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

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

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

| | |
|---|---|
| Indications and Usage (1) | 11/2020 |
| Dosage and Administration (2) | 11/2020 |
| Warnings and Precautions (5) | 11/2020 |

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

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

Urothelial 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)
- for the treatment of patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy. (1.7)

Microsatellite Instability-High or Mismatch Repair Deficient Cancer
- for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)
  - solid tumors 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, 2.1)
- Limitations of Use: The safety and effectiveness of KEYTRUDA in pediatric patients with MSI-H central nervous system cancers have not been established.

Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer (CRC)
- for the first-line treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC). (1.9, 2.1)

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] (1.10, 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. (1.11, 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] (1.12, 2.1)

Hepatocellular Carcinoma (HCC)
- for the treatment of patients with HCC who have been previously treated with sorafenib.[1] (1.13)

Merkel Cell Carcinoma (MCC)
- for the treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma.[1] (1.14)

Renal Cell Carcinoma (RCC)
- in combination with axitinib, for the first-line treatment of patients with advanced RCC. (1.15)

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] (1.16)

Tumor Mutational Burden-High (TMB-H) Cancer
- for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.[1] (1.17, 2.1)

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

Cutaneous Squamous Cell Carcinoma (cSCC)

- for the treatment of patients with recurrent or metastatic cutaneous squamous cell carcinoma that is not curable by surgery or radiation. (1.18)

Triple-Negative Breast Cancer (TNBC)

- in combination with chemotherapy, for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA approved test.[2] (1.19, 2.1)

Adult Indications: Additional Dosing Regimen of 400 mg Every 6 Weeks

- for use at an additional recommended dosage of 400 mg every 6 weeks for all approved adult indications.[3] (1.20, 2.2)

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

[2] This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

[3] This indication is approved under accelerated approval based on pharmacokinetic data, the relationship of exposure to efficacy, and the relationship of exposure to safety. Continued approval for this dosing may be contingent upon verification and description of clinical benefit in the confirmatory trials.

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

- Melanoma: 200 mg every 3 weeks or 400 mg every 6 weeks. (2.2)
- NSCLC: 200 mg every 3 weeks or 400 mg every 6 weeks. (2.2)
- SCLC: 200 mg every 3 weeks or 400 mg every 6 weeks. (2.2)
- HNSCC: 200 mg every 3 weeks or 400 mg every 6 weeks. (2.2)
- cHL or PMBCL: 200 mg every 3 weeks or 400 mg every 6 weeks for adults; 2 mg/kg (up to 200 mg) every 3 weeks for pediatrics. (2.2)
- Urothelial Carcinoma: 200 mg every 3 weeks or 400 mg every 6 weeks. (2.2)
- MSI-H or dMMR Cancer: 200 mg every 3 weeks or 400 mg every 6 weeks for adults; 2 mg/kg (up to 200 mg) every 3 weeks for pediatrics. (2.2)
- MSI-H or dMMR CRC: 200 mg every 3 weeks or 400 mg every 6 weeks. (2.2)
- Gastric Cancer: 200 mg every 3 weeks or 400 mg every 6 weeks. (2.2)
- Esophageal Cancer: 200 mg every 3 weeks or 400 mg every 6 weeks. (2.2)
- Cervical Cancer: 200 mg every 3 weeks or 400 mg every 6 weeks. (2.2)
- HCC: 200 mg every 3 weeks or 400 mg every 6 weeks. (2.2)
- MCC: 200 mg every 3 weeks or 400 mg every 6 weeks for adults; 2 mg/kg (up to 200 mg) every 3 weeks for pediatrics. (2.2)
- RCC: 200 mg every 3 weeks or 400 mg every 6 weeks with axitinib 5 mg orally twice daily. (2.2)
- Endometrial Carcinoma: 200 mg every 3 weeks or 400 mg every 6 weeks with lenvatinib 20 mg orally once daily for tumors that are not MSI-H or dMMR. (2.2)
- TMB-H Cancer: 200 mg every 3 weeks or 400 mg every 6 weeks for adults; 2 mg/kg (up to 200 mg) every 3 weeks for pediatrics. (2.2)
- cSCC: 200 mg every 3 weeks or 400 mg every 6 weeks. (2.2)
- TNBC: 200 mg every 3 weeks or 400 mg every 6 weeks. (2.2)

Administer KEYTRUDA as an intravenous infusion over 30 minutes.

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

- Injection: 100 mg/4 mL (25 mg/mL) solution in a single-dose vial (3)

**----------CONTRAINDICATIONS----------**

None. (4)

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

- Immune-Mediated Adverse Reactions (5.1)
  - Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue, including the following: immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated nephritis with renal dysfunction, immune-mediated dermatologic adverse reactions, and solid organ transplant rejection.
  - Monitor for early identification and management. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment.
  - Withhold or permanently discontinue based on severity and type of reaction.
- Infusion-related reactions: Interrupt, slow the rate of infusion, or permanently discontinue KEYTRUDA based on the severity of reaction. (5.2)
- Complications of allogeneic HSCT: Fatal and other serious complications can occur in patients who receive allogeneic HSCT before or after being treated with a PD-1/PD-L1 blocking antibody. (5.3)
- Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials. (5.4)
- Embryo-Fetal toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective method of contraception. (5.5, 8.1, 8.3)

**---------- ADVERSE REACTIONS ----------**

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

- KEYTRUDA as a single agent: fatigue, musculoskeletal pain, 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, stomatitis, and headache. (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: 03/2021**

**FULL PRESCRIBING INFORMATION: CONTENTS***


**1 INDICATIONS AND USAGE**
- 1.1 Melanoma
- 1.2 Non-Small Cell Lung Cancer
- 1.3 Small Cell Lung Cancer
- 1.4 Head and Neck Squamous Cell Cancer
- 1.5 Classical Hodgkin Lymphoma
- 1.6 Primary Mediastinal Large B-Cell Lymphoma
- 1.7 Urothelial Carcinoma
- 1.8 Microsatellite Instability-High or Mismatch Repair Deficient Cancer

1.9 Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer
1.10 Gastric Cancer
1.11 Esophageal Cancer
1.12 Cervical Cancer
1.13 Hepatocellular Carcinoma
1.14 Merkel Cell Carcinoma
1.15 Renal Cell Carcinoma
1.16 Endometrial Carcinoma
1.17 Tumor Mutational Burden-High Cancer
1.18 Cutaneous Squamous Cell Carcinoma
1.19 Triple-Negative Breast Cancer
1.20 Adult Indications: Additional Dosing Regimen of 400 mg Every 6 Weeks
**2 DOSAGE AND ADMINISTRATION**
2.1 Patient Selection for NSCLC, HNSCC, Urothelial Carcinoma, Gastric Cancer, Esophageal Cancer, Cervical Cancer, MSI-H or dMMR Cancer, MSI-H or dMMR CRC, TMB-H Cancer, or TNBC
2.2 Recommended Dosage
2.3 Dose Modifications
2.4 Preparation and Administration
**3 DOSAGE FORMS AND STRENGTHS**
**4 CONTRAINDICATIONS**
**5 WARNINGS AND PRECAUTIONS**
5.1 Severe and Fatal Immune-Mediated Adverse Reactions
5.2 Infusion-Related Reactions
5.3 Complications of Allogeneic HSCT
5.4 Increased Mortality in Patients with Multiple Myeloma when KEYTRUDA is Added to a Thalidomide Analogue and Dexamethasone
5.5 Embryo-Fetal Toxicity
**6 ADVERSE REACTIONS**
6.1 Clinical Trials Experience
6.2 Immunogenicity
**8 USE IN SPECIFIC POPULATIONS**
8.1 Pregnancy
8.2 Lactation
8.3 Females and Males of Reproductive Potential
8.4 Pediatric Use
8.5 Geriatric Use
**11 DESCRIPTION**
**12 CLINICAL PHARMACOLOGY**
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
**13 NONCLINICAL TOXICOLOGY**
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
**14 CLINICAL STUDIES**
14.1 Melanoma
14.2 Non-Small Cell Lung Cancer
14.3 Small Cell Lung Cancer
14.4 Head and Neck Squamous Cell Cancer
14.5 Classical Hodgkin Lymphoma
14.6 Primary Mediastinal Large B-Cell Lymphoma
14.7 Urothelial Carcinoma
14.8 Microsatellite Instability-High or Mismatch Repair Deficient Cancer
14.9 Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer
14.10 Gastric Cancer
14.11 Esophageal Cancer
14.12 Cervical Cancer
14.13 Hepatocellular Carcinoma
14.14 Merkel Cell Carcinoma
14.15 Renal Cell Carcinoma
14.16 Endometrial Carcinoma
14.17 Tumor Mutational Burden-High Cancer
14.18 Cutaneous Squamous Cell Carcinoma
14.19 Triple-Negative Breast Cancer
14.20 Adult Indications: Additional Dosing Regimen of 400 mg Every 6 Weeks
**16 HOW SUPPLIED/STORAGE AND HANDLING**
**17 PATIENT COUNSELING INFORMATION**

*****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 patients with relapsed or refractory classical Hodgkin lymphoma (cHL).

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



Reference ID: 4761679

### 1.6 Primary Mediastinal Large B-Cell Lymphoma

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

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

### 1.7 Urothelial 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.

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

### 1.8 Microsatellite Instability-High or Mismatch Repair Deficient Cancer

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

- solid tumors 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 Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer

KEYTRUDA is indicated for the first-line treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC).

### 1.10 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 (14.10)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.



Reference ID: 4761679

### 1.11 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.

### 1.12 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 (14.12)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

### 1.13 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 (14.13)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

### 1.14 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 (14.14)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

### 1.15 Renal Cell Carcinoma

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

### 1.16 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 (14.16)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

### 1.17 Tumor Mutational Burden-High Cancer

KEYTRUDA is indicated for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test *[see Dosage and Administration (2.1)]*, that have progressed following prior treatment and who have no satisfactory alternative treatment options.

This indication is approved under accelerated approval based on tumor response rate and durability of response *[see Clinical Studies (14.17)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

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



Reference ID: 4761679

### 1.18 Cutaneous Squamous Cell Carcinoma

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

### 1.19 Triple-Negative Breast Cancer

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

This indication is approved under accelerated approval based on progression-free survival *[see Clinical Studies (14.19)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

### 1.20 Adult Indications: Additional Dosing Regimen of 400 mg Every 6 Weeks

KEYTRUDA is indicated for use at an additional recommended dosage of 400 mg every 6 weeks for all approved adult indications *[see Indications and Usage (1.1-1.19) and Dosage and Administration (2.2)]*. This indication is approved under accelerated approval based on pharmacokinetic data, the relationship of exposure to efficacy, and the relationship of exposure to safety *[see Clinical Pharmacology (12.2) and Clinical Studies (14.20)]*. Continued approval for this dosing 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, Cervical Cancer, MSI-H or dMMR Cancer, MSI-H or dMMR CRC, TMB-H Cancer, or TNBC

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 (14.10)]*. 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 (14.11)]*.
- recurrent or metastatic cervical cancer *[see Clinical Studies (14.12)]*.

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

For the TMB-H indication, select patients for treatment with KEYTRUDA as a single agent based on TMB-H status in tumor specimens *[see Clinical Studies (14.17)].*

Because the effect of prior chemotherapy on test results for tumor mutation burden (TMB-H), MSI-H, or dMMR in patients with high-grade gliomas is unclear, it is recommended to test for these markers in the primary tumor specimens obtained prior to initiation of temozolomide chemotherapy in patients with high-grade gliomas.

Select patients for treatment with KEYTRUDA in combination with chemotherapy based on the presence of positive PD-L1 expression in:

- locally recurrent unresectable or metastatic TNBC *[see Clinical Studies (14.19)]*.

Information on FDA-approved tests for the detection of PD-L1 expression and TMB status is available at: http://www.fda.gov/CompanionDiagnostics. An FDA-approved test for the detection of MSI-H or dMMR is not currently available.



Reference ID: 4761679

## 2.2 Recommended Dosage

**Table 1: Recommended Dosage**

| Indication | Recommended Dosage of KEYTRUDA | Duration/Timing of Treatment |
|---|---|---|
| **Monotherapy** | | |
| Adult patients with unresectable or metastatic melanoma | 200 mg every 3 weeks*<br>or<br>400 mg every 6 weeks* | Until disease progression or unacceptable toxicity |
| Adjuvant treatment of adult patients with melanoma | 200 mg every 3 weeks*<br>or<br>400 mg every 6 weeks* | Until disease recurrence, unacceptable toxicity, or up to 12 months |
| Adult patients with NSCLC, SCLC, HNSCC, cHL, PMBCL, locally advanced or metastatic Urothelial Carcinoma, MSI-H or dMMR Cancer, MSI-H or dMMR CRC, Gastric Cancer, Esophageal Cancer, Cervical Cancer, HCC, MCC, TMB-H Cancer, or cSCC | 200 mg every 3 weeks*<br>or<br>400 mg every 6 weeks* | Until disease progression, unacceptable toxicity, or up to 24 months |
| Adult patients with high-risk BCG-unresponsive NMIBC | 200 mg every 3 weeks*<br>or<br>400 mg every 6 weeks* | Until persistent or recurrent high-risk NMIBC, disease progression, unacceptable toxicity, or up to 24 months |
| Pediatric patients with cHL, PMBCL, MSI-H Cancer, MCC, or TMB-H Cancer | 2 mg/kg every 3 weeks (up to a maximum of 200 mg)* | Until disease progression, unacceptable toxicity, or up to 24 months |
| **Combination Therapy**† | | |
| Adult patients with NSCLC or HNSCC | 200 mg every 3 weeks*<br>or<br>400 mg every 6 weeks*<br>Administer KEYTRUDA prior to chemotherapy when given on the same day. | Until disease progression, unacceptable toxicity, or up to 24 months |
| Adult patients with RCC | 200 mg every 3 weeks*<br>or<br>400 mg every 6 weeks*<br>Administer KEYTRUDA in combination with axitinib 5 mg orally twice daily.‡ | Until disease progression, unacceptable toxicity, or for KEYTRUDA, up to 24 months |
| Adult patients with Endometrial Carcinoma | 200 mg every 3 weeks*<br>or<br>400 mg every 6 weeks*<br>Administer KEYTRUDA in combination with lenvatinib 20 mg orally once daily. | Until disease progression, unacceptable toxicity, or for KEYTRUDA, up to 24 months |
| Adult patients with locally recurrent unresectable or metastatic TNBC | 200 mg every 3 weeks*<br>or<br>400 mg every 6 weeks*<br>Administer KEYTRUDA prior to chemotherapy when given on the same day. | Until disease progression, unacceptable toxicity, or up to 24 months |

* 30-minute intravenous infusion

† Refer to the Prescribing Information for the agents administered in combination with KEYTRUDA for recommended dosing information, as appropriate.

‡ When axitinib is used in combination with KEYTRUDA, dose escalation of axitinib above the initial 5 mg dose may be considered at intervals of six weeks or longer.

## 2.3 Dose Modifications

No dose reduction for KEYTRUDA is recommended. In general, withhold KEYTRUDA for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue KEYTRUDA for Life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions



Reference ID: 4761679

that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating steroids.

Dosage modifications for KEYTRUDA for adverse reactions that require management different from these general guidelines are summarized in Table 2.

**Table 2: Recommended Dosage Modifications for Adverse Reactions**

| Adverse Reaction | Severity* | Dosage Modification |
|---|---|---|
| **Immune-Mediated Adverse Reactions** *[see Warnings and Precautions (5.1)]* | | |
| Pneumonitis | Grade 2 | Withhold† |
| | Grade 3 or 4 | Permanently discontinue |
| Colitis | Grade 2 or 3 | Withhold† |
| | Grade 4 | Permanently discontinue |
| Hepatitis with no tumor involvement of the liver<br><br>For liver enzyme elevations in patients treated with combination therapy with axitinib, see Table 3. | AST or ALT increases to more than 3 and up to 8 times ULN<br>or<br>Total bilirubin increases to more than 1.5 and up to 3 times ULN | Withhold† |
| | AST or ALT increases to more than 8 times ULN<br>or<br>Total bilirubin increases to more than 3 times ULN | Permanently discontinue |
| Hepatitis with tumor involvement of the liver‡ | Baseline AST or ALT is more than 1 and up to 3 times ULN and increases to more than 5 and up to 10 times ULN<br>or<br>Baseline AST or ALT is more than 3 and up to 5 times ULN and increases to more than 8 and up to 10 times ULN | Withhold† |
| | ALT or AST increases to more than 10 times ULN<br>or<br>Total bilirubin increases to more than 3 times ULN | Permanently discontinue |
| Endocrinopathies | Grade 3 or 4 | Withhold until clinically stable or permanently discontinue depending on severity |
| Nephritis with Renal Dysfunction | Grade 2 or 3 increased blood creatinine | Withhold† |
| | Grade 4 increased blood creatinine | Permanently discontinue |
| Exfoliative Dermatologic Conditions | Suspected SJS, TEN, or DRESS | Withhold† |
| | Confirmed SJS, TEN, or DRESS | Permanently discontinue |
| Myocarditis | Grade 2, 3, or 4 | Permanently discontinue |
| Neurological Toxicities | Grade 2 | Withhold† |
| | Grade 3 or 4 | Permanently discontinue |
| Hematologic toxicity in patients with cHL or PMBCL | Grade 4 | Withhold until resolution to Grades 0 or 1 |



Reference ID: 4761679

| Adverse Reaction | Severity* | Dosage Modification |
|---|---|---|
| **Other Adverse Reactions** | | |
| Infusion-related reactions *[see Warnings and Precautions (5.2)]* | Grade 1 or 2 | Interrupt or slow the rate of infusion |
| | Grade 3 or 4 | Permanently discontinue |

* Based on Common Terminology Criteria for Adverse Events (CTCAE), version 4.0
† Resume in patients with complete or partial resolution (Grades 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating steroids or inability to reduce prednisone to 10 mg per day or less (or equivalent) within 12 weeks of initiating steroids.
‡ If AST and ALT are less than or equal to ULN at baseline, withhold or permanently discontinue KEYTRUDA based on recommendations for hepatitis with no liver involvement.
ALT = alanine aminotransferase, AST = aspartate aminotransferase, DRESS = Drug Rash with Eosinophilia and Systemic Symptoms, SJS = Stevens Johnson Syndrome, TEN = toxic epidermal necrolysis, ULN = upper limit normal

The following table represents dosage modifications that are different from those described above for KEYTRUDA or in the Full Prescribing Information for the drug administered in combination.

**Table 3: Recommended Specific Dosage Modifications for Adverse Reactions for Combination**

| Treatment | Adverse Reaction | Severity | Dosage Modification |
|---|---|---|---|
| KEYTRUDA in combination with axitinib | Liver enzyme elevations* | ALT or AST increases to at least 3 times but less than 10 times ULN without concurrent total bilirubin at least 2 times ULN | Withhold both KEYTRUDA and axitinib until resolution to Grades 0 or 1† |
| | | ALT or AST increases to more than 3 times ULN with concurrent total bilirubin at least 2 times ULN or ALT or AST ≥10 times ULN | Permanently discontinue both KEYTRUDA and axitinib |

* Consider corticosteroid therapy
† Based on Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Consider rechallenge with a single drug or sequential rechallenge with both drugs after recovery. If rechallenging with axitinib, consider dose reduction as per the axitinib Prescribing Information.
ALT = alanine aminotransferase, AST = aspartate aminotransferase, ULN = upper limit normal

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.

### 2.4 Preparation and Administration

Preparation for Intravenous Infusion

- Visually inspect the solution for particulate matter and discoloration. The solution is clear to slightly opalescent, colorless to slightly yellow. Discard the vial if visible particles are observed.
- Dilute KEYTRUDA injection (solution) prior to intravenous administration.
- Withdraw the required volume from the vial(s) of KEYTRUDA and transfer into an intravenous (IV) bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. **Mix diluted solution by gentle inversion.** Do not shake. The final concentration of the diluted solution should be between 1 mg/mL to 10 mg/mL.
- Discard any unused portion left in the vial.

Storage of Diluted Solution

The product does not contain a preservative.
Store the diluted solution from the KEYTRUDA 100 mg/4 mL vial either:

- At room temperature for no more than 6 hours from the time of dilution. This includes room temperature storage of the diluted solution, and the duration of infusion.
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 96 hours from the time of dilution. If refrigerated, allow the diluted solution to come to room temperature prior to administration. Do not shake.



Reference ID: 4761679

Discard after 6 hours at room temperature or after 96 hours under refrigeration.

Do not freeze.

Administration

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

## 3 DOSAGE FORMS AND STRENGTHS

- Injection: 100 mg/4 mL (25 mg/mL) clear to slightly opalescent, colorless to slightly yellow solution in a single-dose vial

## 4 CONTRAINDICATIONS

None.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Severe and Fatal Immune-Mediated Adverse Reactions

KEYTRUDA is a monoclonal antibody that belongs to a class of drugs that bind to either the programmed death-receptor 1 (PD-1) or the PD-ligand 1 (PD-L1), blocking the PD-1/PD-L1 pathway, thereby removing inhibition of the immune response, potentially breaking peripheral tolerance and inducing immune-mediated adverse reactions. Important immune-mediated adverse reactions listed under WARNINGS AND PRECAUTIONS may not include all possible severe and fatal immune-mediated adverse reactions.

Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue and can affect more than one body system simultaneously. Immune-mediated adverse reactions can occur at any time after starting treatment with a PD-1/PD-L1 blocking antibody. While immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1 blocking antibodies, immune-mediated adverse reactions can also manifest after discontinuation of PD-1/PD-L1 blocking antibodies.

Early identification and management of immune-mediated adverse reactions are essential to ensure safe use of PD-1/PD-L1 blocking antibodies. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse reactions. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected immune-mediated adverse reactions, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue KEYTRUDA depending on severity *[see Dosage and Administration (2.3)]*. In general, if KEYTRUDA requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy.

Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (e.g., endocrinopathies and dermatologic reactions) are discussed below.

Immune-Mediated Pneumonitis

KEYTRUDA can cause immune-mediated pneumonitis. The incidence of pneumonitis is higher in patients who have received prior thoracic radiation. Immune-mediated pneumonitis occurred in 3.4% (94/2799) of patients receiving KEYTRUDA, including fatal (0.1%), Grade 4 (0.3%), Grade 3 (0.9%), and Grade 2 (1.3%) adverse reactions. Systemic corticosteroids were required in 67% (63/94) of patients with pneumonitis. Pneumonitis led to permanent discontinuation of KEYTRUDA in 1.3% (36) of patients and withholding of KEYTRUDA in 0.9% (26) of patients. All patients who were withheld reinitiated KEYTRUDA



Reference ID: 4761679

after symptom improvement; of these, 23% had recurrence of pneumonitis. Pneumonitis resolved in 59% of the 94 patients.

In clinical studies enrolling 389 adult patients with cHL who received KEYTRUDA as a single agent, pneumonitis occurred in 31 (8%) patients, including Grades 3-4 pneumonitis in 2.3% of patients. Patients received high-dose corticosteroids for a median duration of 10 days (range: 2 days to 53 months). Pneumonitis rates were similar in patients with and without prior thoracic radiation. Pneumonitis led to discontinuation of KEYTRUDA in 21 (5.4%) patients. Of the patients who developed pneumonitis, 42% interrupted KEYTRUDA, 68% discontinued KEYTRUDA, and 77% had resolution.

Immune-Mediated Colitis

KEYTRUDA can cause immune-mediated colitis, which may present with diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. Immune-mediated colitis occurred in 1.7% (48/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (1.1%), and Grade 2 (0.4%) adverse reactions. Systemic corticosteroids were required in 69% (33/48) of patients with colitis. Additional immunosuppressant therapy was required in 4.2% of patients. Colitis led to permanent discontinuation of KEYTRUDA in 0.5% (15) of patients and withholding of KEYTRUDA in 0.5% (13) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement; of these, 23% had recurrence of colitis. Colitis resolved in 85% of the 48 patients.

Hepatotoxicity and Immune-Mediated Hepatitis

*KEYTRUDA as a Single Agent*

KEYTRUDA can cause immune-mediated hepatitis. Immune-mediated hepatitis occurred in 0.7% (19/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (0.4%), and Grade 2 (0.1%) adverse reactions. Systemic corticosteroids were required in 68% (13/19) of patients with hepatitis. Eleven percent of these patients required additional immunosuppressant therapy. Hepatitis led to permanent discontinuation of KEYTRUDA in 0.2% (6) of patients and withholding of KEYTRUDA in 0.3% (9) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement; of these, none had recurrence of hepatitis. Hepatitis resolved in 79% of the 19 patients.

*KEYTRUDA with Axitinib*

KEYTRUDA in combination with axitinib can cause hepatic toxicity with higher than expected frequencies of Grades 3 and 4 ALT and AST elevations compared to KEYTRUDA alone. Monitor liver enzymes before initiation of and periodically throughout treatment. Consider more frequent monitoring of liver enzymes as compared to when the drugs are administered as single agents. For elevated liver enzymes, interrupt KEYTRUDA and axitinib, and consider administering corticosteroids as needed *[see Dosage and Administration (2.3)]*.

With the combination of KEYTRUDA and axitinib, Grades 3 and 4 increased ALT (20%) and increased AST (13%) were seen. Fifty-nine percent of the patients with increased ALT received systemic corticosteroids. In patients with ALT ≥3 times ULN (Grades 2-4, n=116), ALT resolved to Grades 0-1 in 94%. Among the 92 patients who were rechallenged with either KEYTRUDA (n=3) or axitinib (n=34) administered as a single agent or with both (n=55), recurrence of ALT ≥3 times ULN was observed in 1 patient receiving KEYTRUDA, 16 patients receiving axitinib, and 24 patients receiving both KEYTRUDA and axitinib. All patients with a recurrence of ALT ≥3 ULN subsequently recovered from the event.

Immune-Mediated Endocrinopathies

*Adrenal Insufficiency*

KEYTRUDA can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold KEYTRUDA depending on severity *[see Dosage and Administration (2.3)].*

Adrenal insufficiency occurred in 0.8% (22/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (0.3%), and Grade 2 (0.3%) adverse reactions. Systemic corticosteroids were required



Reference ID: 4761679

in 77% (17/22) of patients with adrenal insufficiency; of these, the majority remained on systemic corticosteroids. Adrenal insufficiency led to permanent discontinuation of KEYTRUDA in <0.1% (1) of patients and withholding of KEYTRUDA in 0.3% (8) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement.

*Hypophysitis*

KEYTRUDA can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as indicated. Withhold or permanently discontinue KEYTRUDA depending on severity *[see Dosage and Administration (2.3)]*.

Hypophysitis occurred in 0.6% (17/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (0.3%), and Grade 2 (0.2%) adverse reactions. Systemic corticosteroids were required in 94% (16/17) of patients with hypophysitis; of these, the majority remained on systemic corticosteroids. Hypophysitis led to permanent discontinuation of KEYTRUDA in 0.1% (4) of patients and withholding of KEYTRUDA in 0.3% (7) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement.

*Thyroid Disorders*

KEYTRUDA can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement for hypothyroidism or institute medical management of hyperthyroidism as clinically indicated. Withhold or permanently discontinue KEYTRUDA depending on severity *[see Dosage and Administration (2.3)].*

Thyroiditis occurred in 0.6% (16/2799) of patients receiving KEYTRUDA, including Grade 2 (0.3%). No patients discontinued KEYTRUDA due to thyroiditis. KEYTRUDA was withheld in <0.1% (1) of patients.

Hyperthyroidism occurred in 3.4% (96/2799) of patients receiving KEYTRUDA, including Grade 3 (0.1%) and Grade 2 (0.8%). Hyperthyroidism led to permanent discontinuation of KEYTRUDA in <0.1% (2) of patients and withholding of KEYTRUDA in 0.3% (7) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement.

Hypothyroidism occurred in 8% (237/2799) of patients receiving KEYTRUDA, including Grade 3 (0.1%) and Grade 2 (6.2%). Hypothyroidism led to permanent discontinuation of KEYTRUDA in <0.1% (1) of patients and withholding of KEYTRUDA in 0.5% (14) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. The majority of patients with hypothyroidism required long-term thyroid hormone replacement.

The incidence of new or worsening hypothyroidism was higher in 1185 patients with HNSCC, occurring in 16% of patients receiving KEYTRUDA as a single agent or in combination with platinum and FU, including Grade 3 (0.3%) hypothyroidism. The incidence of new or worsening hypothyroidism was higher in 389 patients with cHL (17%) receiving KEYTRUDA as a single agent, including Grade 1 (6.2%) and Grade 2 (10.8%) hypothyroidism.

*Type 1 Diabetes Mellitus, which can present with Diabetic Ketoacidosis*

Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold KEYTRUDA depending on severity *[see Dosage and Administration (2.3)]*.

Type 1 diabetes mellitus occurred in 0.2% (6/2799) of patients receiving KEYTRUDA. Type 1 diabetes mellitus led to permanent discontinuation in <0.1% (1) of patients and withholding of KEYTRUDA in <0.1% (1) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement. All patients with Type 1 diabetes mellitus required long-term insulin therapy.

<u>Immune-Mediated Nephritis with Renal Dysfunction</u>

KEYTRUDA can cause immune-mediated nephritis. Immune-mediated nephritis occurred in 0.3% (9/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (0.1%), and Grade 2 (0.1%) adverse reactions. Systemic corticosteroids were required in 89% (8/9) of patients with nephritis. Nephritis led to permanent discontinuation of KEYTRUDA in 0.1% (3) of patients and withholding of



Reference ID: 4761679

KEYTRUDA in 0.1% (3) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement; of these, none had recurrence of nephritis. Nephritis resolved in 56% of the 9 patients.

Immune-Mediated Dermatologic Adverse Reactions

KEYTRUDA can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens Johnson Syndrome, DRESS, and toxic epidermal necrolysis (TEN), has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold or permanently discontinue KEYTRUDA depending on severity *[see Dosage and Administration (2.3)]*.

Immune-mediated dermatologic adverse reactions occurred in 1.4% (38/2799) of patients receiving KEYTRUDA, including Grade 3 (1%) and Grade 2 (0.1%) adverse reactions. Systemic corticosteroids were required in 40% (15/38) of patients with immune-mediated dermatologic adverse reactions. Immune-mediated dermatologic adverse reactions led to permanent discontinuation of KEYTRUDA in 0.1% (2) of patients and withholding of KEYTRUDA in 0.6% (16) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement; of these, 6% had recurrence of immune-mediated dermatologic adverse reactions. Immune-mediated dermatologic adverse reactions resolved in 79% of the 38 patients.

Other Immune-Mediated Adverse Reactions

The following clinically significant immune-mediated adverse reactions occurred at an incidence of <1% (unless otherwise noted) in patients who received KEYTRUDA or were reported with the use of other PD-1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions.

*Cardiac/Vascular:* Myocarditis, pericarditis, vasculitis

*Nervous System:* Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy

*Ocular:* Uveitis, iritis and other ocular inflammatory toxicities can occur. Some cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada-like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss.

*Gastrointestinal:* Pancreatitis, to include increases in serum amylase and lipase levels, gastritis, duodenitis

*Musculoskeletal and Connective Tissue:* Myositis/polymyositis, rhabdomyolysis (and associated sequelae, including renal failure), arthritis (1.5%), polymyalgia rheumatica

*Endocrine:* Hypoparathyroidism

*Hematologic/Immune:* Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection

### 5.2 Infusion-Related Reactions

KEYTRUDA can cause severe or life-threatening infusion-related reactions, including hypersensitivity and anaphylaxis, which have been reported in 0.2% of 2799 patients receiving KEYTRUDA. Monitor patients for signs and symptoms of infusion-related reactions including rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever. Interrupt or slow the rate of infusion for mild (Grade 1) or moderate (Grade 2) infusion-related reactions. For severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions, stop infusion and permanently discontinue KEYTRUDA *[see Dosage and Administration (2.3)]*.

### 5.3 Complications of Allogeneic HSCT

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/PD-L1 blocking antibody.



Reference ID: 4761679

Transplant-related complications include hyperacute graft-versus-host-disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between PD-1/PD-L1 blockade and allogeneic HSCT.

Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1/PD-L1 blocking antibody prior to or after an allogeneic HSCT.

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

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

### 5.5 Embryo-Fetal Toxicity

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

## 6 ADVERSE REACTIONS

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

- Severe and fatal immune-mediated adverse reactions *[see Warnings and Precautions (5.1)]*.
- Infusion-related reactions *[see Warnings and Precautions (5.2)].*

### 6.1 Clinical Trials Experience

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

The data described in the WARNINGS AND PRECAUTIONS reflect exposure to KEYTRUDA as a single agent in 2799 patients in three randomized, open-label, active-controlled trials (KEYNOTE-002, KEYNOTE-006, and KEYNOTE-010), which enrolled 912 patients with melanoma and 682 patients with NSCLC, and one single-arm trial (KEYNOTE-001), which enrolled 655 patients with melanoma and 550 patients with NSCLC. In addition to the 2799 patients, certain subsections in the WARNINGS AND PRECAUTIONS describe adverse reactions observed with exposure to KEYTRUDA as a single agent in a non-randomized, open-label, multi-cohort trial (KEYNOTE-012), a non-randomized, open-label, single-cohort trial (KEYNOTE-055), and two randomized, open-label, active-controlled trials (KEYNOTE-040 and KEYNOTE-048 single agent arms), which enrolled 909 patients with HNSCC; in two non-randomized, open-label trials (KEYNOTE-013 and KEYNOTE-087) and one randomized, open-label, active-controlled trial (KEYNOTE-204), which enrolled 389 patients with cHL; in a randomized, open-label, active-controlled trial (KEYNOTE-048 combination arm), which enrolled 276 patients with HNSCC; in combination with axitinib in a randomized, active-controlled trial (KEYNOTE 426), which enrolled 429 patients with RCC; and in post-marketing use. Across all trials, KEYTRUDA was administered at doses of 2 mg/kg intravenously every 3 weeks, 10 mg/kg intravenously every 2 weeks, 10 mg/kg intravenously every 3 weeks, or 200 mg intravenously every 3 weeks. Among the 2799 patients, 41% were exposed for 6 months or more and 21% were exposed for 12 months or more.

<u>Melanoma</u>

*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



Reference ID: 4761679

investigated in KEYNOTE-006. KEYNOTE-006 was a multicenter, open-label, active-controlled trial where patients were randomized (1:1:1) and received KEYTRUDA 10 mg/kg every 2 weeks (n=278) or KEYTRUDA 10 mg/kg every 3 weeks (n=277) until disease progression or unacceptable toxicity or ipilimumab 3 mg/kg every 3 weeks for 4 doses unless discontinued earlier for disease progression or unacceptable toxicity (n=256) *[see Clinical Studies (14.1)]*. Patients with autoimmune disease, a medical condition that required systemic corticosteroids or other immunosuppressive medication; a history of interstitial lung disease; or active infection requiring therapy, including HIV or hepatitis B or C, were ineligible.

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

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

In KEYNOTE-006, the adverse reaction profile was similar for the every 2 week and every 3 week schedule, therefore summary safety results are provided in a pooled analysis (n=555) of both KEYTRUDA arms. Adverse reactions leading to permanent discontinuation of KEYTRUDA occurred in 9% of patients. Adverse reactions leading to discontinuation of KEYTRUDA in more than one patient were colitis (1.4%), autoimmune hepatitis (0.7%), allergic reaction (0.4%), polyneuropathy (0.4%), and cardiac failure (0.4%). Adverse reactions leading to interruption of KEYTRUDA occurred in 21% of patients; the most common (≥1%) was diarrhea (2.5%). Tables 4 and 5 summarize selected adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-006.

**Table 4: Selected* Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-006**

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

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

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

**Table 5: Selected* Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Melanoma Patients Receiving KEYTRUDA in KEYNOTE-006**

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

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

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

‡ Graded per NCI CTCAE v4.0

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

*Ipilimumab-Refractory Melanoma*

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

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

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

In KEYNOTE-002, the adverse reaction profile was similar for the 2 mg/kg dose and 10 mg/kg dose, therefore summary safety results are provided in a pooled analysis (n=357) of both KEYTRUDA arms. Adverse reactions resulting in permanent discontinuation occurred in 12% of patients receiving KEYTRUDA; the most common (≥1%) were general physical health deterioration (1%), asthenia (1%), dyspnea (1%), pneumonitis (1%), and generalized edema (1%). Adverse reactions leading to interruption of KEYTRUDA occurred in 14% of patients; the most common (≥1%) were dyspnea (1%), diarrhea (1%), and maculo-papular rash (1%). Tables 6 and 7 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-002.



Reference ID: 4761679

**Table 6: Selected* Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-002**

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

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

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

**Table 7: Selected* Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Melanoma Patients Receiving KEYTRUDA in KEYNOTE-002**

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

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

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

*Adjuvant Treatment of Resected 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



Reference ID: 4761679

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

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

Two patients treated with KEYTRUDA died from causes other than disease progression; causes of death were drug reaction with eosinophilia and systemic symptoms and autoimmune myositis with respiratory failure. Serious adverse reactions occurred in 25% of patients receiving KEYTRUDA. Adverse reactions leading to permanent discontinuation occurred in 14% of patients receiving KEYTRUDA; the most common (≥1%) were pneumonitis (1.4%), colitis (1.2%), and diarrhea (1%). Adverse reactions leading to interruption of KEYTRUDA occurred in 19% of patients; the most common (≥1%) were diarrhea (2.4%), pneumonitis (2%), increased ALT (1.4%), arthralgia (1.4%), increased AST (1.4%), dyspnea (1%), and fatigue (1%). Tables 8 and 9 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-054.

**Table 8: Selected* Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-054**

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

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



Reference ID: 4761679

**Table 9: Selected* Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Melanoma Patients Receiving KEYTRUDA in KEYNOTE-054**

| Laboratory Test† | KEYTRUDA 200 mg every 3 weeks | | Placebo | |
|---|---|---|---|---|
| | All Grades‡ % | Grades 3-4 % | All Grades % | Grades 3-4 % |
| **Chemistry** | | | | |
| Increased ALT | 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 10 and 11 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-189.



Reference ID: 4761679

**Table 10: Adverse Reactions Occurring in ≥20% of Patients in KEYNOTE-189**

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

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

**Table 11: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients in KEYNOTE-189**

| Laboratory Test* | KEYTRUDA 200 mg every 3 weeks Pemetrexed Platinum Chemotherapy | | Placebo Pemetrexed Platinum Chemotherapy | |
|---|---|---|---|---|
| | All Grades† % | Grades 3-4 % | All Grades % | Grades 3-4 % |
| **Hematology** | | | | |
| Anemia | 85 | 17 | 81 | 18 |
| Lymphopenia | 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*



Reference ID: 4761679

*Clinical Studies (14.2)]*. Safety data are available for the first 203 patients who received KEYTRUDA and chemotherapy (n=101) or placebo and chemotherapy (n=102). Patients with autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible.

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

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

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

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

*Previously Untreated NSCLC*

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

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

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

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

Tables 12 and 13 summarize the adverse reactions and laboratory abnormalities, respectively, in patients treated with KEYTRUDA in KEYNOTE-042.



Reference ID: 4761679

**Table 12: Adverse Reactions Occurring in ≥10% of Patients in KEYNOTE-042**

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

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

**Table 13: Laboratory Abnormalities Worsened from Baseline in ≥20% of Patients in KEYNOTE-042**

| Laboratory Test* | KEYTRUDA 200 mg every 3 weeks | | Chemotherapy | |
|---|---|---|---|---|
| | All Grades† % | Grades 3-4 % | All Grades % | Grades 3-4 % |
| **Chemistry** | | | | |
| Hyperglycemia | 52 | 4.7 | 51 | 5 |
| Increased ALT | 33 | 4.8 | 34 | 2.9 |
| Hypoalbuminemia | 33 | 2.2 | 29 | 1.0 |
| Increased AST | 31 | 3.6 | 32 | 1.7 |
| Hyponatremia | 31 | 9 | 32 | 8 |
| Increased alkaline phosphatase | 29 | 2.3 | 29 | 0.3 |
| Hypocalcemia | 25 | 2.5 | 19 | 0.7 |
| Hyperkalemia | 23 | 3.0 | 20 | 2.2 |
| Increased prothrombin INR | 21 | 2.0 | 15 | 2.9 |
| **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 14 and 15 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-010.

**Table 14: Selected* Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-010**

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

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

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



Reference ID: 4761679

**Table 15: Selected* Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of NSCLC Patients Receiving KEYTRUDA in KEYNOTE-010**

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

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



Reference ID: 4761679

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

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

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

| Laboratory Test* | KEYTRUDA 200 mg every 3 weeks | | KEYTRUDA 200 mg every 3 weeks Platinum FU | | Cetuximab Platinum FU | |
|---|---|---|---|---|---|---|
| | All Grades† (%) | Grades 3-4 (%) | All Grades† (%) | Grades 3-4 (%) | All Grades† (%) | Grades 3-4 (%) |
| **Hematology** | | | | | | |
| Lymphopenia | 54 | 25 | 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 (5.1)]*.

Relapsed or Refractory cHL

*KEYNOTE-204*

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

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

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

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

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

Table 18 summarizes adverse reactions in KEYNOTE-204.



Reference ID: 4761679

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

| Adverse Reaction | KEYTRUDA 200 mg every 3 weeks N=148 | | Brentuximab Vedotin 1.8 mg/kg every 3 weeks N=152 | |
|---|---|---|---|---|
| | All Grades* (%) | Grades 3- 4 (%) | All Grades* (%) | Grades 3- 4[†] (%) |
| **Infections** | | | | |
| Upper respiratory tract infection[‡] | 41 | 1.4 | 24 | 0 |
| Urinary tract infection | 11 | 0 | 3 | 0.7 |
| **Musculoskeletal and Connective Tissue** | | | | |
| Musculoskeletal pain[§] | 32 | 0 | 29 | 1.3 |
| **Gastrointestinal** | | | | |
| Diarrhea[¶] | 22 | 2.7 | 17 | 1.3 |
| Nausea | 14 | 0 | 24 | 0.7 |
| Vomiting | 14 | 1.4 | 20 | 0 |
| Abdominal pain[#] | 11 | 0.7 | 13 | 1.3 |
| **General** | | | | |
| Pyrexia | 20 | 0.7 | 13 | 0.7 |
| Fatigue[þ] | 20 | 0 | 22 | 0.7 |
| **Skin and Subcutaneous Tissue** | | | | |
| Rash[β] | 20 | 0 | 19 | 0.7 |
| Pruritus | 18 | 0 | 12 | 0 |
| **Respiratory, Thoracic and Mediastinal** | | | | |
| Cough[à] | 20 | 0.7 | 14 | 0.7 |
| Pneumonitis[è] | 11 | 5 | 3 | 1.3 |
| Dyspnea[ò] | 11 | 0.7 | 7 | 0.7 |
| **Endocrine** | | | | |
| Hypothyroidism | 19 | 0 | 3 | 0 |
| **Nervous System** | | | | |
| Peripheral neuropathy[ø] | 11 | 0.7 | 43 | 7 |
| Headache[ý] | 11 | 0 | 11 | 0 |

* Graded per NCI CTCAE v4.0
† Adverse reactions in BV arm were Grade 3 only.
‡ Includes acute sinusitis, nasopharyngitis, pharyngitis, pharyngotonsillitis, rhinitis, sinusitis, sinusitis bacterial, tonsillitis, upper respiratory tract infection, viral upper respiratory tract infection
§ Includes arthralgia, back pain, bone pain, musculoskeletal discomfort, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, pain in extremity
¶ Includes diarrhea, gastroenteritis, colitis, enterocolitis
\# Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper
Þ Includes fatigue, asthenia
β Includes dermatitis acneiform, dermatitis atopic, dermatitis allergic, dermatitis contact, dermatitis exfoliative, dermatitis psoriasiform, eczema, rash, rash erythematous, rash follicular, rash maculo-papular, rash papular, rash pruritic, toxic skin eruption
à Includes cough, productive cough
è Includes pneumonitis, interstitial lung disease
ò Includes dyspnea, dyspnea exertional, wheezing
ø Includes dysaesthesia, hypoaesthesia, neuropathy peripheral, paraesthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, polyneuropathy
ý Includes headache, migraine, tension headache

Clinically relevant adverse reactions in <10% of patients who received KEYTRUDA included herpes virus infection (9%), pneumonia (8%), oropharyngeal pain (8%), hyperthyroidism (5%), hypersensitivity (4.1%), infusion reactions (3.4%), altered mental state (2.7%), and in 1.4% each, uveitis, myocarditis, thyroiditis, febrile neutropenia, sepsis, and tumor flare.

Table 19 summarizes laboratory abnormalities in KEYNOTE-204.



Reference ID: 4761679

**Table 19: Laboratory Abnormalities (≥15%) That Worsened from Baseline in Patients with cHL in KEYNOTE-204**

| Laboratory Abnormality* | KEYTRUDA 200 mg every 3 weeks | | Brentuximab Vedotin 1.8 mg/kg every 3 weeks | |
|---|---|---|---|---|
| | All Grades† (%) | Grades 3-4 (%) | All Grades† (%) | Grades 3-4 (%) |
| **Chemistry** | | | | |
| Hyperglycemia | 46 | 4.1 | 36 | 2.0 |
| Increased AST | 39 | 5 | 41 | 3.9 |
| Increased ALT | 34 | 6 | 45 | 5 |
| Hypophosphatemia | 31 | 5 | 18 | 2.7 |
| Increased creatinine | 28 | 3.4 | 14 | 2.6 |
| Hypomagnesemia | 25 | 0 | 12 | 0 |
| Hyponatremia | 24 | 4.1 | 20 | 3.3 |
| Hypocalcemia | 22 | 2.0 | 16 | 0 |
| Increased alkaline phosphatase | 21 | 2.1 | 22 | 2.6 |
| Hyperbilirubinemia | 16 | 2.0 | 9 | 1.3 |
| Hypoalbuminemia | 16 | 0.7 | 19 | 0.7 |
| Hyperkalemia | 15 | 1.4 | 8 | 0 |
| **Hematology** | | | | |
| Lymphopenia | 35 | 9 | 32 | 13 |
| Thrombocytopenia | 34 | 10 | 26 | 5 |
| Neutropenia | 28 | 8 | 43 | 17 |
| Anemia | 24 | 5 | 33 | 8 |

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (range: 143 to 148 patients) and BV (range: 146 to 152 patients); hypomagnesemia: KEYTRUDA n=53 and BV n=50.

† Graded per NCI CTCAE v4.0

*KEYNOTE-087*

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

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



Reference ID: 4761679

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

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

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

Clinically relevant adverse reactions in <10% of patients who received KEYTRUDA included infusion reactions (9%), hyperthyroidism (3%), pneumonitis (3%), uveitis and myositis (1% each), and myelitis and myocarditis (0.5% each).

**Table 21: Select Laboratory Abnormalities (≥15%) That Worsened from Baseline in Patients with cHL who Received KEYTRUDA in KEYNOTE-087**

| Laboratory Abnormality* | KEYTRUDA 200 mg every 3 weeks | |
|---|---|---|
| | All Grades† (%) | Grades 3-4 (%) |
| **Chemistry** | | |
| Hypertransaminasemia‡ | 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 who received KEYTRUDA in KEYNOTE-170 *[see Clinical Studies (14.6)],* the median duration of exposure to KEYTRUDA was 3.5 months (range: 1 day to 22.8 months). Serious adverse reactions occurred in 26% of patients. Serious adverse reactions that occurred in >2% of patients included arrhythmia (4%), cardiac tamponade (2%), myocardial infarction (2%), pericardial effusion (2%), and pericarditis (2%). Six (11%) patients died within 30 days of start of treatment. Permanent discontinuation of KEYTRUDA due to an adverse reaction occurred in 8% of patients and dosage interruption due to an adverse reaction occurred in 15%. Twenty-five percent of patients had an adverse reaction requiring systemic corticosteroid therapy. Tables 22 and 23 summarize adverse reactions and laboratory abnormalities, respectively, in KEYNOTE-170.

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

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

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

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

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

| Laboratory Abnormality* | KEYTRUDA 200 mg every 3 weeks | |
|---|---|---|
| | All Grades† (%) | Grades 3-4 (%) |
| **Hematology** | | |
| Anemia | 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 24 summarizes adverse reactions in patients on KEYTRUDA in KEYNOTE-052.



Reference ID: 4761679

**Table 24: 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** | | |
| RashÞ | 21 | 0.5 |
| Pruritus | 19 | 0.3 |
| Edema peripheralβ | 14 | 1.1 |
| **Infections** | | |
| Urinary tract infection | 19 | 9 |
| **Blood and Lymphatic System** | | |
| Anemia | 17 | 7 |
| **Respiratory, Thoracic, and Mediastinal** | | |
| Cough | 14 | 0 |
| Dyspnea | 11 | 0.5 |
| **Renal and Urinary** | | |
| Increased blood creatinine | 11 | 1.1 |
| Hematuria | 13 | 3.0 |

* Graded per NCI CTCAE v4.0
† Includes fatigue, asthenia
‡ Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, pain in extremity, spinal pain
§ Includes diarrhea, colitis, enterocolitis, gastroenteritis, frequent bowel movements
¶ Includes abdominal pain, pelvic pain, flank pain, abdominal pain lower, tumor pain, bladder pain, hepatic pain, suprapubic pain, abdominal discomfort, abdominal pain upper
\# Includes autoimmune hepatitis, hepatitis, hepatitis toxic, liver injury, increased transaminases, hyperbilirubinemia, increased blood bilirubin, increased alanine aminotransferase, increased aspartate aminotransferase, increased hepatic enzymes, increased liver function tests
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
β Includes edema peripheral, peripheral swelling

*Previously Treated Urothelial Carcinoma*

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



Reference ID: 4761679

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 25 and 26 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-045.

**Table 25: Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-045**

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

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



Reference ID: 4761679

**Table 26: 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

*BCG-unresponsive High-risk NMIBC*

The safety of KEYTRUDA was investigated in KEYNOTE-057, a multicenter, open-label, single-arm trial that enrolled 148 patients with high-risk non-muscle invasive bladder cancer (NMIBC), 96 of whom had BCG-unresponsive carcinoma in situ (CIS) with or without papillary tumors. Patients received KEYTRUDA 200 mg every 3 weeks until unacceptable toxicity, persistent or recurrent high-risk NMIBC or progressive disease, or up to 24 months of therapy without disease progression.

The median duration of exposure to KEYTRUDA was 4.3 months (range: 1 day to 25.6 months).

KEYTRUDA was discontinued due to adverse reactions in 11% of patients. The most common adverse (>1%) reaction resulting in permanent discontinuation of KEYTRUDA was pneumonitis (1.4%). Adverse reactions leading to interruption of KEYTRUDA occurred in 22% of patients; the most common (≥2%) were diarrhea (4%) and urinary tract infection (2%). Serious adverse reactions occurred in 28% of KEYTRUDA-treated patients. The most frequent serious adverse reactions (≥2%) in KEYTRUDA-treated patients were pneumonia (3%), cardiac ischemia (2%), colitis (2%), pulmonary embolism (2%), sepsis (2%), and urinary tract infection (2%). Tables 27 and 28 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-057.

**Table 27: Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-057**

| Adverse Reaction | KEYTRUDA 200 mg every 3 weeks N=148 | |
|---|---|---|
| | All Grades* (%) | Grades 3–4 (%) |
| **General** | | |
| Fatigue† | 29 | 0.7 |
| Peripheral edema‡ | 11 | 0 |
| **Gastrointestinal** | | |
| Diarrhea§ | 24 | 2.0 |
| Nausea | 13 | 0 |
| Constipation | 12 | 0 |
| **Skin and Subcutaneous Tissue** | | |
| Rash¶ | 24 | 0.7 |
| Pruritus | 19 | 0.7 |
| **Musculoskeletal and Connective Tissue** | | |
| Musculoskeletal pain# | 19 | 0 |
| Arthralgia | 14 | 1.4 |
| **Renal and Urinary** | | |
| Hematuria | 19 | 1.4 |
| **Respiratory, Thoracic, and Mediastinal** | | |
| Cough⊳ | 19 | 0 |
| **Infections** | | |
| Urinary tract infection | 12 | 2.0 |
| Nasopharyngitis | 10 | 0 |
| **Endocrine** | | |
| Hypothyroidism | 11 | 0 |

* Graded per NCI CTCAE v4.03
† Includes asthenia, fatigue, malaise
‡ Includes edema peripheral, peripheral swelling
§ Includes diarrhea, gastroenteritis, colitis
¶ Includes rash maculo-papular, rash, rash erythematous, rash pruritic, rash pustular, erythema, eczema, eczema asteatotic, lichenoid keratosis, urticaria, dermatitis
\# Includes back pain, myalgia, musculoskeletal pain, pain in extremity, musculoskeletal chest pain, neck pain
⊳ Includes cough, productive cough

**Table 28: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of BCG-unresponsive NMIBC Patients Receiving KEYTRUDA in KEYNOTE-057**

| Laboratory Test* | KEYTRUDA 200 mg every 3 weeks | |
|---|---|---|
| | All Grades† (%) | Grades 3-4 (%) |
| **Chemistry** | | |
| Hyperglycemia | 59 | 8 |
| Increased ALT | 25 | 3.4 |
| Hyponatremia | 24 | 7 |
| Hypophosphatemia | 24 | 6 |
| Hypoalbuminemia | 24 | 2.1 |
| Hyperkalemia | 23 | 1.4 |
| Hypocalcemia | 22 | 0.7 |
| Increased AST | 20 | 3.4 |
| Increased creatinine | 20 | 0.7 |
| **Hematology** | | |
| Anemia | 35 | 1.4 |
| Lymphopenia | 29 | 1.6 |

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (range: 124 to 147 patients)
† Graded per NCI CTCAE v4.03



Reference ID: 4761679

Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer

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

Gastric Cancer

Among the 259 patients with gastric cancer enrolled in KEYNOTE-059 *[see Clinical Studies (14.10)]*, 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 (14.11)]* treated with KEYTRUDA, the median duration of exposure to KEYTRUDA was 2.1 months (range: 1 day to 24.4 months). Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible. Adverse reactions occurring in patients with esophageal cancer were similar to those occurring in 2799 patients with melanoma or NSCLC treated with KEYTRUDA as a single agent.

Cervical Cancer

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

KEYTRUDA was discontinued due to adverse reactions in 8% of patients. Serious adverse reactions occurred in 39% of patients receiving KEYTRUDA. The most frequent serious adverse reactions reported included anemia (7%), fistula (4.1%), hemorrhage (4.1%), and infections [except UTIs] (4.1%). Tables 29 and 30 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-158.



Reference ID: 4761679

**Table 29: Adverse Reactions Occurring in ≥10% of Patients with Cervical Cancer in KEYNOTE-158**

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

* Graded per NCI CTCAE v4.0
† Includes asthenia, fatigue, lethargy, malaise
‡ Includes breast pain, cancer pain, dysesthesia, dysuria, ear pain, gingival pain, groin pain, lymph node pain, oropharyngeal pain, pain, pain of skin, pelvic pain, radicular pain, stoma site pain, toothache
§ Includes edema peripheral, peripheral swelling
¶ Includes arthralgia, back pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, myositis, neck pain, non-cardiac chest pain, pain in extremity
\# Includes colitis, diarrhea, gastroenteritis
Þ Includes abdominal discomfort, abdominal distension, abdominal pain, abdominal pain lower, abdominal pain upper
ß Includes epistaxis, hematuria, hemoptysis, metrorrhagia, rectal hemorrhage, uterine hemorrhage, vaginal hemorrhage
à Includes bacterial pyelonephritis, pyelonephritis acute, urinary tract infection, urinary tract infection bacterial, urinary tract infection pseudomonal, urosepsis
è Includes cellulitis, clostridium difficile infection, device-related infection, empyema, erysipelas, herpes virus infection, infected neoplasm, infection, influenza, lower respiratory tract congestion, lung infection, oral candidiasis, oral fungal infection, osteomyelitis, pseudomonas infection, respiratory tract infection, tooth abscess, upper respiratory tract infection, uterine abscess, vulvovaginal candidiasis
ð Includes dermatitis, drug eruption, eczema, erythema, palmar-plantar erythrodysesthesia syndrome, rash, rash generalized, rash maculo-papular



Reference ID: 4761679

**Table 30: 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 (14.13)]*, 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 (14.14)]*, 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 (14.15)]*. 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).



Reference ID: 4761679

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 31 and 32 summarize the adverse reactions and laboratory abnormalities, respectively, that occurred in at least 20% of patients treated with KEYTRUDA and axitinib in KEYNOTE-426.



Reference ID: 4761679

**Table 31: 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



Reference ID: 4761679

**Table 32: 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 (14.16)]*. 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 33 and 34 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in combination with lenvatinib.



Reference ID: 4761679

**Table 33: 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 painÞ | 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



Reference ID: 4761679

**Table 34: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% (All Grades) or ≥3% (Grades 3-4) 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).

TMB-H Cancer

The safety of KEYTRUDA was investigated in 105 patients with TMB-H cancer enrolled in KEYNOTE-158 *[see Clinical Studies (14.17)].* The median duration of exposure to KEYTRUDA was 4.9 months (range: 0.03 to 35.2 months). Adverse reactions occurring in patients with TMB-H cancer were similar to those occurring in patients with other solid tumors who received KEYTRUDA as a single agent.

cSCC

Among the 105 patients with cSCC enrolled in KEYNOTE-629 *[see Clinical Studies (14.18)]*, the median duration of exposure to KEYTRUDA was 5.8 months (range 1 day to 16.1 months). Patients with autoimmune disease or a medical condition that required systemic corticosteroids or other immunosuppressive medications were ineligible. Adverse reactions occurring in patients with cSCC were similar to those occurring in 2799 patients with melanoma or NSCLC treated with KEYTRUDA as a single agent. Laboratory abnormalities (Grades 3-4) that occurred at a higher incidence included lymphopenia (11%).

TNBC

The safety of KEYTRUDA in combination with paclitaxel, paclitaxel protein-bound, or gemcitabine and carboplatin was investigated in KEYNOTE-355, a multicenter, double-blind, randomized (2:1), placebo-controlled trial in patients with locally recurrent unresectable or metastatic TNBC who had not been previously treated with chemotherapy in the metastatic setting *[see Clinical Studies (14.19)]*. A total of 596 patients (including 34 patients from a safety run-in) received KEYTRUDA 200 mg every 3 weeks in combination with paclitaxel, paclitaxel protein-bound, or gemcitabine and carboplatin.

The median duration of exposure to KEYTRUDA was 5.7 months (range: 1 day to 33.0 months).

Fatal adverse reactions occurred in 2.5% of patients receiving KEYTRUDA in combination with chemotherapy, including cardio-respiratory arrest (0.7%) and septic shock (0.3%).

Serious adverse reactions occurred in 30% of patients receiving KEYTRUDA in combination with paclitaxel, paclitaxel protein-bound, or gemcitabine and carboplatin. Serious adverse reactions in ≥2% of patients were pneumonia (2.9%), anemia (2.2%), and thrombocytopenia (2%).

KEYTRUDA was discontinued for adverse reactions in 11% of patients. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA (≥1%) were increased ALT (2.2%), increased AST (1.5%), and pneumonitis (1.2%). Adverse reactions leading to the interruption of KEYTRUDA occurred in 50% of patients. The most common adverse reactions leading to interruption of KEYTRUDA (≥2%) were neutropenia (22%), thrombocytopenia (14%), anemia (7%), increased ALT (6%), leukopenia (5%), increased AST (5%), decreased white blood cell count (3.9%), and diarrhea (2%).

Tables 35 and 36 summarize the adverse reactions and laboratory abnormalities in patients on KEYTRUDA in KEYNOTE-355.

**Table 35: Adverse Reactions Occurring in ≥20% of Patients Receiving KEYTRUDA with Chemotherapy in KEYNOTE-355**

| Adverse Reaction | KEYTRUDA 200 mg every 3 weeks with chemotherapy n=596 | | Placebo every 3 weeks with chemotherapy n=281 | |
|---|---|---|---|---|
| | All Grades* (%) | Grades 3-4 (%) | All Grades* (%) | Grades 3-4 (%) |
| **General** | | | | |
| Fatigue† | 48 | 5 | 49 | 4.3 |
| **Gastrointestinal** | | | | |
| Nausea | 44 | 1.7 | 47 | 1.8 |
| Diarrhea | 28 | 1.8 | 23 | 1.8 |
| Constipation | 28 | 0.5 | 27 | 0.4 |
| Vomiting | 26 | 2.7 | 22 | 3.2 |
| **Skin and Subcutaneous Tissue** | | | | |
| Alopecia | 34 | 0.8 | 35 | 1.1 |
| Rash‡ | 26 | 2 | 16 | 0 |
| **Respiratory, Thoracic and Mediastinal** | | | | |
| Cough§ | 23 | 0 | 20 | 0.4 |
| **Metabolism and Nutrition** | | | | |
| Decreased appetite | 21 | 0.8 | 14 | 0.4 |
| **Nervous System** | | | | |
| Headache¶ | 20 | 0.7 | 23 | 0.7 |

* Graded per NCI CTCAE v4.03
† Includes fatigue and asthenia
‡ Includes rash, rash maculo-papular, rash pruritic, rash pustular, rash macular, rash papular, butterfly rash, rash erythematous, eyelid rash
§ Includes cough, productive cough, upper-airway cough syndrome
¶ Includes headache, migraine, tension headache



Reference ID: 4761679

**Table 36: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients Receiving KEYTRUDA with Chemotherapy in KEYNOTE-355**

| Laboratory Test* | KEYTRUDA 200 mg every 3 weeks with chemotherapy | | Placebo every 3 weeks with chemotherapy | |
|---|---|---|---|---|
| | All Grades† % | Grades 3-4 % | All Grades† % | Grades 3-4 % |
| **Hematology** | | | | |
| Anemia | 90 | 20 | 85 | 19 |
| Leukopenia | 85 | 39 | 86 | 39 |
| Neutropenia | 76 | 49 | 77 | 52 |
| Lymphopenia | 70 | 26 | 70 | 19 |
| Thrombocytopenia | 54 | 19 | 53 | 21 |
| **Chemistry** | | | | |
| Increased ALT | 60 | 11 | 58 | 8 |
| Increased AST | 57 | 9 | 55 | 6 |
| Hyperglycemia | 52 | 4.4 | 51 | 2.2 |
| Hypoalbuminemia | 37 | 2.2 | 32 | 2.2 |
| Increased alkaline phosphatase | 35 | 3.9 | 39 | 2.2 |
| Hypocalcemia | 29 | 3.3 | 27 | 1.8 |
| Hyponatremia | 28 | 5 | 26 | 6 |
| Hypophosphatemia | 21 | 7 | 18 | 4.8 |
| Hypokalemia | 20 | 4.4 | 18 | 4.0 |

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA + chemotherapy (range: 566 to 592 patients) and placebo + chemotherapy (range: 269 to 280 patients).

† Graded per NCI CTCAE v4.03

### 6.2 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.



Reference ID: 4761679

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 (5.5), 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 as a single agent have been established in pediatric patients with cHL, PMBCL, MCC, MSI-H cancer, and TMB-H cancer. Use of KEYTRUDA in pediatric patients for these indications is supported by evidence from adequate and well-controlled studies in adults with additional pharmacokinetic and safety data in pediatric patients *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical Studies (14.5, 14.6, 14.8, 14.14, 14.17)]*.

In KEYNOTE-051, 161 pediatric patients (62 pediatric patients aged 6 months to younger than 12 years and 99 pediatric patients aged 12 to 17 years) with advanced melanoma, lymphoma, or PD-L1 positive solid tumors received KEYTRUDA 2 mg/kg every 3 weeks. The median duration of exposure was 2.1 months (range: 1 day to 24 months). Adverse reactions that occurred at a ≥10% higher rate in pediatric patients when compared to adults included pyrexia (33%), vomiting (30%), upper respiratory tract infection (29%), and headache (25%). Laboratory abnormalities that occurred at a ≥10% higher rate in pediatric patients when compared to adults were leukopenia (30%), neutropenia (26%), and Grade 3 anemia (17%).

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

### 8.5 Geriatric Use

Of 3781 patients with melanoma, NSCLC, HNSCC, or urothelial carcinoma who were treated with KEYTRUDA in clinical studies, 48% were 65 years and over and 17% were 75 years and over. No overall differences in safety or effectiveness were observed between elderly patients and younger patients.



Reference ID: 4761679

Of 389 adult patients with cHL who were treated with KEYTRUDA in clinical studies, 46 (12%) were 65 years and over. Patients aged 65 years and over had a higher incidence of serious adverse reactions (50%) than patients aged younger than 65 years (24%). Clinical studies of KEYTRUDA in cHL did not include sufficient numbers of patients aged 65 years and over to determine whether effectiveness differs from that in younger patients.

Of 596 adult patients with TNBC who were treated with KEYTRUDA in combination with paclitaxel, paclitaxel protein-bound, or gemcitabine and carboplatin in KEYNOTE-355, 137 (23%) were 65 years and over. No overall differences in safety or effectiveness were observed between elderly patients and younger patients.

## 11 DESCRIPTION

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

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

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

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

### 12.2 Pharmacodynamics

Based on the modeling of dose/exposure efficacy and safety relationships and observed pharmacokinetic data from an interim analysis of 41 patients with melanoma treated with pembrolizumab 400 mg every 6 weeks, there are no anticipated clinically significant differences in efficacy and safety between pembrolizumab doses of 200 mg or 2 mg/kg every 3 weeks or 400 mg every 6 weeks.

### 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.

<u>Distribution</u>

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

<u>Elimination</u>

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%).



Reference ID: 4761679

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 (10 months 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).



Reference ID: 4761679

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.

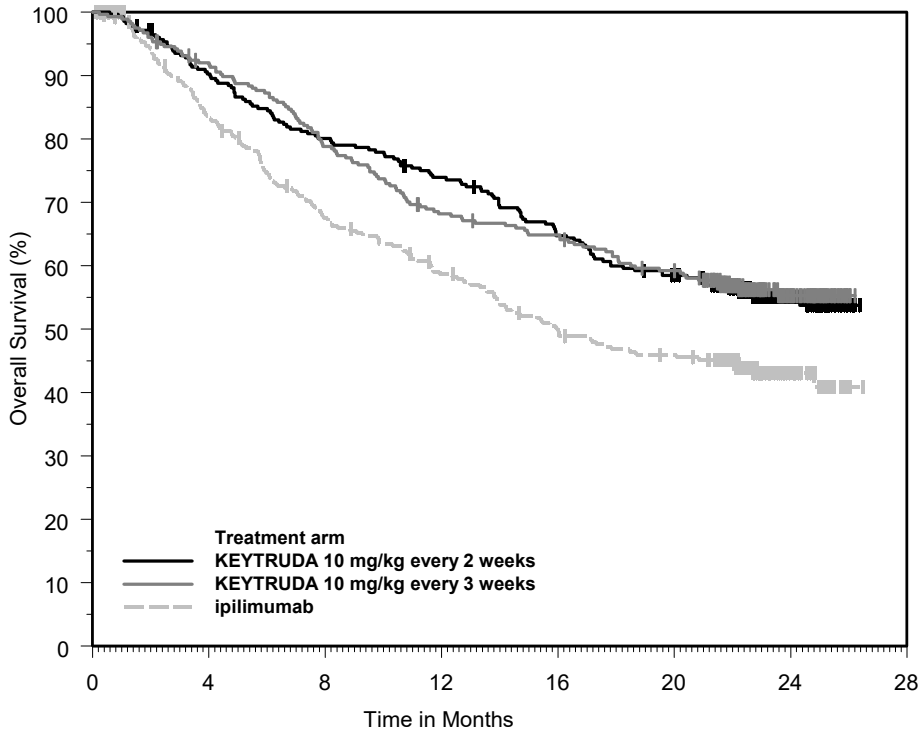
The study demonstrated statistically significant improvements in OS and PFS for patients randomized to KEYTRUDA as compared to ipilimumab. Among the 91 patients randomized to KEYTRUDA 10 mg/kg every 3 weeks with an objective response, response durations ranged from 1.4+ to 8.1+ months. Among the 94 patients 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 37 and Figure 1.

**Table 37: 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 38.

**Table 38: Efficacy Results in KEYNOTE-002**

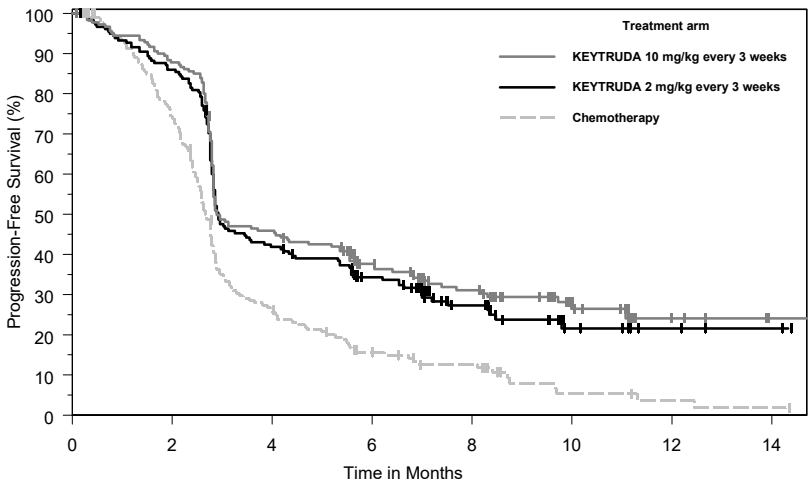
| Endpoint | KEYTRUDA 2 mg/kg every 3 weeks n=180 | KEYTRUDA 10 mg/kg every 3 weeks n=181 | Chemotherapy n=179 |
|---|---|---|---|
| **PFS** | | | |
| Number of Events, n (%) | 129 (72%) | 126 (70%) | 155 (87%) |
| Progression, n (%) | 105 (58%) | 107 (59%) | 134 (75%) |
| Death, n (%) | 24 (13%) | 19 (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 39 and Figure 3.

**Table 39: 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± | |

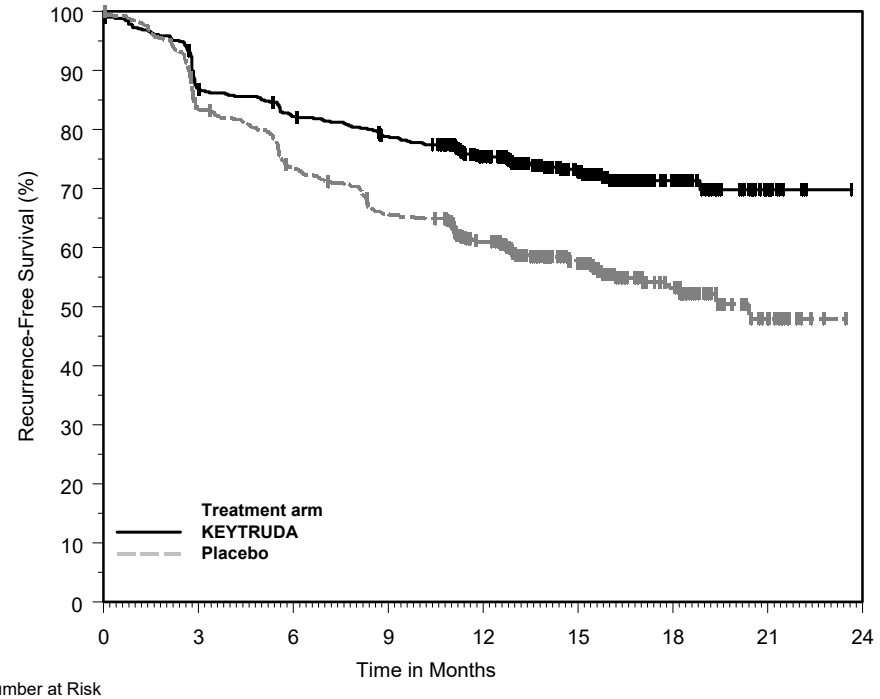
* Based on the stratified Cox proportional hazard model
† Stratified by American Joint Committee on Cancer 7th edition (AJCC) stage
± p-Value is compared with 0.008 of the allocated alpha for this interim analysis.
NR = not reached

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.



Reference ID: 4761679

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




| Number at Risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| KEYTRUDA: | 514 | 438 | 413 | 392 | 313 | 182 | 73 | 15 | 0 |
| Placebo: | 505 | 415 | 363 | 323 | 264 | 157 | 60 | 15 | 0 |

## 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



Reference ID: 4761679

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 40 and Figure 4 summarize the efficacy results for KEYNOTE-189.

**Table 40: Efficacy Results in KEYNOTE-189**

| **Endpoint** | **KEYTRUDA 200 mg every 3 weeks Pemetrexed Platinum Chemotherapy n=410** | **Placebo Pemetrexed Platinum Chemotherapy n=206** |
|---|---|---|
| **OS** | | |
| Number (%) of patients with event | 127 (31%) | 108 (52%) |
| Median in months (95% CI) | NR (NR, NR) | 11.3 (8.7, 15.1) |
| Hazard ratio* (95% CI) | 0.49 (0.38, 0.64) | |
| p-Value† | <0.0001 | |
| **PFS** | | |
| Number of patients with event (%) | 245 (60%) | 166 (81%) |
| Median in months (95% CI) | 8.8 (7.6, 9.2) | 4.9 (4.7, 5.5) |
| Hazard ratio* (95% CI) | 0.52 (0.43, 0.64) | |
| p-Value† | <0.0001 | |
| **Objective Response Rate** | | |
| ORR‡ (95% CI) | 48% (43, 53) | 19% (14, 25) |
| Complete response | 0.5% | 0.5% |
| Partial response | 47% | 18% |
| p-Value§ | <0.0001 | |
| **Duration of Response** | | |
| Median in months (range) | 11.2 (1.1+, 18.0+) | 7.8 (2.1+, 16.4+) |

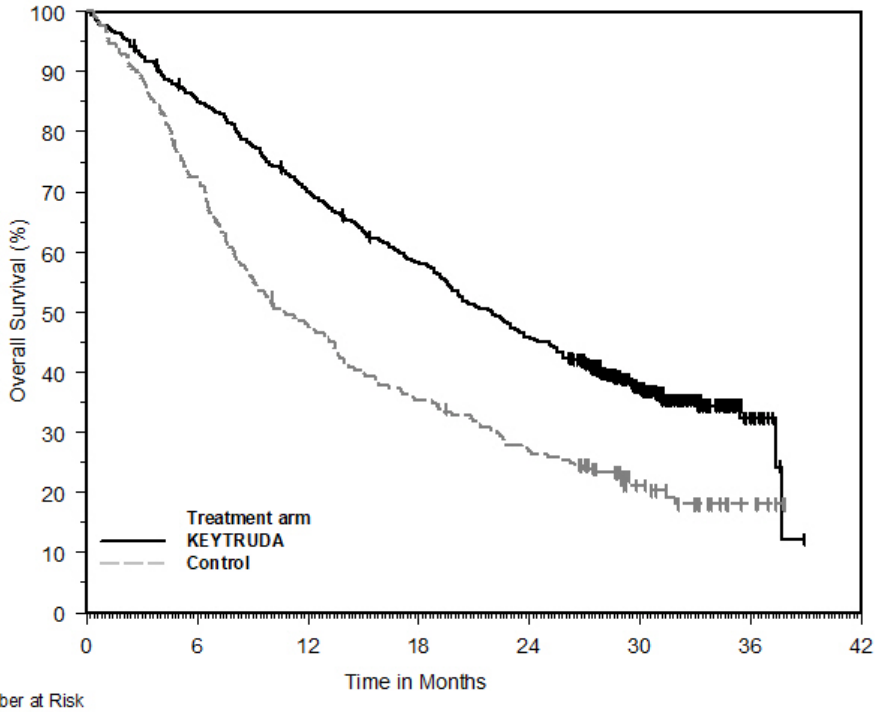
* Based on the stratified Cox proportional hazard model
† Based on a stratified log-rank test.
‡ Response: Best objective response as confirmed complete response or partial response
§ Based on Miettinen and Nurminen method stratified by PD-L1 status, platinum chemotherapy, and smoking status
NR = not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

At the protocol-specified final OS analysis, the median in the KEYTRUDA in combination with pemetrexed and platinum chemotherapy arm was 22.0 months (95% CI: 19.5, 24.5) compared to 10.6 months (95% CI: 8.7, 13.6) in the placebo with pemetrexed and platinum chemotherapy arm, with an HR of 0.56 (95% CI: 0.46, 0.69).



Reference ID: 4761679

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




| Number at Risk | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| KEYTRUDA: | 410 | 347 | 283 | 234 | 184 | 86 | 12 | 0 |
| Control: | 206 | 149 | 98 | 72 | 55 | 25 | 5 | 0 |

*Based on the protocol-specified final OS analysis

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

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

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

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

of disease progression. Assessment of tumor status was performed every 6 weeks through Week 18, every 9 weeks through Week 45 and every 12 weeks thereafter. The main efficacy outcome measures were PFS and ORR as assessed by BICR using RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, and OS. An additional efficacy outcome measure was DoR as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

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

The trial demonstrated a statistically significant improvement in OS, PFS and ORR in patients randomized to KEYTRUDA in combination with carboplatin and either paclitaxel or paclitaxel protein-bound chemotherapy compared with patients randomized to placebo with carboplatin and either paclitaxel or paclitaxel protein-bound chemotherapy. Table 41 and Figure 5 summarize the efficacy results for KEYNOTE-407.

**Table 41: Efficacy Results in KEYNOTE-407**

| **Endpoint** | **KEYTRUDA 200 mg every 3 weeks Carboplatin Paclitaxel/Paclitaxel protein-bound n=278** | **Placebo Carboplatin Paclitaxel/Paclitaxel protein-bound n=281** |
|---|---|---|
| **OS** | | |
| Number of events (%) | 85 (31%) | 120 (43%) |
| Median in months (95% CI) | 15.9 (13.2, NE) | 11.3 (9.5, 14.8) |
| Hazard ratio* (95% CI) | 0.64 (0.49, 0.85) | |
| p-Value† | 0.0017 | |
| **PFS** | | |
| Number of events (%) | 152 (55%) | 197 (70%) |
| Median in months (95% CI) | 6.4 (6.2, 8.3) | 4.8 (4.2, 5.7) |
| Hazard ratio* (95% CI) | 0.56 (0.45, 0.70) | |
| p-Value† | <0.0001 | |
| | **n=101** | **n=103** |
| **Objective Response Rate‡** | | |
| ORR (95% CI) | 58% (48, 68) | 35% (26, 45) |
| Difference (95% CI) | 23.6% (9.9, 36.4) | |
| p-Value§ | 0.0008 | |
| **Duration of Response‡** | | |
| Median duration of response in months (range) | 7.2 (2.4, 12.4+) | 4.9 (2.0, 12.4+) |

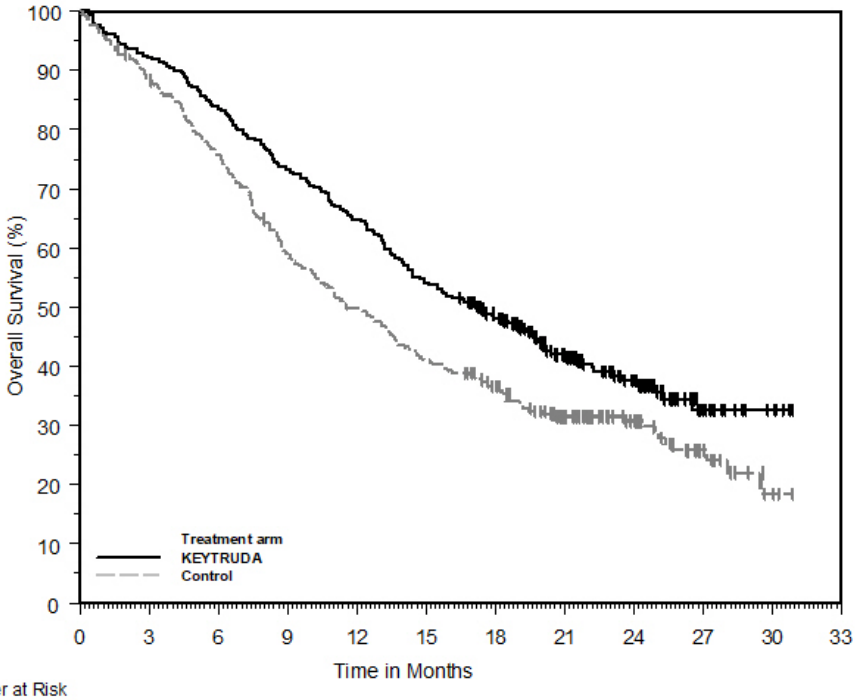
* Based on the stratified Cox proportional hazard model
† Based on a stratified log-rank test
‡ ORR primary analysis and DoR analysis were conducted with the first 204 patients enrolled.
§ Based on a stratified Miettinen-Nurminen test
NE = not estimable

At the protocol-specified final OS analysis, the median in the KEYTRUDA in combination with carboplatin and either paclitaxel or paclitaxel protein-bound chemotherapy arm was 17.1 months (95% CI: 14.4, 19.9) compared to 11.6 months (95% CI: 10.1, 13.7) in the placebo with carboplatin and either paclitaxel or paclitaxel protein-bound chemotherapy arm, with an HR of 0.71 (95% CI: 0.58, 0.88).



Reference ID: 4761679

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




| Number at Risk | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| KEYTRUDA: | 278 | 256 | 232 | 203 | 180 | 150 | 119 | 80 | 46 | 14 | 4 | 0 |
| Control: | 281 | 245 | 210 | 163 | 137 | 113 | 91 | 61 | 36 | 16 | 3 | 0 |

*Based on the protocol-specified final OS analysis

First-line treatment of metastatic NSCLC as a single agent

*KEYNOTE-042*

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

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

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



Reference ID: 4761679

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

**Table 42: Efficacy Results of All Randomized Patients (TPS ≥1% and TPS ≥50%) in KEYNOTE-042**

| | **TPS ≥1%** | | **TPS ≥50%** | |
|---|---|---|---|---|
| **Endpoint** | **KEYTRUDA 200 mg every 3 weeks n=637** | **Chemotherapy n=637** | **KEYTRUDA 200 mg every 3 weeks n=299** | **Chemotherapy n=300** |
| **OS** | | | | |
| Number of events (%) | 371 (58%) | 438 (69%) | 157 (53%) | 199 (66%) |
| Median in months (95% CI) | 16.7 (13.9, 19.7) | 12.1 (11.3, 13.3) | 20.0 (15.4, 24.9) | 12.2 (10.4, 14.2) |
| Hazard ratio* (95% CI) | 0.81 (0.71, 0.93) | | 0.69 (0.56, 0.85) | |
| p-Value† | 0.0036 | | 0.0006 | |
| **PFS** | | | | |
| Number of events (%) | 507 (80%) | 506 (79%) | 221 (74%) | 233 (78%) |
| Median in months (95% CI) | 5.4 (4.3, 6.2) | 6.5 (6.3, 7.0) | 6.9 (5.9, 9.0) | 6.4 (6.1, 6.9) |
| Hazard ratio*,‡ (95% CI) | 1.07 (0.94, 1.21) | | 0.82 (0.68, 0.99) | |
| p-Value† | -‡ | | NS§ | |
| **Objective Response Rate** | | | | |
| ORR‡ (95% CI) | 27% (24, 31) | 27% (23, 30) | 39% (33.9, 45.3) | 32% (26.8, 37.6) |
| Complete response rate | 0.5% | 0.5% | 0.7% | 0.3% |
| Partial response rate | 27% | 26% | 39% | 32% |
| **Duration of Response** | | | | |
| % with duration ≥12 months¶ | 47% | 16% | 42% | 17% |
| % with duration ≥18 months¶ | 26% | 6% | 25% | 5% |

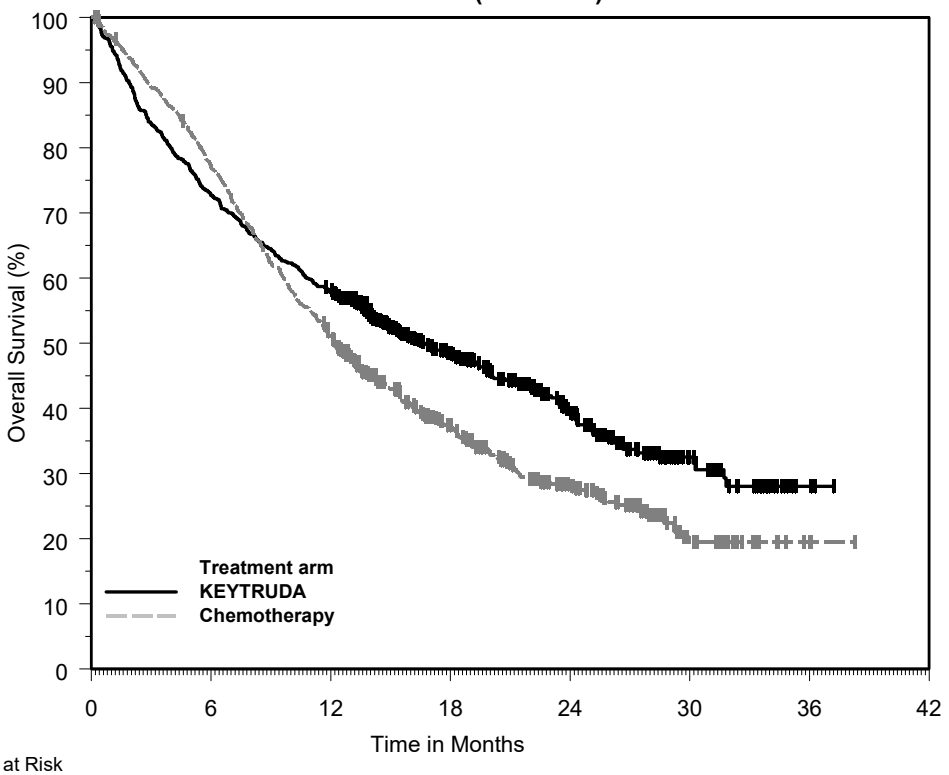
* Based on the stratified Cox proportional hazard model
† Based on a stratified log-rank test; compared to a p-Value boundary of 0.0291
‡ Not evaluated for statistical significance as a result of the sequential testing procedure for the secondary endpoints
§ Not significant compared to a p-Value boundary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

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



Reference ID: 4761679

**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 43 and Figure 7 summarize the efficacy results for KEYNOTE-024.

**Table 43: 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.

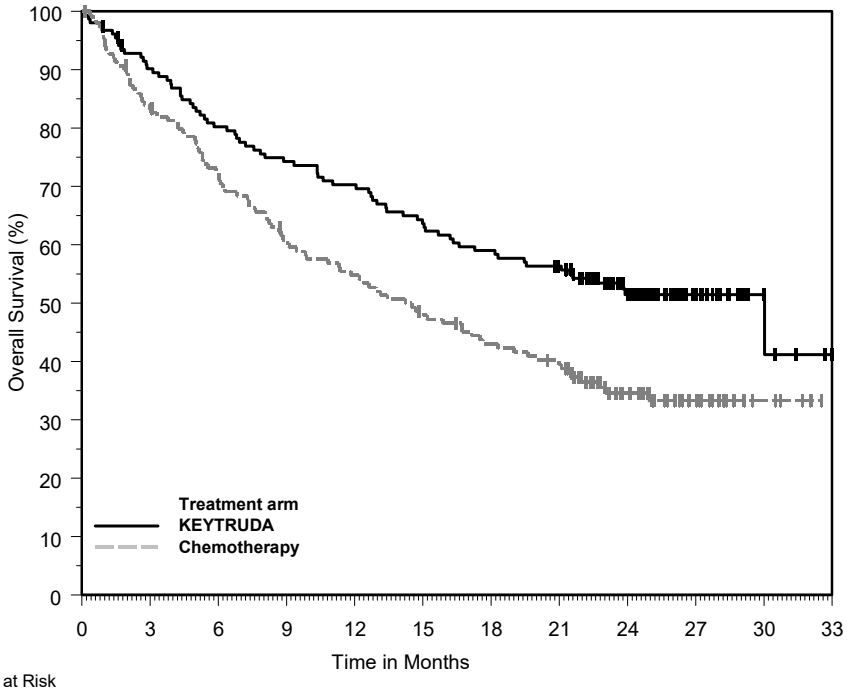
‡ p-Value is compared with 0.0118 of the allocated alpha for the interim analysis

NR = not reached



Reference ID: 4761679

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




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

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

Previously treated NSCLC

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



Reference ID: 4761679

Tables 44 and 45 and Figure 8 summarize efficacy results in the subgroup with TPS ≥50% population and in all patients, respectively.

**Table 44: 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 45: 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

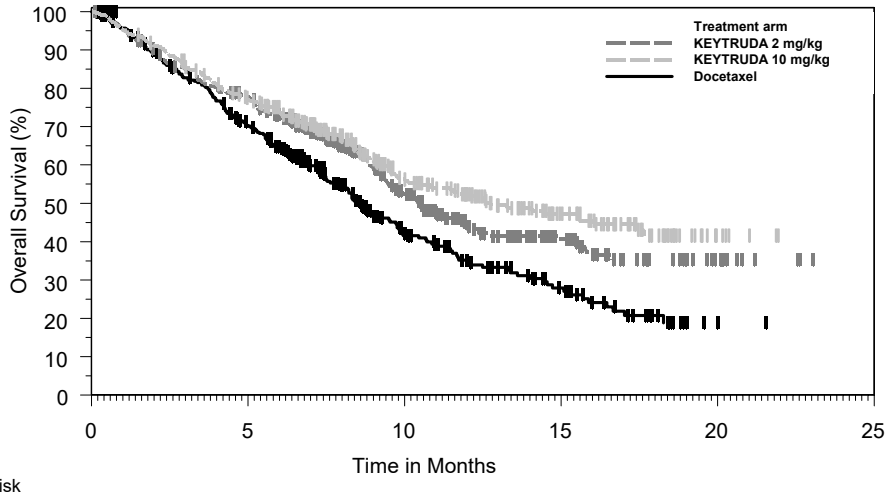
† All responses were partial responses

NR = not reached



Reference ID: 4761679

**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 46.

**Table 46: 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. Table 47 and Figure 9 summarize efficacy results for KEYTRUDA in combination with chemotherapy.

**Table 47: Efficacy Results* for KEYTRUDA plus Platinum/Fluorouracil in KEYNOTE-048**

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

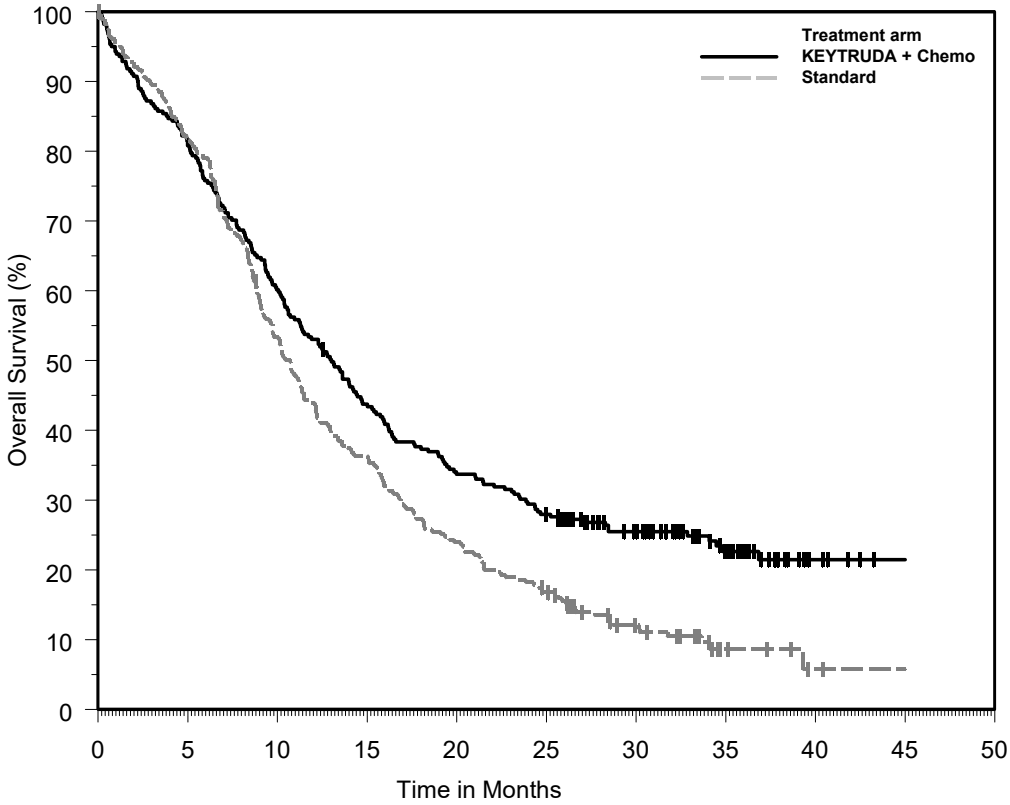
* Results at a pre-specified interim analysis
† Based on the stratified Cox proportional hazard model
‡ Based on stratified log-rank test
§ Response: Best objective response as confirmed complete response or partial response

At the pre-specified final OS analysis for the ITT population, the hazard ratio was 0.72 (95% CI: 0.60, 0.87). In addition, KEYNOTE-048 demonstrated a statistically significant improvement in OS for the subgroups of patients with PD-L1 CPS ≥1 (HR=0.65, 95% CI: 0.53, 0.80) and CPS ≥20 (HR=0.60, 95% CI: 0.45, 0.82).



Reference ID: 4761679

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




| Number at Risk | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| KEYTRUDA + Chemo: | 281 | 227 | 169 | 122 | 94 | 77 | 55 | 29 | 5 | 0 | 0 |
| Standard: | 278 | 227 | 147 | 100 | 66 | 45 | 23 | 6 | 1 | 0 | 0 |

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

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

Table 48 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 48: Efficacy Results* for KEYTRUDA as a Single Agent in KEYNOTE-048 (CPS ≥1 and CPS ≥20)**

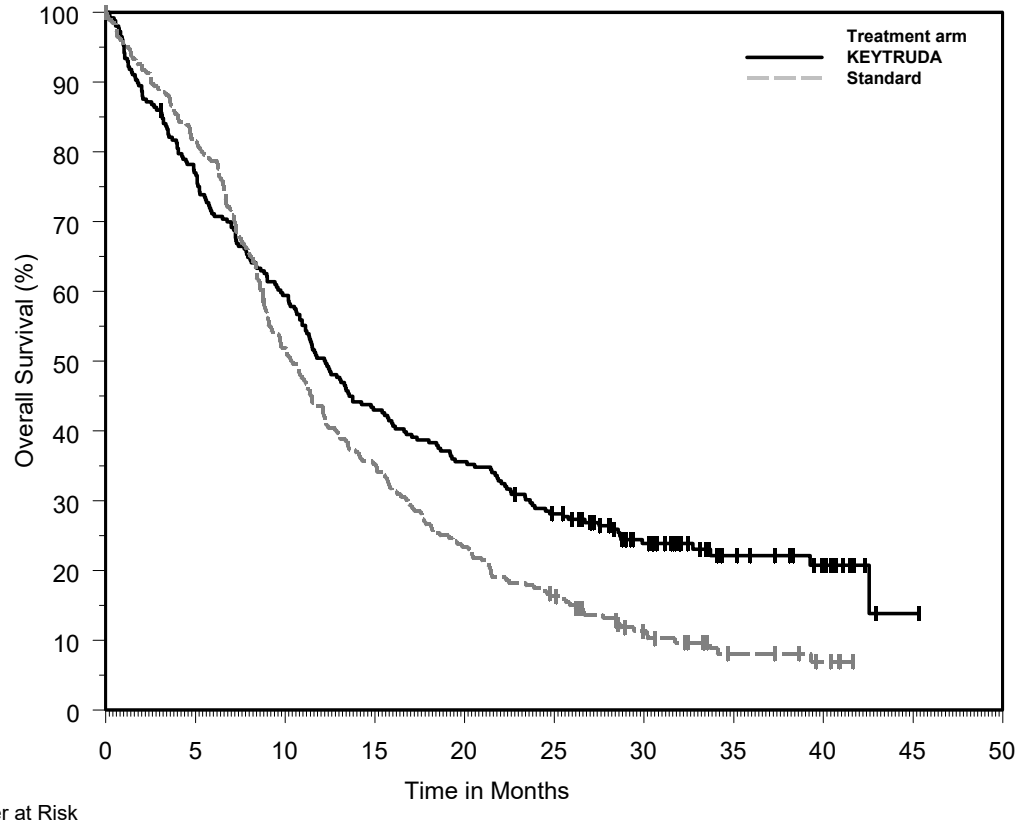
| Endpoint | CPS ≥1 | | CPS ≥20 | |
|---|---|---|---|---|
| | KEYTRUDA 200 mg every 3 weeks n=257 | Cetuximab Platinum FU n=255 | KEYTRUDA 200 mg every 3 weeks n=133 | Cetuximab Platinum FU n=122 |
| **OS** | | | | |
| Number of events (%) | 177 (69%) | 206 (81%) | 82 (62%) | 95 (78%) |
| Median in months (95% CI) | 12.3 (10.8, 14.9) | 10.3 (9.0,11.5) | 14.9 (11.6, 21.5) | 10.7 (8.8, 12.8) |
| Hazard ratio† (95% CI) | 0.78 (0.64, 0.96) | | 0.61 (0.45, 0.83) | |
| p-Value‡ | 0.0171 | | 0.0015 | |
| **PFS** | | | | |
| Number of events (%) | 225 (88%) | 231 (91%) | 113 (85%) | 111 (91%) |
| Median in months (95% CI) | 3.2 (2.2, 3.4) | 5.0 (4.8, 5.8) | 3.4 (3.2, 3.8) | 5.0 (4.8, 6.2) |
| Hazard ratio† (95% CI) | 1.15 (0.95, 1.38) | | 0.97 (0.74, 1.27) | |
| **Objective Response Rate** | | | | |
| ORR§ (95% CI) | 19% (14.5, 24.4) | 35% (29.1, 41.1) | 23% (16.4, 31.4) | 36% (27.6, 45.3) |
| Complete response rate | 5% | 3% | 8% | 3% |
| Partial response rate | 14% | 32% | 16% | 33% |
| **Duration of Response** | | | | |
| Median in months (range) | 20.9 (1.5+, 34.8+) | 4.5 (1.2+, 28.6+) | 20.9 (2.7, 34.8+) | 4.2 (1.2+, 22.3+) |

* Results at a pre-specified interim analysis
† Based on the stratified Cox proportional hazard model
‡ Based on a stratified log-rank test
§ Response: Best objective response as confirmed complete response or partial response

At the pre-specified final OS analysis comparing KEYTRUDA as a single agent to cetuximab in combination with chemotherapy, the hazard ratio for the subgroup of patients with CPS ≥1 was 0.74 (95% CI: 0.61, 0.90) and the hazard ratio for the subgroup of patients with CPS ≥20 was 0.58 (95% CI: 0.44, 0.78).

In an exploratory subgroup analysis for patients with CPS 1-19 HNSCC at the time of the pre-specified final OS analysis, the median OS was 10.8 months (95% CI: 9.0, 12.6) for KEYTRUDA as a single agent and 10.1 months (95% CI: 8.7, 12.1) for cetuximab in combination with chemotherapy, with an HR of 0.86 (95% CI: 0.66, 1.12).

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




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

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

Previously treated recurrent or metastatic HNSCC

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

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

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

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

### 14.5 Classical Hodgkin Lymphoma

*KEYNOTE-204*

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

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

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

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

Efficacy is summarized in Table 49 and Figure 11.

**Table 49: Efficacy Results in Patients with cHL in KEYNOTE-204**

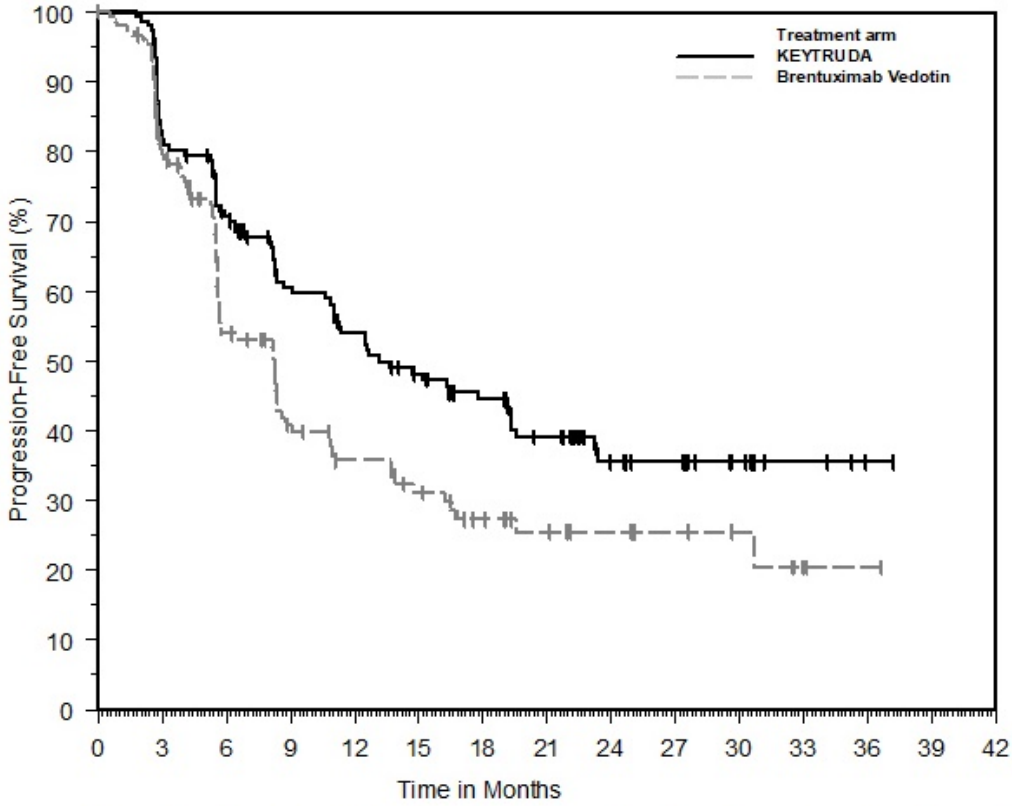
| Endpoint | KEYTRUDA 200 mg every 3 weeks n=151 | Brentuximab Vedotin 1.8 mg/kg every 3 weeks n=153 |
|---|---|---|
| **PFS** | | |
| Number of patients with event (%) | 81 (54%) | 88 (58%) |
| Median in months (95% CI)* | 13.2 (10.9, 19.4) | 8.3 (5.7, 8.8) |
| Hazard ratio† (95% CI) | 0.65 (0.48, 0.88) | |
| p-Value‡ | 0.0027 | |
| **Objective Response Rate** | | |
| ORR§ (95% CI) | 66% (57, 73) | 54% (46, 62) |
| Complete response | 25% | 24% |
| Partial response | 41% | 30% |
| **Duration of Response** | | |
| Median in months (range)* | 20.7 (0.0+, 33.2+) | 13.8 (0.0+, 33.9+) |

* Based on Kaplan-Meier estimates.
† Based on the stratified Cox proportional hazard model.
‡ Based on a stratified log-rank test. One-sided p-value, with a prespecified boundary of 0.0043.
§ Difference in ORR is not statistically significant.
\+ Denotes a censored value.



Reference ID: 4761679

**Figure 11: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-204**




| Number at Risk | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| KEYTRUDA: | 151 | 116 | 96 | 74 | 65 | 55 | 44 | 35 | 18 | 15 | 9 | 4 | 1 | 0 | 0 |
| Brentuximab Vedotin: | 153 | 103 | 63 | 41 | 32 | 26 | 19 | 14 | 10 | 7 | 5 | 2 | 1 | 0 | 0 |

*KEYNOTE-087*

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

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

Efficacy results for KEYNOTE-087 are summarized in Table 50.

**Table 50: Efficacy Results in Patients with cHL in KEYNOTE-087**

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

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

## 14.6 Primary Mediastinal Large B-Cell Lymphoma

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

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

For the 24 responders, the median time to first objective response (complete or partial response) was 2.8 months (range 2.1 to 8.5 months). Efficacy results for KEYNOTE-170 are summarized in Table 51.

**Table 51: Efficacy Results in Patients with PMBCL in KEYNOTE-170**

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

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

## 14.7 Urothelial 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 and DoR as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

The study population characteristics were: median age of 74 years; 77% male; and 89% White. Eighty-seven percent had M1 disease, and 13% had M0 disease. Eighty-one percent had a primary tumor in the lower tract, and 19% of patients had a primary tumor in the upper tract. Eighty-five percent of patients had visceral metastases, including 21% with liver metastases. 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 52.

**Table 52: 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 response
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.



Reference ID: 4761679

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 53 and Figure 12 summarize the efficacy results for KEYNOTE-045.



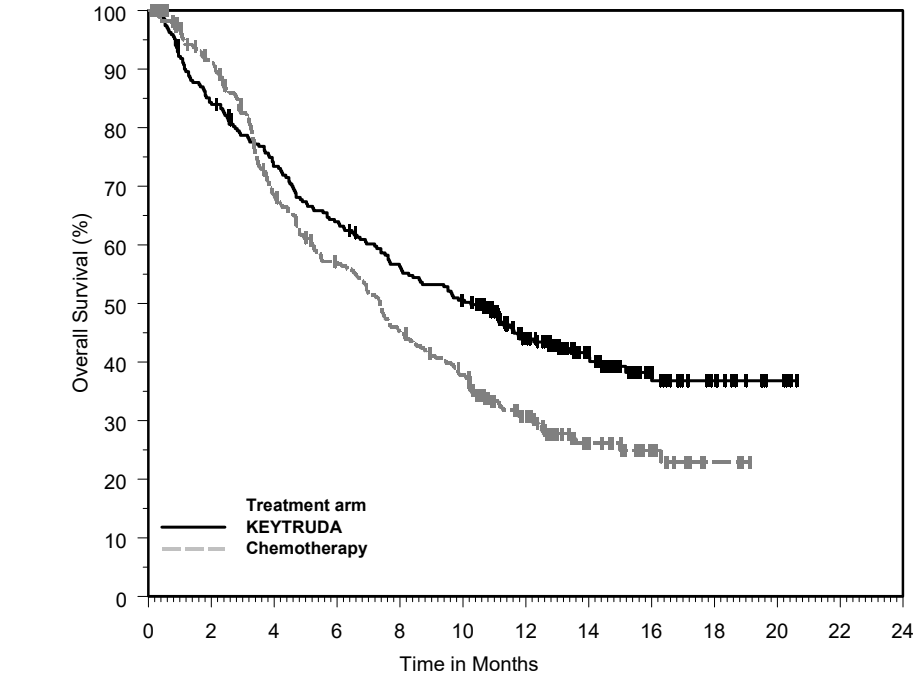
Reference ID: 4761679

**Table 53: Efficacy Results in KEYNOTE-045**

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

* Hazard ratio (KEYTRUDA compared to chemotherapy) based on the stratified Cox proportional hazard model
\+ Denotes ongoing response
NR = not reached

**Figure 12: Kaplan-Meier Curve for Overall Survival in KEYNOTE-045**




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

BCG-unresponsive High-Risk Non-Muscle Invasive Bladder Cancer

The efficacy of KEYTRUDA was investigated in KEYNOTE-057 (NCT02625961), a multicenter, open-label, single-arm trial in 96 patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy. BCG-unresponsive high-risk NMIBC was



Reference ID: 4761679

defined as persistent disease despite adequate BCG therapy, disease recurrence after an initial tumor-free state following adequate BCG therapy, or T1 disease following a single induction course of BCG. Adequate BCG therapy was defined as administration of at least five of six doses of an initial induction course plus either of: at least two of three doses of maintenance therapy or at least two of six doses of a second induction course. Prior to treatment, all patients had undergone transurethral resection of bladder tumor (TURBT) to remove all resectable disease (Ta and T1 components). Residual CIS (Tis components) not amenable to complete resection was allowed. The trial excluded patients with muscle invasive (i.e., T2, T3, T4) locally advanced non-resectable or metastatic urothelial carcinoma, concurrent extra-vesical (i.e., urethra, ureter or renal pelvis) non-muscle invasive transitional cell carcinoma of the urothelium, or autoimmune disease or a medical condition that required immunosuppression.

Patients received KEYTRUDA 200 mg every 3 weeks until unacceptable toxicity, persistent or recurrent high-risk NMIBC, or progressive disease. Assessment of tumor status was performed every 12 weeks for two years and then every 24 weeks for three years, and patients without disease progression could be treated for up to 24 months. The major efficacy outcome measures were complete response (as defined by negative results for cystoscopy [with TURBT/biopsies as applicable], urine cytology, and computed tomography urography [CTU] imaging) and duration of response.

The study population characteristics were: median age of 73 years (range: 44 to 92); 44% age ≥75; 84% male; 67% White; and 73% and 27% with an ECOG performance status of 0 or 1, respectively. Tumor pattern at study entry was CIS with T1 (13%), CIS with high grade TA (25%), and CIS (63%). Baseline high-risk NMIBC disease status was 27% persistent and 73% recurrent. The median number of prior instillations of BCG was 12.

The median follow-up time was 28.0 months (range: 4.6 to 40.5 months). Efficacy results are summarized in Table 54.

**Table 54: Efficacy Results in KEYNOTE-057**

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

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

\+ Denotes ongoing response

### 14.8 Microsatellite Instability-High or Mismatch Repair Deficient Cancer

The efficacy of KEYTRUDA was investigated in 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.



Reference ID: 4761679

**Table 55: MSI-H Trials**

| Study | Design and Patient Population | Number of Patients | MSI-H/dMMR Testing | Dosage | Prior Therapy |
|---|---|---|---|---|---|
| **KEYNOTE-016**<br>NCT01876511 | • prospective, investigator-initiated<br>• 6 sites<br>• patients with CRC and other tumors | 28 CRC<br><br>30 non-CRC | local PCR or IHC | 10 mg/kg every 2 weeks | • CRC: ≥ 2 prior regimens<br>• Non-CRC: ≥1 prior regimen |
| **KEYNOTE-164**<br>NCT02460198 | • prospective international multi-center<br>• CRC | 61 | local PCR or IHC | 200 mg every 3 weeks | Prior fluoropyrimidine, oxaliplatin, and irinotecan +/- anti-VEGF/EGFR mAb |
| **KEYNOTE-012**<br>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**<br>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**<br>NCT02628067 | • prospective international multi-center enrollment of patients with MSI-H/dMMR non-CRC<br>• 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 56 and 57.



Reference ID: 4761679

**Table 56: 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 57: Response by Tumor Type**

| | N | Objective Response Rate n (%) | 95% CI | Duration of Response 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 Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer

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

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

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

Treatment with KEYTRUDA or chemotherapy continued until RECIST v1.1-defined progression of disease as determined by the investigator or unacceptable toxicity. Patients treated with KEYTRUDA without disease progression could be treated for up to 24 months. Assessment of tumor status was performed every 9 weeks. Patients randomized to chemotherapy were offered KEYTRUDA at the time of

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

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

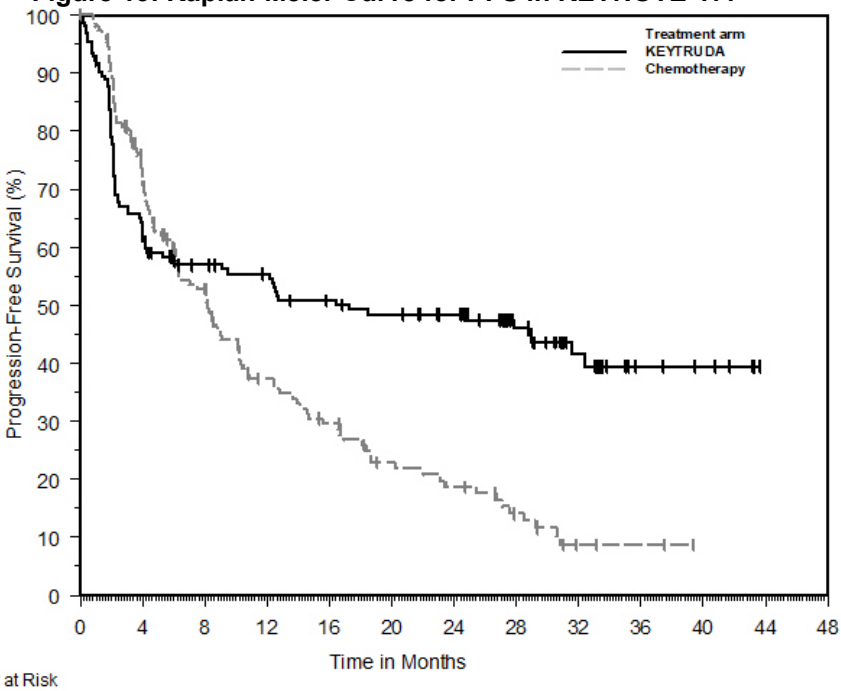
The trial demonstrated a statistically significant improvement in PFS for patients randomized to KEYTRUDA compared with chemotherapy. At the time of the PFS analysis, the overall survival data were not mature (66% of the required number of events for the OS final analysis). The median follow-up time was 27.6 months (range: 0.2 to 48.3 months). Table 58 and Figure 13 summarize the key efficacy measures for KEYNOTE-177.

**Table 58: Efficacy Results in Patients with MSI-H or dMMR CRC in KEYNOTE-177**

| **Endpoint** | **KEYTRUDA 200 mg every 3 weeks n=153** | **Chemotherapy n=154** |
|---|---|---|
| **PFS** | | |
| Number (%) of patients with event | 82 (54%) | 113 (73%) |
| Median in months (95% CI) | 16.5 (5.4, 32.4) | 8.2 (6.1, 10.2) |
| Hazard ratio* (95% CI) | 0.60 (0.45, 0.80) | |
| p-Value† | 0.0004 | |
| **Objective Response Rate‡** | | |
| ORR (95% CI) | 44% (35.8, 52.0) | 33% (25.8, 41.1) |
| Complete response rate | 11% | 4% |
| Partial response rate | 33% | 29% |
| **Duration of Response‡,§** | | |
| Median in months (range) | NR (2.3+, 41.4+) | 10.6 (2.8, 37.5+) |
| % with duration ≥12 months¶ | 75% | 37% |
| % with duration ≥24 months¶ | 43% | 18% |

* Based on Cox regression model
† Two-sided p-value based on log-rank test (compared to a significance level of 0.0234)
‡ Based on confirmed response by BICR review
§ Based on n=67 patients with a response in the KEYTRUDA arm and n=51 patients with a response in the chemotherapy arm
¶ Based on observed duration of response
\+ Denotes ongoing response
NR = not reached

**Figure 13: Kaplan-Meier Curve for PFS in KEYNOTE-177**




| Number at Risk | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| KEYTRUDA: | 153 | 96 | 77 | 72 | 64 | 60 | 55 | 37 | 20 | 7 | 5 | 0 | 0 |
| Chemotherapy: | 154 | 100 | 68 | 43 | 33 | 22 | 18 | 11 | 4 | 3 | 0 | 0 | 0 |

### 14.10 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.

### 14.11 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 59 and Figure 14 summarize the key efficacy measures for KEYNOTE-181 for patients with ESCC CPS ≥10.



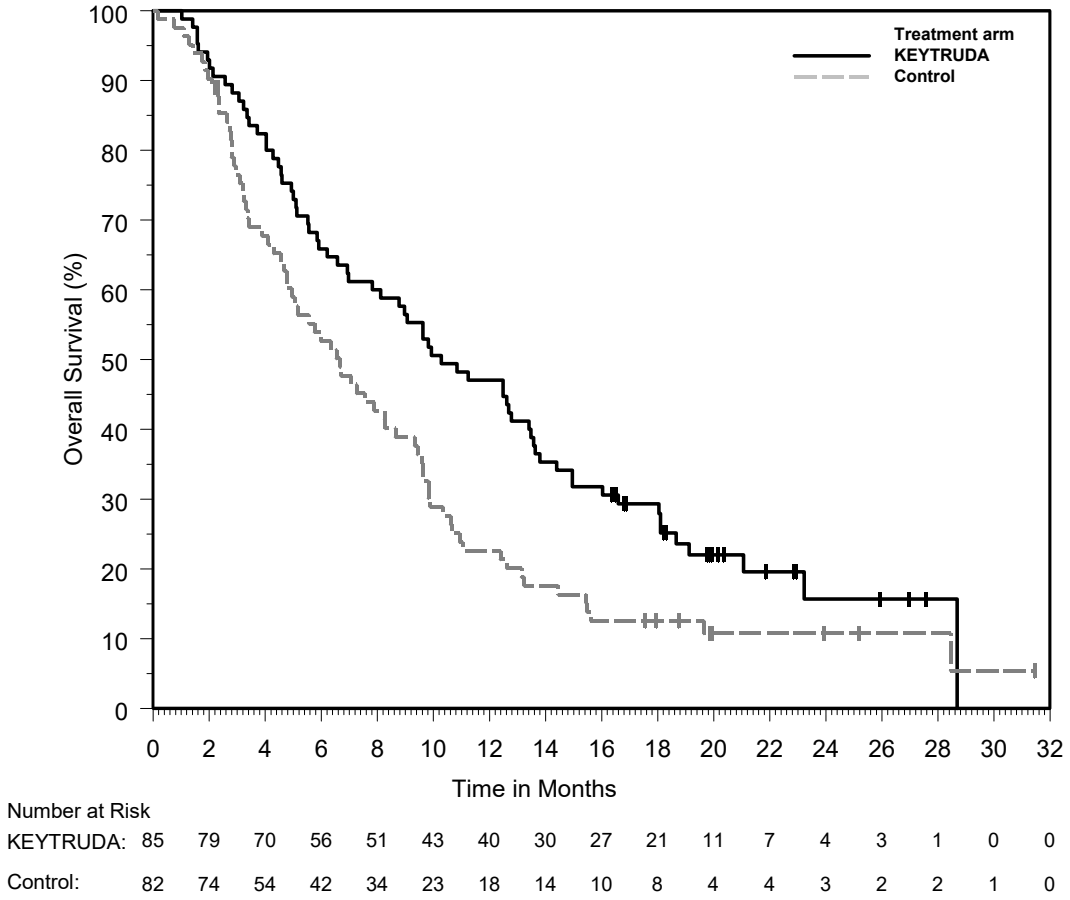
Reference ID: 4761679

**Table 59: 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 14: 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



Reference ID: 4761679

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

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

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

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

### 14.12 Cervical Cancer

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

**Table 60: Efficacy Results in Patients with Recurrent or Metastatic Cervical Cancer (CPS ≥1) in KEYNOTE-158**

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

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

### 14.13 Hepatocellular Carcinoma

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



Reference ID: 4761679

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 61.

**Table 61: 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

### 14.14 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 62.



Reference ID: 4761679

**Table 62: 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.
\+ Denotes ongoing response

### 14.15 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 63 and Figure 15 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.



Reference ID: 4761679

**Table 63: Efficacy Results in KEYNOTE-426**

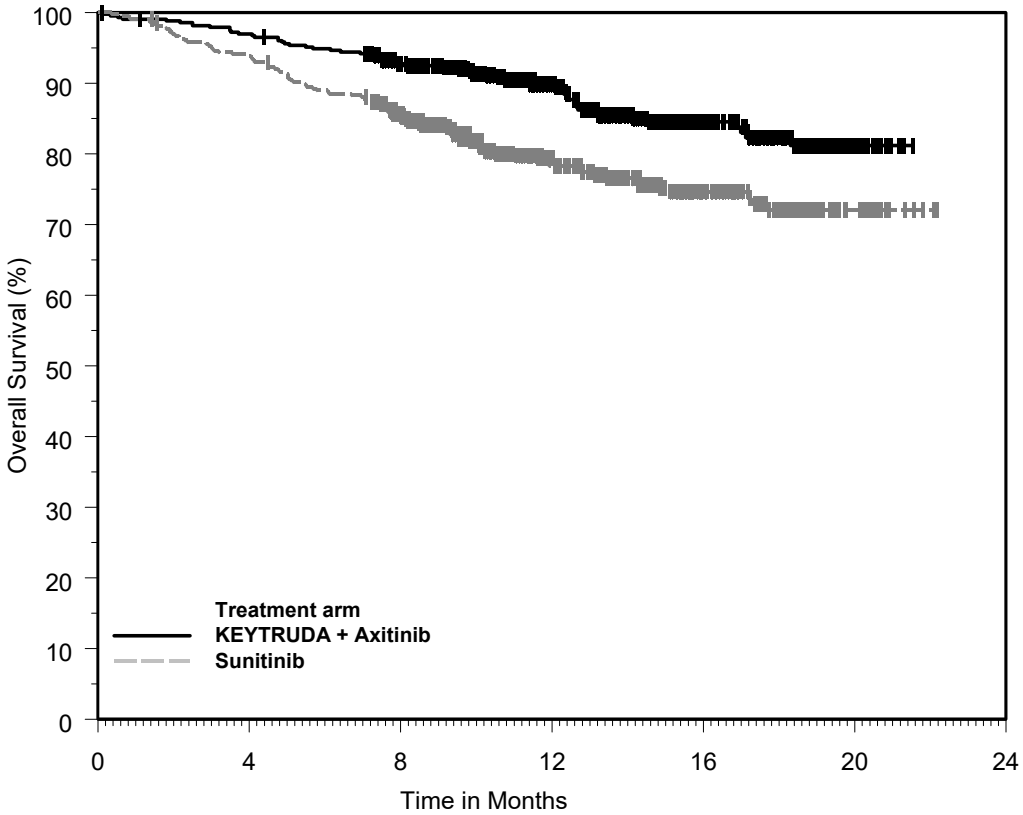
| Endpoint | KEYTRUDA 200 mg every 3 weeks and Axitinib n=432 | Sunitinib n=429 |
|---|---|---|
| **OS** | | |
| Number of patients with event (%) | 59 (14%) | 97 (23%) |
| Median in months (95% CI) | NR (NR, NR) | NR (NR, NR) |
| Hazard ratio* (95% CI) | 0.53 (0.38, 0.74) | |
| p-Value† | <0.0001‡ | |
| 12-month OS rate | 90% (86, 92) | 78% (74, 82) |
| **PFS** | | |
| Number of patients with event (%) | 183 (42%) | 213 (50%) |
| Median in months (95% CI) | 15.1 (12.6, 17.7) | 11.0 (8.7, 12.5) |
| Hazard ratio* (95% CI) | 0.69 (0.56, 0.84) | |
| p-Value† | 0.0001§ | |
| **Objective Response Rate** | | |
| ORR¶ (95% CI) | 59% (54, 64) | 36% (31, 40) |
| Complete response rate | 6% | 2% |
| Partial response rate | 53% | 34% |
| p-Value# | <0.0001 | |

* Based on the stratified Cox proportional hazard model
† Based on stratified log-rank test
‡ p-Value (one-sided) is compared with the allocated alpha of 0.0001 for this interim analysis (with 39% of the planned number of events for final analysis).
§ p-Value (one-sided) is compared with the allocated alpha of 0.0013 for this interim analysis (with 81% of the planned number of events for final analysis).
¶ Response: Best objective response as confirmed complete response or partial response
\# Based on Miettinen and Nurminen method stratified by IMDC risk group and geographic region
NR = not reached



Reference ID: 4761679

**Figure 15: Kaplan-Meier Curve for Overall Survival in KEYNOTE-426**




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

### 14.16 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 ORR and DoR as assessed by BICR 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 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; 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 64.

**Table 64: 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 response
NR = not reached

### 14.17 Tumor Mutational Burden-High Cancer

The efficacy of KEYTRUDA was investigated in a prospectively-planned retrospective analysis of 10 cohorts (A through J) of patients with various previously treated unresectable or metastatic solid tumors with high tumor mutation burden (TMB-H) who were enrolled in a multicenter, non-randomized, open-label trial, KEYNOTE-158 (NCT02628067). The trial excluded patients who previously received an anti-PD-1 or other immune-modulating monoclonal antibody, or who had an autoimmune disease, or a medical condition that required immunosuppression. Patients received KEYTRUDA 200 mg intravenously every 3 weeks until unacceptable toxicity or documented disease progression. Assessment of tumor status was performed every 9 weeks for the first 12 months and every 12 weeks thereafter.

The statistical analysis plan pre-specified ≥10 and ≥13 mutations per megabase using the FoundationOne CDx assay as cutpoints to assess TMB. Testing of TMB was blinded with respect to clinical outcomes. The major efficacy outcome measures were ORR and DoR in patients who received at least one dose of KEYTRUDA as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

In KEYNOTE-158, 1050 patients were included in the efficacy analysis population. TMB was analyzed in the subset of 790 patients with sufficient tissue for testing based on protocol-specified testing requirements. Of the 790 patients, 102 (13%) had tumors identified as TMB-H, defined as TMB ≥10 mutations per megabase. Among the 102 patients with TMB-H advanced solid tumors, the study population characteristics were: median age of 61 years (range: 27 to 80), 34% age 65 or older; 34% male; 81% White; and 41% ECOG PS of 0 and 58% ECOG PS of 1. Fifty-six percent of patients had at least two prior lines of therapy.

Efficacy results are summarized in Tables 65 and 66.

**Table 65: Efficacy Results for Patients with TMB-H Cancer in KEYNOTE-158**

| Endpoint | KEYTRUDA 200 mg every 3 weeks | |
|---|---|---|
| | TMB ≥10 mut/Mb n=102* | TMB ≥13 mut/Mb n=70 |
| **Objective Response Rate** | | |
| ORR (95% CI) | 29% (21, 39) | 37% (26, 50) |
| Complete response rate | 4% | 3% |
| Partial response rate | 25% | 34% |
| **Duration of Response** | n=30 | n=26 |
| Median in months (range)† | NR (2.2+, 34.8+) | NR (2.2+, 34.8+) |
| % with duration ≥12 months | 57% | 58% |
| % with duration ≥24 months | 50% | 50% |

* Median follow-up time of 11.1 months
† From product-limit (Kaplan-Meier) method for censored data
\+ Denotes ongoing response
NR = not reached

**Table 66: Response by Tumor Type (TMB ≥10 mut/Mb)**

| | N | Objective Response Rate n (%) | 95% CI | Duration of Response range (months) |
|---|---|---|---|---|
| **Overall*** | 102 | 30 (29%) | (21%, 39%) | (2.2+, 34.8+) |
| Small cell lung cancer | 34 | 10 (29%) | (15%, 47%) | (4.1, 32.5+) |
| Cervical cancer | 16 | 5 (31%) | (11%, 59%) | (3.7+, 34.8+) |
| Endometrial cancer | 15 | 7 (47%) | (21%, 73%) | (8.4+, 33.9+) |
| Anal cancer | 14 | 1 (7%) | (0.2%, 34%) | 18.8+ |
| Vulvar cancer | 12 | 2 (17%) | (2%, 48%) | (8.8, 11.0) |
| Neuroendocrine cancer | 5 | 2 (40%) | (5%, 85%) | (2.2+, 32.6+) |
| Salivary cancer | 3 | PR, SD, PD | | 31.3+ |
| Thyroid cancer | 2 | CR, CR | | (8.2, 33.2+) |
| Mesothelioma cancer | 1 | PD | | |

* No TMB-H patients were identified in the cholangiocarcinoma cohort
CR = complete response
PR = partial response
SD = stable disease
PD = progressive disease

In an exploratory analysis in 32 patients enrolled in KEYNOTE-158 whose cancer had TMB ≥10 mut/Mb and <13 mut/Mb, the ORR was 13% (95% CI: 4%, 29%), including two complete responses and two partial responses.

### 14.18 Cutaneous Squamous Cell Carcinoma

The efficacy of KEYTRUDA was investigated in patients with recurrent or metastatic cSCC enrolled in KEYNOTE-629 (NCT03284424), a multicenter, multi-cohort, non-randomized, open-label trial. The trial excluded patients with autoimmune disease or a medical condition that required immunosuppression.

Patients received KEYTRUDA 200 mg intravenously every 3 weeks until documented disease progression, unacceptable toxicity, or a maximum of 24 months. Patients with initial radiographic disease progression could receive additional doses of KEYTRUDA during confirmation of progression unless disease progression was symptomatic, rapidly progressive, required urgent intervention, or occurred with a decline in performance status.

Assessment of tumor status was performed every 6 weeks during the first year, and every 9 weeks during the second year. The major efficacy outcome measures were ORR and DoR as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

Among the 105 patients treated, the study population characteristics were: median age of 72 years (range: 29 to 95), 71% age 65 or older; 76% male; 71% White, 25% race unknown; 34% ECOG PS of 0 and 66% ECOG PS of 1. Forty-five percent of patients had locally recurrent only cSCC, 24% had

metastatic only cSCC, and 31% had both locally recurrent and metastatic cSCC. Eighty-seven percent received one or more prior lines of therapy; 74% received prior radiation therapy.

Efficacy results are summarized in Table 67.

**Table 67: Efficacy Results in KEYNOTE-629**

| Endpoint | KEYTRUDA n=105 |
|---|---|
| **Objective Response Rate** | |
| ORR (95% CI) | 34% (25, 44) |
| Complete response rate | 4% |
| Partial response rate | 31% |
| **Duration of Response*** | n=36 |
| Median in months (range) | NR (2.7, 13.1+)† |
| % with duration ≥6 months | 69% |

* Median follow-up time of 9.5 months
† Based on patients (n=36) with a confirmed response by independent review
\+ Denotes ongoing response

### 14.19 Triple-Negative Breast Cancer

The efficacy of KEYTRUDA in combination with paclitaxel, paclitaxel protein-bound, or gemcitabine and carboplatin was investigated in KEYNOTE-355 (NCT02819518), a multicenter, double-blind, randomized, placebo-controlled trial conducted in 847 patients with locally recurrent unresectable or metastatic TNBC, regardless of tumor PD-L1 expression, who had not been previously treated with chemotherapy in the metastatic setting. Patients with active autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Randomization was stratified by chemotherapy treatment (paclitaxel or paclitaxel protein-bound vs. gemcitabine and carboplatin), tumor PD-L1 expression (CPS ≥1 vs. CPS <1) according to the PD-L1 IHC 22C3 pharmDx kit, and prior treatment with the same class of chemotherapy in the neoadjuvant setting (yes vs. no).

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

- KEYTRUDA 200 mg on Day 1 every 3 weeks in combination with paclitaxel protein-bound 100 mg/m$^2$ on Days 1, 8 and 15 every 28 days, paclitaxel 90 mg/m$^2$ on Days 1, 8, and 15 every 28 days, or gemcitabine 1000 mg/m$^2$ and carboplatin AUC 2 mg/mL/min on Days 1 and 8 every 21 days.
- Placebo on Day 1 every 3 weeks in combination with paclitaxel protein-bound 100 mg/m$^2$ on Days 1, 8 and 15 every 28 days, paclitaxel 90 mg/m$^2$ on Days 1, 8, and 15 every 28 days, or gemcitabine 1000 mg/m$^2$ and carboplatin AUC 2 mg/mL/min on Days 1 and 8 every 21 days.

Assessment of tumor status was performed at Weeks 8, 16, and 24, then every 9 weeks for the first year, and every 12 weeks thereafter. The main efficacy outcome 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 tested in the subgroup of patients with CPS ≥10. Additional efficacy outcome measures were OS as well as ORR and DoR as assessed by BICR.

The study population characteristics for patients were: median age of 53 years (range: 22 to 85), 21% age 65 or older; 100% female; 68% White, 21% Asian, and 4% Black; 60% ECOG PS of 0 and 40% ECOG PS of 1; and 68% were post-menopausal status. Seventy-five percent of patients had tumor PD-L1 expression CPS ≥1 and 38% had tumor PD-L1 expression CPS ≥10.

Table 68 and Figure 16 summarize the efficacy results for KEYNOTE-355.



Reference ID: 4761679

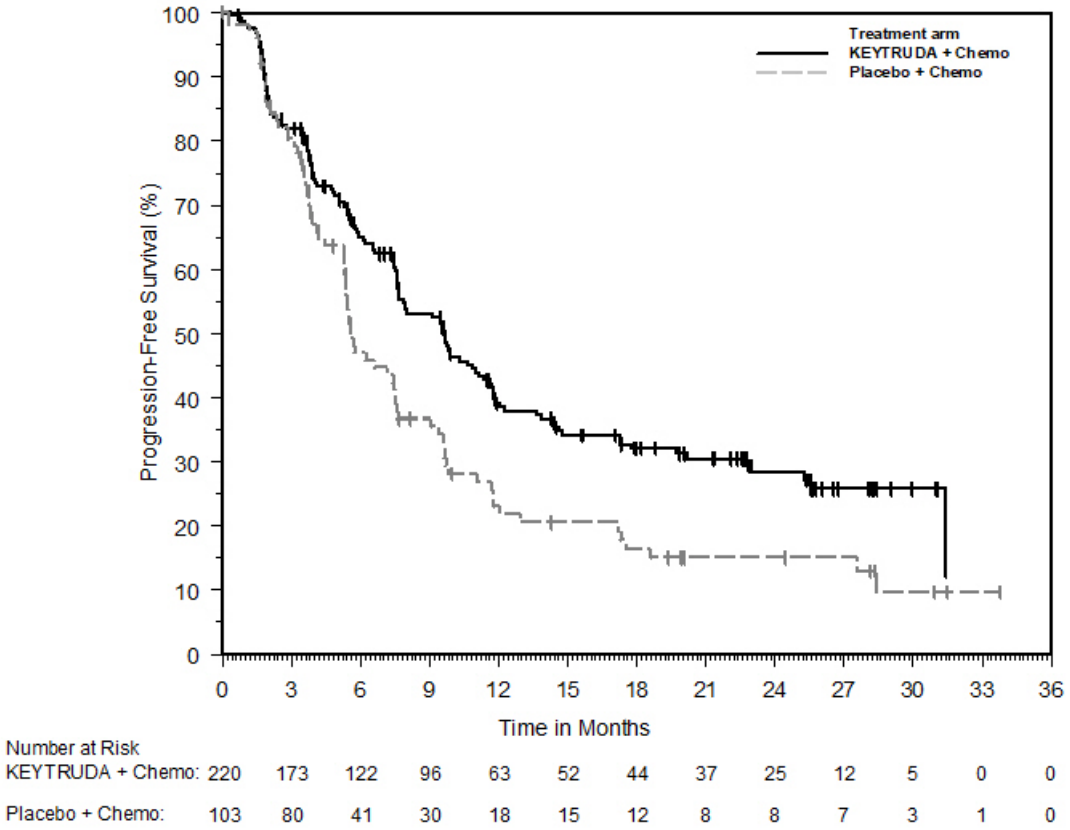
**Table 68: Efficacy Results in KEYNOTE-355 (CPS ≥10)**

| Endpoint | KEYTRUDA 200 mg every 3 weeks with chemotherapy n=220 | Placebo every 3 weeks with chemotherapy n=103 |
|---|---|---|
| **PFS** | | |
| Number of patients with event (%) | 136 (62%) | 79 (77%) |
| Median in months (95% CI) | 9.7 (7.6, 11.3) | 5.6 (5.3, 7.5) |
| Hazard ratio* (95% CI) | 0.65 (0.49, 0.86) | |
| p-Value† | 0.0012 | |
| **ORR** | | |
| Objective confirmed response rate (95% CI) | 53% (46, 60) | 40% (30, 50) |
| Complete response rate | 17% | 13% |
| Partial response rate | 36% | 27% |
| **DoR** | | |
| Median in months (95% CI) | 19.3 (9.9, 29.8) | 7.3 (5.3, 15.8) |

* Based on stratified Cox regression model

† One-sided p-Value based on stratified log-rank test

**Figure 16: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-355 (CPS ≥10)**




### 14.20 Adult Indications: Additional Dosing Regimen of 400 mg Every 6 Weeks

The efficacy and safety of KEYTRUDA using a dosage of 400 mg every 6 weeks for all approved adult indications was primarily based on the modeling of dose/exposure efficacy and safety relationships and observed pharmacokinetic data in patients with melanoma *[see Clinical Pharmacology (12.2)].*

## 16 HOW SUPPLIED/STORAGE AND HANDLING

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

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

## 17 PATIENT COUNSELING INFORMATION

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

Immune-Mediated Adverse Reactions

- Inform patients of the risk of immune-mediated adverse reactions that may be severe or fatal, may occur after discontinuation of treatment, and may require corticosteroid treatment and interruption or discontinuation of KEYTRUDA. These reactions may include:
  - Pneumonitis: Advise patients to contact their healthcare provider immediately for new or worsening cough, chest pain, or shortness of breath *[see Warnings and Precautions (5.1)]*.
  - Colitis: Advise patients to contact their healthcare provider immediately for diarrhea or severe abdominal pain *[see Warnings and Precautions (5.1)]*.
  - Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, or easy bruising or bleeding *[see Warnings and Precautions (5.1)]*.
  - Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of adrenal insufficiency, hypophysitis, hypothyroidism, hyperthyroidism, or Type 1 diabetes mellitus *[see Warnings and Precautions (5.1)]*.
  - Nephritis: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis *[see Warnings and Precautions (5.1)]*.
  - Severe skin reactions: Advise patients to contact their healthcare provider immediately for any signs or symptoms of severe skin reactions, SJS or TEN *[see Warnings and Precautions (5.1)]*.
  - Other immune-mediated adverse reactions:
    - Advise patients that immune-mediated adverse reactions can occur and may involve any organ system, and to contact their healthcare provider immediately for any new or worsening signs or symptoms *[see Warnings and Precautions (5.1)]*.
    - Advise patients of the risk of solid organ transplant rejection and to contact their healthcare provider immediately for signs or symptoms of organ transplant rejection *[see Warnings and Precautions (5.1)]*.

Infusion-Related Reactions

- Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion-related reactions *[see Warnings and Precautions (5.2)]*.

Complications of Allogeneic HSCT

- Advise patients of the risk of post-allogeneic hematopoietic stem cell transplantation complications *[see Warnings and Precautions (5.3)].*

Embryo-Fetal Toxicity

- Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.5), Use in Specific Populations (8.1, 8.3)].*

- Advise females of reproductive potential to use effective contraception during treatment with KEYTRUDA and for 4 months after the last dose *[see Warnings and Precautions (5.5), Use in Specific Populations (8.1, 8.3)]*.



Reference ID: 4761679

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 (5.1)]*.

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