CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125514Orig1s065

Trade Name:	KEYTRUDA
Generic or Proper Name:	pembrolizumab
Sponsor:	Merck Sharp & Dohme Corp.
Approval Date:	September 17, 2019
Indication:	Keytruda is a programmed death receptor-1 (PD-1)-blocking antibody indicated: Melanoma • for the treatment of patients with unresectable or metastatic melanoma. • for the adjuvant treatment of patients with melanoma with involvement of lymph node(s) following complete resection. Non-Small Cell Lung Cancer (NSCLC) • in combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic nonsquamous NSCLC, with no EGFR or ALK genomic tumor aberrations. • in combination with carboplatin and either paclitaxel or paclitaxel protein-bound, as first-line treatment of patients with metastatic squamous NSCLC. • as a single agent for the first-line treatment of patients with NSCLC expressing PD-L1 [Tumor Proportion Score (TPS) ≥1%] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, and is:

    - stage III where patients are not candidates for surgical resection or definitive chemoradiation, or
    - metastatic.
- as a single agent for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA.

Small Cell Lung Cancer (SCLC)

- for the treatment of patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy.[1]

Head and Neck Squamous Cell Cancer (HNSCC)

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

Classical Hodgkins Lymphoma (cHL)

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

Primary Mediastinal Large B-Cell Lymphoma (PMBCL)

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

Urothelial Carcinoma

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

Microsatellite Instability-High Cancer

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

Gastric Cancer

- for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors espress PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test, with disease progression on or after 2 or more prior lines ot therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy.[1]

Esophageal Cancer

- for the treatment of patients with recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA-approved test, with disease progression after one or more prior lines of systemic 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 [Combined Positive Score (CPS) ≥10] as determined by an FDA-approved test.[1]

Hepatocellular Carcinoma (HCC)

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

Merkel Cell Carcinoma (MCC)

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

Renal Cell Carcinoma (RCC)

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

Endometrial Carcinoma

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

1 This 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

125514Orig1s065

CONTENTS

Reviews / Information Included in this NDA Review.

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s065

APPROVAL LETTER

BLA 125514/S-065

ACCELERATED APPROVAL

Merck Sharp & Dohme Corp.,
a subsidiary of Merck & Co., Inc.
Attention: Lynn May Brown, PhD
Director, Global Regulatory Affairs
126 E. Lincoln Avenue, RY34-B293, P.O. Box 2000
Rahway, NJ 07065

Dear Dr. Brown:

Please refer to your supplemental biologics license application (sBLA), dated June 17, 2019, received June 17, 2019, 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/4 mL.

This Prior Approval supplemental new drug application provides for the following indication: KEYTRUDA®, in combination with lenvatinib, is indicated for the treatment of patients with advanced endometrial carcinoma that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trial.

APPROVAL & LABELING

We have completed our review of this application. It is approved under the provisions of accelerated approval regulations (21 CFR 314.500), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

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

CONTENT OF LABELING

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

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

and Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements.

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

The SPL will be accessible via publicly available labeling repositories.

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

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 601.41, require further adequate and well-controlled studies/clinical trials to verify and describe clinical benefit. You are required to conduct such studies/clinical trials with due diligence. If postmarketing studies/clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 601.43(b), withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated September 16, 2019. This requirement, along with required completion dates, is listed below.

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

3700-1 Submit the analyses and datasets with the final report for PFS and OS for the ongoing clinical trial E7080-G000-309/KEYNOTE-775, entitled, "A Randomized, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib in Combination With Pembrolizumab Versus Treatment of Physician's Choice in Participants With Advanced Endometrial Cancer" to verify and describe the clinical benefit of the lenvatinib and pembrolizumab combination for patients with not-microsatellite instability high or mismatch repair proficient tumors.

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

Draft Protocol Submission:	09/2017
Final Protocol Submission:	03/2018
Trial Completion:	09/2022
Interim /Other (Last Patient Enrolled)	04/2020
Final Report Submission:	03/2023

Submit clinical protocols to your IND 122753 for this product. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each requirement in your annual report to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial.

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

REQUIRED PEDIATRIC ASSESSMENTS

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

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable in children. Endometrial cancer occurs, for the most part, in the adult population. The incidence of this cancer type in pediatric patients is extremely rare and as such, clinical pediatric studies are impossible or highly impracticable.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3700-2 Submit the analyses and datasets with the final report for PFS for the ongoing clinical trial E7080-G000-313/MK-7902-001, entitled, "A Phase 3 Randomized, Open-Label, Study of Pembrolizumab (MK-3475) Plus Lenvatinib Versus Chemotherapy for Firstline Treatment of Advanced or Recurrent Endometrial Carcinoma" to verify and describe the clinical benefit of the lenvatinib and pembrolizumab combination for patients with not-microsatellite instability high or mismatch repair proficient tumors.

The timetable you submitted on September 16, 2019, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	02/2019
Trial Completion:	09/2022
Final Report Submission:	03/2023

If PFS is negative, the CSR will not be produced until positive OS interim analysis or when final OS analysis is reached. If PFS is positive at IA2 and OS is negative, the study will continue for OS**.**

3700-3 Submit the analyses and datasets with the final report for OS for the ongoing clinical trial E7080-G000-313/MK-7902-001, entitled, “A Phase 3 Randomized, Open-Label, Study of Pembrolizumab (MK-3475) Plus Lenvatinib Versus Chemotherapy for Firstline Treatment of Advanced or Recurrent Endometrial Carcinoma” to verify and describe the clinical benefit of the lenvatinib and pembrolizumab combination for patients with not-microsatellite instability high or mismatch repair proficient tumors.

The timetable you submitted on September 16, 2019, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	02/2019
Trial Completion:	11/2023
Final Report Submission:	05/2024

3700-4 Commitment to support the availability of an immunohistochemistry-based in vitro diagnostic device that is essential to the safe and effective use of the lenvatinib and pembrolizumab combination for patients with tumors that are mismatch repair proficient through an appropriate analytical and clinical validation study using clinical trial data that will support labeling.

The timetable you submitted on September 16, 2019, states that you will conduct this study according to the following schedule:

Final Report Submission:	09/2023

3700-5 Commitment to support the availability of a nucleic acid-based in vitro diagnostic device that is essential to the safe and effective use of the lenvatinib and pembrolizumab combination for patients with tumors that are not microsatellite instability-high through an appropriate analytical and clinical validation study using clinical trial data that will support labeling.

The timetable you submitted on September 16, 2019, states that you will conduct this study according to the following schedule:

Final Report Submission: 09/2024

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 122753 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

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

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

Send each submission directly to:

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

Alternatively, you may submit promotional materials for accelerated approval products electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry.[3]

REPORTING REQUIREMENTS

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

If you have any questions, contact Rajesh Venugopal, Senior Regulatory Project Manager, at (301) 796-4730.

Sincerely,

{See appended electronic signature page}

Julia Beaver, MD
Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide

[3] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

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/

JULIA A BEAVER
09/17/2019 10:05:16 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s065

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)	09/2019
Dosage and Administration (2)	09/2019
Warnings and Precautions (5)	06/2019

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

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

Melanoma

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

Non-Small Cell Lung Cancer (NSCLC)

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

Small Cell Lung Cancer (SCLC)

- for the treatment of patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy.[1] (1.3)

Head and Neck Squamous Cell Cancer (HNSCC)

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

Classical Hodgkin Lymphoma (cHL)

- for the treatment of adult and pediatric patients with refractory cHL, or who have relapsed after 3 or more prior lines of therapy.[1] (1.5)

Primary Mediastinal Large B-Cell Lymphoma (PMBCL)

- for the treatment of adult and pediatric patients with refractory PMBCL, or who have relapsed after 2 or more prior lines of therapy.[1] (1.6)
- Limitations of Use: KEYTRUDA is not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy.

Urothelial Carcinoma

- for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA-approved test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.[1] (1.7, 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. (1.7)

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] (1.8)
- 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

- 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 2 or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy.[1] (1.9, 2.1)

Esophageal Cancer

- for the treatment of patients with recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA-approved test, with disease progression after one or more prior lines of systemic therapy. (1.10, 2.1)

Cervical Cancer

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

Hepatocellular Carcinoma (HCC)

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

Merkel Cell Carcinoma (MCC)

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

Renal Cell Carcinoma (RCC)

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

Endometrial Carcinoma

- in combination with lenvatinib, for the treatment of patients with advanced endometrial carcinoma that is not MSI-H or dMMR, who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation.[1] (1.15)

[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)
- SCLC: 200 mg every 3 weeks (2.4)
- HNSCC: 200 mg every 3 weeks. (2.5)
- cHL or PMBCL: 200 mg every 3 weeks for adults; 2 mg/kg (up to 200 mg) every 3 weeks for pediatrics. (2.6, 2.7)
- Urothelial Carcinoma: 200 mg every 3 weeks. (2.8)
- MSI-H Cancer: 200 mg every 3 weeks for adults and 2 mg/kg (up to 200 mg) every 3 weeks for pediatrics. (2.9)
- Gastric Cancer: 200 mg every 3 weeks. (2.10)
- Esophageal Cancer: 200 mg every 3 weeks. (2.11)
- Cervical Cancer: 200 mg every 3 weeks. (2.12)

- HCC: 200 mg every 3 weeks. (2.13)
- MCC: 200 mg every 3 weeks for adults; 2 mg/kg (up to 200 mg) every 3 weeks for pediatrics. (2.14)
- RCC: 200 mg every 3 weeks with axitinib 5 mg orally twice daily. (2.15)
- Endometrial Carcinoma: 200 mg every 3 weeks with lenvatinib 20 mg orally once daily for tumors that are not MSI-H or dMMR. (2.16)

Administer KEYTRUDA as an intravenous infusion over 30 minutes.

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

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

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

None. (4)

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

- Immune-mediated pneumonitis: Withhold for moderate, and permanently discontinue for severe, life-threatening or recurrent moderate pneumonitis. (5.1)
- Immune-mediated colitis: Withhold for moderate or severe, and permanently discontinue for life-threatening colitis. (5.2)
- Immune-mediated hepatitis (KEYTRUDA) and hepatotoxicity (KEYTRUDA in combination with axitinib): Monitor for changes in hepatic function. Based on severity of liver enzyme elevations, withhold or discontinue KEYTRUDA, axitinib, or KEYTRUDA and axitin b. Consider corticosteroid therapy. (2.17, 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 poss ble organ rejection. (5.7)
- Infusion-related reactions: Stop infusion and permanently discontinue KEYTRUDA for severe or life-threatening infusion reactions. (5.8)
- Complications of allogeneic HSCT (5.9):
  - Allogeneic HSCT after treatment with KEYTRUDA: Monitor for hepatic veno-occlusive disease, grade 3-4 acute GVHD including hyperacute GVHD, steroid-requiring febrile syndrome, and other immune-mediated adverse reactions. Transplant-related mortality has occurred.
  - Allogeneic HSCT prior to treatment with KEYTRUDA: In patients with a history of allogeneic HSCT, consider the benefit of treatment with KEYTRUDA versus the risk of GVHD.
- Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking ant body in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials. (5.10)
- Embryo-Fetal toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective method of contraception. (5.11, 8.1, 8.3)

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

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

- KEYTRUDA as a single agent: fatigue, musculoskeletal pain, decreased appetite, pruritus, diarrhea, nausea, rash, pyrexia, cough, dyspnea, constipation, pain, and abdominal pain. (6.1)
- KEYTRUDA in combination with chemotherapy: fatigue/asthenia, nausea, constipation, diarrhea, decreased appetite, rash, vomiting, cough, dyspnea, pyrexia, alopecia, peripheral neuropathy, mucosal inflammation, and stomatitis. (6.1)
- KEYTRUDA in combination with axitinib: diarrhea, fatigue/asthenia, hypertension, hepatotoxicity, hypothyroidism, decreased appetite, palmar-plantar erythrodysesthesia, nausea, stomatitis/mucosal inflammation, dysphonia, rash, cough, and constipation. (6.1)
- KEYTRUDA in combination with lenvatinib: fatigue, hypertension, musculoskeletal pain, diarrhea, decreased appetite, hypothyroidism, nausea, stomatitis, vomiting, decreased weight, abdominal pain, headache, constipation, urinary tract infection, dysphonia, hemorrhagic events, hypomagnesemia, palmar-plantar erythrodysesthesia, dyspnea, cough, and rash. (6.1)

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

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

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 09/2019

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 NSCLC expressing PD-L1 [Tumor Proportion Score (TPS) ≥1%] as determined by an FDA-approved test *[see Dosage and Administration (2.1)]*, with no EGFR or ALK genomic tumor aberrations, and is:

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

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

1.3 Small Cell Lung Cancer

KEYTRUDA is indicated for the treatment of patients with metastatic small cell lung cancer (SCLC) with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy.

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 confirmatory trials.

1.4 Head and Neck Squamous Cell Cancer

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

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

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

1.5 Classical Hodgkin Lymphoma

KEYTRUDA is indicated for the treatment of adult 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 (14.5)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

1.6 Primary Mediastinal Large B-Cell Lymphoma

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

This indication is approved under accelerated approval based on tumor response rate and durability 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.

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

1.7 Urothelial Carcinoma

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

This indication is approved under accelerated approval based on tumor response rate and duration of response *[see Clinical Studies (14.7)]*. 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.

1.8 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 (dMMR)

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

This indication is approved under accelerated approval based on tumor response rate and durability of response *[see Clinical Studies (14.8)]*. 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.

1.9 Gastric Cancer

KEYTRUDA is indicated for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test *[see Dosage and Administration (2.1)]*, with disease progression on or after 2 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 (14.9)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

1.10 Esophageal Cancer

KEYTRUDA is indicated for the treatment of patients with recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus whose tumors express PD-L1 (CPS ≥10) as determined by

an FDA-approved test *[see Dosage and Administration (2.1)]*, with disease progression after one or more prior lines of systemic therapy.

1.11 Cervical Cancer

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

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

1.12 Hepatocellular Carcinoma

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

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

1.13 Merkel Cell Carcinoma

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

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

1.14 Renal Cell Carcinoma

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

1.15 Endometrial Carcinoma

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

This indication is approved under accelerated approval based on tumor response rate and durability of response *[see Clinical Studies (14.15)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

2 DOSAGE AND ADMINISTRATION

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

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

- stage III NSCLC who are not candidates for surgical resection or definitive chemoradiation *[see Clinical Studies (14.2)]*.
- metastatic NSCLC *[see Clinical Studies (14.2)].*
- first-line treatment of metastatic or unresectable, recurrent HNSCC *[see Clinical Studies (14.4)]*.
- metastatic urothelial carcinoma *[see Clinical Studies (14.7)]*.
- metastatic gastric cancer *[see Clinical Studies (14.9)]*. If PD-L1 expression is not detected in an archival gastric cancer specimen, evaluate the feasibility of obtaining a tumor biopsy for PD-L1 testing.
- metastatic esophageal cancer *[see Clinical Studies (14.10)]*.
- recurrent or metastatic cervical cancer *[see Clinical Studies (14.11)]*.

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 SCLC

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 HNSCC

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

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

2.6 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.

2.7 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.

2.8 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.

2.9 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.

2.10 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.

2.11 Recommended Dosage for Esophageal 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.

2.12 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.

2.13 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.

2.14 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.

2.15 Recommended Dosage for RCC

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

2.16 Recommended Dosage for Endometrial Carcinoma

The recommended dose of KEYTRUDA is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks in combination with lenvatinib 20 mg orally once daily until disease progression, unacceptable toxicity, or for KEYTRUDA, up to 24 months in patients without disease progression.

Refer to the lenvatinib prescribing information for recommended dosing information.

2.17 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†

Adverse Reaction	Severity*	Dose Modification for KEYTRUDA
For liver enzyme elevations in RCC patients treated with combination therapy, see dosing guidelines following this table.	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
Recurrent immune-mediated adverse reactions	Recurrent Grade 2 pneumonitis Recurrent Grades 3 or 4	Permanently discontinue
Inability to taper corticosteroid	Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks after last dose of KEYTRUDA	Permanently discontinue
Persistent Grade 2 or 3 adverse reaction (excluding endocrinopathy)	Grades 2 or 3 adverse reactions lasting 12 weeks or longer after last dose of KEYTRUDA	Permanently discontinue
Infusion-related reactions	Grades 1 or 2	Interrupt or slow the rate of infusion
	Grades 3 or 4	Permanently discontinue

* Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events. Version 4.0 (NCI CTCAE v4)

† Resume in patients with complete or partial resolution (Grades 0 to 1) after corticosteroid taper.

‡ Resume in HCC patients when AST or ALT and total bilirubin recover to Grades 0-1 or to baseline.

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

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

When administering KEYTRUDA in combination with lenvatinib for the treatment of endometrial carcinoma, interrupt one or both as appropriate. No dose reductions are recommended for KEYTRUDA. Withhold, dose reduce, or discontinue lenvatinib in accordance with the instructions in the lenvatinib prescribing information.

2.18 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 (2.17) and Adverse Reactions (6.1)].*

In clinical studies enrolling 2799 patients with various cancers who received KEYTRUDA as a single agent, pneumonitis occurred in 94 (3.4%) patients, including Grade 1 (0.8%), Grade 2 (1.3%), Grade 3

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

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

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

5.2 Immune-Mediated Colitis

KEYTRUDA can cause immune-mediated colitis. Monitor patients for signs and symptoms of colitis. Administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper) for Grade 2 or greater colitis. Withhold KEYTRUDA for moderate (Grade 2) or severe (Grade 3) colitis, and permanently discontinue KEYTRUDA for life-threatening (Grade 4) colitis *[see Dosage and Administration (2.17) and Adverse Reactions (6.1)].*

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

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

Immune-Mediated Hepatitis

KEYTRUDA can cause immune-mediated hepatitis. Monitor patients for changes in liver function. Administer corticosteroids (initial dose of 0.5 to 1 mg/kg/day [for Grade 2 hepatitis] and 1 to 2 mg/kg/day [for Grade 3 or greater hepatitis] prednisone or equivalent followed by a taper) and, based on severity of liver enzyme elevations, withhold or discontinue KEYTRUDA *[see Dosage and Administration (2.17) and Adverse Reactions (6.1)].*

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

Hepatotoxicity in Combination with Axitinib

KEYTRUDA in combination with axitinib can cause hepatic toxicity with higher than expected frequencies of Grades 3 and 4 ALT and AST elevations compared to KEYTRUDA alone. Monitor liver enzymes before initiation of and periodically throughout treatment. Consider more frequent monitoring of liver enzymes as compared to when the drugs are administered as single agents. For elevated liver enzymes, interrupt KEYTRUDA and axitinib and consider administering corticosteroids as needed *[see Dosage and Administration (2.17)]*.

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

5.4 Immune-Mediated Endocrinopathies

Hypophysitis

KEYTRUDA can cause hypophysitis. Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency). Administer corticosteroids and hormone replacement as clinically indicated. Withhold KEYTRUDA for moderate (Grade 2) hypophysitis and withhold or discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) hypophysitis *[see Dosage and Administration (2.17) 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 (2.17) and Adverse Reactions (6.1)].*

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

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

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

Type 1 Diabetes mellitus

KEYTRUDA can cause type 1 diabetes mellitus, including diabetic ketoacidosis, which have been reported in 6 (0.2%) of 2799 patients receiving KEYTRUDA. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Administer insulin for type 1 diabetes and withhold KEYTRUDA and administer anti-hyperglycemics in patients with severe hyperglycemia *[see Dosage and Administration (2.17) 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 (2.17) 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 (2.17)].*

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 (2.17) 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 (2.17)]*.

5.9 Complications of Allogeneic HSCT

Allogeneic HSCT after treatment with KEYTRUDA

Immune-mediated complications, including fatal events, occurred in patients who underwent allogeneic hematopoietic stem cell transplantation (HSCT) after being treated with KEYTRUDA. Of 23 patients with cHL who proceeded to allogeneic HSCT after treatment with KEYTRUDA on any trial, 6 patients (26%) developed graft-versus-host-disease (GVHD), one of which was fatal, and 2 patients (9%) developed severe hepatic veno-occlusive disease (VOD) after reduced-intensity conditioning, one of which was fatal. Cases of fatal hyperacute GVHD after allogeneic HSCT have also been reported in patients with lymphoma who received a PD-1 receptor blocking antibody before transplantation. These complications may occur despite intervening therapy between PD-1 blockade and allogeneic HSCT. Follow patients closely for early evidence of transplant-related complications such as hyperacute GVHD, severe (Grade 3 to 4) acute GVHD, steroid-requiring febrile syndrome, hepatic VOD, and other immune-mediated adverse reactions, and intervene promptly.

Allogeneic HSCT prior to treatment with KEYTRUDA

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

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

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

5.11 Embryo-Fetal Toxicity

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

6 ADVERSE REACTIONS

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

- Immune-mediated pneumonitis *[see Warnings and Precautions (5.1)]*.
- Immune-mediated colitis *[see Warnings and Precautions (5.2)]*.
- Immune-mediated hepatitis (KEYTRUDA) and hepatotoxicity (KEYTRUDA in combination with axitinib) *[see Warnings and Precautions (5.3)]*.
- Immune-mediated endocrinopathies *[see Warnings and Precautions (5.4)]*.

- Immune-mediated nephritis and renal dysfunction *[see Warnings and Precautions (5.5)]*.
- Immune-mediated skin adverse reactions *[see Warnings and Precautions (5.6)]*.
- Other immune-mediated adverse reactions *[see Warnings and Precautions (5.7)]*.
- Infusion-related reactions *[see Warnings and Precautions (5.8)].*

6.1 Clinical Trials Experience

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

The data described in the WARNINGS AND PRECAUTIONS reflect exposure to KEYTRUDA as a single agent in 2799 patients in three randomized, open-label, active-controlled trials (KEYNOTE-002, KEYNOTE-006, and KEYNOTE-010), which enrolled 912 patients with melanoma and 682 patients with NSCLC, and one single-arm trial (KEYNOTE-001), which enrolled 655 patients with melanoma and 550 patients with NSCLC. In addition to the 2799 patients, certain subsections in the WARNINGS AND PRECAUTIONS describe adverse reactions observed with exposure to KEYTRUDA as a single agent in two randomized, open-label, active-controlled clinical trials (KEYNOTE-042 and KEYNOTE-024), which enrolled 790 patients with NSCLC; in a non-randomized, open-label, multi-cohort trial (KEYNOTE-012), a non-randomized, open-label, single-cohort trial (KEYNOTE-055), and two randomized, open-label, active-controlled trials (KEYNOTE-040 and KEYNOTE-048 single agent arms), which enrolled 909 patients with HNSCC; in two non-randomized, open-label trials (KEYNOTE-013 and KEYNOTE-087), which enrolled 241 patients with cHL; in combination with chemotherapy in a randomized, active-controlled trial (KEYNOTE-189), which enrolled 405 patients with nonsquamous NSCLC; in a randomized, open-label, active-controlled trial (KEYNOTE-048 combination arm), which enrolled 276 patients with HNSCC; in combination with axitinib in a randomized, active-controlled trial (KEYNOTE 426), which enrolled 429 patients with RCC; and in post-marketing use. Across all trials, KEYTRUDA was administered at doses of 2 mg/kg intravenously every 3 weeks, 10 mg/kg intravenously every 2 weeks, 10 mg/kg intravenously every 3 weeks, or 200 mg intravenously every 3 weeks. Among the 2799 patients, 41% were exposed for 6 months or more and 21% were exposed for 12 months or more.

The data described in this section were obtained in ten randomized, controlled trials (KEYNOTE-002, KEYNOTE-006, KEYNOTE-010, KEYNOTE-042, KEYNOTE-045, KEYNOTE-048, KEYNOTE-189, KEYNOTE-407, KEYNOTE-181, and KEYNOTE-426) and ten non-randomized, open-label trials (KEYNOTE-028, KEYNOTE-012, KEYNOTE-087, KEYNOTE-170, KEYNOTE-052, KEYNOTE-059, KEYNOTE-158, KEYNOTE-224, KEYNOTE-017, and KEYNOTE-146). The data described in this section also included a single randomized, double-blind, placebo-controlled trial (KEYNOTE-054) in which KEYTRUDA was administered for the adjuvant treatment of 509 patients with melanoma with involvement of lymph node(s) following complete surgical resection. In these trials, KEYTRUDA was administered at 2 mg/kg every 3 weeks, 200 mg every 3 weeks, or 10 mg/kg every 2 or 3 weeks.

Melanoma

Ipilimumab-Naive Melanoma

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

The median duration of exposure was 5.6 months (range: 1 day to 11.0 months) for KEYTRUDA and similar in both treatment arms. Fifty-one and 46% of patients received KEYTRUDA 10 mg/kg every 2 or

3 weeks, respectively, for ≥6 months. No patients in either arm received treatment for more than one year.

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

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

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

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

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

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

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

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

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

† Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (520 to 546 patients) and ipilimumab (237 to 247 patients); hypertriglyceridemia: KEYTRUDA n=429 and ipilimumab n=183; hypercholesterolemia: KEYTRUDA n=484 and ipilimumab n=205.

‡ Graded per NCI CTCAE v4.0

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

Ipilimumab-Refractory Melanoma

The safety of KEYTRUDA in patients with unresectable or metastatic melanoma with disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor, was investigated in KEYNOTE-002. KEYNOTE-002 was a multicenter, partially blinded (KEYTRUDA dose), randomized (1:1:1), active-controlled trial in which 528 patients received KEYTRUDA 2 mg/kg (n=178) or 10 mg/kg (n=179) every 3 weeks or investigator's choice of chemotherapy (n=171), consisting of dacarbazine (26%), temozolomide (25%), paclitaxel and carboplatin (25%), paclitaxel (16%), or carboplatin (8%) *[see Clinical Studies (14.1)]*. Patients with autoimmune disease, severe immune-related toxicity related to ipilimumab, defined as any Grade 4 toxicity or Grade 3 toxicity requiring corticosteroid treatment (greater than 10 mg/day prednisone or equivalent dose) for greater than 12 weeks; medical conditions that required systemic corticosteroids or other immunosuppressive medication; a history of interstitial lung disease; or an active infection requiring therapy, including HIV or hepatitis B or C, were ineligible.

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

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

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

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

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

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

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

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

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

* Laboratory abnormalities occurring at same or higher incidence than in chemotherapy arm.
† Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (range: 320 to 325 patients) and chemotherapy (range: 154 to 161 patients); hypertriglyceridemia: KEYTRUDA n=247 and chemotherapy n=116; decreased bicarbonate: KEYTRUDA n=263 and chemotherapy n=123.
‡ Graded per NCI CTCAE v4.0

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

Adjuvant Treatment of Resected Melanoma

The safety of KEYTRUDA as a single agent was investigated in KEYNOTE-054, a randomized (1:1) double-blind trial in which 1019 patients with completely resected stage IIIA (>1 mm lymph node metastasis), IIIB or IIIC melanoma received 200 mg of KEYTRUDA by intravenous infusion every 3 weeks

(n=509) or placebo (n=502) for up to one year *[see Clinical Studies (14.1)]*. Patients with active autoimmune disease or a medical condition that required immunosuppression or mucosal or ocular melanoma were ineligible. Seventy-six percent of patients received KEYTRUDA for 6 months or longer.

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

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

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

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

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

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

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

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

NSCLC

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

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

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

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

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

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

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

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

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

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

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA/pemetrexed/platinum chemotherapy (range: 381 to 401 patients) and placebo/pemetrexed/platinum chemotherapy (range: 184 to 197 patients).
† Graded per NCI CTCAE v4.03

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

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

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

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

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

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

Previously Untreated NSCLC

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

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

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

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

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

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

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

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

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

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

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (range: 598 to 610 patients) and chemotherapy (range: 588 to 597 patients); increased prothrombin INR: KEYTRUDA n=203 and chemotherapy n=173.
† Graded per NCI CTCAE v4.03

Previously Treated NSCLC

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

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

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

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

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

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

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

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

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

Laboratory Test†	KEYTRUDA 2 or 10 mg/kg every 3 weeks		Docetaxel 75 mg/m^2 every 3 weeks	
	All Grades‡ %	Grades 3-4 %	All Grades‡ %	Grades 3-4 %
Chemistry				
Hyponatremia	32	8	27	2.9
Increased a kaline 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).

SCLC

Among the 131 patients with previously treated SCLC who received KEYTRUDA in KEYNOTE-158 Cohort G (n=107) and KEYNOTE-028 Cohort C1 (n=24) *[see Clinical Studies (14.3)]*, the median duration of exposure to KEYTRUDA was 2 months (range: 1 day to 2.25 years). Patients with autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Adverse reactions occurring in patients with SCLC were similar to those occurring in patients with other solid tumors who received KEYTRUDA as a single agent.

HNSCC

First-line treatment of metastatic or unresectable, recurrent HNSCC

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

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

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

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

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

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

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

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

* Graded per NCI CTCAE v4.0

† Includes fatigue, asthenia

‡ Includes diarrhea, colitis, hemorrhagic diarrhea, microscopic colitis

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

¶ Includes cough, productive cough

Includes dyspnea, exertional dyspnea

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

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

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

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

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

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

† Graded per NCI CTCAE v4.0

Previously treated recurrent or metastatic HNSCC

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

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

KEYTRUDA was discontinued due to adverse reactions in 17% of patients. Serious adverse reactions occurred in 45% of patients receiving KEYTRUDA. The most frequent serious adverse reactions reported in at least 2% of patients were pneumonia, dyspnea, confusional state, vomiting, pleural effusion, and respiratory failure. The incidence of adverse reactions, including serious adverse reactions, was similar between dosage regimens (10 mg/kg every 2 weeks or 200 mg every 3 weeks); therefore, summary safety results are provided in a pooled analysis. The most common adverse reactions (occurring in ≥20% of patients) were fatigue, decreased appetite, and dyspnea. Adverse reactions occurring in patients with HNSCC were generally similar to those occurring in 2799 patients with melanoma or NSCLC treated with KEYTRUDA as a single agent, with the exception of increased incidences of facial edema (10% all Grades; 2.1% Grades 3-4) and new or worsening hypothyroidism *[see Warnings and Precautions (5.4)]*.

cHL

Among the 210 patients with cHL enrolled in KEYNOTE-087 *[see Clinical Studies (14.5)]*, the median duration of exposure to KEYTRUDA was 8.4 months (range: 1 day to 15.2 months). KEYTRUDA was discontinued due to adverse reactions in 5% of patients, and treatment was interrupted due to adverse reactions in 26%. Fifteen percent (15%) of patients had an adverse reaction requiring systemic

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

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

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

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

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

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

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

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

† Graded per NCI CTCAE v4.0

‡ Includes elevation of AST or ALT

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

PMBCL

Among the 53 patients with PMBCL treated in KEYNOTE-170 *[see Clinical Studies (14.6)],* the median duration of exposure to KEYTRUDA was 3.5 months (range: 1 day to 22.8 months).

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

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

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

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

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

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

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

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

Urothelial Carcinoma

Cisplatin Ineligible Patients with Urothelial Carcinoma

The safety of KEYTRUDA was investigated in KEYNOTE-052, a single-arm trial that enrolled 370 patients with locally advanced or metastatic urothelial carcinoma who were not eligible for cisplatin-containing chemotherapy. Patients with autoimmune disease or medical conditions that required systemic corticosteroids or other immunosuppressive medications were ineligible *[see Clinical Studies (14.7)]*. Patients received KEYTRUDA 200 mg every 3 weeks until unacceptable toxicity or either radiographic or clinical disease progression.

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

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

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

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

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

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

* Graded per NCI CTCAE v4.0

† Includes fatigue, asthenia

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

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

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

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

Þ Includes dermatitis, dermatitis bullous, eczema, erythema, rash, rash macular, rash maculo-papular, rash pruritic, rash pustular, skin reaction, dermatitis acneiform, seborrheic dermatitis, palmar-plantar erythrodysesthesia syndrome, rash generalized

Previously Treated Urothelial Carcinoma

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

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

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

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

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

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

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

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

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

† Graded per NCI CTCAE v4.0

Gastric Cancer

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

Esophageal Cancer

Among the 314 patients with esophageal cancer enrolled in KEYNOTE-181 *[see Clinical Studies (14.10)]* treated with KEYTRUDA, the median duration of exposure to KEYTRUDA was 2.1 months (range: 1 day to 24.4 months). Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible. Adverse reactions occurring in patients with esophageal cancer were similar to those occurring in 2799 patients with melanoma or NSCLC treated with KEYTRUDA as a single agent.

Cervical Cancer

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

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

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

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

* Graded per NCI CTCAE v4.0

† Includes asthenia, fatigue, lethargy, malaise

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

§ Includes edema peripheral, peripheral swelling

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

Includes colitis, diarrhea, gastroenteritis

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

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

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

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

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

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

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

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

† Graded per NCI CTCAE v4.0

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

HCC

Among the 104 patients with HCC who received KEYTRUDA in KEYNOTE-224 *[see Clinical Studies (14.12)]*, the median duration of exposure to KEYTRUDA was 4.2 months (range: 1 day to 1.5 years). Adverse reactions occurring in patients with HCC were generally similar to those in 2799 patients with melanoma or NSCLC treated with KEYTRUDA as a single agent, with the exception of increased incidences of ascites (8% Grades 3-4) and immune-mediated hepatitis (2.9%). Laboratory abnormalities (Grades 3-4) that occurred at a higher incidence were elevated AST (20%), ALT (9%), and hyperbilirubinemia (10%).

MCC

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

RCC

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

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

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

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

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

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

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

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

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

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

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks and Axitinib n=429		Sunitinib n=425	
	All Grades* (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Gastrointestinal				
Diarrhea†	56	11	45	5
Nausea	28	0.9	32	0.9
Constipation	21	0	15	0.2
General				
Fatigue/Asthenia	52	5	51	10
Vascular				
Hypertension‡	48	24	48	20
Hepatobiliary				
Hepatotoxicity§	39	20	25	4.9
Endocrine				
Hypothyroidism	35	0.2	32	0.2
Metabolism and Nutrition				
Decreased appetite	30	2.8	29	0.7
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysaesthesia syndrome	28	5	40	3.8
Stomatitis/Mucosal inflammation	27	1.6	41	4
Rash¶	25	1.4	21	0.7
Respiratory, Thoracic and Mediastinal				
Dysphonia	25	0.2	3.3	0
Cough	21	0.2	14	0.5

* Graded per NCI CTCAE v4.03

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

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

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

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

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

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks and Axitinib		Sunitinib	
	All Grades† %	Grades 3-4 %	All Grades %	Grades 3-4 %
Chemistry				
Hyperglycemia	62	9	54	3.2
Increased ALT	60	20	44	5
Increased AST	57	13	56	5
Increased creatinine	43	4.3	40	2.4
Hyponatremia	35	8	29	8
Hyperkalemia	34	6	22	1.7
Hypoalbuminemia	32	0.5	34	1.7
Hypercalcemia	27	0.7	15	1.9
Hypophosphatemia	26	6	49	17
Increased alkaline phosphatase	26	1.7	30	2.7
Hypocalcemia‡	22	0.2	29	0.7
Blood bilirubin increased	22	2.1	21	1.9
Activated partial thromboplastin time prolonged§	22	1.2	14	0
Hematology				
Lymphopenia	33	11	46	8
Anemia	29	2.1	65	8
Thrombocytopenia	27	1.4	78	14

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

Endometrial Carcinoma

The safety of KEYTRUDA in combination with lenvatinib (20 mg orally once daily) was investigated in KEYNOTE-146, a single-arm, multicenter, open-label trial in 94 patients with endometrial carcinoma whose tumors had progressed following one line of systemic therapy and were not MSI-H or dMMR *[see Clinical Studies (14.15)]*. The median duration of study treatment was 7 months (range: 0.03 to 37.8 months). The median duration of exposure to KEYTRUDA was 6 months (range: 0.03 to 23.8 months). KEYTRUDA was continued for a maximum of 24 months; however, treatment with lenvatinib could be continued beyond 24 months.

Fatal adverse reactions occurred in 3% of patients receiving KEYTRUDA and lenvatinib, including gastrointestinal perforation, reversible posterior leukoencephalopathy syndrome (RPLS) with intraventricular hemorrhage, and intracranial hemorrhage.

Serious adverse reactions occurred in 52% of patients receiving KEYTRUDA and lenvatinib. Serious adverse reactions in ≥3% of patients were hypertension (9%), abdominal pain (6%), musculoskeletal pain (5%), hemorrhage (4%), fatigue (4%), nausea (4%), confusional state (4%), pleural effusion (4%), adrenal insufficiency (3%), colitis (3%), dyspnea (3%), and pyrexia (3%).

KEYTRUDA was discontinued for adverse reactions (Grade 1-4) in 19% of patients, regardless of action taken with lenvatinib. The most common adverse reactions (≥ 2%) leading to discontinuation of KEYTRUDA were adrenal insufficiency (2%), colitis (2%), pancreatitis (2%), and muscular weakness (2%).

Adverse reactions leading to interruption of KEYTRUDA occurred in 49% of patients; the most common adverse reactions leading to interruption of KEYTRUDA (≥2%) were: fatigue (14%), diarrhea (6%), decreased appetite (6%), rash (5%), renal impairment (4%), vomiting (4%), increased lipase (4%), decreased weight (4%), nausea (3%), increased blood alkaline phosphatase (3%), skin ulcer (3%),

adrenal insufficiency (2%), increased amylase (2%), hypocalcemia (2%), hypomagnesemia (2%), hyponatremia (2%), peripheral edema (2%), musculoskeletal pain (2%), pancreatitis (2%), and syncope (2%).

Tables 27 and 28 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in combination with lenvatinib.

Table 27: Adverse Reactions Occurring in ≥20% of Patients with Endometrial Carcinoma in KEYNOTE-146

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks with Lenvatinib N=94	
	All Grades (%)	Grades 3-4 (%)
General		
Fatigue*	65	17
Musculoskeletal and Connective Tissue		
Musculoskeletal pain†	65	3
Vascular		
Hypertension‡	65	38
Hemorrhagic events§	28	4
Gastrointestinal		
Diarrhea¶	64	4
Nausea	48	5
Stomatitis#	43	0
Vomiting	39	0
Abdominal pain Þ	33	6
Constipation	32	0
Metabolism		
Decreased appetiteß	52	0
Hypomagnesemia	27	3
Endocrine		
Hypothyroidismà	51	1
Investigations		
Decreased weight	36	3
Nervous System		
Headache	33	1
Infections		
Urinary tract infectionè	31	4
Respiratory, Thoracic and Mediastinal		
Dysphonia	29	0
Dyspneað	24	2
Cough	21	0
Skin and Subcutaneous Tissue		
Palmar-plantar erythrodysesthesia syndrome	26	3
Rashø	21	3

* Includes asthenia, fatigue, and malaise

† Includes arthralgia, arthritis, back pain, breast pain, musculoskeletal chest pain, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, non-cardiac chest pain, pain in extremity

‡ Includes essential hypertension, hypertension, and hypertensive encephalopathy

§ Includes catheter site bruise, contusion, epistaxis, gastrointestinal hemorrhage, hematemesis, hematuria, hemorrhage intracranial, injection site hemorrhage, intraventricular hemorrhage, large intestinal hemorrhage, metrorrhagia, mouth hemorrhage, uterine hemorrhage, and vaginal hemorrhage

¶ Includes diarrhea, gastroenteritis, gastrointestinal viral infection, and viral diarrhea

Includes glossitis, mouth ulceration, oral discomfort, oral mucosal blistering, oropharyngeal pain, and stomatitis

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

ß Includes decreased appetite and early satiety

à Includes increased blood thyroid stimulating hormone and hypothyroidism

è Includes cystitis and urinary tract infection

ð Includes dyspnea and exertional dyspnea

ø Includes rash, rash generalized, rash macular, and rash maculo-papular

Table 28: Laboratory Abnormalities Worsened from Baseline Occurring in ≥3% of Patients with Endometrial Carcinoma in KEYNOTE-146

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks with Lenvatinib	
	All Grades %†	Grade 3-4 %†
Chemistry		
Increased creatinine	80	7
Hypertriglyceridemia	58	4
Hyperglycemia	53	1
Hypercholesteremia	49	6
Hypoalbuminemia	48	0
Hypomagnesemia	47	2
Increased aspartate aminotransferase	43	4
Hyponatremia	42	13
Increased lipase	42	18
Increased alanine aminotransferase	35	3
Increased alkaline phosphatase	32	1
Hypokalemia	27	5
Increased amylase	19	6
Hypocalcemia	14	3
Hypermagnesemia	4	3
Hematology		
Thrombocytopenia	48	0
Leukopenia	38	2
Lymphopenia	36	7
Anemia	35	1
Increased INR	21	3
Neutropenia	12	3

* With at least 1 grade increase from baseline
† Laboratory abnormality percentage is based on the number of patients who had both baseline and at least one post-baseline laboratory measurement for each parameter (range: 71 to 92 patients).

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 (14.5, 14.6, 14.8), Clinical Pharmacology (12.3)]*.

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

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

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

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

8.5 Geriatric Use

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

11 DESCRIPTION

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

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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

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

12.3 Pharmacokinetics

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

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

Distribution

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

Elimination

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

Specific Populations

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

13.2 Animal Toxicology and/or Pharmacology

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

14 CLINICAL STUDIES

14.1 Melanoma

Ipilimumab-Naive Melanoma

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

Tumors [RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ]). Additional efficacy outcome measures were objective response rate (ORR) and duration of response (DoR).

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

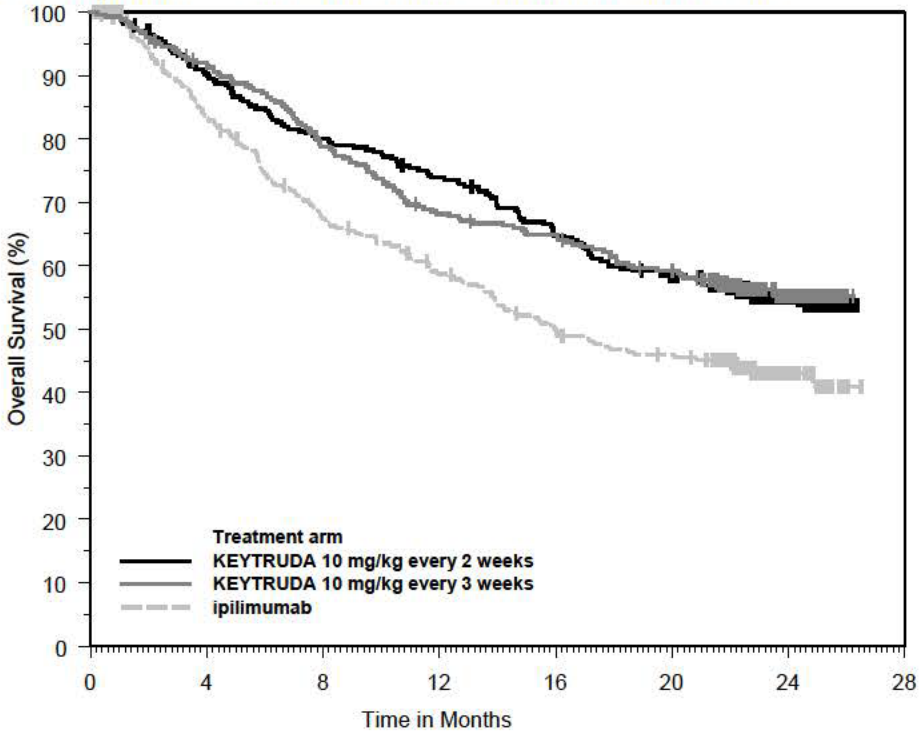
The study demonstrated statistically significant improvements in OS and PFS for patients randomized to KEYTRUDA as compared to ipilimumab. Among the 91 patients randomized to KEYTRUDA 10 mg/kg every 3 weeks with an objective response, response durations ranged from 1.4+ to 8.1+ months. Among the 94 patients randomized to KEYTRUDA 10 mg/kg every 2 weeks with an objective response, response durations ranged from 1.4+ to 8.2 months. Efficacy results are summarized in Table 29 and Figure 1.

Table 29: Efficacy Results in KEYNOTE-006

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

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

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



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

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

Ipilimumab-Refractory Melanoma

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

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

The study demonstrated a statistically significant improvement in PFS for patients randomized to KEYTRUDA as compared to control arm. There was no statistically significant difference between KEYTRUDA 2 mg/kg and chemotherapy or between KEYTRUDA 10 mg/kg and chemotherapy in the OS analysis in which 55% of the patients who had been randomized to receive chemotherapy had crossed over to receive KEYTRUDA. Among the 38 patients randomized to KEYTRUDA 2 mg/kg with an objective response, response durations ranged from 1.3+ to 11.5+ months. Among the 46 patients randomized to KEYTRUDA 10 mg/kg with an objective response, response durations ranged from 1.1+ to 11.1+ months. Efficacy results are summarized in Table 30.

Table 30: Efficacy Results in KEYNOTE-002

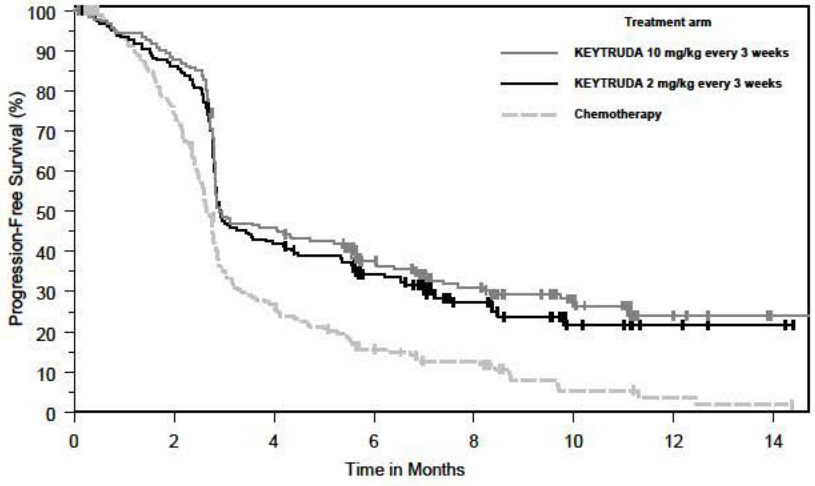
Endpoint	KEYTRUDA 2 mg/kg every 3 weeks n=180	KEYTRUDA 10 mg/kg every 3 weeks n=181	Chemotherapy n=179
PFS			
Number of Events, n (%)	129 (72%)	126 (70%)	155 (87%)
Progression, n (%)	105 (58%)	107 (59%)	134 (75%)
Death, n (%)	24 (13%)	19 (10%)	21 (12%)
Median in months (95% CI)	2.9 (2.8, 3.8)	2.9 (2.8,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

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

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

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

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



Number at Risk

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

Adjuvant Treatment of Resected Melanoma

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

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

The trial demonstrated a statistically significant improvement in RFS for patients randomized to the KEYTRUDA arm compared with placebo. Efficacy results are summarized in Table 31 and Figure 3.

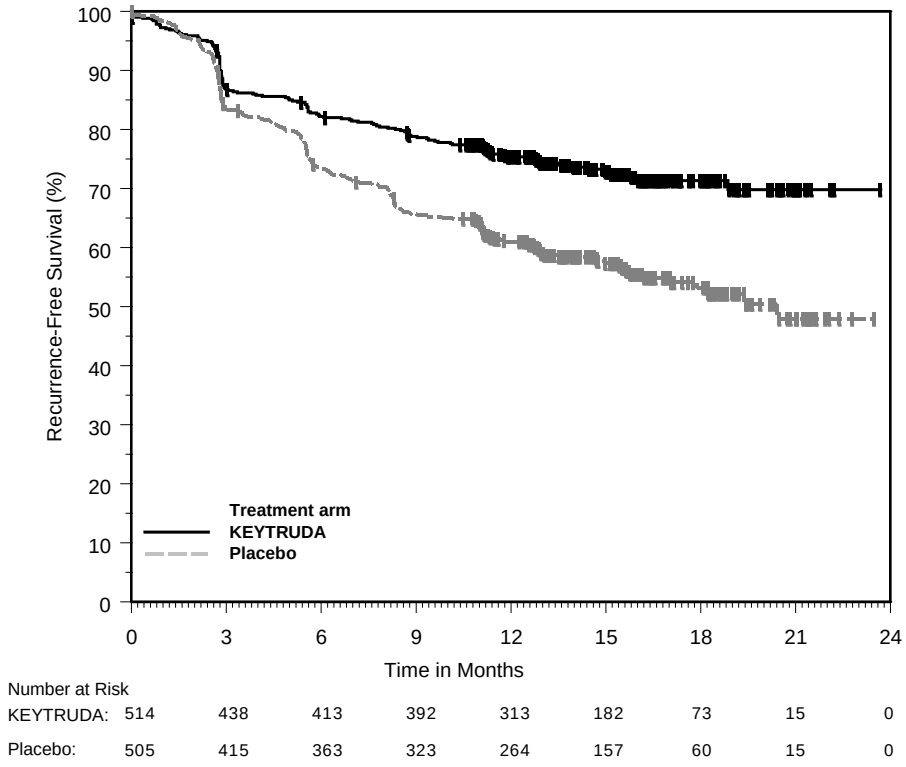
Table 31: Efficacy Results in KEYNOTE-054

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

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

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

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



14.2 Non-Small Cell Lung Cancer

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

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

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

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

was performed at Week 6, Week 12, and then every 9 weeks thereafter. The main efficacy outcome measures were OS and PFS as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Additional efficacy outcome measures were ORR and DoR, as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

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

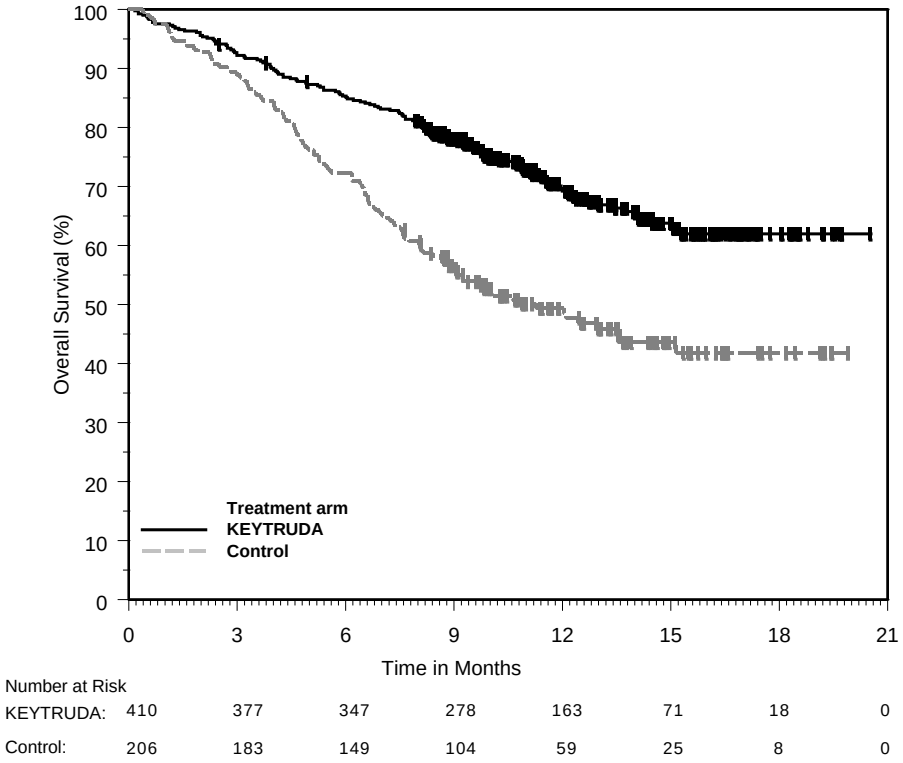
The trial demonstrated a statistically significant improvement in OS and PFS for patients randomized to KEYTRUDA in combination with pemetrexed and platinum chemotherapy compared with placebo, pemetrexed, and platinum chemotherapy. Table 32 and Figure 4 summarize the efficacy results for KEYNOTE-189.

Table 32: Efficacy Results in KEYNOTE-189

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

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

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



Number at Risk

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

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

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

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

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

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

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

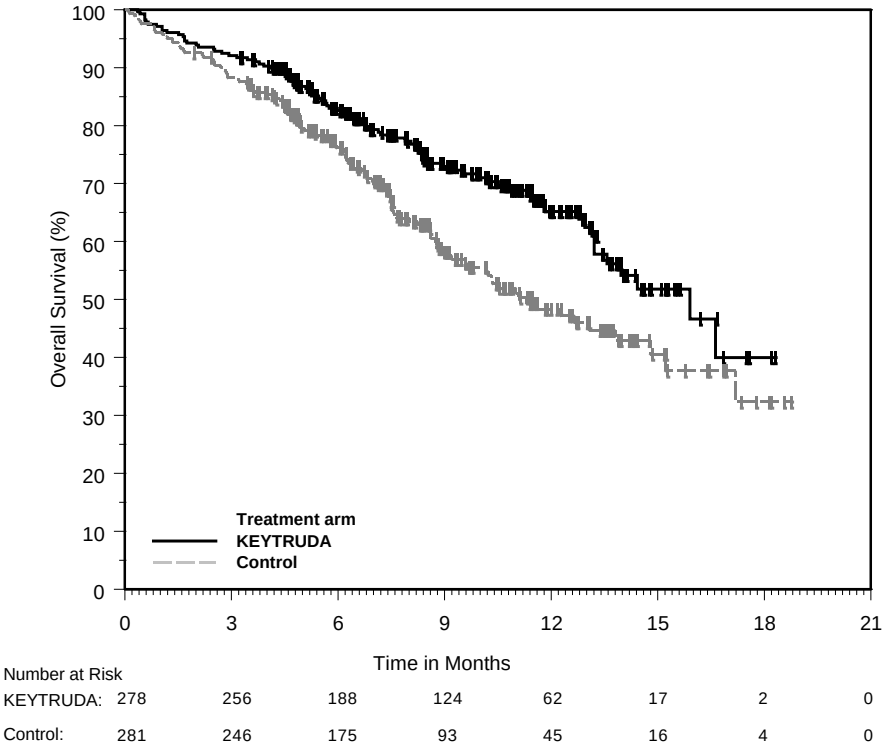
The trial demonstrated a statistically significant improvement in OS, PFS and ORR in patients randomized to KEYTRUDA in combination with carboplatin and either paclitaxel or paclitaxel protein-bound chemotherapy compared with patients randomized to placebo with carboplatin and either paclitaxel or paclitaxel protein-bound chemotherapy. Table 33 and Figure 5 summarize the efficacy results for KEYNOTE-407.

Table 33: Efficacy Results in KEYNOTE-407

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

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

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



Number at Risk

KEYTRUDA:	278	256	188	124	62	17	2	0
Control:	281	246	175	93	45	16	4	0

First-line treatment of metastatic NSCLC as a single agent

KEYNOTE-042

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

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

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

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

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

The trial demonstrated a statistically significant improvement in OS for patients (PD-L1 TPS ≥50%, TPS ≥20%, TPS ≥1%) randomized to KEYTRUDA as compared with chemotherapy. Table 34 and Figure 6 summarize the efficacy results in the subgroup of patients with TPS ≥50% and in all randomized patients with TPS ≥1%.

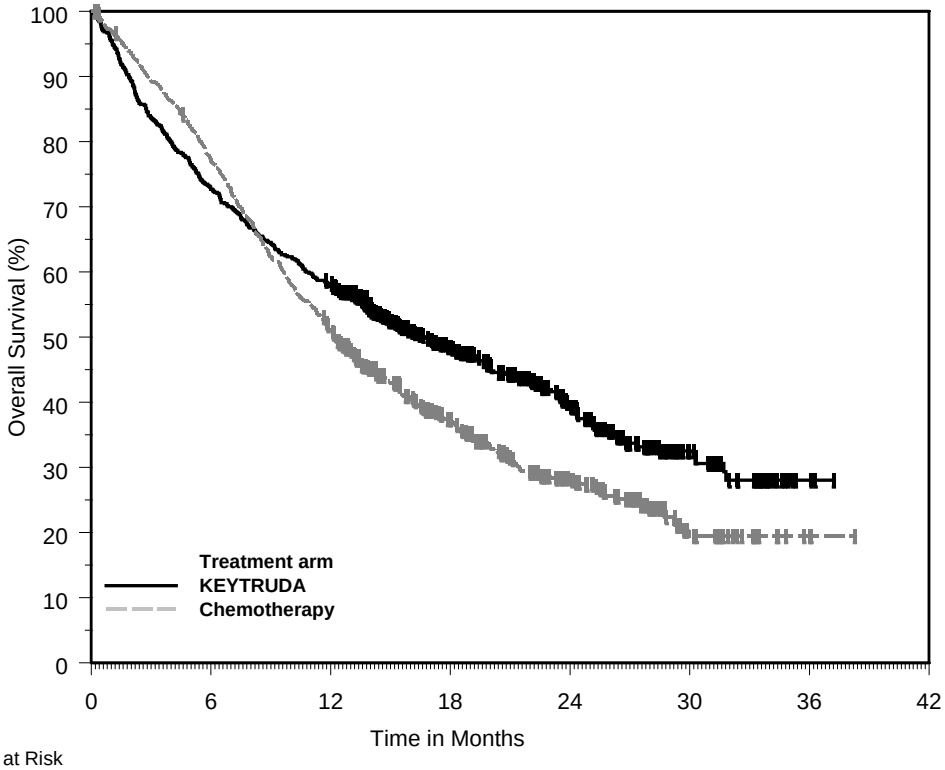
Table 34: Efficacy Results of All Randomized Patients (TPS ≥1% and TPS ≥50%) in KEYNOTE-042

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

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

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

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



Number at Risk

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

KEYNOTE-024

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

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

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

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

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

The trial demonstrated a statistically significant improvement in both PFS and OS for patients randomized to KEYTRUDA as compared with chemotherapy. Table 35 and Figure 7 summarize the efficacy results for KEYNOTE-024.

Table 35: 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+)

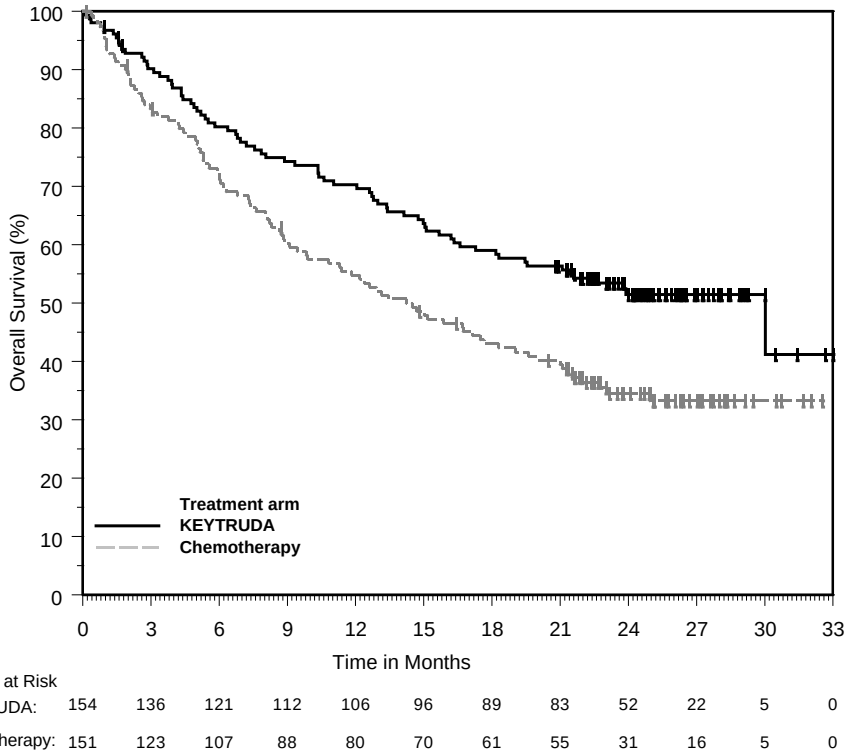
* Based on the stratified Cox proportional hazard model for the interim analysis

† 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*



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

Previously treated NSCLC

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

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

Tables 36 and 37 and Figure 8 summarize efficacy results in the subgroup with TPS ≥50% population and in all patients, respectively.

Table 36: 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 37: Efficacy Results of All Randomized Patients (TPS ≥1%) in KEYNOTE-010

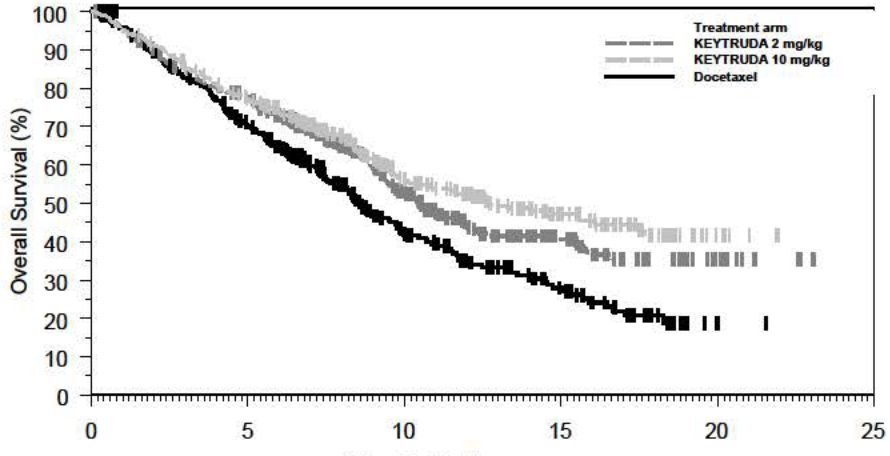
Endpoint	KEYTRUDA 2 mg/kg every 3 weeks n=344	KEYTRUDA 10 mg/kg every 3 weeks n=346	Docetaxel 75 mg/m^2 every 3 weeks n=343
OS			
Deaths (%)	172 (50%)	156 (45%)	193 (56%)
Median in months (95% CI)	10.4 (9.4, 11.9)	12.7 (10.0, 17.3)	8.5 (7.5, 9.8)
Hazard ratio* (95% CI)	0.71 (0.58, 0.88)	0.61 (0.49, 0.75)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

The efficacy of KEYTRUDA was investigated in 83 patients with SCLC who had disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy enrolled in one of two multicenter, multi-cohort, non-randomized, open label trials: KEYNOTE-028 (NCT02054806), Cohort C1, or KEYNOTE-158 (NCT02628067), Cohort G. The trials excluded patients with autoimmune disease or a medical condition that required immunosuppression.

Patients received either KEYTRUDA 200 mg intravenously every 3 weeks (n=64) or 10 mg/kg intravenously every 2 weeks (n=19). Treatment with KEYTRUDA continued until documented disease progression, unacceptable toxicity, or a maximum of 24 months. Patients with initial radiographic disease progression could receive additional doses of KEYTRUDA during confirmation of progression unless disease progression was symptomatic, was rapidly progressive, required urgent intervention, or occurred with a decline in performance status.

Assessment of tumor status was performed every 8 weeks for the first 6 months in KEYNOTE-028, every 9 weeks for the first 12 months in KEYNOTE-158, and every 12 weeks thereafter for both studies. The major efficacy outcome measures were ORR and DoR as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

The study population characteristics were: median age of 62 years (range: 24 to 84); 40% age 65 or older; 64% male; 63% White, 25% Asian, and 2% Black; 30% ECOG PS of 0 and 69% ECOG PS of 1; 7% had M0 disease and 93% had M1 disease; and 16% had a history of brain metastases. Sixty-four percent received two prior lines of therapy and 36% received three or more lines of therapy; 60% received prior thoracic radiation therapy; 51% received prior radiation therapy to the brain.

Efficacy results are summarized in Table 38.

Table 38: Efficacy Results in Patients with Small Cell Lung Cancer

Endpoint	KEYTRUDA n=83
Objective Response Rate	
ORR (95% CI)	19% (11, 29)
Complete response rate	2%
Partial response rate	17%
Duration of Response	n=16
Range (months)	4.1, 35.8+
% with duration ≥6 months	94%
% with duration ≥12 months	63%
% with duration ≥18 months	56%

\+ Denotes ongoing response

14.4 Head and Neck Squamous Cell Cancer

First-line treatment of metastatic or unresectable, recurrent HNSCC

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

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

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

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

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

The trial demonstrated a statistically significant improvement in OS for patients randomized to KEYTRUDA in combination with chemotherapy compared to those randomized to cetuximab in combination with chemotherapy at a pre-specified interim analysis in the overall population. The trial also demonstrated a statistically significant improvement in OS for the subgroup of patients with PD-L1 CPS ≥1 randomized to KEYTRUDA as a single agent compared to those randomized to cetuximab in combination with chemotherapy. At the time of the interim analysis, there was no significant difference in OS between the KEYTRUDA single agent arm and the control arm for the overall population. Table 39 and Figure 9 summarize efficacy results for KEYTRUDA in combination with chemotherapy.

Table 39: Efficacy Results for KEYTRUDA plus Platinum/Fluorouracil in KEYNOTE-048

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

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

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

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

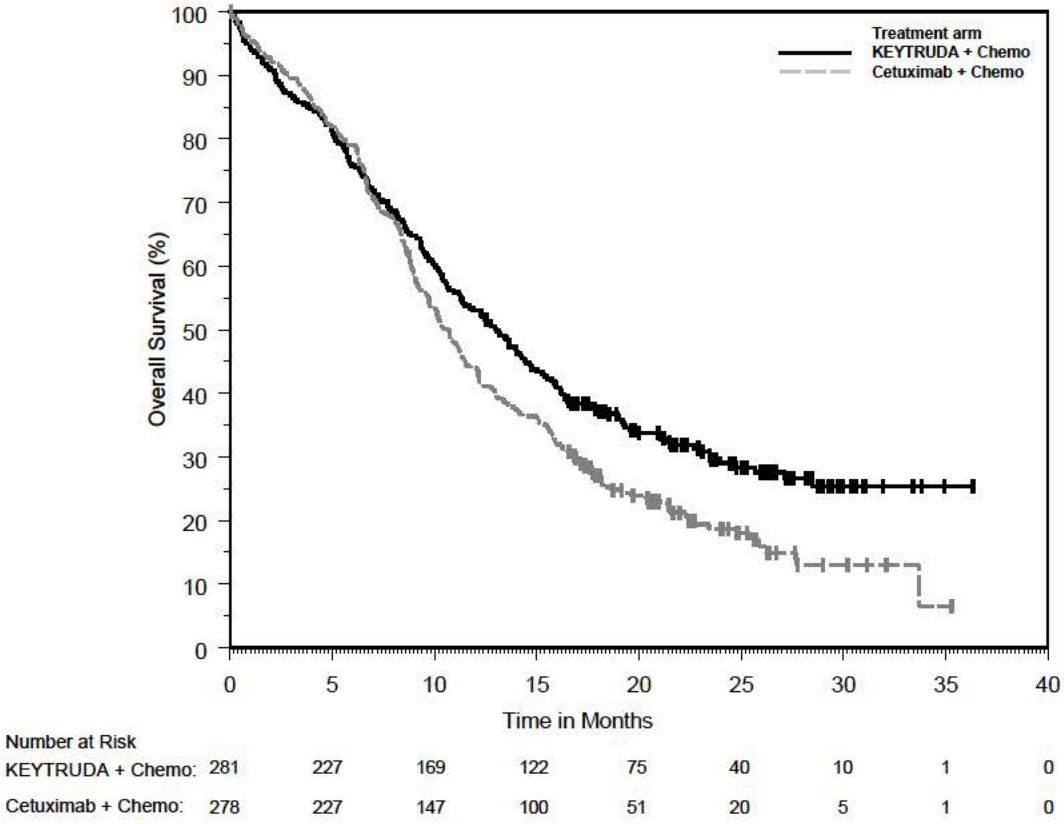


Table 40 summarizes efficacy results for KEYTRUDA as a single agent in the subgroups of patients with CPS ≥1 HNSCC and CPS ≥20 HNSCC. Figure 10 summarizes the OS results in the subgroup of patients with CPS ≥1 HNSCC.

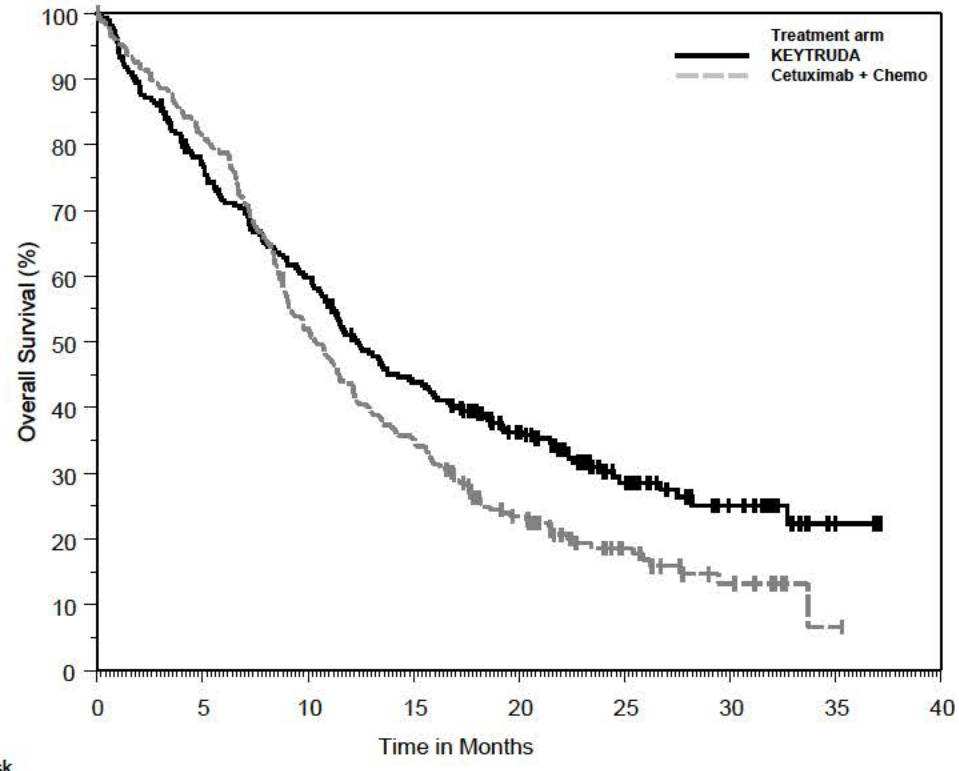
Table 40: Efficacy Results for KEYTRUDA as a Single Agent in KEYNOTE-048 (CPS ≥1 and CPS ≥20)

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

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

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

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



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

Previously treated recurrent or metastatic HNSCC

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

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

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

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

14.5 Classical Hodgkin Lymphoma

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

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

Efficacy results for KEYNOTE-087 are summarized in Table 41.

Table 41: Efficacy Results in KEYNOTE-087

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

* Median follow-up time of 9.4 months

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

14.6 Primary Mediastinal Large B-Cell Lymphoma

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

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

For the 24 responders, the median time to first objective response (complete or partial response) was 2.8 months (range 2.1 to 8.5 months). Efficacy results for KEYNOTE-170 are summarized in Table 42.

Table 42: Efficacy Results in KEYNOTE-170

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

* Median follow-up time of 9.7 months

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

NR = not reached

14.7 Urothelial Carcinoma

Cisplatin Ineligible Patients with Urothelial Carcinoma

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

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

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

The median follow-up time for 370 patients treated with KEYTRUDA was 7.8 months (range 0.1 to 20 months). Efficacy results are summarized in Table 43.

Table 43: Efficacy Results in KEYNOTE-052

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

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

Previously Untreated Urothelial Carcinoma

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

Previously Treated Urothelial Carcinoma

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

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

The study population characteristics were: median age of 66 years (range: 26 to 88), 58% age 65 or older; 74% male; 72% White and 23% Asian; 42% ECOG PS of 0 and 56% ECOG PS of 1; and 96% M1 disease and 4% M0 disease. Eighty-seven percent of patients had visceral metastases, including 34% with liver metastases. Eighty-six percent had a primary tumor in the lower tract and 14% had a primary tumor in the upper tract. Fifteen percent of patients had disease progression following prior platinum-containing neoadjuvant or adjuvant chemotherapy. Twenty-one percent had received 2 or more prior systemic regimens in the metastatic setting. Seventy-six percent of patients received prior cisplatin, 23% had prior carboplatin, and 1% were treated with other platinum-based regimens.

The study demonstrated statistically significant improvements in OS and ORR for patients randomized to KEYTRUDA as compared to chemotherapy. There was no statistically significant difference between KEYTRUDA and chemotherapy with respect to PFS. The median follow-up time for this trial was 9.0 months (range: 0.2 to 20.8 months). Table 44 and Figure 11 summarize the efficacy results for KEYNOTE-045.

Table 44: Efficacy Results in KEYNOTE-045

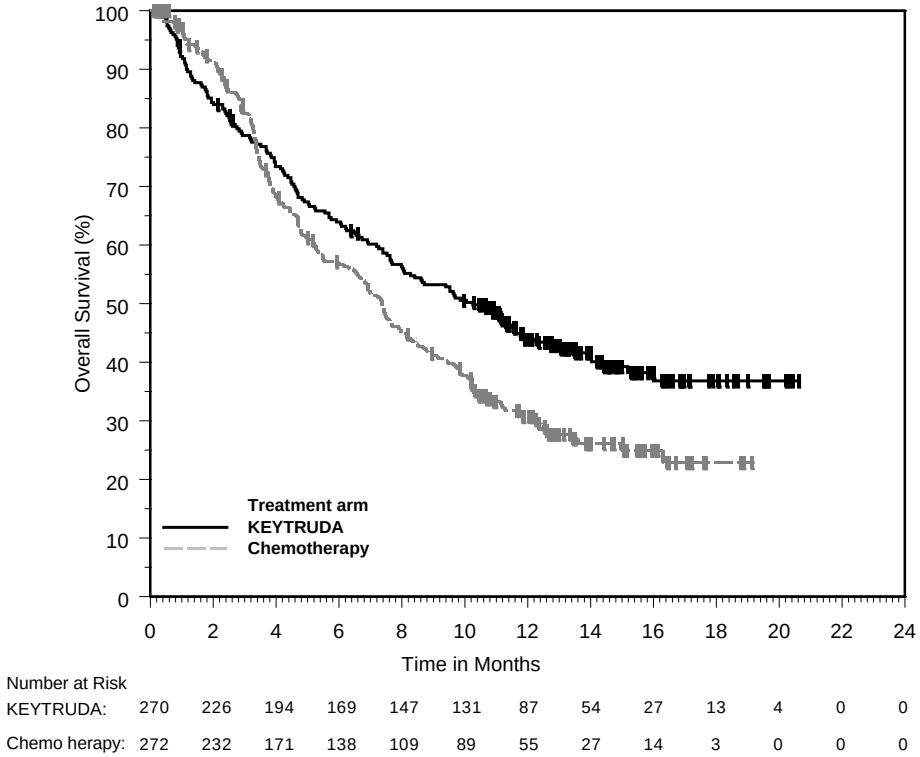
	KEYTRUDA 200 mg every 3 weeks n=270	**Chemotherapy n=272**
OS		
Deaths (%)	155 (57%)	179 (66%)
Median in months (95% CI)	10.3 (8.0, 11.8)	7.4 (6.1, 8.3)
Hazard ratio* (95% CI)	0.73 (0.59, 0.91)	
p-Value (stratified log-rank)	0.004	
PFS by BICR		
Events (%)	218 (81%)	219 (81%)
Median in months (95% CI)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

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

\+ Denotes ongoing

NR = not reached

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



14.8 Microsatellite Instability-High Cancer

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

Table 45: MSI-H Trials

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

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

A total of 149 patients with MSI-H or dMMR cancers were identified across the five trials. Among these 149 patients, the baseline characteristics were: median age of 55 years, 36% age 65 or older; 56% male; 77% White, 19% Asian, and 2% Black; and 36% ECOG PS of 0 and 64% ECOG PS of 1. Ninety-eight percent of patients had metastatic disease and 2% had locally advanced, unresectable disease. The median number of prior therapies for metastatic or unresectable disease was two. Eighty-four percent of patients with metastatic CRC and 53% of patients with other solid tumors received two or more prior lines of therapy.

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

Efficacy results are summarized in Tables 46 and 47.

Table 46: Efficacy Results for Patients with MSI-H/dMMR Cancer

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

NR = not reached

Table 47: 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

14.9 Gastric Cancer

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

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

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

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

14.10 Esophageal Cancer

KEYNOTE-181
The efficacy of KEYTRUDA was investigated in KEYNOTE-181 (NCT02564263), a multicenter, randomized, open-label, active-controlled trial that enrolled 628 patients with recurrent locally advanced or metastatic esophageal cancer who progressed on or after one prior line of systemic treatment for advanced disease. Patients with HER2/neu positive esophageal cancer were required to have received treatment with approved HER2/neu targeted therapy. All patients were required to have tumor specimens for PD-L1 testing at a central laboratory; PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx kit. Patients with a history of non-infectious pneumonitis that required steroids or current pneumonitis, active autoimmune disease, or a medical condition that required immunosuppression were ineligible.

Patients were randomized (1:1) to receive either KEYTRUDA 200 mg every 3 weeks or investigator's choice of any of the following chemotherapy regimens, all given intravenously: paclitaxel 80-100 mg/m^2 on Days 1, 8, and 15 of every 4-week cycle, docetaxel 75 mg/m^2 every 3 weeks, or irinotecan 180 mg/m^2 every 2 weeks. Randomization was stratified by tumor histology (esophageal squamous cell carcinoma [ESCC] vs. esophageal adenocarcinoma [EAC]/Siewert type I EAC of the gastroesophageal junction [GEJ]), and geographic region (Asia vs. ex-Asia). Treatment with KEYTRUDA or chemotherapy continued until unacceptable toxicity or disease progression. Patients randomized to KEYTRUDA were permitted to continue beyond the first RECIST v1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ)-defined disease progression if clinically stable until the first radiographic evidence of disease progression was confirmed at least 4 weeks later with repeat imaging. Patients treated with KEYTRUDA without disease progression could be treated for up to 24 months. Assessment of tumor status was performed every 9 weeks. The major efficacy outcome measure was OS evaluated in the following co-primary populations: patients with ESCC, patients with tumors expressing PD-L1 CPS ≥10, and all randomized patients. Additional efficacy outcome measures were PFS, ORR, and DoR, according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, as assessed by BICR.

A total of 628 patients were enrolled and randomized to KEYTRUDA (n=314) or investigator's treatment of choice (n=314). Of these 628 patients, 167 (27%) had ESCC that expressed PD-L1 with a CPS ≥10. Of these 167 patients, 85 patients were randomized to KEYTRUDA and 82 patients to investigator's treatment of choice [paclitaxel (n=50), docetaxel (n=19), or irinotecan (n=13)]. The baseline characteristics of these 167 patients were: median age of 65 years (range: 33 to 80), 51% age 65 or older; 84% male; 32% White and 68% Asian; 38% had an ECOG PS of 0 and 62% had an ECOG PS of 1. Ninety percent had M1 disease and 10% had M0 disease. Prior to enrollment, 99% of patients had received platinum-based treatment and 84% had also received treatment with a fluoropyrimidine. Thirty-three percent of patients received prior treatment with a taxane.

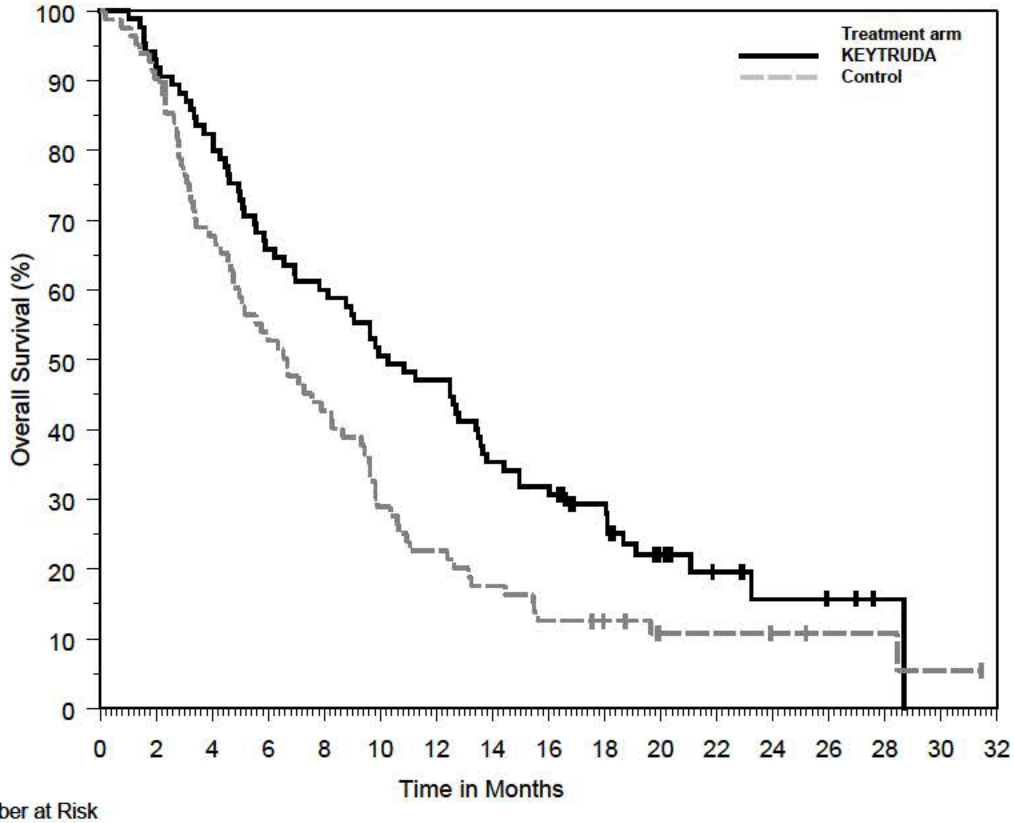
The observed OS hazard ratio was 0.77 (95% CI: 0.63, 0.96) in patients with ESCC, 0.70 (95% CI: 0.52, 0.94) in patients with tumors expressing PD-L1 CPS ≥10, and 0.89 (95% CI: 0.75, 1.05) in all randomized patients. On further examination in patients whose ESCC tumors expressed PD-L1 (CPS ≥10), an improvement in OS was observed among patients randomized to KEYTRUDA as compared with chemotherapy. Table 48 and Figure 12 summarize the key efficacy measures for KEYNOTE-181 for patients with ESCC CPS ≥10.

Table 48: Efficacy Results in Patients with Recurrent or Metastatic ESCC (CPS ≥10) in KEYNOTE-181

Endpoint	KEYTRUDA 200 mg every 3 weeks n=85	Chemotherapy n=82
OS		
Number (%) of patients with event	68 (80%)	72 (88%)
Median in months (95% CI)	10.3 (7.0, 13.5)	6.7 (4.8, 8.6)
Hazard ratio* (95% CI)	0.64 (0.46, 0.90)	
PFS		
Number (%) of patients with event	76 (89%)	76 (93%)
Median in months (95% CI)	3.2 (2.1, 4.4)	2.3 (2.1, 3.4)
Hazard ratio* (95% CI)	0.66 (0.48, 0.92)	
Objective Response Rate		
ORR (95% CI)	22 (14, 33)	7 (3, 15)
Number (%) of complete responses	4 (5)	1 (1)
Number (%) of partial responses	15 (18)	5 (6)
Median duration of response in months (range)	9.3 (2.1+, 18.8+)	7.7 (4.3, 16.8+)

* Based on the Cox regression model stratified by geographic region (Asia vs. ex-Asia)

Figure 12: Kaplan-Meier Curve for Overall Survival in KEYNOTE-181 (ESCC CPS ≥10)



KEYNOTE-180

The efficacy of KEYTRUDA was investigated in KEYNOTE-180 (NCT02559687), a multicenter, non-randomized, open-label trial that enrolled 121 patients with locally advanced or metastatic esophageal cancer who progressed on or after at least 2 prior systemic treatments for advanced disease. With the

exception of the number of prior lines of treatment, the eligibility criteria were similar to and the dosage regimen identical to KEYNOTE-181.

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

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

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

14.11 Cervical Cancer

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

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

No responses were observed in patients whose tumors did not have PD-L1 expression (CPS <1). Efficacy results are summarized in Table 49 for patients with PD-L1 expression (CPS ≥1).

Table 49: Efficacy Results in Patients with Recurrent or Metastatic Cervical Cancer (CPS ≥1) in KEYNOTE-158

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

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

14.12 Hepatocellular Carcinoma

The efficacy of KEYTRUDA was investigated in KEYNOTE-224 (NCT02702414), a single-arm, multicenter trial in 104 patients with HCC who had disease progression on or after sorafenib or were

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

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

Efficacy results are summarized in Table 50.

Table 50: Efficacy Results in KEYNOTE-224

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

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

14.13 Merkel Cell Carcinoma

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

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

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

Efficacy results are summarized in Table 51.

Table 51: Efficacy Results in KEYNOTE-017

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

* The median duration of response was not reached.

14.14 Renal Cell Carcinoma

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

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

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

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

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

The main efficacy outcome measures were OS and PFS as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Additional efficacy outcome measures included ORR, as assessed by BICR. A statistically significant improvement in OS was demonstrated at the pre-specified interim analysis in patients randomized to KEYTRUDA in combination with axitinib compared with sunitinib. The trial also demonstrated statistically significant improvements in PFS and ORR. Table 52 and Figure 13 summarize the efficacy results for KEYNOTE-426. The median follow-up time was 12.8 months (range 0.1 to 22.0 months). Consistent results were observed across pre-specified subgroups, IMDC risk categories and PD-L1 tumor expression status.

Table 52: Efficacy Results in KEYNOTE-426

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

* Based on the stratified Cox proportional hazard model

† Based on stratified log-rank test

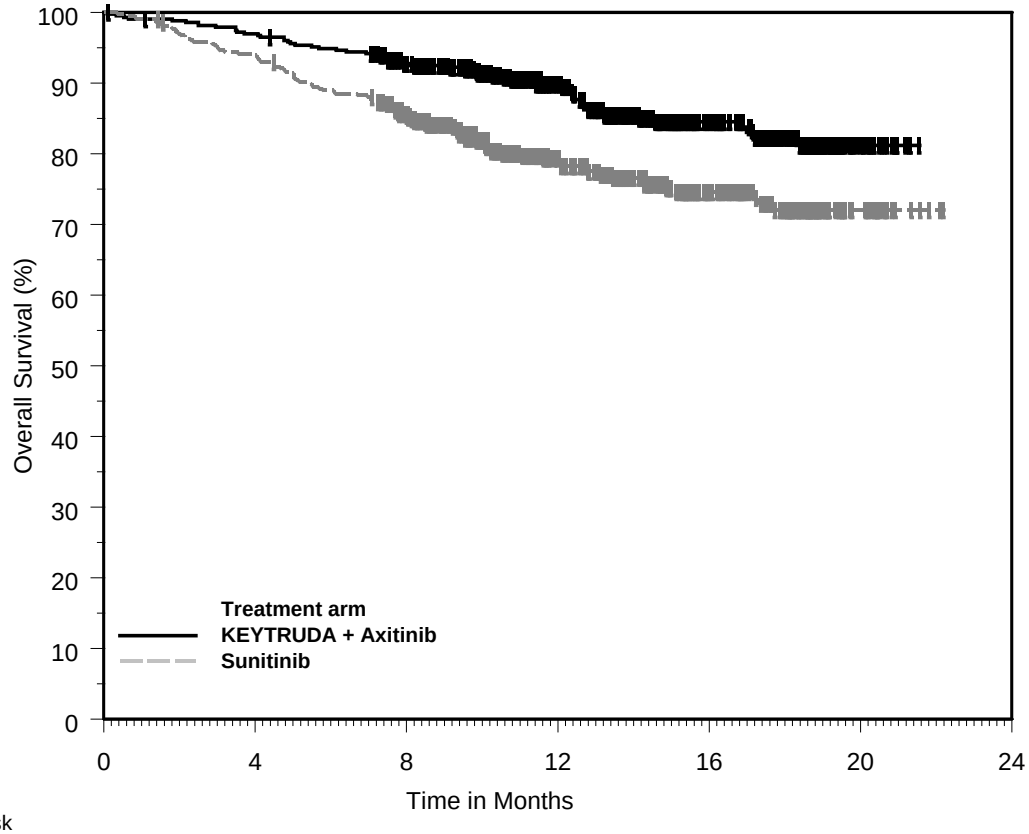
‡ p-Value (one-sided) is compared with the allocated alpha of 0.0001 for this interim analysis (with 39% of the planned number of events for final analysis).

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

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

NR = not reached

Figure 13: Kaplan-Meier Curve for Overall Survival in KEYNOTE-426



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

14.15 Endometrial Carcinoma

The efficacy of KEYTRUDA in combination with lenvatinib was investigated in KEYNOTE-146 (NCT02501096), a single-arm, multicenter, open-label, multi-cohort trial that enrolled 108 patients with metastatic endometrial carcinoma that had progressed following at least one prior systemic therapy in any setting. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible. Patients were treated with KEYTRUDA 200 mg intravenously every 3 weeks in combination with lenvatinib 20 mg orally once daily until unacceptable toxicity or disease progression as determined by the investigator. The major efficacy outcome measures were objective response rate (ORR) and duration of response (DOR) by independent radiologic review committee (IRC) using RECIST 1.1.

Administration of KEYTRUDA and lenvatinib was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered by the investigator to be deriving clinical benefit. KEYTRUDA dosing was continued for a maximum of 24 months; however, treatment with lenvatinib could be continued beyond 24 months. Assessment of tumor status was performed at baseline and then every 6 weeks until week 24, followed by every 9 weeks thereafter.

Among the 108 patients, 87% (n= 94) had tumors that were not MSI-H or dMMR, 10% (n=11) had tumors that were MSI-H or dMMR, and in 3% (n=3) the status was not known. Tumor MSI status was determined using a polymerase chain reaction (PCR) test. Tumor MMR status was determined using an immunohistochemistry (IHC) test. The baseline characteristics of the 94 patients with tumors that were not MSI-H or dMMR were: median age of 66 years, 62% age 65 or older; and 86% White, 6% Black, 4% Asian, and 3% other races; and ECOG PS of 0 (52%) or 1 (48%). All 94 of these patients received prior

systemic therapy for endometrial carcinoma: 51% had one, 38% had two, and 11% had three or more prior systemic therapies.

Efficacy results are summarized in Table 53.

Table 53: Efficacy Results in KEYNOTE-146

Endpoint	KEYTRUDA 200 mg every 3 weeks with lenvatinib n=94*
Objective Response Rate	
ORR (95% CI)	38.3% (29, 49)
Complete response rate	10.6%
Partial response rate	27.7%
Response duration	
Median in months (range)	NR (1.2+, 33.1+)†
% with duration ≥6 months	69%

* Median follow-up time of 18.7 months
† Based on patients (n=36) with a response by independent review
\+ Denotes ongoing
NR = 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)
Carton containing two 100 mg/4 mL (25 mg/mL), single-dose vials (NDC 0006-3026-04)
Store vials under refrigeration at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze. Do not shake.

17 PATIENT COUNSELING INFORMATION

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

Immune-Mediated Adverse Reactions

- Inform patients of the risk of immune-mediated adverse reactions that may be severe or fatal, may occur after discontinuation of treatment, and may require corticosteroid treatment and interruption or discontinuation of KEYTRUDA. These reactions may include:
  - Pneumonitis: Advise patients to contact their healthcare provider immediately for new or worsening cough, chest pain, or shortness of breath *[see Warnings and Precautions (5.1)]*.
  - Colitis: Advise patients to contact their healthcare provider immediately for diarrhea or severe abdominal pain *[see Warnings and Precautions (5.2)]*.
  - Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, or easy bruising or bleeding *[see Warnings and Precautions (5.3)]*.
  - Hypophysitis: Advise patients to contact their healthcare provider immediately for persistent or unusual headache, extreme weakness, dizziness or fainting, or vision changes *[see Warnings and Precautions (5.4)]*.
  - Hyperthyroidism and Hypothyroidism: Advise patients to contact their healthcare provider immediately for signs or symptoms of hyperthyroidism and hypothyroidism *[see Warnings and Precautions (5.4)].*
  - Type 1 Diabetes Mellitus: Advise patients to contact their healthcare provider immediately for signs or symptoms of type 1 diabetes *[see Warnings and Precautions (5.4)].*

- Nephritis: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis *[see Warnings and Precautions (5.5)]*.
- Severe skin reactions: Advise patients to contact their healthcare provider immediately for any signs or symptoms of severe skin reactions, SJS or TEN *[see Warnings and Precautions (5.6)]*.
- Other immune-mediated adverse reactions:
  - Advise patients that immune-mediated adverse reactions can occur and may involve any organ system, and to contact their healthcare provider immediately for any new signs or symptoms *[see Warnings and Precautions (5.7)]*.
  - Advise patients of the risk of solid organ transplant rejection and to contact their healthcare provider immediately for signs or symptoms of organ transplant rejection *[see Warnings and Precautions (5.7)]*.

Infusion-Related Reactions

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

Complications of Allogeneic HSCT

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

Embryo-Fetal Toxicity

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

Lactation

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

Laboratory Tests

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

Manufactured by: Merck Sharp & Dohme Corp., a subsidiary of
MERCK & CO., INC., Whitehouse Station, NJ 08889, USA
U.S. License No. 0002

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

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

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

uspi-mk3475-iv-1909r030

MEDICATION GUIDE

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

What is KEYTRUDA?

KEYTRUDA is a prescription medicine used to treat:

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

- you have received 2 or more types of chemotherapy, including one that contains platinum, and it did not work or is no longer working.

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

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

What should I tell my doctor before receiving KEYTRUDA?

Before you receive KEYTRUDA, tell your doctor if you:

- have immune system problems such as Crohn's disease, ulcerative colitis, or lupus
- have received an organ transplant, such as a kidney or liver

- have received or plan to receive a stem cell transplant that uses donor stem cells (allogeneic)
- have lung or breathing problems
- have liver problems
- have any other medical problems
- are pregnant or plan to become pregnant
    - KEYTRUDA can harm your unborn baby.

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

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

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

How will I receive KEYTRUDA?

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

What are the possible side effects of KEYTRUDA?

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

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

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

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

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

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 informa ion: www.merck.com/product/patent/home.html

usmg-mk3475-iv-1909r027

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s065

MULTI-DISCIPLINE REVIEW

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

NDA/BLA Multi-disciplinary Review and Evaluation

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

Application Type	Efficacy Supplement- SE1
Application Number(s)	NDA 206947/S-11 (Eisai, E); BLA 125514/S-65 (Merck, M)
Priority or Standard	Priority
Submit Date	June 17, 2019
Received Date	June 17, 2019
PDUFA Goal Date	December 17, 2019
Division/Office	Division of Oncology Products 1/OHOP
Review Completion Date	September 13, 2019
Established Name	(E) Lenvatinib; (M) Pembrolizumab
Trade Name	(E) LENVIMA; (M) KEYTRUDA
Pharmacologic Class	Tyrosine Kinase Inhibitor and monoclonal antibody
Applicant	Eisai Inc; Merck Sharp & Dohme Corp.
Formulation(s)	(E) Capsules; (M) Powder for Soln for Infusion/ Soln for Infusion
Dosing Regimen	(E) 4 mg and 10 mg; (M) 50 mg; 100 mg
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	(E) in combination with pembrolizumab, for the treatment of patients with advanced endometrial carcinoma that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation. (M) in combination with lenvatinib, for the treatment of patients with advanced endometrial carcinoma that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation.

Table of Contents

Table of Tables

APPEARS THIS WAY ON ORIGINAL

Table of Figures

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OSE= Office of Surveillance and Epidemiology OSI=Office of Scientific Investigations
OPDP=Office of Prescription Drug Promotion DMEPA=Division of Medication Error Prevention and Analysis

Glossary

131I	iodine-131
2L+	second-line or greater
AA	accelerated approval
AC	advisory committee
ACS	American Cancer Society
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AEOSI	adverse event(s) of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
BOR	best overall response
BP	blood pressure
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
cHL	classical Hodgkin lymphoma
CI	confidence interval
ClinRo	clinician reported outcome
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
CPMP	Committee for Proprietary Medicinal Products
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CPS	combined positive score
CR	complete response
CRA	Clinical Research Associate
CRC	colorectal cancer
CrCl	creatinine clearance
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSE	clinically significant event
CSR	clinical study report
CSS	Controlled Substance Staff
CTCAE	Common Terminology Criteria for Adverse Events
CTD	Common Technical Document

DLT	dose limiting toxicity
DMC	data monitoring committee
dMMR	mismatch repair deficient
DOR	duration of response
DTC	differentiated thyroid cancer
EC	endometrial carcinoma
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
ECOG PS	Eastern Cooperative Oncology Group performance status
eCTD	electronic Common Technical Document
ETASU	elements to assure safe use
EU	European Union
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
GERD	gastroesophageal reflux disease
GI	gastrointestinal
GRMP	good review management practice
HCC	hepatocellular carcinoma
HCL	hydrochloride
HNSCC	head and neck squamous cell carcinoma
HTN	hypertension
ICH	International Conference on Harmonization
IIR	independent imaging review
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
irRECIST	immune-related Response Evaluation Criteria in Solid Tumors
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IV	intravenous
KIF5B-RET	KIF5B-RET fusion gene
KM	Kaplan-Meier
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MARRS	Merck Adverse Event Reporting and Review System
MCC	Merkel cell carcinoma
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MMR	mismatch repair

mRECIST 1.1	modified RECIST 1.1
MSI	microsatellite instability
MSI-H	microsatellite instability-high
MTD	maximum tolerated dose
MUGA	multigated acquisition (scan)
NA	not available
N/A	not applicable
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NCCN	National Comprehensive Cancer Network
NDA	new drug application
NME	new molecular entity
NSCLC	non-small cell lung cancer
ObsRO	observer reported outcome
OCE	Oncology Center of Excellence
OCP	Office of Combination Products (FDA)/Office of Clinical Pharmacology (FDA)
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
ORR	objective response rate
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics/progressive disease
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PD-L1+	PD-L1-positive
PD-L2	programmed cell death ligand 2
PerfO	performance outcome
PFS	progression-free survival
PI	prescribing information
PK	pharmacokinetics
PMBCL	primary mediastinal large B-cell lymphoma
PMC	postmarketing commitment
pMMR	mismatch repair proficient
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PR	partial response
PREA	Pediatric Research Equity Act
PRES	posterior reversible encephalopathy syndrome
PRO	patient reported outcome
PSUR	Periodic Safety Update Report
PT	preferred term

QD	once a day
Q3W	every 3 weeks
RCC	renal cell carcinoma
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
REMS	risk evaluation and mitigation strategy
RP2D	recommended Phase 2 dose
RSD	Reference Safety Dataset
RTOR	Real Time Oncology Review
SAE	serious adverse event
SAP	statistical analysis plan
sBLA	supplemental biologics licensing application
SD	stable disease/standard deviation
SFU	survival follow-up
SGE	special government employee
sNDA	supplemental new drug application
SOC	standard of care/system organ class
SOP	standard operating procedure
TE	therapeutic equivalence
TEAE	treatment-emergent adverse event
TTR	time to response
UC	urothelial carcinoma
US	United States
US 21 CFR	Title 21 of the United States Code of Federal Regulations
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor

1 Executive Summary

1.1 Product Introduction

Lenvatinib (LENVIMA) is a kinase inhibitor that inhibits the kinase activities of vascular endothelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4). The drug also inhibits other kinases that have been implicated in pathogenic angiogenesis, tumor growth, and cancer progression in addition to their normal cellular functions, including fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4; platelet derived growth factor receptor alpha (PDGFRα); KIT; and RET. Lenvatinib has previously been approved in the United States for treatment of differentiated thyroid cancer, unresectable hepatocellular carcinoma, and in combination with everolimus for the treatment of advanced renal cell carcinoma. This is the first application for marketing approval for the treatment of patients with not-MSI-H/dMMR endometrial cancer.

The applicant's proposed indication at the time of supplemental BLA submission on June 27, 2019, was:

LENVIMA is a kinase inhibitor that is indicated:

- (b) (4)

The recommended indication for accelerated approval is:

LENVIMA is a kinase inhibitor that is indicated:

- **in combination with pembrolizumab, for the treatment of patients with advanced endometrial carcinoma that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation.**

Pembrolizumab (KEYTRUDA) is a humanized monoclonal antibody that binds to the programmed death receptor-1 (PD-1) and blocks its interaction with its ligands programmed death ligand-1 (PD-L1) and programmed death ligand-2 (PD-L2). Blocking of this interaction between PD-1 and its ligands can release PD-1-mediated T-cell inhibitory regulation and thus reduce inhibition of the antitumor immune response. It is an FDA-approved therapy for multiple solid and hematological malignancies, including treatment-refractory MSI-H endometrial cancer. This is the first application for marketing approval for the treatment of patients with not-MSI-H/dMMR endometrial cancers.

The applicant's proposed indication at the time of supplemental BLA submission on June 27, 2019, was:

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

- [redacted] (b) (4)

The recommended indication for accelerated approval is:

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

- **in combination with lenvatinib, for the treatment of patients with advanced endometrial carcinoma that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation.**

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

The recommended dose for this combination is lenvatinib 20 mg orally once daily, in combination with pembrolizumab 200 mg as an intravenous infusion every three weeks.

1.2 Conclusions on the Substantial Evidence of Effectiveness

The review team recommends the combination of lenvatinib and pembrolizumab (L+P) for accelerated approval in accordance with Title 21 of the Code of Federal Regulations (21CFR601.41 and 21CFR314 subpart H), supported by substantial evidence of safety and effectiveness provided by submitted data from a single arm, open-label, Phase 1b/2 study of the combination of lenvatinib plus pembrolizumab in subjects with selected confirmed metastatic tumor types, including endometrial cancer (EC). This conclusion is based on demonstration of the tumor response rate and durability that provide meaningful therapeutic benefit to patients over existing treatments. Currently, there are no FDA-approved treatments for patients with not-MSI-H/pMMR endometrial cancer who progress following one line of systemic therapy, and patients are generally offered single-agent cytotoxic chemotherapy with low response rates and brief responses based on evidence from small studies.

The EC cohort of Study E7080-A001-111/KEYNOTE-146 (hereafter referred to as Study 111)

included patients with either previously untreated EC or EC that had progressed after up to 2 prior lines of therapy. A total of 124 patients were enrolled in this EC cohort, of whom 108 had had prior systemic therapy; of these, 94 patients had tumors which were not MSI-H or dMMR. The efficacy and safety populations in this application comprise these 94 patients, who were treated with lenvatinib 20 mg orally daily and pembrolizumab 200 mg intravenously every three weeks. The primary endpoint for this study was objective response rate (ORR) and duration of response (DOR) as assessed by independent imaging review (IIR) according to RECISTv.1.1.

Testing for tumor MSI/MMR status was not required for enrollment into Study 111. Available tumor samples were tested centrally to determine tumor MSI/MMR status. Additionally, if available, local testing results for both MSI and MMR status were also collected. No premarket approval application was submitted to FDA's Center for Devices and Radiological Health for contemporaneous approval of a companion diagnostic device for this indication.

Results from Study 111 demonstrated that patients treated with L+P had a confirmed IIR-assessed RECISTv.1.1 OR of 38.3% (95% CI: 28.5, 48.9) with 10.6% of patients achieving a complete response (CR) and 27.7% of patients achieving a partial response (PR). The median DOR was not reached (range: 1.2+ to 33.1+ months) after a median study follow-up time of 18.7 months. A total of 25 patients (69% of the 36 responders) had a DOR of at least six months. The ORR and DOR of lenvatinib in combination with pembrolizumab for the recommended indication is considered an improvement over available therapy, which is generally single-agent cytotoxic chemotherapy.

The safety of L+P was assessed in comparison to the safety profiles of each of the monotherapies in the EC patient population. All safety analyses compared adverse event trends between L+P (study 111), lenvatinib monotherapy (study 204) and pembrolizumab monotherapy (KN-158 and KN-028). Compared to monotherapies, there were high rates of treatment discontinuations, interruptions and reductions in the patients treated with L+P. There were also increased frequencies of clinically significant events (CSEs) and adverse events of special interest (AESIs) in study 111, compared to the monotherapy studies; however, no new safety signals were identified.

Notable toxicities for patients treated with L+P included a high incidence of fatigue, hypertension, musculoskeletal pain, diarrhea, decreased appetite, hypothyroidism, nausea, stomatitis, vomiting, decreased weight, abdominal pain, headache, constipation, urinary tract infection, dysphonia, hemorrhagic events, hypomagnesemia, palmar-plantar erythrodysesthesia, dyspnea, cough, and rash. Despite the higher frequency of adverse events observed in Study 111, in comparison to the submitted data from three monotherapy studies, the overall safety profile of L+P is consistent with previous knowledge of the safety profiles of the individual agents and is considered acceptable in the context of the proposed indication.

This supplement is approved with one post-marketing requirement (PMR) and four post-marketing commitments (PMC) agreements. The Accelerated Approval PMR requires submission of the analyses and datasets with the final report for PFS and OS for the ongoing clinical trial E7080-G000-309/KEYNOTE-775, to verify and describe the clinical benefit L+P for patients with not-MSI-H/pMMR endometrial cancers (b) (4) **The four PMCs include submission of analyses and datasets with the final report for PFS and OS for the ongoing clinical trial trial E7080- G000-313/MK-7902-001, a randomized trial of L+P in the first-line setting, and development of a nucleic acid-based and an immunohistochemistry-based in vitro diagnostic devices essential to the safe and effective use of L+P in patients with tumors that are not-microsatellite instability high or mismatch repair proficient respectively, through appropriate analytical and clinical validation studies.**

Given the marked improvement in ORR and DoR seen with L+P, including a substantial proportion of complete responses, compared to the two monotherapy agents and the unmet medical need in this population with no approved systemic options, as well as the acceptable safety profile, all disciplines were in agreement with this accelerated approval, and did not identify any outstanding issues that precluded approval.

In summary, lenvatinib in combination with pembrolizumab, for the treatment of patients with advanced endometrial carcinoma that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation, demonstrates a favorable benefit-risk profile with sufficient evidence to recommend accelerated approval.

1.3 Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Lenvatinib, a tyrosine kinase inhibitor, in combination with pembrolizumab, an anti- PD-1 inhibitory antibody, is recommended for accelerated approval for the following indication:

- **for the treatment of patients with advanced endometrial carcinoma that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior systemic therapy, and are not candidates for curative surgery or radiation.**

Endometrial cancer (EC) is the most common gynecologic malignancy in the United States, and its prevalence is increasing. Approximately 75 percent of EC is diagnosed at an early stage (FIGO stage I) and is typically curable with total hysterectomy and bilateral salpingo-ophorectomy. Women with advanced endometrial cancer are generally treated with surgery and radiation in combination with standard front-line systemic therapy: carboplatin plus paclitaxel. For patients with recurrent disease following local therapy or metastatic endometrial cancer, first-line systemic chemotherapy with carboplatin and paclitaxel may provide response rates of about 40%-62%, with expected overall survival of around 13 to 29 months. In this setting, patients are seldom cured and usually experience disease progression, though a minority of these women who present with indolent localized or oligometastatic disease may still be curable through surgery or radiation. Upon progression after initial systemic therapy, there are no FDA-approved systemic options. Usually, single-agent cytotoxic chemotherapy is applied based on results from small, non-randomized studies with response rates generally below 20% and durations of response less than six months. These agents include liposomal doxorubicin, topotecan, docetaxel, bevacizumab, and temsirolimus.

Genomic and transcriptomic analyses of endometrial cancers have defined a 25% to 30% of tumors that present with a high frequency of somatic mutations that are attributable to deficiencies in DNA mismatch repair (dMMR), which results in chromosomal changes (expansion or reduction in the length of repetitive sequences in tumor DNA compared with normal DNA) referred to as microsatellite instability-high (MSI-H). This alteration in chromosomal biology and resultant high mutation rate is thought to result in the increased expression of tumor-associated neoantigens, making MSI-H tumors logical targets for the application of immunotherapy. Pembrolizumab as a single agent received accelerated approval for refractory MSI-H solid tumors, including endometrial cancer, where it demonstrated a 36% ORR (5 of 14 treated patients had an objective RECISTv.1.1 response). However, patients with tumors that are not MSI-H or dMMR represent an unmet

medical need due to lack of treatment options.

The safety and efficacy of the lenvatinib and pembrolizumab combination (L+P) for the current supplemental application submission was demonstrated in one clinical trial, Study E7080-A001-111/KEYNOTE-146 (hereafter referred to as Study 111), an ongoing, open-label, phase 1b/2 study of lenvatinib in combination with pembrolizumab in subjects with selected metastatic tumor types, including EC, non-small cell lung cancer, renal cell carcinoma, urothelial cancer, and melanoma. The primary objective of phase 1b was to determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) for lenvatinib to be used in combination with pembrolizumab 200 mg IV Q3W. Testing for tumor MSI/MMR status was not required for enrollment into the study. Available tumor samples were tested centrally to determine tumor MSI/MMR status using the Promega PCR MSI Analysis System and the Ventana MMR IHC assay. Additionally, if available, local testing results for both MSI and MMR status were also collected.

A total of 94 patients had previously treated metastatic endometrial cancer which were not MSI-H/dMMR and were the focus of the efficacy and safety review in this application. The primary endpoint for this study was objective response rate (ORR) and adequate duration of response (DOR) by independent imaging review (IIR). The trial demonstrated an ORR of 38.3% (95% CI: 28.5, 48.9) including 10.6% of patients with a complete response (CR) and 27.7% with a partial response (PR). At the time of the data cutoff (January 10, 2019), the median DOR was not reached (range: 1.2+ to 33.1+ months) with a median follow-up of 18.7 months. A total of 25 patients (69% of the 36 responders) had a response duration of at least six months.

The safety profile of L+P was adequately represented in the submitted database. Fatal adverse reactions (AR) occurred in 3% of patients receiving L+P, including gastrointestinal perforation, reversible posterior leukoencephalopathy syndrome (RPLS) with intraventricular hemorrhage, and intracranial hemorrhage. Permanent discontinuation due to adverse reaction occurred in 17% of patients who received L+P. The combination was reasonably well-tolerated with AR manageable with dose reduction and/or interruptions, although the rate of AR and dose modifications was higher in study 111 compared to the monotherapy studies. Serious adverse reactions occurred in 52% of patients receiving L+P. In study 111, lenvatinib alone was dose modified (interrupted and/or reduced) in 88% of the patients (regardless of action with pembrolizumab) and pembrolizumab alone was dose interrupted in 49% (regardless of action with lenvatinib). Despite the high rate, the adverse reactions that led to dose interruption and reduction are consistent with the known safety profiles of lenvatinib and pembrolizumab.

The key ARs of interest with lenvatinib, identified as clinically significant events (CSEs, which include ARs that have been identified in clinical trials across the lenvatinib development program), occurred in 86 (91.5%) patients. Adverse events (AE) of special interest (AESIs – immune-mediated AEs or nonimmune-mediated events of infusion-related reactions) with pembrolizumab occurred in 57% of patients. Both CSEs

and AESIs occurred at higher frequencies in study 111 compared to monotherapy studies, study 204 and KN-158, respectively.

Notable toxicities for L+P included a high incidence of fatigue, hypertension, musculoskeletal pain, diarrhea, decreased appetite, hypothyroidism, nausea, stomatitis, vomiting, decreased weight, abdominal pain, headache, constipation, urinary tract infection, dysphonia, hemorrhagic events, hypomagnesemia, palmar-plantar erythrodysesthesia, dyspnea, cough, and rash. Based on the frequency of AEs observed in the monotherapy trials, it is important to note that the incidence of AEs was higher in the combination study 111; however, no new safety concerns were identified based on the safety data submitted in this sNDA. The safety profile is acceptable for this patient population with a serious and life-threatening disease with limited additional treatment options.

An important consideration in the benefit-risk evaluation for this approval action is that it represents the first approved therapy for patients with EC that has progressed following prior systemic therapy whose tumors are not MSI-H or dMMR, across various histologies. The only other approval for women with EC was pembrolizumab monotherapy, which received accelerated approval in May 2017, with an ORR of 36% (95% CI:13%, 65%) for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or MMR deficient (dMMR) solid tumors, including endometrial cancer, that have progressed following prior treatment and who have no satisfactory alternative treatment options.

Although the data presented in this application evaluated women on Study 111 with metastatic EC who had been treated with at least one prior platinum-based systemic therapy, the indication recommended by the review team is for women with EC who have progressed following any prior systemic therapy, which includes women who may have been ineligible for up-front platinum-based treatment; similarly, the recommended indication for accelerated approval is for women with endometrial cancer who are not candidates for curative surgery or radiation, and not only women with metastatic disease. Thus, the indication favored by the review team is applicable to a slightly broader population of women than that included in the EC cohort for this supplemental application, but the characteristics of the additional patients included in the review team's suggested indication should respond similarly to the combination. The type of historical systemic therapy, and whether platinum vs. non-platinum, would not be thought to affect responsiveness to L+P from a mechanistic standpoint; similarly, for women with incurable EC, the presence or absence of metastatic lesions should not biologically affect a patient's chance of responding to L+P, and women with locally advanced disease not amenable to curative surgery or radiation and metastatic disease may similarly benefit from the combination.

Uncertainties regarding the benefit of exposure to L+P stem from the small sample size in this clinical trial. Given that study 111 was a single-arm trial, no inferential procedures were employed to evaluate the outcome; instead, the trial relied on the demonstration of improvement over available therapy based on the magnitude of response rate and duration of those responses.

Additionally, the contribution to the treatment effect of each component in the combination could not be isolated based on this single-arm study design. The applicant provided three single-arm monotherapy studies including Study 204 (lenvatinib) and KEYNOTE-158 and KEYNOTE-028 (pembrolizumab) to allow an assessment of the contribution of each component to the efficacy of the combination treatment. Exploratory cross-trial comparisons showed that there appeared to be a substantially numerically higher ORR with the combination therapy over the individual treatments. FDA conducted exploratory analyses using propensity score matching and weighting methods to account for observed imbalances in selected demographics and baseline characteristics. The results are consistent with those seen in an unadjusted comparison of the combination treatment as providing a numerically higher ORR than lenvatinib or pembrolizumab individually in this population.

The large proportion of patients that experienced SAEs, grade 3-4 AEs, AEs leading to dose reductions, interruptions and discontinuation indicate that the lenvatinib and pembrolizumab combination is less tolerable than lenvatinib or pembrolizumab as monotherapy.

Patients with advanced EC that is not MSI-H/pMMR that has progressed following systemic therapy and who are not candidates for curative surgery or radiation have a serious and life-threatening disease for which no FDA-approved therapies currently exist. The review team concluded that the treatment effect seen with L+P, an ORR of 38.3%, with median DOR not reached at the time of data cutoff and the majority of responses durable for at least six months, is of sufficient magnitude to serve as evidence that is reasonably likely to predict clinical benefit over available therapies in support of accelerated approval. All disciplines agree that L+P has a favorable benefit-risk profile in the indicated population and did not identify any outstanding issues that would preclude approval. The recommendation is for accelerated approval with a post-marketing requirement that the sponsor provide results of the ongoing randomized trial in this setting to confirm direct clinical benefit.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Endometrial cancer is the most common gynecological malignancy in the United States, and its prevalence is increasing. • Most patients present with early-stage disease, typically curable with surgery. • 20-30% of EC present with a high frequency of somatic mutations, that can be attributed to deficiencies in DNA mismatch repair	• **Advanced endometrial cancer is a serious and life-threatening disease with a significant unmet medical need for more effective therapies.**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	(dMMR), leading to the microsatellite instability-high (MSI-H) phenotype.	
Current Treatment Options	• Single-agent chemotherapy is the mainstay of treatment for women with advanced endometrial cancer that progresses following initial curative therapy, where response rates and response durations are generally low. There are no FDA approved drugs for this specific indication.	• **Patients with advanced endometrial cancer that is not MSI-H/dMMR could benefit from treatment that provides a more favorable response rate and prolonged duration of response compared to available therapies.**
Benefit	• An ORR of 38.3% (95% CI: 28.5, 48.9) with 10.6% of patients achieving a complete response and 27.7% of patients achieving a partial response. • The median DOR that was not reached (range: 1.2+ to 33.1+ months) with a median follow-up of 18.7 months. A total of 25 patients (69% of the 36 responders) had a duration of response ≥6 months.	• **Evidence of effectiveness was supported by an objective response rate greater than typically seen with cytotoxic chemotherapy in this disease setting.** • **A PMR is required to verify clinical benefit in a randomized study.**
Risk	• The most common adverse reactions experienced by at least 20% of patients with lenvatinib and pembrolizumab were fatigue, hypertension, musculoskeletal pain, diarrhea, decreased appetite, hypothyroidism, nausea, stomatitis, vomiting, decreased weight, abdominal pain, headache, constipation, urinary tract infection, dysphonia, hemorrhagic events, hypomagnesemia, palmar-plantar erythrodysesthesia, dyspnea, cough, and rash.	• **Higher frequency of adverse events was observed with the lenvatinib and pembrolizumab combination, compared to monotherapy, but the overall safety profile is consistent with knowledge of safety with individual agents.**
Risk and Risk Management	• Lenvatinib and pembrolizumab combination is intended to be prescribed by oncologists. • Oncologists are well-versed in the identification and management of the toxicities associated with lenvatinib and pembrolizumab. • Labeling details dose interruption, reduction, or discontinuation.	• **The overall safety profile of lenvatinib and pembrolizumab combination for the treatment of patients with advanced endometrial cancer is consistent with the known safety profile of lenvatinib and**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Laboratory and vital sign monitoring are recommended before and during treatment.	**pembrolizumab and acceptable for the intended population, and current risk mitigation strategies are sufficient.** • **The safe use of lenvatinib and pembrolizumab can be managed through accurate labeling and routine oncology care. No REMS is indicated.**

1.4 Patient Experience Data

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

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

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

X _____

Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1 Analysis of Condition

The Applicant's Position:

Uterine cancer is the fourth most common cancer among females and the most common malignancy of the gynecological system in the US [1]. The American Cancer Society (ACS) estimates that approximately 1 in 40 women in the US will develop uterine cancer in their lifetime with 61,880 new cases and 12,160 deaths to occur in 2019 [1].

Adenocarcinoma of the endometrium is the most common histologic type of uterine cancer. Endometrial adenocarcinomas are often classified into 2 histologic categories—Type 1 or Type 2. Type 1 tumors are more common than Type 2 and are less aggressive, accounting for 70% to 80% of new cases, with endometrioid histology being the most common [2].

In contrast, Type 2 tumors are often of non-endometrioid histologies (e.g., clear cell and serous cell types), typically behave more aggressively, carry a worse prognosis and are enriched in the advanced recurrent setting [3] [4] [5] [6] [7] [8].

The population of patients with advanced or recurrent endometrial carcinoma (EC) represents a heterogeneous mix of stage at diagnosis, histologic subtypes and grades, microsatellite instability (MSI) or mismatch repair (MMR) status, prior therapies, duration of recurrence-free intervals, and sites of recurrence (distant or local) [9]. In general, the prognosis is dismal for these patients, with a median survival of only 12 months [5].

The Regulatory Authorities' Assessment[1]:
We agree with the applicant's assessment of endometrial cancer.

2.2 Analysis of Current Treatment Options

The Applicant's Position:

Platinum-based combination chemotherapy is the standard first-line systemic therapy for patients with metastatic, recurrent, or high-risk disease [11] (**Table 1**). Following progression after first-line platinum-based chemotherapy, there is no approved therapy or generally accepted standard treatment approach with the exception of accelerated approval of pembrolizumab for a select subset of patients with MSI-high (MSI-H) or MMR deficient (dMMR) solid tumors, which includes those with EC [12]. The majority of patients with recurrent or metastatic EC will have tumors that are not MSI-H or dMMR [10]. Therefore, despite advances in the understanding of tumor biology, there has been no real improvement in outcomes for

[1] The Regulatory Authorities' assessment made in sections 2 through 4 and 8 through 12 of this review pertain to the US FDA only, and not to the Australian Therapeutic Goods Administration nor HealthCanada.

the majority of patients with advanced or metastatic EC. Since advanced EC (inoperable, recurrent, or metastatic) is typically incurable and is associated with a poor prognosis, the National Comprehensive Cancer Network (NCCN) guidelines strongly encourage these patients to participate in clinical trials, further underscoring this setting as one of significant unmet medical need [11].

In order to better understand the extent of efficacy from therapies studied in this setting, a systematic literature review (SLR) was performed to identify clinical trials assessing the efficacy and safety of systemic treatments for patients with previously treated advanced (unresectable and metastatic) or recurrent EC (Module 2.5, Section 2.5.1.2). Seventy-three (73) studies with 84 treatment arms were included in the meta-analysis. Based on meta-analysis of available data, the estimate of ORR in all studies identified was 9% (95% CI: 7, 11). Furthermore, a subgroup analysis of therapies found in NCCN guidelines was conducted for this meta-analysis, and the estimated ORR was 13% (95% CI: 9, 17). The estimated ORR in the non-NCCN group was 7% (95% CI: 5%, 9%), which included mostly failed experimental agents and highlights the challenge of identifying effective therapies in this setting.

Table 1
Summary of Treatment Armamentarium for Advanced or Recurrent Endometrial Carcinoma

Product Name	Relevant Indication	Year of Approval And Type of Approval *	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
FDA Approved Treatments					
Megestrol acetate	Palliative treatment of advanced endometrial carcinoma	1971	40-320 mg/day in divided doses	Phase 2 trial to assess the efficacy and safety in patients with recurrent/ advanced endometrial carcinoma. A total of 54 patients were evaluated. **ORR**: 24% (95% CI: 13.6, 38.1) **median PFS:** 2.5 months **median OS**: 7.6 months [15]	**Warnings**: Fetal harm when administered to a pregnant woman. Exacerbation of preexisting diabetes with increased insulin requirements.
Pembrolizumab	Single agent for the treatment of adult and pediatric patients with unresectable or metastatic, MSI-H or dMMR solid tumors, that have progressed following prior treatment and who have no satisfactory alternative treatment options	2017 (accelerated approval)	200 mg IV Q3W for adults	A total of 149 participants with MSI-H or dMMR solid tumors who progressed following prior treatment enrolled in 1 of 5 uncontrolled, open-label, multi-cohort, multi-center, single-arm trials, including 14 subjects with endometrial carcinoma. **ORR in 14 EC subjects**: 36% (95% CI: 13%, 65%) [12].	**Warnings and Precautions**: Immune-mediated pneumonitis, colitis, hepatitis, endocrinopathies (hypophysitis, thyroid disorders, Type 1 diabetes mellitus, nephritis, and skin reactions). Withhold or permanently discontinue based on severity.
Non-FDA Approved Treatments (Single-Agent Chemotherapy)					
Paclitaxel	Not approved for second-line treatment of advanced/recurrent EC	Initial approval 1992	175 mg/m^2 Q3W	Phase III randomized trial to determine whether second-line treatment with ixabepilone	**Important Safety and Tolerability Issues:** Alopecia and neuropathy

Product Name	Relevant Indication	Year of Approval And Type of Approval *	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
		(full approval) for relapsed ovarian cancer		resulted in improved OS compared with the control arm (single-agent chemotherapy with doxorubicin or paclitaxel) in locally advanced, recurrent, or metastatic EC after at least 1 prior failed platinum-based chemotherapy regimen. A total of 248 subjects received single-agent therapy with either paclitaxel or doxorubicin. **Results for control arm (paclitaxel or doxorubicin)**: **OS**: 12.3 months (95% CI: 10.7, 15.4) **Median PFS:** 4.0 months (95% CI: 2.7, 4.3) **ORR**: 15.7% (95% CI: 11.2, 21.1). [13]	**Black Box Warning for Paclitaxel**: Anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2%-4% of patients receiving paclitaxel in clinical trials. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving paclitaxel.
Doxorubicin	Not approved for second-line treatment of advanced/recurrent EC	Initial approval 1974	60 mg/m^{2}Q3W	Phase III randomized study comparing Zoptarelin with doxorubicin as second-line therapy for locally advanced, recurrent, or metastatic EC after 1 failed prior chemotherapy with a platinum plus a taxane. A total of 255 subjects received single-agent doxorubicin therapy **Results for doxorubicin arm**: **ORR:** 14.1% (95% CI: 9.8, 18.4) **Median PFS:** 4.7 months (95% CI: 4.1, 6.6) **Median OS:** 10.8 months (95% CI:	**Black Box Warning for doxorubicin**: Cardiomyopathy: Myocardial damage can occur with doxorubicin HCl with incidences from 1% – 20% for cumulative doses from 300 mg/m to 500 mg/m when doxorubicin HCl is administered Q3W. The risk of cardiomyopathy is further increased with concomitant cardiotoxic therapy. Assess LVEF before and regularly

Product Name	Relevant Indication	Year of Approval And Type of Approval *	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
				9.8, 12.6) [13] [14]	during and after treatment with doxorubicin HCl. Secondary Malignancies: Secondary acute myelogenous leukemia and myelodysplastic syndrome occur at a higher incidence in patients treated with anthracyclines, including doxorubicin HCl. Extravasation and Tissue Necrosis: Extravasation of doxorubicin HCl can result in severe local tissue injury and necrosis requiring wide excision and skin grafting. Immediately terminate the drug, and apply ice to the affected area. Severe myelosuppression resulting in serious infection, septic shock, requirement for transfusions, hospitalization, and death may occur.
CI = confidence interval, dMMR = mismatch repair deficient, MSI-H = microsatellite instability high, EC = endometrial carcinoma, IV = intravenous, ORR = objective response rate, OS = overall survival, PFS = progression-free survival, Q3W = every 3 weeks.					

*Accelerated approval or full approval

The Regulatory Authorities' Assessment[1]:

We agree with the applicant's assessment of current treatment options for patients with advanced or recurrent endometrial carcinoma who have progressed after first-line platinum-based chemotherapy.

APPEARS THIS WAY ON ORIGINAL

3 Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Lenvatinib (LENVIMA) is currently marketed in over 50 countries for at least one of the following indications, and all have been approved in the US: as a monotherapy treatment for differentiated thyroid cancer (DTC [13 Feb 2015]) and hepatocellular carcinoma (HCC [15 Aug 2018]), and in combination with everolimus, for the treatment of advanced renal cell carcinoma (RCC [13 May 2016]).

Pembrolizumab (KEYTRUDA) was first approved in the US on 04 Sep 2014. It is registered and approved for at least 1 oncology indication in over 80 countries worldwide. As of mid-June 2019, pembrolizumab was approved in the US for the following indications: unresectable or metastatic melanoma, adjuvant treatment of patients with melanoma with involvement of lymph node(s) following complete resection, first line and metastatic non-small cell lung cancer (NSCLC), locally advanced or metastatic urothelial carcinoma, first-line and recurrent or metastatic head and neck squamous cell carcinoma (HNSCC), refractory classical Hodgkin lymphoma (cHL), refractory primary mediastinal large B-cell lymphoma (PMBCL), locally advanced or metastatic urothelial carcinoma (UC), locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma, recurrent or metastatic cervical cancer, HCC, Merkel cell carcinoma (MCC), and unresectable or metastatic, MSI-H or dMMR solid tumors or colorectal cancer (CRC). Pembrolizumab is approved in combination with pemetrexed and platinum chemotherapy for treatment of nonsquamous NSCLC, and in combination with axitinib for the first-line treatment of advanced RCC. The global registration status of KEYTRUDA is rapidly evolving. Applications are under regulatory agency review worldwide in multiple other indications.

Combination Therapy with Lenvatinib plus Pembrolizumab

In addition to advanced EC that has progressed following prior systemic therapy and is not MSI-H or dMMR (the subject of this supplemental new drug application [sNDA]/supplemental biologics licensing application [sBLA]), the combination of lenvatinib and pembrolizumab is currently in clinical development in a variety of malignancies in which either or both agents have demonstrated preclinical or clinical antitumor activity.

The Regulatory Authorities' Assessment[1]:
We agree with the applicant's history of the approval of lenvatinib (NDA 206947) and pembrolizumab (BLA 125514).

3.2 Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

Advice from the US FDA has been solicited throughout the development program for lenvatinib plus pembrolizumab. A pre-Phase 3 meeting with FDA was conducted in October 2017 to discuss the confirmatory randomized, Phase 3 endometrial carcinoma study (E7080-G000-309/ KEYNOTE-775). Two pre-submission meetings were held between the Sponsors and the FDA regarding submission of an sNDA and sBLA for the combination of lenvatinib plus pembrolizumab for the proposed EC indication. The following table summarizes the major regulatory interactions with FDA to date.

31-Mar-2005	Eisai opened the original lenvatinib IND 072010 for investigation of solid tumors.
23-July- 2013	Eisai opened lenvatinib IND 118808 for investigation of endometrial carcinoma.
17-July-2015	E7080-A001-111/KEYNOTE-146 (Study111) submitted to IND 072010.
26-Oct-2015	Merck opened IND 127548 to conduct multi-tumor study KEYNOTE-158, which includes endometrial Cohorts D (all-comers) and Cohort K-Endometrial MSI-H.
30-Oct-2017	Type B, Pre-Phase 3 meeting to discuss the design of the ongoing Phase 3 study E7080-G000-309/KEYNOTE-775 (IND 118808)
25-July-2018	Eisai received Breakthrough Therapy Designation for lenvatinib in combination with pembrolizumab for the treatment of patients with advanced and/or metastatic non-MSI-H/ mismatch repair proficient (pMMR) EC who have progressed following at least one prior therapy (IND 118808).
08-Aug-2018	Merck received Breakthrough Therapy Designation for pembrolizumab in combination with lenvatinib for the treatment of patients with advanced and/or metastatic non-MSI-H/pMMR EC who have progressed following at least one prior therapy (IND 126191).
10-Jan-2019	Type B, Pre-sNDA/Pre-sBLA teleconference to discuss the format and content of the joint sNDA (206947)/sBLA (125514).
3-Apr-2019	Teleconference between FDA, Eisai, and Merck (IND 118808), where agreement was reached that the endometrial supplemental submissions qualify for the Real-Time Oncology Review pilot program
01-May-2019	Type B, Pre-sNDA/sBLA meeting to gain concurrence with the Division on the acceptability of sNDA (206947)/sBLA (125514) to support potential AA, based upon topline data from Study 111.
08-May-2019	Eisai and Merck submitted the Real Time Oncology Review early packages to NDA 206947 and BLA 125514, respectively.
AA = accelerated approval, dMMR = mismatch repair deficient, DOR = duration of response, EC = endometrial carcinoma, IND = investigational new drug, ORR = objective response rate, MSI-H = microsatellite instability-high, RTOR = Real Time Oncology Review, sBLA = supplemental biologic license application, sNDA = supplemental new drug application, Study 111 = Study E7080-A001-111/KEYNOTE 146, Study 204 = Study E7080-G000-204, Study 309 = Study E7080-G000-309/KEYNOTE-775.	

The Regulatory Authorities' Assessment[1]:

We agree with the applicant's summary of pre-submission regulatory activities in the United States.

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

4.1 Office of Scientific Investigations (OSI)

The Regulatory Authorities' Assessment[1]:

The Office of Scientific Investigations (OSI) was consulted to perform site inspections as part of review of the lenvatinib + pembrolizumab (L+P) combination. Reference is made to the Clinical Inspection Summary by Dr. Navid Homayouni. Two sites were inspected, the classifications given to each site by the clinical reviewer are shown in Table 2: OSI Clinical Inspection Summary.

Table 2: OSI Clinical Inspection Summary

Name of CI, Site #, Location	Study and # of Subjects	Inspection Dates	Final Classification
CI: Matthew Taylor, M.D. Site: 1001 Location: Portland, Oregon	Study 111/KEYNOTE-146 Site enrolled 15 patients	July 15-22, 2019	Final Classification: No Action Indicated (NAI)
CI: Vicky Makker, M.D. Site: 1003 Location: New York, New York	Study 111/KEYNOTE-146 Site enrolled 49 patients	July 29, 2019 to August 1, 2019	Final Classification: NAI

4.2 Product Quality

Not applicable.

4.3 Clinical Microbiology

Not applicable.

4.4 Devices and Companion Diagnostic Issues

The Regulatory Authorities' Assessment[1]:

Testing for tumor MSI/MMR status was not required for enrollment into the study. Available tumor samples were tested centrally to determine tumor MSI/MMR status using the Promega PCR MSI Analysis System and the Ventana MMR IHC assay. Additionally, if available, local testing results for both MSI and MMR status were also collected. Among the 108 patients in the endometrial cancer cohort of Study 111, 87% (n= 94) had tumors that were not MSI-H or dMMR, 10% (n=11) had tumors that were MSI-H or dMMR, and in 3% (n=3) the status was not known. The sponsor's testing strategy of central testing using the Ventana MMR IHC assay and the Promega PCR MSI Analysis System is acceptable. The Ventana MMR IHC assay is FDA cleared for the colorectal cancer indication and as such CDRH believes it was acceptable to use in an investigational setting for the endometrial cancer indication for assessing patient MMR status. The Promega PCR MSI Analysis System is routinely used in the clinical setting for assessing patient MSI status. These two types of tests are within the guidelines for testing MMR and MSI status of patients.

A marketing application for the contemporaneous approval of a companion diagnostic (CDx) has not been submitted to CDRH (Center for Devices and Radiological Health, US FDA). This indication is approved under accelerated approval based on tumor response rate and durability of response by the Center for Drug Evaluation and Research (CDER). Therefore, based on the unmet medical need in this population and the existence of a device that has already been cleared for assessing patient MMR status but in a different indication, it is acceptable that the companion diagnostic does not have a contemporaneous approval in this case. Two post market commitments to develop and support labeling of an immunohistochemistry-based in-vitro diagnostic device and a nucleic acid-based in-vitro diagnostic device to identify patients with endometrial carcinoma who are not mismatch repair deficient (dMMR) dMMR or microsatellite instability high (MSI-H) respectively, will be obtained from the sponsor. See section 12 of this review for description of the device PMCs.

5 Clinical Pharmacology

5.1 Executive Summary

The Regulatory Authorities' Assessment:
In this submission, the applicant is proposing a 20 mg QD lenvatinib in combination with 200 mg Q3W pembrolizumab for the treatment of [redacted] (b) (4) **. The proposed dose was selected based on safety information obtained for the Phase 1b of Study 111, where patients receiving 24 mg QD lenvatinib in combination 200 mg Q3W pembrolizumab experienced DLTs and the 20 mg QD lenvatinib in combination with 200 mg Q3W pembrolizumab was the MTD.**

There is no new pharmacokinetic or pharmacodynamic information submitted in this submission. The applicant proposed a 10 mg starting dose for EC patients with severe renal or hepatic impairment similar to the two-level dose reduction recommendation for the DTC and RCC indications in the current labeling.

5.2 Summary of Clinical Pharmacology Assessment

5.2.1. Pharmacology and Clinical Pharmacokinetics

The Applicant's Position:

No new PK or PK/pharmacodynamic analyses have been performed for combination lenvatinib plus pembrolizumab for this sNDA/sBLA, as Study 111 is ongoing. Module 2.7.2 includes data from the EC cohort of Study 111.

The Regulatory Authorities' Assessment:
We agree.

5.2.2. General Dosing and Therapeutic Individualization

5.2.2.1. General Dosing

The Applicant's Position:

The 20-mg starting dose of lenvatinib, given orally once a day (QD), in combination with a fixed pembrolizumab dose of 200 mg, given intravenously (IV) every 3 weeks (Q3W), is based on the determination of the maximum tolerated dose (MTD) in Phase 1b of Study 111. This regimen appears tolerable in patients with EC (Study 111 CSR, Section 12).

The Regulatory Authorities' Assessment:
We agree with the applicant's statement. In the Phase 1b portion of Study 111, three patients received 24 mg lenvatinib QD in combination with 200 mg pembrolizumab 200 mg Q3W. Two of the three patients experienced DLTs (Grade 3 arthralgia and Grade 3 fatigue) at 24 mg QD in combination with 200 mg Q3W pembrolizumab. Ten patients received 20 mg QD lenvatinib in combination with 200 mg Q3W pembrolizumab and no DLTs were observed. Therefore, 20 mg QD lenvatinib in combination with 200 mg Q3W pembrolizumab was declared the MTD and selected for the Phase 2 study.

5.2.2.2. Therapeutic Individualization

The Applicant's Position:

No new information concerning pharmacology and clinical PK is provided in this sNDA/sBLA.

The Regulatory Authorities' Assessment:
We agree.

5.2.2.3. Outstanding Issues

The Applicant's Position:

Not applicable.

The Regulatory Authorities' Assessment:
We agree.

5.3 Comprehensive Clinical Pharmacology Review

5.3.1. General Pharmacology and Pharmacokinetic Characteristics

The Applicant's Position:

No new information concerning pharmacology and clinical PK is provided in this sNDA/sBLA.

The Regulatory Authorities' Assessment:
We agree.

5.3.2. Clinical Pharmacology Questions

5.3.2.1. Does the clinical pharmacology program provide supportive evidence of effectiveness?

The Applicant's Position:

No new information concerning pharmacology and clinical PK is provided in this sNDA/sBLA.

The Regulatory Authorities' Assessment:
We agree.

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

The Applicant's Position:

The 20-mg starting dose of lenvatinib, given orally QD, in combination with a fixed pembrolizumab dose of 200 mg, given IV Q3W, is based on the determination of the MTD in Phase 1b of Study 111. The proposed dosing regimen is appropriate for the general population for which the indication is being sought.

The Regulatory Authorities' Assessment:
We agree.

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

The Applicant's Position:

An alternative dosing regimen or management strategy is not required for subpopulations based on intrinsic patient factors (Module 2.7.4, Section 2.7.4.5). The currently labeled dose management strategies for patients treated with either lenvatinib or pembrolizumab remain applicable.

The Regulatory Authorities' Assessment:
The applicant did not provide pharmacokinetic information to guide dosing in patients with severe renal or hepatic impairment. Similar to patients with DTC or RCC who have severe renal or hepatic impairment, the applicant is proposing a two-level dose reduction (i.e. 10 mg QD) for lenvatinib. Of note, the two-level dose reduction was approved based on clinical safety information at the time of original NDA submission. The applicant's proposal is acceptable because the safety profile in the EC population appears similar, with respect to dose reductions and discontinuations, to the RCC and DTC indications.

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

The Applicant's Position:

Lenvatinib has been reported to prolong the QT/QTc interval. Avoid coadministration of lenvatinib with medicinal products with a known potential to prolong the QT/QTc interval. Lenvatinib exposure is not affected by the intake of food nor are there any known clinically significant drug-drug interactions with lenvatinib.

There are no known food-drug or drug-drug interactions for pembrolizumab.

No drug interactions are expected between pembrolizumab and lenvatinib because of different metabolic pathways. Pembrolizumab is a monoclonal antibody and is primarily catabolized like other proteins, while lenvatinib is metabolized by enzymatic (CYP3A and aldehyde oxidase) and nonenzymatic processes.

The Regulatory Authorities' Assessment:
We agree.

X _____ X _____

Primary Reviewer Team Leader

6 Sources of Clinical Data

6.1 Table of Clinical Studies

The Applicant's Position:

Table 3 presents a total of 4 studies.

Study 111 contributes efficacy and safety and tolerability data in support of the combination of lenvatinib 20 mg QD orally plus pembrolizumab 200 mg IV Q3W for patients with (b) (4) .

The contribution of lenvatinib monotherapy is presented with data from EC subjects treated with lenvatinib 24 mg QD from the completed Study 204. The contribution of pembrolizumab monotherapy is presented with data from EC subjects from an interim analysis for studies KEYNOTE-158 (200 mg IV Q3W) and KEYNOTE-028 (10 mg/kg IV Q2W).

More information on these studies can be found in the CSRs, located in Module 5.3.5.2 for Study 111 and Modules 5.3.5.4 for Study 204, KEYNOTE-158, and KEYNOTE-028.

Table 3
List of Clinical Trials Relevant to this sNDA

Trial Identity	Trial Design	Regimen/schedule/ route	Study Endpoints Used for Filing	Treatment Duration/ Follow-Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
E7080-A001-111/ KEYNOTE 146 NCT02501096 (Ongoing)	Phase 1b/2, multicenter, open label study of combination lenvatinib plus pembrolizumab	Phase 1b: lenvatinib 24 mg or 20 mg orally QD plus pembrolizumab 200 mg Q3W Phase 2: Lenvatinib 20 mg orally QD, plus pembrolizumab 200 mg, given IV Q3W	Phase 2: ORR and DOR based on RECIST 1.1 by IIR	Until PD, development of unacceptable toxicity, withdrawal of consent, or discontinuation of the study by the sponsor	Phase 2: Total:124 subjects with EC [a, b]	Subjects with EC who received 0 to 2 lines of previous therapies	20 centers in US (15 sites) and Spain (5 sites) [c]
E7080-G000-204 NCT01111461	Phase 2, open label, single arm, multicenter study of lenvatinib monotherapy	Lenvatinib 24 mg orally QD	ORR based on RECIST 1.1 by IIR	Until PD, development of unacceptable toxicity, withdrawal of consent, or discontinuation of the study by the sponsor	133 [d]	Advanced EC following first-line platinum based chemotherapy	50 centers in US and Europe (20 sites each), Russia (10 sites)
KEYNOTE-158 (Ongoing) NCT02628067	Phase 2, open label, single arm, multi cohort, multicenter study of pembrolizumab monotherapy	Pembrolizumab 200 mg IV Q3W	ORR based on modified RECIST 1.1 as determined by IIR	Up to 2 years or until confirmed PD, intolerable toxicity, withdrawal of consent, investigator decision, or	Cohort D: 107 Cohort K-EC: 38 Not MSI-H/ dMMR: 90	Advanced EC after progression of standard of care.	49 centers in US (13 sites); France, Israel, Japan (5 sites each); Australia (4 sites); Russia, Spain (3 sites

				administrative reasons			each); Canada, Denmark, Italy, Norway (2 sites each); Brazil, Republic of Korea, Taiwan (1 site each)
KEYNOTE-028 NCT02054806 (Ongoing)	Phase 1b, open label, single arm, multi cohort, multicenter study of pembrolizumab monotherapy	Pembrolizumab 10 mg/kg IV Q2W	ORR based on modified RECIST 1.1 as determined by IIR	Up to 24 months or until confirmed PD, intolerable toxicity, withdrawal of consent, or investigator decision	Total: 24 Not MSI-H/ dMMR: 18	PD-L1-positive, advanced EC following 1 or more prior lines of therapy.	13 centers in US (7 sites), France (2 sites), Canada, Republic of Korea, Spain, UK (1 site each)

2L+ = second-line or greater, dMMR = mismatch repair deficient, EC = endometrial carcinoma, IIR = independent imaging review, irRECIST = immune-related Response Evaluation Criteria in Solid Tumors, IV = intravenous, MTD = maximum tolerated dose, ORR = objective response rate, MSI-H = microsatellite instability-high, PD = progressive disease, PD-L1 = programmed cell death ligand 1, Q2W = every 2 weeks, Q3W = every 3 weeks, QD = once daily, RECIST 1.1 = Response Evaluation Criteria in Solid Tumors version 1.1, sNDA = supplemental New Drug Application

a: Data cutoff date: 10 Jan 2019.

b: This includes the 108 subjects who received the combination of lenvatinib plus pembrolizumab in the 2L+ setting who had sufficient follow up to provide a median follow-up of at least 12 months, and for all responders, an opportunity for follow up after initial objective response as assessed by the investigator of at least 6 months.

c. This only includes sites that enrolled subjects with EC.

d. Data cutoff date: 21 May 2012.

The Regulatory Authorities' Assessment:
We agree with the summaries of the study 111/KN-146, study 204, KN-158 and KN-028 as presented in the table above.

7 Statistical and Clinical Evaluation

7.1 Review of Relevant Individual Trials Used to Support Efficacy

7.1.1. Study 111

The Applicant's Position:

Trial Design

Study 111

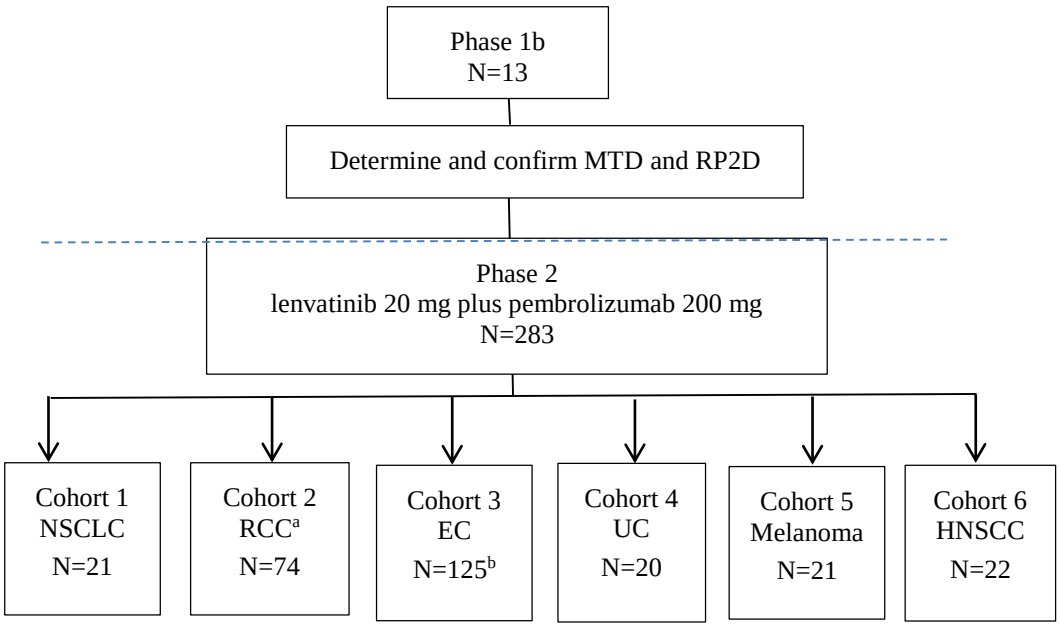
Study 111 is an ongoing, multi-center, open-label, multi-cohort Phase 1b/2 study of lenvatinib in combination with pembrolizumab in subjects with selected metastatic tumor types, including EC, NSCLC, RCC, UC, HNSCC, and melanoma. The primary objective of Phase 1b was to determine the MTD and recommended Phase 2 dose (RP2D) for lenvatinib to be used in combination with pembrolizumab 200 mg IV Q3W.

For this sNDA/sBLA, the primary objective of Phase 2 was to assess ORR and duration of response (DOR) per RECIST 1.1 by IIR of lenvatinib 20 mg orally QD plus pembrolizumab 200 mg IV Q3W in subjects with advanced EC that has progressed following prior systemic therapy and whose tumors are not MSI-H/dMMR.

Both phases of the study included a Pretreatment Phase (a Screening and Baseline Period), a Treatment Phase, and an Extension Phase that consisted of a Treatment Period and a Follow-up Period.

A schematic of the study design and the number of subjects as of the data cutoff date of 10 Jan 2019 is presented in Figure 1. Details of the study design can be found in the Study 111 protocol.

Figure 1 Design of Study 111



EC = endometrial carcinoma, HNSCC = squamous cell carcinoma of the head and neck, MTD = maximum tolerated dose, NSCLC = non-small cell lung cancer, RCC = renal cell carcinoma, RP2D = recommended Phase 2 dose, UC = urothelial carcinoma.

a: As of Protocol Amendment 05, the RCC cohort could be expanded to 120 subjects. Enrollment in the expansion is ongoing

b: One subject with leiomyosarcoma was enrolled in the EC cohort. Data for this subject are included in the Non-EC Set. The EC Set includes 124 subjects

Note: A total of 283 subjects received the RP2D of lenvatinib 20 mg QD plus pembrolizumab 200 mg Q3W in Phase 2, including 10 subjects who were enrolled in Phase 1b and received the RP2D and 273 subjects who were enrolled in Phase 2.

Source: Figure 1 and Table 14.1.4.1.2, Study 111 CSR

Phase 1b

The MTD and RP2D were determined using a dose de-escalation strategy with a 3 + 3 design. The RP2D for the combination was determined to be lenvatinib 20 mg orally QD plus pembrolizumab 200 mg IV Q3W (refer to the Study 111 CSR for further details).

Phase 2

Key Inclusion Criteria: Subjects ≥18 years had to have a life expectancy ≥12 weeks, an ECOG PS score of 0 or 1, adequately controlled blood pressure (BP) with or without antihypertensive medication, and adequate renal, bone marrow, liver, cardiac, and blood coagulation function. Subjects with known brain metastases were eligible if they had completed their primary brain therapy (e.g., whole-brain radiotherapy, stereotactic radiosurgery, complete surgical resection) and if they had remained clinically stable, were asymptomatic, and discontinued steroid use at least 28 days before starting study treatment.

Eligible EC subjects had histologically and/or cytologically confirmed metastatic EC with 0 to 2 prior lines of systemic therapy (unless discussed with the sponsor). If previously treated, the subject must have had PD after previous treatment. Subjects must have had measurable disease per irRECIST by investigator assessment.

Available tumor samples were tested centrally to determine tumor MSI/MMR status. Additionally, if available, local testing results for both MSI and MMR status were also collected. Testing for tumor MSI/MMR status was not required for enrollment into the study.

Complete inclusion criteria during participation in the study are provided in the Study 111 protocol, Section 9.3.1.

Key Exclusion Criteria: Subjects were not eligible for participation if they had significant cardiac impairment within the past 6 months, a history of or current noninfectious pneumonitis that required steroid treatment, a history of organ allograft, or had positive test results for human immunodeficiency virus, hepatitis B or hepatitis C.

A full list of the study exclusion criteria is provided in the Study 111 protocol, Section 9.3.2.

Study Treatment: EC subjects were treated with lenvatinib 20 mg orally QD in combination with pembrolizumab 200 mg IV Q3W.

Dose Modification: Toxicity was managed in accordance with prespecified dose modification instructions for each agent provided in the protocol (Study 111 protocol, Section 9.4.1.1 and Section 9.4.1.2).

Subject Discontinuation: Subjects could receive treatment until progressive disease (PD), development of unacceptable toxicity, withdrawal of consent, or termination of the study by the sponsor. Subjects could receive up to 35 treatments (approximately 2 years) with pembrolizumab. Lenvatinib treatment could be continued as monotherapy thereafter.

Procedures and Schedule: The Schedules of Procedures/Assessments in the Study 111 protocol, Table 9 summarizes the trial procedures to be performed at each visit.

Efficacy Assessments*:* Tumor assessments were performed at Baseline, every 6 weeks during the Treatment Phase until Week 24, and every 9 weeks during treatment cycles in both the Treatment Phase and the Extension Phase. Subjects who discontinued treatment without PD underwent tumor assessments until PD was documented or another anticancer therapy was initiated.

Treatment decisions were based on investigator assessment. Per immune-related Response Evaluation Criteria in Solid Tumors (irRECIST), the decision to continue study treatment after the first evidence of PD per modified RECIST 1.1 (mRECIST 1.1) was at the investigator's discretion based on the clinical status of the subject. Tumor assessments for EC subjects were also performed by IIR using irRECIST, and mRECIST 1.1, and RECIST 1.1 as specified in subsequent protocol amendments.

Safety Assessments*:* Safety was assessed throughout the study by monitoring adverse events (AEs), laboratory evaluations, vital signs, electrocardiograms (ECGs), and echocardiograms (ECHOs). Adverse events were graded according to the guidelines outlined in the National

Cancer Institute CTCAE version 4.03. After the end of study treatment, subjects were followed for AE monitoring for 30 days. Serious AEs, regardless of causality, were collected through 90 days after the last dose or 30 days after the last dose if the subject initiated a new anticancer therapy, whichever was earlier.

Study Endpoints

Primary

*Efficacy Endpoint***:** For this submission, the primary efficacy endpoints are ORR (CR + PR) and DOR based on IIR using standard RECIST 1.1 in the Indication Efficacy Set. A total of 94 subjects with EC that had progressed following prior systemic therapy, whose tumors were not MSI-H/dMMR and who met the criteria for duration of follow-up are included in the Indication Efficacy Set.

Key Secondary and Exploratory Efficacy Endpoints: The key secondary endpoints for the Indication Efficacy Set were PFS and OS. Tumor shrinkage, demonstrating depth of response, was an exploratory endpoint.

*Safety***:** Safety endpoints include treatment-emergent AEs, clinical laboratory parameters, vital signs, 12-lead ECGs, and ECHO/multigated acquisition (MUGA) scan results, including left ventricular ejection fraction (LVEF).

Statistical Analysis Plan and Amendments

Study 111 was conducted as an open-label study, i.e., subjects, investigators, and sponsor personnel were aware of subject treatment. An Addendum Statistical Analysis plan for Study 111 was prepared to document the statistical analyses performed for the EC cohort of Study 111 (dated 21 Feb 2019) for this sNDA/sBLA.

Efficacy Analysis

Indication Efficacy Set: Includes all subjects with histologically confirmed EC whose tumors were not MSI-H/dMMR, were previously treated with at least 1 systemic anticancer therapy, and who had sufficient follow-up to provide a median duration of follow-up of at least 12 months, with the opportunity of at least 6 months of follow-up time from the time of documented response for subjects that responded. All subjects in this analysis set received lenvatinib 20 mg QD plus pembrolizumab 200 mg Q3W. The Indication Analysis Set supports the regulatory purpose of this filing.

The analysis strategy for the primary and key secondary endpoints is presented below. ORR, DOR, and PFS were based on RECIST 1.1 as assessed by IIR.

- For the assessment of ORR, the number and percentage of subjects with a confirmed CR or PR and corresponding 95% confidence intervals (CIs), based on the method of Clopper and Pearson, are presented.
- Duration of response was defined as the time from the date a response was first documented until the date of the first documentation of PD or date of death from any cause, whichever occurred first, and was summarized for subjects with a confirmed CR

or PR. Time to response was summarized with descriptive statistics for subjects with confirmed CR or PR.

- Among the responders, results for DOR, time to response, and DOR ≥6 months and 12 months are summarized. The distribution of DOR was estimated using Kaplan–Meier (KM) methodology, and median DOR and 95% CIs were provided.
- PFS was defined as the time from the date of first dose to the date of PD or death, whichever occurred first. Median PFS and corresponding 95% CIs were provided, and PFS was analyzed using KM product-limit estimates along with KM plots. Three-month, 6-month, 9-month, and 1-year PFS rates were estimated using KM methodology, and corresponding 95% CIs were calculated.
- OS was defined as the time from the first dose date to the date of death due to any cause. Median OS and survival rates at 12, 18, and 24 months were calculated using KM product-limit estimates presented with 2 sided 95% CIs. A KM plot for OS was provided.
- Maximum percentage reduction in the sum of diameters of target lesions (tumor shrinkage) per RECIST 1.1 by IIR is displayed in a waterfall plot.

Safety Analysis: Safety data were summarized for all subjects treated as of the data cutoff date using descriptive statistics. Categorical variables were summarized by number and percentage. Continuous variables were summarized using n (number of subjects with available data), mean, standard deviation, median, and range.

Protocol Amendments

The original protocol was approved on 22-Apr-2015, and was amended 6 times as of the data cut-off date of 10 -Jan-2019. Key changes to the protocol are presented below.

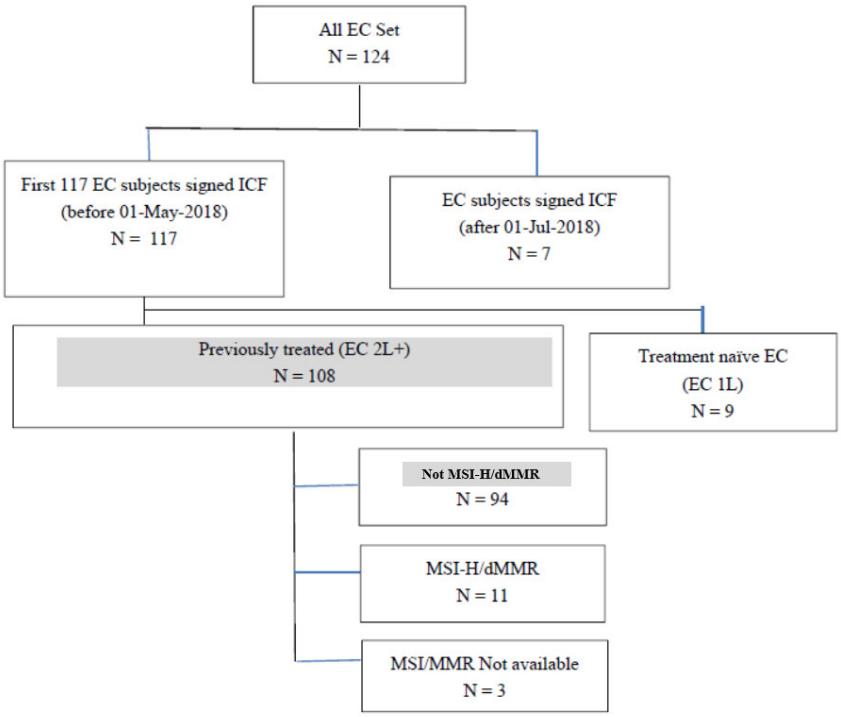
Protocol or Amendment (Date Finalized at Sponsor)	Key Changes
Protocol (22-Apr-2015)	Original Protocol
Amendment 01 (14-Jan-2016)	Changed dose-modification guidelines for pembrolizumab-related AEs to reflect updated guidelines.
Amendment 02 (30-Mar-2016)	Added general guidelines for holding periods of lenvatinib due to minor and major procedures.
Amendment 03 (26-Oct-2016)	In the Phase 2 expansion, added the option to increase enrollment in the EC cohort to up to 120 subjects. Added statistical information of the 2 analyses. New exploratory objective and exploratory endpoint added to allow for evaluation of tumor response in the EC cohort using IIR. Exclusion criterion modified.
Amendment 04 (23-May-2017)	Inclusion criterion modified. Modified requirements for pembrolizumab that specified treatment be discontinued for subjects with recurrent Grade 2 pneumonitis. Clarified the duration that subjects could receive lenvatinib and pembrolizumab.
Amendment 05 (22-DEC-2017)	Updated the 200-mg pembrolizumab dose justification, treatment guidelines for Grades 3 or 4

	infusion reaction, and supportive care guidelines for pembrolizumab based on updated information.
Amendment 06 (31 Jul 2018)	Assessments of tumor response based on IIR using RECIST v1.1 for subjects with EC were added to the exploratory objectives, and exploratory efficacy assessments were added to the corresponding exploratory endpoint. Exclusion Criterion revised to clarify that subjects who have had an allogenic tissue/solid organ transplant were to be excluded, based on the updated pembrolizumab label.

The Regulatory Authorities' Assessment:

The applicant has described protocol amendments and statistical analysis plan above. No statistical inference can be made from a single-arm study and results presented would be considered descriptive. The efficacy evaluation was based on the magnitude of response rate and adequate duration of response. Additionally, although progression-free survival, time to response and overall survival results were summarized, we noted that time-to-event endpoints are uninterpretable without a comparator arm. Due to the single arm design of Study 111/KN-146, the treatment effect of each component in the combination could not be isolated within this study. In order to evaluate whether the combination of L+P was associated with improved efficacy compared to either drug alone, anti-tumor activity for each individual component in the same patient population should be characterized. The applicant submitted data from three clinical studies in which activity of lenvatinib or pembrolizumab monotherapy was investigated to support the evaluation of each product contribution in the combination. The contribution of lenvatinib monotherapy was descriptively assessed with data from Study 204, and the contribution of pembrolizumab monotherapy was descriptively assessed with data from interim analysis for studies KEYNOTE-158 and KEYNOTE-028. FDA further conducted exploratory analyses using a propensity score approach to evaluate the contribution of each component using data from external monotherapy trials (see Section 7.1.6 and Appendix 17.4). Propensity score analyses cannot guarantee that all measured and unmeasured baseline characteristics are balanced across studies and the results of these analyses are considered as exploratory and should be interpreted with caution.

Figure 2: Patients enrolled in the endometrial cohort of Study 111/KN-146



One subject with leiomyosarcoma was enrolled in the EC cohort. Data for this subject are included in the Non-EC Set. The EC Set includes 124 subjects.

7.1.2. Study 111 Results

The Applicant's Position:

Compliance with Good Clinical Practices

Study 111 was conducted in accordance with standard operating procedures (SOPs) of the sponsor (or designee), which are designed to ensure adherence to good clinical practice (GCP) guidelines as required by the following:

Principles of the World Medical Association Declaration of Helsinki 2013

- International Conference on Harmonization (ICH) E6 Guideline for GCP (Committee for Proprietary Medicinal Products [CPMP]/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.
- Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and Institutional Review Board (IRB) regulations and applicable sections of US 21 CFR Part 312.
- European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any European Union (EU) country. All

suspected unexpected serious adverse reactions (SUSARs) were reported, as required, to the Competent Authorities of all involved EU member states.

- Other applicable regulatory authorities

Financial Disclosure

Disclosure of financial interests of the investigators who enrolled subjects with endometrial carcinoma in Study 111, has been obtained and submitted in the FDA Financial Disclosure Form 3454 (Module 1.3.4).

Patient Disposition

A total of 94 subjects with EC tumors that were not MSI-H/dMMR were included in Indication Efficacy Set. As of the data cutoff (10 Jan 2019), 24 (25.5%) subjects were still receiving treatment (Table 7). The most frequent reasons for discontinuation of treatment were due to radiological disease progression by investigator assessment (46.8% of subjects), AEs (9.6% of subjects), and clinical disease progression (8.5% of subjects).

Protocol Violations/Deviations

There was one major protocol deviation related to Investigational Product (IP): this was an accidental overdose (described in Section 12.3.1.4.5 of the Study 111 CSR and Section 7.2.9).

Table of Demographic Characteristics

The majority of subjects in the Indication Efficacy Set were white (86.2%) and from the US (86.2%) (Table 8). Median age was 66.0 years, the Eastern Cooperative Oncology Group (ECOG) score was 0 in 52.1% of subjects and 1 in 47.9% of subjects.

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

All relevant Baseline characteristics are included in Table 8.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance

Records of treatment compliance for each subject were kept during the study. Clinical Research Associates (CRAs) reviewed treatment compliance during site visits and at the completion of the study (Study 111 CSR, Section 9.4.8)

Concomitant Medications

The most common concomitant medications in the Indication Efficacy Set were antihypertensive medications (90.4%), thyroid preparations (74.5%), analgesics and antipyretics (72.3%), and antiemetics and antinauseants (61.7%). Antidiarrheal medication use was reported for 43.6% of subjects, and systemic corticosteroid use for any indication was reported for 31.9% of subjects in the Indication Safety Set (Study 111 CSR, Table 12).

Rescue Medications

Not applicable.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

The ORR for subjects in the Indication Efficacy Set based on IIR using RECIST 1.1 was 38.3% (95% CI: 28.5, 48.9) with 10.6% of subjects achieving a CR and 27.7% of subjects achieving a PR (**Table 4**). The response to lenvatinib plus pembrolizumab combination therapy was durable, with a median DOR that was not reached after a median follow-up of longer than 12 months among subjects in the Indication Efficacy Set (**Figure 3**). Twenty-one of the responders were censored as their disease had not progressed. As of the data cutoff, the longest DOR was 33.1 months and ongoing. Among the 36 responders, 25 subjects had a DOR that lasted at least 6 months; the estimated probability of DOR for at least 6 months was 0.76. Eight subjects had a DOR that lasted at least 1 year; the estimated probability of DOR at least 1 year was 0.51.

Table 4
Objective Response Rate Based on Independent Imaging Review using RECIST 1.1 – Indication Efficacy Set

	Lenvatinib 20 mg + Pembrolizumab 200 mg Indication Efficacy Set[a] (N=94)
BOR, n (%)[b]	
CR	10 (10.6)
PR	26 (27.7)
SD	38 (40.4)
PD	12 (12.8)
Not Evaluable	8 (8.5)
Unknown	0 (0.0)
ORR (CR + PR), [b] n (%)[a]	36 (38.3)
95% CI of ORR[c]	(28.5, 48.9)

Data cutoff date: 10 Jan 2019.

This table summarizes all tumor assessments as long as the subjects did not start a new anticancer therapy. For BOR, PR and CR must be confirmed no less than 4 weeks after initial assessment of response. SD must be achieved at <5 weeks after the first dose study drug administration to be considered BOR. Not evaluable refers to subjects with either no postbaseline tumor assessment(s) or with postbaseline tumor assessment(s) that are not evaluable (ie, due to insufficient data for assessment of response per RECIST 1.1 or an early SD with duration <5 weeks). Unknown refers to subjects with no baseline tumor assessment.

BOR = best overall response, CR = complete response, dMMR = mismatch repair deficient, EC = endometrial cancer, IIR= independent imaging review, MSI-H = microsatellite instability-high, ORR = objective response rate, PD=progressive disease, PR=partial response, RECIST =Response Evaluation Criteria in Solid Tumors, SD= stable disease.

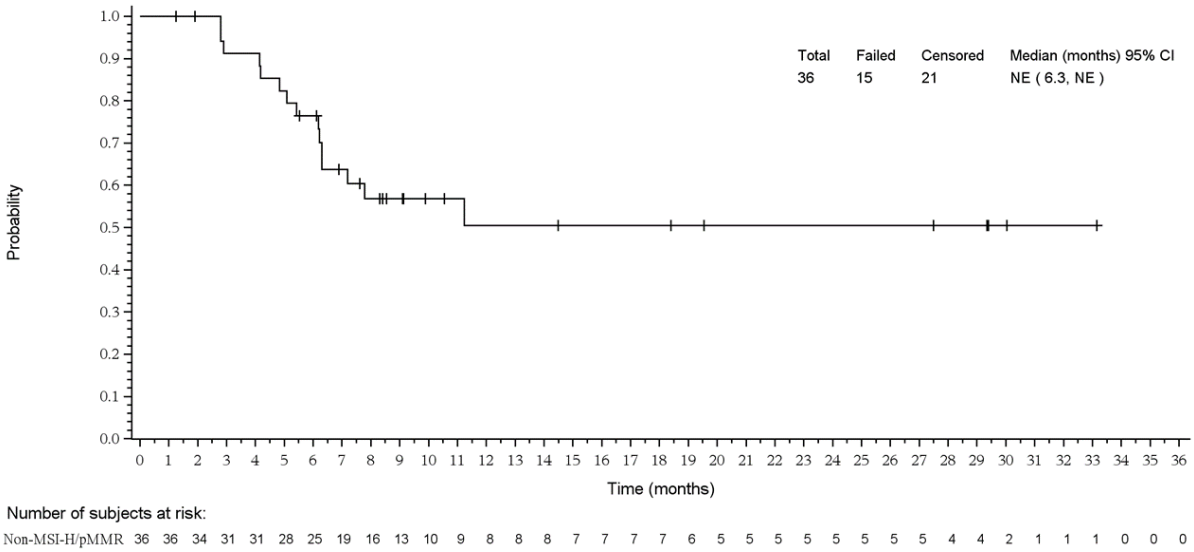
a: Indication Efficacy Set = all subjects with histologically confirmed not MSI-H/dMMR EC who received at least 1 prior systemic anticancer therapy(ies) and who had sufficient follow-up to provide a median follow-up of at least 12 months, and for all responders, an opportunity for follow-up after initial objective response as assessed by the investigator of at least 6 months (ie, enrolled prior to 01Jul2018).

b: Six subjects in the Indication Efficacy Set had no target lesions at Baseline per IIR assessment. Non-CR/Non-PD for subjects with no target lesions at Baseline was treated as, and combined with, SD for purposes of analysis for ORR and BOR.

c: 95% CI was constructed using the method of Clopper and Pearson.

Source: Study 111 EC CSR Table 14.2.1.2.1e, ADaM dataset: ADSL_Study 111, ADEF_Study 111, ADTTE_Study 111.

Figure 3
Kaplan Meier Plot of Duration of Response Based on Independent Imaging Review using RECIST 1.1 – Indication Efficacy Set



Data cutoff date: 10 Jan 2019.
Indication Efficacy Set = all subjects with histologically confirmed not MSI-H/dMMR EC who received at least 1 prior systemic anticancer therapy(ies) and who had sufficient follow up to provide a median follow up of at least 12 months, and for all responders, an opportunity for follow up after initial objective response as assessed by the investigator of at least 6 months (ie, enrolled prior to 01 Jul 2018).
DOR among responders is defined as the time from the date that a confirmed response was first documented as the evidence of CR or PR until the date of the first documentation of disease progression or date of death from any cause, whichever occurred first.
The median was estimated using the Kaplan Meier method and the 95% CI was constructed with a generalized Brookmeyer and Crowley method.
All tumor assessments were considered as long as the subjects did not start a new anticancer therapy.
+ = censored, CR = complete response, dMMR = mismatch repair deficient, DOR = duration of response, EC = endometrial cancer, IIR = independent imaging review, MSI-H = microsatellite instability-high, PR = partial response, RECIST = Response Evaluation Criteria in Solid Tumors.
Source: Study 111 EC CSR Figure 14.2.1.1e; ADaM dataset: ADSL_Study 111, ADTTE_Study 111

Responses were seen early with the combination regimen. The median time to response (TTR) among responders based on IIR using RECIST 1.1 in the Indication Efficacy Set was 1.4 months (range: 1.1 – 8.0), which was approximately at the time of the first scheduled tumor assessment scan per protocol (Study 111 CSR Table 14.2.1.2.1e, ADaM dataset: ADSL_Study 111, ADEF_Study 111, ADTTE_Study 111).

Data Quality and Integrity

Quality and integrity of study data were assured through monitoring of investigational sites, provision of appropriate training for study personnel, and use of data management procedures, as detailed in the Study 111 protocol, Section 9.6.

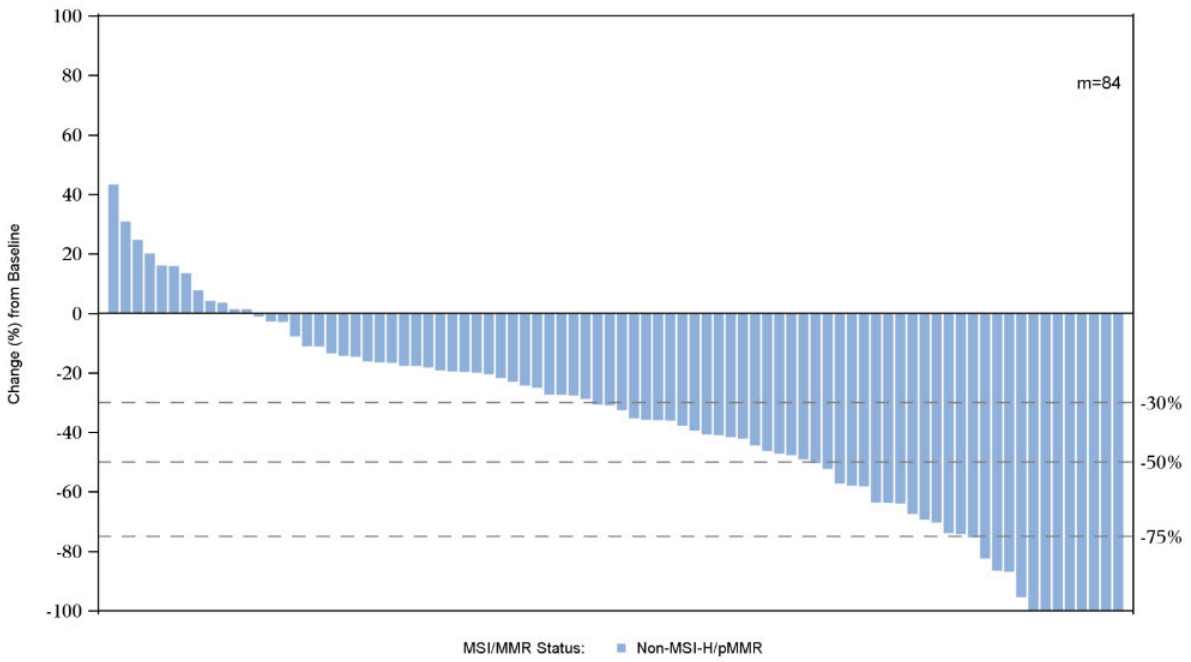
Efficacy Results – Secondary and other relevant endpoints

Tumor Shrinkage

The maximum percentage change from Baseline in the sum of the diameters of target lesions is shown in the waterfall plot in Figure 4 for the 84 evaluable subjects in the Indication Efficacy Set (i.e., with measurable disease as assessed based on IIR using RECIST 1.1 and with target lesions assessed both at Baseline and at least 1 postbaseline time point).

Among the 84 evaluable subjects in the Indication Efficacy Set, the majority (72/84; 85.7%) had tumor shrinkage with 26/84 (31.0%) achieving at least 50% maximal tumor shrinkage, and 13/84 (15.5%) achieving at least 75% maximal tumor shrinkage (Study 111 CSR Table 14.2.1.2.1e; ADaM dataset: ADSL_Study 111, ADEF_Study 111, ADTTE_Study 111). Furthermore, among the 36 responders, 24/36 (66.7%) had at least 50% maximal tumor shrinkage, and 11/36 (30.6%) had at least 75% maximal tumor shrinkage (Study 111 CSR Listing 16.2.6.1.1).

Figure 4
Percentage Change in Sum of Diameters of Target Lesions from Baseline to Postbaseline Nadir Based on Independent Imaging Review using RECIST 1.1 – Indication Efficacy Set



Data cutoff date: 10 Jan 2019.
Indication Efficacy Set = all subjects with histologically confirmed not MSI-H/dMMR EC who received at least 1 prior systemic anticancer therapy(ies) and who had sufficient follow up to provide a median follow up of at least 12 months, and for all responders, an opportunity for follow up after initial objective response as assessed by the investigator of at least 6 months (ie, enrolled prior to 01 Jul 2018).
Figure includes subjects (m) with both Baseline and at least 1 postbaseline target lesion assessment.
Note: 10 subjects were not included in the Waterfall plot, 4 subjects due to no postbaseline assessment and 6 subjects due to no target lesion.
dMMR = mismatch repair deficient, EC = endometrial cancer, MSI = microsatellite instability, RECIST = Response Evaluation Criteria in Solid Tumors.

Source: SCE 2.7.3 Figure 2.7.3-2; ADaM dataset: ADSL_Study 111, ADEF_Study 111

Progression-Free Survival

Treatment with combination lenvatinib plus pembrolizumab resulted in a median PFS of 5.4 months (95% CI: 4.4, 7.6). The PFS rates at 12 and 18 months were 33.2% and 27.2%, respectively (Module 2.7.3 Table 2.7.3-9 and Figure 2.7.3-3).

Overall Survival

As of the cutoff date, median OS was 16.4 months (95% CI: 13.5, 25.9) in the Indication Efficacy Set; the OS rate at 12 months was 69.5% and the OS rate at 24 months was 39.2% (Module 2.7.3 Table 2.7.3-10 and Figure 2.7.3-4).

Subgroup Analyses

A clinically meaningful ORR was observed in all subgroups defined by age, race, region, programmed cell death ligand 1 (PD-L1) status, and histologic subtype. Response rates were generally consistent among the subgroups and with that of the Indication Efficacy Set (Table 5). Responses were seen across various histologies including serous and clear cell subtypes.

Table 5
Subgroup Analysis of Objective Response Rate Based on Independent Imaging Review using RECIST 1.1 – Indication Efficacy Set

	Lenvatinib 20 mg + Pembrolizumab 200 mg Indication Efficacy Set[a]		
	N	Responder	ORR (%) (95% CI)[b]
Overall	94	36	38.3 (28.5, 48.9)
Age Group (years)			
<65	36	13	36.1 (20.8, 53.8)
≥65	58	23	39.7 (27.0, 53.4)
Race			
White	81	31	38.3 (27.7, 49.7)
All others	13	5	38.5 (13.9, 68.4)
Geographic Region			
US	81	30	37.0 (26.6, 48.5)
Non-US	13	6	46.2 (19.2, 74.9)
PD-L1 Status[c]			
Positive	46	16	34.8 (21.4, 50.2)
Negative	39	16	41.0 (25.6, 57.9)
Not Available	9	4	44.4 (13.7, 78.8)
Histologic subtype[d]			

	Lenvatinib 20 mg + Pembrolizumab 200 mg Indication Efficacy Set[a]		
	N	Responder	ORR (%) (95% CI)[b]
Endometrioid adenocarcinoma	46	12	26.1 (14.3, 41.1)
Serous	33	14	42.4 (25.5, 60.8)
Clear cell	5	4	80.0 (28.4, 99.5)

Data cutoff date: 10 Jan 2019.

CI = confidence interval, CPS = combined positive score, dMMR = mismatch repair deficient, EC = endometrial cancer, MSI = microsatellite instability-high, ORR = objective response rate, PD-L1 = programmed cell death ligand 1; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, US = United States.

a: Indication Efficacy Set = all subjects with histologically confirmed not MSI-H/dMMR EC who received at least 1 prior systemic anticancer therapy(ies) and who had sufficient follow-up to provide a median follow-up of at least 12 months, and for all responders, an opportunity for follow-up after initial objective response as assessed by the investigator of at least 6 months (ie, enrolled prior to 01 Jul 2018).

b: 95% CI was calculated using the method of Clopper and Pearson.

c: PD-L1 status is positive; if CPS ≥1 and negative if CPS <1.

d: Eleven patients had other histologies which were predominately mixed histologies.

Source: Study 111 EC CSR Table 14.2.1.2.1e, Table 14.2.1.3.1.e, Table 14.2.1.4.1, Table 14.2.1.5.1, Listing 16.2.4.1.1a and Listing 16.2.6.2.1c; ADaM dataset: ADSL_Study 111, ADEF_Study 111, ADTTE_Study 111.

Dose/Dose Response

Not applicable.

Durability of Response

Duration of response was a primary efficacy endpoint and is summarized above.

Persistence of Effect

Persistence of effect is discussed in previous sections: DOR (Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)) and OS (Efficacy Results – Secondary and other relevant endpoints).

Four subjects in the Indication Efficacy Set completed treatment with pembrolizumab per protocol after receiving the maximum of 35 treatments (approximately 2 years) and continued to receive lenvatinib monotherapy further demonstrating continued benefit and persistence of efficacy (Study 111 EC CSR Table 14.1.1.3.1).

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Not applicable.

Additional Analyses Conducted on the Individual Trial

Not applicable

The Regulatory Authorities' Assessment:

FDA agrees with the efficacy results of Study 111/KN-146 presented by the applicant; however, the single arm design of Study 111/KN-146 did not allow determining the

contribution of each component of the combination. Monotherapy data were collected from three clinical trials and provided supportive information for isolation of treatment effect. FDA conducted exploratory analyses using a propensity score approach to evaluate the contribution of each component using data from external monotherapy trials (see Section 7.1.6 and Appendix 17.4).

The ORR based on independent imaging review (IIR) using RECIST v1.1 was 38.3% (95% CI: 28.5, 48.9) with 10.6% of patients achieving a CR and 27.7% of patients achieving a PR. The applicant stated in the Study 111 EC CSR that the ORR assessed by the investigator was not available based on RECIST v1.1, but available based on modified RECIST (mRECIST) v1.1. The mRECIST v1.1 allowed selection of up to 10 target lesions with up to 5 lesions per organ. The ORR based on mRECIST v1.1 was 36.2% (95 CI: 26.5, 46.7) per investigator and 39.4% (95% CI: 29.4, 50.0) per IIR. Response rates per RECIST v1.1 and mRECIST v1.1 were consistent. Discordance rate of the ORR between the investigator assessment and IIR assessment based on mRECIST 1.1 was 20.2% and is acceptable for ORR assessment in a single-arm study.

The applicant also provided the waterfall plots of maximum percentage change in summed diameter of target lesions from baseline to nadir based on IIR using RECIST v.1.1. The use of waterfall plots to visually convey the benefit seen in cancer clinical trials has gained popularity over time; however, it is noted that the waterfall plot has its own limitations. Not every bar below the -30% line is a response and may have stable disease, partial response, etc. In addition, the waterfall plot only includes patients able to be assessed for response. Therefore, waterfall plots may visually bias the estimate of response rate upward and misrepresent response rates.

Duration of response is considered by the FDA as a secondary endpoint to support the primary endpoint of ORR in a single arm study. To describe duration of response, in addition to providing an estimate of median response duration, FDA often calculates the percentage of patients with response longer than a set time period without considering censoring. In this study, 25 patients (69% of the 36 responders) had a duration of response ≥6 months.

In addition, FDA conducted exploratory analyses of ORR in subgroups defined by ECOG performance status at baseline, number of prior anticancer medication regimens, FIGO Grade for EC and number of metastatic sites. No apparent outliers were observed in these subgroup analyses (Table 6).

Table 6. Subgroup Analysis of Objective Response Rate Based on Independent Imaging Review using RECIST 1.1 – Indication Efficacy Set

	Lenvatinib 20 mg + Pembrolizumab 200 mg Indication Efficacy Set		
	N	Responder	ORR (%) (95% CI)
Overall	94	36	38.3 (28.5, 48.9)

	Lenvatinib 20 mg + Pembrolizumab 200 mg Indication Efficacy Set		
	N	Responder	ORR (%) (95% CI)
ECOG PS at baseline			
0	49	23	46.9 (32.5, 61.7)
1	45	13	28.9 (16.4, 44.3)
Number of prior anticancer medication regimens			
1	48	20	41.7 (26.7, 56.8)
2	36	12	33.3 (18.6, 51.0)
3 or 4	10	4	40.0 (12.2, 73.8)
FIGO Grade for EC			
Grade 1	10	4	40.0 (12.2, 73.8)
Grade 2	15	3	20.0 (44.3, 48.1)
Grade 3	69	29	42.0 (30.2, 54.5)
Number of Metastatic Sites Group			
1	31	15	48.4 (30.2, 66.9)
2	31	13	41.9 (24.6, 60.9)
>=3	32	8	25.0 (11.5, 43.4)
Source: Study 111 – ADSL.xpt, ADDC.xpt, ADEF.xpt			

7.1.3. Study 204

Study 204 is a completed, multicenter, open-label, single-arm, Phase 2 study of lenvatinib monotherapy (24 mg QD orally) in 133 subjects with advanced EC and PD following first-line platinum-based chemotherapy. The primary objective was to assess the ORR (CR+PR) of lenvatinib in subjects with unresectable EC and PD following platinum based, first-line chemotherapy based on IIR using RECIST 1.1.

Key Inclusion Criteria: Females aged 18 years or older; histological confirmation of EC; radiographic evidence of PD according to RECIST 1.1 after 1 prior systemic, platinum-based chemotherapy regimen; measurable disease according to RECIST 1.1; ECOG performance status (PS) score of 0 to 2; adequately controlled BP; and adequate renal, liver, bone marrow, and blood coagulation function. MSI/MMR tumor status was not determined for subjects in this study.

Key Exclusion Criteria: More than 1 prior systemic chemotherapy regimen for metastatic or primary unresectable EC or any treatment targeting vascular endothelial growth factor (VEGF)-directed angiogenesis (there was no restriction regarding prior hormonal therapy) and the presence of brain or leptomeningeal metastases, including stable metastases.

Study Treatment: Subjects received lenvatinib monotherapy with 24 mg QD orally until PD, development of unacceptable toxicity, withdrawal of consent, or discontinuation of lenvatinib development by the sponsor. Subjects received study treatment until PD, development of unacceptable toxicity, withdrawal of consent, or discontinuation of lenvatinib development by the sponsor. All subjects were followed for survival until death or termination of survival follow-up by the sponsor. The data cutoff for the primary analysis was 21 May 2012

Efficacy Assessments: Tumor assessments were performed according to standard RECIST 1.1 every 8 weeks after enrollment until PD.

Safety Assessments: Monitoring and recording of AEs, laboratory evaluations, vital signs, ECGs and ECHOs

Study Endpoints: ORR and DOR, both assessed by IIR.

7.1.4. Study KEYNOTE-158

Study Design

KEYNOTE-158 is an ongoing, multicohort, multicenter, open-label, Phase 2 study in subjects with multiple types of advanced (unresectable and/or metastatic) solid tumors, including EC regardless of PD-L1 expression, which has progressed after standard of care therapy. Subjects with EC were enrolled in Cohort D. Cohort K enrolled subjects with any advanced solid tumor (excluding colorectal carcinoma), including EC, which was MSI-H/dMMR.

The primary objective was to estimate ORR based on IIR using RECIST 1.1 (modified to allow for up to 10 target lesions and up to 5 lesions per organ).

Key Inclusion Criteria: For subjects in Cohort D (biomarker unselected EC) and Cohort K EC (MSI-H/dMMR), key inclusion criteria were: at least 18 years of age; histologically or cytologically documented advanced EC (sarcomas and mesenchymal tumors were excluded); progression of tumor or intolerance to therapies known to provide clinical benefit; measurable disease according to RECIST 1.1; ECOG PS of 0 or 1; and adequate organ function

Key Exclusion Criteria: Received prior therapy with an anti-programmed cell death 1 (anti PD-1), anti PD-L1, anti-programmed cell death ligand 2 (anti-PD-L2), or any other immunomodulating monoclonal antibody (mAb) or drug specifically targeting T-cell co stimulation or checkpoint pathways; known additional malignancy within 2 years prior to enrollment with the exception of curatively treated basal cell carcinoma of the skin, squamous cell carcinoma of the skin and/or curatively resected in situ cancers; known active central nervous system (CNS) metastases and/or carcinomatous meningitis; and known glioblastoma multiforme of the brainstem.

Study Treatment: Subjects were treated with pembrolizumab monotherapy 200 mg Q3W. Subjects could continue to receive pembrolizumab until PD, development of unacceptable toxicity, intercurrent illness that prevented further administration of treatment, investigator's decision to withdraw the subject, subject discontinuation from the study, noncompliance with trial treatment or procedure requirements, subject received 35 administrations of pembrolizumab (approximately 2 years), or administrative reasons requiring the cessation of

treatment. Subjects who stopped pembrolizumab after receiving 35 doses of pembrolizumab without PD, or after achieving a CR may have been eligible for a second course of pembrolizumab treatment for up to 17 additional doses of pembrolizumab (approximately 1 year) upon experiencing PD.

Efficacy Assessments: Subjects were evaluated every 9 weeks with radiological imaging to assess response to treatment for the first 12 months, then every 12 weeks thereafter.

Safety Assessments: Monitoring and recording of AEs, laboratory evaluations, vital signs, and ECGs. MSI testing was done for Cohort D. Cohort K EC enrolled only MSI-H/dMMR EC subjects per local testing results.

Study Endpoints: ORR based on IIR using RECIST 1.1 (modified to allow for up to 10 target lesions and up to 5 lesions per organ).

7.1.5. Study KEYNOTE-028

Study Design

KEYNOTE-028 is a multicohort, multicenter, open-label, Phase 1b study in subjects with PD L1 positive advanced solid tumors, including EC. The primary objective was to evaluate the preliminary signals of potential antitumor activity of pembrolizumab monotherapy in subjects with PD L1 positive advanced solid tumors using ORR based on investigator assessment using RECIST 1.1.

Key Inclusion Criteria: At least 18 years of age; histologically or cytologically documented locally advanced or metastatic EC that progressed after standard therapy, for which no standard therapy exists or for which standard therapy was not considered appropriate; measurable disease according to RECIST 1.1; ECOG PS of 0 or 1; and adequate organ function.

Key Exclusion Criteria: Prior anticancer mAb therapy within 4 weeks of treatment initiation; prior chemotherapy, targeted small-molecule therapy, or radiation therapy within 2 weeks of treatment initiation; prior treatment with an anti-PD-1, anti-PD-L1, or anti-PD-L2 therapy or other immune checkpoint inhibitor; known active CNS metastases; or diagnosis of immunodeficiency, autoimmune disease, interstitial lung disease, or active infection requiring systemic therapy.

Study Treatment: Subjects received pembrolizumab 10 mg/kg IV Q2W for up to 24 months or until confirmed PD, intolerable toxicity, death, withdrawal of consent or investigator decision. Subjects who stopped pembrolizumab after receiving treatment for 24 months or after achieving a CR may have been eligible for a second course of pembrolizumab treatment for an additional year upon experiencing PD.

Efficacy Assessments: Tumor assessments were performed every 8 weeks for the first 6 months and every 12 weeks thereafter.

Safety Assessments: Monitoring and recording of AEs, laboratory evaluations and vital signs.

Study Endpoints for the filing: ORR, and the secondary efficacy endpoint of DOR, both based on IIR using RECIST 1.1 (modified to allow for up to 10 target lesions and up to 5 lesions per organ).

Integrated Review of Effectiveness

7.1.6. Assessment of Efficacy Across Trials

The Applicant's Position:

For assessment of contribution of components, side-by-side evaluations showing the results of Study 111 and the results for Study 204, KEYNOTE-158, and KEYNOTE 028 are provided. Data are included for ORR and DOR based on IIR using RECIST 1.1 for Study 111 and Study 204; and modified RECIST 1.1 for KEYNOTE-158 and KEYNOTE-028.

Notable differences across the studies were the number and type of prior treatments allowed per protocol, the ECOG performance status allowed at study entry, and biomarker testing performed for the studies. Study 111 allowed up to 2 lines of prior therapy, unless discussed with the sponsor, Study 204 required 1 prior line, and the 2 KEYNOTE studies did not have a cap on the number of prior therapies. Study 204 also required subjects to have received prior platinum-based therapy whereas the other studies did not specify. Study 204 allowed subjects to have an ECOG score of 0 to 2; however, the other studies allowed an ECOG score of 0 or 1. Finally, MSI/MMR status and PD-L1 status were evaluated in all studies except Study 204.

Other differences across the studies were the different doses of lenvatinib and pembrolizumab evaluated. The RP2D dose of lenvatinib in combination with pembrolizumab in Study 111 (20 mg QD) is lower than the monotherapy dose used in Study 204 (24 mg QD). The dose of pembrolizumab was 200 mg Q3W in Study 111 and KEYNOTE 158 and 10 mg/kg Q2W in KEYNOTE-028. A comparison of the key features of these studies appears in Module 2.7.3, Table 2.7.3-12.

Patient Disposition

Subject disposition was generally consistent among Study 111, Study 204, KEYNOTE-158, and KEYNOTE-028 (Table 7). The most common reason for discontinuation in all studies was due to radiological disease progression; however, a higher proportion of subjects discontinued due to progression (radiological and clinical) in KEYNOTE-158 than Study 111. A similar proportion of subjects in Study 111 and KEYNOTE 158 discontinued due to AEs; however, a higher proportion discontinued due to AEs in Study 204 and no subjects discontinued treatment due to AEs in KEYNOTE 028.

Demographics

Key baseline characteristics were generally consistent across the Study 111, Study 204, KEYNOTE-158, and KEYNOTE-028 (Table 8). The majority of subjects were white, and the median age across all 4 studies ranged from 62.0 to 67.0 years old. The majority of subjects had an ECOG PS of 0 or 1; Study 204 was the only study to enroll subjects with an ECOG PS of 2 (12 subjects [9.0%]). The location of study sites was well balanced between US and non-US sites in Study 204 and KEYNOTE-028; however, the majority of subjects in the Indication Efficacy Set (81 subjects [86.2%]) were recruited at sites in the US and the majority of not MSI-H/dMMR EC

subjects in KEYNOTE 158 (63 subjects [70.0%]) were recruited at non-US sites. The most common histologic subtype across all studies was endometrioid.

Differences were observed in the number of prior anticancer medication regimens received with the majority of subjects in the Indication Efficacy Set (51.1%) and Study 204 (99.2%) receiving only 1 prior line of therapy compared with 28.9% of not MSI-H/dMMR EC subjects in KEYNOTE 158 and 29.2% of subjects in KEYNOTE 028.

Table 7
Subject Disposition and Reasons For Discontinuation of Treatment Across Study 111 and Monotherapy Studies.

	Lenvatinib 20 mg + Pembrolizumab 200 mg	Lenvatinib Monotherapy	Pembrolizumab Monotherapy	
	Indication Efficacy Set[a] (N=94) n (%)	Study 204[b] (N=133) n (%)	KEYNOTE-158 Not MSI-H/dMMR (N=90) n (%)	KEYNOTE-028[c] (N=24) n (%)
Treatment Ongoing at Cutoff Date	24 (25.5)[d]	25 (18.8)	0	0
On Both Study Drugs	17 (18.1)	Not applicable	Not applicable	Not applicable
On Lenvatinib only	5 (5.3)	25 (18.8)	Not applicable	Not applicable
On Pembrolizumab only	2 (2.1)	Not applicable	0	0
Discontinued Treatment	70 (74.5)[e]	108 (81.2)[f]	90 (100.0)[g]	24 (100.0)[g]
Primary Reason(s) for Discontinuation from Treatment				
Radiological Disease Progression	44 (46.8)	57 (42.9)	63 (70.0)	16 (66.7)
Adverse Event	9 (9.6)	32 (24.1)	7 (7.8)	0
Clinical Disease Progression	8 (8.5)	Not applicable[h]	10 (11.1)	0
Subject Choice	4 (4.3)[i]	11 (8.3)[i]	Not applicable[h]	0
Withdrawal of Consent from Study	2 (2.1)	1 (0.8)	5 (5.6)	2 (8.3)
Lost to Follow-up	1 (1.1)	1 (0.8)	0	0
Completed Treatment	0[j]	Not applicable	5 (5.6)	2 (8.3)
Complete Response	Not applicable[h]	Not applicable[h]	0	0
Physician Decision	Not applicable[h]	Not applicable[h]	0	4 (16.7)
Other	2 (2.1)	6 (4.5)	0	0

Data cutoff date: 10 Jan 2019 for Study 111; 21 May 2012 for Study 204; 06 Dec 2018 for KEYNOTE-158; 23 Jan 2019 for KEYNOTE-028.

CRF = case report form, dMMR = mismatch repair deficient, EC = endometrial carcinoma, MSI-H = microsatellite instability-high, PD-L1 = programmed cell death ligand 1.

a: Indication Efficacy Set = all subjects with histologically confirmed not MSI-H/dMMR EC who received at least 1 prior systemic anticancer therapy(ies) and who had sufficient follow-up to provide a median follow-up of at least 12 months, and for all responders, an opportunity for follow-up after initial objective response as assessed by the investigator of at least 6 months (ie, enrolled prior to 01 Jul 2018).

b: MSI status was not assessed in Study 204.

c: Includes subjects regardless of MSI status (MSI-H/dMMR = 1 subject, not MSI-H/dMMR = 18 subjects, unknown = 5 subjects). All subjects in KEYNOTE-028 were PD-L1 positive.

d: Study 111: Treatment ongoing based on data available in database at time of database cutoff. Subjects deemed to have 'treatment ongoing' in absence of a discontinuation page.

e: Study 111: Discontinued treatment includes subjects who discontinued both lenvatinib and pembrolizumab while treatment ongoing summarizes subjects with at least 1 study drug ongoing.

f: Study 204: subjects were reported as having completed treatment if they had radiological disease progression. The number of subjects who discontinued treatment for the purposes of this summary includes those who completed treatment due to radiological progression and those that prematurely discontinued treatment.

g: For KEYNOTE-158 the number of subjects who discontinued includes 5 subjects with not MSI-H/dMMR EC who completed treatment and for KEYNOTE-028 the number of subjects who discontinued includes 2 subjects who completed treatment.

h: Not collected as a reason for discontinuation per Study CRF.

i: Subject's choice was selected when subjects withdrew from study treatment, but agreed to be followed by survival.

j: Reasons for early discontinuation of one study drug are presented in Study 111 EC CSR Table 14.1.1.3.1, and includes 4 subjects who completed pembrolizumab treatment per protocol, but continued lenvatinib monotherapy.

Source: Study 111 CSR Table 14.1.1.4.1, ADaM dataset: ADSL_EC ISS; Study 204 Primary CSR Table 8; KEYNOTE-158 EC CSR Table 14.1-7 and Table 14.1-8; KEYNOTE-028 EC CSR Table 10-1.

Table 8
Key Baseline Characteristics Across Study 111 and Monotherapy Studies

	Lenvatinib 20 mg + Pembrolizumab 200 mg	Lenvatinib Monotherapy	Pembrolizumab Monotherapy	
	Indication Efficacy Set[a] (N=94)	Study 204[b] (N=133)	KEYNOTE-158 Not MSI-H/dMMR (N=90)	KEYNOTE-028[c] (N=24)
Age (years)				
n	94	133	90	24
Median	66.0	62.0	63.0	67.0
Min, Max	40, 80	38, 80	41, 80	34, 87
Sex, n (%)				
Female	94 (100.0)	133 (100.0)	90 (100.0)	24 (100.0)
Race, n (%)				
White	81 (86.2)	112 (84.2)	67 (74.4)	17 (70.8)
Black or African American	6 (6.4)	10 (7.5)	9 (10.0)	1 (4.2)
Asian	4 (4.3)	6 (4.5)	14 (15.6)	3 (12.5)
American Indian or Alaskan Native	1 (1.1)	1 (0.8)	0	0
Native Hawaiian or other Pacific Islander	0	2 (1.5)	0	0
Other	2 (2.1)	2 (1.5)	0	0
Missing	0	Not applicable	0	3 (12.5)
Geographic region, n (%)				
US	81 (86.2)	58 (43.6)	27 (30.0)	14 (58.3)
Non-US	13 (13.8)	75 (56.4)	63 (70.0)	10 (41.7)
ECOG PS at Baseline				
0	49 (52.1)	50 (37.6)	43 (47.8)	7 (29.2)
1	45 (47.9)	71 (53.4)	47 (52.2)	17 (70.8)
2	Not applicable	12 (9.0)	Not applicable	Not applicable
Histology, n (%)[d]				
Endometrioid	46 (48.9)	89 (66.9)	49 (54.4)	10 (41.7)
Serous	33 (35.1)	0	16 (17.8)	2 (8.3)
Clear Cell	5 (5.3)	10 (7.5)	1 (1.1)	0

	Lenvatinib 20 mg + Pembrolizumab 200 mg	Lenvatinib Monotherapy	Pembrolizumab Monotherapy	
	Indication Efficacy Set[a] (N=94)	Study 204[b] (N=133)	KEYNOTE-158 Not MSI-H/dMMR (N=90)	KEYNOTE-028[c] (N=24)
Adenocarcinoma, not otherwise specified	1 (1.1)	0	22 (24.4)	8 (33.3)
Carcinosarcoma	0	0	0	1 (4.2)
Mucinous Carcinoma	0	0	1 (1.1)	0
Papillary	0	24 (18.0)	0	3 (12.5)
Squamous Cell Carcinoma	0	0	1 (1.1)	0
Other	9 (9.6)[e]	10 (7.5)	0	0
Time Since Original Diagnosis (years)				
Median	2.0	1.7	Not reported	Not reported
Min, Max	0.3, 20.9	0, 12	Not reported	Not reported
Age at Diagnosis (years)				
Median	64.0	61.0	Not reported	Not reported
Min, Max	40, 74	37, 79	Not reported	Not reported
PD-L1 status[f], n (%)				
Positive	46 (48.9)	Not collected	56 (62.2)	24 (100.0)
Negative	39 (41.5)	Not collected	32 (35.6)	Not applicable
Not Available/Not Evaluable	9 (9.6)	Not collected	2 (2.2)	Not applicable
Number of prior anticancer medication regimens, n (%)				
1	48 (51.1)	132 (99.2)	26 (28.9)	7 (29.2)
2	36 (38.3)	1 (0.8)[g]	21 (23.3)	6 (25.0)
≥3	10 (10.6)	0	43 (47.8)	11 (45.8)

Data cutoff date: 10 Jan 2019 for Study 111; 21 May 2012 for Study 204; 06 Dec 2018 for KEYNOTE-158; 23 Jan 2019 for KEYNOTE-028.

CPS = combined positive score, dMMR = mismatch repair deficient, EC = endometrial carcinoma, ECOG PS = Eastern Cooperative Oncology Group performance status, Max = maximum, Min = minimum, MSI-H = microsatellite instability-high, PD-L1 = programmed cell death ligand 1, US = United States.

a: Indication Efficacy Set = all subjects with histologically confirmed not MSI-H/dMMR EC who received at least 1 prior systemic anticancer therapy(ies) and who had sufficient follow-up to provide a median follow-up of at least 12 months, and for all responders, an opportunity for follow-up after initial objective response as assessed by the investigator of at least 6 months (ie, enrolled prior to 01 Jul 2018).

b: MSI status was not assessed in Study 204.

c: Includes subjects regardless of MSI status (MSI-H/dMMR = 1 subject, not MSI-H/dMMR = 18 subjects, unknown = 5 subjects). All subjects in KEYNOTE-028 were PD-L1 positive.

d: Histology types were captured in different categories across the studies and have been combined here for ease of reading.

	Lenvatinib 20 mg + Pembrolizumab 200 mg	Lenvatinib Monotherapy	Pembrolizumab Monotherapy	
	Indication Efficacy Set[a] (N=94)	Study 204[b] (N=133)	KEYNOTE-158 Not MSI-H/dMMR (N=90)	KEYNOTE-028[c] (N=24)

Clear combines the categories clear cell, clear cell adenocarcinoma, and clear cell carcinoma; endometrioid combines endometrioid, endometrioid adenocarcinoma and endometrioid carcinoma; serous combines high grade serous, serous adenocarcinoma, and serous carcinoma; and papillary combines papillary and papillary serous.

e: Histology types listed as "other" were predominately mixed histologies for Study 111.

f: PD-L1 status was positive if CPS ≥1 and negative if CPS <1.

g: One subject received 2 prior systemic chemotherapy regimens: (1) a platinum-based regimen in the adjuvant setting for primary unresectable disease and (2) an additional systemic regimen of topotecan before enrolling on the study. Site personnel were re-educated on inclusion and exclusion criteria, per protocol, and instructed to report this violation to their Institutional Review Board.

Source: Study 111 CSR Table 14.1.4.1.1.1, ADaM dataset: ADSL_Study 111, Table 14.1.4.1.2.1, ADaM datasets: ADSL_Study 111, ADDC_Study 111, Table 14.1.4.2.1.1, and Listing 16.2.4.1.1a; Study 204 Primary CSR Table 10, Table 11, Table 12, and Table 14.1.1.2; KEYNOTE-158 EC CSR Table 14.1-7 and Table 14.1-13; KEYNOTE-028 EC CSR Table 10-3.

Primary Endpoints

The ORR observed with the combination of lenvatinib plus pembrolizumab (38.3%; 95% CI: 28.5, 48.9) was greater than that resulting from treatment with either lenvatinib or pembrolizumab as monotherapy. The lower bound of the 95% CI of the ORR for the combination (28.5%) was greater than that of the observed point estimate for either lenvatinib (14.3%) or pembrolizumab (<10%) administered as monotherapy (Table 9). Furthermore, the observed CR rate (10.6%) was higher in subjects who received lenvatinib plus pembrolizumab compared with those who received lenvatinib (1 subject [0.8%]) or pembrolizumab (no subjects in KEYNOTE 158 and 1 subject [4.8%] in KEYNOTE-028) as a monotherapy (Table 9).

At the time of the data cutoff, for the Indication Efficacy Set, median DOR with combination treatment was not reached (range: 1.2+ to 33.1+ months) compared with 7.2 months (range: 1.02+ to 9.76+ months) for lenvatinib monotherapy (Study 204). Median DOR was also not reached for subjects with not MSI-H/dMMR EC who received pembrolizumab monotherapy in KEYNOTE-158 (range: 8.4+ to 27.6+ months) and in KEYNOTE-028 (range: 49.8+ to 51.0+ months).

Table 9
Summary of Best Overall Tumor Response and Duration of Response Based on Independent Imaging Review using RECIST 1.1 Across Study 111 and Monotherapy Studies

Response Category	Lenvatinib 20 mg + Pembrolizumab 200 mg	Lenvatinib Monotherapy	Pembrolizumab Monotherapy	
	Indication Efficacy Set[a] (N=94)	Study 204[b] (N=133)	KEYNOTE-158 Not MSI-H/dMMR (N=90)	KEYNOTE-028[c] (N=21)
BOR,[d,e] n (%)				
CR	10 (10.6)	1 (0.8)	0	1 (4.8)
PR	26 (27.7)	18 (13.5)	7 (7.8)	1 (4.8)
SD	38 (40.4)	62 (46.6)	24 (26.7)	3 (14.3)
PD	12 (12.8)	24 (18.0)	49 (54.4)	12 (57.1)
Not Evaluable[f]	8 (8.5)	4 (3.0)	2 (2.2)	1 (4.8)
Unknown[g]	0	24 (18.0)	8 (8.9)	3 (14.3)
ORR (CR+PR),[d,e,f] n (%)	36 (38.3)	19 (14.3)	7 (7.8)	2 (9.5)
95% CI of ORR[h]	(28.5, 48.9)	(8.8, 21.4)	(3.2, 15.4)	(1.2, 30.4)
Number (probability[i]) of Subjects with Durable Response				
≥6 months	25 (0.76)	5 (0.73)	7 (1.00)	2 (1.00)
≥12 months	8 (0.51)	0 (NE)	5 (0.83)	2 (1.00)
Duration of Objective Response (months)[j]				
Median (95% CI)	NE (6.3, NE)	7.2 (4.5, NE)	Not reached	Not reached
Range (min, max)	(1.2+, 33.1+)	(1.02+, 9.76+)	(8.4+, 27.6+)	(49.8+, 51.0+)
1st Quartile, 3rd Quartile	6.2, NE	4.5, 8.5	Not reported	Not reported

Data cutoff date: 10 Jan 2019 for Study 111; 21 May 2012 for Study 204; 06 Dec 2018 for KEYNOTE-158; 23 Jan 2019 for KEYNOTE-028.

Tumor assessments for Study 111 and Study 204 are based on RECIST 1.1 criteria, tumor assessments for KEYNOTE-158 and KEYNOTE-028 are based on modified RECIST (allowing up to 10 target lesions/up to 5 per organ). All responses are confirmed responses.

For Study 111, this table summarizes all tumor assessments as long as the subjects did not start a new anticancer therapy.

Study 111: for BOR, PR and CR must be confirmed no less than 4 weeks after initial assessment of response. SD must be achieved at ≥5 weeks after the first dose study drug administration to be considered BOR.

+ indicates that time is censored.

BOR = best overall response, CI = confidence interval, CR = complete response, dMMR = mismatch repair deficient, EC = endometrial carcinoma, max = maximum, min = minimum, MSI-H = microsatellite instability-high, NE = not estimable because it was not reached, ORR = objective response rate, PD = progressive disease, PD-L1 = programmed cell death ligand 1, PR = partial response, RECIST = Response Evaluation Criteria in Solid Tumors, SD = stable disease.

a: Indication Efficacy Set = all subjects with histologically confirmed not MSI-H/dMMR EC who received at least 1 prior systemic anticancer therapy(ies) and who had sufficient follow-up to provide a median follow-up of at least 12 months, and for all responders, an opportunity for follow-up after initial objective response as assessed by the investigator of at least 6 months (ie, enrolled prior to 01 Jul 2018).

b: MSI status was not assessed in Study 204.

c: Includes subjects regardless of MSI status (MSI-H/dMMR = 1 subject, not MSI-H/dMMR = 16 subjects, unknown = 4 subjects). All subjects in KEYNOTE-028 had PD-L1-positive tumors.

d: Percentages were calculated based on the total number of subjects in the column header.

e: Non-CR/Non-PD for subjects with no target lesions at Baseline was treated as, and combined with, SD for purposes of analysis for ORR and BOR. Six subjects in the Indication Efficacy Set had no target lesions at Baseline per IIR assessment. Study 204: SD was defined as SD lasting ≥7 weeks (49 days). KEYNOTE-158 and KEYNOTE-028 a subject had to be on study for at least 42 days without a PD for their response to count.

f: For Study 111, not evaluable refers to subjects with either no postbaseline tumor assessment(s) or with postbaseline tumor assessment(s) that are not evaluable (ie, due to insufficient data for assessment of response per RECIST 1.1 or an early SD with duration <5 weeks). For Study 204, not evaluable includes subjects who did not meet the minimum criteria for SD duration.

g: For Study 111, unknown refers to subjects with no baseline tumor assessment. For Study 204 unknown refers to subjects who did not have postbaseline tumor assessments due to death or clinical progression prior to the first scheduled tumor assessment. For KEYNOTE-158, unknown refers to subjects who had a baseline assessment evaluated by IIR but no postbaseline assessment on the data cutoff date including missing, discontinuing or death before the first postbaseline scan.

h: 95% CI was constructed using the method of Clopper and Pearson.

i: For Study 111 and Study 204, probability was estimated from the Kaplan-Meier method. For KEYNOTE-158 and KEYNOTE-028, from product-limit (Kaplan-Meier) method for censored data.

j: For Study 111 duration of objective response was only summarized among responders (CR or PR). The median and quartiles were estimated using the Kaplan-Meier method and their 95% CIs were constructed with a generalized Brookmeyer and Crowley method. For KEYNOTE-158 and KEYNOTE-028, from product-limit (Kaplan-Meier) method for censored data.

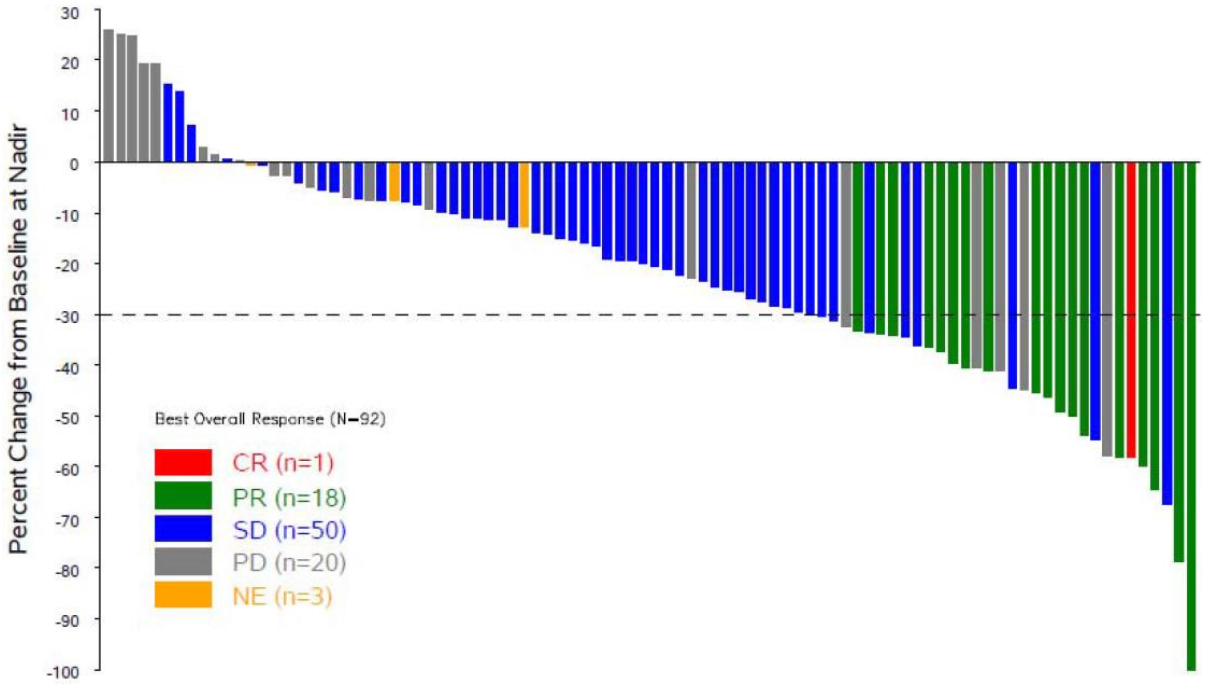
Source: Study 111 EC CSR Table 14.2.1.2.1e, ADaM dataset: ADSL_Study 111, ADEF_Study 111, ADTTE_Study 111; Study 204 ad hoc Table 14.2.3.3; KEYNOTE-158 EC CSR Table 11-5 and Table 11-8; KEYNOTE-028 EC CSR Table 14.2-4, Table 14.2-5, and Table 14.2-7.

Secondary and Other Endpoints

Percentage Change from Baseline in Tumor Burden

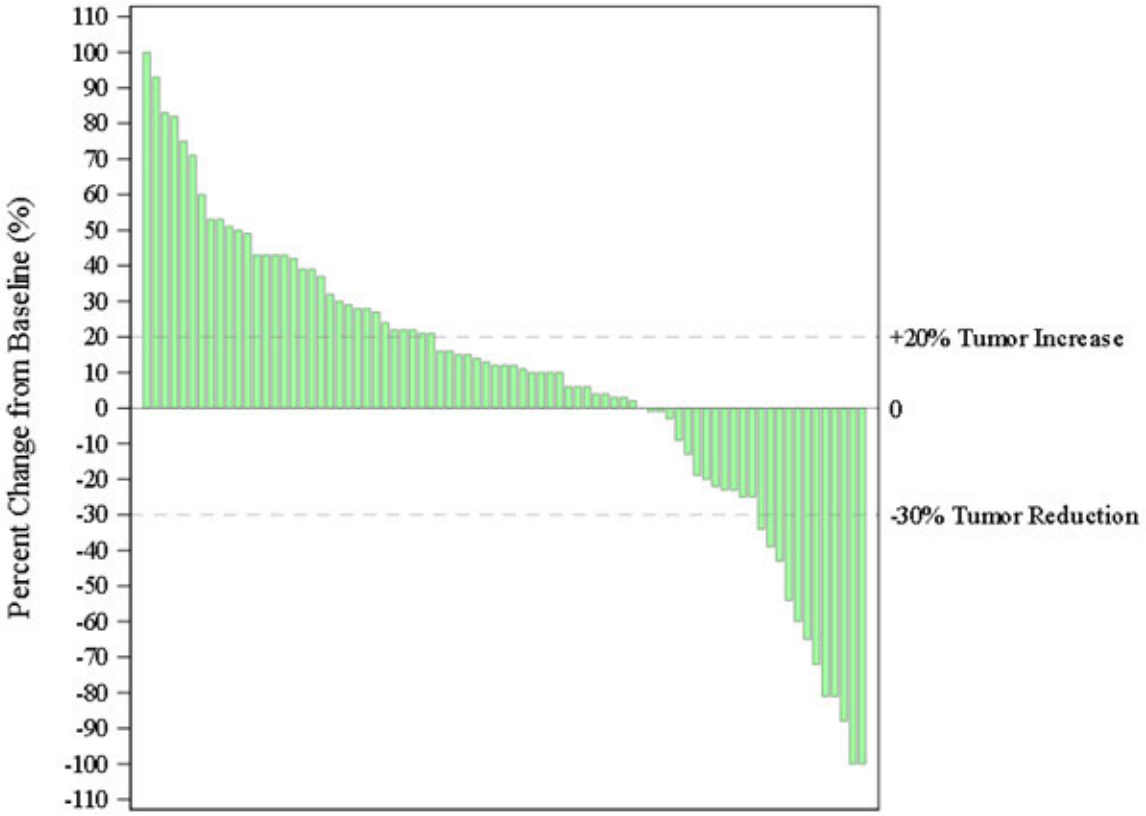
Waterfall plots for the maximum percentage change from Baseline in the sum of the diameters of target lesions are shown in Figure 4 for subjects in the Indication Efficacy Set, Figure 5 for Study 204, Figure 6 for subjects with not MSI-H/dMMR EC in KEYNOTE 158, and Figure 7 for KEYNOTE-028. Overall, the plots show more shrinkage resulting from treatment with the combination of lenvatinib plus pembrolizumab relative to lenvatinib or pembrolizumab administered as monotherapy.

Figure 5
Study 204: Waterfall Plot of Maximum Percentage Change in Summed Diameter of Target Lesions from Baseline to Nadir Based on Independent Imaging Review using RECIST 1.1 – Lenvatinib Monotherapy



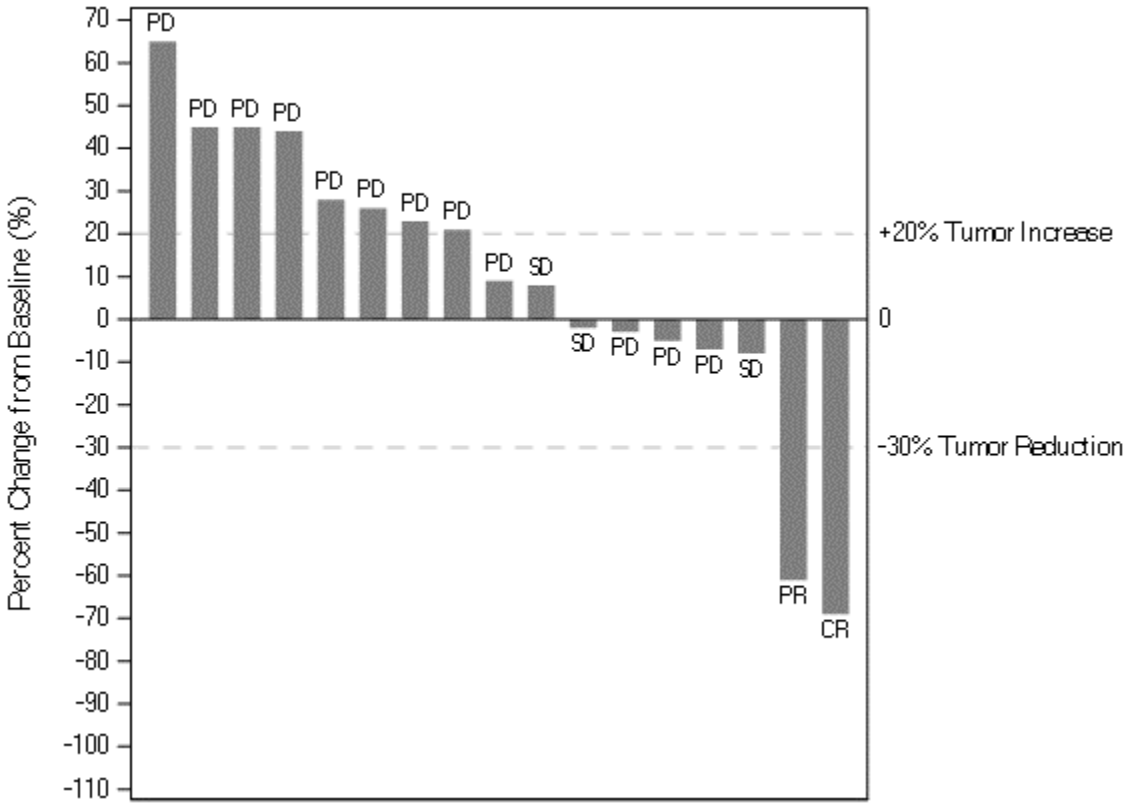
Data cutoff date: 21 May 2012.
CR = complete response, MSI = microsatellite instability; NE = not evaluable, PD = progressive disease, PR = partial response, RECIST = Response Evaluation Criteria for Solid Tumors, SD = stable disease.
RECIST 1.1 used longest diameter for non-nodal lesions and short-axis for nodal lesions in calculating the sum of diameters for tumor response.
Represents each subject percentage changes from baseline in sum of diameters of target tumors at postbaseline nadir.
Note: 41 subjects were not included in the waterfall plot due to no postbaseline assessment (24 subjects), non-CR/non-PD (12 subjects), PD assessment based on non-target lesion (4 subjects), NE assessment based on non-target lesion (1 subject).
MSI status was not assessed in Study 204.
Source: Study 204 Primary CSR Figure 14.2.3.1.

Figure 6
KEYNOTE-158: Waterfall Plot of Best Tumor Change from Baseline Based on Independent Imaging Review using RECIST 1.1 – Not MSI-H/dMMR – Pembrolizumab Monotherapy



Data cutoff date: 06 Dec 2018.
RECIST 1.1 was modified to allow up to 10 target lesions and up to 5 per organ.
Percentage changes over 100% were truncated at 100%.
Subjects with unknown MSI status are not included
dMMR = mismatch repair deficient, MSI-H = microsatellite instability-high, RECIST = Response Evaluation Criteria in Solid Tumors.
Source: KEYNOTE-158 EC CSR Figure 11-4.

Figure 7
KEYNOTE 028: Waterfall Plot of Best Tumor Change from Baseline Based on Independent Imaging Review using RECIST 1.1 – Pembrolizumab Monotherapy



Data cutoff date: 23 Jan 2019.
RECIST 1.1 was modified to allow up to 10 target lesions and up to 5 per organ.
Percentage changes over 100% were truncated at 100%.
Bars are labeled by BOR based on RECIST 1.1 per IIR
Includes subjects regardless of MSI status (MSI-H/dMMR = 1 subject, not MSI-H/dMMR = 16 subjects, unknown = 4 subjects).
BOR = best overall response, CR = complete response, dMMR = mismatch repair deficient, IIR = independent imaging review, MSI-H = microsatellite instability-high, PD = progressive disease, PR = partial response, RECIST = Response Evaluation Criteria in Solid Tumors, SD = stable disease.
Source: KEYNOTE-028 EC CSR Figure 14.2-4 and Table 14.2 5

Subpopulations

Results in subpopulations are presented for the Study 111 Indication Efficacy Set in the Efficacy Results – Secondary and other relevant endpoints section (Table 5).

Additional Efficacy Considerations

<u>The Applicant's Position</u>:

The applicant considers that the conduct of Study 111 is reflective of the proposed study population and that the proposed labeling is reflective of clinical use.

The Regulatory Authorities' Assessment:

The ORR observed with the combination of lenvatinib plus pembrolizumab (38.3%; 95% CI: 28.5, 48.9) was numerically greater than that resulting from treatment with either lenvatinib or pembrolizumab as monotherapy. The use of the lower bound of 95% CI assumes that the treatments came from a randomized clinical trial in the same population using the same frequency of assessments by the same investigator, etc. In order to evaluate whether including both lenvatinib and pembrolizumab in the combination are necessary for the observed treatment effect, the activity of each individual component in the same patient population should be characterized in a randomized clinical trial comparing the combination therapy to each of the monotherapies. However, due to the single-arm design of Study 111/KN-146, the treatment effect of each component in the combination could not be isolated based on this single study. The applicant submitted three single-arm studies including lenvatinib monotherapy Study 204 and pembrolizumab monotherapy data from interim analysis for studies KEYNOTE-158 and KEYNOTE-028 to assess the contribution effect of each component. Given the difference in pembrolizumab dose and limited sample size (n=24), Study KEYNOTE-028 was not used in the cross-trial comparison for treatment effect isolation. Therefore, KEYNOTE-028 was not included in this section. There were considerable differences in patient population among the Study 111/KN-146, Study 204 and KEYNOTE-158 with respect to prior lines of therapy, ECOG performance score, age, gender, geographical region and endometroid histology. The contribution of these differences on the treatment effect as measured by tumor response rate is difficult to assess.

Study period: Study 111/KN-146 was conducted from July 21, 2015 to January 10, 2019; Study 204 was conducted from March 3, 2010 to May 21, 2012; and KEYNOTE-158 was conducted from January 15, 2016 to December 6, 2018. Changes in study population and patient management over time could not be assessed given the differences in the study time between Study 111/KN-146 and Study 204.

Study 111/ KN-146 allowed up to 2 lines of prior therapy, unless discussed with the sponsor, whereas Study 204 required 1 prior line. KEYNOTE-158 did not have a cap on the number of prior therapies.

Study 204 allowed subjects to have an ECOG score of 0 to 2; however, the other studies allowed an ECOG score of 0 or 1.

The median age was 66 in Study 111/KN-146 and nearly 62% of women were ≥65 years of age, which was higher than observed in the other three studies.

The majority of patients in Study 111/KN-146 (81, 86.2%) were recruited at sites in the US and the majority of patients in KEYNOTE-158 (63,70.0%) were recruited at sites outside the US.

More subjects with endometrioid histology were enrolled in Study 204 than in Study 111/ KN-146 or KN158/KN28. This is unlikely to favor Study 111/ KN-146 since endometrioid histology may have better prognosis than higher grade Type II adenocarcinomas.

Also, MSI/MMR status and PD-L1 status were not evaluated in Study 204.

Other differences across the studies were the different doses of lenvatinib and pembrolizumab evaluated. The RP2D dose of lenvatinib in combination with pembrolizumab in Study 111/KN-146 (20 mg QD) is lower than the monotherapy dose used in Study 204 (24 mg QD).

Exploratory Cross-Trial Analyses - Isolation of Treatment Effect

Among the many issues with performing cross-trial comparison, one major concern is that patient populations may not be comparable between trials. Non-randomized studies can be subject to treatment-selection bias in which patients who received combination treatment (treated, L+P) differ systematically from patients who received monotherapy (control, L or P). FDA conducted exploratory analyses using different approaches (propensity score-based matching analysis and weighting analysis) to adjust covariates across trials and balance treatment groups based on statistical model determined scores with respect to important demographic and baseline characteristics with available data.

(1) Isolation of treatment effect for pembrolizumab – Comparison of Study 111/KN-146 (n=94) vs. Study 204 (n=133) using Propensity Score Matching and Weighting Approaches

Propensity scores (Rosenbaum and Rubin 1983) were estimated using a logistic regression model with the binary variable of the treatment versus control as dependent variable and adjusted for baseline covariates including demographic characteristics (age [<65 or ≥65], race [white or non-white], region[USA or rest of world]) and baseline disease characteristics (ECOG PS [0, 1 or 2], histology [endometroid or others], FIGO Grade [Grade 1/2 or Grade3/4] and lesions at baseline [any lymph node target lesions at baseline, any non-lymph node target lesions at baseline, any non-target lesions at baseline]). The covariates chosen were based on what was collected and accessible in the compared trials. Importantly, this approach cannot guarantee that all measured and unmeasured covariates will be balanced.

Two approaches based on propensity scores were used: matching analysis and weighting analysis. In the matching analysis, matched pairs were formed (1:1 matching without replacement) with a similar propensity score using the nearest-neighbor matching algorithm with caliper width of 0.2 of the standard deviation of the logit of the propensity scores (Austin 2011). Matching strategies reduce bias at the expense of sample size which may limit the ability to generalize the results. The weighting approach allows keeping the samples while reducing bias by giving more weight to patients with smaller propensity scores. A stabilized inversed probability treatment weighting (sIPTW) approach was considered. Sensitivity analyses were performed to assess ORR using additional weighting

schemes (i.e., Average Treatment Effect for Overlap Population [ATO], Average Treatment Effects on the Treated [ATT] and Average Treatment Effects on the Control [ATC]).

Based on propensity score matched and weighted methods, the adjusted treatment effects measured by ORR, are shown in Table 10. Compared with unadjusted analyses, the treatment effects from propensity matched or weighted analyses are similar.

The lower bound of 95% confidence interval for the response rate ratio (based on the propensity score matched or weighted method) is greater than 1, suggesting that the combination treatment elicited a better response rate than lenvatinib monotherapy, and that the higher response rate is potentially due to the contribution of pembrolizumab.

Table 10. Efficacy Results – Propensity Score Matched and Weighted Analyses (Lenvatinib + Pembrolizumab vs. Lenvatinib)

	Study 111/KN-146	Study 204
Propensity Score Matched Analysis		
# of patients included the analysis	65	65
# of Responders	27	9
ORR, % (95% CI)	41.5 (29.4, 54.4)	13.9 (6.5, 24.7)
ORR difference, % (95% CI)	27.7 (13.1, 42.3)	
ORR ratio[1] (95% CI)	3.00 (1.53, 5.87)	
Propensity Score Weighted Analysis - sIPTW		
ORR % (95% CI)	38.4 (28.1, 48.8)	12.8 (7.2, 18.5)
ORR difference, % (95% CI)	25.6 (13.8, 37.4)	
ORR ratio (95% CI)	2.99 (1.78, 5.02)	
Source: Study 111 – ADSL.xpt, ADDC.xpt, ADEF.xpt, Study 204 – ADSL.xpt , ADDC.xpt, ADEF.xpt		

[1]*ORR ratio >1 favors Lenvatinib + Pembrolizumab*
[Source: Reviewer's Analysis]

Reviewer's Comments on the Propensity Score Matching and Weighting Approaches

i. ***The covariates were chosen based on data collected and submitted in the trials. The MSI/MMR statuses were not evaluated in Study 204, and therefore were not included in the analyses. The PD-L1 status and number of metastatic sites were also not evaluated in Study 204 and could not be included in the propensity score analyses. All patients in Study 204 received 1 line of prior anticancer therapy except 1 patient received 2 lines of prior therapies. Thus, the number of prior lines of therapy was not included in the analyses. Of note, Study 204 used a higher dose of lenvatinib (24mg) versus Study 111/KN-146 (20mg).***

i. ***Using this propensity score matching analysis, 29 out of 94 patients (30.9%) in Study 111/KN-146 and 25 out of 90 patients (27.8%) in Study 204 were unmatched, and therefore excluded from the propensity score matched analysis. Thus, matched analysis population may not fully represent the study target population, and therefore***

the estimated treatment effect may not represent the true treatment effect in the target population.

ii. The weighted approach can be more efficient than matching in terms of sample size because it keeps all patients in the analysis; however, patients with extreme propensity scores receive very small weights. Weighting based on different schemes showed consistent results (See Appendix 17.4).

iii. In general, propensity score matching/weighting analyses are limited by the observed covariates included in the propensity score model. After propensity score matching/weighting, the patient populations were reasonably comparable between the two studies (See Appendix 17.4).

(2) Isolation of treatment effect for lenvatinib – Comparison of Study 111/KN-146 (n=94) vs. KEYNOTE-158 (n=90) using Propensity Score Matching and Weighting Approaches

Using the same approach as described in (1), propensity score analyses were performed in the comparison of Study 111/KN-146 and KEYNOTE-158. With propensity score matched and weighted methods, the treatment effect in ORR are shown in Table 11. Comparing with unadjusted analyses, the treatment effect from propensity matching or weighting analyses are similar. The lower bound of 95% CI for the ORR ratio based on the propensity score matching or weighting method is greater than 1 suggesting that the combination treatment elicited a better response rate compared to the pembrolizumab monotherapy and that the higher response rate is potentially due to the contribution of lenvatinib.

Table 11. Efficacy Results – Propensity Score Matched and Weighted Analyses (Lenvatinib + Pembrolizumab vs. Pembrolizumab)

	Study 111/KN-146	KEYNOTE-158
Propensity Score Matched Analysis		
# of patients included the analysis	31	31
# of Responders	12	2
ORR, % (95% CI)	38.7 (21.9, 57.8)	6.5 (0.8, 21.4)
ORR difference, % (95% CI)	32.3 (13.1, 51.5)	
ORR ratio[1] (95% CI)	6.00 (1.46, 24.62)	
Propensity Score Weighted Analysis - sIPTW		
ORR, % (95% CI)	38.8 (28.0, 49.6)	5.4 (1.0, 9.7)
ORR difference, % (95% CI)	33.4 (21.8, 45.1)	
ORR ratio (95% CI)	7.23 (3.05, 17.13)	
Source: Study 111 – ADSL.xpt, ADDC.xpt, ADEF.xpt, KEYNOTE 158 – ADSL.xpt, ADRS.xpt		

[1]ORR ratio >1 favors Lenvatinib + Pembrolizumab
[Source: Reviewer's Analysis]

Reviewer's Comments on the Propensity Score Matching and Weighting Approaches

ii. The covariates were chosen based on data collected and submitted in the trials. FIGO Grade (Grade 1/2 or Grade3/4) and lesions at baseline were not available in KEYNOTE-158, and not included in the propensity analyses.

iii. Study 111/KN-146 allowed up to 2 lines of prior therapy, unless discussed with the sponsor (1 line: 51.1%, 2 lines: 38.3%, 3+ lines: 10.6%); KEYNOTE-158 did not have a cap on the number of prior therapies (1 line: 28.9%, 2 lines: 23.3%, 3+ lines: 47.8% in KEYNOTE-158). The majority of patients in Study 111/KN-146 (81, 86.2%) were recruited at sites in the US and the majority of patients in KEYNOTE 158 (63,70.0%) were recruited outside of US sites. The number of lines and region were incorporated in the propensity score model.

iv. With propensity score matching analysis, 63 out of 94 patients (67.0%) in Study 111/KN-146 and 59 out of 90 patients (65.6%) in KEYNOTE-158 were unmatched and excluded from the analysis. Thus, matched analysis population may not fully represent the target study population, and therefore the estimated treatment effect may not represent the true treatment effect in the target study population. The generalizability of the matched samples is a concern.

v. The weighted approach can be more efficient than matching in terms of sample size because it keeps all patients in the analysis, however, patients with extreme propensity scores receive very small weights. Weighting based on different schemes showed consistent results (See Appendix 17.4).

vi. The primary endpoint ORR was based on the RECIST criteria in Study 111/KN-146, but the mRECIST criteria in KEYNOTE-158. Sensitivity analyses were conducted in comparison of the two studies in terms of the ORR based on the mRECIST. The sensitivity analyses showed consistent results using matching or weighting approaches.

vii. In general, propensity score matching/weighting analyses are limited by the observed covariates included in the propensity score model. After propensity score matching/weighting, the patient populations were reasonably comparable between the two studies (See Appendix 17.4).

The non-randomized exploratory cross-trial comparison was performed post-hoc to assess whether the combination therapy is better than either monotherapy. The cross-trial comparison of efficacy across studies shows that the combination had a numerically higher ORR than both individual treatments (lenvatinib and pembrolizumab). The results are consistent with those seen in an unadjusted comparison of the combination treatment vs. each individual treatment. These results were considered exploratory, so no formal hypothesis testing was performed. Acknowledging the lack of a randomized trial and the limitations in the use of external controls, the data and analyses submitted in this application suggest a higher response rate with the combination therapy.

7.1.7. Integrated Assessment of Effectiveness

The Applicant's Position:

The results from Study 111 demonstrate that treatment with the combination of lenvatinib plus pembrolizumab provided compelling antitumor activity in EC that is not MSI-H/dMMR which has progressed following prior systemic therapy. The results were observed across the various histologies, including the high-risk and most aggressive subtypes. In the Indication Efficacy Set, a clinically meaningful ORR (38.3%; 95%CI: 28.5, 48.9) was observed, with 10 subjects(10.6%) achieving a CR and 26 subjects (27.7%) achieving a PR. Responses occurred early with a median TTR of 1.4 months, and were durable, with a median DOR not reached and lower bound of the 95% CI for median DOR greater than 6 months. Of the 36 subjects who responded, 66.7% had at least 50% maximal tumor shrinkage, and 30.6% had at least 75% maximal tumor shrinkage.

Results from Study 111 demonstrate that lenvatinib plus pembrolizumab addresses a significant unmet medical need and represents an effective treatment with an impressive ORR, unprecedented CR rate, long DOR, rapid onset of response, and meaningful tumor shrinkage.

The Regulatory Authorities' Assessment:

The only study designated to support the effectiveness of L+P for endometrial carcinoma that has progressed following prior systemic therapy and that is not microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) was study 111/KN-146. However, in order to evaluate the contribution effect of lenvatinib and pembrolizumab in the combination for the observed treatment effect, exploratory analyses using propensity score matching and weighting methods were conducted. See discussion above concerning the contribution of lenvatinib and pembrolizumab to the combination regimen.

7.2 Review of Safety

The Applicant's Position:

Overall, no new safety signals were observed with lenvatinib plus pembrolizumab (Indication Safety Set) compared with either lenvatinib or pembrolizumab as monotherapies. Treatment with lenvatinib plus pembrolizumab demonstrated an acceptable safety profile, with an incidence of discontinuation consistent with lenvatinib monotherapy. Toxicities were primarily low grade, consistent with the known risks with each drug, and were generally manageable with (if appropriate) study drug treatment interruption and dose reduction, and standard medical care.

The incidences of any Grade ≥3 treatment-emergent adverse events (TEAEs), non-fatal serious adverse events (SAEs), study drug interruption, and study drug discontinuation in the Indication Safety Set were generally comparable with the incidences seen in the Lenvatinib Monotherapy Safety Set and generally higher than that in the Pembrolizumab Monotherapy Safety Set. The incidence of Grade 5 TEAEs in the Indication Safety Set was generally consistent with the All EC

(as defined in Section 7.2.1) and Pembrolizumab Monotherapy Safety Sets and was lower than the Non-EC and Lenvatinib Monotherapy Safety Sets.

There was a higher incidence of TEAEs leading to dose reduction of lenvatinib in the Indication Safety Set (67.0%) than in the Lenvatinib Monotherapy Safety Set (47.5%); however, the incidence of discontinuation of lenvatinib was consistent between the Indication and Lenvatinib Monotherapy Safety Sets.

The incidences of clinically significant events (CSEs) in the Indication Safety Set were generally consistent with those for lenvatinib monotherapy, with the exception of the CSE~~s~~ of hypothyroidism (any grade). The overall frequency of adverse events of special interest (AEOSI) (any) was higher than that seen with pembrolizumab monotherapy, predominantly due to hypothyroidism. Hypothyroidism was almost all low grade and readily manageable with thyroid hormone replacement. Except for hypothyroidism, the overlapping toxicities of clinical interest in the Indication Safety Set were represented by small numbers of subjects. None of the CSEs/AEOSIs or overlapping toxicities of clinical interest (ie, hypothyroidism, nephritis, severe skin reactions, and pancreatitis), were found to impact the benefit risk profile of lenvatinib plus pembrolizumab in the treatment of EC.

The Regulatory Authorities' Assessment:

The safety profile of L+P was assessed in not MSI-H/dMMR women with endometrial cancer who had received at least 1 prior line of therapy (n = 94). To ensure consistency of the safety profile, a safety analysis was also performed for all patients with endometrial carcinoma who had received at least 1 prior line of therapy (EC 2L+; n=108). We also analyzed the safety profiles for lenvatinib in the provided monotherapy trial (study 204) and two pembrolizumab monotherapy trials (KN-158 and KN-028) to assess trends of adverse events observed in monotherapy versus combination therapy and assess the contribution of each drug to the safety profile of the lenvatinib + pembrolizumab combination (L+P). For this review, the size of the study111/KN-146 safety population and the extent of exposure were adequate to allow for sufficient characterization of the safety of lenvatinib and pembrolizumab combination for treatment of this serious and life- threatening condition.

Fatal adverse reactions occurred in 3% of patients receiving L+P, including gastrointestinal perforation, RPLS with intraventricular hemorrhage, and intracranial hemorrhage. Permanent discontinuation due to adverse reaction (Grade 1-4) occurred in 17% of patients who received L+P. The most common adverse reactions (>2%) resulting in discontinuation were gastrointestinal perforation or fistula (2%), muscular weakness (2%), and pancreatitis (2%).

In the not MSI-H group, lenvatinib alone was dose modified (interrupted and/or reduced) due to TEAEs in nearly 88% of the patients (regardless of action with pembrolizumab). Pembrolizumab alone was dose interrupted in 49% (regardless of action with lenvatinib). The rate of dose modifications was much higher in study 111 compared to the monotherapy studies but the AEs that led to dose interruptions and reductions correspond to the known safety profile of lenvatinib and pembrolizumab with hypertension, fatigue, and hemorrhages being common causes for lenvatinib discontinuation. Fatigue was the most common AE that

led to interruption of both lenvatinib and pembrolizumab.

Serious adverse reactions occurred in 52% of patients receiving L+P. Notable toxicities for the L+P combination included a high incidence of fatigue, hypertension, musculoskeletal pain, diarrhea, decreased appetite, hypothyroidism, nausea, stomatitis, vomiting, decreased weight, abdominal pain, headache, constipation, urinary tract infection, dysphonia, hemorrhagic events, hypomagnesemia, palmar-plantar erythrodysesthesia, dyspnea, cough, and rash. Based on the frequency of AEs observed in the monotherapy trials, it is important to note that the incidence of AEs was much higher in the combination study111/KN-146 but many of these are AEs are consistent with the known safety profile of lenvatinib and pembrolizumab and no new safety signals were identified.

In the not MSI-H/dMMR EC 2L+ data set, the key adverse events of interest with lenvatinib, identified as clinically significant events (CSEs - AEs that have been identified in clinical trials across the development program), occurred in 86 (91.5%) patients. The most common CSEs identified were hypertension, hypothyroidism, hemorrhages, palmar-plantar erythrodysesthesia, proteinuria, and renal events. Of the 86 CSEs in the not MSI-H/dMMR EC 2L+ data set, 46 (48.9%) events were Grade ≥3. Grade ≥3 CSEs occurring in ≥2% were hypertension (39%), hepatotoxicity (excluding elevated LFTs, 7%), hemorrhages (3.2%), palmar-plantar erythrodysesthesia (3.2%), and renal events (3.2%). The incidence of CSEs in the not MSI-H/dMMR EC 2L+ data set was compared with that in the lenvatinib monotherapy study 204 to determine which CSEs occurred at a higher incidence rates in patients treated with L+P than with lenvatinib monotherapy. We found a higher frequency of hypothyroidism, palmar-plantar erythrodysesthesia, and renal events in the combination.

The development of adverse events of special interest (AESIs –immune-mediated AEs or nonimmune-mediated events of infusion-related reactions) for pembrolizumab was also evaluated. The incidence of AESIs in the not MSI-H/dMMR EC 2L+ data set was compared with that in the pembrolizumab monotherapy studies (KN-158 and KN-028) to determine which AESIs occurred at a higher rate in patients treated with L+P than with pembrolizumab monotherapy. We found higher frequencies of hypothyroidism, pancreatitis, nephritis and adrenal insufficiency in the combination compared to monotherapy study KN-158. We also looked at steroid use in study 111; nearly a quarter of the patients received systemic corticosteroids with only around 9% needing steroids for immune mediated adverse events.

Overall the safety profile of L+P is consistent with previous knowledge of the safety profile of the individual agents and is considered acceptable in the context of the proposed indication for this serious and life-threatening condition.

7.2.1. Safety Review Approach

The Applicant's Position:

The review of the safety of the combination of lenvatinib 20 mg orally QD plus pembrolizumab 200 mg IV Q3W in support of the proposed indication is based on Study 111, as described in

Section 7.1.1. In addition, pooled safety data from the lenvatinib monotherapy clinical program, and the reference safety dataset (RSD) for pembrolizumab monotherapy support the contribution of each drug to the safety profile of the combination.

Five safety analysis sets were defined, 3 based on Study 111 and 2 that include the pooled monotherapy data for lenvatinib and pembrolizumab. The 3 safety sets based on Study 111 were: the Indication Safety Set (defined below), the All EC Safety Set (N=124; all subjects with EC), and the Non-EC Safety Set (N=159; subjects with a tumor type other than EC). The Indication Safety Set includes 94 subjects with EC that is not MSI-H/dMMR and has progressed following prior systemic therapy, who received at least 1 dose each of lenvatinib plus pembrolizumab as of the data cutoff date of 10 Jan 2019, and who met the prespecified follow-up criteria (the same 94 subjects in the Indication Efficacy Set).

The 2 monotherapy safety sets include pooled data from 11 lenvatinib monotherapy studies and pooled data from 4 pembrolizumab monotherapy studies (Lenvatinib and Pembrolizumab Monotherapy Safety Sets, respectively).

The primary comparison of safety is between the Indication Safety Set and the monotherapy safety sets.

The Regulatory Authorities' Assessment:

The FDA evaluated the datasets submitted by the sponsor and no obvious discrepancies were identified between those datasets and information provided in the Clinical Study Report (CSR). The applicant's categorization of data and coding methods were appropriate. The preferred terms (PTs) listed in the dataset adequately represented the investigator-recorded term and did not raise any concerns of inconsistency. A random audit of 10% of the case report forms to assess the completeness and verify the accuracy of the raw adverse event (AE) datasets did not reveal any issues.

The safety population includes not MSI-H/dMMR women with endometrial cancer who had received at least 1 prior line of therapy (n = 94); however, analyses were also performed for all patients with endometrial carcinoma who had received at least 1 prior line of therapy (EC 2L+; n=108) to ensure consistency of the safety profile. We also analyzed the safety profiles for lenvatinib in the provided monotherapy trial (study 204) and two pembrolizumab monotherapy trials (KN-158 and KN-028) to assess trends of adverse events observed in monotherapy versus combination therapy and assess the contribution of each drug to the safety profile of the lenvatinib + pembrolizumab combination (L+P). Of note, all monotherapy trials incorporated in the analyses enrolled patients with EC that progressed following prior systemic therapy.

While reviewing AEs and safety information for study 111, we compiled a table to aggregate similar AEs for calculating adverse events observed in this study and also used these results to guide a more focused look at specific AEs. The applicant agreed to these pooled terms for use in our analyses, provided any discordance between reviewer findings and the applicant's position would undergo further evaluation for confirmation (refer to appendix section 17.5 for the list of PTs that were used for the safety analyses).

7.2.2. Review of the Safety Database

Overall Exposure

The Applicant's Position:

The number of subjects exposed to combination lenvatinib plus pembrolizumab therapy in Study 111, and the number of subjects included in the pooled lenvatinib monotherapy, and pembrolizumab (RSD) monotherapy sets is presented in Table 12.

Table 12
Safety Population, Size, and Denominators

Study ID	Study Title	Number of participants included in safety dataset
Indication under review		
E7080-A001-111/ KEYNOTE-146	A Multicenter, Open-Label Phase 1b/2 Trial of Lenvatinib (E7080) Plus Pembrolizumab in Subjects With Selected Solid Tumors.	Indication Safety Set: 94[a]
Other Safety Sets contributing to the safety of the combination of lenvatinib plus pembrolizumab		
E7080-A001-111/ KEYNOTE-146	A Multicenter, Open-Label Phase 1b/2 Trial of Lenvatinib (E7080) Plus Pembrolizumab in Subjects With Selected Solid Tumors.	**EC Safety Set: 124** (all subjects with EC) **Non EC Safety Set: 159** (subjects with a tumor type other than EC
Lenvatinib Monotherapy Safety Set (N=1119) for contribution of lenvatinib monotherapy[b]		
E7080-G000-201	Phase 2, Multicenter, Open-label, Single Arm Trial to Evaluate the Safety and Efficacy of Oral E7080 in Medullary and Iodine-131 Refractory, Unresectable Differentiated Thyroid Cancers, Stratified by Histology	114
E7080-G000-203	An Open-Label, Three-Cohort, Phase 2 Study of E7080 in Subjects with Recurrent Malignant Glioma	113
E7080 G000 204	An Open-Label, Single-Arm, Multicenter Phase 2 Study of E7080 [Lenvatinib] in Subjects with Advanced Endometrial Cancer and Disease Progression Following First-Line Chemotherapy	133
E7080-G000-205	An Open-Label, Multicenter Phase 1b/2 Study of E7080 Alone, and in Combination With Everolimus in Subjects With Unresectable Advanced or Metastatic Renal Cell Carcinoma Following One Prior VEGF-Targeted Treatment.	51
E7080-G000-206	An Open-Label, 2-Cohort, Multicenter, Phase 2 Study of E7080 in Previously Treated Subjects With Unresectable Stage III or Stage IV Melanoma	181
E7080-G000-209	A Multicenter, Open-Label, Phase 2 Study of the Safety and Activity of Lenvatinib (E7080) in Subjects With KIF5B-RET-Positive Adenocarcinoma of the Lung.	25
E7080-G000-303	A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Lenvatinib (E7080) in ^{131}I-Refractory Differentiated Thyroid Cancer.	346
E7080-G000-398	An Open-Label, Randomized, Multicenter, Expanded Access Program With Lenvatinib for the Treatment of Radioiodine-Refractory Differentiated Thyroid Cancer	10
E7080-703	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of Oral E7080 (Lenvatinib) in Addition to Best Supportive Care (BSC) versus BSC Alone in Patients	89

	with Locally Advanced or Metastatic Non-Squamous Non-Small Cell Lung Cancer Who Have Failed at least Two Systemic Anticancer Regimens	
E7080-J081-105	A Phase 1 Study of E7080 (lenvatinib) in Subjects with Solid Tumors	6
E7080 J081 208	A Phase 2 Study of E7080 in Subjects With Advanced thyroid Cancer.	51
Pembrolizumab Monotherapy Set (N=2799) for contribution of pembrolizumab monotherapy		
KEYNOTE-001	Phase 1 Study of Single Agent Pembrolizumab (MK-3475) in Patients With Progressive Locally Advanced or Metastatic Carcinoma, Melanoma, and Non-Small Cell Lung Carcinoma	Melanoma: 655 NSCLC: 550
KEYNOTE-002	Randomized, Phase 2 Study of Pembrolizumab (MK-3475) versus Chemotherapy in Patients with Advanced Melanoma (KEYNOTE-002)	Melanoma: 357
KEYNOTE-006	A Multicenter, Randomized, Controlled, Three-Arm, Phase 3 Study to Evaluate the Safety and Efficacy of Two Dosing Schedules of Pembrolizumab (MK-3475) Compared to Ipilimumab in Patients with Advanced Melanoma	Melanoma: 555
KEYNOTE-010	A Phase 2/3 Randomized Trial of Two Doses of MK-3475 (SCH900475) Versus Docetaxel in Previously Treated Subjects With Non-Small Cell Lung Cancer	NSCLC: 682
131I = iodine-131, EC = endothelial carcinoma, KIF5B-RET = KIF5B-RET fusion gene, VEGF = vascular endothelial growth factor a: All subjects received at least 1 dose of lenvatinib plus pembrolizumab. b: Starting dose level of 24 mg orally once daily.		

Duration of treatment for Study in 111 datasets was defined as the number of days the subject received treatment, including dose interruptions. As of the data cutoff date (10 Jan 2019), the median duration of treatment (with either or both study drug[s]) in the Indication Safety Set was 7.38 months and the median duration of treatment with each individual study drug was 7.21 months for lenvatinib and 6.37 months for pembrolizumab (Table 13). The median duration of treatment with either study drug as a monotherapy was shorter than that of the study drugs as combination therapy.

In the Indication Safety Set, the median dose intensity of lenvatinib was 14.34 mg per day, which was slightly lower than the Lenvatinib Monotherapy Safety Set due to the higher starting dose (20 mg QD in Study 111 compared with 24 mg QD in the monotherapy studies). In the Study 111 Indication Safety Set, the median number of doses of pembrolizumab per subject was 9.5 compared with 7.0 doses for the Pembrolizumab Monotherapy Safety Set (EC ISS Table 4.2.2; ADaM dataset: ADSL_EC ISS, ADEXSUM_EC ISS).

Table 13
Duration of Treatment – All Safety Sets

Duration of Treatment, months	Combination Therapy			Monotherapy	
	Lenv 20 mg + Pembro 200 mg			Lenv 24 mg (N=1119)	Pembro (N=2799)
	Indication (N=94)	All EC (N=124)	Non-EC (N=159)		
Overall Study Treatment[a]					
n	94	124	159	N/A	N/A
Mean (SD)	8.36 (7.869)	8.47 (7.966)	8.50 (9.063)	N/A	N/A
Median	7.38	7.21	5.45	N/A	N/A
Lenv[b]					
n	94	124	158	1119	N/A
Mean (SD)	8.21 (7.928)	8.24 (7.986)	8.37 (8.983)	11.61 (14.066)	N/A
Median	7.21	7.01	5.39	5.55	N/A
Pembro[b]					
n	94	124	159	N/A	2799
Mean (SD)	7.21 (6.112)	7.34 (6.133)	7.33 (7.652)	N/A	6.51 (5.931)
Median	6.37	6.24	4.40	N/A	4.17

Data cutoff date for Combination Therapy Safety Sets: 10 Jan 2019.
Data cutoff date for Lenv monotherapy studies: 01 Sep 2016 (ongoing studies), except Study 205 (which had a cutoff date of 15 Mar 2018); earlier for completed studies.
Data cutoff date for the Pembro monotherapy studies: varied by study; range 18 Apr 2014 to 30 Sep 2015.
Indication Safety Set: Subjects from Study 111 with histologically confirmed EC that was not MSI-H/dMMR and that was previously treated with systemic therapy, who received Lenv 20 mg QD + Pembro 200 mg Q3W.
dMMR = mismatch repair deficient, EC = endometrial carcinoma, Lenv = lenvatinib, MSI-H = microsatellite instability-high, NSCLC = non-small-cell lung cancer, Pembro = pembrolizumab, Q3W = once every 3 weeks, QD = once daily, SD = standard deviation.
a: Overall duration of treatment (months) = (date of last dose of study treatments – date of first dose of study treatments + 1) / 30.4375.
b: Duration of treatment (months) = (date of last dose – date of first dose + 1) / 30.4375.
Source: EC ISS Table 4.1; ADaM dataset: ADSL_EC ISS, ADEXSUM_EC ISS.

The Regulatory Authorities' Assessment:

The safety population for Study 111/KN-146 consists of all not MSI-H/dMMR patients who had received at least 1 prior line of therapy (n = 94). For this review, the size of this safety population and the extent of exposure were adequate to allow for sufficient characterization of AEs associated with L+P in the study population. We note that checkpoint inhibitors may have delayed immune-mediated toxicities, but the study follow-up was thought to be adequate to capture the majority of these events.

Relevant characteristics of the safety population:

The Applicant's Position:

Baseline demographics and disease characteristics for the Indication Safety Set and the All EC Safety Set from Study 111 are representative of the overall population with advanced EC, and were generally consistent with baseline demographics and disease characteristics of the EC

subjects included in Study 204 (lenvatinib monotherapy) and KEYNOTE-028 and KEYNOTE-158 (pembrolizumab monotherapy) (Table 8).

There were no apparent major differences across the 5 safety analysis sets that would preclude comparisons across the Study 111 and monotherapy safety sets (Table 14). Observed differences between the Indication Safety Set and the monotherapy safety sets generally were specific to the EC indication: ie, female gender, advanced age, and high BMI.

Table 14
Selected Demographics and Baseline Characteristics – All Safety Sets

Parameter at Baseline Statistic or Category	Combination Therapy			Monotherapy	
	Lenv 20 mg + Pembro 200 mg			Lenv 24 mg (N=1119)	Pembro[a] (N=2799)
	Indication (N=94)	All EC (N=124)	Non-EC (N=159)		
Age (y)					
n	94	124	159	1119	2799
Mean (SD)	65.4 (7.42)	65.3 (7.83)	63.2 (11.30)	59.8 (11.60)	61.0 (12.52)
Median	66.0	66.0	64.0	61.0	62.0
Min, Max	40, 80	40, 85	31, 87	21, 89	15, 94
Age Group, n (%)					
<65 years	36 (38.3)	47 (37.9)	80 (50.3)	700 (62.6)	1587 (56.7)
≥65 years	58 (61.7)	77 (62.1)	79 (49.7)	419 (37.4)	1212 (43.3)
Sex, n (%)					
Female	94 (100.0)	124 (100.0)	42 (26.4)	565 (50.5)	1140 (40.7)
Male	0 (0.0)	0 (0.0)	117 (73.6)	554 (49.5)	1659 (59.3)
Race Group, n (%)					
White	81 (86.2)	108 (87.1)	140 (88.1)	900 (80.4)	2474 (88.4)
All Others	13 (13.8)	16 (12.9)	18 (11.3)	219 (19.6)	303 (10.8)
Missing	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	22 (0.8)
Ethnicity, n (%)					
Hispanic or Latino	1 (1.1)	3 (2.4)	12 (7.5)	43 (3.8)	128 (4.6)
Not Hispanic or Latino	93 (98.9)	121 (97.6)	147 (92.5)	1069 (95.5)	2582 (92.2)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	7 (0.6)	89 (3.2)
Geographic Region, n (%)					
US	81 (86.2)	101 (81.5)	155 (97.5)	423 (37.8)	1250 (44.7)
Non-US	13 (13.8)	23 (18.5)	4 (2.5)	696 (62.2)	1549 (55.3)
Body Mass Index (kg/m^2)					
n	94	123	159	1082	NA
Mean (SD)	30.3 (7.86)	30.1 (7.43)	28.1 (6.57)	27.1 (6.65)	NA
Median	30.7	30.1	26.7	26.1	NA
Min, Max	14, 58.6	14, 58.6	18, 61	13.9, 122.4	NA
ECOG PS, n (%)					
0	49 (52.1)	62 (50.0)	77 (48.4)	492 (44.0)	1446 (51.7)
1	45 (47.9)	62 (50.0)	82 (51.6)	452 (40.4)	1347 (48.1)

Parameter at Baseline Statistic or Category	Combination Therapy			Monotherapy	
	Lenv 20 mg + Pembro 200 mg			Lenv 24 mg (N=1119)	Pembro[a] (N=2799)
	Indication (N=94)	All EC (N=124)	Non-EC (N=159)		
≥2	0 (0.0)	0 (0.0)	0 (0.0)	51 (4.6)	1 (< 0.1)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	124 (11.1)	5 (0.2)
Hypertension, n (%)					
Yes	60 (63.8)	79 (63.7)	95 (59.7)	NA	NA
No	34 (36.2)	45 (36.3)	64 (40.3)	NA	NA
Renal Function,[a] n (%)					
Normal	74 (78.7)	100 (80.6)	112 (70.4)	933 (83.4)	NA
Impaired	20 (21.3)	24 (19.4)	46 (28.9)	157 (14.0)	NA
Missing	0 (0.0)	0 (0.0)	1 (0.6)	29 (2.6)	NA
Hepatic Function,[b] n (%)					
Normal	84 (89.4)	110 (88.7)	141 (88.7)	937 (83.7)	2383 (85.1)
Impaired	10 (10.6)	14 (11.3)	17 (10.7)	155 (13.9)	414 (14.8)
Missing	0 (0.0)	0 (0.0)	1 (0.6)	27 (2.4)	2 (0.1)

Data cutoff date for Combination Therapy Safety Sets: 10 Jan 2019.
Data cutoff date for Lenv monotherapy studies: 01 Sep 2016 (ongoing studies), except Study 205 (which had a cutoff date of 15 Mar 2018); earlier for completed studies.
Data cutoff date for the Pembro monotherapy studies: varied by study; range 18 Apr 2014 to 30 Sep 2015.
Percentages are based on total number of subjects within the respective safety set.
ALT = alanine aminotransferase, AST = aspartate aminotransferase, CrCl = creatinine clearance, EC = endometrial carcinoma, ECOG PS = Eastern Cooperative Oncology Group Performance Status, Lenv = lenvatinib, Max = maximum, Min = minimum, NA = not available, NSCLC = non-small cell lung cancer, Pembro = pembrolizumab, Q3W = once every 3 weeks, QD = once daily, SD standard deviation, US = United States, y = year.
a: Normal: CrCl ≥60 mL/min; Impaired: CrCl <60 mL/min.
b. Normal: No CTCAE Grade 1 AST, ALT, and bilirubin; Impaired: CTCAE Grade ≥1 AST, ALT, or bilirubin.
Source: EC ISS Table 2.1; 111 EC CSR Table 14.1.4.1.3.1; ADaM dataset: ADSL_EC ISS, ADSL_Study 111, ADMH_Study 111

The Regulatory Authorities' Assessment:

We conducted our own analyses to confirm that the demographics and baseline disease characteristics between the L+P combination therapy and monotherapy studies (study 204, KN-158 and KN-028) were well balanced between the trials and adequately represented the broader population of women with endometrial cancer after first-line systemic therapy. We agree with the applicant's assessment of this section and note that a higher percentage of patients in the *not MSI-H/dMMR EC 2L+* dataset were ≥65 years of age compared to the monotherapy safety datasets.

Table 15: Select Demographic Characteristics – All Safety Sets

Demographic Group	Not MSI-H/dMMR EC 2L+ N=94 n(%)	All previously Treated (EC 2L+) N=108 n(%)	Lenvatinib Study 204 N=133 n(%)	KEYNOTE-158 Non MSI-H/dMMR N=90 n(%)	KEYNOTE-028 Non MSI-H/dMMR N=18 n(%)
Age					

Demographic Group	Not MSI-H/dMMR EC 2L+ N=94 n(%)	All previously Treated (EC 2L+) N=108 n(%)	Lenvatinib Study 204 N=133 n(%)	KEYNOTE-158 Non MSI-H/dMMR N=90 n(%)	KEYNOTE-028 Non MSI-H/dMMR N=18 n(%)
<65	36 (38)	41 (38)	81 (61)	50 (56)	8 (44)
>=65	58 (62)	67 (62)	52 (39)	40 (44)	10 (56)
Median (Range)	66 (40–80)	66 (40–80)	62 (38–80)	63 (41–80)	66.5 (34–74)
Sex					
F	94 (100)	108 (100)	133 (100)	90 (100)	18 (100)
Race					
American Indian or Alaska Native	1 (1.1)	1 (0.9)	1 (0.8)	0 (0)	0 (0)
Asian	4 (4.3)	5 (4.6)	6 (4.5)	14 (16)	3 (17)
Black or African American	6 (6)	6 (6)	10 (8)	9 (10)	1 (6)
Native Hawaiian or Other Pacific Islander	0 (0)	1 (0.9)	2 (1.5)	0 (0)	0 (0)
Other	2 (2.1)	2 (1.9)	2 (1.5)	0 (0)	0 (0)
White	81 (86)	93 (86)	112 (84)	67 (74)	12 (67)
Baseline ECOG Status					
0	49 (52)	53 (49)	50 (38)	43 (48)	6 (33)
1	45 (48)	55 (51)	71 (53)	47 (52)	12 (67)
2	0 (0)	0 (0)	12 (9)	0 (0)	0 (0)
Source: Study 111 - adsl.xpt; Study 204 – adsl.xpt, KN-158 – adsl.xpt, KN-028 – adsl.xpt					

Table 16: Select Baseline Disease Characteristics – All Safety Sets

Baseline disease characteristic	Not MSI-H/dMMR EC 2L+ N=94	All previously Treated (EC 2L+) N=108	Lenvatinib Study 204 N=133
Baseline Body Mass Index (BMIBL)			
Mean (SD)	30.3 (7.9)	30.3 (7.7)	30.7 (10.8)

Baseline disease characteristic	Not MSI-H/dMMR EC 2L+ N=94	All previously Treated (EC 2L+) N=108	Lenvatinib Study 204 N=133
Median (Range)	30.6 (14–58.6)	30.6 (14–58.6)	28.6 (18.3–122.4)
Baseline Renal Function Group 1 (RENLGR1)			
Total	94 (100)	108 (100)	133 (100)
Not Available	0 (0)	0 (0)	0 (0)
Impaired	20 (21)	23 (21)	39 (29)
Normal	74 (79)	85 (79)	94 (71)
Baseline Hepatic Function Group 1 (HEPAGR1)			
Total	94 (100)	108 (100)	133 (100)
Not Available	0 (0)	0 (0)	0 (0)
Impaired	10 (11)	11 (10)	22 (17)
Normal	84 (89)	97 (90)	111 (83)
Hypertension (AVAL)			
Total	94 (100)	108 (100)	133 (100)
False	37 (39)	39 (36)	31 (23)
True	57 (61)	69 (64)	102 (77)
Source: Study 111 - EC ISS adsl.xpt Data for pembrolizumab monotherapy studies KN-028 and KN-158 was not available to do this analysis.			

Adequacy of the safety database:

The Applicant's Position:

The clinical safety data supporting the combination of lenvatinib plus pembrolizumab in this sNDA/sBLA are primarily derived from the Indication Safety Set from Study 111 (N=94), which is identical to the Indication Efficacy Set. Safety data from the lenvatinib monotherapy clinical program and the pembrolizumab monotherapy RSD, which include 1119 and 2799 subjects, respectively, support the contribution of each drug to the safety profile of the combination.

Thus, the applicant considers that the safety database for the combination of lenvatinib plus pembrolizumab is of adequate size, considering exposure to the appropriate dose of the combination, duration of treatment, patient demographics, and disease characteristics, and contribution of monotherapy components in the US target EC population.

The Regulatory Authorities' Assessment:

The size of the safety database and duration of exposure were sufficient to characterize the safety of the L+P for the proposed indication. Datasets for monotherapy studies for lenvatinib (study 204), and pembrolizumab (KN-158 and KN-028) were also adequate to assess the contribution of each drug to the safety profile of the combination.

7.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:

Clinical development of lenvatinib and pembrolizumab has proceeded in accordance with the appropriate US FDA and ICH jurisdictional guidelines. Site visit audits were made periodically by the sponsor's or the contract research organization's (CRO's) qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study. There were no issues with data integrity or analysis that precluded the inclusion of data in the safety analysis.

The sNDA/sBLA submission contains all required components of the electronic Common Technical Document (eCTD). The overall quality and integrity of the application is sufficient for substantive review to be completed.

The Regulatory Authorities' Assessment:

We agree with the applicant's assessment.

Categorization of Adverse Event

The Applicant's Position:

Treatment-emergent AEs included AEs reported up to 30 days after the subject's last dose of study drug (if no anticancer treatment started during that time). Serious AEs, regardless of causality, were collected through the termination visit and for 30 days (lenvatinib monotherapy studies) or 90 days (Study 111 and pembrolizumab monotherapy studies) after study drug discontinuation or until resolution, whichever was longer.

The AE profile for lenvatinib plus pembrolizumab in the Indication Safety Set was comparable with that for the Lenvatinib Monotherapy Safety Set, except for an increased incidence of TEAEs leading to a dose reduction of lenvatinib; however, the incidence of discontinuation of lenvatinib was consistent between the Indication and Lenvatinib Monotherapy Safety Sets.

Table 17
Overview of Treatment-Emergent Adverse Events – All Safety Sets

Subjects With at Least 1 of the Following:	Combination Therapy			Monotherapy	
	Lenv 20 mg + Pembro 200 mg			Lenv 24 mg (N=1119) n (%)	Pembro (N=2799) n (%)
	Indication (N=94) n (%)	All EC (N=124) n (%)	Non-EC (N=159) n (%)		
Any TEAE	94 (100.0)	124 (100.0)	158 (99.4)	1108 (99.0)	2727 (97.4)
TEAE With Worst CTCAE Grade[b] of					
≥3	80 (85.1)	103 (83.1)	123 (77.4)	899 (80.3)	1273 (45.5)
3	68 (72.3)	84 (67.7)	82 (51.6)	701 (62.6)	1020 (36.4)
4	9 (9.6)	13 (10.5)	23 (14.5)	103 (9.2)	143 (5.1)
5	3 (3.2)	6 (4.8)	18 (11.3)	95 (8.5)	110 (3.9)
Any Related TEAE[a]	92 (97.9)	120 (96.8)	149 (93.7)	1060 (94.7)	2064 (73.7)
Related TEAE With Worst CTCAE Grade of[a,b]					
≥3	66 (70.2)	83 (66.9)	89 (56.0)	724 (64.7)	387 (13.8)
3	58 (61.7)	74 (59.7)	72 (45.3)	644 (57.6)	336 (12.0)
4	6 (6.4)	7 (5.6)	15 (9.4)	53 (4.7)	40 (1.4)
5	2 (2.1)	2 (1.6)	2 (1.3)	27 (2.4)	11 (0.4)
Serious AEs	49 (52.1)	61 (49.2)	81 (50.9)	613 (54.8)	1042 (37.2)
Nonfatal SAEs	49 (52.1)	61 (49.2)	77 (48.4)	580 (51.8)	984 (35.2)
Number of Subjects With[c]					
TEAEs Leading to Study Drug Discontinuation of					
Both	15 (16.0)	22 (17.7)	32 (20.1)	N/A	N/A
Lenv[d]	21 (22.3)	30 (24.2)	38 (23.9)	299 (26.7)	N/A
Pembro[e]	19 (20.2)	26 (21.0)	39 (24.5)	N/A	334 (11.9)
TEAEs Leading to Dose Reduction of Lenv	63 (67.0)	80 (64.5)	88 (55.3)	531 (47.5)	N/A
TEAEs Leading to Study Drug Interruption of					
Both	36 (38.3)	53 (42.7)	61 (38.4)	N/A	N/A
Lenv[d]	71 (75.5)	93 (75.0)	115 (72.3)	757 (67.6)	N/A
Pembro[e]	46 (48.9)	64 (51.6)	80 (50.3)	N/A	622 (22.2)

Data cutoff date for Combination Therapy Safety Sets: 10 Jan 2019.
Data cutoff date for Lenv monotherapy studies: 01 Sep 2016 (ongoing studies), except Study 205 (which had a cutoff date of 15 Mar 2018); earlier for completed studies.
Data cutoff date for the Pembro monotherapy studies: varied by study; range 18 Apr 2014 to 30 Sep 2015.
Percentages based on total number of subjects within the respective safety set.
Adverse events were graded using CTCAE version 4.03.
Rows containing only zeroes have been omitted from this in-text table.
AE = adverse event, CRF = case report form, CTCAE = Common Terminology Criteria for Adverse Events, EC = endometrial carcinoma, Lenv = lenvatinib, Pembro = pembrolizumab, SAE = serious adverse event, TEAE = treatment-emergent adverse event.
a: Related TEAEs include TEAEs that were considered by the investigator to be possibly or probably related to study treatment or TEAEs with a missing causality on the CRF, except for the Pembro Monotherapy Safety Set.
b: If a subject had more than 1 TEAE, the subject was only counted once at the worst grade.
c: Drug action taken is for Lenv or/and Pembro.
d: Drug action taken for Lenv, regardless of action taken for Pembro.

Subjects With at Least 1 of the Following:	Combination Therapy			Monotherapy	
	Lenv 20 mg + Pembro 200 mg			Lenv 24 mg (N=1119) n (%)	Pembro (N=2799) n (%)
	Indication (N=94) n (%)	All EC (N=124) n (%)	Non-EC (N=159) n (%)		

e. Drug action taken for Pembro, regardless of action taken for Lenv.
Source: EC ISS Tables 5.1 and 6.1; ADaM dataset: ADSL_EC ISS, ADAE_EC ISS.

The Regulatory Authorities' Assessment:

The Agencies agree with the applicant's categorization of safety and tolerability assessment based on the frequency of deaths, AEs, serious adverse events (SAEs), AEs leading to discontinuation, AEs leading to interruptions, and AEs leading to dose reductions. AEs were coded using MedDRA version 21.1. AEs and laboratory values were graded for severity using NCI CTCAE version 4.03. Adverse events were categorized by System Organ Class (SOC) and PT. The PT listed in the dataset adequately represented the investigator-recorded term and did not raise any significant issues. During review of the AE datasets, the reviewers pooled selected PTs so as not to underestimate the incidence of some AEs with multiple similar or overlapping PTs; this pooling of terms was discussed with the applicant (see Appendix 17.5).

Table 18: Overview of Adverse Events in Study 111/KN-146

AE category	Study 111/KN-146	
	Not MSI-H/dMMR EC 2L+ N=94; n(%)	All previously Treated EC 2L+ N=108; n(%)
Any AE	94 (100)	108 (100)
Grade 3-4 AEs	69 (73.4)	79 (73.1)
Grade 3	62 (66)	71 (65.7)
Grade 4	7 (7.4)	8 (7.4)
Grade 5 (includes deaths due to disease progression)	12 (12.8)	14 (13)
Serious AEs (SAEs)	50 (53.2)	57 (52.8)
Any treatment discontinuation due to AEs	22 (23.4)	26 (24.1)
Any dose interruption due to TEAEs	71 (75.5)	83 (76.9)
Any dose reduction due to TEAEs	63 (67)	72 (66.7)
Source: Study 111 – adsl.xpt, adae.xpt		

Routine Clinical Tests

The Applicant's Position:

The schedule of assessments for Study 111 shown in the study protocol (Table 9), shows the frequency of laboratory testing, vital signs, physical examination, and AE monitoring.

The Regulatory Authorities' Assessment:
Based on the protocol-mandated safety assessment schedule, the clinical testing of patients enrolled in the trial appeared adequate.

7.2.4. Safety Results

Deaths

The Applicant's Position:

In the Indication Safety Set, 44 (46.8%) subjects died as of the data cutoff date of 10 Jan 2019; most of these subjects died during survival follow-up and a cause of death may not have been recorded (Table ; ADaM data set: ADSL_Study 111, ADAE_Study 111).

The incidence rate of fatal AEs in the Indication Safety Set (3.2%) was generally consistent between the All EC (4.8%) and Pembrolizumab Monotherapy (3.9%) Safety Sets and was lower than that in the Non-EC (11.3%) and Lenvatinib Monotherapy (8.7%) Safety Sets (EC ISS Table 8.1; ADaM dataset: ADSL_EC ISS, ADAE_EC ISS).

In the Indication Safety Set, 3 subjects had a fatal AE; 2 subjects had fatal AEs that were considered by the investigator to be related to study treatment and not related to PD (intracranial hemorrhage and Escherichia sepsis), and 1 subject had a fatal AE that was related to PD and considered by the investigator to be unrelated to study treatment (gastrointestinal [GI] perforation).

Three additional deaths occurred in the All EC Safety Set (total of 6 EC subjects, 4.8%): intestinal obstruction (unrelated to study treatment and not related to PD), general physical health deterioration, and metabolic encephalopathy (both related to PD and unrelated to study treatment).

Summary narratives are provided for subjects in the All EC Set whose death was considered not due to disease progression.

- Subject A (Non-MSI-H/pMMR) had a fatal intracranial hemorrhage. The subject did not take lenvatinib from Day 40 to Day 42. On Day 43, the subject experienced hypertension (Grade 3), with blood pressure of 154/71 mmHg and was hospitalized for intracranial hemorrhage (Grade 4). A CT scan of head showed intraparenchymal hemorrhage and no evidence of infarction. The subject underwent intubation for airway protection, intracerebral hematoma evacuation, and ventricular drainage (placement of left ventricular catheter). Lenvatinib was interrupted due to intracranial hemorrhage. On Day 56, the subject was withdrawn from the study due to intracranial hemorrhage. The subject received the last dose of lenvatinib on Day 39 and pembrolizumab on Day 41. On Day 56, 17 days after the last dose of lenvatinib and 15 days after the last dose of pembrolizumab, the subject died due to intracranial hemorrhage. The investigator considered intracranial hemorrhage related to the study drugs and hypertension not related to the study drugs.
- Subject B (Non-MSI-H/pMMR) had fatal sepsis (*E. coli*). The subject missed the dose of lenvatinib from Day 23 to Day 33. On Day 34, the subject was hospitalized for Escherichia sepsis (unknown source; Grade 4, white blood cell (WBC) count 11.7 × 10^9/L) and was

withdrawn from the study due to Escherichia sepsis. On Day 47, 25 days after the last dose of lenvatinib and 46 days after the last dose of pembrolizumab, the subject died due to Escherichia sepsis. The investigator considered Escherichia sepsis related to the study drugs.

- Subject C (MSI-H/dMMR EC) had a fatal intestinal obstruction. Prior therapy included radiotherapy to a right pelvic mass. On Day 243, the subject was hospitalized for intestinal obstruction (Grade 3 and was treated with fentanyl, metoclopramide, morphine, corticosteroids, and piperacillin/tazobactam. The subject received the last dose of lenvatinib on Day 246 and pembrolizumab on Day 235. On Day 260, 14 days after the last dose of lenvatinib and 25 days after the last dose of pembrolizumab, the subject died due to intestinal obstruction. The investigator considered the event not related to the study drugs.

Refer to Module 2.7.4, Section 2.7.4.2.1.3 for details on deaths due to AEs.

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Table 19
Summary of Deaths – Safety Analysis Set

	Lenvatinib 20 mg QD + Pembrolizumab 200 mg Q3W n (%)					
	EC 2L+					
	Total (N=108)	Indication (N=94)	MSI-H/ dMMR (N=11)	All EC (N=124)	Non-EC (N=159)	All EC + Non-EC (N=283)
All Deaths[a]	49 (45.4)	44 (46.8)	3 (27.3)	51 (41.1)	63 (39.6)	114 (40.3)
AEs Leading to Death	14 (13.0)	12 (12.8)	2 (18.2)	16 (12.9)	28 (17.6)	44 (15.5)
Due to Disease Progression	11 (10.2)	10 (10.6)	1 (9.1)	13 (10.5)	16 (10.1)	29 (10.2)
Not Due to Disease Progression	3 (2.8)	2 (2.1)	1 (9.1)	3 (2.4)	12 (7.5)	15 (5.3)
Other Deaths During the Survival Follow-up	35 (32.4)	32 (34.0)	1 (9.1)	35 (28.2)	35 (22.0)	70 (24.7)

Data cutoff date: 10 Jan 2019.
Percentages were based on total number of subjects within the relevant treatment group in the Safety Analysis Set.
EC 2L+ = subjects with histologically confirmed EC that was previously treated with at least 1 systemic anticancer therapy, and who had sufficient follow-up to provide a median follow-up of at least 12 months, and for all responders, an opportunity for follow-up after initial objective response as assessed by the investigator of at least 6 months. Subjects with a status of Non-MSI-H/pMMR (n=94; Indication Safety Set) or MSI-H/dMMR (n=11), or whose MSI status was not available (n=3), are included in total EC 2L+ Set (N=108).
All EC = subjects with histologically confirmed EC regardless of prior anticancer therapy or length of follow-up as of the data cutoff date.
Non-EC = subjects from tumor cohorts other than EC; it includes 1 subject with leiomyosarcoma who was enrolled in the EC cohort.
2L+ = second line or greater, dMMR = mismatch repair deficient, EC = endometrial carcinoma, MSI-H = microsatellite instability high, pMMR = mismatch repair proficient, Q3W = every 3 weeks, QD = once daily, TEAE = treatment-emergent adverse event.
a: The majority of these deaths occurred during survival follow-up and the cause of death may not have been recorded.
Source: Study 111 Table 14.3.2.1.1.

The Regulatory Authorities Assessment:

The sponsor reported a total of 14 deaths in study 111. Of these, 11 deaths were clearly attributed to disease progression; however, in the remaining three patients, death causality was confounded. During our review of death cases, we discovered one additional death that was drug related; Table 21: Narratives Reports of Deaths due to Causes Other than Disease Progression in Patients Enrolled in Not MSI-H/dMMR EC 2L+ Dataset for Study 111/KN-146 **presents an overview of these four deaths.**

There were 32 deaths that occurred in the indication data set during survival follow-up; however, the case report form did not collect the cause of death for patients who died during the survival follow-up period. In the non-EC (n=159) cohort, 12 deaths occurred from adverse events that were not related to disease progression. Table 22: Adverse events that resulted in

death of 12 patients in Non-EC population (n=159) **provides the adverse events that resulted in death for these 12 subjects.**

Table 20: Adverse events leading to death in Study111/KN-146

Adverse events leading to death	Not MSI-H/dMMR EC 2L+ N=94 n(%)	All previously Treated EC 2L+ N=108 n(%)
ALL AEs	14 (14.89)	16 (14.81)
[SOC] NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	11 (11.7)	12 (11.1)
Malignant neoplasm progression*	10 (10.6)	11 (10.2)
Metastases to peritoneum	1 (1.1)	1 (0.9)
[SOC] GASTROINTESTINAL DISORDERS	1 (1.1)	2 (1.9)
Gastrointestinal perforation	1 (1.1)	1 (0.9)
Intestinal obstruction	0 (0)	1 (0.9)
[SOC] INFECTIONS AND INFESTATIONS	1 (1.1)	1 (0.9)
Escherichia sepsis	1 (1.1)	1 (0.9)
[SOC] NERVOUS SYSTEM DISORDERS	1 (1.1)	1 (0.9)
Haemorrhage intracranial	1 (1.1)	1 (0.9)
*One death case described as malignant neoplasm progression was identified as a TEAE by the FDA reviewer. Please see narratives below for detail. Source: Study 111 – adsl.xpt, adae.xpt		

Table 21: Narratives Reports of Deaths due to Causes Other than Disease Progression in Patients Enrolled in Not MSI-H/dMMR EC 2L+ Dataset for Study 111/KN-146

Subject ID	Narrative	Reviewer's Comments
(b) (6)	Primary Reported Cause of Death: Hemorrhage intracranial	Reviewer Assessed Cause of Death: **Intracranial hemorrhage**

65-year-old female with EC with PMH of anemia, angle closure glaucoma, arthralgia, carpal tunnel syndrome, cholelithotomy, fibromyalgia, hyperglycemia, hypertriglyceridemia, migraine, and proctalgia. Previous anticancer therapies included hysterosalpingo-oophorectomy, carboplatin, and paclitaxel. At screening, tumor assessments of target/nontarget lesions via CT scan showed lesions at the left pelvis, central peritoneum/omentum, and left peritoneum/omentum. The ECOG performance score was 1. The patient began treatment with L+P combination on (b) (6) (Day 1) and on Day 43, patient experienced hypertension (Grade 3), with blood pressure of 154/71 mmHg and was hospitalized for Grade 4 intracranial hemorrhage (CT scan). Lenvatinib was interrupted due to intracranial hemorrhage and pembrolizumab did not change. On Day 56, patient withdrew from the study and died later that day (intracranial hemorrhage did not recover), 17 days after the last dose of lenvatinib and 15 days after the last dose of pembrolizumab.		**Given the temporal association between L+P administration and the onset of hypertension and intracranial hemorrhage, we assess that the death was probably related to study drugs. It is important to note that patient did not have any predisposing factors, prior hemorrhage or brain metastasis. Hemorrhagic events are listed under the *Warnings and Precautions* section of the lenvatinib label.**
(b) (6)	Primary Reported Cause of Death: Escherichia sepsis	Reviewer Assessed Cause of Death: **Escherichia sepsis**
71-year-old female with EC with PMH of abdominal pain, anemia, anxiety, arthritis, atrial fibrillation, breast cancer, breast conserving surgery, chronic kidney disease, decreased appetite, depression, dyspnea, fatigue, gastroesophageal reflux disease, hernia hiatus repair, hypercholesterolemia, hypertension, knee arthroplasty, malignant ascites, muscular weakness, urinary incontinence, and vitamin D deficiency. Previous anticancer therapies included hysterectomy, carboplatin, and paclitaxel. At screening, tumor assessments of target/nontarget lesions via CT scan showed left upper quadrant nodule, uterine mass, and para-aortic and posterior esophageal lymphadenopathies. The ECOG performance score was 0. The patient began treatment with L+P combination on (b) (6) (Day 1) and on Day 34 was hospitalized for Escherichia sepsis and withdrew from the study. Patient underwent "abdominal cavity drainage" due to ongoing dyspnea. Treatment with antibiotics was started. On Day 47, 25 days after the last dose of lenvatinib and 46 days after the last dose of pembrolizumab, the subject died due to Escherichia sepsis.		**Despite the temporal association between L+P administration, and onset of sepsis, lack of predisposing factors and no prior neutropenia make it difficult to assess causality. Even though cases of sepsis have been reported in patients treated with pembrolizumab and/or lenvatinib, the role of disease progression and procedures (abdominal cavity drainage) cannot be disregarded.**
(b) (6)	Primary Reported Cause of Death: Gastrointestinal perforation related to disease progression	Reviewer Assessed Cause of Death: **Gastrointestinal perforation related to**

		disease progression
62-year-old female with EC with PMH of allergic rhinitis, anemia, anxiety, appendectomy, arthritis, bronchitis, depression, dry mouth, exertional dyspnea, fatigue, gastroesophageal reflux disease, headache, hematuria, hiatus hernia, hypertension, hysterectomy, micturition urgency, nail toxicity, peripheral edema, peripheral sensory neuropathy, pollakiuria, proctitis, sinus congestion, urinary incontinence, urinary retention, vaginal hemorrhage, and vitreous floaters. Previous anticancer therapies included hysterosalpingo-oophorectomy, carboplatin, paclitaxel, radiotherapy to vaginal mass, brachytherapy to vaginal cuff, anastrozole, and megestrol. At screening, tumor assessments of target and nontarget lesions via CT scan showed omental mass, pelvic mass at superior left iliac crest, and thoracic vertebral mass at the anterior midline of T7; bilateral upper quadrant peritoneal fluid; right pleural effusion; and right paracentral pretracheal and left infraclavicular lymphadenopathies. The ECOG performance score was 1. The patient began treatment with L+P combination on (b) (6) (Day 1) and on Day 143 was hospitalized for gastrointestinal perforation (Grade 3) and was treated with pantoprazole. The CT scan of abdomen and pelvis showed pneumoperitoneum and suspected GI perforation. Exploratory laparotomy revealed extensive mesenteric matting due to endometrial cancer and a sequestered loop of ischemic small bowel. On Day 148, the subject was withdrawn from the study and transferred to inpatient hospice for palliative care. On Day 152 (23 days after last dose of lenvatinib and 38 days after the last dose of pembrolizumab), the subject died due to gastrointestinal perforation.	**Despite the temporal association between L+P administration, and onset of GI perforation, death was most likely caused due to ischemic small bowel and disease progression (based on the case narrative).**

(b) (6) *	Primary Reported Cause of Death: Malignant neoplasm progression	Reviewer Assessed Cause of Death: **Intraventricular hemorrhage and PRES**
62-year-old female with EC with PMH of anxiety, appendicitis, central venous catheterization, fatigue, gastroesophageal reflux disease, hypertension, hypothyroidism, insomnia, peripheral sensory neuropathy, and proteinuria. Previous anticancer therapies included endocervical curettage, hysterectomy, cystoscopy, lymphadenectomy, sigmoidoscopy, lung biopsy, bevacizumab, cisplatin, docetaxel, carboplatin, paclitaxel, and radiotherapy to the right upper and lower lung lobe mass. Prior and concomitant medications included alprazolam, calcium, carvedilol, clonidine, dexamethasone, gabapentin, haloperidol, hydralazine, hydromorphone, hyoscine, irbesartan, levothyroxine, lorazepam, nicardipine, omeprazole, sertraline, temazepam, and vitamins. At screening, tumor assessments of target/nontarget lesions via CT scan showed right lateral lung mass, right inferior lung cyst, and right infrahilar consolidation. The ECOG performance score was 0. The patient began treatment with L+P combination on (b) (6) (Day 1) and was hospitalized for seizure on Day 10 at which time she also had BP of 217/107 mmHg and Grade 3 headache. Lenvatinib was interrupted and resumed at a lower dose on Day 20. On Day 36, patient had BP of 190/100 mmHg and was hospitalized. Next day she experienced a Grade 3 intraventricular haemorrhage (CT scan). On Day 38 Grade 3 posterior reversible encephalopathy syndrome (PRES) was considered and lenvatinib was interrupted. On Day 40, patient withdrew from the study and died on Day 48 (intraventricular hemorrhage and PRES did not recover), 12 days after last dose of lenvatinib and 28 days after last dose of pembrolizumab.		**Given the temporal association between L+P administration and onset of seizure, hypertension, intraventricular hemorrhage, and PRES we assess that the death was probably related to study drugs. It is important to note that PRES (also known as RPLS) and hemorrhagic events are labeled under the *Warnings and Precautions* section of the lenvatinib label.**
* This case was described as malignant neoplasm progression by the sponsor but was identified as a TEAE by the FDA reviewer		

Table 22: Adverse events that resulted in death of 12 patients in Non-EC population (n=159)

Patient Identifier	Cause of Death
E7080-A001-111-(b) (6)	Myocardial infarction
E7080-A001-111-(b) (6)	Aspiration
E7080-A001-111-(b) (6)	Pulmonary haemorrhage

Patient Identifier	Cause of Death
E7080-A001-111-(b) (6)	Sepsis
E7080-A001-111-(b) (6)	Pneumonia aspiration
E7080-A001-111-(b) (6)	Pneumonia aspiration
E7080-A001-111-(b) (6)	Pneumonia
E7080-A001-111-(b) (6)	Gastrointestinal haemorrhage
E7080-A001-111-(b) (6)	Portal vein thrombosis
E7080-A001-111-(b) (6)	Pneumothorax
E7080-A001-111-(b) (6)	Pneumonia aspiration
E7080-A001-111-(b) (6)	Urosepsis
Source: Data requested via information request from Sponsor	

Serious Adverse Events

The Applicant's Position:

In the Indication Safety Set, SAEs and nonfatal SAEs were reported for 52.1% of subjects (Table 17). Fatal AEs are discussed in the **Deaths** section above.

In the Indication Safety Set, the most frequently reported nonfatal SAEs (≥4% of subjects), by decreasing incidence rate, were hypertension (HTN), abdominal pain, confusional state, nausea, and pleural effusion (Table 23).

All nonfatal SAEs that occurred in ≥4% of subjects in the Indication Safety Set occurred at a similar incidence rate in the All EC Safety Set and at a higher incidence rate than in the Non-EC Safety Set, which was generally consistent with the Lenvatinib Monotherapy or Pembrolizumab Monotherapy Safety Set.

The higher rate of abdominal pain and nausea SAEs is consistent with the higher rate of TEAEs within the GI disorders system organ class (SOC) seen in the EC safety sets compared with that in the monotherapy safety sets.

Although there was a higher incidence rate of SAEs of HTN, the incidence rate of severe (Grade 3 or 4) TEAEs of HTN was comparable in the Indication, All EC, and Lenvatinib Monotherapy Safety Sets.

Table 23
Nonfatal Serious Adverse Events Occurring in 4% or More of Subjects by Preferred Term – All Safety Sets

MedDRA Preferred Term	Combination Therapy			Monotherapy	
	Lenv 20 mg + Pembro 200 mg			Lenv 24 mg (N=1119) n (%)	Pembro (N=2799) n (%)
	Indication (N=94) n (%)	All EC (N=124) n (%)	Non-EC (N=159) n (%)		
Subjects With Any Nonfatal SAE	*49 (52.1)*	*61 (49.2)*	*77 (48.4)*	*580 (51.8)*	*984 (35.2)*
Hypertension	7 (7.4)	7 (5.6)	3 (1.9)	28 (2.5)	0 (0.0)
Abdominal pain	5 (5.3)	6 (4.8)	2 (1.3)	27 (2.4)	22 (0.8)
Confusional state	4 (4.3)	4 (3.2)	1 (0.6)	10 (0.9)	15 (0.5)
Nausea	4 (4.3)	5 (4.0)	3 (1.9)	17 (1.5)	18 (0.6)
Pleural effusion	4 (4.3)	4 (3.2)	0 (0.0)	8 (0.7)	48 (1.7)

Data cutoff date for Combination Therapy Safety Sets: 10 Jan 2019.
Data cutoff date for Lenv monotherapy studies: 01 Sep 2016 (ongoing studies), except Study 205 (which had a cutoff date of 15 Mar 2018); earlier for completed studies.
Data cutoff date for the Pembro monotherapy studies: varied by study; range 18 Apr 2014 to 30 Sep 2015.
Adverse event terms were coded using MedDRA version 21.1.
Subject Incidence: Subjects with 2 or more SAEs reported in the same PT were counted only once. Percentages are based on the total number of subjects in the relevant safety set.
Preferred terms are included in this table if they occurred within the % parameter for the primary population of interest for this submission, the Indication Safety Set.
EC = endometrial carcinoma, Lenv = lenvatinib, MedDRA = Medical Dictionary for Regulatory Activities,
Pembro = pembrolizumab, PT = preferred term, SAE = serious adverse event.
Source: EC ISS Table 7.2.1; ADaM dataset: ADSL_EC ISS, ADAE_EC ISS.

The Regulatory Authorities' Assessment:

Our analyses showed that SAEs were more common in patients receiving L+P compared to either monotherapy, as expected. Comparing the incidence of frequent SAEs observed in study 111/KN-146 with the monotherapy studies, higher frequencies of hypertension, pancreatitis, confusional state, encephalopathy, pleural effusion and adrenal insufficiency were observed. Though not combined in the applicant's submission, reviewers pooled PTs in the process described above and in Appendix 17.5, revealing that musculoskeletal pain, hemorrhage, renal impairment, and fatigue were frequent SAEs. Of note, hypertension and hemorrhagic events are known AEs with VEGF inhibitors and are listed in the *Warnings and Precautions* section of the lenvatinib label.

Table 24: Frequent serious adverse events by pooled preferred term for Study111/KN-146

	Lenvatinib + Pembrolizumab	Lenvatinib + Pembrolizumab	Lenvatinib monotherapy Study 204	Pembrolizumab monotherapy KN-158	Pembrolizumab monotherapy KN-028
	Not MSI-H/dMMR EC 2L+	All previously treated EC 2L+		Not (MSI-H/dMMR)	Not (MSI-H/dMMR)

	N=94 n (%)		N=108 n (%)		N=133 n (%)		N=90 n (%)		N=18 n (%)	
	G1-5	G3-4	G1-5	G3-4	G1-5	G3-4	G1-5	G3-4	G1-5	G3-4
All SAEs	50 (53.2)	34 (36.2)	57 (52.8)	38 (35.2)	65 (48.9)	45 (33.8)	39 (43)	18 (20)	8 (44)	3 (17)
Hypertension	8 (8.5)	8 (8.5)	8 (7.4)	8 (7.4)	6 (4.5)	6 (4.5)	0 (0)	0 (0)	0 (0)	0 (0)
Musculoskeletal pain	6 (6.4)	4 (4.3)	6 (5.6)	4 (3.7)	0 (0)	0 (0)	2 (2.2)	2 (2.2)	0 (0)	0 (0)
Abdominal pain	5 (5.3)	5 (5.3)	6 (5.6)	5 (4.6)	7 (5.3)	6 (4.5)	0 (0)	0 (0)	0 (0)	0 (0)
Hemorrhage	4 (4.3)	2 (2.1)	5 (4.6)	3 (2.8)	4 (3.0)	2 (1.5)	0 (0)	0 (0)	1 (6)	1 (6)
Fatigue	4 (4.3)	3 (3.2)	4 (3.7)	3 (2.8)	7 (5.3)	4 (3)	0 (0)	0 (0)	0 (0)	0 (0)
Nausea	4 (4.3)	1 (1.1)	5 (4.6)	1 (0.9)	3 (2.3)	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)
Pleural effusion	4 (4.3)	2 (2.1)	4 (3.7)	2 (1.9)	2 (1.5)	2 (1.5)	1 (1.1)	1 (1.1)	0 (0)	0 (0)
Adrenal insufficiency	3 (3.2)	3 (3.2)	3 (2.8)	3 (2.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Confusional state	3 (3.2)	2 (2.1)	3 (3.2)	2 (1.9)	1 (0.8)	0 (0)	1 (1.1)	1 (1.1)	0 (0)	0 (0)
Colitis	3 (3.2)	3 (3.2)	3 (2.8)	3 (2.8)	2 (1.5)	2 (1.5)	0 (0)	0 (0)	0 (0)	0 (0)
Dyspnea	3 (3.2)	2 (2.1)	3 (2.8)	2 (1.9)	2 (1.5)	2 (1.5)	1 (1.1)	1 (1.1)	0 (0)	0 (0)
Pyrexia	3 (3.2)	0 (0)	3 (2.8)	0 (0)	1 (0.8)	0 (0)	2 (2.2)	2 (2.2)	1 (6)	1 (6)
Encephalopathy	3 (3.2)	3 (3.2)	3 (2.8)	3 (2.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Pancreatitis	3 (3.2)	2 (2.1)	3 (2.8)	2 (1.9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Renal impairment	3 (3.2)	3 (3.2)	4 (3.7)	4 (3.7)	7 (5.3)	4 (3)	1 (1.1)	1 (1.1)	0 (0)	0 (0)
Lenvatinib + pembrolizumab analysis performed with 90-day safety update dataset. Pancreatitis and renal impairment were the 2 AEs where the % changed from 2% to 3% based on the 90-day safety update.										
Source: Study 111 – adsl.xpt, adae.xpt; Study 204 - adsl.xpt, adae.xpt; KN-158 - adsl.xpt, adae.xpt; KN-028 - adsl.xpt, adae.xpt Study 111 90-day safety update - adsl.xpt, adae.xpt Information in the label for lenvatinib and pembrolizumab does not incorporate the information from the 90-day safety update as no significant change to the safety profile of lenvatinib plus pembrolizumab compared with that previously reported in the EC submission was observed.										

Dropouts and/or Discontinuations Due to Adverse Effects

The Applicant's Position:

Discontinuation of Lenvatinib and Pembrolizumab: In the Indication Safety Set, the overall incidence of TEAEs leading to simultaneous discontinuation of both lenvatinib and pembrolizumab was 16.0%. There was a low incidence rate of individual events and no pattern was identified. TEAEs of muscular weakness and pancreatitis led to simultaneous discontinuation of both study drugs in 2 (2.1%) subjects and all other TEAEs that led to simultaneous discontinuation of both study drugs were each reported by 1 subject (Table 25).

Table 25
Treatment-Emergent Adverse Events Leading to Simultaneous Treatment Discontinuation of Both Lenvatinib and Pembrolizumab – Combination Therapy Safety Sets

MedDRA Preferred Term	Lenv 20 mg + Pembro 200 mg		
	Indication (N=94) n (%)	All EC (N=124) n (%)	Non-EC (N=159) n (%)
Subjects With Any TEAEs Leading to Treatment Discontinuation of Lenv and Pembro	*15 (16.0)*	*22 (17.7)*	*32 (20.1)*
Muscular weakness	2 (2.1)	2 (1.6)	0 (0.0)
Pancreatitis	2 (2.1)	2 (1.6)	0 (0.0)
Abdominal pain	1 (1.1)	1 (0.8)	0 (0.0)
Adrenal insufficiency	1 (1.1)	1 (0.8)	0 (0.0)
Colitis ischaemic	1 (1.1)	1 (0.8)	0 (0.0)
Diverticulitis	1 (1.1)	1 (0.8)	0 (0.0)
Encephalopathy	1 (1.1)	1 (0.8)	0 (0.0)
Escherichia sepsis	1 (1.1)	1 (0.8)	0 (0.0)
Female genital tract fistula	1 (1.1)	1 (0.8)	0 (0.0)
Gastrointestinal perforation	1 (1.1)	1 (0.8)	0 (0.0)
General physical health deterioration	1 (1.1)	2 (1.6)	0 (0.0)
Haemorrhage intracranial	1 (1.1)	1 (0.8)	0 (0.0)
Intraventricular haemorrhage	1 (1.1)	1 (0.8)	0 (0.0)
Posterior reversible encephalopathy syndrome	1 (1.1)	1 (0.8)	0 (0.0)

Data cutoff date for Combination Therapy Safety Sets: 10 Jan 2019.
Rows containing only zeroes have been omitted from this in-text table.
Display is in decreasing order of TEAE rate of PTs.
Adverse event terms were coded using MedDRA version 21.1.
Subject Incidence: Subjects with 2 or more TEAEs reported in the same PT were counted only once. Percentages are based on the total number of subjects in the relevant safety set.
Preferred terms are included in this table if they occurred within the % parameter for the primary population of interest for this submission, the Indication Safety Set.
EC = endometrial carcinoma, Lenv = lenvatinib, MedDRA = Medical Dictionary for Regulatory Activities,
Pembro = pembrolizumab, PT = preferred term, TEAE = treatment-emergent adverse event.
Source: EC ISS Table 5.6.3; ADaM Dataset:. ADSL_EC ISS, ADAE_EC ISS

Discontinuation of Lenvatinib: The overall incidence of TEAEs leading to discontinuation of lenvatinib (only or with pembrolizumab) in the Indication Safety Set was 22.3%. The TEAEs of muscular weakness and pancreatitis each led to discontinuation of lenvatinib in 2 (2.1%) subjects, respectively. All other TEAEs leading to lenvatinib discontinuation were each reported by 1 (1.1%) subject. There was no common etiology identified for the events leading to discontinuation (EC ISS Table 5.6.1; ADaM dataset: ADSL_EC ISS, ADAE_EC ISS).

***Discontinuation of Pembrolizumab*:** The incidence rate of TEAEs leading to discontinuation of pembrolizumab (only or with lenvatinib) was higher in the Indication Safety Set (20.2%) than in the Pembrolizumab Monotherapy Safety Set (11.9%). Those TEAEs that led to discontinuation of pembrolizumab but are not a known risk of pembrolizumab include ischemic colitis, muscular weakness, diverticulitis, encephalopathy, GI perforation, and posterior reversible encephalopathy syndrome (PRES). Most TEAEs were single events and there was no common etiology identified for the events leading to discontinuation (EC ISS Table 5.6.2; ADaM Dataset: ADSL_EC ISS, ADAE_EC ISS).

The Regulatory Authorities' Assessment:

Our analyses of study drug discontinuations in the L+P group are consistent with the applicant's findings presented above. We also analyzed AEs leading to discontinuation of L+P, L and P alone in study 111/KN-146 (Table 26: Frequent adverse events leading to discontinuation of both lenvatinib and pembrolizumab in Study111/KN-146**) and compared the trends to discontinuation frequency observed in monotherapy studies (Table 27**: Frequent adverse events leading to discontinuation of lenvatinib in Study111/KN-146 **and Table 28**: Frequent adverse events leading to discontinuation of pembrolizumab in Study111/KN-146**). As shown in Table 26**: Frequent adverse events leading to discontinuation of both lenvatinib and pembrolizumab in Study111/KN-146**, we observed a higher incidence of discontinuation of L+P in the indicated population (patients with not MSI-H/dMMR endometrial cancer treated in the second line or later), and the rates of AEs leading to discontinuation were similar to the larger set of patients, women with endometrial cancer treated in the second line or later (n=108).**

We also calculated the time to drug discontinuation (regardless of reason for discontinuation) by using the time period between date of first exposure and date of first AE leading to modification for study 111, and compared with lenvatinib and pembrolizumab discontinuation in study 204 and KN-158.

- **For lenvatinib: In study 111 (n=94), a total of 23 patients experienced lenvatinib discontinuation (only or with pembrolizumab), with median time to discontinuation of 2.5 (range: 0.07 – 16.8) months. In study 204 (n=133), 38 patients experienced lenvatinib discontinuation, with median time to discontinuation of 1.2 (range: 0.2 – 9.7) months.**

- **For pembrolizumab: In study 111 (n=94), a total of 20 patients experienced pembrolizumab discontinuation (only or with lenvatinib), with median time to discontinuation of 2.4 (range: 0.07 – 22.4) months. In KN-158 (n=90), 20 patients experienced pembrolizumab discontinuation, with median time to discontinuation of 2 (range: 0.5 – 15.1) months.**

Median time to discontinuation was longer for L in study 111 and the number of discontinuations for L and P in the combination study were comparable to the monotherapy studies.

Table 26: Frequent adverse events leading to discontinuation of both lenvatinib and pembrolizumab in Study111/KN-146

	Lenvatinib + Pembrolizumab	Lenvatinib + Pembrolizumab
	Not MSI-H/dMMR EC 2L+	All previously treated EC 2L+

	N=94; n (%)		N=108; n (%)	
	G1-5	G3-4	G1-5	G3-4
Patients with at least 1 TEAE leading to discontinuation of lenvatinib **and** pembrolizumab	**16 (17)**	**9 (9.6)**	**19 (17.6)**	**11 (10.2)**
Pancreatitis	2 (2.1)	1 (1.1)	2 (1.9)	1 (0.9)
Muscular weakness	2 (2.1)	1 (1.1)	2 (1.9)	1 (0.9)
Adrenal insufficiency	1 (1.1)	0 (0)	1 (0.9)	0 (0)
Colitis ischaemic	1 (1.1)	1 (1.1)	1 (0.9)	1 (0.9)
Diverticulitis	1 (1.1)	0 (0)	1 (0.9)	0 (0)
Encephalopathy	1 (1.1)	1 (1.1)	1 (0.9)	1 (0.9)
Escherichia sepsis	1 (1.1)	1 (1.1)	1 (0.9)	1 (0.9)
Female genital tract fistula	1 (1.1)	0 (0)	1 (0.9)	0 (0)
Gastrointestinal perforation	1 (1.1)	1 (1.1)	1 (0.9)	1 (0.9)
General physical health deterioration	1 (1.1)	1 (1.1)	1 (0.9)	1 (0.9)
Haemorrhage intracranial	1 (1.1)	0 (0)	1 (0.9)	0 (0)
Intraventricular haemorrhage	1 (1.1)	1 (1.1)	1 (0.9)	1 (0.9)
Malignant neoplasm progression	1 (1.1)	0 (0)	1 (0.9)	0 (0)
Posterior reversible encephalopathy syndrome (PRES)	1 (1.1)	1 (1.1)	1 (0.9)	1 (0.9)
Abdominal pain	1 (1.1)	1 (1.1)	1 (0.9)	1 (0.9)
Elevated LFTs	1 (1.1)	1 (1.1)	0 (0)	0 (0)
Autoimmune nephritis	0 (0)	0 (0)	1 (0.9)	1 (0.9)
Intestinal obstruction	0 (0)	0 (0)	1 (0.9)	0 (0)
Gastric perforation	0 (0)	0 (0)	1 (0.9)	1 (0.9)
Intraventricular hemorrhage and PRES occurred in the same patient leading to withdrawal of both drugs.				
Source: Study 111 – adsl.xpt, adae.xpt; Study 111 90-day safety update - adsl.xpt, adae.xpt				

Table 27: Frequent adverse events leading to discontinuation of lenvatinib in Study111/KN-146

	Lenvatinib + Pembrolizumab Not MSI-H/dMMR EC 2L+		Lenvatinib + Pembrolizumab All previously treated EC 2L+	
	N=94; n (%)		**N=108; n (%)**	
	G1-5	G3-4	G1-5	G3-4
Patients with at least 1 TEAE leading to discontinuation of lenvatinib	**6 (6.4)**	**2 (2.1)**	**7 (6.5)**	**3 (2.8)**
GI fistula	1 (1.1)	0 (0)	1 (0.9)	0 (0)
Acute kidney injury	1 (1.1)	1 (1.1)	1 (0.9)	1 (0.9)
Pneumoperitoneum	1 (1.1)	0 (0)	1 (0.9)	0 (0)
Rectal ulcer	1 (1.1)	1 (1.1)	1 (0.9)	1 (0.9)
Fatigue	1 (1.1)	0 (0)	1 (0.9)	0 (0)
Diarrhea	1 (1.1)	0 (0)	1 (0.9)	0 (0)
Hypertension	0 (0)	0 (0)	1 (0.9)	1 (0.9)

Pancreatitis	0 (0)	0 (0)	1 (0.9)	0 (0)
Source: Study 111 – adsl.xpt, adae.xpt; Study 111 90-day safety update - adsl.xpt, adae.xpt				

Table 28: Frequent adverse events leading to discontinuation of pembrolizumab in Study111/KN-146

	Lenvatinib + Pembrolizumab		Lenvatinib + Pembrolizumab	
	Not MSI-H/dMMR EC 2L+		All previously treated EC 2L+	
	N=94; n (%)		**N=108; n (%)**	
	G1-5	G3-4	G1-5	G3-4
Patients with at least 1 TEAE leading to discontinuation of pembrolizumab	**4 (4.3)**	**3 (3.2)**	**4 (3.7)**	**3 (2.8)**
Elevated LFTs	2 (2.1)	1 (1.1)	2 (1.9)	1 (0.9)
Colitis ischaemic	1 (1.1)	1 (1.1)	1 (0.9)	1 (0.9)
Hypopituitarism	1 (1.1)	1 (1.1)	1 (0.9)	1 (0.9)
Adrenal insufficiency	1 (1.1)	1 (1.1)	1 (0.9)	1 (0.9)
Adrenal insufficiency and hypopituitarism occurred in the same patient leading to pembrolizumab withdrawal. Source: Study 111 – adsl.xpt, adae.xpt; Study 111 90-day safety update - adsl.xpt, adae.xpt				

Dose Interruption/Reduction Due to Adverse Effect

The Applicant's Position:

Lenvatinib Dose Modification: In the Indication Safety Set, 88.3% of subjects had TEAEs leading to a lenvatinib dose modification (dose interruption or reduction), 75.5% had TEAEs leading to a dose interruption, and 67.0% had TEAEs leading to a dose reduction. In the Indication Safety Set, the TEAEs that most frequently led to a lenvatinib dose modification (≥10% of subjects), by decreasing incidence, were hypertension, fatigue, diarrhea, nausea, palmar-plantar erythrodysesthesia (PPE) syndrome, vomiting, and decreased appetite; these TEAEs are consistent with the lenvatinib safety profile. The incidence of TEAEs leading to a dose modification of lenvatinib was comparable in the Indication and Lenvatinib Monotherapy Safety Sets (Table 29; ADaM dataset: ADSL_EC ISS, ADAE_EC ISS).

Pembrolizumab Dose Interruption: In the Indication Safety Set, the overall incidence of TEAEs leading to a dose interruption of pembrolizumab was 48.9%. The TEAEs that most frequently led to a pembrolizumab dose interruption (≥5% of subjects) in the Indication Safety Set, by decreasing incidence, were fatigue, diarrhea, asthenia, and decreased appetite. The incidence of TEAEs leading to a dose interruption of pembrolizumab was higher in the Indication Safety Set than in the Pembrolizumab Monotherapy Safety Set (22.2%) (; ADaM dataset: ADSL_EC ISS, ADAE_EC ISS).

Table 29
Treatment-Emergent Adverse Events Leading to Dose Modification of Lenvatinib by System Organ Class and Preferred Term - ISS Safety Analysis Set

	Lenv 20 mg + Pembro 200 mg			
System Organ Class Preferred Term	**Indication (N=94) n (%)**	**All EC (N=124) n (%)**	**Non-EC (N=159) n (%)**	**Lenv Monotx 24mg (N=1119) n (%)**
Subjects with any TEAEs Leading to Dose Modification of Lenvatinib	83 (88.3)	106 (85.5)	129 (81.1)	835 (74.6)
Blood and lymphatic system disorders	4 (4.3)	4 (3.2)	4 (2.5)	51 (4.6)
Thrombocytopenia	3 (3.2)	3 (2.4)	1 (0.6)	28 (2.5)
Neutropenia	1 (1.1)	1 (0.8)	1 (0.6)	9 (0.8)
Anaemia	0 (0.0)	0 (0.0)	1 (0.6)	10 (0.9)
Leukocytosis	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Leukopenia	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.4)
Lymphopenia	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.4)
Polycythaemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Splenic haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Splenic infarction	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Spontaneous haematoma	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Cardiac disorders	2 (2.1)	3 (2.4)	11 (6.9)	29 (2.6)
Angina pectoris	1 (1.1)	1 (0.8)	1 (0.6)	2 (0.2)
Cardiac failure	1 (1.1)	1 (0.8)	0 (0.0)	4 (0.4)
Palpitations	1 (1.1)	1 (0.8)	1 (0.6)	1 (0.1)
Acute coronary syndrome	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Acute myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Aortic valve stenosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Atrial fibrillation	0 (0.0)	1 (0.8)	1 (0.6)	5 (0.4)
Atrial flutter	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.3)
Bradycardia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Cardiac failure chronic	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Cardiac failure congestive	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Coronary artery disease	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Cyanosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Intracardiac thrombus	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Left ventricular dysfunction	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Left ventricular failure	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Myocardial infarction	0 (0.0)	0 (0.0)	2 (1.3)	2 (0.2)
Myocardial ischaemia	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Postural orthostatic tachycardia syndrome	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Sinus tachycardia	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.3)
Supraventricular extrasystoles	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Supraventricular tachycardia	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Tachycardia	0 (0.0)	0 (0.0)	1 (0.6)	4 (0.4)
Ventricular hypokinesia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Ear and labyrinth disorders	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.4)
Deafness transitory	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
External ear inflammation	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Vertigo	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.3)
Endocrine disorders	5 (5.3)	6 (4.8)	3 (1.9)	15 (1.3)
Adrenal insufficiency	3 (3.2)	3 (2.4)	1 (0.6)	0 (0.0)
Hypothyroidism	2 (2.1)	3 (2.4)	2 (1.3)	13 (1.2)
Hypopituitarism	1 (1.1)	1 (0.8)	0 (0.0)	0 (0.0)
Hyperthyroidism	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.4)

Table 29
Treatment-Emergent Adverse Events Leading to Dose Modification of Lenvatinib by System Organ Class and Preferred Term - ISS Safety Analysis Set

	Lenv 20 mg + Pembro 200 mg			
System Organ Class Preferred Term	Indication (N=94) n (%)	All EC (N=124) n (%)	Non-EC (N=159) n (%)	Lenv Monotx 24mg (N=1119) n (%)
Inappropriate antidiuretic hormone secretion	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Eye disorders	2 (2.1)	2 (1.6)	3 (1.9)	15 (1.3)
Retinal vein occlusion	1 (1.1)	1 (0.8)	0 (0.0)	1 (0.1)
Ulcerative keratitis	1 (1.1)	1 (0.8)	0 (0.0)	0 (0.0)
Cataract	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.3)
Diplopia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Dry eye	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Eye disorder	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Eye pain	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.3)
Eyelid function disorder	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Eyelid oedema	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Eyelid ptosis	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Lacrimation increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Retinal detachment	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Retinal tear	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Retinal vein thrombosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Vision blurred	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Gastrointestinal disorders	44 (46.8)	62 (50.0)	60 (37.7)	374 (33.4)
Diarrhoea	17 (18.1)	26 (21.0)	31 (19.5)	175 (15.6)
Nausea	12 (12.8)	15 (12.1)	14 (8.8)	103 (9.2)
Vomiting	12 (12.8)	14 (11.3)	9 (5.7)	77 (6.9)
Stomatitis	7 (7.4)	9 (7.3)	11 (6.9)	59 (5.3)
Abdominal pain	4 (4.3)	5 (4.0)	6 (3.8)	52 (4.6)
Abdominal pain upper	2 (2.1)	3 (2.4)	2 (1.3)	34 (3.0)
Dysphagia	2 (2.1)	2 (1.6)	2 (1.3)	11 (1.0)
Oral pain	2 (2.1)	2 (1.6)	4 (2.5)	10 (0.9)
Abdominal discomfort	1 (1.1)	1 (0.8)	0 (0.0)	1 (0.1)
Abdominal distension	1 (1.1)	2 (1.6)	1 (0.6)	3 (0.3)
Colitis	1 (1.1)	3 (2.4)	5 (3.1)	4 (0.4)
Colitis ischaemic	1 (1.1)	1 (0.8)	0 (0.0)	0 (0.0)
Constipation	1 (1.1)	1 (0.8)	2 (1.3)	12 (1.1)
Dental caries	1 (1.1)	1 (0.8)	0 (0.0)	5 (0.4)
Dry mouth	1 (1.1)	2 (1.6)	0 (0.0)	3 (0.3)
Gastrointestinal haemorrhage	1 (1.1)	2 (1.6)	0 (0.0)	1 (0.1)
Odynophagia	1 (1.1)	1 (0.8)	0 (0.0)	3 (0.3)
Oral dysaesthesia	1 (1.1)	1 (0.8)	1 (0.6)	5 (0.4)
Pancreatitis	1 (1.1)	3 (2.4)	2 (1.3)	6 (0.5)
Pancreatitis acute	1 (1.1)	1 (0.8)	0 (0.0)	0 (0.0)
Small intestinal obstruction	1 (1.1)	1 (0.8)	0 (0.0)	2 (0.2)
Abdominal pain lower	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.3)
Anal fistula	0 (0.0)	0 (0.0)	1 (0.6)	4 (0.4)
Anal incontinence	0 (0.0)	0 (0.0)	1 (0.6)	2 (0.2)
Aphthous ulcer	0 (0.0)	1 (0.8)	0 (0.0)	2 (0.2)
Apical granuloma	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Cheilitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Diverticular perforation	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Dyspepsia	0 (0.0)	0 (0.0)	1 (0.6)	9 (0.8)

Table 29
Treatment-Emergent Adverse Events Leading to Dose Modification of Lenvatinib by System Organ Class and Preferred Term - ISS Safety Analysis Set

	Lenv 20 mg + Pembro 200 mg			
System Organ Class Preferred Term	Indication (N=94) n (%)	All EC (N=124) n (%)	Non-EC (N=159) n (%)	Lenv Monotx 24mg (N=1119) n (%)
Enteritis	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Enterocutaneous fistula	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Enterovesical fistula	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Epigastric discomfort	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Flatulence	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Gastric haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Gastric ulcer	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Gastritis	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.4)
Gastroduodenal ulcer	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Gastrointestinal inflammation	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Gastrointestinal pain	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.3)
Gastrooesophageal reflux disease	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.3)
Gingival bleeding	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Gingival pain	0 (0.0)	0 (0.0)	1 (0.6)	2 (0.2)
Glossitis	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.3)
Glossodynia	0 (0.0)	0 (0.0)	0 (0.0)	8 (0.7)
Haematochezia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Haemorrhoidal haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Haemorrhoids	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.4)
Ileus	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Impaired gastric emptying	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Inguinal hernia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Intestinal obstruction	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Intestinal perforation	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Mouth ulceration	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Oesophageal stenosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Oesophagitis	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Oral discomfort	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Pancreatic pseudocyst	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Paraesthesia oral	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Periodontal disease	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Pneumatosis intestinalis	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Proctalgia	0 (0.0)	0 (0.0)	1 (0.6)	2 (0.2)
Rectal haemorrhage	0 (0.0)	0 (0.0)	1 (0.6)	3 (0.3)
Saliva altered	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Salivary hypersecretion	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Subileus	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Swollen tongue	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Tongue oedema	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Tongue ulceration	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Tooth disorder	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Tooth loss	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Toothache	0 (0.0)	0 (0.0)	2 (1.3)	3 (0.3)
General disorders and administration site conditions	32 (34.0)	40 (32.3)	38 (23.9)	267 (23.9)
Fatigue	23 (24.5)	28 (22.6)	30 (18.9)	150 (13.4)
Asthenia	7 (7.4)	9 (7.3)	2 (1.3)	72 (6.4)

Table 29
Treatment-Emergent Adverse Events Leading to Dose Modification of Lenvatinib by System Organ Class and Preferred Term - ISS Safety Analysis Set

	Lenv 20 mg + Pembro 200 mg			
System Organ Class Preferred Term	Indication (N=94) n (%)	All EC (N=124) n (%)	Non-EC (N=159) n (%)	Lenv Monotx 24mg (N=1119) n (%)
Oedema peripheral	3 (3.2)	3 (2.4)	2 (1.3)	21 (1.9)
Gait disturbance	1 (1.1)	1 (0.8)	1 (0.6)	3 (0.3)
Pyrexia	1 (1.1)	1 (0.8)	1 (0.6)	10 (0.9)
Chest discomfort	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Discomfort	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Early satiety	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Face oedema	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.3)
General physical health deterioration	0 (0.0)	0 (0.0)	0 (0.0)	6 (0.5)
Generalised oedema	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Hyperpyrexia	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Impaired healing	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Influenza like illness	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Loss of control of legs	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Malaise	0 (0.0)	0 (0.0)	3 (1.9)	22 (2.0)
Mucosal inflammation	0 (0.0)	0 (0.0)	0 (0.0)	6 (0.5)
Non-cardiac chest pain	0 (0.0)	1 (0.8)	1 (0.6)	0 (0.0)
Pain	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Performance status decreased	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.3)
Peripheral swelling	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Swelling	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Hepatobiliary disorders	1 (1.1)	2 (1.6)	4 (2.5)	35 (3.1)
Cholecystitis acute	1 (1.1)	1 (0.8)	1 (0.6)	6 (0.5)
Bile duct stone	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Biliary dilatation	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Cholecystitis	0 (0.0)	0 (0.0)	2 (1.3)	11 (1.0)
Cholecystitis chronic	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Cholelithiasis	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Cholestatic liver injury	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Drug-induced liver injury	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Gallbladder mucocoele	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Gallbladder obstruction	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Hepatic function abnormal	0 (0.0)	0 (0.0)	0 (0.0)	6 (0.5)
Hepatitis	0 (0.0)	1 (0.8)	1 (0.6)	0 (0.0)
Hepatocellular injury	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Hyperbilirubinaemia	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Liver injury	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Immune system disorders	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.1)
Contrast media allergy	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.1)
Infections and infestations	9 (9.6)	12 (9.7)	25 (15.7)	144 (12.9)
Urinary tract infection	2 (2.1)	2 (1.6)	2 (1.3)	9 (0.8)
Appendicitis	1 (1.1)	1 (0.8)	0 (0.0)	6 (0.5)
Bronchitis	1 (1.1)	1 (0.8)	0 (0.0)	3 (0.3)
Clostridium difficile infection	1 (1.1)	1 (0.8)	2 (1.3)	0 (0.0)
Diverticulitis	1 (1.1)	1 (0.8)	1 (0.6)	5 (0.4)
Fungal infection	1 (1.1)	1 (0.8)	0 (0.0)	0 (0.0)
Influenza	1 (1.1)	1 (0.8)	0 (0.0)	4 (0.4)
Oral candidiasis	1 (1.1)	1 (0.8)	1 (0.6)	2 (0.2)

Table 29
Treatment-Emergent Adverse Events Leading to Dose Modification of Lenvatinib by System Organ Class and Preferred Term - ISS Safety Analysis Set

	Lenv 20 mg + Pembro 200 mg			
System Organ Class Preferred Term	Indication (N=94) n (%)	All EC (N=124) n (%)	Non-EC (N=159) n (%)	Lenv Monotx 24mg (N=1119) n (%)
Pelvic abscess	1 (1.1)	1 (0.8)	0 (0.0)	0 (0.0)
Pneumonia	1 (1.1)	1 (0.8)	3 (1.9)	27 (2.4)
Respiratory tract infection	1 (1.1)	1 (0.8)	0 (0.0)	5 (0.4)
Abdominal infection	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Abscess intestinal	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Abscess limb	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Abscess rupture	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Abscess soft tissue	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Acute sinusitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Anal abscess	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Anorectal infection	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Appendicitis perforated	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Bacteraemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Biliary tract infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Blister infected	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Candida infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Cellulitis	0 (0.0)	0 (0.0)	1 (0.6)	2 (0.2)
Cholecystitis infective	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.1)
Chronic sinusitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Colonic abscess	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Cystitis	0 (0.0)	0 (0.0)	2 (1.3)	5 (0.4)
Dengue fever	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Device related infection	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Epididymitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Erysipelas	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Escherichia urinary tract infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Folliculitis	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Fungal skin infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Gastroenteritis	0 (0.0)	2 (1.6)	0 (0.0)	8 (0.7)
Gastroenteritis viral	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.3)
Gastrointestinal infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Gastrointestinal viral infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Gingival abscess	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Gingivitis	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Herpes simplex	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Herpes virus infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Herpes zoster	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.3)
Implant site infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Intervertebral discitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Labyrinthitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Laryngitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Localised infection	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Lower respiratory tract infection	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.4)
Lung infection	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.3)
Lung infection pseudomonal	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Meningitis viral	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Nasopharyngitis	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.4)

Table 29
Treatment-Emergent Adverse Events Leading to Dose Modification of Lenvatinib by System Organ Class and Preferred Term - ISS Safety Analysis Set

	Lenv 20 mg + Pembro 200 mg			
System Organ Class Preferred Term	Indication (N=94) n (%)	All EC (N=124) n (%)	Non-EC (N=159) n (%)	Lenv Monotx 24mg (N=1119) n (%)
Oral infection	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Osteomyelitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Otitis media	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Paronychia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Parotitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Pericoronitis	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Perineal abscess	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Periodontitis	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.3)
Perirectal abscess	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Pharyngitis	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Pneumonia necrotising	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Pneumonia staphylococcal	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Pseudomonas infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Psoas abscess	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Pulpitis dental	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Pyelonephritis	0 (0.0)	1 (0.8)	1 (0.6)	1 (0.1)
Rotavirus infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Sepsis	0 (0.0)	0 (0.0)	1 (0.6)	5 (0.4)
Sialoadenitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Sinusitis	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Skin infection	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Staphylococcal sepsis	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Subcutaneous abscess	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Tooth abscess	0 (0.0)	0 (0.0)	2 (1.3)	6 (0.5)
Tooth infection	0 (0.0)	0 (0.0)	1 (0.6)	4 (0.4)
Tracheitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Upper respiratory tract infection	0 (0.0)	0 (0.0)	7 (4.4)	8 (0.7)
Urosepsis	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Wound infection	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Injury, poisoning and procedural complications	3 (3.2)	4 (3.2)	7 (4.4)	22 (2.0)
Tooth fracture	1 (1.1)	1 (0.8)	0 (0.0)	0 (0.0)
Wound	1 (1.1)	1 (0.8)	0 (0.0)	1 (0.1)
Wound complication	1 (1.1)	1 (0.8)	0 (0.0)	0 (0.0)
Accidental overdose	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Brain contusion	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Craniocerebral injury	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Eschar	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Face injury	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Facial bones fracture	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Fall	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Femur fracture	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Hypobarism	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Incision site complication	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Joint dislocation	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Joint injury	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Pancreatic injury	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Post procedural haemorrhage	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)

Table 29
Treatment-Emergent Adverse Events Leading to Dose Modification of Lenvatinib by System Organ Class and Preferred Term - ISS Safety Analysis Set

	Lenv 20 mg + Pembro 200 mg			
System Organ Class Preferred Term	**Indication (N=94) n (%)**	**All EC (N=124) n (%)**	**Non-EC (N=159) n (%)**	**Lenv Monotx 24mg (N=1119) n (%)**
Postoperative wound complication	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Rib fracture	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Skin abrasion	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.3)
Spinal compression fracture	0 (0.0)	0 (0.0)	3 (1.9)	1 (0.1)
Stoma site erythema	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Sunburn	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Thermal burn	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Vascular pseudoaneurysm	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Wound dehiscence	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.1)
Wound necrosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Wound secretion	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Investigations	23 (24.5)	27 (21.8)	23 (14.5)	221 (19.7)
Weight decreased	6 (6.4)	7 (5.6)	9 (5.7)	105 (9.4)
Lipase increased	5 (5.3)	5 (4.0)	4 (2.5)	16 (1.4)
Alanine aminotransferase increased	3 (3.2)	4 (3.2)	6 (3.8)	19 (1.7)
Aspartate aminotransferase increased	3 (3.2)	4 (3.2)	4 (2.5)	14 (1.3)
Amylase increased	2 (2.1)	2 (1.6)	2 (1.3)	10 (0.9)
Blood alkaline phosphatase increased	2 (2.1)	3 (2.4)	3 (1.9)	5 (0.4)
Blood bilirubin increased	2 (2.1)	2 (1.6)	3 (1.9)	5 (0.4)
Blood creatinine increased	2 (2.1)	2 (1.6)	1 (0.6)	13 (1.2)
Ejection fraction decreased	2 (2.1)	3 (2.4)	3 (1.9)	13 (1.2)
Electrocardiogram QT prolonged	2 (2.1)	2 (1.6)	1 (0.6)	13 (1.2)
Electrocardiogram T wave abnormal	1 (1.1)	1 (0.8)	0 (0.0)	0 (0.0)
Electrocardiogram T wave inversion	1 (1.1)	1 (0.8)	0 (0.0)	1 (0.1)
Neutrophil count decreased	1 (1.1)	1 (0.8)	0 (0.0)	5 (0.4)
Blood albumin decreased	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Blood alkaline phosphatase abnormal	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Blood chloride increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Blood cholesterol increased	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Blood creatine phosphokinase	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Blood creatine phosphokinase increased	0 (0.0)	0 (0.0)	0 (0.0)	7 (0.6)
Blood glucose increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Blood magnesium increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Blood pressure immeasurable	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Blood pressure increased	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.4)
Blood thromboplastin increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Blood thyroid stimulating hormone increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Blood urea increased	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Blood uric acid increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Eastern Cooperative Oncology Group performance status worsened	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Electrocardiogram ST-T segment abnormal	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Electrocardiogram T wave amplitude decreased	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Electrocardiogram repolarisation abnormality	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Gamma-glutamyltransferase increased	0 (0.0)	0 (0.0)	0 (0.0)	6 (0.5)
Glomerular filtration rate decreased	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)

Table 29
Treatment-Emergent Adverse Events Leading to Dose Modification of Lenvatinib by System Organ Class and Preferred Term - ISS Safety Analysis Set

	Lenv 20 mg + Pembro 200 mg			
System Organ Class Preferred Term	Indication (N=94) n (%)	All EC (N=124) n (%)	Non-EC (N=159) n (%)	Lenv Monotx 24mg (N=1119) n (%)
Haematocrit decreased	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Haematocrit increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Hepatic enzyme increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
International normalised ratio increased	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.3)
Liver function test increased	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Lymphocyte count decreased	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Mean cell haemoglobin decreased	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Occult blood positive	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Platelet count decreased	0 (0.0)	0 (0.0)	1 (0.6)	16 (1.4)
Protein urine present	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.4)
Red blood cell count decreased	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Staphylococcus test positive	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Transaminases increased	0 (0.0)	0 (0.0)	1 (0.6)	2 (0.2)
Troponin increased	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Wall motion score index abnormal	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
White blood cell count decreased	0 (0.0)	0 (0.0)	0 (0.0)	6 (0.5)
Metabolism and nutrition disorders	19 (20.2)	27 (21.8)	40 (25.2)	162 (14.5)
Decreased appetite	11 (11.7)	13 (10.5)	24 (15.1)	112 (10.0)
Dehydration	2 (2.1)	2 (1.6)	13 (8.2)	31 (2.8)
Hypocalcaemia	2 (2.1)	2 (1.6)	0 (0.0)	9 (0.8)
Hypomagnesaemia	2 (2.1)	4 (3.2)	2 (1.3)	2 (0.2)
Hyponatraemia	2 (2.1)	4 (3.2)	5 (3.1)	9 (0.8)
Failure to thrive	1 (1.1)	1 (0.8)	1 (0.6)	2 (0.2)
Hypokalaemia	1 (1.1)	3 (2.4)	2 (1.3)	3 (0.3)
Food intolerance	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Gout	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Hypercalcaemia	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Hypercalcitoninaemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Hypercholesterolaemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Hyperglycaemia	0 (0.0)	0 (0.0)	1 (0.6)	2 (0.2)
Hyperkalaemia	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.1)
Hyperlipasaemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Hypertriglyceridaemia	0 (0.0)	0 (0.0)	1 (0.6)	3 (0.3)
Hypoalbuminaemia	0 (0.0)	1 (0.8)	0 (0.0)	4 (0.4)
Hypophagia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Hypophosphataemia	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Hypoproteinaemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Hypovolaemia	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.1)
Increased appetite	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Lactic acidosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Malnutrition	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Musculoskeletal and connective tissue disorders	12 (12.8)	15 (12.1)	21 (13.2)	105 (9.4)
Arthralgia	7 (7.4)	8 (6.5)	10 (6.3)	33 (2.9)
Back pain	2 (2.1)	2 (1.6)	2 (1.3)	9 (0.8)
Muscular weakness	2 (2.1)	2 (1.6)	3 (1.9)	10 (0.9)
Musculoskeletal pain	1 (1.1)	1 (0.8)	1 (0.6)	5 (0.4)
Myalgia	1 (1.1)	2 (1.6)	4 (2.5)	19 (1.7)

Table 29
Treatment-Emergent Adverse Events Leading to Dose Modification of Lenvatinib by System Organ Class and Preferred Term - ISS Safety Analysis Set

	Lenv 20 mg + Pembro 200 mg			
System Organ Class Preferred Term	Indication (N=94) n (%)	All EC (N=124) n (%)	Non-EC (N=159) n (%)	Lenv Monotx 24mg (N=1119) n (%)
Pain in extremity	1 (1.1)	2 (1.6)	1 (0.6)	14 (1.3)
Bone pain	0 (0.0)	0 (0.0)	0 (0.0)	6 (0.5)
Fistula discharge	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Flank pain	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.1)
Foot deformity	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Joint range of motion decreased	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Joint swelling	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.1)
Mobility decreased	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Muscle contracture	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Muscle spasms	0 (0.0)	0 (0.0)	1 (0.6)	3 (0.3)
Muscle tightness	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Musculoskeletal stiffness	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Myopathy	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.1)
Myositis	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Neck mass	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Neck pain	0 (0.0)	0 (0.0)	1 (0.6)	3 (0.3)
Osteitis	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Osteoarthritis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Osteolysis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Osteonecrosis of jaw	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Pain in jaw	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.1)
Pathological fracture	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Periarthritis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Plantar fasciitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Polyarthritis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Rhabdomyolysis	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0)	0 (0.0)	1 (0.6)	7 (0.6)
Cancer pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Infected neoplasm	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Malignant pleural effusion	0 (0.0)	0 (0.0)	1 (0.6)	3 (0.3)
Metastases to meninges	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Squamous cell carcinoma of skin	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Tumour necrosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Nervous system disorders	16 (17.0)	19 (15.3)	7 (4.4)	116 (10.4)
Headache	5 (5.3)	6 (4.8)	2 (1.3)	37 (3.3)
Syncope	3 (3.2)	3 (2.4)	0 (0.0)	7 (0.6)
Haemorrhage intracranial	2 (2.1)	2 (1.6)	0 (0.0)	2 (0.2)
Seizure	2 (2.1)	2 (1.6)	1 (0.6)	9 (0.8)
Dysgeusia	1 (1.1)	2 (1.6)	0 (0.0)	10 (0.9)
Encephalopathy	1 (1.1)	1 (0.8)	0 (0.0)	1 (0.1)
Hypertensive encephalopathy	1 (1.1)	1 (0.8)	0 (0.0)	0 (0.0)
Peripheral sensory neuropathy	1 (1.1)	1 (0.8)	0 (0.0)	2 (0.2)
Transient ischaemic attack	1 (1.1)	1 (0.8)	0 (0.0)	4 (0.4)
Tremor	1 (1.1)	1 (0.8)	0 (0.0)	1 (0.1)
Ageusia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Aphasia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)

Table 29
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	Lenv 20 mg + Pembro 200 mg			
System Organ Class Preferred Term	Indication (N=94) n (%)	All EC (N=124) n (%)	Non-EC (N=159) n (%)	Lenv Monotx 24mg (N=1119) n (%)
Ataxia	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Balance disorder	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Brain oedema	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Burning sensation	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.1)
Carotid artery occlusion	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Carotid artery stenosis	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Cerebral haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Cerebral ischaemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Cerebrovascular accident	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Cervical radiculopathy	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Cognitive disorder	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.1)
Diabetic encephalopathy	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Dizziness	0 (0.0)	0 (0.0)	1 (0.6)	14 (1.3)
Dizziness postural	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Dysarthria	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Dyskinesia	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Facial paresis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Ischaemic stroke	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Lacunar infarction	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Lethargy	0 (0.0)	0 (0.0)	1 (0.6)	3 (0.3)
Loss of consciousness	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Memory impairment	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.4)
Mental impairment	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Metabolic encephalopathy	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Monoparesis	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Myoclonus	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Paraesthesia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Posterior reversible encephalopathy syndrome	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.1)
Presyncope	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Sciatica	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Somnolence	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Speech disorder	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Spinal cord compression	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Subarachnoid haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Toxic encephalopathy	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Vocal cord paralysis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Product issues	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Device breakage	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Psychiatric disorders	3 (3.2)	3 (2.4)	1 (0.6)	25 (2.2)
Confusional state	1 (1.1)	1 (0.8)	0 (0.0)	10 (0.9)
Depression	1 (1.1)	1 (0.8)	0 (0.0)	5 (0.4)
Restlessness	1 (1.1)	1 (0.8)	0 (0.0)	0 (0.0)
Aggression	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Agitation	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Anxiety	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Bradyphrenia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)

Table 29
Treatment-Emergent Adverse Events Leading to Dose Modification of Lenvatinib by System Organ Class and Preferred Term - ISS Safety Analysis Set

	Lenv 20 mg + Pembro 200 mg			
System Organ Class Preferred Term	Indication (N=94) n (%)	All EC (N=124) n (%)	Non-EC (N=159) n (%)	Lenv Monotx 24mg (N=1119) n (%)
Depressed mood	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.3)
Depression suicidal	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Hallucination	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Mental status changes	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.1)
Mood altered	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Suicide attempt	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Renal and urinary disorders	10 (10.6)	19 (15.3)	24 (15.1)	185 (16.5)
Proteinuria	5 (5.3)	14 (11.3)	16 (10.1)	166 (14.8)
Acute kidney injury	2 (2.1)	2 (1.6)	4 (2.5)	9 (0.8)
Haematuria	2 (2.1)	2 (1.6)	0 (0.0)	6 (0.5)
Autoimmune nephritis	1 (1.1)	1 (0.8)	1 (0.6)	0 (0.0)
Nephritis	1 (1.1)	1 (0.8)	0 (0.0)	0 (0.0)
Nephrolithiasis	1 (1.1)	1 (0.8)	1 (0.6)	0 (0.0)
Renal failure	1 (1.1)	1 (0.8)	0 (0.0)	2 (0.2)
Chronic kidney disease	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Dysuria	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.1)
Hydronephrosis	0 (0.0)	0 (0.0)	2 (1.3)	0 (0.0)
Kidney small	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Leukocyturia	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Nephrotic syndrome	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Renal haematoma	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Renal impairment	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Renal tubular necrosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Urethral obstruction	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Urinary hesitation	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Urinary retention	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.1)
Urinary tract pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Reproductive system and breast disorders	1 (1.1)	1 (0.8)	0 (0.0)	10 (0.9)
Vaginal haemorrhage	1 (1.1)	1 (0.8)	0 (0.0)	3 (0.3)
Cystocele	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Genital lesion	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Genital prolapse	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Penile pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Postmenopausal haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Prostatomegaly	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Rectocele	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Uterine prolapse	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Vulval ulceration	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Respiratory, thoracic and mediastinal disorders	12 (12.8)	16 (12.9)	25 (15.7)	93 (8.3)
Dysphonia	3 (3.2)	4 (3.2)	4 (2.5)	17 (1.5)
Dyspnoea	2 (2.1)	2 (1.6)	4 (2.5)	19 (1.7)
Pleural effusion	2 (2.1)	2 (1.6)	2 (1.3)	2 (0.2)
Apnoea	1 (1.1)	1 (0.8)	0 (0.0)	0 (0.0)
Epistaxis	1 (1.1)	2 (1.6)	0 (0.0)	8 (0.7)
Oropharyngeal pain	1 (1.1)	1 (0.8)	7 (4.4)	11 (1.0)
Pleuritic pain	1 (1.1)	1 (0.8)	0 (0.0)	0 (0.0)
Pneumonitis	1 (1.1)	1 (0.8)	2 (1.3)	2 (0.2)

Table 29
Treatment-Emergent Adverse Events Leading to Dose Modification of Lenvatinib by System Organ Class and Preferred Term - ISS Safety Analysis Set

	Lenv 20 mg + Pembro 200 mg			
System Organ Class Preferred Term	Indication (N=94) n (%)	All EC (N=124) n (%)	Non-EC (N=159) n (%)	Lenv Monotx 24mg (N=1119) n (%)
Pneumothorax	1 (1.1)	1 (0.8)	0 (0.0)	4 (0.4)
Pulmonary embolism	1 (1.1)	2 (1.6)	1 (0.6)	12 (1.1)
Atelectasis	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Bronchial fistula	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Bronchospasm	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Chronic obstructive pulmonary disease	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.1)
Cough	0 (0.0)	1 (0.8)	0 (0.0)	10 (0.9)
Dyspnoea exertional	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.3)
Haemoptysis	0 (0.0)	0 (0.0)	1 (0.6)	3 (0.3)
Haemothorax	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Hydrothorax	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Laryngeal haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Laryngeal stenosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Lung disorder	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Nasal congestion	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Pharyngeal inflammation	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Pneumonia aspiration	0 (0.0)	0 (0.0)	1 (0.6)	2 (0.2)
Pulmonary granuloma	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Pulmonary mass	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Pulmonary oedema	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.1)
Respiratory alkalosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Respiratory distress	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Respiratory failure	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Rhinorrhoea	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Stridor	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Tonsillar inflammation	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Tracheal fistula	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Tracheal stenosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Skin and subcutaneous tissue disorders	20 (21.3)	28 (22.6)	20 (12.6)	135 (12.1)
Palmar-plantar erythrodysaesthesia syndrome	12 (12.8)	16 (12.9)	13 (8.2)	88 (7.9)
Rash maculo-papular	4 (4.3)	5 (4.0)	2 (1.3)	3 (0.3)
Skin ulcer	4 (4.3)	4 (3.2)	0 (0.0)	5 (0.4)
Rash	1 (1.1)	1 (0.8)	1 (0.6)	12 (1.1)
Alopecia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Angioedema	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Blister	0 (0.0)	0 (0.0)	0 (0.0)	6 (0.5)
Decubitus ulcer	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Dermal cyst	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Dermatitis	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Dermatitis allergic	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Erythema	0 (0.0)	1 (0.8)	1 (0.6)	3 (0.3)
Exfoliative rash	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Hand dermatitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Hyperkeratosis	0 (0.0)	0 (0.0)	1 (0.6)	2 (0.2)
Lichen planus	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Onychalgia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)

Table 29

Treatment-Emergent Adverse Events Leading to Dose Modification of Lenvatinib by System Organ Class and Preferred Term - ISS Safety Analysis Set

	Lenv 20 mg + Pembro 200 mg			
System Organ Class Preferred Term	Indication (N=94) n (%)	All EC (N=124) n (%)	Non-EC (N=159) n (%)	Lenv Monotx 24mg (N=1119) n (%)
Palmar erythema	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Papule	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Pruritus	0 (0.0)	0 (0.0)	1 (0.6)	2 (0.2)
Rash erythematous	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Rash macular	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Rash pruritic	0 (0.0)	1 (0.8)	1 (0.6)	0 (0.0)
Skin exfoliation	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Skin haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Skin hypertroph	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Skin induration	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.4)
Skin lesion	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)
Splinter haemorrhages	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Urticaria	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.1)
Social circumstances	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Loss of personal independence in daily activities	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Vascular disorders	24 (25.5)	33 (26.6)	25 (15.7)	216 (19.3)
Hypertension	24 (25.5)	31 (25.0)	22 (13.8)	192 (17.2)
Hypotension	2 (2.1)	2 (1.6)	1 (0.6)	17 (1.5)
Aortic aneurysm	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Deep vein thrombosis	0 (0.0)	2 (1.6)	1 (0.6)	3 (0.3)
Haematoma	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Hypertensive crisis	0 (0.0)	0 (0.0)	1 (0.6)	2 (0.2)
Lymphoedema	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Orthostatic hypotension	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Pelvic venous thrombosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Raynaud's phenomenon	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Subclavian vein thrombosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)

Percentages are based on the total number of subjects in the respective safety set.
Dose modification includes dose reduction or drug interruption.
MedDRA preferred terms “Neoplasm Progression”, “Malignant Neoplasm Progression” and “Disease Progression” which are unrelated to the study drug are excluded.
Subjects with two or more adverse events in the same system organ class (or with the same preferred term) were counted only once for that system organ class (or preferred term).
Adverse event terms were coded using Medical Dictionary for Drug Regulatory Activities (MedDRA) version 21.1.
TEAE = treatment-emergent adverse event.
Data cutoff date: 10 Jan 2019 for Study 111/KN146; for all other studies, the clinical cutoff date for each study was used.
Source: EC ISS Table 5.7

Table 30

Treatment-Emergent Adverse Events Leading to Drug Interruption of Pembrolizumab by System Organ Class and Preferred Term - ISS Safety Analysis Set

	Lenv 20 mg + Pembro 200 mg			
System Organ Class Preferred Term	**Indication (N=94) n (%)**	**All EC (N=124) n (%)**	**Non-EC (N=159) n (%)**	**Pembro Monotx (N=2799) n (%)**
Subjects with any TEAE Leading to Drug Interruption of Pembrolizumab	46 (48.9)	64 (51.6)	80 (50.3)	622 (22.2)
Blood and lymphatic system disorders	1 (1.1)	2 (1.6)	0 (0.0)	28 (1.0)
Thrombocytopenia	1 (1.1)	1 (0.8)	0 (0.0)	3 (0.1)
Anaemia	0 (0.0)	1 (0.8)	0 (0.0)	20 (0.7)
Leukopenia	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Neutropenia	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Normocytic anaemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Splenomegaly	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Cardiac disorders	0 (0.0)	1 (0.8)	9 (5.7)	20 (0.7)
Acute coronary syndrome	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Angina pectoris	0 (0.0)	0 (0.0)	2 (1.3)	0 (0.0)
Angina unstable	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Atrial fibrillation	0 (0.0)	1 (0.8)	1 (0.6)	4 (0.1)
Atrial thrombosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Bradycardia	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Cardiac failure	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Cardiac failure congestive	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Cardiac tamponade	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Cardio-respiratory arrest	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Coronary artery disease	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Intracardiac thrombus	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Myocardial infarction	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Palpitations	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Pericardial effusion	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.2)
Postural orthostatic tachycardia syndrome	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Supraventricular extrasystoles	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Supraventricular tachycardia	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Tachycardia	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Congenital, familial and genetic disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Pyloric stenosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Ear and labyrinth disorders	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Deafness	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Vertigo	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Endocrine disorders	4 (4.3)	5 (4.0)	3 (1.9)	34 (1.2)
Adrenal insufficiency	2 (2.1)	2 (1.6)	3 (1.9)	8 (0.3)
Hyperthyroidism	1 (1.1)	1 (0.8)	0 (0.0)	7 (0.3)
Hypothyroidism	1 (1.1)	2 (1.6)	0 (0.0)	13 (0.5)
Hypophysitis	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.2)
Hypopituitarism	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Hypothalamo-pituitary disorder	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Myxoedema	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Thyroiditis	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Eye disorders	0 (0.0)	0 (0.0)	0 (0.0)	14 (0.5)
Cataract	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Conjunctival haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Eye irritation	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Eye pruritus	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Eyelash discolouration	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Iritis	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Papilloedema	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)

Table 30

Treatment-Emergent Adverse Events Leading to Drug Interruption of Pembrolizumab by System Organ Class and Preferred Term - ISS Safety Analysis Set

	Lenv 20 mg + Pembro 200 mg			
System Organ Class Preferred Term	Indication (N=94) n (%)	All EC (N=124) n (%)	Non-EC (N=159) n (%)	Pembro Monotx (N=2799) n (%)
Retinal tear	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Uveitis	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.1)
Vision blurred	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Visual impairment	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Gastrointestinal disorders	14 (14.9)	26 (21.0)	28 (17.6)	101 (3.6)
Diarrhoea	6 (6.4)	12 (9.7)	13 (8.2)	45 (1.6)
Vomiting	4 (4.3)	5 (4.0)	2 (1.3)	11 (0.4)
Nausea	3 (3.2)	4 (3.2)	7 (4.4)	14 (0.5)
Abdominal pain upper	1 (1.1)	1 (0.8)	1 (0.6)	1 (< 0.1)
Colitis	1 (1.1)	2 (1.6)	5 (3.1)	13 (0.5)
Dysphagia	1 (1.1)	1 (0.8)	1 (0.6)	1 (< 0.1)
Pancreatitis	1 (1.1)	3 (2.4)	1 (0.6)	3 (0.1)
Pancreatitis acute	1 (1.1)	1 (0.8)	0 (0.0)	0 (0.0)
Pneumoperitoneum	1 (1.1)	1 (0.8)	0 (0.0)	0 (0.0)
Stomatitis	1 (1.1)	1 (0.8)	1 (0.6)	1 (< 0.1)
Abdominal pain	0 (0.0)	1 (0.8)	2 (1.3)	6 (0.2)
Abdominal pain lower	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Aphthous ulcer	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Constipation	0 (0.0)	0 (0.0)	2 (1.3)	4 (0.1)
Dry mouth	0 (0.0)	1 (0.8)	0 (0.0)	2 (0.1)
Faeces soft	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Gastric haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Gastric perforation	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Gastritis	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Gastritis erosive	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Gastroduodenal ulcer	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Gastrointestinal disorder	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Gastrointestinal haemorrhage	0 (0.0)	1 (0.8)	0 (0.0)	1 (< 0.1)
Glossitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Haematochezia	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Intestinal obstruction	0 (0.0)	1 (0.8)	0 (0.0)	1 (< 0.1)
Intussusception	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Irritable bowel syndrome	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Large intestinal obstruction	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Melaena	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Proctalgia	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Rectal haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Small intestinal obstruction	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.1)
Small intestinal perforation	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Upper gastrointestinal haemorrhage	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	15 (16.0)	20 (16.1)	15 (9.4)	86 (3.1)
Fatigue	7 (7.4)	10 (8.1)	11 (6.9)	27 (1.0)
Asthenia	6 (6.4)	8 (6.5)	2 (1.3)	10 (0.4)
Oedema peripheral	2 (2.1)	2 (1.6)	1 (0.6)	6 (0.2)
Adverse drug reaction	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)

Table 30

Treatment-Emergent Adverse Events Leading to Drug Interruption of Pembrolizumab by System Organ Class and Preferred Term - ISS Safety Analysis Set

	Lenv 20 mg + Pembro 200 mg			
System Organ Class Preferred Term	Indication (N=94) n (%)	All EC (N=124) n (%)	Non-EC (N=159) n (%)	Pembro Monotx (N=2799) n (%)
Chest discomfort	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Chest pain	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.1)
Chills	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.1)
Face oedema	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Feeling hot	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
General physical health deterioration	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Generalised oedema	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Inflammation	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Influenza like illness	0 (0.0)	0 (0.0)	0 (0.0)	6 (0.2)
Infusion site extravasation	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Injection site extravasation	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Localised oedema	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Malaise	0 (0.0)	0 (0.0)	2 (1.3)	6 (0.2)
Mucosal inflammation	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.1)
Nodule	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Oedema	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Pain	0 (0.0)	0 (0.0)	1 (0.6)	3 (0.1)
Pyrexia	0 (0.0)	0 (0.0)	0 (0.0)	14 (0.5)
Systemic inflammatory response syndrome	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Hepatobiliary disorders	1 (1.1)	2 (1.6)	2 (1.3)	20 (0.7)
Autoimmune hepatitis	1 (1.1)	1 (0.8)	0 (0.0)	5 (0.2)
Bile duct obstruction	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Bile duct stenosis	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Biliary dilatation	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Cholecystitis	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Cholestasis	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Drug-induced liver injury	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Hepatic function abnormal	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Hepatic pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Hepatitis	0 (0.0)	1 (0.8)	1 (0.6)	3 (0.1)
Hepatocellular injury	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Hepatomegaly	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Hyperbilirubinaemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Liver disorder	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Immune system disorders	0 (0.0)	0 (0.0)	1 (0.6)	8 (0.3)
Anaphylactic reaction	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Contrast media allergy	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Drug hypersensitivity	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Hypersensitivity	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.2)
Infections and infestations	8 (8.5)	11 (8.9)	16 (10.1)	119 (4.3)
Appendicitis	1 (1.1)	1 (0.8)	0 (0.0)	0 (0.0)
Bronchitis	1 (1.1)	1 (0.8)	0 (0.0)	4 (0.1)
Clostridium difficile infection	1 (1.1)	1 (0.8)	1 (0.6)	0 (0.0)
Diverticulitis	1 (1.1)	1 (0.8)	1 (0.6)	3 (0.1)
Fungal infection	1 (1.1)	1 (0.8)	0 (0.0)	0 (0.0)
Pelvic abscess	1 (1.1)	1 (0.8)	0 (0.0)	1 (< 0.1)

Table 30

Treatment-Emergent Adverse Events Leading to Drug Interruption of Pembrolizumab by System Organ Class and Preferred Term - ISS Safety Analysis Set

	Lenv 20 mg + Pembro 200 mg			
System Organ Class Preferred Term	Indication (N=94) n (%)	All EC (N=124) n (%)	Non-EC (N=159) n (%)	Pembro Monotx (N=2799) n (%)
Pneumonia	1 (1.1)	1 (0.8)	2 (1.3)	21 (0.8)
Respiratory tract infection	1 (1.1)	1 (0.8)	0 (0.0)	5 (0.2)
Urinary tract infection	1 (1.1)	1 (0.8)	3 (1.9)	8 (0.3)
Abdominal infection	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Appendicitis perforated	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Arthritis bacterial	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Aspergillus infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Atypical pneumonia	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Catheter site infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Cellulitis	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.1)
Cellulitis streptococcal	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Cholecystitis infective	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Conjunctivitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Cystitis	0 (0.0)	0 (0.0)	2 (1.3)	0 (0.0)
Erysipelas	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Folliculitis	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Gastroenteritis	0 (0.0)	2 (1.6)	0 (0.0)	3 (0.1)
Herpes simplex	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Herpes zoster	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Infected dermal cyst	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Infectious colitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Infectious pleural effusion	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Infective exacerbation of chronic obstructive airways disease	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Influenza	0 (0.0)	0 (0.0)	0 (0.0)	6 (0.2)
Lower respiratory tract infection	0 (0.0)	0 (0.0)	0 (0.0)	6 (0.2)
Lung infection	0 (0.0)	0 (0.0)	0 (0.0)	6 (0.2)
Nasopharyngitis	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.1)
Oesophageal candidiasis	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Oral candidiasis	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Pneumonia cryptococcal	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Pneumonia klebsiella	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Pneumonia pneumococcal	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Pneumonia viral	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Pyelonephritis	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Rash pustular	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Respiratory tract infection viral	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Sepsis	0 (0.0)	0 (0.0)	1 (0.6)	4 (0.1)
Sinusitis	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Skin infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Soft tissue infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Spinal cord infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Staphylococcal infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Staphylococcal sepsis	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Tooth abscess	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Tooth infection	0 (0.0)	0 (0.0)	1 (0.6)	2 (0.1)

Table 30

Treatment-Emergent Adverse Events Leading to Drug Interruption of Pembrolizumab by System Organ Class and Preferred Term - ISS Safety Analysis Set

	Lenv 20 mg + Pembro 200 mg			
System Organ Class Preferred Term	Indication (N=94) n (%)	All EC (N=124) n (%)	Non-EC (N=159) n (%)	Pembro Monotx (N=2799) n (%)
Tuberculosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Upper respiratory tract infection	0 (0.0)	0 (0.0)	3 (1.9)	17 (0.6)
Urosepsis	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Viral infection	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.1)
Injury, poisoning and procedural complications	0 (0.0)	0 (0.0)	3 (1.9)	23 (0.8)
Hip fracture	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Infusion related reaction	0 (0.0)	0 (0.0)	0 (0.0)	16 (0.6)
Ligament sprain	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Post procedural haemorrhage	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Post procedural urine leak	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Procedural pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Radiation necrosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Radiation pneumonitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Skin laceration	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Spinal compression fracture	0 (0.0)	0 (0.0)	2 (1.3)	0 (0.0)
Investigations	14 (14.9)	16 (12.9)	11 (6.9)	72 (2.6)
Lipase increased	4 (4.3)	4 (3.2)	3 (1.9)	0 (0.0)
Weight decreased	4 (4.3)	4 (3.2)	1 (0.6)	6 (0.2)
Blood alkaline phosphatase increased	3 (3.2)	4 (3.2)	1 (0.6)	4 (0.1)
Amylase increased	2 (2.1)	2 (1.6)	3 (1.9)	2 (0.1)
Blood creatinine increased	2 (2.1)	2 (1.6)	0 (0.0)	8 (0.3)
Alanine aminotransferase increased	1 (1.1)	1 (0.8)	3 (1.9)	28 (1.0)
Aspartate aminotransferase increased	1 (1.1)	1 (0.8)	2 (1.3)	28 (1.0)
Electrocardiogram T wave abnormal	1 (1.1)	1 (0.8)	0 (0.0)	0 (0.0)
Bilirubin conjugated increased	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Blood bilirubin increased	0 (0.0)	1 (0.8)	1 (0.6)	10 (0.4)
Blood corticotrophin decreased	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Blood creatine phosphokinase increased	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Blood prolactin increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Blood testosterone decreased	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
C-reactive protein increased	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.1)
Cardiac murmur functional	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Cortisol decreased	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Ejection fraction decreased	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Electrocardiogram QT prolonged	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Gamma-glutamyltransferase increased	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.1)
Haemoglobin decreased	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Liver function test abnormal	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Liver function test increased	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Platelet count decreased	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Quality of life decreased	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Transaminases increased	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.1)
Metabolism and nutrition disorders	12 (12.8)	16 (12.9)	14 (8.8)	61 (2.2)
Decreased appetite	6 (6.4)	7 (5.6)	5 (3.1)	14 (0.5)
Hypocalcaemia	2 (2.1)	2 (1.6)	1 (0.6)	0 (0.0)
Hypomagnesaemia	2 (2.1)	3 (2.4)	1 (0.6)	1 (< 0.1)

Table 30

Treatment-Emergent Adverse Events Leading to Drug Interruption of Pembrolizumab by System Organ Class and Preferred Term - ISS Safety Analysis Set

	Lenv 20 mg + Pembro 200 mg			
System Organ Class Preferred Term	Indication (N=94) n (%)	All EC (N=124) n (%)	Non-EC (N=159) n (%)	Pembro Monotx (N=2799) n (%)
Hyponatraemia	2 (2.1)	3 (2.4)	0 (0.0)	13 (0.5)
Dehydration	1 (1.1)	1 (0.8)	7 (4.4)	9 (0.3)
Failure to thrive	1 (1.1)	1 (0.8)	0 (0.0)	2 (0.1)
Cell death	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Diabetic metabolic decompensation	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Gout	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Hyperamylasaemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Hypercalcaemia	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.1)
Hyperglycaemia	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Hyperkalaemia	0 (0.0)	0 (0.0)	1 (0.6)	1 (< 0.1)
Hypermagnesaemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Hyperphosphataemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Hypertriglyceridaemia	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.1)
Hyperuricaemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Hypoalbuminaemia	0 (0.0)	1 (0.8)	0 (0.0)	1 (< 0.1)
Hypokalaemia	0 (0.0)	1 (0.8)	1 (0.6)	3 (0.1)
Hypophosphataemia	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.1)
Hypovolaemia	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Lactic acidosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Type 1 diabetes mellitus	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Musculoskeletal and connective tissue disorders	2 (2.1)	4 (3.2)	9 (5.7)	56 (2.0)
Arthralgia	1 (1.1)	1 (0.8)	3 (1.9)	18 (0.6)
Back pain	1 (1.1)	1 (0.8)	1 (0.6)	10 (0.4)
Arthritis	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.2)
Arthropathy	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Bone pain	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Chondrocalcinosis pyrophosphate	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Intervertebral disc protrusion	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Muscle spasms	0 (0.0)	0 (0.0)	2 (1.3)	1 (< 0.1)
Muscular weakness	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Musculoskeletal chest pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Musculoskeletal pain	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.1)
Myalgia	0 (0.0)	1 (0.8)	0 (0.0)	8 (0.3)
Myopathy	0 (0.0)	0 (0.0)	1 (0.6)	1 (< 0.1)
Myositis	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Pain in extremity	0 (0.0)	1 (0.8)	1 (0.6)	0 (0.0)
Pain in jaw	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Pathological fracture	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Polyarthritis	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Spinal osteoarthritis	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Synovitis	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Tendonitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0)	0 (0.0)	1 (0.6)	11 (0.4)
Intestinal metastasis	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Leiomyosarcoma	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)

Table 30

Treatment-Emergent Adverse Events Leading to Drug Interruption of Pembrolizumab by System Organ Class and Preferred Term - ISS Safety Analysis Set

	Lenv 20 mg + Pembro 200 mg			
System Organ Class Preferred Term	Indication (N=94) n (%)	All EC (N=124) n (%)	Non-EC (N=159) n (%)	Pembro Monotx (N=2799) n (%)
Malignant pleural effusion	0 (0.0)	0 (0.0)	1 (0.6)	1 (< 0.1)
Metastases to central nervous system	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Metastatic malignant melanoma	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Neoplasm malignant	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Oncologic complication	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Pericardial effusion malignant	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Tumour haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Tumour pain	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Nervous system disorders	6 (6.4)	7 (5.6)	3 (1.9)	35 (1.3)
Syncope	2 (2.1)	2 (1.6)	0 (0.0)	3 (0.1)
Cerebral ischaemia	1 (1.1)	1 (0.8)	0 (0.0)	2 (0.1)
Encephalopathy	1 (1.1)	1 (0.8)	0 (0.0)	0 (0.0)
Seizure	1 (1.1)	1 (0.8)	1 (0.6)	2 (0.1)
Tremor	1 (1.1)	1 (0.8)	0 (0.0)	0 (0.0)
Amnesia	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Aphasia	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Cerebrovascular accident	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Cognitive disorder	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Dizziness	0 (0.0)	0 (0.0)	1 (0.6)	4 (0.1)
Dysgeusia	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)
Epilepsy	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Headache	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.2)
Hemiparesis	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Hydrocephalus	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Ischaemic stroke	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Meningitis noninfective	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Myasthenic syndrome	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Neuralgia	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Neuropathy peripheral	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.1)
Normal pressure hydrocephalus	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Polyneuropathy	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Presyncope	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Restless legs syndrome	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Ruptured cerebral aneurysm	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Transient ischaemic attack	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Vasogenic cerebral oedema	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Psychiatric disorders	1 (1.1)	1 (0.8)	1 (0.6)	8 (0.3)
Confusional state	1 (1.1)	1 (0.8)	0 (0.0)	4 (0.1)
Anxiety	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Binge eating	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Depression	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Insomnia	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Mental status changes	0 (0.0)	0 (0.0)	1 (0.6)	1 (< 0.1)
Renal and urinary disorders	5 (5.3)	8 (6.5)	6 (3.8)	17 (0.6)
Acute kidney injury	1 (1.1)	1 (0.8)	2 (1.3)	4 (0.1)
Hydronephrosis	1 (1.1)	1 (0.8)	0 (0.0)	0 (0.0)

Table 30

Treatment-Emergent Adverse Events Leading to Drug Interruption of Pembrolizumab by System Organ Class and Preferred Term - ISS Safety Analysis Set

	Lenv 20 mg + Pembro 200 mg			
System Organ Class Preferred Term	Indication (N=94) n (%)	All EC (N=124) n (%)	Non-EC (N=159) n (%)	Pembro Monotx (N=2799) n (%)
Nephritis	1 (1.1)	1 (0.8)	0 (0.0)	0 (0.0)
Nephrolithiasis	1 (1.1)	1 (0.8)	0 (0.0)	0 (0.0)
Renal failure	1 (1.1)	1 (0.8)	0 (0.0)	6 (0.2)
Autoimmune nephritis	0 (0.0)	0 (0.0)	2 (1.3)	0 (0.0)
Chronic kidney disease	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Dysuria	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Microalbuminuria	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Proteinuria	0 (0.0)	3 (2.4)	2 (1.3)	1 (< 0.1)
Tubulointerstitial nephritis	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.1)
Urinary bladder polyp	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Respiratory, thoracic and mediastinal disorders	4 (4.3)	5 (4.0)	10 (6.3)	95 (3.4)
Dysphonia	1 (1.1)	2 (1.6)	0 (0.0)	0 (0.0)
Pleural effusion	1 (1.1)	1 (0.8)	2 (1.3)	8 (0.3)
Pneumonitis	1 (1.1)	1 (0.8)	1 (0.6)	24 (0.9)
Pneumothorax	1 (1.1)	1 (0.8)	0 (0.0)	2 (0.1)
Atelectasis	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Bronchiectasis	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Bronchospasm	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Chronic obstructive pulmonary disease	0 (0.0)	0 (0.0)	0 (0.0)	6 (0.2)
Cough	0 (0.0)	0 (0.0)	0 (0.0)	11 (0.4)
Dyspnoea	0 (0.0)	0 (0.0)	5 (3.1)	20 (0.7)
Haemoptysis	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.1)
Hypercapnia	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Hypoxia	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Interstitial lung disease	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Laryngeal inflammation	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Lung disorder	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Nasal congestion	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Obstructive airways disorder	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Pharyngeal inflammation	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Pneumonia aspiration	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Pneumothorax spontaneous	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Productive cough	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Pulmonary embolism	0 (0.0)	0 (0.0)	0 (0.0)	10 (0.4)
Pulmonary granuloma	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Pulmonary oedema	0 (0.0)	0 (0.0)	1 (0.6)	3 (0.1)
Pulmonary thrombosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Pulmonary vascular disorder	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Respiratory failure	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Rhinorrhoea	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Tachypnoea	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Throat tightness	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Skin and subcutaneous tissue disorders	9 (9.6)	11 (8.9)	9 (5.7)	50 (1.8)
Rash maculo-papular	3 (3.2)	3 (2.4)	0 (0.0)	12 (0.4)
Skin ulcer	3 (3.2)	3 (2.4)	1 (0.6)	0 (0.0)
Rash	2 (2.1)	2 (1.6)	0 (0.0)	14 (0.5)

Table 30

Treatment-Emergent Adverse Events Leading to Drug Interruption of Pembrolizumab by System Organ Class and Preferred Term - ISS Safety Analysis Set

	Lenv 20 mg + Pembro 200 mg			
System Organ Class Preferred Term	Indication (N=94) n (%)	All EC (N=124) n (%)	Non-EC (N=159) n (%)	Pembro Monotx (N=2799) n (%)
Palmar-plantar erythrodysaesthesia syndrome	1 (1.1)	2 (1.6)	3 (1.9)	1 (< 0.1)
Dermatitis	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Drug eruption	0 (0.0)	0 (0.0)	1 (0.6)	1 (< 0.1)
Eczema	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Erythema	0 (0.0)	0 (0.0)	1 (0.6)	1 (< 0.1)
Erythema multiforme	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Hyperkeratosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Lichen planus	0 (0.0)	1 (0.8)	0 (0.0)	2 (0.1)
Lichenoid keratosis	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Neutrophilic dermatosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Night sweats	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Pain of skin	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Pemphigoid	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Penile ulceration	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Pruritus	0 (0.0)	0 (0.0)	1 (0.6)	6 (0.2)
Psoriasis	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Rash erythematous	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Rash generalised	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.1)
Rash macular	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
Rash pruritic	0 (0.0)	1 (0.8)	1 (0.6)	0 (0.0)
Vitiligo	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Vascular disorders	2 (2.1)	5 (4.0)	2 (1.3)	14 (0.5)
Hypertension	1 (1.1)	3 (2.4)	2 (1.3)	4 (0.1)
Hypotension	1 (1.1)	1 (0.8)	0 (0.0)	2 (0.1)
Aortic stenosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Deep vein thrombosis	0 (0.0)	2 (1.6)	0 (0.0)	0 (0.0)
Embolism	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Flushing	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Pallor	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Peripheral ischaemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Superior vena cava occlusion	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Superior vena cava syndrome	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)
Thrombosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)

Percentages are based on the total number of subjects in the respective safety set.
MedDRA preferred terms “Neoplasm Progression”, “Malignant Neoplasm Progression” and “Disease Progression” which are unrelated to the study drug are excluded.
Subjects with two or more adverse events in the same system organ class (or with the same preferred term) were counted only once for that system organ class (or preferred term).
Adverse event terms were coded using Medical Dictionary for Drug Regulatory Activities (MedDRA) version 21.1.
TEAE = treatment-emergent adverse event.
Data cutoff date: 10 Jan 2019 for Study 111/KN146; for all other studies, the clinical cutoff date for each study was used.
Source: EC ISS Table 5.8

The Regulatory Authorities’ Assessment:

Our analyses of TEAEs leading to dose interruptions and reductions agrees with the

applicant's findings presented above.

Lenvatinib: In the not-MSI-H/dMMR EC 2L+ group, TEAEs leading to lenvatinib dose interruptions (interruptions - 65%:Grade 1-5 and 34%: Grade 3-4 AEs) occured at a similar rate compared to monotherapy study 204 and reference safety dataset (RSD; N=1119; includes pooled data from 11 lenvatinib monotherapy studies), but the rate of dose reductions was higher in study 111/KN-146 (reductions - 66%:Grade 1-5 and 34%: Grade 3-4 AEs). It is important to note that study 204 used a higher dose of lenvatinib (24mg) versus study 111/KN-146 (20mg). Also, adverse reactions led to dose modifications (includes reduction and/or interruption) in 88% of patients receiving lenvatinib (regardless of the action taken with pembrolizumab).

The most common AEs leading to treatment interruption for lenvatinib alone were hypertension (15%), diarrhea (11%), fatigue (7%), and hemorrhages (6%). The most common AEs leading to dose reduction for lenvatinib alone were fatigue (25%), palmar-plantar erythrodysesthesia (13%), hypertension (12%), diarrhea (10%), and decreased appetite (9%). Overall the dose interruptions and reductions in nature corresponding to the known safety profile of lenvatinib.

We also calculated the time to dose modification (reduction and interruption) by using the time period between date of first exposure and date of first AE leading to modification for study 111 and study 204.

- **For study 111 (n=94), a total of 71 patients experienced dose interruption, with median time to dose interruption of 1.4 (range: 0.03 – 11) months. Also, a total of 63 patients experienced dose reduction, with median time to dose reduction of 1.3 (range: 0.03 – 17.5) months.**

- **For study 204 (n=133), a total of 78 patients experienced dose interruption, with median time to dose interruption of 0.95 (range: 0.07 – 9.7) months. Also, a total of 40 patients experienced dose reduction, with median time to dose reduction of 0.97 (range: 0.03 –7.4) months.**

Pembrolizumab: In the not MSI-H/dMMR EC 2L+ group, pembrolizumab alone was dose interrupted 26% owing to TEAEs, most commonly due to fatigue (7%), diarrhea (4%) and rash (3%). The incidence of TEAEs leading to a dose interruption of pembrolizumab was higher in the not-MSI-H/dMMR EC 2L+ group than in the pembrolizumab monotherapy studies KN-028, KN-158 and RSD (N=2799; data from melanoma and NSCLC trials). Not many dose reductions of pembrolizumab alone were observed. Of note, adverse reactions led to dose modifications (includes reduction and/or interruption) in 49% of patients receiving pembrolizumab (regardless of the action taken with lenvatinib).

We also calculated the time to dose modification (reduction and interurruption) by using the time period between date of first exposure and date of first AE leading to modification for

study 111/KN-146 and KN-158.

- **For study 111/KN-146 (n=94), a total of 46 patients experienced dose interruption, with median time to dose interruption of 2.6 (range: 0.13 – 22.2) months. Also, two patients experienced dose reduction, with median time to dose reduction of 3 (range: 1.1 – 5) months.**

- **For KN-158 (n=90), no dose reductions were reported, however, 21 patients experienced dose interruption, with median time to dose interruption of 2.1 (range: 0.07 – 9.6) months.**

Overall, dose reductions for lenvatinib were much higher in study 111/KN-146 compared to study 204 (despite the use of a higher dose of 24mg in study 204). The timelines for dose modifications were comparable between the studies for both L and P.

Table 31: Overview of drug interruptions and reductions in Study 111/KN-146

	Not MSI-H/dMMR EC 2L+ N=94; n (%)		All previously Treated EC 2L+ N=108; n (%)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Lenvatinib				
Interruptions	61 (65)	32 (34)	68 (63)	37 (34)
Reductions	62 (66)	32 (34)	71 (66)	37 (34)
Pembrolizumab				
Interruptions	24 (26)	10 (11)	30 (28)	13 (12)
Reductions	1 (1)	0 (0)	1 (1)	0 (0)
L and P Together				
Interruptions	36 (38)	16 (17)	46 (43)	21 (19)
Reductions	1 (1)	0 (0)	1 (1)	0 (0)
Source: Study 111 – adsl.xpt, adae.xpt; Study 111 90-day safety update - adsl.xpt, adae.xpt				

Significant Adverse Events

The Applicant's Position:

Clinically Significant Events for Lenvatinib

The incidence rate of CSEs (defined in Module 2.7.4, Section 2.7.4.1.1) observed in the Indication Safety Set was generally comparable to the Lenvatinib Monotherapy Safety Set, with the exception of the CSEs of hypothyroidism (any grade: 51.1% vs 19.8%, respectively) and hemorrhage events (Grade ≥3; 4.3% [4 subjects] vs 2.1%. respectively) (Table 32; ADaM dataset: ADSL_EC ISS, ADAE_EC ISS). Review of hemorrhage events indicates that, overall, severe (Grade ≥3) hemorrhage events are rare; however, there is a risk of severe hemorrhage associated with tumor shrinkage/necrosis following lenvatinib therapy and lenvatinib plus pembrolizumab may result in a slightly higher incidence of severe hemorrhage events.

Conclusions are limited due to the small number of subjects with these events. Nearly all individual hypothyroidism events were Grade 1 or 2. Hypothyroidism is discussed below in **Overlapping Toxicities of Clinical Interest**. Overall, the majority of CSEs can be managed with adequate monitoring, dose reduction and interruption, and standard medical care. Details are provided in Module 2.7.4, Section 2.7.4.2.1.7.

Table 32
Overview of Clinically Significant Treatment-Emergent Adverse Events (CSAEs) for Lenvatinib - ISS Safety Analysis Set

	Lenv 20 mg + Pembro 200 mg			
	Indication (N=94) n (%)	**All EC (N=124) n (%)**	**Non-EC (N=159) n (%)**	**Lenv Monotx 24mg (N=1119) n (%)**
Subjects with Any Clinically Significant TEAEs (CSAEs) for Lenvatinib	86 (91.5)	116 (93.5)	138 (86.8)	975 (87.1)
Worst CTCAE Grade of[a]				
1	6 (6.4)	8 (6.5)	17 (10.7)	100 (8.9)
2	34 (36.2)	46 (37.1)	53 (33.3)	315 (28.2)
>=3	46 (48.9)	62 (50.0)	68 (42.8)	560 (50.0)
3	40 (42.6)	53 (42.7)	55 (34.6)	502 (44.9)
4	4 (4.3)	6 (4.8)	7 (4.4)	31 (2.8)
5	2 (2.1)	3 (2.4)	6 (3.8)	27 (2.4)
Serious CSAEs	20 (21.3)	25 (20.2)	32 (20.1)	200 (17.9)
CSAEs Leading to Drug Withdrawal of Lenvatinib	7 (7.4)	12 (9.7)	15 (9.4)	108 (9.7)
CSAEs Leading to Study Drug Modification[b]	49 (52.1)	67 (54.0)	62 (39.0)	477 (42.6)
Dose Reduction of Lenvatinib	31 (33.0)	42 (33.9)	38 (23.9)	264 (23.6)
Drug Interruption of Lenvatinib	35 (37.2)	49 (39.5)	46 (28.9)	378 (33.8)

Percentages are based on the total number of subjects in the respective safety set.
For each row category, a subject with two or more adverse events in that category is counted only once.
TEAE = treatment-emergent adverse event, CSAE = clinically significant TEAE.
a: If a subject had more than one CSAE, the subject is only counted once at the worst CTCAE grade.
b: Study drug modification includes dose reduction or drug interruption. A subject may be counted in both categories if the subject had TEAEs leading to both dose reduction and/or drug interruption.
Data cutoff date: 10 Jan 2019 for Study 111/KN146; for all other studies, the clinical cutoff date for each study was used.
Source: ECI ISS Table 9.1.2

Adverse Events of Special Interest for Pembrolizumab

While the overall incidence of AEOSIs (defined in Module 2.7.4, Section 2.7.4.1.1) in the Indication Safety Set (57.4%) was higher than that in the Pembrolizumab Monotherapy Safety Set (21.3%), most AEOSIs reported were mild to moderate in severity (Grade 1 or 2) and the incidence of Grade ≥3 AEOSIs was 11.7% compared with 5.5% in the Pembrolizumab Monotherapy Safety Set (Table 33; ADaM dataset: ADSL_EC ISS, ADAE_EC ISS). The incidence of AEOSIs leading to treatment discontinuation of pembrolizumab in the Indication Safety Set was consistent with that in the Pembrolizumab Monotherapy Safety Set (4.3% vs 3.0%, respectively). The higher incidence of AEOSIs in the Indication Safety Set compared with the

Pembrolizumab Monotherapy Safety Set was primarily driven by thyroid-related events, most notably hypothyroidism (48.9% vs 8.5%, respectively), as well as hyperthyroidism (5.3% vs 3.4%) and thyroiditis (3.2% vs 0.6%) (Table 33; ADaM dataset: ADSL_EC ISS, ADAE_EC ISS). In the Indication Safety Set, all thyroid-related events were Grade 1 or 2, except for a single Grade 3 event of hypothyroidism. In addition, the incidences of the following AEOSIs were higher in the Indication Safety Set in comparison with the Pembrolizumab Monotherapy Safety Set for adrenal insufficiency, colitis, pancreatitis, severe skin reactions, and nephritis; however, the small number of events prevents drawing a meaningful conclusion regarding these differences. The AEOSIs were managed with dose interruption and appropriate treatment, rarely requiring discontinuation. Hypothyroidism, nephritis, severe skin reactions, and pancreatitis are discussed below in **Overlapping Toxicities of Clinical Interest**.

Table 33
Overview of Treatment-Emergent Adverse Events of Special Interest (AEOSI) for Pembrolizumab - ISS Safety Analysis Set

	Lenv 20 mg + Pembro 200 mg			
	Indication (N=94) n (%)	**All EC (N=124) n (%)**	**Non-EC (N=159) n (%)**	**Pembro Monotx (N=2799) n (%)**
Subjects with Any TEAEs of Special Interest (AEOSI) for Pembrolizumab	54 (57.4)	71 (57.3)	79 (49.7)	597 (21.3)
Worst CTCAE Grade of[a]				
1	5 (5.3)	8 (6.5)	9 (5.7)	153 (5.5)
2	38 (40.4)	48 (38.7)	54 (34.0)	290 (10.4)
>=3	11 (11.7)	15 (12.1)	16 (10.1)	154 (5.5)
3	11 (11.7)	15 (12.1)	14 (8.8)	133 (4.8)
4	0 (0.0)	0 (0.0)	2 (1.3)	17 (0.6)
5	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.1)
Serious AEOSIs	9 (9.6)	10 (8.1)	10 (6.3)	161 (5.8)
AEOSIs Leading to Drug Withdrawal of Pembrolizumab	4 (4.3)	5 (4.0)	10 (6.3)	83 (3.0)
AEOSIs Leading to Drug Interruption of Pembrolizumab	9 (9.6)	14 (11.3)	13 (8.2)	132 (4.7)

Percentages are based on the total number of subjects in the respective safety set.
For each row category, a subject with two or more adverse events in that category is counted only once.
TEAE = treatment-emergent adverse event.
a: Subjects with two or more of the same AEOSI reported will be counted only once in the worst CTCAE grade.
Data cutoff date: 10 Jan 2019 for Study 111/KN146; for all other studies, the clinical cutoff date for each study was used.
Source: EC ISS Table 9.2.2

The Regulatory Authorities' Assessment:

The sponsor created pre-specified custom data queries to assess the frequency of clinically significant events (CSEs - *AEs that have been identified in clinical trials across the development program*) for lenvatinib and adverse events of special interest (AESIs –*immune-*

***mediated AEs or nonimmune-mediated events of infusion-related reactions*) for pembrolizumab. Each CSE/AESI represented a single medical concept/event but may be composed of multiple preferred terms (PTs).**

CSEs: In general, the sponsor's approach to the analysis of CSEs was acceptable. FDA also independently analyzed each of the CSE events. In the *not MSI-H/dMMR EC 2L+* data set, there were 86 (91.5%) patients with 1 or more CSEs with lenvatinib. The most common CSEs identified were hypertension, hypothyroidism, hemorrhages, palmar-plantar erythrodysaesthesia, proteinuria, and renal events. Of the 86 CSEs in the *not MSI-H/dMMR EC 2L+* data set, 46 (48.9%) events were Grade ≥3. Grade ≥3 CSEs occurring in ≥2% were hypertension (39%), hepatotoxicity (excluding elevated LFTs; 7%), hemorrhages (3.2%), Palmar Plantar erythrodysaesthesia (3.2%), and renal events (3.2%).

The incidence of CSEs in the *not MSI-H/dMMR EC 2L+* data set was compared with that in the lenvatinib monotherapy study 204 to determine which CSEs occurred at a higher incidence rate in patients treated with L+P than with lenvatinib monotherapy. We found a higher frequency of hypothyroidism and palmar-plantar erythrodysesthesia in the combination; importantly, renal events were similar across the studies. It is important to note that study 204 used a higher dose of lenvatinib (24mg) versus study 111/KN-146 (20mg). We also compared the safety results of our CSE analyses to the safety findings from the lenvatinib RSD (N=1119; includes pooled data from 11 lenvatinib monotherapy studies). See Table 34 for these individual CSEs.

Table 34: Clinically significant events (CSE) in ≥10% of Patients in Study 111/KN-146

	Lenvatinib + Pembrolizumab Not MSI-H/dMMR EC 2L+ N=94 n (%)		Lenvatinib + Pembrolizumab All previously treated EC 2L+ N=108 n (%)		Lenvatinib monotherapy Study 204 N=133 n (%)		Lenvatinib RSD N=1119 n (%)
	G1-5	G3-4	G1-5	G3-4	G1-5	G3-4	G1-5
CSE - Hypertension	**61 (64.9)**	**36 (38.8)**	**69 (63.9)**	**39 (36.1)**	76 (57.1)	46 (34.6)	703 (62.8)
CSE - Hypothyroidism Events*	**48 (51.1)**	**1 (1.1)**	**53 (49.1)**	**1 (0.9)**	33 (24.8)	3 (2.3)	222 (19.8)
CSE – Hemorrhage Events	26 (27.7)	3 (3.2)	30 (27.8)	4 (3.7)	32 (24.1)	2 (1.5)	366 (32.7)
CSE – Palmar Plantar Erythrodysesthesia Events	**24 (25.5)**	**3 (3.2)**	**29 (26.9)**	**3 (2.8)**	13 (9.8)	3 (2.3)	233 (20.8)
CSE - Proteinuria	18 (19.1)	1 (1.1)	24 (22.2)	4 (3.7)	33 (24.8)	11 (8.3)	395 (35.3)

CSE – Renal Events	**11 (11.7)**	**3 (3.2)**	**13 (12)**	**4 (3.7)**	12 (9.0)	5 (3.8)	112 (10)
* Hypothyroidism events are an overlapping toxicity and were part of CSE and AESI analyses. Source: Study 111 – adsl.xpt, adae.xpt; Study 111 90-day safety update - adsl.xpt, adae.xpt; : Study 204 – adsl.xpt, adae.xpt; EC ISS Table 9.1.2 used for RSD data							

AESIs: The applicant's choice of terms underestimates the incidence of AESIs, as the list of PTs used in their analyses is limited, and because laboratory abnormalities thought to be clinically significant and reported as adverse events have been excluded. The reviewers independently analyzed each of the AESIs, but the list of PTs included in each query was expanded to ensure that the grouping of terms robustly captured the medical concept/event (see Appendix 17.5 for pooling of PTs). The incidence of AESIs in the *not MSI-H/dMMR EC 2L+* data set was compared with that in the pembrolizumab monotherapy studies (KN-158 and KN-028) to determine which AESIs occurred at a higher rate in patients treated with L+P than with pembrolizumab monotherapy. We found higher frequencies of hypothyroidism, pancreatitis, nephritis and adrenal insufficiency in the combination compared to monotherapy study KN-158. We also compared the safety results of our AESI analyses to the safety findings from the pembrolizumab RSD (N=2799; data from melanoma and NSCLC trials), which per the applicant reflects the established safety profile for pembrolizumab. See Table 35 for these individual AESIs below. We also looked at steroid use in study 111 (see), nearly a quarter of the patients received systemic corticosteroids with only around 9% needing steroids for immune mediated adverse events.

Table 35: Adverse Events of Special Interest (AESI) in ≥10% of Patients in Study 111/KN-146

	Lenvatinib + Pembrolizumab		Lenvatinib + Pembrolizumab		Pembrolizumab monotherapy KN-158		Pembro-lizumab RSD
	Not MSI-H/dMMR EC 2L+		All previously treated EC 2L+		Not (MSI-H/dMMR)		
	N=94 n (%)		**N=108 n (%)**		**N=90 n (%)**		**N=2799 n (%)**
	G1-5	G3-4	G1-5	G3-4	G1-5	G3-4	G1-5
AESI - Hypothyroidism Events*	**48 (51.1)**	**1 (1.1)**	**53 (49.1)**	**1 (0.9)**	7 (7.8)	0 (0)	237 (8.5)
AESI – Pancreatitis Events	**4 (4.3)**	**3 (3.2)**	**6 (5.6)**	**3 (2.8)**	1 (1.1)	1 (1.1)	7 (0.3)
AESI – Adrenal insufficiency Events	**3 (3.2)**	**3 (3.2)**	**4 (3.7)**	**3 (2.8)**	0 (0)	0 (0)	22 (0.8)
AESI – Nephritis Events	**2 (2.1)**	**1 (1.1)**	**3 (2.8)**	**2 (1.9)**	0 (0)	0 (0)	9 (0.3)
AESI – Hypopituitarism Events	**1 (1.1)**	**1 (1.1)**	**1 (0.9)**	**1 (0.9)**	0 (0)	0 (0)	8 (0.3)

* Hypothyroidism events are an overlapping toxicity and were part of CSE and AESI analyses. Study KN-028 (n=18) was not included in this table as there were no cases of hypothyroidism, pancreatitis, adrenal insufficiency, nephritis or hypopituitarism reported.
Source: Study 111 – adsl.xpt, adae.xpt; Study 111 90-day safety update - adsl.xpt, adae.xpt; Study 204 – adsl.xpt, adae.xpt; EC ISS Table 9.2.2 used for RSD data

Table 36: Systemic Corticosteroid use and AESIs in Study 111/KN-146

	Lenvatinib + Pembrolizumab Not MSI-H/dMMR EC 2L+ (n=94)	
	Number of Adverse Events	Patients; n (%)
Systemic corticosteroid administered	57	26 (28)
AESI		
Total	74	54 (57.4)
Requiring systemic steroids	16	8 (8.5)

Source: Study 111 – adsl.xpt, adae.xpt; Study 111 90-day safety update - adsl.xpt, adae.xpt; Information also requested as part of IR from sponsor

Treatment Emergent Adverse Events and Adverse Reactions

The Applicant's Position:

In the Indication Safety Set, the most commonly reported TEAEs (>30% of subjects; Table 37) were, by decreasing incidence, hypertension, diarrhea, fatigue, decreased appetite, hypothyroidism, nausea, vomiting, stomatitis, decreased weight, arthralgia, headache, and constipation. The incidence and type of TEAEs observed in the Indication Safety Set were generally consistent with the Lenvatinib Monotherapy or Pembrolizumab Monotherapy Safety Sets, except for the following events that occurred at a higher incidence in the Indication Safety Set than in both monotherapy safety sets: diarrhea, dehydration, hyponatremia, hypomagnesemia, hypothyroidism, urinary tract infection, maculo-papular rash, increased lipase, gastroesophageal reflux disease (GERD), and vaginal discharge.

- The incidences of diarrhea (any grade) and hypomagnesemia were higher in the EC safety sets than in the Non-EC Safety Set and in both monotherapy safety sets; the difference in incidence of diarrhea was driven by Grade 1 events. One subject discontinued lenvatinib treatment because of diarrhea and no subjects discontinued treatment because of dehydration, hyponatremia, or hypomagnesemia; all of these TEAEs could generally be managed by dose modification and supportive care.
- Hypothyroidism is a CSE for lenvatinib, an AEOSI for pembrolizumab, and is discussed further in **Overlapping Toxicities of Clinical Interest.**
- The incidence of urinary tract infection was higher in the EC safety sets than in the Non-EC Safety Set and both monotherapy safety sets, indicating this may be related to the underlying disease, as well as subject characteristics.

- Events of maculo-papular rash in the Indication Safety Set were generally low grade while higher grade events were managed through dose modification and did not require discontinuation of study treatment.
- Lipase was monitored routinely in Study 111, but not monitored routinely in the studies comprising the monotherapy safety sets; therefore, a comparison of the incidences for increased lipase is not possible. Overall, increased lipase events were manageable through dose modification, and no subjects discontinued treatment.
- The increased incidence of GERD was limited to the EC safety sets, all TEAEs were Grade 1 or 2 and there were no dose modifications.

See Module 2.7.4, Section 2.7.4.2.1.2 for details of common TEAEs.

Table 37
Treatment Emergent Adverse Events Occurring in 10% or More of Subjects in the Indication Safety Set, by MedDRA Preferred Term – All Safety Sets

MedDRA Preferred Term	Safety Set				
	Combination Therapy			Monotherapy	
	Lenv 20 mg + Pembro 200 mg			Lenv 24 mg (N=1119) n (%)	Pembro (N=2799) n (%)
	Indication (N=94) n (%)	All EC (N=124) n (%)	Non-EC (N=159) n (%)		
Subjects With at Least 1 TEAE	*94 (100.0)*	*124 (100.0)*	*158 (99.4)*	*1108 (99.0)*	*2727 (97.4)*
Hypertension	60 (63.8)	76 (61.3)	58 (36.5)	672 (60.1)	106 (3.8)
Diarrhoea	59 (62.8)	78 (62.9)	83 (52.2)	580 (51.8)	625 (22.3)
Fatigue	51 (54.3)	64 (51.6)	96 (60.4)	537 (48.0)	1044 (37.3)
Decreased appetite	48 (51.1)	64 (51.6)	70 (44.0)	509 (45.5)	630 (22.5)
Nausea	45 (47.9)	58 (46.8)	72 (45.3)	475 (42.4)	685 (24.5)
Hypothyroidism	46 (48.9)	59 (47.6)	59 (37.1)	146 (13.0)	236 (8.4)
Vomiting	37 (39.4)	49 (39.5)	46 (28.9)	373 (33.3)	387 (13.8)
Stomatitis	34 (36.2)	40 (32.3)	44 (27.7)	310 (27.7)	59 (2.1)
Weight decreased	34 (36.2)	39 (31.5)	41 (25.8)	390 (34.9)	220 (7.9)
Arthralgia	31 (33.0)	44 (35.5)	45 (28.3)	281 (25.1)	504 (18.0)
Headache	31 (33.0)	40 (32.3)	25 (15.7)	357 (31.9)	400 (14.3)
Constipation	30 (31.9)	34 (27.4)	43 (27.0)	300 (26.8)	498 (17.8)
Dysphonia	27 (28.7)	36 (29.0)	51 (32.1)	351 (31.4)	68 (2.4)
Urinary tract infection	27 (28.7)	34 (27.4)	23 (14.5)	119 (10.6)	162 (5.8)
Abdominal pain	25 (26.6)	34 (27.4)	22 (13.8)	231 (20.6)	274 (9.8)
Hypomagnesaemia	25 (26.6)	32 (25.8)	16 (10.1)	51 (4.6)	80 (2.9)
Dyspnoea	23 (24.5)	25 (20.2)	38 (23.9)	202 (18.1)	534 (19.1)
Palmar-plantar erythrodysaesthesia syndrome	24 (25.5)	31 (25.0)	30 (18.9)	233 (20.8)	9 (0.3)
Cough	20 (21.3)	28 (22.6)	50 (31.4)	245 (21.9)	615 (22.0)
Myalgia	20 (21.3)	26 (21.0)	19 (11.9)	168 (15.0)	253 (9.0)
Back pain	19 (20.2)	22 (17.7)	28 (17.6)	200 (17.9)	349 (12.5)
Proteinuria	18 (19.1)	31 (25.0)	51 (32.1)	389 (34.8)	14 (0.5)
Dehydration	17 (18.1)	19 (15.3)	27 (17.0)	105 (9.4)	106 (3.8)
Dry mouth	17 (18.1)	21 (16.9)	18 (11.3)	147 (13.1)	142 (5.1)
Oedema peripheral	16 (17.0)	22 (17.7)	26 (16.4)	192 (17.2)	286 (10.2)
Musculoskeletal pain	15 (16.0)	17 (13.7)	16 (10.1)	144 (12.9)	226 (8.1)
Rash maculo-papular	14 (14.9)	19 (15.3)	14 (8.8)	15 (1.3)	100 (3.6)
Dizziness	13 (13.8)	17 (13.7)	18 (11.3)	153 (13.7)	244 (8.7)
Lipase increased	13 (13.8)	16 (12.9)	14 (8.8)	41 (3.7)	5 (0.2)
Asthenia	12 (12.8)	22 (17.7)	13 (8.2)	193 (17.2)	362 (12.9)
Dry skin	12 (12.8)	14 (11.3)	14 (8.8)	117 (10.5)	166 (5.9)
Hyponatraemia	11 (11.7)	13 (10.5)	23 (14.5)	66 (5.9)	146 (5.2)

MedDRA Preferred Term	Safety Set				
	Combination Therapy			Monotherapy	
	Lenv 20 mg + Pembro 200 mg				
	Indication (N=94) n (%)	All EC (N=124) n (%)	Non-EC (N=159) n (%)	Lenv 24 mg (N=1119) n (%)	Pembro (N=2799) n (%)
Muscular weakness	11 (11.7)	15 (12.1)	21 (13.2)	79 (7.1)	89 (3.2)
Gastrooesophageal reflux disease	10 (10.6)	15 (12.1)	7 (4.4)	62 (5.5)	74 (2.6)
Hypokalaemia	10 (10.6)	15 (12.1)	15 (9.4)	96 (8.6)	124 (4.4)
Pyrexia	10 (10.6)	12 (9.7)	13 (8.2)	134 (12.0)	357 (12.8)

Data cutoff date for Combination Therapy Safety Sets: 10 Jan 2019.

Data cutoff date for Lenv monotherapy studies: 01 Sep 2016 (ongoing studies), except Study 205 (which had a cutoff date of 15 Mar 2018); earlier for completed studies.

Data cutoff date for the Pembro monotherapy studies: varied by study; range 18 Apr 2014 to 30 Sep 2015.

Preferred terms are included in this table if they occurred within the percentage parameter for the primary population of interest for this submission, the Indication Safety Set.

Display is by decreasing order of AE incidence of PTs in the Indication Safety Set.

Adverse event terms were coded using MedDRA version 21.1.

Subjects with 2 or more TEAEs reported in the same SOC or PT were counted only once. Percentages are based on the total number of subjects in the relevant safety set.

AE = adverse event, EC = endometrial carcinoma, Lenv = lenvatinib, MedDRA = Medical Dictionary for Regulatory Activities, Pembro = pembrolizumab, PT = preferred term, SOC = system organ class, TEAE = treatment-emergent adverse event.

Source: EC ISS Table 5.5; ADaM dataset: ADSL_EC ISS, ADAE_EC ISS.

In the Indication Safety Set, 85.1% of subjects had a severe (worst postbaseline Grade ≥3) TEAE. The majority of subjects had a Grade 3 TEAE (72.3%) and 9.6% of subjects had a Grade 4 TEAE (Table 17). The most frequently reported Grade 3 TEAE was hypertension (36.2%); 2 (2.1%) subjects had Grade 4 hypertension. Other commonly reported Grade 3 TEAEs (occurring in ≥5% of subjects) were, by decreasing incidence: fatigue, increased lipase, asthenia, hyponatremia, abdominal pain, and nausea. Grade 4 TEAEs of hypertension and hypomagnesemia were each reported in 2 (2.1%) subjects in the Indication Safety Set. The incidence and type of severe TEAEs observed in the Indication Safety Set were generally consistent with either the Lenvatinib Monotherapy or the Pembrolizumab Monotherapy Safety Set, with the exceptions of Grades 3 and 4 increased lipase, Grades 3 and 4 hypokalemia, and Grade 3 hyponatremia. The incidence of severe hypokalemia was higher in the EC safety sets than in both monotherapy safety sets (EC ISS Table 5.3; ADaM dataset: ADSL_EC ISS, ADAE_EC ISS).

The Regulatory Authorities' Assessment:

The reviewers conducted an independent assessment of TEAEs and the results are shown in Table 38: Adverse Reactions in Study111/KN-146 Occurring in ≥10% of Patients in the Not MSI-H/dMMR EC 2L+ Data Set. To ensure consistency of the safety profile, a safety analysis was also performed for all patients with endometrial carcinoma who had received at least 1 prior line of therapy (EC 2L+; n=108) in Study 111/KN-146 (ie, including MSI-H/dMMR (n=14) as well as the not MSI-H/dMMR group (n=94)). The most common AEs (>50%) in the *not MSI-H/dMMR EC 2L+* data set were fatigue, hypertension, musculoskeletal disorders, diarrhea, decreased appetite and hypothyroidism, whereas common Grade 3-4 AEs were hypertension, fatigue, and lipase increase. The reviewers pooled several PTs, resulting in hemorrhage,

elevated LFTs, and renal impairment also being frequent AEs reported in the *not MSI-H/dMMR EC 2L+* data set.

We compared the safety results of our analyses to the safety findings of the monotherapy studies. In the lenvatinib monotherapy trial (study 204 used a higher dose of lenvatinib at 24mg compared to 20mg used in study 111/KN-146), the most notable Grade 3-4 AEs include hypertension, fatigue, and proteinuria. For pembrolizumab monotherapy, common Grade 3-4 AEs include UTI, dyspnea and hyponatremia.

We note that the incidence of Grade 1-5 TEAEs is higher in L+P versus the monotherapies, as expected; however, no new safety signal was identified. The adverse events in the lenvatinib and pembrolizumab monotherapy studies were consistent with their known safety profile, and the adverse events in L+P were consistent with the known AEs of each drug.

Table 38: Adverse Reactions in Study111/KN-146 Occurring in ≥10% of Patients in the Not MSI-H/dMMR EC 2L+ Data Set

	Lenvatinib + Pembrolizumab		Lenvatinib + Pembrolizumab		Lenvatinib monotherapy Study 204		Pembrolizumab monotherapy KN-158		Pembrolizumab monotherapy KN-028	
	Not MSI-H/dMMR EC 2L+		All previously treated EC 2L+				Not (MSI-H/dMMR)		Not (MSI-H/dMMR)	
PTs	**N=94; n (%)**		**N=108; n (%)**		**N=133; n (%)**		**N=90; n (%)**		**N=18; n (%)**	
	G1-5	G3-4	G1-5	G3-4	G1-5	G3-4	G1-5	G3-4	G1-5	G3-4
All AEs	94 (100)	69 (73.4)	108 (100)	79 (73.1)	126 (94.7)	86 (64.7)	88 (97.8)	35 (38.9)	17 (94.4)	4 (22.2)
Fatigue	61 (64.9)	17 (18.1)	73 (67.6)	18 (16.7)	83 (62.4)	29 (21.8)	38 (42.2)	3 (3.3)	7 (38.9)	0 (0)
Musculoskeletal pain	62 (66)	5 (5.3)	74 (68.5)	7 (6.5)	37 (27.8)	1 (0.8)	38 (42.2)	2 (2.2)	5 (27.8)	0 (0)
Hypertension	61 (64.9)	36 (38.3)	69 (63.9)	39 (36.1)	76 (57.1)	46 (34.6)	1 (1.1)	0 (0)	0 (0)	0 (0)
Diarrhea	60 (63.8)	4 (4.3)	69 (63.9)	8 (7.4)	48 (36.1)	8 (6.0)	16 (17.8)	1 (1.1)	3 (16.7)	1 (5.6)
Decreased appetite	50 (53.1)	1 (1.1)	57 (52.8)	1 (0.9)	48 (36.1)	3 (2.3)	24 (26.7)	1 (1.1)	4 (22.2)	0 (0)
Hypothyroidism	48 (51.1)	1 (1.1)	53 (49.1)	1 (0.9)	33 (24.8)	3 (2.3)	8 (8.9)	0 (0)	0 (0)	0 (0)
Nausea	47 (50)	5 (5.3)	54 (50)	5 (4.6)	45 (33.8)	4 (3)	27 (30)	2 (2.2)	3 (16.7)	0 (0)
Stomatitis	41 (43.6)	0 (0)	46 (42.6)	0 (0)	41 (30.8)	3 (2.3)	3 (3.3)	0 (0)	2 (11.1)	0 (0)
Vomiting	37 (39.4)	0 (0)	42 (38.9)	0 (0)	36	4 (3)	15	1 (1.1)	2	0 (0)

PTs	Lenvatinib + Pembrolizumab Not MSI-H/dMMR EC 2L+ N=94; n (%)		Lenvatinib + Pembrolizumab All previously treated EC 2L+ N=108; n (%)		Lenvatinib monotherapy Study 204 N=133; n (%)		Pembrolizumab monotherapy KN-158 Not (MSI-H/dMMR) N=90; n (%)		Pembrolizumab monotherapy KN-028 Not (MSI-H/dMMR) N=18; n (%)	
	G1-5	G3-4	G1-5	G3-4	G1-5	G3-4	G1-5	G3-4	G1-5	G3-4
					(27.1)		(16.7)		(11.1)	
Weight decreased	34 (36.2)	3 (3.2)	37 (34.3)	4 (3.7)	31 (23.3)	5 (3.8)	8 (8.9)	0 (0)	0 (0)	0 (0)
Headache	31 (33)	1 (1.1)	35 (32.4)	1 (0.9)	35 (26.3)	3 (2.3)	8 (8.9)	0 (0)	4 (22.2)	0 (0)
Constipation	30 (31.9)	0 (0)	33 (30.6)	0 (0)	26 (19.5)	1 (0.8)	12 (13.3)	1 (1.1)	1 (5.6)	0 (0)
UTI	30 (31.9)	4 (4.3)	33 (30.6)	5 (4.6)	21 (15.8)	3 (2.3)	15 (16.7)	6 (6.7)	0 (0)	0 (0)
Abdominal pain	28 (29.8)	5 (5.3)	36 (33.3)	5 (4.6)	39 (29.3)	8 (6)	18 (20)	0 (0)	2 (11.1)	0 (0)
Dysphonia	27 (28.7)	0 (0)	31 (28.7)	0 (0)	27 (20.3)	0 (0)	2 (2.2)	0 (0)	0 (0)	0 (0)
Hemorrhages	26 (27.7)	3 (3.2)	30 (27.8)	4 (3.7)	32 (24.1)	2 (1.5)	11 (12.2)	0 (0)	2 (11.1)	1 (5.6)
Hypomagnesaemia	25 (26.6)	3 (3.2)	29 (26.9)	4 (3.7)	11 (8.3)	2 (1.5)	1 (1.1)	1 (1.1)	5 (27.8)	0 (0)
Palmar-plantar erythrodysesthesia	25 (26.6)	3 (3.2)	30 (27.8)	3 (2.8)	13 (9.8)	3 (2.3)	0 (0)	0 (0)	0 (0)	0 (0)
Dyspnea	23 (24.5)	2 (2.1)	26 (24.1)	2 (1.9)	22 (16.5)	5 (3.8)	16 (17.8)	3 (3.3)	2 (11.1)	0 (0)
Cough	20 (21.3)	0 (0)	25 (23.1)	1 (0.9)	20 (15.0)	3 (2.3)	15 (16.7)	0 (0)	1 (5.6)	0 (0)
Rash	20 (21.3)	3 (3.2)	25 (23.1)	3 (2.8)	8 (6.0)	0 (0)	9 (10)	1 (1.1)	2 (11.1)	1 (5.6)
Proteinuria	18 (19.1)	1 (1.1)	24 (22.2)	4 (3.7)	33 (24.8)	11 (8.3)	2 (2.2)	0 (0)	0 (0)	0 (0)
Dehydration	17 (18.1)	2 (2.1)	18 (16.7)	2 (1.9)	12 (9.0)	8 (6.0)	2 (2.2)	1 (1.1)	0 (0)	0 (0)
Dry mouth	17 (18.1)	0 (0)	19 (17.6)	0 (0)	16 (12.0)	0 (0)	4 (4.4)	1 (1.1)	0 (0)	0 (0)
Edema peripheral	17 (18.1)	0 (0)	21 (19.4)	0 (0)	20 (15.0)	1 (0.8)	9 (10)	1 (1.1)	0 (0)	0 (0)
Lipase increased	13 (13.8)	9 (9.6)	15 (13.9)	10 (9.3)	2 (1.5)	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)

	Lenvatinib + Pembrolizumab		Lenvatinib + Pembrolizumab		Lenvatinib monotherapy Study 204		Pembrolizumab monotherapy KN-158		Pembrolizumab monotherapy KN-028	
	Not MSI-H/dMMR EC 2L+		All previously treated EC 2L+				Not (MSI-H/dMMR)		Not (MSI-H/dMMR)	
PTs	N=94; n (%)		N=108; n (%)		N=133; n (%)		N=90; n (%)		N=18; n (%)	
	G1-5	G3-4	G1-5	G3-4	G1-5	G3-4	G1-5	G3-4	G1-5	G3-4
Dizziness	13 (13.8)	0 (0)	16 (14.8)	0 (0)	21 (15.8)	0 (0)	3 (3.3)	0 (0)	3 (16.7)	0 (0)
Dry skin	12 (12.8)	0 (0)	13 (12)	0 (0)	7 (5.3)	0 (0)	3 (3.3)	0 (0)	1 (5.6)	0 (0)
Peripheral neuropathy	12 (12.8)	0 (0)	12 (11.1)	0 (0)	9 (6.8)	0 (0)	12 (13.3)	1 (1.1)	1 (5.6)	0 (0)
Hyponatremia	11 (11.7)	6 (6.4)	12 (11.1)	7 (6.5)	5 (3.8)	1 (0.8)	3 (3.3)	3 (3.3)	2 (11.1)	1 (5.6)
Muscular weakness	11 (11.7)	2 (2.1)	14 (13)	2 (1.9)	4 (3)	2 (1.5)	2 (2.2)	0 (0)	0 (0)	0 (0)
Elevated LFTs	11 (11.7)	3 (3.2)	14 (13)	5 (4.6)	15 (11.3)	5 (3.8)	9 (10)	1 (1.1)	1 (5.6)	1 (5.6)
Renal impairment	11 (11.7)	3 (3.2)	13 (12)	4 (3.7)	12 (9.0)	5 (3.8)	9 (10)	2 (2.2)	0 (0)	0 (0)
Gastro-esophageal reflux disease	10 (10.6)	0 (0)	12 (11.1)	0 (0)	5 (3.8)	0 (0)	3 (3.3)	0 (0)	1 (5.6)	0 (0)
Hypokalemia	10 (10.6)	5 (5.3)	12 (11.1)	6 (5.6)	18 (13.5)	5 (3.8)	2 (2.2)	0 (0)	1 (5.6)	0 (0)
Pyrexia	10 (10.6)	0 (0)	12 (11.1)	0 (0)	6 (4.5)	0 (0)	13 (14.4)	0 (0)	2 (11.1)	0 (0)

Lenvatinib + pembrolizumab analysis performed with 90-day safety update dataset. Information in the label for lenvatinib and pembrolizumab does not incorporate the information from the 90-day safety update as no significant change to the safety profile of lenvatinib plus pembrolizumab compared with that previously reported in the EC submission was observed.

Source: Study 111 – adsl.xpt, adae.xpt; Study 111 90-day safety update - adsl.xpt, adae.xpt; Study 204 – adsl.xpt, adae.xpt; KN-158 – adsl.xpt, adae.xpt; KN-028 – adsl.xpt, adae.xpt.

Laboratory Findings

The Applicant's Position:

The clinical laboratory evaluations focused on parameters of potential clinical interest given the AE profile of lenvatinib and pembrolizumab as monotherapies. Summaries of changes from baseline and shifts in laboratory toxicities (based on CTCAE v4.03 grading of laboratory values) were assessed (Table 39, Table 40, Table 41, Table 42) . In the Indication Safety Set, there were no clinically meaningful changes from Baseline in median hematologic parameters and no

remarkable differences from each study drug used as a monotherapy in clinical chemistry laboratory values throughout treatment (see Module 2.7.4, Sections 2.7.4.2.1.6, 2.7.4.2.1.7, and 2.7.4.3 for details).

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Table 39
Treatment-Emergent Grade 3 or 4 Laboratory Results for Hematology Tests – All Safety Sets

Hematology Parameter Worst Postbaseline Grade	Combination Therapy			Monotherapy	
	Lenv 20 mg + Pembro 200 mg			Lenv 24 mg (N=1119) n (%)	Pembro (N=2799) n (%)
	Indication (N=94) n (%)	All EC (N=124) n (%)	Non-EC (N=159) n (%)		
Hemoglobin decreased					
Overall, n[a]	92	121	151	1065	2685
Grade 3, n (%)	1 (1.1)	2 (1.7)	6 (4.0)	20 (1.9)	112 (4.2)
Grade 4, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (0.3)
Platelet count decreased					
Overall, n[a]	92	121	151	1060	2686
Grade 3, n (%)	0 (0.0)	0 (0.0)	2 (1.3)	20 (1.9)	13 (0.5)
Grade 4, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	23 (0.9)
White blood cells decreased					
Overall, n[a]	92	121	151	1064	2680
Grade 3, n (%)	2 (2.2)	3 (2.5)	3 (2.0)	7 (0.7)	5 (0.2)
Grade 4, n (%)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.1)	8 (0.3)
Neutrophil count decreased					
Overall, n[a]	92	121	151	1057	2326
Grade 3, n (%)	2 (2.2)	2 (1.7)	4 (2.6)	14 (1.3)	15 (0.6)
Grade 4, n (%)	1 (1.1)	2 (1.7)	1 (0.7)	4 (0.4)	13 (0.6)

Data cutoff date for Combination Therapy Safety Sets: 10 Jan 2019.
Data cutoff date for Lenv monotherapy studies: 01 Sep 2016 (ongoing studies), except Study 205 (which had a cutoff date of 15 Mar 2018); earlier for completed studies.
Data cutoff date for the Pembro monotherapy studies: varied by study; range 18 Apr 2014 to 30 Sep 2015.
Percentages are based on total number of subjects within the respective safety set.
Rows containing only zeroes have been omitted from this in-text table.
Subjects are counted only once for each row.
Grade 3, Grade 4 = the number of subjects with an increase of at least 1 CTCAE grade from baseline to the worst postbaseline value that is Grade 3 or 4.
Laboratory Results were graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.
dMMR = mismatch repair deficient, EC = endometrial carcinoma, Lenv = lenvatinib, MSI-H = microsatellite instability-high, NA = not available, NSCLC = non-small-cell lung cancer, Pembro = pembrolizumab, Q3W = once every 3 weeks, QD = once daily.
a: Indicates the number of subjects with nonmissing baseline and postbaseline data; this number was used to calculate percentages within each laboratory test.
Source: EC ISS Table 11.3.1.

Table 40
Treatment-Emergent Grade 3 or 4 Laboratory Results for Clinical Chemistry Tests
All Safety Sets

Clinical Chemistry Parameter Worst Postbaseline Grade	Combination Therapy			Monotherapy	
	Lenv 20 mg + Pembro 200 mg			Lenv 24 mg (N=1119) n (%)	Pembro (N=2799) n (%)
	Indication (N=94) n (%)	All EC (N=124) n (%)	Non-EC (N=159) n (%)		
Blood calcium decreased					
Overall, n[a]	91	121	151	555	2672
Grade 3, n (%)	1 (1.1)	1 (0.8)	1 (0.7)	10 (1.8)	17 (0.6)
Grade 4, n (%)	2 (2.2)	2 (1.7)	0 (0.0)	7 (1.3)	15 (0.6)
Lipase increased					
Overall, n[a]	89	118	147	727	NA
Grade 3, n (%)	12 (13.5)	13 (11.0)	7 (4.8)	29 (4.0)	NA
Grade 4, n (%)	4 (4.5)	7 (5.9)	13 (8.8)	12 (1.7)	NA
Serum amylase increased					
Overall, n[a]	89	118	146	753	1
Grade 3, n (%)	5 (5.6)	7 (5.9)	11 (7.5)	22 (2.9)	0 (0.0)
Grade 4, n (%)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.1)	0 (0.0)
Blood magnesium decreased					
Overall, n[a]	91	120	149	NA	2560
Grade 3, n (%)	0 (0.0)	1 (0.8)	0 (0.0)	NA	0 (0.0)
Grade 4, n (%)	2 (2.2)	2 (1.7)	1 (0.7)	NA	4 (0.2)
Blood potassium decreased					
Overall, n[a]	92	122	151	1069	2678
Grade 3, n (%)	4 (4.3)	7 (5.7)	9 (6.0)	44 (4.1)	39 (1.5)
Grade 4, n (%)	1 (1.1)	2 (1.6)	2 (1.3)	5 (0.5)	10 (0.4)
Blood sodium decreased					
Overall, n[a]	92	122	151	1070	2684
Grade 3, n (%)	11 (12.0)	14 (11.5)	21 (13.9)	63 (5.9)	149 (5.6)
Grade 4, n (%)	1 (1.1)	1 (0.8)	4 (2.6)	8 (0.7)	39 (1.5)
Alanine aminotransferase increased					
Overall, n[a]	92	122	151	1069	2673
Grade 3, n (%)	3 (3.3)	4 (3.3)	3 (2.0)	32 (3.0)	51 (1.9)
Grade 4, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.4)	8 (0.3)
Alkaline phosphatase increased					
Overall, n[a]	91	121	151	1070	2668
Grade 3, n (%)	1 (1.1)	3 (2.5)	3 (2.0)	16 (1.5)	55 (2.1)
Grade 4, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.1)
Aspartate aminotransferase increased					

Table 40
Treatment-Emergent Grade 3 or 4 Laboratory Results for Clinical Chemistry Tests
All Safety Sets

Clinical Chemistry Parameter Worst Postbaseline Grade	Combination Therapy			Monotherapy	
	Lenv 20 mg + Pembro 200 mg			Lenv 24 mg (N=1119) n (%)	Pembro (N=2799) n (%)
	Indication (N=94) n (%)	All EC (N=124) n (%)	Non-EC (N=159) n (%)		
Overall, n[a]	92	122	151	1070	2670
Grade 3, n (%)	4 (4.3)	5 (4.1)	6 (4.0)	28 (2.6)	45 (1.7)
Grade 4, n (%)	0 (0.0)	1 (0.8)	1 (0.7)	3 (0.3)	11 (0.4)
Blood bilirubin increased					
Overall, n[a]	91	121	151	1070	2675
Grade 3, n (%)	1 (1.1)	1 (0.8)	4 (2.6)	9 (0.8)	35 (1.3)
Grade 4, n (%)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.1)	7 (0.3)
Creatinine increased					
Overall, n[a]	92	122	151	1072	2688
Grade 3, n (%)	5 (5.4)	5 (4.1)	5 (3.3)	20 (1.9)	12 (0.4)
Grade 4, n (%)	1 (1.1)	1 (0.8)	1 (0.7)	0 (0.0)	7 (0.3)

Data cutoff date for Combination Therapy Safety Sets: 10 Jan 2019.
Data cutoff date for Lenv monotherapy studies: 01 Sep 2016 (ongoing studies), except Study 205 (which had a cutoff date of 15 Mar 2018); earlier for completed studies.
Data cutoff date for the Pembro monotherapy studies: varied by study; range 18 Apr 2014 to 30 Sep 2015.
Percentages are based on total number of subjects within the respective safety set.
Rows containing only zeroes have been omitted from this in-text table.
Subjects are counted only once for each row.
Grade 3, Grade 4 = the number of subjects with an increase of at least 1 CTCAE grade from baseline to the worst postbaseline value that is Grade 3 or 4.
Laboratory Results were graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.
dMMR = mismatch repair deficient, EC = endometrial carcinoma, Lenv = lenvatinib, MSI-H = microsatellite instability-high, NA = not available, NSCLC = non-small-cell lung cancer, Pembro = pembrolizumab, Q3W = once every 3 weeks, QD = once daily.
a: Indicates the number of subjects with nonmissing baseline and postbaseline data; this number was used to calculate percentages within each laboratory test.
Source: EC ISS Tables 11.3.2 and 11.3.3.

Table 41
Thyroid Function Tests at Baseline and Worst Postbaseline Value – Combination Therapy and Lenvatinib Monotherapy Safety Sets

Parameter Visit Category	Combination Therapy			Monotherapy
	Lenv 20 mg + Pembro 200 mg			Lenv 24 mg (N=1119) n (%)
	Indication (N=94) n (%)	All EC (N=124) n (%)	Non-EC (N=159) n (%)	
TSH				
Baseline				
≤ULN	77/89 (86.5)	105/118 (89.0)	120/139 (86.3)	891/950 (93.8)
>ULN	12/89 (13.5)	13/118 (11.0)	19/139 (13.7)	59/950 (6.2)
Worst Postbaseline Value				
≤ULN	17/89 (19.1)	24/118 (20.3)	30/139 (21.6)	384/950 (40.4)
>ULN	72/89 (80.9)	94/118 (79.7)	109/139 (78.4)	566/950 (59.6)
Free T_4 levels				
Baseline				
≤ULN	82/86 (95.3)	110/115 (95.7)	130/136 (95.6)	NA
>ULN	4/86 (4.7)	5/115 (4.3)	6/136 (4.4)	NA
Worst Postbaseline Value				
≤ULN	59/86 (68.6)	74/115 (64.3)	107/136 (78.7)	NA
>ULN	27/86 (31.4)	41/115 (35.7)	29/136 (21.3)	NA

Data cutoff date for Combination Therapy Safety Sets: 10 Jan 2019.
Data cutoff date for Lenv monotherapy studies: 01 Sep 2016 (ongoing studies), except Study 205 (which had a cutoff date of 15 Mar 2018); earlier for completed studies.
Percentages were based on the number of subjects with nonmissing data at both Baseline and any postbaseline visit in the Safety Analysis Set and the upper limit of the standardized normal range.
dMMR = mismatch repair deficient, EC = endometrial carcinoma, Lenv = lenvatinib, MSI-H = microsatellite instability-high, NA = not available, Pembro = pembrolizumab, Q3W = once every 3 weeks, QD = once daily, T_4 = thyroxine, TSH = thyroid stimulating hormone, ULN = upper limit of normal.
Source: EC ISS Table 11.2.6.

Table 42 Proteinuria from 24-Hour Urine Collection at Postbaseline - Combination Therapy and Lenvatinib Monotherapy Safety Sets				
	Combination Therapy			Monotherapy
	Lenv 20 mg + Pembro 200 mg			Lenv 24 mg (N=1119) n (%)
	Indication (N=94) n (%)	All EC (N=124) n (%)	Non-EC (N=159) n (%)	
Number of Subjects with 24-Hour Urine Collection at Postbaseline	21 (22.3)	30 (24.2)	44 (27.7)	294 (26.3)
Number of Subjects with Proteinuria at Postbaseline	20 (21.3)	29 (23.4)	43 (27.0)	228 (20.4)
Worst Grade of Proteinuria				
Grade 0	1 (1.1)	1 (0.8)	1 (0.6)	65 (5.8)
Grade 1	13 (13.8)	16 (12.9)	19 (11.9)	108 (9.7)
Grade 2	6 (6.4)	10 (8.1)	14 (8.8)	64 (5.7)
Grade 3	1 (1.1)	3 (2.4)	10 (6.3)	56 (5.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Proteinuria data from 24-Hour Urine Collection are not available for Pembro Monotx Safety Set. Percentages are based on the total number of subjects in the respective safety set. Grades of Proteinuria are based on 24-hour urine protein collection per CTCAE version 4.03. Data cutoff date: 10 Jan 2019 for Study 111/KN146; for all other studies, the clinical cutoff date for each study was used. Source: EC !SS Table 11.2.5				

The Regulatory Authorities' Assessment:

Our analyses of laboratory abnormalities are consistent with the applicant's findings presented above.

Vital Signs

The Applicant's Position:

Summaries of changes from baseline and shifts to worst postbaseline values (based on CTCAE v4.03 grading of vital sign values) were assessed (Table 24). No clinically meaningful trends over time were observed in vital signs or body weight in the Indication Safety Set. Mean changes from Baseline in systolic BP and diastolic BP ranges in the Indication Safety Set were similar to those observed for the Lenvatinib Monotherapy Safety Set. In the Indication Safety Set, a slight decrease from Baseline in median body weight occurred by Cycle 1. The maximum decrease from Baseline in median body weight was 15.50 kg. Results for the Lenvatinib Monotherapy Safety Set were similar to those for the Indication Safety Set.

See Module 2.7.4, Sections 2.7.4.4.1.1 and 2.7.4.4.1.2 for further details.

Table 43 Hypertension Determined by Vital Signs: Shifts from Baseline to Worst Postbaseline CTCAE Grade				
	Baseline Grade			
Analysis Set **Worst Postbaseline Grade**	**Grade 0** **n (%)**	**Grade 1** **n (%)**	**Grade 2** **n (%)**	**Grade 3** **n (%)**
Indication EC 2L+ Non-MSI-H/pMMR Lenv+Pembro (m[a]=92)				
Grade 0	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)
Grade 1	13 (14.1)	6 (6.5)	1 (1.1)	0 (0.0)
Grade 2	14 (15.2)	18 (19.6)	5 (5.4)	0 (0.0)
Grade 3	10 (10.9)	19 (20.7)	5 (5.4)	0 (0.0)
All EC Lenv+Pembro (m[a]=121)				
Grade 0	1 (0.8)	1 (0.8)	0 (0.0)	0 (0.0)
Grade 1	14 (11.6)	8 (6.6)	2 (1.7)	0 (0.0)
Grade 2	18 (14.9)	28 (23.1)	6 (5.0)	0 (0.0)
Grade 3	12 (9.9)	25 (20.7)	6 (5.0)	0 (0.0)
Non-EC Lenv+Pembro (m[a]=151)				
Grade 0	6 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 1	24 (15.9)	24 (15.9)	2 (1.3)	0 (0.0)
Grade 2	26 (17.2)	25 (16.6)	5 (3.3)	1 (0.7)
Grade 3	7 (4.6)	28 (18.5)	3 (2.0)	0 (0.0)
Lenv Monotx 24 mg (m[a]=1071)				
Grade 0	16 (1.5)	6 (0.6)	0 (0.0)	0 (0.0)
Grade 1	116 (10.8)	95 (8.9)	5 (0.5)	1 (0.1)
Grade 2	138 (12.9)	231 (21.6)	49 (4.6)	2 (0.2)
Grade 3	90 (8.4)	234 (21.8)	83 (7.7)	5 (0.5)

Vital sign data are not available for Pembro Monotx Safety Set.
Hypertension results were graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.
CTCAE= Common Terminology Criteria for adverse Events, Lenv = lenvatinib, MSI-H = microsatellite instability-high, Pembro = pembrolizumab, pMMR= mistmatch repair proficient
a: Indicates the number of subjects with both non-missing baseline and at least one postbaseline result in the respective safety set; this number is used to calculate percentages.
Data cutoff date: 10 Jan 2019 for Study 111/KN146; for all other studies, the clinical cutoff date for each study was used.
Source: EC ISS Table 12.2

The Regulatory Authorities' Assessment:

Our analyses of vital signs (hypertension) corroborate the applicant's findings presented above.

Electrocardiograms (ECGs)

The Applicant's Position:

ECG testing was routinely performed during Study 111 as specified in the study protocol (Table 9). Clinically significant abnormal findings were not identified.

The Regulatory Authorities' Assessment:
We agree with the applicant's statement above.

QT

The Applicant's Position:

QT prolongation and decreased left ventricular ejection fraction are CSEs for lenvatinib. Based on ECG and echocardiogram data, there was no increased incidence of these events in the combination-therapy safety sets compared with the Lenvatinib Monotherapy Safety Set. These data are described in Module 2.7.4, Sections 2.7.4.2.1.7, 2.7.4.4.3.1, and 2.7.4.4.3.3.

The Regulatory Authorities' Assessment:
We agree with the applicant's statement above.

Immunogenicity

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The Applicant's Position:

The development of anti-drug antibodies against pembrolizumab were not measured in Study 111.

The Regulatory Authorities' Assessment:
We agree with the applicant's statement above.

7.2.5. Analysis of Submission-Specific Safety Issues

The Applicant's Position:

Overlapping Toxicities of Clinical Interest

Overlapping toxicities of clinical interest are defined by the sponsors as known or established risks, common to both lenvatinib and pembrolizumab, that are seen more frequently above a defined threshold in the Indication Safety Set (refer to Module 2.7.4, Section 2.7.4.2.1.8 for the threshold definition). These overlapping toxicities are hypothyroidism, pancreatitis, skin reactions, and nephritis.

- The incidence of hypothyroidism events was 48.9% in the Indication Safety Set (Table 37) compared with 18.9% in the non-thyroid cancer subset of the Lenvatinib Monotherapy and 8.4% in the Pembrolizumab Monotherapy Safety Sets (Table 44; ADaM dataset: ADSL_EC ISS, ADAE_EC ISS). No subjects discontinued lenvatinib or pembrolizumab treatment because of hypothyroidism, and no subjects had a lenvatinib dose reduction because of the TEAE. Hypothyroidism events were primarily Grade 1 or 2 and, if appropriate, managed with thyroid hormone replacement.

Table 44
Overview of the CSE and AEOSI of Hypothyroidism – Indication and Monotherapy Safety Sets

CSE or AEOSI Category Preferred Term	Lenv 20 mg + Pembro 200 mg	Monotherapy		
	Indication (N=94) n (%)	Lenv 24 mg (N=1119) n (%)	Lenv 24 mg (non-thyroid cancer subjects only) (N=598) n (%)	Pembro (N=2799) n (%)
CSE of Hypothyroidism	48 (51.1)	222 (19.8)	149 (24.9)	N/A
Hypothyroidism	46 (48.9)	146 (13.0)	113 (18.9)	236 (8.4)
Blood TSH increased	3 (3.2)	80 (7.1)	39 (6.5)	37 (1.3)
Blood TSH abnormal	0 (0.0)	1 (0.1)	1 (0.2)	0 (0.0)
AEOSI of Hypothyroidism	46 (48.9)	N/A	N/A	237 (8.5)
Hypothyroidism	46 (48.9)	146 (13.0)	113 (18.9)	236 (8.4)
Myxoedema	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)
Primary hypothyroidism	0 (0.0)	0 (0.0)	0 (0.0)	1 (<0.1)

Data cutoff date for Combination Therapy Safety Sets: 10 Jan 2019.
Data cutoff date for Lenv monotherapy studies: 01 Sep 2016 (ongoing studies), except Study 205 (which had a cutoff date of 15 Mar 2018); earlier for completed studies.

Table 44
Overview of the CSE and AEOSI of Hypothyroidism – Indication and Monotherapy Safety Sets

Data cutoff date for the Pembro monotherapy studies: varied by study; range 18 Apr 2014 to 30 Sep 2015.
Percentages are based on the total number of subjects in the relevant safety set.
AEOSI = adverse event of special interest, CSE = clinically significant event, Lenv = lenvatinib, N/A = not applicable, Pembro = pembrolizumab, TSH = thyroid-stimulating hormone.
Source: EC ISS Table 9.1.6, EC ISS Table 9.1.1, EC ISS Table 9.2.1, EC ISS Table 5.4.

- The events of pancreatitis, nephritis, and skin reactions were reported at higher incidences than in either monotherapy (EC ISS Tables 5.2 and 5.3; ADaM datasets: ADSL_EC ISS, ADAE_EC ISS). Skin reaction events were manageable with lenvatinib and/or pembrolizumab dose interruption as appropriate. There were small numbers of pancreatitis and nephritis events; therefore, no conclusions can be drawn regarding their incidences.

See Module 2.7.4, Section 2.7.4.2.1.8 for details of overlapping toxicity.

The Regulatory Authorities' Assessment:
We performed an in-depth analysis of the CSE for lenvatinib (Table 34) and AESI for pembrolizumab (Table 35). Despite the small numbers, L+P had a higher incidence of adverse events compared to both monotherapies, as expected. Hypothyroidism occurred in 51%, pancreatitis in 4% and nephritis in 2% of the patients in the *not MSI-H/dMMR EC 2L+* group.

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

The Applicant's Position:

Patient reported outcomes were not assessed in Study 111.

The Regulatory Authorities' Assessment:
Not Applicable

7.2.7. Safety Analyses by Demographic Subgroups

The Applicant's Position:

Subgroup analyses were conducted for the intrinsic factors of age (<65 years vs ≥65 years), sex (male vs female), and race (White vs All Others), and the extrinsic factor of geographic region (US, other). In general, no meaningful differences among subgroups were observed for the overall AE profile of lenvatinib plus pembrolizumab (Table 45, Table 46, Table 47; ADaM dataset: ADSL_EC ISS, ADAE_EC ISS).

In general, the incidence rate of TEAEs in the Indication Safety Set was similar for subjects from both the US and the non-US regions, which was consistent with that in the monotherapy safety

sets. The small sample size of the non-US group limits meaningful interpretation (Table 47, ADaM dataset: ADSL_EC ISS, ADAE_EC ISS).

Table 45
Overview of Incidence of Treatment-Emergent Adverse Events by Age Group – All Safety Sets

Subjects With:	Combination Therapy						Monotherapy			
	Lenv 20 mg + Pembro 200 mg						Lenv 24 mg (N=1119)		Pembro (N=2799)	
	Indication (N=94)		All EC (N=124)		Non-EC (N=159)					
	<65 y (N=36) n (%)	≥65 y (N=58) n (%)	<65 y (N=47) n (%)	≥65 y (N=77) n (%)	<65 y (N=80) n (%)	≥65 y (N=79) n (%)	<65 y (N=700) n (%)	≥65 y (N=419) n (%)	<65 y (N=1587) n (%)	≥65 y (N=1212) n (%)
Any TEAE	36 (100.0)	58 (100.0)	47 (100.0)	77 (100.0)	79 (98.8)	79 (100.0)	692 (98.9)	416 (99.3)	1547 (97.5)	1180 (97.4)
Related[a] TEAEs	35 (97.2)	57 (98.3)	45 (95.7)	75 (97.4)	76 (95.0)	73 (92.4)	660 (94.3)	400 (95.5)	1164 (73.3)	900 (74.3)
Grade[b] ≥3 TEAEs	31 (86.1)	49 (84.5)	40 (85.1)	63 (81.8)	58 (72.5)	65 (82.3)	542 (77.4)	357 (85.2)	695 (43.8)	578 (47.7)
Related[a] Grade[b] ≥3 TEAEs	23 (63.9)	43 (74.1)	30 (63.8)	53 (68.8)	41 (51.3)	48 (60.8)	418 (59.7)	306 (73.0)	202 (12.7)	185 (15.3)
Any SAE[c]	20 (55.6)	29 (50.0)	23 (48.9)	38 (49.4)	34 (42.5)	47 (59.5)	370 (52.9)	243 (58.0)	553 (34.8)	489 (40.3)
Fatal AEs	0 (0.0)	3 (5.2)	0 (0.0)	6 (7.8)	5 (6.3)	13 (16.5)	57 (8.1)	40 (9.5)	46 (2.9)	64 (5.3)
Nonfatal SAEs	20 (55.6)	29 (50.0)	23 (48.9)	38 (49.4)	34 (42.5)	43 (54.4)	353 (50.4)	227 (54.2)	526 (33.1)	458 (37.8)
TEAEs Leading to Study Drug										
Withdrawal	6 (16.7)	18 (31.0)	9 (19.1)	24 (31.2)	15 (18.8)	27 (34.2)	172 (24.6)	127 (30.3)	164 (10.3)	170 (14.0)
Of Both Drugs	4 (11.1)	11 (19.0)	6 (12.8)	16 (20.8)	13 (16.3)	19 (24.1)	N/A	N/A	N/A	N/A
Of Lenv[d]	4 (11.1)	17 (29.3)	7 (14.9)	23 (29.9)	14 (17.5)	24 (30.4)	172 (24.6)	127 (30.3)	N/A	N/A
Of Pembro[e]	6 (16.7)	13 (22.4)	8 (17.0)	18 (23.4)	14 (17.5)	25 (31.6)	N/A	N/A	164 (10.3)	170 (14.0)
Dose Reduction of Lenv	25 (69.4)	38 (65.5)	31 (66.0)	49 (63.6)	44 (55.0)	44 (55.7)	303 (43.3)	228 (54.4)	N/A	N/A

Data cutoff date for Combination Therapy Safety Sets: 10 Jan 2019.
Data cutoff date for Lenv monotherapy studies: 01 Sep 2016 (ongoing studies), except Study 205 (which had a cutoff date of 15 Mar 2018); earlier for completed studies.
Data cutoff date for the Pembro monotherapy studies: varied by study; range 18 Apr 2014 to 30 Sep 2015.
Percentages are based on total number of subjects within the respective safety set.
Rows containing only zeroes have been omitted from this in-text table. Subjects are counted only once for each row.
CRF = case report form, dMMR = mismatch repair deficient, EC = endometrial carcinoma, Lenv = lenvatinib, MSI-H = microsatellite instability-high, NSCLC = non-small-cell lung cancer, Pembro = pembrolizumab, Q3W = once every 3 weeks, QD = once daily, SAE = serious adverse events, TEAE = treatment-emergent adverse event.
a: Related TEAEs included TEAEs that were considered by the Investigator to be possibly or probably related to the study drugs and TEAEs with a missing causality on the CRF.
b: Adverse events were graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.
c: For combination of Lenv 20 mg + Pembro, the SAE follow-up window is 90 days after the last dose. For Lenv Monotherapy and Pembro Monotherapy, the window is 30 days and 90 days after the last dose, respectively.
d: Drug withdrawal for Lenv, regardless action taken for Pembro.
e: Drug withdrawal for Pembro, regardless action taken for Lenv.
Source: EC ISS Table 10.1.

Table 46

Overview of Incidence of Treatment-Emergent Adverse Events by Race Group – All Safety Sets

Subjects With:	Combination Therapy						Monotherapy			
	Lenv 20 mg + Pembro 200 mg						Lenv 24 mg (N=1119)		Pembro (N=2799)	
	Indication (N=94)		All EC (N=124)		Non-EC (N=159)					
	White (N=81) n (%)	All Others (N=13) n (%)	White (N=108) n (%)	All Others (N=16) n (%)	White (N=140) n (%)	All Others (N=19) n (%)	White (N=900) n (%)	Other (N=219) n (%)	White (N=2474) n (%)	Other (N=325) n (%)
Any TEAE	81 (100.0)	13 (100.0)	108 (100.0)	16 (100.0)	140 (100.0)	18 (94.7)	889 (98.8)	219 (100.0)	2414 (97.6)	313 (96.3)
Related[a] TEAEs	80 (98.8)	12 (92.3)	106 (98.1)	14 (87.5)	133 (95.0)	16 (84.2)	844 (93.8)	216 (98.6)	1844 (74.5)	220 (67.7)
Grade[b] ≥3 TEAEs	68 (84.0)	12 (92.3)	88 (81.5)	15 (93.8)	110 (78.6)	13 (68.4)	719 (79.9)	180 (82.2)	1131 (45.7)	142 (43.7)
Related[a] Grade[b] ≥3 TEAEs	57 (70.4)	9 (69.2)	72 (66.7)	11 (68.8)	79 (56.4)	10 (52.6)	568 (63.1)	156 (71.2)	346 (14.0)	41 (12.6)
Any SAE[c]	40 (49.4)	9 (69.2)	51 (47.2)	10 (62.5)	76 (54.3)	5 (26.3)	497 (55.2)	116 (53.0)	925 (37.4)	117 (36.0)
Fatal AEs	3 (3.7)	0 (0.0)	6 (5.6)	0 (0.0)	17 (12.1)	1 (5.3)	80 (8.9)	17 (7.8)	89 (3.6)	21 (6.5)
Nonfatal SAEs	40 (49.4)	9 (69.2)	51 (47.2)	10 (62.5)	72 (51.4)	5 (26.3)	469 (52.1)	111 (50.7)	877 (35.4)	107 (32.9)
TEAEs Leading to Study Drug										
Withdrawal	20 (24.7)	4 (30.8)	28 (25.9)	5 (31.3)	40 (28.6)	2 (10.5)	256 (28.4)	43 (19.6)	302 (12.2)	32 (9.8)
Of Both Drugs	13 (16.0)	2 (15.4)	19 (17.6)	3 (18.8)	31 (22.1)	1 (5.3)	N/A	N/A	N/A	N/A
Of Lenv[d]	18 (22.2)	3 (23.1)	26 (24.1)	4 (25.0)	36 (25.7)	2 (10.5)	256 (28.4)	43 (19.6)	N/A	N/A
Of Pembro[e]	16 (19.8)	3 (23.1)	22 (20.4)	4 (25.0)	37 (26.4)	2 (10.5)	N/A	N/A	302 (12.2)	32 (9.8)
Dose Reduction of Lenv	55 (67.9)	8 (61.5)	71 (65.7)	9 (56.3)	77 (55.0)	11 (57.9)	391 (43.4)	140 (63.9)	N/A	N/A

Data cutoff date for Combination Therapy Safety Sets: 10 Jan 2019.
Data cutoff date for Lenv monotherapy studies: 01 Sep 2016 (ongoing studies), except Study 205 (which had a cutoff date of 15 Mar 2018); earlier for completed studies.
Data cutoff date for the Pembro monotherapy studies: varied by study; range 18 Apr 2014 to 30 Sep 2015.
Percentages are based on total number of subjects within the respective safety set.
Rows containing only zeroes have been omitted from this in-text table.
Subjects are counted only once for each row.
CRF = case report form, dMMR = mismatch repair deficient, EC = endometrial carcinoma, Lenv = lenvatinib, MSI-H = microsatellite instability-high, NSCLC = non-small-cell lung cancer, Pembro = pembrolizumab, Q3W = once every 3 weeks, QD = once daily, SAE = serious adverse events, TEAE = treatment-emergent adverse event.
a: Related TEAEs included TEAEs that were considered by the Investigator to be possibly or probably related to the study drugs and TEAEs with a missing causality on the CRF.
b: Adverse events were graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.
c: For combination of Lenv 20 mg + Pembro, the SAE follow-up window is 90 days after the last dose. For Lenv Monotherapy and Pembro Monotherapy, the window is 30 days and 90 days after the last dose, respectively.

Table 46

Overview of Incidence of Treatment-Emergent Adverse Events by Race Group – All Safety Sets

d: Drug withdrawal for Lenv, regardless action taken for Pembro.
e: Drug withdrawal for Pembro, regardless action taken for Lenv.
Source: EC ISS Table 10.1.

Table 47

Overview of Incidence of Treatment-Emergent Adverse Events by Region – All Safety Sets

	Combination Therapy						Monotherapy			
	Lenv 20 mg + Pembro 200 mg						Lenv 24 mg (N=1119)		Pembro (N=2799)	
	Indication (N=94)		All EC (N=124)		Non-EC (N=159)					
Subjects With:	US (N=81) n (%)	Non-US (N=13) n (%)	US (N=101) n (%)	Non-US (N=23) n (%)	US (N=155) n (%)	Non-US (N=4) n (%)	US (N=423) n (%)	Non-US (N=696) n (%)	US (N=1250) n (%)	Non-US (N=1549) n (%)
Any TEAE	81 (100.0)	13 (100.0)	101 (100.0)	23 (100.0)	154 (99.4)	4 (100.0)	422 (99.8)	686 (98.6)	1223 (97.8)	1504 (97.1)
Related[a] TEAEs	80 (98.8)	12 (92.3)	98 (97.0)	22 (95.7)	145 (93.5)	4 (100.0)	413 (97.6)	647 (93.0)	928 (74.2)	1136 (73.3)
Grade[b] ≥3 TEAEs	70 (86.4)	10 (76.9)	84 (83.2)	19 (82.6)	121 (78.1)	2 (50.0)	340 (80.4)	559 (80.3)	579 (46.3)	694 (44.8)
Related[a] Grade[b] ≥3 TEAEs	57 (70.4)	9 (69.2)	68 (67.3)	15 (65.2)	87 (56.1)	2 (50.0)	280 (66.2)	444 (63.8)	157 (12.6)	230 (14.8)
Any SAE[c]	45 (55.6)	4 (30.8)	51 (50.5)	10 (43.5)	80 (51.6)	1 (25.0)	217 (51.3)	396 (56.9)	459 (36.7)	583 (37.6)
Fatal AEs	3 (3.7)	0 (0.0)	4 (4.0)	2 (8.7)	18 (11.6)	0 (0.0)	18 (4.3)	79 (11.4)	31 (2.5)	79 (5.1)
Nonfatal SAEs	45 (55.6)	4 (30.8)	51 (50.5)	10 (43.5)	76 (49.0)	1 (25.0)	211 (49.9)	369 (53.0)	442 (35.4)	542 (35.0)
TEAEs Leading to Study Drug										
Withdrawal	22 (27.2)	2 (15.4)	27 (26.7)	6 (26.1)	42 (27.1)	0 (0.0)	127 (30.0)	172 (24.7)	149 (11.9)	185 (11.9)
Of Both Drugs	14 (17.3)	1 (7.7)	17 (16.8)	5 (21.7)	32 (20.6)	0 (0.0)	N/A	N/A	N/A	N/A
Of Lenv[d]	19 (23.5)	2 (15.4)	24 (23.8)	6 (26.1)	38 (24.5)	0 (0.0)	127 (30.0)	172 (24.7)	N/A	N/A
Of Pembro[e]	18 (22.2)	1 (7.7)	21 (20.8)	5 (21.7)	39 (25.2)	0 (0.0)	N/A	N/A	149 (11.9)	185 (11.9)
Dose Reduction of Lenv	54 (66.7)	9 (69.2)	67 (66.3)	13 (56.5)	88 (56.8)	0 (0.0)	192 (45.4)	339 (48.7)	N/A	N/A

Data cutoff date for Combination Therapy Safety Sets: 10 Jan 2019.
Data cutoff date for Lenv monotherapy studies: 01 Sep 2016 (ongoing studies), except Study 205 (which had a data cutoff date of 15 Mar 2018); earlier for completed studies.
Data cutoff date for the Pembro monotherapy studies: varied by study; range 18 Apr 2014 to 30 Sep 2015.
Percentages are based on total number of subjects within the respective safety set.
Rows containing only zeroes have been omitted from this in-text table.

Table 47
Overview of Incidence of Treatment-Emergent Adverse Events by Region – All Safety Sets

Subjects are counted only once for each row.
CRF = case report form, dMMR = mismatch repair deficient, EC = endometrial carcinoma, Lenv = lenvatinib, MSI-H = microsatellite instability-high, NSCLC = non-small-cell lung cancer, Pembro = pembrolizumab, Q3W = once every 3 weeks, QD = once daily, SAE = serious adverse events, TEAE = treatment-emergent adverse event.
a: Related TEAEs included TEAEs that were considered by the Investigator to be possibly or probably related to the study drugs and TEAEs with a missing causality on the CRF.
b: Adverse events were graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.
c: For combination of Lenv 20 mg + Pembro, the SAE follow-up window is 90 days after the last dose. For Lenv Monotherapy and Pembro Monotherapy, the window is 30 days and 90 days after the last dose, respectively.
d: Drug withdrawal for Lenv, regardless of action taken for Pembro.
e: Drug withdrawal for Pembro, regardless of action taken for Lenv.
Source: EC ISS Table 10.1.

The Regulatory Authorities' Assessment:
We agree with the applicant's assessment above.

7.2.8. Specific Safety Studies/Clinical Trials

The Applicant's Position:

Not applicable.

The Regulatory Authorities' Assessment:
We agree with the applicant's statement above.

7.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

APPEARS THIS WAY
ON ORIGINAL

The Applicant's Position:

No new information concerning human carcinogenicity or tumor development is provided in this sNDA/sBLA.

The Regulatory Authorities' Assessment:
We agree with the applicant's statement above.

Human Reproduction and Pregnancy

The Applicant's Position:

No pregnancies have been reported with the combination of lenvatinib plus pembrolizumab as of the data cutoff date for Study 111 (10 Jan 2019). See Module 2.7.4, Section 2.7.4.5.6 for a pregnancy risk summary for lenvatinib and pembrolizumab.

The Regulatory Authorities' Assessment:
We agree with the applicant's statement above.

Pediatrics and Assessment of Effects on Growth

The Applicant's Position:

Not applicable.

The Regulatory Authorities' Assessment:
We agree with the applicant's statement above.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position:

Overdose: One case of overdose has been reported with lenvatinib administered in combination with pembrolizumab as of the data cutoff date (10 Jan 2019) for Study 111, and is discussed in the Study 111 EC CSR Section 12.3.1.4.5. The subject received lenvatinib 20 mg as planned for 35 days. From Day 36 to 38 the subject took lenvatinib 20 mg twice a day instead of QD. Upon report of the overdose, drug was interrupted for 7 days and then resumed at the appropriate schedule. The subject received lenvatinib for a total of 2.7 months before discontinuing due to PD. The subject had 3 events of confusional state; the initial SAE of confusional state on Day 30 was considered related to study drug and predated the accidental drug overdose, possibly leading to the dosing error (Module 2.7.4, Section 2.7.4.5.7).

The current product information for lenvatinib (LENVIMA PI, 2018) states that: "Due to high plasma protein binding, lenvatinib is not expected to be dialyzable. Death due to multiorgan dysfunction occurred in a patient who received a single dose of LENVIMA 120 mg orally."

The current product information for pembrolizumab (KEYTRUDA PI, 2019) states that: "There is no information on overdosage with KEYTRUDA."

Drug Abuse: Not applicable, as VEGF/vascular endothelial growth factor receptor [VEGFR] targeted therapies, including lenvatinib, and PD L1 inhibitors, including pembrolizumab, do not have the potential for drug abuse.

The Regulatory Authorities' Assessment:
We agree with the applicant's statement above.

7.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:

The combination of lenvatinib plus pembrolizumab has not been approved in any country. For postmarketing data for each individual study drug, refer to the most recent periodic safety update report (LENVIMA PSUR and KEYTRUDA PSUR).

The Regulatory Authorities' Assessment:
The U.S. periodic safety update report (PSUR) for lenvatinib [covering period February 13, 2018 to February 12, 2019 (submitted April 11, 2019)] and periodic adverse experience report (PAER) for pembrolizumab [covering period September 4, 2017 to September 3, 2018 (submitted October 25, 2018)] were reviewed for the purposes of this application.

Lenvatinib: During the reporting period, the information related to nephrotic syndrome, wound healing complications labeling changes were made to the U.S. label and the U.S. Medication Guide.

Pembrolizumab: During the reporting period, FDA posted a notice to their web site alerting health care professionals, oncology clinical investigators, and the public about decreased survival associated with the use of pembrolizumab as monotherapy in clinical trial KEYNOTE-361 to treat patients with metastatic urothelial cancer who have not received prior therapy and who have low expression of the protein programmed death ligand 1 (PD-L1). The U.S. label was revised to reflect the restricted use of pembrolizumab for patients with locally advanced or metastatic urothelial cancer who are not eligible for cisplatin-containing therapy. Also, during this reporting period, the U.S. label was updated to reflect the FDA not recommending the use of pembrolizumab with a thalidomide analogue and dexamethasone outside of controlled clinical trials due to increased mortality observed in two randomized clinical trials in patients with multiple myeloma.

The FDA reviewer performed a search of the post-marketing cases in the FAERS database, but due to the presence of confounding factors, lack of sufficient clinical information in a majority of reports, or limited number of FAERS reports, no new safety signal was identified. FDA will continue routine postmarket pharmacovigilance activities for lenvatinib and pembrolizumab.

Expectations on Safety in the Postmarket Setting

The Applicant's Position:

Postmarketing data are routinely reviewed for lenvatinib and pembrolizumab (ie, Merck Adverse Event Reporting and Review System [MARRS]) via their separate safety reporting databases. The safety signal detection activities include review of reported AEs from postmarket sources, including health care providers, consumers, and competent authorities worldwide, and by review of the scientific literature relevant to lenvatinib and pembrolizumab. The Sponsors continue to monitor postmarket data associated with lenvatinib and with pembrolizumab for new findings or trends.

There are no specific safety concerns associated with subpopulations not adequately represented in the safety databases for lenvatinib and pembrolizumab. There are no specific safety concerns not already included in the lenvatinib labeling and pembrolizumab labeling expected from off-label use.

The Regulatory Authorities' Assessment:
Both lenvatinib and pembrolizumab have been marketed in the U.S. for several years and their safety profile is well understood. FDA will continue post-marketing safety surveillance.

7.2.11. Integrated Assessment of Safety

The Applicant's Position:

Overall, no new safety signals were observed with lenvatinib plus pembrolizumab compared with either lenvatinib or pembrolizumab as monotherapies in a study population representative of patients in the setting of 2L+ treatment of EC that is not MSI-H/dMMR (Study 111, Indication Safety Set). Treatment with lenvatinib plus pembrolizumab demonstrated an acceptable safety profile, with an incidence of discontinuation consistent with lenvatinib monotherapy. Toxicities were primarily low grade, consistent with the known risks with each drug, and were generally manageable with (if appropriate) study drug treatment interruption and dose reduction, and standard medical care.

The key safety and tolerability findings from the Indication Safety Set of Study 111 were:

- The incidences of any Grade ≥3 TEAEs, non-fatal SAEs, study drug interruption, and study drug discontinuation in the Indication Safety Set were generally comparable with the incidences seen in the Lenvatinib Monotherapy Safety Set and generally higher than that in the Pembrolizumab Monotherapy Safety Set. The incidence of Grade 5 TEAEs in the Indication Safety Set was generally consistent with the All EC and Pembrolizumab Monotherapy Safety Sets and was lower than the Non-EC and Lenvatinib Monotherapy Safety Sets.
- There was a higher incidence of TEAEs leading to dose reduction of lenvatinib in the Indication Safety Set (67.0%) than in the Lenvatinib Monotherapy Safety Set (47.5%); however, the incidence of discontinuation of lenvatinib was consistent between the Indication and Lenvatinib Monotherapy Safety Sets. These findings suggest that the majority of TEAEs can be managed through dose modification rather than

discontinuation.

- The incidences of CSEs in the Indication Safety Set were generally consistent with those for lenvatinib monotherapy, with the exception of the CSEs of hypothyroidism (any grade). The overall frequency of AEOSI (any) was higher than that seen with pembrolizumab monotherapy, predominantly due to hypothyroidism. Hypothyroidism was almost all low grade and readily manageable with thyroid hormone replacement.
- Except for hypothyroidism, the overlapping toxicities of clinical interest in the Indication Safety Set were represented by small numbers of subjects. None of the CSEs/AEOSI or overlapping toxicities of clinical interest (ie, hypothyroidism, nephritis, severe skin reactions, and pancreatitis), were found to impact the benefit risk profile of lenvatinib plus pembrolizumab in the treatment of EC.

The Regulatory Authorities' Assessment:

Safety for the L+P combination was assessed in context of the safety profile of each of the monotherapies in the EC patient population. All safety analyses compared AE trends between L+P (study 111/KN-146), lenvatinib monotherapy (study 204) and pembrolizumab monotherapy (KN-158 and KN-028). Compared to monotherapies, there were a high rate of treatment discontinuations, interruptions and reductions, in the L+P combination (frequency was higher for lenvatinib compared to pembrolizumab). There were also increased frequency of certain AEs, CSEs and AESIs in study 111 but no new safety signals identified. Overall, the safety profile of L+P is consistent with previous knowledge of the safety profile of the individual agents and considered acceptable in the context of the proposed indication. Detailed summary of safety is provided in section 7.2.

We do not recommend a Risk Evaluation and Mitigation Strategy (REMS) given the current safety profile of lenvatinib and pembrolizumab and the experience of the medical community in managing clinically significants events related to lenvatinib and immune-mediated adverse reactions with pembrolizumab. Recommendations for safe and effective use of lenvatinib and pembrolizumab, including monitoring for adverse events, have been included in the label. In summary, the safety profile of lenvatinib and pembrolizumab combination is acceptable for the intended population.

SUMMARY AND CONCLUSIONS

7.3 Statistical Issues

The Regulatory Authorities' Assessment:

The applicant submitted an sNDA for lenvatinib plus pembrolizumab combination therapy in patients with advanced EC in the second line or greater (2L+) setting in Study 111/KN-146, whose tumors are not MSI-H or dMMR. The ORR based on IIR using RECIST 1.1 was 38.3% (95% CI: 28.5, 48.9) with 10.6% of patients achieving a CR and 27.7% of patients achieving a PR. At the time of the data cutoff (January 10, 2019), the median DOR that was not reached (range: 1.2+ to 33.1+ months) with a median follow-up of 18.7 months. A total of 25 patients (69% of the 36 responders) had a duration of response ≥6 months. We reiterate that no

inferential procedures can be used to evaluate results from this single arm study. Instead, the efficacy evaluation was based on the magnitude of response rate and adequate duration of response. Additionally, although progression-free survival, time to response, and overall survival results were summarized, we noted that time-to-event endpoints are uninterpretable without a comparator arm.

To evaluate the contribution effect of lenvatinib and pembrolizaumab in the combination for the observed treatment effect, activity for each individual component in the same patient population should be characterized in a randomized clinical trial comparing the combination therapy to each of the monotherapies. However, due to the single-arm design of Study 111/KN-146, the treatment effect of each component in the combination could not be isolated based on this single study. The applicant provided three single-arm studies including Study 204 (lenvatinib) and KEYNOTE-158 and KEYNOTE-028 (pembrolizumab) to help assess contribution of each component to the efficacy of the combination treatment. Exploratory post-hoc cross-trial comparisons showed that there appeared to be a numerically higher ORR with the combination therapy over the individual treatments. FDA conducted exploratory analyses using propensity score matching and weighting methods to account for observed imbalances in selected demographics and baseline characteristics. The results are consistent with those seen in an unadjusted comparison of the combination treatment vs. each individual treatment. These analyses results were considered exploratory and no formal hypothesis testing was performed. Acknowledging the lack of a randomized trial and the limitations in the use of external controls, the data and analyses submitted in this application suggest a higher response rate with the combination therapy.

7.4 Conclusions and Recommendations

The Regulatory Authorities' Assessment:

The review team recommends accelerated approval for lenvatinib and pembrolizumab combination for the following indication:

- **In combination with pembrolizumab, for the treatment of patients with advanced endometrial carcinoma that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation.**

The recommendation is based upon review of the results from the study 111/KN-146, which was a multicenter, open-label study of lenvatinib plus pembrolizumab combination. The study enrolled patients with metastatic tumors and had 6 tumor indication cohorts, including endometrial cancer. Study 111/KN-146 had 2 phases, the Phase 1b part of the study determined the recommended Phase 2 dose to be 20 mg lenvatinib PO daily in combination with 200 mg pembrolizumab IV Q3W.

A total of 124 patients were enrolled in EC cohort, of which 108 patients had been previously treated EC and 94 of those had tumors which were not MSI-H/dMMR and were the focus for

efficacy and safety review in this application. The primary endpoint for this study was objective response rate and duration of response by independent imaging review (IIR). The trial demonstrated an ORR of 38.3% (95% CI: 28.5, 48.9) with 10.6% of patients achieving a CR and 27.7% of subjects achieving a PR. At the time of the data cutoff (January 10, 2019), the median DOR that was not reached (range: 1.2+ to 33.1+ months) with a median follow-up of 18.7 months. A total of 25 patients (69% of the 36 responders) had a duration of response ≥6 months.

The safety profile of the L+P combination was adequately assessed in the submitted database. The combination was generally tolerated with adverse reactions manageable with dose reduction and/or interruptions, although the rate of dose modifications was fairly high in study 111 compared to monotherapy studies. In study 111, lenvatinib alone was dose modified (interrupted and/or reduced) in 88% of the patients (regardless of action with pembrolizumab) and pembrolizumab alone was dose interrupted in 49% (regardless of action with lenvatinib). Despite the high rate, the TEAEs that led to dose interruptions and reductions correspond to the known safety profile of lenvatinib and pembrolizumab with hypertension, fatigue, and hemorrhages being common causes for lenvatinib discontinuation. Fatigue was the most common AE that led to interruption of both lenvatinib and pembrolizumab.

Fatal adverse reactions occurred in 3% of patients receiving L+P combination, including gastrointestinal perforation, RPLS with intraventricular hemorrhage, and intracranial hemorrhage. Permanent discontinuation due to adverse reaction (Grade 1-4) occurred in 17% of patients who received L+P combination. The most common adverse reactions (>2%) resulting in discontinuation were gastrointestinal perforation or fistula (2%), muscular weakness (2%), and pancreatitis (2%).

The key adverse events of interest with lenvatinib, identified as clinically significant events (CSEs - AEs that have been identified in clinical trials across the development program), occurred in 86 (91.5%) patients. The most common CSEs identified were hypertension, hypothyroidism, hemorrhages, palmar-plantar erythrodysaesthesia, proteinuria, and renal events.

Adverse events of special interest (AESIs – immune-mediated AEs or nonimmune-mediated events of infusion-related reactions) with pembrolizumab occurred in 57% of patients. Adverse events such as hypothyroidism, pancreatitis, nephritis and adrenal insufficiency occurred at a higher frequencies in study 111 compared to monotherapy study KN-158. Nearly a quarter of the patients received systemic corticosteroids with only around 9% needing steroids for immune mediated adverse events.

Serious adverse reactions occurred in 52% of patients receiving L+P combination. No new safety concerns have been identified based on the safety data submitted in this sNDA. Notable toxicities for the L+P combination included a high incidence of fatigue, hypertension, musculoskeletal pain, diarrhea, decreased appetite, hypothyroidism, nausea, stomatitis,

vomiting, decreased weight, abdominal pain, headache, constipation, urinary tract infection, dysphonia, hemorrhagic events, hypomagnesemia, palmar-plantar erythrodysesthesia, dyspnea, cough, and rash. Based on the frequency of AEs observed in the monotherapy trials, it is important to note that the incidence of AEs was higher in the combination study111/KN-146, though no new safety signals were identified. The safety profile is acceptable for this patient population with a serious and life-threatening disease. All disciplines agreed that the L+P combination had a favorable risk-benefit profile, and did not identify any outstanding issues that precluded approval.

X X

Primary Statistical Reviewer Statistical Team Leader

X X

Primary Clinical Reviewer Clinical Team Leader

8 Advisory Committee Meeting and Other External Consultations

The Regulatory Authorities' Assessment[1]:
Not applicable.

9 Pediatrics

The Applicant's Position:

The combination of lenvatinib plus pembrolizumab was not studied in pediatric patients. The applicant has submitted a PREA waiver.

The Regulatory Authorities' Assessment[1]:
Not applicable.

10 Labeling Recommendations

10.1 Prescription Drug Labeling

The Applicant's Position:

The Sponsors have provided the proposed labeling in the submission in Module 1.14.1.3. The proposed indications are:

- LENVIMA, in combination with pembrolizumab, is indicated for the treatment of [redacted] (b) (4)
- KEYTRUDA, in combination with lenvatinib, is indicated for the treatment of [redacted] (b) (4)

The Regulatory Authorities' Assessment[1]:
The table below summarizes significant changes to the proposed prescribing information made by FDA. This labeling was under negotiation at the time of this review. See the final approved prescribing information for lenvatinib and pembrolizumab accompanying the NDA 208558 and BLA 125514 approval letters for more information.

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Applicant's Proposed Labeling**	**FDA's proposed Labeling**
Highlights of Labeling		
Indications and Usage	*See the Full Prescribing Information (FPI), Section 1 below.*	See the Full Prescribing Information (FPI), Section 1 below.
Dosage and Administration	…	FDA agreed with the proposed dosage and administration statements with format revisions.

Adverse Reactions	*…: fatigue, hypertension, diarrhea,* (b) (4) *decreased appetite, hypothyroidism, nausea, vomiting, stomatitis, decreased weight, abdominal pain, headache, constipation, dysphonia, urinary tract infection, hemorrhagic events, hypomagnesemia, palmar-plantar erythrodysesthesia, dyspnea, cough, and rash. (6.1)*	FDA revised the most common adverse reactions (ARs) statement to add musculoskeletal pain based on the FDA safety review.
Full Prescribing Information		
1. Indications and Usage	1.4 Endometrial Carcinoma (LENVIMA) 1.15 Endometrial Carcinoma (KEYTRUDA) *…, in combination with pembrolizumab, is indicated for the treatment of* (b) (4)	FDA revised the indication statement to the following: … in combination with pembrolizumab, is indicated for the treatment of patients with advanced endometrial carcinoma that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation.
2. Dosage and Administration	2.5 Recommended Dosage for Endometrial Carcinoma (LENVIMA) 2 (b) (4) Recommended Dosage for Endometrial Carcinoma (KEYTRUDA)	FDA accepted the proposed recommended dosage of lenvatinib 20 mg orally once daily in combination with pembrolizumab 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until unacceptable toxicity or disease progression.
	2.6 Dosage Modifications for Adverse Reactions (LENVIMA)	FDA agreed to the following with minor revisions: …, interrupt one or both drugs

	2 (b)(4) Dose Modifications (KEYTRUDA)	or dose reduce LENVIMA as appropriate. No dose reductions are recommended for pembrolizumab. KEYTRUDA: Withhold, dose reduce, or discontinue lenvatinib in accordance with the instructions in the lenvatinib prescribing information. LENVIMA: Withhold or discontinue pembrolizumab in accordance with the instructions in the pembrolizumab prescribing information.
6 Adverse Reactions	6.1 Clinical Trials Experience …	FDA revised this section as follows: • Added the recommended lenvatinib dosage used in combination with pembrolizumab to the study description. • Clarified that KEYNOTE 148/Study 111 was conducted in patients who had progressed following one line of systemic therapy. • Added statements to describe the fatal and serious adverse reactions in patients treated with pembolizumab and lenvatinib. • Revised the information for permanent discontinuation due to ARs to provide the most common ARs that led to permanent

		discontinuation in > 2% of patients [KEYRUDA}. Gastrointestinal perforation or fistula (2%) [LENVIMA] was added based on FDA safety review. • Revised the information for ARs that led to dose reduction or interruption based on FDA safety review. This included revisions to the incidence rates for the reported ARs and revisions and reordering of proposed ARs where applicable. • Revised the AR table [LENVIMA Table 9; KEYTRUDA Table (b) (4)] to add musculoskeletal pain (pooled term (b) (4) and made minor revisions to incidence rates based on FDA safety review findings. • Revised the Laboratory Abnormality (LAs) table [LENVIMA Table 10; KEYTRUDA Table (b) (4)] to include all grades of LAs in addition to the proposed Grade 3-4 LAs in these tables. This resulted in the addition of LAs for hyperglycemia, hypoalbimunemia, hypomagnesemia, increased alkaline phosphatase, increased amylase, thrombocytopenia,

		aenemia, and increased INR.
12. Clinical Pharmacology	*The applicant proposes to update this section with clinical pharmacology data from the use of lenvatinib in combination with pembrolizumab:* 12.1 Mechanism of Action (b) (4) [redacted]	Based on the data reviewed from published literature from studies conducted by the Applicant, the Pharmacology/Toxicology team revised the Applicant's proposed statements in section 12.1 to include a concise summary of the established mechanism of action and avoid speculative and misleading claims. The Applicant agreed to revise the proposed statements in section 12.1 to (b) (4) [redacted]
14. Clinical Studies	14.4 Endometrial Carcinoma (LENVIMA) 14.15 Endometrial Carcinoma (KEYTRUDA)	FDA revised the study description in this section to clarify KEYNOTE 146 was a single arm trial and added key exclusion criteria proposed in KEYTRUDA to the LENVIMA Study 111 description (i.e., "active autoimmune disease or a medical condition that required immunosuppression were ineligible").

		FDA added the following: "Tumor MSI status was determined using a polymerase chain reaction (PCR) test. Tumor MMR status was determined using an immunohistochemistry (IHC) test." FDA accepted the efficacy results tables [LENVIMA Table 14; KEYTRUDA Table 53] with format revisions and revised the duration of response ≥ 6 months from (b) (4) to 69% [LENVIMA] based on the FDA statistical review.
17 Patient Counseling Information	…	(b) (4)

10.2 Patient Labeling

The Regulatory Authorities' Assessment[1]:

Patient Labeling for LENVIMA and KEYTRUDA was reviewed and revised. This labeling was under negotiation at the time of this review. See the final approved Patient Information for lenvatinib and pembrolizumab accompanying the NDA.

The following is a summary of high level revisions that were made to the Patient Information for LENVIMA and KEYTRUDA:

- **FDA accepted the addition of information to the Patient Labeling in the *What is LENVIMA/KEYTRUDA* section for use of lenvatinib and pembrolizumab in endometrial cancer with minor revisions for consistency with the Indications and Usage information in Section 1.**
- **In the *What are the possible side effects of LENVIMA/KEYTRUDA* section, FDA revised the common side effects to reflect the ARs and order of common ARs listed in the USPI for this dosage regimen.**
- **Additional revisions were made to the LENVIMA Patient Information to reduce redundancy.**

See the FDA OPDP/DMPP review filed under this NDA/BLA for more information.

11 Risk Evaluation and Mitigation Strategies (REMS)

The Applicant's Position:

The safety profile of lenvatinib and the safety profile of pembrolizumab administered as monotherapy are well characterized in the product labeling. Overall, no new safety signals were observed with lenvatinib plus pembrolizumab in the Indication Safety Set compared with either lenvatinib or pembrolizumab as monotherapies. Therefore, a REMS is not necessary for the combination of lenvatinib plus pembrolizumab for the proposed indication.

The Regulatory Authorities' Assessment[1]:
Not applicable.

12 Postmarketing Requirements and Commitment

The Regulatory Authorities' Assessment[1]:
NDA 206947/S-11; will be approved with one PMR and four PMC agreements. BLA 125514/S-65 will also have the same PMR and four PMCs, numbered beginning with sequence 3700.

3696-1, 3700-1 Post-Marketing Requirement
Submit the analyses and datasets with the final report for PFS and OS for the ongoing clinical trial E7080-G000-309/KEYNOTE-775, entitled, "A Randomized, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib in Combination With Pembrolizumab Versus Treatment of Physician's Choice in Participants With Advanced Endometrial Cancer" to verify and describe the clinical benefit of the lenvatinib and pembrolizumab combination for patients with not-microsatellite instability high or mismatch repair proficient tumors.

Draft Protocol Submission:	**09/2017**
Final Protocol Submission:	**03/2018**
Trial Completion:	**09/2022**
Interim /Other (Last Patient Enrolled):	**04/2020**
Final Report Submission:	**03/2023**

3696-2, 3700-2 Post-Marketing Commitment
Submit the analyses and datasets with the final report for PFS for the ongoing clinical trial E7080-G000-313/MK-7902-001, entitled, "A Phase 3 Randomized, Open-Label, Study of Pembrolizumab (MK-3475) Plus Lenvatinib Versus Chemotherapy for Firstline Treatment of Advanced or Recurrent Endometrial Carcinoma" to verify and describe the clinical benefit of the lenvatinib and pembrolizumab combination for patients with not-microsatellite instability high or mismatch repair proficient tumors.

Final Protocol Submission:	**02/2019**
Trial Completion:	**09/2022**
Final Report Submission:	**03/2023**

3696-3, 3700-3 Post-Marketing Commitment
Submit the analyses and datasets with the final report for OS for the ongoing clinical trial E7080-G000-313/MK-7902-001, entitled, "A Phase 3 Randomized, Open-Label, Study of Pembrolizumab (MK-3475) Plus Lenvatinib Versus Chemotherapy for Firstline Treatment of Advanced or Recurrent Endometrial Carcinoma" to verify and describe the clinical benefit of the lenvatinib and pembrolizumab combination for patients with not-microsatellite instability high or mismatch repair proficient tumors.

Final Protocol Submission:	**02/2019**

Trial Completion: **11/2023**
Final Report Submission: **05/2024**

3696-4, 3700-4 Post-Marketing Commitment
Commitment to support the availability of an immunohistochemistry-based in vitro diagnostic device that is essential to the safe and effective use of the lenvatinib and pembrolizumab combination for patients with tumors that are mismatch repair proficient through an appropriate analytical and clinical validation study using clinical trial data that will support labeling.

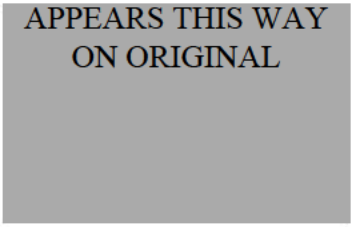
Final Report Submission: **09/2023**

3696-5, 3700-5 Post-Marketing Commitment
Commitment to support the availability of a nucleic acid-based in vitro diagnostic device that is essential to the safe and effective use of the lenvatinib and pembrolizumab combination for patients with tumors that are not microsatellite instability-high through an appropriate analytical and clinical validation study using clinical trial data that will support labeling.

Final Report Submission: **09/2024**

13 Division Director (OCP)

X _____



14 Division Director (OB)

X _____

APPEARS THIS WAY ON ORIGINAL

15 Division Director (Clinical)

X _____

APPEARS THIS WAY ON ORIGINAL

16 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.

APPEARS THIS WAY ON ORIGINAL

17 Appendices

17.1 References

The Applicant's References:

[1] American Cancer Society. Cancer Facts Cancer Facts and Figures, 2019. Atlanta: American Cancer Society; 2019. Available from: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2019/cancer-facts-and-figures-2019.pdf. Accessed 08 Apr 2019.

[2] Kerr SE. Molecular testing in gynecologic cancer. In: Coleman WB, Tsongalis GJ, editors. Diagnostic Molecular Pathology. A guide to applied molecular testing. 1st edition. New York: Elsevier; 2017. pp 361-379.

[3] Fleming GF. Second-line therapy for endometrial cancer: The need for better options. J Clin Oncol. 2015;33(31):3535-40.

[4] Tran A-Q, Gehrig P. Recent advances in endometrial cancer. F1000Research. 2017;6:81. doi: 10.12688/f1000research.10020.1.

[5] Makker V, Green A, Wenham R, Mutch D, Davidson B, Miller D. New therapies for advanced, recurrent, and metastatic endometrial cancers. Gyn Oncol Res Practice 2017;4:19. doi: 10.1186/s40661-017-0056-7.

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[7] Ramondetta L, Burke TW, Levenback C, et al. Treatment of uterine serous papillary carcinoma with paclitaxel. Gynecol Oncol. 2001;82(1):156-61.

[8] Slomovitz BM, Burke TW, Eifel PJ, et al. Uterine papillary serous carcinoma (UPSC): a single institution review of 129 cases. Gynecol Oncol. 2003;91(3):463-9.

[9] Obel JC, Friberg G, Fleming, GF. Chemotherapy in Endometrial Cancer. Clin Adv Hematol Oncol. 2006 Jun;4(6):459-68.

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[11] National Comprehensive Cancer Network. Clinical Practice Guidelines in

Oncology. Uterine Neoplasms, Version 3.2019. Available from: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp.

[12] U.S. Prescribing Information: KEYTRUDA (pembrolizumab) for injection, for intravenous use; KEYTRUDA (pembrolizumab) injection, for intravenous use: Apr 2019.

[13] McMeekin S, Dizon D, Barter J, Scambia G, Manzyuk L, Lisyanskaya A, et al. Phase III randomized trial of second-line ixabepilone versus paclitaxel or doxorubicin in women with advanced endometrial cancer. Gynecol Oncol. 2015;138(1):18-23.

[14] Miller DS, Scambia G, Bondarenko I, Westermann AM, Oaknin A, Oza AM, et al. ZoptEC: Phase III randomized controlled study comparing zoptarelin with doxorubicin as second line therapy for locally advanced, recurrent, or metastatic endometrial cancer (NCT01767155). Proceedings of the ASCO annual meeting 2018.

[15] Lentz SS, Brady MF, Major FJ, Reid GC, Soper JT. High-dose megesterol acetate in advanced or recurrent endometrial carcinoma: a Gynecoloic Oncology Group Study. J Clin Oncol. 1996;14(2):357-61.

The FDA's References:

[1] Austin, P. C. (2009) Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Statistics in Medicine, 28: 3083–3107.

[2] Austin P.C. (2011) Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. Pharmaceutical Statistics, 10: 150-161

[3] D'Agostino (1998) Propensity score method for bias reduction in the comparison of a treatment to a non-randomized control group. Statistic in Medicine, 17: 2265-2281.

[4] Ho, D. E., Imai, K., King, G., and Stuart, E. A. (2007). Matching as nonparametric preprocessing for reducing model dependence in parametric causal inference. Political Analysis 15(3): 199-236.

[5] Li, F., Morgan, K.L., and Zaslavsky A. M. (2015) Balancing Covariates via Propensity Score Weighting. Journal of the American Statistical Association, 113: 390-400

[6] **Rosenbaum, P. R. and Rubin, D. B. (1983) Assessing sensitivity to an unobserved binary covariate in an observational study with binary outcome. Journal of the Royal Statistical Society Series B 45, 2, 212-218.**

[7] **Rosenbaum, P.R., Rubin D.B. (1983) The central role of the propensity score in observational studies for causal effects. Biometrika, 70(1): 41–55.**

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[9] **Rubin, D. B. (2006). Matched Sampling for Causal Inference. Cambridge University Press, Cambridge, England.**

[10] **Stuart, E.A. (2010). Matching methods for causal inference: A review and look forward. Statistical Science 25(1): 1-21.**

17.2 Financial Disclosure

The Applicant's Position:

Study 111 was considered as covered by the "Financial Disclosure for Clinical Investigators" rule. All investigators were assessed for equity interest, significant payments, proprietary interest, and other compensation.

The FDA's Assessment:

Financial disclosure did not reveal any information that might raise concerns about the reliability of the submitted data or the conduct of the pivotal clinical trial.

Covered Clinical Study (Name and/or Number):* E7080-A001-111

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: **35**		
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): **3**		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR		

54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: **0** Significant payments of other sorts: **3** Proprietary interest in the product tested held by investigator: **0** Significant equity interest held by investigator in study: **0** Sponsor of covered study: **0**		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
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 Applicant)

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

17.3 OCP Appendices (Technical documents supporting OCP recommendations)

Not Applicable.

17.4 FDA Exploratory Propensity Score-based Cross-Trial Analyses - Isolation of Treatment Effect

This appendix includes assessment on comparability of patients across trials before and after propensity score matching or weighting analyses, and results from weighting analyses based on different weighting schemes.

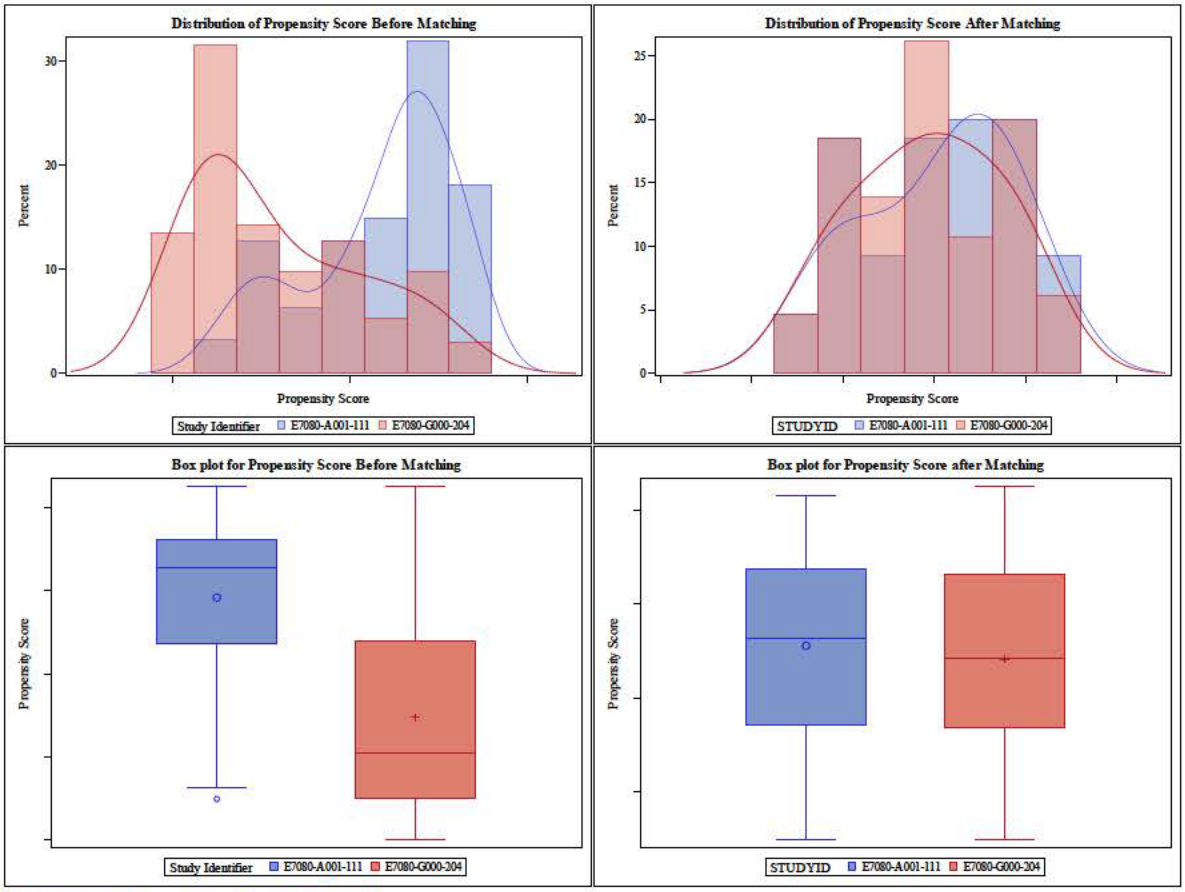
1. Isolation of treatment effect for pembrolizumab – Comparison of Study 111/KN-146 (n=94) vs. Study 204 (n=133)

(a) Propensity Score Matching Approach

Matched pairs were formed (1:1 matching without replacement) with a similar propensity score using nearest-neighbour matching algorithm with caliper width of 0.2 of the standard deviation of the logit of the propensity scores (Austin 2011). The following histograms and boxplots represented the distribution of propensity score by treated

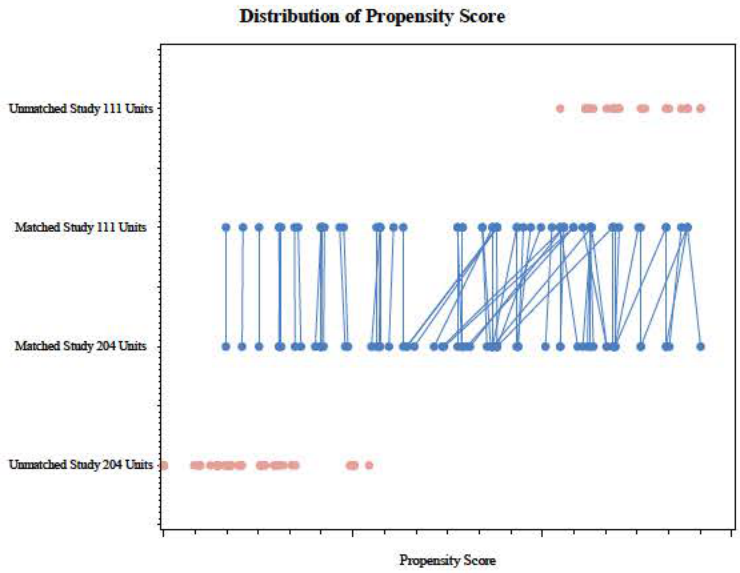
(Study 111/KN-146) or control (Study 204), before or after matching. With 1 to 1 matching method, there were 65 patients from Study 111/KN-146 matched with 65 patients from Study 204. The difference was reduced after matching (Figure 8). There were 29 out of 94 patients (30.9%) in Study 111/KN-146 and 25 out of 90 patients (27.8%) in Study 204 who were unmatched in the analysis (Figure 9).

Figure 8. Distribution of Propensity Score Before and After Matching (Lenvatinib + Pembrolizumab vs. Lenvatinib)



[Source: Reviewer's Analysis]

Figure 9. Distribution of Propensity Score including Matched and Unmatched Patients (Lenvatinib + Pembrolizumab vs. Lenvatinib)



[Source: Reviewer's Analysis]

To assess the quality of matching, examination of the balance of baseline covariates between treated and control patients in the matched sample were performed. This was done by computing the absolute standardized mean difference (SMD) between the two groups for the covariates. Rubin (2001) and Stuart (2010) indicated that the propensity score analysis may reasonably adjust for covariates if the SMD <0.25. A summary of baseline covariates used for assessing the comparability of Study 111/KN-146 and Study 204 prior to any adjustment is presented in Table 48 (see "Unadjusted" column). The covariates appear to be adequately balanced after matching based on SMD (see "Matching" column).

Table 48. Summary of Baseline Covariates Before and After Propensity Score Matching (Lenvatinib + Pembrolizumab vs. Lenvatinib)

	Unadjusted			Matching		
	Study 111/KN-146	Study 204	SMD - unadjusted	Study 111/KN-146	Study 204	SMD - matched
	N=94	N=133		N=65	N=65	
Age Group			0.464			0.123
<65	36 (38.3)	81 (60.9)		34 (52.3)	30 (46.2)	
≥65	58 (61.7)	52 (39.1)		31 (47.7)	35 (53.9)	
Race			0.055			0.147
White	81 (86.1)	112 (84.2)		52 (80.0)	48 (73.9)	
Non-White	13 (13.8)	21 (15.8)		13 (20.0)	17 (26.2)	
Geographic Region			0.996			<0.001
US	81 (86.1)	58 (43.6)		52 (80.0)	52 (80.0)	
Non-US	13 (13.8)	75 (56.4)		13 (20.0)	13 (20.0)	
ECOG PS at Baseline			0.498			<0.001

	Unadjusted			Matching		
	Study 111/KN-146	Study 204	SMD - unadjusted	Study 111/KN-146	Study 204	SMD - matched
	N=94	N=133		N=65	N=65	
0	49 (52.1)	50 (37.6)		34 (52.3)	35 (53.9)	
1	45 (47.9)	83 (62.4)		31 (47.7)	30 (46.2)	
2	0	12 (9.0)		0	0	
Histology			0.370			0.218
Endometroid	46 (48.9)	89 (66.9)		33 (50.8)	40 (61.5)	
Others	48 (51.1)	44 (33.1)		32 (49.2)	25 (38.5)	
FIGO Grade			0.231			0.034
Grade 1/2	25 (26.6)	47 (25.4)		18 (27.7)	19 (29.2)	
Grade 3/4	69 (73.4)	85 (63.9)		47 (72.3)	46 (70.8)	
Not Available	0	1 (0.1)		0	0	
Any Lymph Node TL at Baseline			0.122			0.031
Yes	34 (36.2)	56 (42.1)		27 (41.5)	28 (43.1)	
No	60 (63.8)	77 (57.9)		38 (58.5)	37 (56.9)	
Any Non-Lymph Node TL at Baseline			0.107			0.159
Yes	82 (87.2)	111 (83.5)		55 (84.6)	51 (78.5)	
No	12 (12.8)	22 (16.5)		10 (15.4)	14 (21.5)	
Any Non-Target Lesions at Baseline			0.069			0.154
Yes	86 (91.5)	119 (89.5)		60 (92.3)	57 (87.7)	
No	8 (8.5)	14 (10.5)		5 (7.7)	8 (12.3)	
Source: Study 111 – ADSL.xpt, ADDC.xpt, ADEF.xpt, Study 204 – ADSL.xpt , ADDC.xpt, ADEF.xpt						

(b) Propensity Score Weighting Approach

A stabilized inversed probability treatment weighting (sIPTW) approach was used as the primary weighting method. Sensitivity analyses were performed to assess ORR using additional weighting schemes (i.e., Average Treatment Effect for Overlap Population [ATO], Average Treatment Effects on the Treated [ATT] and Average Treatment Effects on the Control [ATC]).

To examine the balance of baseline covariates between treated and control patients in the different approaches, the absolute SMD between the two groups were summarized in Table 49. The covariates appear to be adequately balanced across treatment and comparison groups in the propensity score weighted sample based on the SMD, except for ECOG score at baseline using sIPTW and ATC approaches.

Table 49. Summary of Standardized Mean Difference (Lenvatinib + Pembrolizumab vs. Lenvatinib).

	Unadjusted	Matched	sIPTW	ATT	ATC
Age Group	0.464	0.123	0.069	0.044	0.127
Race	0.055	0.147	0.073	0.006	0.138
Geographic Region	0.996	<0.001	0.138	0.020	0.190
ECOG PS at Baseline	0.498	<0.001	0.341	0.013	0.461
Histology	0.370	0.218	0.083	0.004	0.134
FIGO Grade	0.231	0.034	0.113	0.004	0.157
Any Lymph Node TL at Baseline	0.122	0.031	0.021	0.118	0.136
Any Non-Lymph Node TL at Baseline	0.107	0.159	0.048	0.110	0.167
Any Non-Target Lesions at Baseline	0.069	0.154	0.056	0.005	0.099
Source: Study 111 – ADSL.xpt, ADDC.xpt, ADEF.xpt, Study 204 – ADSL.xpt , ADDC.xpt, ADEF.xpt					

The treatment effects in ORR based on different weighting methods are shown in Table 50. The treatment effects estimated from all different propensity score weighting approaches are consistent with unadjusted analysis and propensity score matching analysis.

Table 50. Efficacy Results – Propensity Score Weighting Analyses (Lenvatinib + Pembrolizumab vs. Lenvatinib).

	Study 111/KN-146	Study 204
sIPTW		
ORR, % (95% CI)	38.4 (28.1, 48.8)	12.8 (7.2, 18.5)
ORR difference, % (95% CI)	25.6 (13.8, 37.4)	
ORR ratio (95% CI)	2.99 (1.78, 5.02)	
ATO		
ORR, % (95% CI)	37.8 (28.8, 46.7)	13.6 (7.3, 19.9)
ORR difference, % (95% CI)	24.1 (13.2, 35.1)	
ORR ratio (95% CI)	2.77 (1.65, 4.66)	
ATT		
ORR, % (95% CI)	38.3 (28.5, 48.1)	10.8 (4.6, 17.0)
ORR difference, % (95% CI)	27.5 (15.9, 39.1)	
ORR ratio (95% CI)	3.55 (1.89, 6.68)	
ATC		
ORR, % (95% CI)	38.5 (29.5, 47.5)	14.3 (8.3, 20.2)
ORR difference, % (95% CI)	24.2 (13.4, 35.0)	
ORR ratio (95% CI)	2.69 (1.67, 4.35)	
Source: Study 111 – ADSL.xpt, ADDC.xpt, ADEF.xpt, Study 204 – ADSL.xpt , ADDC.xpt, ADEF.xpt		

Reviewer's Comments on the Propensity Score Matching and Weighting Approaches

i. Study 204 allowed subjects to have an ECOG score of 0 to 2; however, Study 111/KN-146 allowed an ECOG score of 0 or 1. Twelve patients with ECOG score of 2 in Study 204 were unmatched.

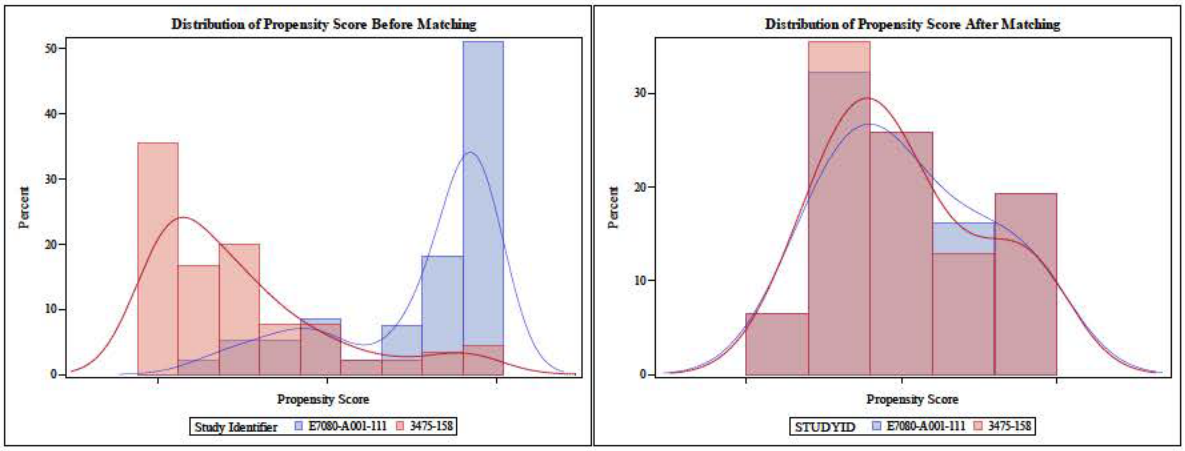
In sIPTW and ATC weighted approaches, ECOG score at baseline appears to have some imbalance (SMD>0.25) after weighting. It is unclear if the imbalance is due to small sample size or other important factors that were not included.

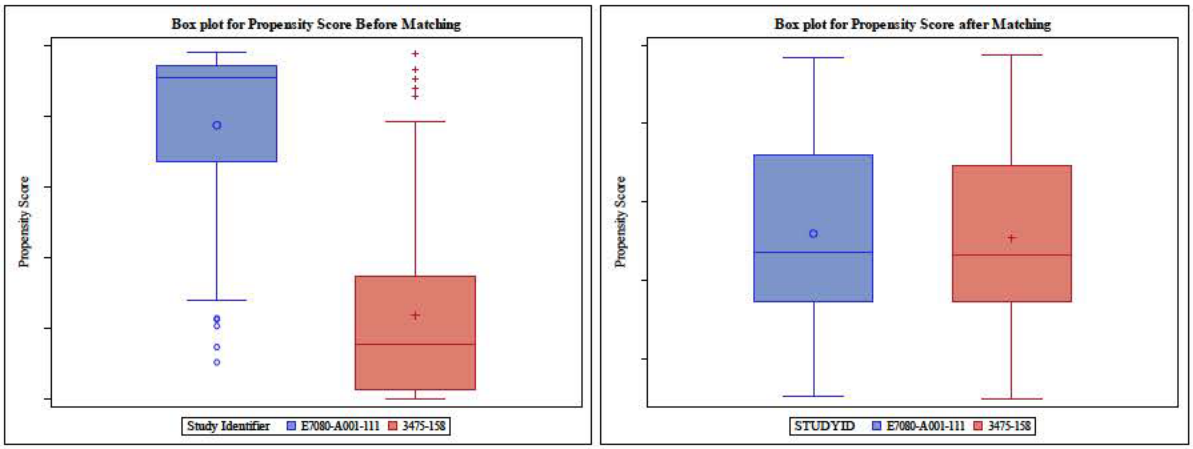
2. Isolation of treatment effect for lenvatinib – Comparison of Study 111/KN-146 (n=94) vs. KEYNOTE-158 (n=90)

(a) Propensity Score Matching Approach

Matched pairs were formed (1:1 matching without replacement) with a similar propensity score using nearest-neighbour matching algorithm with caliper width of 0.2 of the standard deviation of the logit of the propensity scores (Austin 2011). The following histograms and boxplots represented the distribution of propensity score by treated (Study 111/KN-146) or control (KEYNOTE-158), before or after matching. With 1 to 1 matching method, there were 31 patients from Study 111/KN-146 matched with 31 patients from KEYNOTE-158. The difference was reduced after matching (Figure 10). There were 63 out of 94 patients (67.0%) in Study 111/KN-146 and 59 out of 90 patients (65.6%) in KEYNOTE-158 who were unmatched in the analysis (Figure 11).

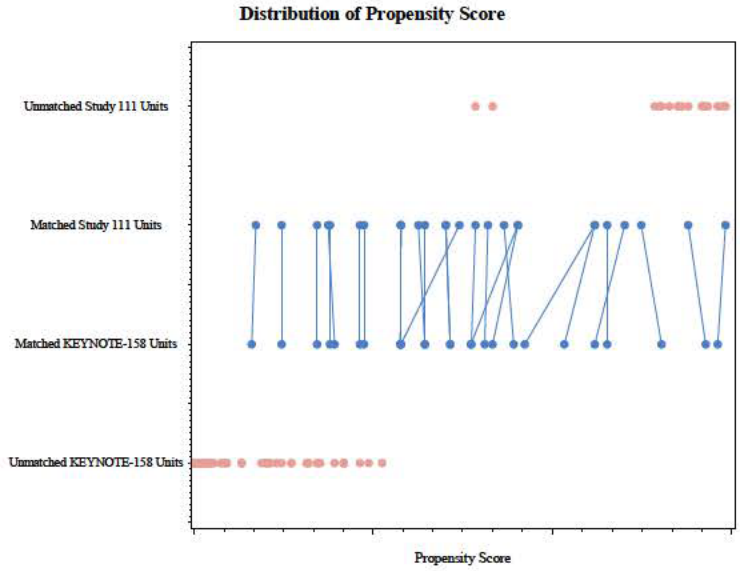
Figure 10. Distribution of Propensity Score Before and After Matching (Lenvatinib + Pembrolizumab vs. Pembrolizumab)





[Source: Reviewer's Analysis]

Figure 11. Distribution of Propensity Score including Matched and Unmatched Patients (Lenvatinib + Pembrolizumab vs. Pembrolizumab)



[Source: Reviewer's Analysis]

A summary of baseline covariates used for assessing the comparability of Study 111/KN-146 and KEYNOTE-158 prior to any adjustment is presented in Table 51 (see "Unadjusted" column). It appears to have some minor imbalance, e.g. PD-L1 status and Histology based on the matching method (see "Matching" column). This may be due to the subset of patients after matching which more than 65% of patients in each study were unmatched, and the imbalance in the original studies.

Table 51. Summary of Baseline Covariates Before and After Propensity Score Matching (Lenvatinib + Pembrolizumab vs. Pembrolizumab)

	Unadjusted	Matching

	Study 111/KN-146	KEYNOTE-158	SMD - unadjusted	Study 111/KN-146	KEYNOTE-158	SMD - matched
	N=94	N=90		N=31	N=31	
Age Group			0.351			0.066
<65	36 (38.3)	50 (55.6)		13 (41.9)	12 (38.7)	
≥65	58 (61.7)	40 (44.4)		18 (58.1)	19 (61.3)	
Race			0.298			0.092
White	81 (86.1)	67 (74.4)		26 (83.9)	27 (87.1)	
Non-White	13 (13.8)	23 (25.6)		5 (16.1)	4 (12.9)	
Geographic Region			1.385			0.067
US	81 (86.1)	27 (30.0)		20 (64.5)	19 (61.3)	
Non-US	13 (13.8)	63 (70.0)		11 (35.5)	12 (38.7)	
ECOG PS at Baseline			0.087			0.130
0	49 (52.1)	43 (47.8)		13 (41.9)	15 (48.4)	
1	45 (47.9)	47 (52.2)		18 (58.1)	16 (51.6)	
PD-L1 Status			0.370			0.310
Positive	46 (48.9)	56 (62.2)		16 (51.6)	18 (58.1)	
Negative	39 (41.5)	32 (35.6)		15 (48.4)	12 (39.7)	
Not Available	9 (9.6)	2 (2.2)		0	1 (3.2)	
Number of Prior Anti-Cancer Regimen			0.895			0.156
1	48 (51.1)	26 (28.9)		12 (38.7)	14 (45.2)	
2	36 (38.3)	21 (23.3)		10 (32.3)	8 (25.8)	
3+	10 (10.6)	43 (47.8)		9 (29.0)	9 (29.0)	
Histology			0.110			0.330
Endometroid	46 (48.9)	49 (54.4)		20 (64.5)	15 (48.4)	
Others	48 (51.1)	41 (45.6)		11 (35.5)	16 (51.6)	
Source: Study 111 – ADSL.xpt, ADDC.xpt, ADEF.xpt, KEYNOTE 158 – ADSL.xpt, ADRS.xpt						

(b) Propensity Score Weighting Approach

A stabilized inversed probability treatment weighting (sIPTW) approach was used as the primary weighting method. Sensitivity analyses were performed to assess ORR using additional weighting schemes (i.e., Average Treatment Effect for Overlap Population [ATO], Average Treatment Effects on the Treated [ATT] and Average Treatment Effects on the Control [ATC]).

To examine the balance of baseline covariates between treated and control patients in the different approaches, the absolute SMD between the two groups were summarized in Table 52. The covariates appear to have minor imbalance between treatment and compared group in the sIPTW sample (ie, number of prior anticancer regimen based on the sIPTW [SMD = 0.323]). This may be due to the small sample size and the imbalance in the original studies.

Table 52. Summary of Standardized Mean Difference (Lenvatinib + Pembrolizumab vs. Pembrolizumab).

	Unadjusted	Matched	sIPTW	ATT	ATC
Age Group	0.351	0.066	0.115	0.335	0.116
Race	0.298	0.092	0.067	0.304	0.473
Geographic Region	1.385	0.067	0.106	0.103	0.232
ECOG PS at Baseline	0.087	0.130	0.100	0.179	0.015
PD-L1 Status	0.37	0.310	0.250	0.362	0.185
Number of Prior Anti-Cancer Regimen	0.895	0.156	0.323	0.484	0.548
Histology	0.11	0.330	0.085	0.114	0.066
Source: Study 111 – ADSL.xpt, ADDC.xpt, ADEF.xpt, KEYNOTE 158 – ADSL.xpt, ADRS.xpt					

The treatment effects in ORR based on different weighting methods are shown in Table 53. The treatment effects estimated from all different propensity score weighting approaches are consistent with unadjusted analysis and propensity score matching analysis.

Table 53. Efficacy Results – Propensity Score Weighting Analyses (Lenvatinib + Pembrolizumab vs. Lenvatinib).

	Study 111/KN-146	KEYNOTE-158
sIPTW		
ORR, % (95% CI)	38.8 (28.0, 49.6)	5.4 (1.0, 9.7)
ORR difference, % (95% CI)	33.4 (21.8, 45.1)	
ORR ratio (95% CI)	7.23 (3.05, 17.13)	
ATO		
ORR, % (95% CI)	38.7 (28.7, 48.6)	6.0 (1.2, 10.9)
ORR difference, % (95% CI)	32.7 (21.6, 43.7)	
ORR ratio (95% CI)	6.43 (2.75, 15.00)	
ATT		
ORR, % (95% CI)	38.3 (28.5, 48.1)	3.5 (0.2, 6.9)
ORR difference, % (95% CI)	34.8 (24.4, 45.2)	
ORR ratio (95% CI)	10.87 (4.09, 28.90)	
ATC		
ORR, % (95% CI)	39.6 (27.1., 52.1)	7.8 (2.2, 13.3)
ORR difference, % (95% CI)	31.8 (18.2, 45.5)	
ORR ratio (95% CI)	5.09 (2.34, 11.08)	
Source: Study 111 – ADSL.xpt, ADDC.xpt, ADEF.xpt, KEYNOTE 158 – ADSL.xpt, ADRS.xpt		

Based on the cross-trial comparison results presented in Section 7.1.6, additional information summarized showd in this Appendix. Acknowledging the lack of a randomized trial and the limitations in the use of external controls, the data and analyses submitted in this application suggest a higher response rate with the combination therapy.

17.5 List of Pooled Preferred Terms used for Safety Analysis

To review the AE datasets, the following terms, as shown in table below were pooled for this review. These pooled terms are used for safety analysis.

	Category	AEDECOD
1	Fatigue	Asthenia; Fatigue; decreased activity; Malaise; Lethargy
2	Abdominal pain	abdominal pain; upper abdominal pain; lower abdominal pain; abdominal tenderness; abdominal discomfort; epigastric discomfort; gastrointestinal pain; Abdominal pain generalized; Abdominal pain localized
3	Hypothyroidism	hypothyroidism; blood thyroid hormone increased; autoimmune hypothyroidism; hypothyroidic goiter; secondary hypothyroidism; tertiary hypothyroidism; primary hypothyroidism; post procedural hypothyroidism; blood thyroid stimulating hormone increased
4	Hemorrhage (SMQ)	Abdominal wall haematoma; Abdominal wall haemorrhage; Abnormal withdrawal bleeding; Achenbach syndrome; Acute haemorrhagic leukoencephalitis; Acute haemorrhagic ulcerative colitis; Administration site bruise; Administration site haematoma; Administration site haemorrhage; Adrenal haematoma; Adrenal haemorrhage; Anal fissure haemorrhage; Anal haemorrhage; Anal ulcer haemorrhage; Anastomotic haemorrhage; Anastomotic ulcer haemorrhage; Aneurysm ruptured; Angina bullosa haemorrhagica; Anorectal varices haemorrhage; Aortic aneurysm rupture; Aortic dissection rupture; Aortic intramural haematoma; Aortic perforation; Aortic rupture; Aponeurosis contusion; Application site bruise; Application site haematoma; Application site haemorrhage; Application site purpura; Arterial haemorrhage; Arterial intramural haematoma; Arterial perforation; Arterial rupture; Arteriovenous fistula site haematoma; Arteriovenous fistula site haemorrhage; Arteriovenous graft site haematoma; Arteriovenous graft site haemorrhage; Astringent therapy; Atrial rupture; Auricular haematoma; Basal ganglia haematoma; Basal ganglia haemorrhage; Basilar artery perforation; Bladder tamponade; Bleeding varicose vein; Blood blister; Blood loss anaemia; Blood urine; Blood urine present; Bloody discharge; Bloody peritoneal effluent; Bone contusion; Bone marrow haemorrhage; Brain

		contusion; Brain stem haematoma; Brain stem haemorrhage; Brain stem microhaemorrhage; Breast haematoma; Breast haemorrhage; Broad ligament haematoma; Bronchial haemorrhage; Bronchial varices haemorrhage; Bursal haematoma; Cardiac contusion; Carotid aneurysm rupture; Carotid artery perforation; Catheter site bruise; Catheter site haematoma; Catheter site haemorrhage; Central nervous system haemorrhage; Cephalhaematoma; Cerebellar haematoma; Cerebellar haemorrhage; Cerebellar microhaemorrhage; Cerebral aneurysm perforation; Cerebral aneurysm ruptured syphilitic; Cerebral arteriovenous malformation haemorrhagic; Cerebral artery perforation; Cerebral cyst haemorrhage; Cerebral haematoma; Cerebral haemorrhage; Cerebral haemorrhage foetal; Cerebral haemorrhage neonatal; Cerebral microhaemorrhage; Cervix haematoma uterine; Cervix haemorrhage uterine; Chest wall haematoma; Choroidal haematoma; Choroidal haemorrhage; Chronic gastrointestinal bleeding; Chronic pigmented purpura; Ciliary body haemorrhage; Coital bleeding; Colonic haematoma; Conjunctival haemorrhage; Contusion; Corneal bleeding; Cullen's sign; Cystitis haemorrhagic; Deep dissecting haematoma; Diarrhoea haemorrhagic; Disseminated intravascular coagulation; Diverticulitis intestinal haemorrhagic; Diverticulum intestinal haemorrhagic; Duodenal ulcer haemorrhage; Duodenitis haemorrhagic; Dysfunctional uterine bleeding; Ear haemorrhage; Ecchymosis; Encephalitis haemorrhagic; Enterocolitis haemorrhagic; Epidural haemorrhage; Epistaxis; Exsanguination; Extra-axial haemorrhage; Extradural haematoma; Extravasation blood; Eye contusion; Eye haematoma; Eye haemorrhage; Eyelid bleeding; Eyelid contusion; Eyelid haematoma; Femoral artery perforation; Femoral vein perforation; Foetal-maternal haemorrhage; Fothergill sign positive; Gastric haemorrhage; Gastric ulcer haemorrhage; Gastric ulcer haemorrhage, obstructive; Gastric varices haemorrhage; Gastritis alcoholic haemorrhagic; Gastritis haemorrhagic; Gastroduodenal haemorrhage; Gastrointestinal haemorrhage; Gastrointestinal polyp haemorrhage; Gastrointestinal ulcer haemorrhage; Gastrointestinal vascular malformation haemorrhagic; Genital contusion; Genital haemorrhage; Gingival bleeding; Graft haemorrhage; Grey Turner's sign; Haemarthrosis; Haematemesis; Haematochezia; Haematocoele; Haematoma; Haematoma evacuation; Haematoma infection; Haematoma muscle; Haematosalpinx; Haematospermia; Haematotympanum; Haematuria; Haematuria traumatic; Haemobilia; Haemophilic arthropathy; Haemophilic

		pseudotumour; Haemoptysis; Haemorrhage; Haemorrhage coronary artery; Haemorrhage foetal; Haemorrhage in pregnancy; Haemorrhage intracranial; Haemorrhage neonatal; Haemorrhage subcutaneous; Haemorrhage subepidermal; Haemorrhage urinary tract; Haemorrhagic adrenal infarction; Haemorrhagic arteriovenous malformation; Haemorrhagic ascites; Haemorrhagic breast cyst; Haemorrhagic cerebral infarction; Haemorrhagic cyst; Haemorrhagic diathesis; Haemorrhagic disease of newborn; Haemorrhagic disorder; Haemorrhagic erosive gastritis; Haemorrhagic hepatic cyst; Haemorrhagic infarction; Haemorrhagic necrotic pancreatitis; Haemorrhagic ovarian cyst; Haemorrhagic stroke; Haemorrhagic thyroid cyst; Haemorrhagic transformation stroke; Haemorrhagic tumour necrosis; Haemorrhagic urticaria; Haemorrhagic vasculitis; Haemorrhoidal haemorrhage; Haemostasis; Haemothorax; Henoch-Schonlein purpura; Hepatic haemangioma rupture; Hepatic haematoma; Hepatic haemorrhage; Hereditary haemorrhagic telangiectasia; Hyperfibrinolysis; Hyphaema; Iliac artery perforation; Iliac artery rupture; Iliac vein perforation; Immune thrombocytopenic purpura; Implant site bruising; Implant site haematoma; Implant site haemorrhage; Incision site haematoma; Incision site haemorrhage; Increased tendency to bruise; Induced abortion haemorrhage; Inferior vena cava perforation; Infusion site bruising; Infusion site haematoma; Infusion site haemorrhage; Injection site bruising; Injection site haematoma; Injection site haemorrhage; Instillation site bruise; Instillation site haematoma; Instillation site haemorrhage; Internal haemorrhage; Intestinal haematoma; Intestinal haemorrhage; Intestinal varices haemorrhage; Intra-abdominal haematoma; Intra-abdominal haemorrhage; Intracerebral haematoma evacuation; Intracranial haematoma; Intracranial tumour haemorrhage; Intraocular haematoma; Intrapartum haemorrhage; Intraventricular haemorrhage; Intraventricular haemorrhage neonatal; Iris haemorrhage; Joint microhaemorrhage; Kidney contusion; Lacrimal haemorrhage; Large intestinal haemorrhage; Large intestinal ulcer haemorrhage; Laryngeal haematoma; Laryngeal haemorrhage; Lip haematoma; Lip haemorrhage; Liver contusion; Lower gastrointestinal haemorrhage; Lower limb artery perforation; Lymph node haemorrhage; Mallory-Weiss syndrome; Mediastinal haematoma; Mediastinal haemorrhage; Medical device site bruise; Medical device site haematoma; Medical device site haemorrhage; Melaena; Melaena neonatal; Meningorrhagia; Menometrorrhagia; Menorrhagia; Mesenteric haematoma;

		Mesenteric haemorrhage; Metrorrhagia; Mouth haemorrhage; Mucocutaneous haemorrhage; Mucosal haemorrhage; Muscle contusion; Muscle haemorrhage; Myocardial haemorrhage; Myocardial rupture; Naevus haemorrhage; Nail bed bleeding; Nasal septum haematoma; Neonatal gastrointestinal haemorrhage; Nephritis haemorrhagic; Nipple exudate bloody; Ocular retrobulbar haemorrhage; Oesophageal haemorrhage; Oesophageal intramural haematoma; Oesophageal ulcer haemorrhage; Oesophageal varices haemorrhage; Oesophagitis haemorrhagic; Optic disc haemorrhage; Optic nerve sheath haemorrhage; Oral contusion; Oral mucosa haematoma; Osteorrhagia; Ovarian haematoma; Ovarian haemorrhage; Palpable purpura; Pancreatic haemorrhage; Pancreatitis haemorrhagic; Papillary muscle haemorrhage; Paranasal sinus haematoma; Paranasal sinus haemorrhage; Parathyroid haemorrhage; Parotid gland haemorrhage; Pelvic haematoma; Pelvic haematoma obstetric; Pelvic haemorrhage; Penile contusion; Penile haematoma; Penile haemorrhage; Peptic ulcer haemorrhage; Pericardial haemorrhage; Perineal haematoma; Periorbital haematoma; Periorbital haemorrhage; Periosteal haematoma; Peripartum haemorrhage; Peripheral artery aneurysm rupture; Peripheral artery haematoma; Perirenal haematoma; Peritoneal haematoma; Peritoneal haemorrhage; Periventricular haemorrhage neonatal; Petechiae; Pharyngeal haematoma; Pharyngeal haemorrhage; Pituitary apoplexy; Pituitary haemorrhage; Placenta praevia haemorrhage; Polymenorrhagia; Post abortion haemorrhage; Post procedural contusion; Post procedural haematoma; Post procedural haematuria; Post procedural haemorrhage; Post transfusion purpura; Postmenopausal haemorrhage; Postpartum haemorrhage; Post-traumatic punctate intraepidermal haemorrhage; Premature separation of placenta; Procedural haemorrhage; Proctitis haemorrhagic; Prostatic haemorrhage; Pulmonary alveolar haemorrhage; Pulmonary contusion; Pulmonary haematoma; Pulmonary haemorrhage; Pulmonary haemorrhage neonatal; Puncture site bruise; Puncture site haematoma; Puncture site haemorrhage; Purpura; Purpura fulminans; Purpura neonatal; Purpura non-thrombocytopenic; Purpura senile; Putamen haemorrhage; Radiation associated haemorrhage; Rectal haemorrhage; Rectal ulcer haemorrhage; Renal artery perforation; Renal cyst haemorrhage; Renal haematoma; Renal haemorrhage; Respiratory tract haemorrhage; Respiratory tract haemorrhage neonatal; Retinal aneurysm rupture; Retinal haemorrhage; Retinopathy haemorrhagic;

		Retroperitoneal haematoma; Retroperitoneal haemorrhage; Retroplacental haematoma; Ruptured cerebral aneurysm; Scleral haemorrhage; Scrotal haematocoele; Scrotal haematoma; Shock haemorrhagic; Skin haemorrhage; Skin neoplasm bleeding; Skin ulcer haemorrhage; Small intestinal haemorrhage; Small intestinal ulcer haemorrhage; Soft tissue haemorrhage; Spermatic cord haemorrhage; Spinal cord haematoma; Spinal cord haemorrhage; Spinal epidural haematoma; Spinal epidural haemorrhage; Spinal subarachnoid haemorrhage; Spinal subdural haematoma; Spinal subdural haemorrhage; Spleen contusion; Splenic artery perforation; Splenic haematoma; Splenic haemorrhage; Splenic varices haemorrhage; Splinter haemorrhages; Spontaneous haematoma; Spontaneous haemorrhage; Stoma site haemorrhage; Stomatitis haemorrhagic; Subarachnoid haematoma; Subarachnoid haemorrhage; Subarachnoid haemorrhage neonatal; Subchorionic haematoma; Subchorionic haemorrhage; Subclavian artery perforation; Subclavian vein perforation; Subcutaneous haematoma; Subdural haematoma; Subdural haematoma evacuation; Subdural haemorrhage; Subdural haemorrhage neonatal; Subendocardial haemorrhage; Subgaleal haematoma; Subgaleal haemorrhage; Subretinal haematoma; Superior vena cava perforation; Testicular haemorrhage; Thalamus haemorrhage; Third stage postpartum haemorrhage; Thoracic haemorrhage; Thrombocytopenic purpura; Thrombotic thrombocytopenic purpura; Thyroid haemorrhage; Tongue haematoma; Tongue haemorrhage; Tonsillar haemorrhage; Tooth pulp haemorrhage; Tooth socket haemorrhage; Tracheal haemorrhage; Traumatic haematoma; Traumatic haemorrhage; Traumatic haemothorax; Traumatic intracranial haematoma; Traumatic intracranial haemorrhage; Tumour haemorrhage; Ulcer haemorrhage; Umbilical cord haemorrhage; Umbilical haematoma; Umbilical haemorrhage; Upper gastrointestinal haemorrhage; Ureteric haemorrhage; Urethral haemorrhage; Urinary bladder haemorrhage; Urogenital haemorrhage; Uterine haematoma; Uterine haemorrhage; Vaccination site bruising; Vaccination site haematoma; Vaccination site haemorrhage; Vaginal haematoma; Vaginal haemorrhage; Varicose vein ruptured; Vascular access site bruising; Vascular access site haematoma; Vascular access site haemorrhage; Vascular access site rupture; Vascular graft haemorrhage; Vascular pseudoaneurysm ruptured; Vascular purpura; Vascular rupture; Vein rupture; Venous haemorrhage; Venous perforation; Ventricle rupture; Vertebral artery perforation; Vessel puncture site bruise; Vessel puncture site

		haematoma; Vessel puncture site haemorrhage; Vitreous haematoma; Vitreous haemorrhage; Vulval haematoma; Vulval haematoma evacuation; Vulval haemorrhage; Withdrawal bleed; Wound haematoma; Wound haemorrhage
5	Hepatotoxicity	Ascites; Autoimmune hepatitis; Hepatitis; Hepatic encephalopathy; Metabolic encephalopathy; Hepatic failure; Hepatic function abnormal; Hyperbilirubinemia; Hyperammonemia; Jaundice cholestatic; Hepatic pain; jaundice; Urine bilirubin increased; Hepatic cirrhosis; Coma hepatic; Edema due to hepatic disease; Varices esophageal; Portal hypertensive gastropathy
6	Elevated LFTs	Blood bilirubin Increased; Aspartate transaminase increased; Alanine aminotransferase increased; Gamma-glutamyltransferase increased; hyperbilirubinemia; transaminases increased; Blood alkaline phosphatase increased
7	Hypertension	Accelerated hypertension; Blood pressure ambulatory increased; Blood pressure diastolic increased; Blood pressure inadequately controlled; Blood pressure increased; Blood pressure management; Blood pressure orthostatic increased; Blood pressure systolic increased; Cardiometabolic syndrome; Catecholamine crisis; Diastolic hypertension; Eclampsia; Endocrine hypertension; Essential hypertension; Gestational hypertension; HELLP syndrome; Hyperaldosteronism; Hypertension; Hypertension neonatal; Hypertensive angiopathy; Hypertensive cardiomegaly; Hypertensive cardiomyopathy; Hypertensive cerebrovascular disease; Hypertensive crisis; Hypertensive emergency; Hypertensive encephalopathy; Hypertensive end-organ damage; Hypertensive heart disease; Hypertensive nephropathy; Hypertensive urgency; Labile hypertension; Malignant hypertension; Malignant hypertensive heart disease; Malignant renal hypertension; Maternal hypertension affecting foetus; Mean arterial pressure increased; Neurogenic hypertension; Orthostatic hypertension; Page kidney; Postoperative hypertension; Pre-eclampsia; Prehypertension; Procedural hypertension; Renal hypertension; Renal sympathetic nerve ablation; Renovascular hypertension; Retinopathy hypertensive; Secondary aldosteronism; Secondary hypertension; Supine hypertension; Systolic hypertension; Withdrawal hypertension; Aldosterone urine abnormal; Aldosterone urine increased; Angiotensin converting enzyme increased; Angiotensin I increased; Angiotensin II increased; Angiotensin II receptor type 1 antibody positive; Blood aldosterone abnormal; Blood aldosterone increased; Blood catecholamines abnormal; Blood catecholamines increased; Blood pressure abnormal; Blood

		pressure ambulatory abnormal; Blood pressure diastolic abnormal; Blood pressure fluctuation; Blood pressure orthostatic abnormal; Blood pressure systolic abnormal; Catecholamines urine abnormal; Catecholamines urine increased; Diuretic therapy; Ectopic aldosterone secretion; Ectopic renin secretion; Epinephrine abnormal; Epinephrine increased; Labile blood pressure; Metanephrine urine abnormal; Metanephrine urine increased; Non-dipping; Norepinephrine abnormal; Norepinephrine increased; Normetanephrine urine increased; Pseudoaldosteronism; Renin abnormal; Renin increased; Renin-angiotensin system inhibition; Tyramine reaction
8	Rhabdomyolysis	Muscle necrosis; Myoglobin blood increased; Myoglobin blood present; Myoglobin urine present; Myoglobinaemia; Myoglobinuria; Myopathy; Myopathy toxic; Necrotising myositis; Rhabdomyolysis; Thyrotoxic myopathy
9	GI perforation fistula	Abdominal hernia perforation; Acquired tracheo-oesophageal fistula; Anal fistula; Anal fistula excision; Anal fistula infection; Anastomotic ulcer perforation; Anovulvar fistula; Aortoenteric fistula; Aorto-oesophageal fistula; Appendicitis perforated; Arterioenteric fistula; Atrio-oesophageal fistula; Chemical peritonitis; Colon fistula repair; Colonic fistula; Diverticular fistula; Diverticular perforation; Duodenal perforation; Duodenal ulcer perforation; Duodenal ulcer perforation, obstructive; Duodenal ulcer repair; Enterocolonic fistula; Enterocutaneous fistula; Enterovesical fistula; Fistula of small intestine; Gastric fistula; Gastric fistula repair; Gastric perforation; Gastric ulcer perforation; Gastric ulcer perforation, obstructive; Gastrointestinal anastomotic leak; Gastrointestinal fistula; Gastrointestinal fistula repair; Gastrointestinal perforation; Gastrointestinal ulcer perforation; Gastropleural fistula; Gastrosplenic fistula; Ileal perforation; Ileal ulcer perforation; Inguinal hernia perforation; Intestinal fistula; Intestinal fistula infection; Intestinal fistula repair; Intestinal perforation; Intestinal ulcer perforation; Jejunal perforation; Jejunal ulcer perforation; Large intestinal ulcer perforation; Large intestine perforation; Lower gastrointestinal perforation; Neonatal intestinal perforation; Oesophageal fistula; Oesophageal fistula repair; Oesophageal perforation; Oesophageal rupture; Oesophageal ulcer perforation; Oesophagobronchial fistula; Oesophagopleural fistula; Pancreatic fistula; Pancreatic fistula repair; Peptic ulcer perforation; Peptic ulcer perforation, obstructive; Perforated peptic ulcer oversewing; Perforated ulcer; Peritoneocutaneous fistula; Peritonitis; Peritonitis bacterial; Procedural intestinal perforation; Rectal fistula repair; Rectal perforation;

		Rectoprostatic fistula; Rectourethral fistula; Small intestinal perforation; Small intestinal ulcer perforation; Umbilical hernia perforation; Upper gastrointestinal perforation
10	Renal impairment	Acute Kidney Injury; Renal impairment; Renal Failure; Anuria; Azotemia; Oliguria; Renal tubular necrosis; blood creatinine increased; Urine output decreased; Nephritis NEC HLT
11	Musculoskeletal pain	Musculoskeletal pain; Musculoskeletal chest pain; myalgia; arthralgia; Musculoskeletal stiffness; Musculoskeletal discomfort; bone pain; non-cardiac chest pain; Breast pain; arthritis; Back Pain; Pain in Jaw; pain in extremity; Joint Pain; neck pain
12	Pancreatitis	Pancreatitis; pancreatitis acute; Pancreatic enzymes increased; Pancreatic enzymes abnormal; Pancreatic pseudocyst; Pancreatic cyst; Pancreatic haemorrhage; Pancreatic necrosis
13	Palmar-plantar erythrodysesthesia	Palmar-plantar erythrodysaesthesia syndrome; Skin reaction; Palmar erythema; Plantar erythema
14	Rash	Rashes, eruptions and exanthems NEC
15	Peripheral neuropathy	autoimmune neuropathy; peripheral sensory neuropathy; paraesthesia; neuropathy peripheral; hypoaesthesia; neuralgia; polyneuropathy; peripheral motor neuropathy; peripheral sensorimotor neuropathy; dysesthesia
16	Proteinuria	Albumin globulin ratio increased; Albumin urine present; Albuminuria; Bence Jones protein urine present; Bence Jones proteinuria; Beta 2 microglobulin urine increased; Globulinuria; Microalbuminuria; Myoglobinuria; Orthostatic proteinuria; Protein urine; Protein urine present; Proteinuria; Urine albumin/creatinine ratio increased; Urine protein/creatinine ratio abnormal; Urine protein/creatinine ratio increased
17	Abscess	Abdominal abscess; Abdominal wall abscess; Abscess intestinal; Anal abscess; Appendiceal abscess; Colonic abscess; Douglas' abscess; Mesenteric abscess; Paraoesophageal abscess; Perineal abscess; Perirectal abscess; Peritoneal abscess; Rectal abscess; Retroperitoneal abscess; Abscess; abdominal Abscess; pelvic Abscess; vulval abscess; subcutaneous abscess; tooth Abscess
18	Stomatitis	Mucositis; stomatitis; aphthous ulcer; mouth ulceration; chelitis; oral discomfort; tongue ulceration; mucosal inflammation; mucositis; apthous ulcer; glossitis; mucosal hyperaemia; oral mucosal blistering; gingival erosion; oropharyngeal pain; gingival ulceration; pharyngeal inflammation; oral mucosal erythema; aphthous stomatitis
19	Colitis	Colitis; colitis ischaemic
20	Diarrhea	viral diarrhoea; gastroenteritis; gastrointestinal viral infection; Diarrhoea

21	Chest pain	angina pectoris; chest discomfort; chest pain
22	Decreased appetite	Decreased appetite; Early satiety
23	Dyspnea	Dyspnoea; Dyspnoea at rest; Dyspnoea exertional; Shortness of breath; Difficulty in breathing
24	UTI	pyelonephritis; urinary tract infection; cystitis
25	Cardiac Failure	cardiac failure; cardiac failure congestive; ejection fraction decreased
27	Depressed mood	adjustment disorder with depressed mood; Depressed mood; Depression

17.6 Information Requests sent to the Sponsors during the review cycle

1.	Date: June 25, 2019; Agency sending IR: FDA

This IR refers to your pending applications for Lenvima and Keytruda (NDA 206947/S-011 and BLA 125514/S-065). Below is an information request from the clinical team:
Update the Assessment Aid document to include the following tables (in a format consistent with other tables in section 7.2). In your response include a version with tracked changes and a clean version. Provide a response by noon on Thursday, June 27, 2019.
1. Overview of Deaths in Safety Population due to adverse event whilst on study drug or during study follow-up
a) Apart from the table, also include the narratives reports of deaths due to causes other than disease progression
2. Dose Interruption/Reduction Due to Adverse Effect
3. Overview of AESIs for pembrolizumab observed in the Safety Population
4. Overview of Clinically significant events for lenvatinib observed in the Safety Population
5. Overview of Overlapping Toxicities of Clinical Interest
6. Incidence of Laboratory Abnormalities
7. Shift from baseline to worst post-baseline CTCAE Grade for vital signs
8. Safety Analyses by Demographic Subgroups – age, race and geographical region

Response reveived: June 27, 2019. Updated assessment aid was provided by the sponsor.

2.	Date: July 3, 2019; Agency sending IR: FDA

In the datasets submitted for study 111/KN-146, we cannot locate patients treated with systemic corticosteroids (indicated with CORTFL flag) or the patients that experienced immune-mediated adverse events (indicated with AEOSIFL in the dataset).
Also, the studies KN-028 and KN-158 are not part of the ISS safety dataset. Either identify the location for the above stated or provide updated datasets.

Response reveived: June 27, 2019
Within the ADCM dataset for Study 111, patients treated with corticosteroids are flagged with the variable ACMEDFL. In the ADAE dataset for Study 111, patients that experienced adverse events of special interest (AEOSI) for pembrolizumab are indicated by 20 flag variables,

CQPE01FL-CQPE20FL, corresponding to grouped terms; variables CQ01NAM - CQ20NAM contain the AEOSI grouped term names. All grouped terms are considered immune-mediated adverse events except for the grouped term in CQPE19FL, which identifies infusion reactions.

3. Date: July 3, 2019; Agency sending IR: FDA

A). In reference to Efficacy Supplement 11 (SDN 461 submitted on 5/8/2019), submit data by COB July 12, 2019– or provide eCTD location if already submitted – to support the proposed USPI update "[redacted (b) (4)]" in section 12.3.

B). Provide one dataset consisting of the 94 patients in the not MSI-H/dMMR EC 2L+ set, listing all AEs that required any corticosteroid use (flag) and how many AEs were considered AEOSI (flag), without the custom queries.

C). Provide a rationale for the following:
For Subject ID [redacted (b) (6)], provide a rationale for not considering this death occurred due to AE of the study drugs.
For Subject ID [redacted (b) (6)], provide a rationale for considering this death occurred due to AE of the study drugs.
Provide a clarification for the numbers (in red font) in the table below:
What were the cause of deaths for these events that occurred in the indication data set during survival follow-up
Though not part of this application, provide the cause for the 12 deaths that occurred in the Non-EC data set, that were not due to disease progression.

Table 17
Summary of Deaths – Safety Analysis Set

	Lenvatinib 20 mg QD + Pembrolizumab 200 mg Q3W n (%)					
	EC 2L+					
	Total (N=108)	Indication (N=94)	MSI-H/ dMMR (N=11)	All EC (N=124)	Non-EC (N=159)	All EC + Non-EC (N=283)
All Deaths[a]	49 (45.4)	44 (46.8)	3 (27.3)	51 (41.1)	63 (39.6)	114 (40.3)
AEs Leading to Death	14 (13.0)	12 (12.8)	2 (18.2)	16 (12.9)	28 (17.6)	44 (15.5)
Due to Disease Progression	11 (10.2)	10 (10.6)	1 (9.1)	13 (10.5)	16 (10.1)	29 (10.2)
Not Due to Disease Progression	3 (2.8)	2 (2.1)	1 (9.1)	3 (2.4)	12 (7.5)	15 (5.3)
Other Deaths During the Survival Follow-up	35 (32.4)	32 (34.0)	1 (9.1)	35 (28.2)	35 (22.0)	70 (24.7)

Data cutoff date: 10 Jan 2019.

Response reveived: June 27, 2019

Response to Clinical RFI dated 10

4.	Date: July 10, 2019; Agency sending IR: Health Canada

HC Questions_0710201

Response reveived: July 18, 2019

Responses_HC Questions_0710201

5.	Date: July 11, 2019; Agency sending IR: FDA

Provide a status update for Study E7080-G000-313/MK-7902-001, A Phase 3 Randomized, Open- Label, Study of Pembrolizumab (MK-3475) Plus Lenvatinib Versus Chemotherapy for Firstline Treatment of Advanced or Recurrent Endometrial Carcinoma.

Response reveived: July 23, 2019

(b) (4)

(b) (4)

6. Date: August 1, 2019; Agency sending IR: Health Canada

1. Enrolled EC patients in pivotal Study 111 were restricted to those with metastatic disease previously treated with systemic therapy. (b) (4)

   a. (b) (4)

   b. The pre-submission meeting briefing package indicates that the confirmatory Study 309/KN775 is being conducted in patients with 'Advanced Endometrial Cancer', whereas the meeting slides indicate that those EC patients with 'advanced, metastatic, or recurrent' disease would be eligible. Please describe how this populations differ, and clarify the EC patient population being enrolled in this confirmatory study with respect to stage of disease. (b) (4)

2. For patients with severe renal or severe hepatic impairment, the Product Monograph instructs that the starting dose of Lenvima be reduced to 14 mg QD (from 24 mg) for the treatment of DTC, and reduced to 10 mg (from 18 mg QD) for the treatment of RCC.
   a. Please discuss the necessity of a reduced lenvatinib dose for patients with severe renal impairment when used in combination with pembrolizumab for the proposed indication. If a specific reduced starting dose is recommended, please provide a sufficient justification for its derivation.
   b. It is noted from the FDA analysis of safety that Renal Adverse Events, including Grade 3/4 AEs, were notably higher in the 'Indication Safety Set' (lenvatinib in combination with pembrolizumab) compared to the lenvatinib monotherapy (Study 204). Please further discuss the impact of this finding on your response to comment 2a above with respect to the dosing of lenvatinib in patients with severe renal impairment, as well as for those with mild and moderate renal impairment.
   c. Please discuss the necessity of a reduced lenvatinib dose for patients with severe

hepatic impairment when used in combination with pembrolizumab for the proposed indication. If a specific reduced starting dose is recommended, please provide a sufficient justification for its derivation.

Response received: August 8, 2019


Response to Health Canada RFI Dated 0


Response to Health Canada RFI Dated 0


Response to Health Canada RFI Dated 0


Response to Health Canada RFI Dated 0

5.	Date: September 5, 2019; Agency sending IR: FDA

Provide the total number of investigators involved in study111/KN-146. Also, for investigators with disclosable financial interests/arrangements, provide a description of the steps taken to minimize potential bias.

Response received: September 5, 2019

The total number of investigators participating in Study 111 is 35. Fifteen of the 35 investigators enrolled subjects in the endometrial cohort at the time of data cutoff.

Study 111 is a single-arm, open label trial. To minimize potential bias, the Sponsors implemented the same measures across all study sites:

The primary efficacy analyses were based on data from an independent imaging review. The radiologists that evaluated the images for tumor assessments had no knowledge as to which investigators enrolled subjects.

Clinical monitoring of Study 111 was performed throughout the study with a minimum visit interval of every 6 weeks. This included ensuring that study assessments and procedures were performed appropriately and within the correct time frames, and that adverse events and serious adverse events were accurately recorded in the case report form and reported in a timely fashion.

6. Date: September 11, 2019; Agency sending IR: FDA

Upon review of the milestones of the PMXs you provided, our clinical review team are requesting your response to the following comment:

Please provide the rationale for your proposed timelines for the development of the two companion diagnostic devices for this indication.

Response received:

The Sponsors identified an error in the PMR dates that were submitted to FDA on 06 September 2019. The original and corrected projections for PMR1 are shown below in tracked changes.

PMR 1/ Description

Submit the analyses and datasets with the final report for PFS and OS for the ongoing clinical trial E7080-G000-309/KEYNOTE-775, entitled, "A Randomized, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib in Combination With Pembrolizumab Versus Treatment of Physician's Choice in Participants With Advanced Endometrial Cancer" to verify and describe the clinical benefit of the lenvatinib and pembrolizumab combination for patients with not-microsatellite instability high or mismatch repair proficient tumors.

PMR 1 Schedule Milestones

Draft Protocol Submission: **09 /2017**
Final Protocol Submission: **03 /2018**
Trial Completion: (b) (4) **09/2022**
Interim/Other (Last Patient In) 04/2020
Final Report Submission: (b) (4) **03/2023**

Rationale for timelines of the companion diagnostic devices

The proposed timelines for the development of the two companion diagnostic devices for this indication are based upon the timelines for the clinical trial E7080-G000-309/KEYNOTE-775 (PMR1). The trial completion date and final report submission date have been corrected to add 3 months to each date. With the amended PMR final report date, the proposed date for the IHC companion diagnostic device is 6 months later, not 9 months later. The nucleic acid-based companion diagnostic development timeline is later, as discussed in the PMC 4 section as follows.

PMC 3 Description

Commitment to support the availability of an immunohistochemistry-based in vitro diagnostic device that is essential to the safe and effective use of the lenvatinib and pembrolizumab combination for patients with tumors that are mismatch repair proficient through an appropriate analytical and clinical validation study using clinical trial data that will support labeling.

PMC 3 Schedule Milestones

Final Report Submission: 09/2023

Following FDA input on Study 111, the testing method for assessing tumor MSI status by PCR used in that study was replaced by IHC to determine tumor MMR status (30 October 2017 Type

B Pre-Phase 3 Meeting). For Study 111, 41 (44%) of 94 subjects were tested using the IHC assay, and 53 of 94 subjects (56%) are missing IHC results. Study 111 subjects with missing IHC results can no longer be retrospectively re-tested. Given the large proportion of missing data, use of Study 111 to support clinical validation of the CDx device will depend heavily on the assumptions arising from missing data, which may be difficult to assess (based on FDA input to Merck, obtained for a similar topic at the 11 December 2018 meeting regarding Merck's PMCs #3213-3 and #3213-4 for BLA 125514/S-14 approved on 23 May 2017).

Study 309 has utilized the Ventana IHC test from the beginning of the trial to identify MMR status of subjects prior to randomization as a stratification marker. MMR results will therefore be available for all randomized subjects, and importantly there will not be substantial missing data, as will be the case for Study 111.

Therefore, the timelines for development of the immunohistochemistry-based in vitro diagnostic device are based on the following considerations:

- Completion of Study 309 (an event driven analysis) (Sep 2022)
- Final report submission from Study 309 (Mar 2023)
- The time needed to prepare the PMA submission (Sep 2023)

PMC 4 Description

Commitment to support the availability of a nucleic acid-based in vitro diagnostic device that is essential to the safe and effective use of the lenvatinib and pembrolizumab combination for patients with tumors that are not microsatellite instability-high through an appropriate analytical and clinical validation study using clinical trial data that will support labeling.

PMC 4 Schedule Milestones

Final Report Submission: 09/2024

The timelines for development of the nucleic acid-based in vitro diagnostic device are based on the following considerations:

(b) (4)

[redacted]

7. Date: September 10, 2019; Agency sending IR: FDA
Since two different MedDRA dictionaries were used for coding data from Study 204, please provide tables for comparison of AEs, SAEs, and CSEs using the original (MedDRA 15) coding and the updated (MedDRA 21) coding methodologies, incorporating the pooling of preferred terms as denoted by FDA in the output. Please provide these tables by 9:00 AM EDT 9/12/19. We may request additional AE tables for this comparison, so any additional tables you might supply would be helpful. Response reviewed: September 12, 2019 Please note that differences identified in the AEs, SAEs, and CSEs between the Study 204 CSR and Study 204 ISS are due to both upversioned coding and differing data cut-off dates. The Study 204 CSR (MedDRA version 15.0) had a data cut-off date of 21 May 2012, and the Study 204 data used in the ISS (MedDRA version 21.1) had a data cut-off date of 01 September 2016. There are 22 Preferred Terms (PT) based on the Study 204 CSR data cut that were affected by the upversioning from MedDRA 15.0 to MedDRA 21.1, as a result, 27 AEs were impacted. This was caused by the remapping of lower level terms (LLT) to a new dictionary hierarchy and re-coding of the reported verbatim to a more appropriate LLT (see Table 204-2019-09-10-IR). In addition, there were also 32 adverse events reported to 28 new PTs in the ISS data cut which were coded using MedDRA 21.1. As requested, the Sponsor has provided comparison tables for AE, SAEs and CSEs incorporating the pooling of PTs as denoted by FDA.    T9-1-1-204-in-ISS-FDAgroup-terms.rtf  T9-1-10-204-FDAgroup-terms.rtf  T9-1-1-204-CSR-FDAgroup-terms.rtf

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/s/

RAJESH VENUGOPAL
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TIFFANY RICKS on behalf of WIMOLNUT N MANHENG
09/16/2019 03:56:51 PM

TIFFANY RICKS
09/16/2019 03:58:02 PM

SALAHELDIN HAMED
09/16/2019 06:15:23 PM

PENGFEI SONG
09/16/2019 06:27:23 PM

WEI ZHANG
09/16/2019 06:40:58 PM

LIJUN ZHANG
09/16/2019 06:42:13 PM

SHENGHUI TANG
09/16/2019 07:21:46 PM

SANJEEVE BALASUBRAMANIAM on behalf of SHAILY ARORA
09/16/2019 07:36:03 PM

WILLIAM F PIERCE
09/17/2019 07:24:20 AM

SANJEEVE BALASUBRAMANIAM
09/17/2019 07:53:09 AM

JULIA A BEAVER
09/17/2019 10:04:25 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s065

STATISTICAL REVIEW(S)

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	sNDA 206947/sBLA 125514
Drug Name:	LENVIMA (lenvatinib) and KEYTRUDA (pembrolizumab)
Indication:	Lenvatinib in combination with pembrolizumab, for the treatment of patients with advanced endometrial carcinoma that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation
Applicant:	Eisai and Merck
Date(s):	Submission date: June 17, 2019
	PDUFA date: December 17, 2019
Review Priority:	Priority
Biometrics Division:	Division of Biometrics V
Statistical Reviewer:	Wei Zhang
Concurring Reviewers:	Lijun Zhang, Team Leader (Acting)
	Shenghui Tang, Associate Director (Acting)
Medical Division:	Division of Oncology Products I
Clinical Team:	Shaily Arora, Clinical Reviewer
	Sanjeeve Balasubramaniam, CDTL
Project Manager:	Rajesh Venugopal

The statistical review is complete and has been added to the Multidisciplinary Review and Evaluation. Refer to the Multidisciplinary Review and Evaluation for additional details. From a statistical standpoint, my recommendation for this application is approval.

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/s/

WEI ZHANG
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LIJUN ZHANG
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s065

OTHER REVIEW(S)

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:	September 10, 2019
To:	Julia Beaver, MD Director **Division of Oncology Products 1 (DOP 1)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Ruth Mayrosh, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Rachael Conklin, MS, RN Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name), Dosage Form and Route:	KEYTRUDA (pembrolizumab) for injection, for intravenous use KEYTRUDA (pembrolizumab) injection, for intravenous use
Application Type/Number:	BLA 125514
Supplement Number:	S-065
Applicant:	Merck Sharp & Dohme Corp.

1 INTRODUCTION

On May 8, 2019, May 22, 2019, and May 23, 2019, Merck Sharp & Dohme Corp. submitted presubmission material as agreed to with the Agency as a part of the Real-Time Oncology Review (RTOR) Pilot for a Prior Approval Supplement (PAS) – Efficacy to their approved Biologics License Application (BLA) 125514/S-065 for KEYTRUDA (pembrolizumab) for injection and KEYTRUDA (pembrolizumab) injection. On June 17, 2019, the Applicant submitted the final submission material for the proposed indication of KEYTRUDA (pembrolizumab) for injection and KEYTRUDA (pembrolizumab) injection, in combination with lenvatinib, for (b) (4) [redacted]

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 1 (DOP 1) on June 18, 2019 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 June 17, 2019, and received by DMPP and OPDP on September 6, 2019.
- Draft KEYTRUDA (pembrolizumab) for injection and KEYTRUDA (pembrolizumab) injection Prescribing Information (PI) received on June 17, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 6, 2019.
- Patient Labeling Review for LENVIMA (lenvatinib) capsules Patient Package Insert (PPI) dated August 29, 2019.

3 REVIEW METHODS

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

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

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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/s/

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

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

Memorandum

Date: August 29, 2019

To: Rajesh Venugopal, MPH, MBA
Senior Regulatory Health Project Manager
Division of Oncology Products 1 (DOP 1)

Bill Pierce, Associate Director for Labeling, DOP 1

From: Carole Broadnax, Pharm.D., Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, Team Leader, OPDP

Subject: OPDP Labeling Comments for LENVIMA (lenvatinib) capsules, for oral use

NDA: 206947/Supplement 011

In response to the DOP 1 consult request dated June 18, 2019, OPDP has reviewed the proposed product labeling (PI) and patient package insert (PPI) for LENVIMA (lenvatinib). This supplemental application (S-011) provides for the use of the combination of lenvatinib and pembrolizumab for the treatment of patients with endometrial carcinoma based on data from two Merck-sponsored pembrolizumab monotherapy studies (KEYNOTE-028 and KEYNOTE-158) and two Eisai-sponsored studies; one investigating lenvatinib monotherapy (Study E7080-G000-204) and the other investigating the combination of pembrolizumab and lenvatinib in endometrial carcinoma (Study E7080-A001-111/ KEYNOTE-146).

PI and PPI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DOP 1 (Rajesh Venugopal) on August 16, 2019, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI were sent under separate cover on August 29, 2019.

Thank you for your consult. If you have any questions, please contact Carole Broadnax at (301) 796-0575 or carole.broadnax@fda.hhs.gov.

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/s/

CAROLE C BROADNAX
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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:	August 29, 2019
To:	Julia Beaver, MD Director **Division of Oncology Products 1 (DOP 1)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Ruth Mayrosh, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Carole Broadnax, RPh, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	LENVIMA (lenvatinib)
Dosage Form and Route:	capsules, for oral use
Application Type/Number:	NDA 206947
Supplement Number:	S-011
Applicant:	Eisai Inc.

1 INTRODUCTION

On May 8, 2019, Eisai Inc. submitted presubmission material as agreed to with the Agency as a part of the Real-Time Oncology Review (RTOR) Pilot for a Prior Approval Supplement (PAS) – Efficacy to their approved New Drug Application (NDA) 206947/S-011 for LENVIMA (lenvatinib) capsules. On June 17, 2019, the Applicant submitted the final submission material for the proposed indication of LENVIMA (lenvatinib) in combination with pembrolizumab, for the treatment of patients with (b) (4)

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 1 (DOP 1) on June 18, 2019 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for LENVIMA (lenvatinib) capsules.

2 MATERIAL REVIEWED

- Draft LENVIMA (lenvatinib) capsules PPI received on June 17, 2019, and received by DMPP and OPDP on August 16, 2019.
- Draft LENVIMA (lenvatinib) capsules Prescribing Information (PI) received on June 17, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 16, 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 PPI we:

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

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

4 CONCLUSIONS

The PPI 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 PPI 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 PPI.

Please let us know if you have any questions.

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08/29/2019 10:52:46 AM

LASHAWN M GRIFFITHS
08/29/2019 11:51:59 AM

Clinical Inspection Summary

Date	August 13, 2019
From	Navid Homayouni, M.D., Medical Officer Susan Thompson, M.D., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Rajesh Venugopal, Regulatory Project Manager Shaily Arora, M.D., Clinical Reviewer Sanjeeve Balasubramaniam, M.D., Team Leader Division of Oncology Products 2
NDA/BLA #	NDA 206947 S-11 & BLA 125514 S-65
Applicant	Eisai, Inc. and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
Drug	Lenvatinib and Pembrolizumab
NME	No
Therapeutic Classification	Standard
Proposed Indication	(b) (4) [redacted]
Consultation Request Date	June 14, 2019
Summary Goal Date	August 14, 2019
Action Goal Date	September 17, 2019
PDUFA Date	December 17, 2019

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The data from Study Protocol E7080-A001-111/KEYNOTE-146 (from now on called Study 111/KEYNOTE-146) was submitted to the FDA in support of proposed indications for NDA 206947 S-11 (lenvatinib) and BLA 125514 S-65 (pembrolizumab). This is an ongoing, multicenter, open-label, Phase 1b/2 study of the combination of lenvatinib plus pembrolizumab in subjects with selected solid tumors.

The data for Study 111/KEYNOTE-146 submitted by the Sponsor to the Agency in support of sNDA 206947 and sBLA 125514 appear reliable based on available information from the inspections of two domestic clinical sites.

Two clinical sites, Matthew Taylor, M.D. (Site 1001) and Vicky Makker, M.D. (Site 1003) were selected for audit. There were no significant inspectional observations for the Clinical Investigators, Matthew Taylor, M.D. and Vicky Makker, M.D. Conclusions noted above are preliminary and based on the Form FDA 483 and communications with the field investigator.

A Clinical Inspections Summary Addendum will be provided if conclusions for the inspection of the Clinical Investigators, Drs. Taylor and Makker, is significantly different following receipt and review of the Establishment Inspection Report.

II. BACKGROUND

Eisai, Inc., as sponsor of NDA 206947 seeks accelerated approval for the use of lenvatinib in combination with pembrolizumab for the treatment of (b) (4) Merck is the Sponsor of BLA 125514.

Eisai and Merck are collaboratively evaluating the combination of lenvatinib and pembrolizumab in patients with advanced endometrial carcinoma. The pivotal study providing the data supporting the sNDA/sBLA is Study 111/KEYNOTE-146.

Study 111/KEYNOTE-146 was conducted at 30 sites in the United States, 7 sites in Spain, and 1 site in Norway. The study was conducted in 2 phases, Phase 1b and Phase 2. Both phases of the study included a Pretreatment Phase, a Treatment Phase, and an Extension Phase. Phase 1b was conducted to determine the maximum tolerated dose (MTD) for lenvatinib when administered in combination with pembrolizumab 200 mg intravenous every 3 weeks. Phase 1b is complete. Phase 2 was conducted to assess the efficacy and safety of the MTD in each of the tumor types. Phase 2 is ongoing.

During Phase 2, subjects were assigned by tumor type to 1 of 6 cohorts which included endometrial carcinoma (EC), renal cell carcinoma (RCC), non-small-cell lung cancer (NSCLC), urothelial carcinoma (UC), squamous cell carcinoma of the head and neck (HNSCC), and melanoma to receive oral lenvatinib 20 mg daily plus pembrolizumab 200 mg intravenous every 3 weeks.

Endometrial carcinoma (EC) subjects were enrolled across 20 sites, 15 sites in the U.S. and 5 sites in Spain. At the data cutoff date, a total of 108 subjects were treated in the EC cohort including 94 non-MSI-H / pMMR (proficient MMR) subjects, 11 MSI-H / dMMR subjects, and 3 subjects who were not evaluable for MSI / MMR.

For Phase 2, eligible subjects had histologically and/or cytologically confirmed metastatic selected solid tumor types with 0 to 2 prior lines of systemic therapy. If previously treated, subjects must have had progressive disease (PD) after previous treatment. Subjects must have had measurable disease per immune-related Response Evaluation Criteria in Solid Tumors (irRECIST) by investigator assessment.

During Phase 2, subjects received a minimum of 8 cycles (24 weeks) of treatment in the Treatment Phase for evaluation of the primary efficacy endpoint.

Subjects continued to receive study drug in the Extension Phase until PD, development of unacceptable toxicity, withdrawal of consent, or sponsor termination of the study. Subjects

could receive up to 35 treatments (approximately 2 years) with pembrolizumab. Lenvatinib treatment could be continued as monotherapy thereafter.
The primary efficacy endpoint was Objective Response Rate (ORR). ORR was defined as the percent of patients who achieved a Best Overall Response (BOR; including Complete Response [CR] or Partial Response [PR]) and duration of response (DOR) using Response RECIST v1.1 per independent imaging review of lenvatinib 20 mg daily plus pembrolizumab 200 mg intravenously every 3 weeks in subjects with endometrial carcinoma.

GCP inspection was conducted at two domestic Clinical Investigator (CI) sites. The CI sites were chosen primarily based on high enrollment and high number of reported SAEs and subject deaths and discontinuations.

III. RESULTS (by site):

1. Matthew Taylor, M.D., Portland, Oregon (Site 1001)

The focus of this clinical inspection was on the EC cohort. The inspection was conducted on July 15-22, 2019. The site screened (b) (4) subjects and (b) (4) were enrolled and received treatment. (b) (4) subjects remain on open-label treatment, (b) (4) subjects are off treatment but in long term follow up, and (b) (4) subjects died due to clinical disease progression.

The inspection evaluated all subject's informed consent forms. An audit of all subject's records enrolled in the EC cohort was conducted, focusing on eligibility criteria, adverse events reporting, adherence to protocol and efficacy endpoint data. Study source documents of the audited subjects were compared to the data listings and found to be the same.

(b) (4)

(b) (4)

There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, was issued. The investigator determined primary efficacy endpoint data were verifiable. There was no evidence of under reporting of AEs. Study conduct at the site appeared to be in compliance with good clinical practice. The data from Site 1001 appear reliable based on available information.

2. Vicky Makker, M.D., New York, New York (Site 1003)

The focus of this clinical inspection was on the EC cohort. The inspection dates were July 29, 2019 to August 1, 2019. The site screened (b) (4) subjects and (b) (4) were enrolled. (b) (4) subjects remain on open-label treatment. (b) (4) subjects are off treatment but in long term follow up, and (b) (4) subjects died due to clinical disease progression.

All subject's informed consent forms were reviewed. An audit of (b) (4) enrolled subjects' data was conducted, focusing on primary and secondary endpoints, protocol deviations, concomitant meds, inclusion/exclusion criteria and adverse events reporting. Additional records reviewed during the inspection included monitoring logs, delegation logs, enrollment logs, Institutional Review Board (IRB) correspondence and approvals, drug accountability records, Sponsor correspondence, dosing, lab results and electronic case report forms (eCRF). Study source documents of the audited subjects were compared to the data listings and found to be the same.

There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, was issued. The investigator determined primary efficacy endpoint data were verifiable. There was no evidence of under reporting of AEs. Study conduct at the site appeared to be in compliance with good clinical practice. The data from Site 1003 appear reliable based on available information.

{See appended electronic signature page}

Navid Homayouni, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Susan Thompson, M.D., Team Leader, Acting for
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LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	July 3, 2019
Requesting Office or Division:	Division of Oncology Products 1 (DOP1)
Application Type and Number:	NDA 206947/S-011
Product Name and Strength:	Lenvima (lenvatinib) Capsules, 4 mg and 10 mg
Applicant/Sponsor Name:	Eisai, Inc.
Application Type and Number:	BLA 125514/S-065
Product Name and Strength:	Keytruda (pembrolizumab) for Injection, 50 mg/vial Keytruda (pembrolizumab) Injection, 100 mg/4 mL
Applicant/Sponsor Name:	Merck Sharp & Dohme Corp.
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
FDA Received Date:	May 8, 2019 (for Lenvima) and June 17, 2019 (for Keytruda)
OSE RCM #:	2019-955
DMEPA Safety Evaluator:	Tingting Gao, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

Eisai and Merck collaboratively submitted an Efficacy Supplement for Lenvima and Keytruda under the Real-Time Oncology Review (RTOR) to add new indication for both products:

(b) (4)

Subsequently, the Division of Oncology Products 1 (DOP1) requested that we review the proposed Lenvima PI and Keytruda PI for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the proposed additions to Section 2 Dosage and Administration of the Lenvima and Keytruda PIs and determined that the proposed additions are acceptable from a medication error perspective. We noted that there are no changes to Section 3 Dosage Forms and Strengths and Section 16 How Supplied/Storage and Handling.

4 CONCLUSION & RECOMMENDATIONS

Our evaluation of the proposed Lenvima PI and Keytruda PI did not identify areas of vulnerability that may lead to medication errors. We have no recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Lenvima received on May 8, 2019 from Eisai, Inc., and Keytruda received on June 17, 2019 from Merck.

Table 2. Relevant Product Information for Lenvima and the Listed Drug		
Product Name	Lenvima	Keytruda
Initial Approval Date	February 13, 2015	September 4, 2014
Active Ingredient	lenvatinib	pembrolizumab
Indication	Currently approved: • For the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer (DTC). • In combination with everolimus, for the treatment of patients with advanced renal cell carcinoma (RCC) following one prior anti-angiogenic therapy. • For the first-line treatment of patients with unresectable hepatocellular carcinoma (HCC). Proposed: • (b) (4)	Currently approved: Melanoma Non-Small Cell Lung Cancer (NSCLC) Head and Neck Squamous Cell Cancer (HNSCC) Classical Hodgkin Lymphoma (cHL) Primary Mediastinal Large B-Cell Lymphoma (PMBCL) Urothelial Carcinoma Microsatellite Instability- High Cancer Gastric Cancer Cervical Cancer Hepatocellular Carcinoma (HCC) Merkel Cell Carcinoma (MCC) Renal Cell Carcinoma (RCC) Proposed: (b) (4)
Route of Administration	Oral	Intravenous
Dosage Form	Capsules	For Injection Injection
Strength	4 mg and 10 mg	50 mg/vial 100 mg/4 mL
Dose and Frequency	Currently approved: • DTC: The recommended dosage is 24 mg orally once daily. • RCC: The recommended dosage is 18 mg orally once daily with everolimus 5 mg orally once daily. • HCC: The recommended dosage is based on actual body weight: o 12 mg orally once daily for patients greater than or equal to 60 kg o 8 mg orally once daily for patients less than 60 kg.	Currently approved: • Melanoma: 200 mg every 3 weeks. • NSCLC: 200 mg every 3 weeks. • HNSCC: 200 mg every 3 weeks. • cHL or PMBCL: 200 mg every 3 weeks for adults; 2 mg/kg (up to 200 mg) every 3 weeks for pediatrics. • Urothelial Carcinoma: 200 mg every 3 weeks. • MSI-H Cancer: 200 mg every 3 weeks for adults and 2 mg/kg (up to 200 mg) every 3 weeks for pediatrics.

Table 2. Relevant Product Information for Lenvima and the Listed Drug		
Product Name	Lenvima	Keytruda
	<u>Proposed:</u> • Endometrial Carcinoma: The recommended dosage is 20 mg orally once daily with pembrolizumab 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks.	• Gastric Cancer: 200 mg every 3 weeks. • Cervical Cancer: 200 mg every 3 weeks. • HCC: 200 mg every 3 weeks. • MCC: 200 mg every 3 weeks for adults; 2 mg/kg (up to 200 mg) every 3 weeks for pediatrics. • RCC: 200 mg every 3 weeks with axitinib 5 mg orally twice daily. <u>Proposed:</u> • Endometrial Carcinoma: The recommended dose of KEYTRUDA is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks in combination with lenvatinib 20 mg orally once daily until disease progression, unacceptable toxicity, or for KEYTRUDA, up to 24 months in patients without disease progression.
How Supplied	Cartons of 6 cards. Each card is a 5-day blister card as follows: • 24 mg, carton with 6 cards (ten 10 mg capsules and five 4 mg capsules per card) • 20 mg, carton with 6 cards (ten 10 mg capsules per card) • 18 mg, carton with 6 cards (five 10 mg capsules and ten 4 mg capsules per card) • 14 mg, carton with 6 cards (five 10 mg capsules and five 4 mg capsules per card) • 12 mg, carton with 6 cards (fifteen 4 mg capsules per card) • 10 mg, carton with 6 cards (five 10 mg capsules per card) • 8 mg, carton with 6 cards (ten 4 mg capsules per card). • 4 mg, carton with 6 cards (five 4 mg capsules per card)	50 mg/vial: Carton of one single-dose vial 100 mg/4 mL: Carton of one single-dose vial Carton of two single-dose vials
Storage	Store at 25°C (77°F); excursions permitted to 15 – 30°C (59 – 86°F)	Both 50 mg/vial and 100 mg/4 mL: Store vials under refrigeration at 2°C to 8°C (36°F to 46°F). Injection: Store in original carton to protect from light. Do not freeze.
Container Closure	Blister pack	Single-dose vial

APPENDIX B. PREVIOUS DMEPA REVIEWS

On June 24, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, Lenvima and Keytruda. Our search identified 1 previous review[a] for Lenvima since December 29, 2017[b], and 1 previous review[c] for Keytruda since January 24, 2019[d], and we confirmed that our previous recommendations were implemented.

[a] Stewart, J. Label and Labeling Review for Lenvima (NDA 206947/S-007). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Jan 23. RCM No.: 2017-1917.

[b] Date of last search in Stewart, J. Label and Labeling Review for Lenvima (NDA 206947/S-007). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Jan 23. RCM No.: 2017-1917.

[c] Gao, T. Label and Labeling Review for Keytruda (BLA 125514/S-054). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Mar 6. RCM No.: 2019-42.

[d] Date of last search in Gao, T. Label and Labeling Review for Keytruda (BLA 125514/S-054). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Mar 6. RCM No.: 2019-42.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[e] along with postmarket medication error data, we reviewed the following Lenvima labels and labeling submitted by Eisai, Inc. and Keytruda labels and labeling submitted by Merck.

- Lenvima Prescribing Information (Image not shown) received on May 8, 2019
- Keytruda Prescribing Information (Image not shown) received on June 17, 2019

G.2 Label and Labeling Images

N/A

[e] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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