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**KEYTRUDA® 100 mg/4 mL (pembrolizumab)  
Concentrate for Solution for Intravenous Infusion**

**Patient Card**

The marketing of KEYTRUDA is subject to a risk management plan (RMP) including a Patient Card. The Patient Card emphasizes important safety information that the patient should be aware of before and during treatment. Please explain to the patient the need to review the card before starting treatment.

## **1 THERAPEUTIC INDICATIONS**

### **1.1 Melanoma**

KEYTRUDA is indicated for the treatment of adult and pediatric (12 years and older) patients with unresectable or metastatic melanoma.

KEYTRUDA is indicated for the adjuvant treatment of adult and pediatric (12 years and older) patients with Stage IIB, IIC, or III melanoma following complete resection.

### **1.2 Non-Small Cell Lung Cancer**

KEYTRUDA, in combination with pemetrexed and carboplatin, is indicated for the first-line treatment of patients with metastatic nonsquamous non-small cell lung cancer (NSCLC) negative for 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 treatment of patients with metastatic NSCLC whose tumors express PD-L1 [Tumor Proportion Score (TPS)  $\geq 50\%$ ] as determined by a validated test. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on or after platinum-containing chemotherapy and an approved therapy for these aberrations prior to receiving KEYTRUDA

KEYTRUDA, as a single agent, is indicated for the treatment of patients with advanced NSCLC whose tumors express PD-L1 as determined by a validated test, with disease progression on or after platinum containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on approved therapy for these aberrations prior to receiving KEYTRUDA

KEYTRUDA, as a single agent, is indicated as adjuvant treatment following resection and platinum-based chemotherapy for adult patients with Stage IB (T2a  $\geq 4$  cm), II, or IIIA NSCLC.

### **1.3 Head and Neck 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)  $\geq 1$ ] as determined by a validated test [see *Dosage and Administration (2.1)*].

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

### **1.4 Classical Hodgkin Lymphoma**

KEYTRUDA is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL).

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

### **1.5 Primary Mediastinal large B-Cell Lymphoma**

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

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

### **1.6 Urothelial Cancer**

KEYTRUDA, as a single agent, is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (CPS  $\geq 10$ ) as determined by a validated test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.

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

### **1.7 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 systemic treatment and who have no satisfactory alternative treatment options, or
- colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan

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

### **1.8 Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer (CRC)**

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

### **1.9 Gastric Cancer**

KEYTRUDA, in combination with trastuzumab, fluoropyrimidine and platinum-containing chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction (GEJ) adenocarcinoma in adults whose tumors express PD-L1 with a CPS  $\geq 1$  as determined by a validated test.

KEYTRUDA, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adults with locally advanced unresectable or metastatic HER2-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1 with a CPS  $\geq 10$  or MSI-High, as determined by a validated test.

### **1.10 Esophageal Cancer**

KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic esophageal or gastroesophageal junction (GEJ) (Siewert type I) carcinoma that is not amenable to surgical resection or definitive chemoradiation in combination with platinum- and fluoropyrimidine-based chemotherapy.

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  $\geq 10$ ) as determined by a validated test, with disease progression after one or more prior lines of systemic therapy.

### **1.11 Cervical Cancer**

KEYTRUDA, in combination with chemotherapy, with or without bevacizumab, is indicated for the treatment of patients with persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1 (CPS  $\geq 1$ ) as determined by a validated test.

KEYTRUDA, as a single agent, is indicated for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS  $\geq 1$ ) as determined by a validated test.

### **1.12 Biliary Tract Cancer**

KEYTRUDA, in combination with gemcitabine and cisplatin, is indicated for the treatment of patients with locally advanced unresectable or metastatic biliary tract cancer (BTC).

### **1.13 Merkel Cell Carcinoma**

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

### **1.14 Renal Cell Carcinoma**

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

KEYTRUDA, in combination with lenvatinib, is indicated for the first-line treatment of adult patients with advanced RCC.

KEYTRUDA is indicated for the adjuvant treatment of patients with RCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.

### **1.15 Endometrial Carcinoma**

Keytruda, in combination with lenvatinib, is indicated for the treatment of advanced or recurrent endometrial carcinoma in adults who have disease progression on or following prior treatment with a platinum-containing therapy and who are not candidates for curative surgery or radiation.

### **1.16 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) [ $\geq 10$  mutations/megabase (mut/Mb)] solid tumors, as determined by a validated test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.

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

### **1.17 Cutaneous Squamous Cell Carcinoma**

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

### **1.18 Triple Negative Breast Cancer**

KEYTRUDA is indicated for the treatment of patients with high-risk early-stage triple-negative breast cancer (TNBC) in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.

KEYTRUDA, in combination with chemotherapy, is indicated for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 (CPS  $\geq 10$ ) as determined by a validated test.

## **2 DOSAGE AND ADMINISTRATION**

### **2.1 Patient Selection**

#### Patient Selection for Single Agent Treatment

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

- metastatic NSCLC [see *Clinical Studies (14.2)*].

- first-line treatment of metastatic or unresectable, recurrent HNSCC [see *Clinical Studies (14.3)*].
- metastatic urothelial carcinoma [see *Clinical Studies (14.6)*].
- previously treated recurrent locally advanced or metastatic esophageal cancer [see *Clinical Studies (14.10)*].
- recurrent or metastatic cervical cancer with disease progression on or after chemotherapy [see *Clinical Studies (14.11)*].

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 (14.7, 14.8)*].

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 (14.16)*].

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.

#### Patient Selection for Combination Therapy

For use of KEYTRUDA in combination with chemotherapy and trastuzumab, select patients based on the presence of positive PD-L1 expression (CPS  $\geq 1$ ) in locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma [see *Clinical Studies (14.9)*].

For use of KEYTRUDA in combination with chemotherapy, with or without bevacizumab, select patients based on the presence of positive PD-L1 expression in persistent, recurrent, or metastatic cervical cancer [see *Clinical Studies (14.11)*].

For use of KEYTRUDA in combination with chemotherapy, select patients based on the presence of positive PD-L1 expression in locally recurrent unresectable or metastatic TNBC [see *Clinical Studies (14.18)*].

## **2.2 Recommended Dosage for Melanoma**

The recommended dose of KEYTRUDA in patients with unresectable or metastatic melanoma is 200 mg or 2 mg/kg, according to treating physician's discretion, administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity.

The recommended dose of KEYTRUDA for the treatment of pediatric patients (12 years and older) with unresectable or metastatic melanoma is 2 mg/kg (up to a maximum of 200 mg) administered as an intravenous infusion over 30 minutes every 3 weeks until disease recurrence or unacceptable toxicity.

The recommended dose of KEYTRUDA for the adjuvant treatment of adult patients with melanoma is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease recurrence, unacceptable toxicity, or for up to 12 months.

The recommended dose of KEYTRUDA for the adjuvant treatment of pediatric patients (12 years and older) with melanoma is 2 mg/kg (up to a maximum of 200 mg) administered as an intravenous infusion over 30 minutes every 3 weeks until disease recurrence, unacceptable toxicity, or up to 12 months.

## **2.3 Recommended Dosage for NSCLC**

For first-line treatment:

The recommended dose of KEYTRUDA is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months.

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

For second-line or greater treatment:

The recommended dose of KEYTRUDA is 200 mg or 2 mg/kg, according to treating physician's discretion, administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months.

For adjuvant treatment:

The recommended dose of KEYTRUDA for the adjuvant treatment of adult patients with NSCLC is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease recurrence, unacceptable toxicity, or for up to 12 months.

#### **2.4 Recommended Dosage for HNSCC**

The recommended dose of KEYTRUDA is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months.

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

#### **2.5 Recommended Dosage for cHL**

The recommended dose of KEYTRUDA in adults is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity, or up to 24 months.

The recommended dose of KEYTRUDA in pediatric patients is 2 mg/kg (up to a maximum of 200 mg), administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity, or up to 24 months.

#### **2.6 Recommended Dosage for PMBCL**

The recommended dose of KEYTRUDA in adults is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months.

The recommended dose of KEYTRUDA in pediatric patients is 2 mg/kg (up to a maximum of 200 mg), administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity, or up to 24 months.

#### **2.7 Recommended Dosage for Urothelial Cancer**

The recommended dose of KEYTRUDA in patients with locally advanced or metastatic urothelial carcinoma is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity, or up to 24 months.

The recommended dose of KEYTRUDA in patients with high-risk BCG-unresponsive non-muscle invasive bladder cancer is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until persistent or recurrent high-risk NMIBC, disease progression or unacceptable toxicity, or up to 24 months.

#### **2.8 Recommended Dosage for MSI-H or dMMR Cancer**

The recommended dose of KEYTRUDA in adults is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months.

The recommended dose of KEYTRUDA in children is 2 mg/kg (up to a maximum of 200 mg), administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity, or up to 24 months.

#### **2.9 Recommended Dosage for MSI-H or dMMR colorectal cancer (CRC)**

The recommended dose of KEYTRUDA in adults is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months.

#### **2.10 Recommended Dosage for Gastric Cancer**

The recommended dose of KEYTRUDA in adult is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months.

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

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

### **2.11 Recommended Dosage for Esophageal Cancer**

The recommended dose of KEYTRUDA is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months. When administering KEYTRUDA in combination with chemotherapy, administer KEYTRUDA prior to chemotherapy when given on the same day. Refer to the Prescribing Information for the chemotherapy agents administered in combination with KEYTRUDA, for recommended dosing information, as appropriate.

### **2.12 Recommended Dosage for Cervical Cancer**

The recommended dose of KEYTRUDA in adults is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or for KEYTRUDA up to 24 months.

For combination therapy, administer KEYTRUDA prior to chemotherapy with or without bevacizumab when given on the same day. Refer to the Prescribing Information for the agents administered in combination with KEYTRUDA for recommended dosing information, as appropriate.

### **2.13 Recommended Dosage for Biliary Tract Cancer**

The recommended dose of KEYTRUDA is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months.

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

### **2.14 Recommended Dosage for MCC**

The recommended dose of KEYTRUDA in adults is 200 mg or 2 mg/kg, according to treating physician's discretion, administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months.

The recommended dose of KEYTRUDA in pediatric patients is 2 mg/kg (up to a maximum of 200 mg), administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity, or up to 24 months.

### **2.15 Recommended Dosage for RCC**

The recommended dose of KEYTRUDA is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks in combination with 5 mg axitinib orally twice daily or in combination with lenvatinib 20 mg orally once daily until disease progression, unacceptable toxicity, or for KEYTRUDA, up to 24 months. 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. Refer to the Prescribing Information for the agents administered in combination with KEYTRUDA for recommended dosing information, as appropriate.

The recommended dose of KEYTRUDA for the adjuvant treatment of adult patients with RCC is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease recurrence, unacceptable toxicity, or for up to 12 months.

### **2.16 Recommended Dosage for Endometrial Carcinoma**

The recommended dose of KEYTRUDA is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks in combination with lenvatinib 20 mg orally once daily until disease progression, unacceptable toxicity, or for KEYTRUDA, up to 24 months. Refer to the Prescribing Information for the agents administered in combination with KEYTRUDA for recommended dosing information, as appropriate.

### 2.17 Recommended Dosage for TMB-H Cancer

The recommended dose of KEYTRUDA in adults is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months.

The recommended dose of KEYTRUDA in pediatric is 2 mg/kg (up to a maximum of 200 mg), administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity, or up to 24 months.

### 2.18 Recommended Dosage for cSCC

The recommended dose of KEYTRUDA in adults is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months.

### 2.19 Recommended Dosage for TNBC

The recommended dose of KEYTRUDA in adult patients with high-risk early-stage TNBC for neoadjuvant treatment is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks in combination with chemotherapy for 24 weeks (8 doses of 200mg every 3 weeks) or until disease progression or unacceptable toxicity, followed by adjuvant treatment with KEYTRUDA as a single agent for up to 27 weeks (9 doses of 200 mg every 3 weeks) or until disease recurrence or unacceptable toxicity.

Administer KEYTRUDA prior to chemotherapy when given on the same day. Refer to the Prescribing Information for the chemotherapy agents administered in combination with KEYTRUDA, for recommended dosing information, as appropriate. Patients who experience disease progression or unacceptable toxicity related to KEYTRUDA with neoadjuvant treatment in combination with chemotherapy should not receive adjuvant single agent KEYTRUDA.

The recommended dose of KEYTRUDA in patients with locally recurrent unresectable or metastatic TNBC is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks in combination to chemotherapy until disease progression, unacceptable toxicity, or up to 24 months.

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

### 2.20 Dose Modifications

No dose reduction for KEYTRUDA is recommended. In general, withhold KEYTRUDA for severe (Grade 3) immune-mediated adverse reactions. Permanently discontinue KEYTRUDA for Life-threatening (Grade 4) immune-mediated adverse reactions, recurrent severe (Grade 3) immune-mediated reactions that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating steroids.

Dosage modifications for KEYTRUDA for adverse reactions that require management different from these general guidelines are summarized in Table 1

Table 1 : Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity*	Dosage Modification
<b>Immune-Mediated Adverse Reactions</b> [see Warnings and Precautions (5.1)]		
Pneumonitis	Grade 2	Withhold <sup>†</sup>
	Grade 3 or 4	Permanently discontinue
Colitis	Grade 2 or 3	Withhold <sup>†</sup>
	Grade 4	Permanently discontinue
Hepatitis with no tumor involvement of the liver  For liver enzyme elevations in patients treated with combination	AST or ALT increases to more than 3 and up to 8 times ULN or Total bilirubin increases to more than 1.5 and up to 3 times ULN	Withhold <sup>†</sup>

Adverse Reaction	Severity*	Dosage Modification
therapy with axitinib, see Table 2.	AST or ALT increases to more than 8 times ULN or Total bilirubin increases to more than 3 times ULN	Permanently discontinue
Hepatitis with tumor involvement of the liver†	Baseline AST or ALT is more than 1 and up to 3 times ULN and increases to more than 5 and up to 10 times ULN or Baseline AST or ALT is more than 3 and up to 5 times ULN and increases to more than 8 and up to 10 times ULN	Withhold‡
	ALT or AST increases to more than 10 times ULN or Total bilirubin increases to more than 3 times ULN	Permanently discontinue
Endocrinopathies	Grade 3 or 4	Withhold until clinically stable or permanently discontinue depending on severity
Nephritis with Renal Dysfunction	Grade 2 or 3 increased blood creatinine	Withhold‡
	Grade 4 increased blood creatinine	Permanently discontinue
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold‡
	Confirmed SJS, TEN, or DRESS	Permanently discontinue
Myocarditis	Grade 2, 3, or 4	Permanently discontinue
Neurological Toxicities	Grade 2	Withhold‡
	Grade 3 or 4	Permanently discontinue
Hematologic toxicity in patients with cHL or PMBCL	Grade 4	Withhold until resolution to Grades 0 or 1
<b>Other Adverse Reactions</b>		
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

Table 2 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 2: Recommended Specific Dosage Modifications for Adverse Reactions for KEYTRUDA in Combination with Axitinib**

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



Treatment	Adverse Reaction	Severity	Dosage Modification
		ALT or AST increases to more than 3 times ULN with concurrent total bilirubin at least 2 times ULN or ALT or AST $\geq$ 10 times ULN	Permanently discontinue both KEYTRUDA and axitinib

\* Consider corticosteroid therapy

† Based on Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Consider rechallenge with a single drug or sequential rechallenge with both drugs after recovery. If rechallenging with axitinib, consider dose reduction as per the axitinib Prescribing Information.

ALT = alanine aminotransferase, AST = aspartate aminotransferase, ULN = upper limit normal

### Recommended Dose Modifications for Adverse Reactions for KEYTRUDA in Combination with Lenvatinib

When administering KEYTRUDA in combination with lenvatinib, modify the dosage of one or both drugs. Withhold or discontinue KEYTRUDA as shown in Table 1. Refer to lenvatinib prescribing information for additional dose modification information.

## 2.21 Preparation and Administration

### Preparation for Intravenous Infusion

- Visually inspect the solution for particulate matter and discoloration prior to administration. The solution is clear to slightly opalescent, colorless to slightly yellow. Discard the vial if visible particles are observed.
- Dilute KEYTRUDA 100 mg/4 mL (concentrated 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.

From a microbiological point of view, the product, once diluted, should be used immediately. If not used immediately, 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 for no more than 96 hours from the time of dilution. If refrigerated, allow the diluted solution to come to room temperature prior to administration. Do not shake.

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

Do not freeze.

### Administration

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

## 3 DOSAGE FORMS AND STRENGTHS

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

## 4 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 11.

## 5 WARNINGS AND PRECAUTIONS

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

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

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

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

Withhold or permanently discontinue KEYTRUDA depending on severity [see *Dosage and Administration* (2.20)]. In general, if KEYTRUDA requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reactions are not controlled with corticosteroid therapy.

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

#### Immune-Mediated Pneumonitis

KEYTRUDA can cause immune-mediated pneumonitis. The incidence of pneumonitis is higher in patients who have received prior thoracic radiation. Immune-mediated pneumonitis occurred in 3.4% (94/2799) of patients receiving KEYTRUDA, including fatal (0.1%), Grade 4 (0.3%), Grade 3 (0.9%), and Grade 2 (1.3%) adverse reactions. Systemic corticosteroids were required in 67% (63/94) of patients with pneumonitis. Pneumonitis led to permanent discontinuation of KEYTRUDA in 1.3% (36) of patients and withholding of KEYTRUDA in 0.9% (26) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement; of these, 23% had recurrence of pneumonitis. Pneumonitis resolved in 59% of the 94 patients.

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

In a clinical study enrolling 580 adult patients with resected NSCLC (KEYNOTE-091) who received KEYTRUDA as a single agent for adjuvant treatment, pneumonitis occurred in 41 (7%) patients, including fatal (0.2%), Grade 4 (0.3%), and Grade 3 (1%) adverse reactions. Patients received high-dose corticosteroids for a median duration of 10 days (range: 1 day to 2.3 months). Pneumonitis led to discontinuation of KEYTRUDA in 26 (4.5%) of patients. Of the patients who developed pneumonitis, 54% interrupted KEYTRUDA, 63% discontinued KEYTRUDA, and 71% had resolution.

#### Immune-Mediated Colitis

KEYTRUDA can cause immune-mediated colitis, which may present with diarrhea. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies. Immune-mediated colitis occurred in 1.7% (48/2799) of patients receiving KEYTRUDA, including

Grade 4 (<0.1%), Grade 3 (1.1%), and Grade 2 (0.4%) adverse reactions. Systemic corticosteroids were required in 69% (33/48) of patients with colitis. Additional immunosuppressant therapy was required in 4.2% of patients. Colitis led to permanent discontinuation of KEYTRUDA in 0.5% (15) of patients and withholding of KEYTRUDA in 0.5% (13) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement; of these, 23% had recurrence of colitis. Colitis resolved in 85% of the 48 patients.

#### Hepatotoxicity and Immune-Mediated Hepatitis

##### *KEYTRUDA as a Single Agent*

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

##### *KEYTRUDA with Axitinib*

KEYTRUDA in combination with axitinib can cause hepatic toxicity with higher than expected frequencies of Grades 3 and 4 ALT and AST elevations compared to KEYTRUDA alone. Monitor liver enzymes before initiation of and periodically throughout treatment. Consider more frequent monitoring of liver enzymes as compared to when the drugs are administered as single agents. For elevated liver enzymes, interrupt KEYTRUDA and axitinib, and consider administering corticosteroids as needed [see *Dosage and Administration* (2.20)].

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  $\geq 3$  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  $\geq 3$  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  $\geq 3$  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* (2.20)].

Adrenal insufficiency occurred in 0.8% (22/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (0.3%), and Grade 2 (0.3%) adverse reactions. Systemic corticosteroids were required in 77% (17/22) of patients with adrenal insufficiency; of these, the majority remained on systemic corticosteroids. Adrenal insufficiency led to permanent discontinuation of KEYTRUDA in <0.1% (1) of patients and withholding of KEYTRUDA in 0.3% (8) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement.

##### *Hypophysitis*

KEYTRUDA can cause immune-mediated hypophysitis. Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism. Initiate hormone replacement as indicated. Withhold or permanently discontinue KEYTRUDA depending on severity [see *Dosage and Administration* (2.20)].

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. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders. Consider frequent monitoring of thyroid function when KEYTRUDA is administered in combination with axitinib or in combination with lenvatinib. 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* (2.20)].

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

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

The incidence of new or worsening hyperthyroidism was higher in 580 patients with resected NSCLC, occurring in 11% of patients receiving KEYTRUDA as a single agent as adjuvant treatment (KEYNOTE-091), including Grade 3 (0.2%) hyperthyroidism.

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

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

The incidence of new or worsening hypothyroidism was higher in 580 patients with resected NSCLC, occurring in 22% of patients receiving KEYTRUDA as a single agent as adjuvant treatment (KEYNOTE-091), including Grade 3 (0.3%) hypothyroidism.

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

Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold KEYTRUDA depending on severity [see *Dosage and Administration* (2.20)].

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

#### Immune-Mediated Nephritis with Renal Dysfunction

KEYTRUDA can cause immune-mediated nephritis. Immune-mediated nephritis occurred in 0.3% (9/2799) of patients receiving KEYTRUDA, including Grade 4 (<0.1%), Grade 3 (0.1%), and Grade 2 (0.1%) adverse reactions. Systemic corticosteroids were required in 89% (8/9) of patients with nephritis. Nephritis led to permanent discontinuation of KEYTRUDA in 0.1% (3) of patients and withholding of KEYTRUDA in 0.1% (3) of patients. All patients who were withheld reinitiated KEYTRUDA after symptom improvement; of these, none had recurrence of nephritis. Nephritis resolved in 56% of the 9 patients.

#### Immune-Mediated Dermatologic Adverse Reactions

KEYTRUDA can cause immune-mediated rash or dermatitis. Exfoliative dermatitis, including Stevens Johnson Syndrome, DRESS, and toxic epidermal necrolysis (TEN), has occurred with PD-1/PD-L1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes. Withhold or permanently discontinue KEYTRUDA depending on severity [see *Dosage and Administration* (2.20)].

Immune-mediated dermatologic adverse reactions occurred in 1.4% (38/2799) of patients receiving KEYTRUDA, including Grade 3 (1%) and Grade 2 (0.1%) adverse reactions. Systemic corticosteroids were

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

#### Other Immune-Mediated Adverse Reactions

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

*Cardiac/Vascular:* Myocarditis, pericarditis, vasculitis

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

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

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

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

*Endocrine:* Hypoparathyroidism

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

## **5.2 Infusion-Related Reactions**

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

For severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions, stop infusion and permanently discontinue KEYTRUDA [see *Dosage and Administration* (2.20)].

## **5.3 Complications of Allogeneic HSCT**

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/PD-L1 blocking antibody. Transplant-related complications include hyperacute graft-versus-host-disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease (VOD) after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between PD-1/PD-L1 blockade and allogeneic HSCT.

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

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

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

## 5.5 Embryo-Fetal Toxicity

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

## 5.6 Esophageal Cancer and Upper Gastrointestinal Hemorrhage

In the KEYTRUDA arm of the esophageal studies after one or more prior lines of therapy, there were 4 fatal events due to upper GI hemorrhage, in patients who had a history of prior radiation therapy to that area. A possible causal association between the events and pembrolizumab use cannot be ruled out.

## 5.7 Use of pembrolizumab in urothelial carcinoma for patients who are considered ineligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with CPS $\geq$ 10

The baseline and prognostic disease characteristics of the study population of KEYNOTE-052 included a proportion of patients eligible for a carboplatin-based combination, for whom the benefit has been assessed in a comparative study (KEYNOTE-361). In KEYNOTE-361, a higher number of deaths within 6 months of treatment initiation followed by a long-term survival benefit was observed with pembrolizumab monotherapy compared to chemotherapy (see section 14.6). No specific factor(s) associated with early deaths could be identified. Physicians should consider the delayed onset of pembrolizumab effect before initiating treatment in patients with urothelial carcinoma who are considered eligible for carboplatin-based combination chemotherapy. KEYNOTE-052 also included patients eligible for mono-chemotherapy, for whom no randomised data are available. In addition, no safety and efficacy data are available in frailer patients (e.g. ECOG performance status 3) considered not eligible for chemotherapy. In the absence of these data, pembrolizumab should be used with caution in this population after careful consideration of the potential risk-benefit on an individual basis.

## 6 ADVERSE REACTIONS

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

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

### 6.1 Clinical Trials Experience

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

The data described in the WARNINGS AND PRECAUTIONS reflect exposure to KEYTRUDA as a single agent in 2799 patients in three randomized, open-label, active-controlled trials (KEYNOTE 002, KEYNOTE 006, and KEYNOTE 010), which enrolled 912 patients with melanoma and 682 patients with NSCLC, and one single-arm trial (KEYNOTE 001), which enrolled 655 patients with melanoma and 550 patients with NSCLC. In addition to the 2799 patients, certain subsections in the WARNINGS AND PRECAUTIONS describe adverse reactions observed with exposure to KEYTRUDA as a single agent in a randomized, placebo-controlled trial (KEYNOTE-091), which enrolled 580 patients with resected NSCLC, a non-randomized, open-label, multi-cohort trial (KEYNOTE 012), a non-randomized, open-label, single-cohort trial (KEYNOTE-055), and two randomized, open-label, active controlled trials (KEYNOTE-040 and KEYNOTE-048 single agent arms), which enrolled 909 patients with HNSCC; in two non-randomized, open-label trials (KEYNOTE-013 and KEYNOTE-087), and one randomized, open-label, active-controlled trial (KEYNOTE-204), which enrolled 389 patients with cHL; in a randomized, open-label, active-controlled trial (KEYNOTE-048 combination arm), which enrolled 276 patients with HNSCC; in combination with axitinib in a randomized, active-controlled trial (KEYNOTE-426), which enrolled 429 patients with RCC; and in post-marketing use. Across all trials, KEYTRUDA was administered at doses of 2 mg/kg intravenously every 3 weeks, 10 mg/kg intravenously every 2 weeks, 10 mg/kg intravenously every 3 weeks, or 200 mg intravenously every 3 weeks. Among the 2799 patients, 41% were exposed for 6 months or more and 21% were exposed for 12 months or more.

## Melanoma

### *Ipilimumab-Naive Melanoma*

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

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

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

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

**Table 3: Selected\* Adverse Reactions Occurring in  $\geq 10\%$  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 <sup>†</sup> (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
<b>General</b>				
Fatigue	28	0.9	28	3.1
<b>Skin and Subcutaneous Tissue</b>				
Rash <sup>‡</sup>	24	0.2	23	1.2
Vitiligo <sup>§</sup>	13	0	2	0
<b>Musculoskeletal and Connective Tissue</b>				
Arthralgia	18	0.4	10	1.2
Back pain	12	0.9	7	0.8
<b>Respiratory, Thoracic and Mediastinal</b>				
Cough	17	0	7	0.4
Dyspnea	11	0.9	7	0.8
<b>Metabolism and Nutrition</b>				
Decreased appetite	16	0.5	14	0.8
<b>Nervous System</b>				
Headache	14	0.2	14	0.8

\* Adverse reactions occurring at same or higher incidence than in the ipilimumab arm

<sup>†</sup> Graded per NCI CTCAE v4.0

<sup>‡</sup> Includes rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, and exfoliative rash.

<sup>§</sup> Includes skin hypopigmentation

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

**Table 4: 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 %
<b>Chemistry</b>				
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
<b>Hematology</b>				
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 maculopapular rash (1%). Tables 5 and 6 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-002.



**Table 5: 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 (%)
<b>Skin and Subcutaneous Tissue</b>				
Pruritus	28	0	8	0
Rash§	24	0.6	8	0
<b>Gastrointestinal</b>				
Constipation	22	0.3	20	2.3
Diarrhea	20	0.8	20	2.3
Abdominal pain	13	1.7	8	1.2
<b>Respiratory, Thoracic and Mediastinal</b>				
Cough	18	0	16	0
<b>General</b>				
Pyrexia	14	0.3	9	0.6
Asthenia	10	2.0	9	1.8
<b>Musculoskeletal and Connective Tissue</b>				
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 6: 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 %
<b>Chemistry</b>				
Hyperglycemia	49	6	44	6
Hypoalbuminemia	37	1.9	33	0.6
Hyponatremia	37	7	24	3.8
Hypertriglyceridemia	33	0	32	0.9
Increased alkaline phosphatase	26	3.1	18	1.9
Increased AST	24	2.2	16	0.6
Decreased bicarbonate	22	0.4	13	0
Hypocalcemia	21	0.3	18	1.9
Increased ALT	21	1.8	16	0.6

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

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

‡ Graded per NCI CTCAE v4.0

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

#### *Adjuvant Treatment of Resected Stage IIB or IIC Melanoma*

Among the 969 patients with Stage IIB or IIC melanoma enrolled in KEYNOTE-716 [see *Clinical Studies (14.1)*] treated with KEYTRUDA, the median duration of exposure to KEYTRUDA was 9.9 months (range: 0 to 15.4 months). Patients with autoimmune disease or a medical condition that required immunosuppression or mucosal or ocular melanoma were ineligible. Adverse reactions occurring in patients with Stage IIB or IIC melanoma were similar to those occurring in 1011 patients with Stage III melanoma from KEYNOTE-054 or the 2799 patients with melanoma or NSCLC treated with KEYTRUDA as a single agent.

#### *Adjuvant Treatment of Stage III Resected Melanoma*

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

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

Two patients treated with KEYTRUDA died from causes other than disease progression; causes of death were drug reaction with eosinophilia and systemic symptoms and autoimmune myositis with respiratory failure. Serious adverse reactions occurred in 25% of patients receiving KEYTRUDA. Adverse reactions leading to permanent discontinuation occurred in 14% of patients receiving KEYTRUDA; the most common (≥1%) were pneumonitis (1.4%), colitis (1.2%), and diarrhea (1%). Adverse reactions leading to interruption of KEYTRUDA occurred in 19% of patients; the most common (≥1%) were diarrhea (2.4%), pneumonitis (2%), increased ALT (1.4%), arthralgia (1.4%), increased AST (1.4%), dyspnea (1%), and fatigue (1%). Tables 7 and 8 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-054.

**Table 7: 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 <sup>†</sup> (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
<b>Gastrointestinal</b>				
Diarrhea	28	1.2	26	1.2
Nausea	17	0.2	15	0
<b>Skin and Subcutaneous Tissue</b>				
Pruritus	19	0	12	0
Rash	13	0.2	9	0
<b>Musculoskeletal and Connective Tissue</b>				
Arthralgia	16	1.2	14	0
<b>Endocrine</b>				
Hypothyroidism	15	0	2.8	0
Hyperthyroidism	10	0.2	1.2	0
<b>Respiratory, Thoracic and Mediastinal</b>				
Cough	14	0	11	0
<b>General</b>				
Asthenia	11	0.2	8	0
Influenza like illness	11	0	8	0
<b>Investigations</b>				
Weight loss	11	0	8	0

\* Adverse reactions occurring at same or higher incidence than in placebo arm

† Graded per NCI CTCAE v4.03

**Table 8: Selected\* Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Melanoma Patients Receiving KEYTRUDA in KEYNOTE-054**

Laboratory Test <sup>†</sup>	KEYTRUDA 200 mg every 3 weeks		Placebo	
	All Grades <sup>‡</sup> %	Grades 3-4 %	All Grades %	Grades 3-4 %
<b>Chemistry</b>				
Increased ALT	27	2.4	16	0.2
Increased AST	24	1.8	15	0.4
<b>Hematology</b>				

Lymphopenia	24	1	16	1.2
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\* 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  $\geq 6$  months. Seventy-two percent of patients received carboplatin.

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

KEYTRUDA was discontinued for adverse reactions in 20% of patients. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA were pneumonitis (3%) and acute kidney injury (2%). Adverse reactions leading to the interruption of KEYTRUDA occurred in 53% of patients; the most common adverse reactions or laboratory abnormalities leading to interruption of KEYTRUDA ( $\geq 2\%$ ) were neutropenia (13%), asthenia/fatigue (7%), anemia (7%), thrombocytopenia (5%), diarrhea (4%), pneumonia (4%), increased blood creatinine (3%), dyspnea (2%), febrile neutropenia (2%), upper respiratory tract infection (2%), increased ALT (2%), and pyrexia (2%). Tables 9 and 10 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-189.

**Table 9: Adverse Reactions Occurring in  $\geq 20\%$  of Patients in KEYNOTE-189**

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks Pemetrexed Platinum Chemotherapy n=405		Placebo Pemetrexed Platinum Chemotherapy n=202	
	All Grades* (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
<b>Gastrointestinal</b>				
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
<b>General</b>				
Fatigue†	56	12	58	6
Pyrexia	20	0.2	15	0
<b>Metabolism and Nutrition</b>				
Decreased appetite	28	1.5	30	0.5
<b>Skin and Subcutaneous Tissue</b>				
Rash‡	25	2.0	17	2.5
<b>Respiratory, Thoracic and Mediastinal</b>				

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 10: Laboratory Abnormalities Worsened from Baseline Occurring in  $\geq 20\%$  of Patients in KEYNOTE-189**

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks Pemetrexed Platinum Chemotherapy		Placebo Pemetrexed Platinum Chemotherapy	
	All Grades <sup>†</sup> %	Grades 3-4 %	All Grades %	Grades 3-4 %
<b>Hematology</b>				
Anemia	85	17	81	18
Lymphopenia	64	22	64	25
Neutropenia	48	20	41	19
Thrombocytopenia	30	12	29	8
<b>Chemistry</b>				
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 KEYNOTE407, a multicenter, double-blind, randomized (1:1), placebo-controlled trial in 558 patients with previously untreated, metastatic squamous NSCLC [see *Clinical Studies (14.2)*]. Safety data are available for the first 203 patients who received KEYTRUDA and chemotherapy (n=101) or placebo and chemotherapy (n=102). Patients with autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible.

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

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

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

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

### Previously 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<sup>2</sup> 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 11 and 12 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-010.

**Table 11: 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 <sup>2</sup> every 3 weeks n=309	
	All Grades <sup>†</sup> (%)	Grades 3-4 (%)	All Grades <sup>†</sup> (%)	Grades 3-4 (%)
<b>Metabolism and Nutrition</b>				
Decreased appetite	25	1.5	23	2.6
<b>Respiratory, Thoracic and Mediastinal</b>				
Dyspnea	23	3.7	20	2.6
Cough	19	0.6	14	0
<b>Gastrointestinal</b>				
Nausea	20	1.3	18	0.6
Constipation	15	0.6	12	0.6
Vomiting	13	0.9	10	0.6
<b>Skin and Subcutaneous Tissue</b>				
Rash <sup>‡</sup>	17	0.4	8	0
Pruritus	11	0	3	0.3
<b>Musculoskeletal and Connective Tissue</b>				
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

<sup>†</sup> Graded per NCI CTCAE v4.0

<sup>‡</sup> Includes rash, rash erythematous, rash macular, rash maculo-papular, rash papular, and rash pruritic

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

**Table 12: Selected\* Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of NSCLC Patients Receiving KEYTRUDA in KEYNOTE 010**

Laboratory Test <sup>†</sup>	KEYTRUDA 2 or 10 mg/kg every 3 weeks		Docetaxel 75 mg/m <sup>2</sup> every 3 weeks	
	All Grades <sup>‡</sup> %	Grades 3-4 %	All Grades <sup>‡</sup> %	Grades 3-4 %
<b>Chemistry</b>				
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.

<sup>†</sup> 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).

<sup>‡</sup> 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).

#### *Adjuvant Treatment of Resected NSCLC*

The safety of KEYTRUDA as a single agent was investigated in KEYNOTE-091, a multicenter, randomized (1:1), triple-blind, placebo-controlled trial in patients with completely resected Stage IB (T2a ≥4 cm), II, or IIIA NSCLC; adjuvant chemotherapy up to 4 cycles was optional [see *Clinical Studies (14.2)*]. A total of 1161 patients received KEYTRUDA 200 mg (n=580) or placebo (n=581) every 3 weeks. Patients were ineligible if they had active autoimmune disease, were on chronic immunosuppressive agents, or had a history of interstitial lung disease or pneumonitis.

The median duration of exposure to KEYTRUDA was 11.7 months (range: 1 day to 18.9 months). Sixty-eight percent of patients in the KEYTRUDA arm were exposed to KEYTRUDA for ≥6 months.

The adverse reactions observed in KEYNOTE-091 were generally similar to those occurring in other patients with NSCLC receiving KEYTRUDA as a single agent, with the exception of hypothyroidism (22%), hyperthyroidism (11%), and pneumonitis (7%). Two fatal adverse reactions of myocarditis occurred.

#### HNSCC

##### *First-line treatment of metastatic or unresectable, recurrent HNSCC*

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

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

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

KEYTRUDA was discontinued for adverse reactions in 16% of patients in the combination arm. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA were pneumonia (2.5%), pneumonitis (1.8%), and septic shock (1.4%). Adverse reactions leading to the interruption of KEYTRUDA occurred in 45% of patients; the most common adverse reactions leading to interruption of KEYTRUDA ( $\geq 2\%$ ) were neutropenia (14%), thrombocytopenia (10%), anemia (6%), pneumonia (4.7%), and febrile neutropenia (2.9%). Tables 13 and 14 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-048.

**Table 13: Adverse Reactions Occurring in  $\geq 10\%$  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 (%)
<b>General</b>						
Fatigue <sup>†</sup>	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
<b>Gastrointestinal</b>						
Constipation	20	0.3	37	0	33	1.4
Nausea	17	0	51	6	51	6
Diarrhea <sup>‡</sup>	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
<b>Skin</b>						
Rash <sup>§</sup>	20	2.3	17	0.7	70	8
Pruritus	11	0	8	0	10	0.3
<b>Respiratory, Thoracic and Mediastinal</b>						
Cough <sup>¶</sup>	18	0.3	22	0	15	0
Dyspnea <sup>#</sup>	14	2.0	10	1.8	8	1.0
<b>Endocrine</b>						
Hypothyroidism	18	0	15	0	6	0
<b>Metabolism and Nutrition</b>						
Decreased appetite	15	1.0	29	4.7	30	3.5
Weight loss	15	2	16	2.9	21	1.4
<b>Infections</b>						
Pneumonia <sup>p</sup>	12	7	19	11	13	6
<b>Nervous System</b>						
Headache	12	0.3	11	0.7	8	0.3
Dizziness	5	0.3	10	0.4	13	0.3
Peripheral sensory neuropathy <sup>β</sup>	1	0	14	1.1	7	1
<b>Musculoskeletal</b>						
Myalgia <sup>a</sup>	12	1.0	13	0.4	11	0.3
Neck pain	6	0.7	10	1.1	7	0.7
<b>Psychiatric</b>						
Insomnia	7	0.7	10	0	8	0

\* Graded per NCI CTCAE v4.0

<sup>†</sup> Includes fatigue, asthenia

<sup>‡</sup> Includes diarrhea, colitis, hemorrhagic diarrhea, microscopic colitis

<sup>§</sup> 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

- <sup>†</sup> Includes cough, productive cough  
<sup>#</sup> Includes dyspnea, exertional dyspnea  
<sup>‡</sup> Includes pneumonia, atypical pneumonia, bacterial pneumonia, staphylococcal pneumonia, aspiration pneumonia, lower respiratory tract infection, lung infection, lung infection pseudomonal  
<sup>β</sup> Includes peripheral sensory neuropathy, peripheral neuropathy, hypoesthesia, dysesthesia  
<sup>α</sup> Includes back pain, musculoskeletal chest pain, musculoskeletal pain, myalgia

**Table 14: 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 <sup>†</sup> (%)	Grades 3- 4 (%)	All Grades <sup>†</sup> (%)	Grades 3- 4 (%)	All Grades <sup>†</sup> (%)	Grades 3-4 (%)
<b>Hematology</b>						
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
<b>Chemistry</b>						
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).

<sup>†</sup> Graded per NCI CTCAE v4.0

#### Previously treated recurrent or metastatic HNSCC

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

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

KEYTRUDA was discontinued due to adverse reactions in 17% of patients. Serious adverse reactions occurred in 45% of patients receiving KEYTRUDA. The most frequent serious adverse reactions reported in at least 2% of patients were pneumonia, dyspnea, confusional state, vomiting, pleural effusion, and respiratory failure. The incidence of adverse reactions, including serious adverse reactions, was similar between dosage regimens (10 mg/kg every 2 weeks or 200 mg every 3 weeks); therefore, summary safety results are provided in a pooled analysis. The most common adverse reactions (occurring in ≥20% of patients) were fatigue, decreased appetite, and dyspnea. Adverse reactions occurring in patients with HNSCC were generally similar to those occurring in 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 (14.4)*]. Adults with relapsed or refractory cHL received KEYTRUDA 200 mg intravenously every 3 weeks (n=148) or brentuximab vedotin (BV) 1.8 mg/kg intravenously every 3 weeks (n=152). The trial required an ANC  $\geq 1000/\mu\text{L}$ , platelet count  $\geq 75,000/\mu\text{L}$ , hepatic transaminases  $\leq 2.5$  times the upper limit of normal (ULN), bilirubin  $\leq 1.5$  times ULN, and ECOG performance status of 0 or 1. The trial excluded patients with active non-infectious pneumonitis, prior pneumonitis requiring steroids, active autoimmune disease, a medical condition requiring immunosuppression, or allogeneic HSCT within the past 5 years. The median duration of exposure to KEYTRUDA was 10 months (range: 1 day to 2.2 years), with 68% receiving at least 6 months of treatment and 48% receiving at least 1 year of treatment.

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

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

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

Table 15 summarizes adverse reactions in KEYNOTE-204.

**Table 15: 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† (%)
<b>Infections</b>				
Upper respiratory tract infection‡	41	1.4	24	0
Urinary tract infection	11	0	3	0.7
<b>Musculoskeletal and Connective Tissue</b>				
Musculoskeletal pain§	32	0	29	1.3
<b>Gastrointestinal</b>				
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
<b>General</b>				
Pyrexia	20	0.7	13	0.7
Fatigue▷	20	0	22	0.7
<b>Skin and Subcutaneous Tissue</b>				
Rashβ	20	0	19	0.7
Pruritus	18	0	12	0
<b>Respiratory, Thoracic and Mediastinal</b>				
Cough <sup>α</sup>	20	0.7	14	0.7
Pneumonitis <sup>ε</sup>	11	5	3	1.3
Dyspnea <sup>ο</sup>	11	0.7	7	0.7
<b>Endocrine</b>				
Hypothyroidism	19	0	3	0
<b>Nervous System</b>				
Peripheral neuropathy <sup>ο</sup>	11	0.7	43	7
Headache <sup>ϑ</sup>	11	0	11	0

\* Graded per NCI CTCAE v4.0

† Adverse reactions in BV arm were Grade 3 only.

‡ Includes acute sinusitis, nasopharyngitis, pharyngitis, pharyngotonsillitis, rhinitis, sinusitis, sinusitis bacterial, tonsillitis, upper respiratory tract infection, viral upper respiratory tract infection

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

¶ Includes diarrhea, gastroenteritis, colitis, enterocolitis

# Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper

▷ Includes fatigue, asthenia

β Includes dermatitis acneiform, dermatitis atopic, dermatitis allergic, dermatitis contact, dermatitis exfoliative, dermatitis psoriasiform, eczema, rash, rash erythematous, rash follicular, rash maculo-papular, rash papular, rash pruritic, toxic skin eruption

α Includes cough, productive cough

ε Includes pneumonitis, interstitial lung disease

ο Includes dyspnea, dyspnea exertional, wheezing

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

ϑ 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 16 summarizes laboratory abnormalities in KEYNOTE-204.

**Table 16: 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 <sup>†</sup> (%)	Grades 3-4 (%)	All Grades <sup>†</sup> (%)	Grades 3-4 (%)
<b>Chemistry</b>				
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
<b>Hematology</b>				
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 (14.4)*], 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 17 and 18 summarize adverse reactions and laboratory abnormalities, respectively, in KEYNOTE-087.

**Table 17: 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 (%)
<b>General</b>		
Fatigue <sup>†</sup>	26	1.0
Pyrexia	24	1.0
<b>Respiratory, Thoracic and Mediastinal</b>		
Cough <sup>‡</sup>	24	0.5
Dyspnea <sup>§</sup>	11	1.0
<b>Musculoskeletal and Connective Tissue</b>		
Musculoskeletal pain <sup>¶</sup>	21	1.0
Arthralgia	10	0.5
<b>Gastrointestinal</b>		
Diarrhea <sup>#</sup>	20	1.4
Vomiting	15	0
Nausea	13	0
<b>Skin and Subcutaneous Tissue</b>		
Rash <sup>Ⓟ</sup>	20	0.5
Pruritus	11	0
<b>Endocrine</b>		
Hypothyroidism	14	0.5
<b>Infections</b>		
Upper respiratory tract infection	13	0
<b>Nervous System</b>		
Headache	11	0.5
Peripheral neuropathy <sup>β</sup>	10	0

\* Graded per NCI CTCAE v4.0

† Includes fatigue, asthenia

‡ Includes cough, productive cough

§ Includes dyspnea, dyspnea exertional, wheezing

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

# Includes diarrhea, gastroenteritis, colitis, enterocolitis

Ⓟ Includes rash, rash maculo-papular, drug eruption, eczema, eczema asteatotic, dermatitis, dermatitis acneiform, dermatitis contact, rash erythematous, rash macular, rash papular, rash pruritic, seborrheic dermatitis, dermatitis psoriasiform

β Includes neuropathy peripheral, peripheral sensory neuropathy, hypoesthesia, paresthesia, dysesthesia, polyneuropathy

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

**Table 18: 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 <sup>†</sup> (%)	Grades 3-4 (%)
<b>Chemistry</b>		
Hypertransaminasemia <sup>‡</sup>	34	2
Increased alkaline phosphatase	17	0
Increased creatinine	15	0.5
<b>Hematology</b>		
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 (14.5)*], 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 19 and 20 summarize adverse reactions and laboratory abnormalities, respectively, in KEYNOTE-170.

**Table 19: 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 (%)
<b>Musculoskeletal and Connective Tissue</b>		
Musculoskeletal pain <sup>†</sup>	30	0
<b>Infections</b>		
Upper respiratory tract infection <sup>‡</sup>	28	0
<b>General</b>		
Pyrexia	28	0
Fatigue <sup>§</sup>	23	2
<b>Respiratory, Thoracic and Mediastinal</b>		
Cough <sup>¶</sup>	26	2
Dyspnea	21	11
<b>Gastrointestinal</b>		
Diarrhea <sup>#</sup>	13	2
Abdominal pain <sup>Ⓟ</sup>	13	0
Nausea	11	0
<b>Cardiac</b>		
Arrhythmia <sup>β</sup>	11	4
<b>Nervous System</b>		
Headache	11	0

\* Graded per NCI CTCAE v4.0

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

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

§ Includes fatigue, asthenia

¶ Includes allergic cough, cough, productive cough

# Includes diarrhea, gastroenteritis

Ⓟ Includes abdominal pain, abdominal pain upper

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

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

**Table 20: 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 <sup>†</sup> (%)	Grades 3-4 (%)
<b>Hematology</b>		
Anemia	47	0
Leukopenia	35	9
Lymphopenia	32	18
Neutropenia	30	11
<b>Chemistry</b>		
Hyperglycemia	38	4
Hypophosphatemia	29	10
Hypertransaminasemia <sup>‡</sup>	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 Cancer

#### *Cisplatin Ineligible Patients with Urothelial Carcinoma*

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

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

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

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

Table 21 summarizes adverse reactions in patients on KEYTRUDA in KEYNOTE-052.

**Table 21: 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 (%)
<b>General</b>		
Fatigue <sup>†</sup>	38	6
Pyrexia	11	0.5
Weight loss	10	0
<b>Musculoskeletal and Connective Tissue</b>		
Musculoskeletal pain <sup>‡</sup>	24	4.9
Arthralgia	10	1.1
<b>Metabolism and Nutrition</b>		
Decreased appetite	22	1.6
Hyponatremia	10	4.1
<b>Gastrointestinal</b>		
Constipation	21	1.1
Diarrhea <sup>§</sup>	20	2.4
Nausea	18	1.1
Abdominal pain <sup>¶</sup>	18	2.7
Elevated LFTs <sup>#</sup>	13	3.5
Vomiting	12	0
<b>Skin and Subcutaneous Tissue</b>		
Rash <sup>♯</sup>	21	0.5
Pruritus	19	0.3
Edema peripheral <sup>β</sup>	14	1.1
<b>Infections</b>		
Urinary tract infection	19	9
<b>Blood and Lymphatic System</b>		
Anemia	17	7
<b>Respiratory, Thoracic, and Mediastinal</b>		
Cough	14	0
Dyspnea	11	0.5
<b>Renal and Urinary</b>		
Increased blood creatinine	11	1.1
Hematuria	13	3.0

\* Graded per NCI CTCAE v4.0

<sup>†</sup> Includes fatigue, asthenia

<sup>‡</sup> Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, pain in extremity, spinal pain

<sup>§</sup> Includes diarrhea, colitis, enterocolitis, gastroenteritis, frequent bowel movements

<sup>¶</sup> Includes abdominal pain, pelvic pain, flank pain, abdominal pain lower, tumor pain, bladder pain, hepatic pain, suprapubic pain, abdominal discomfort, abdominal pain upper

<sup>#</sup> 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

<sup>♯</sup> 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

<sup>β</sup> 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 (14.6)*]. Patients with autoimmune disease or a medical condition that required systemic corticosteroids or other immunosuppressive medications were ineligible.

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

KEYTRUDA was discontinued due to adverse reactions in 8% of patients. The most common adverse reaction resulting in permanent discontinuation of KEYTRUDA was pneumonitis (1.9%). Adverse reactions leading to interruption of KEYTRUDA occurred in 20% of patients; the most common ( $\geq 1\%$ ) were urinary tract infection (1.5%), diarrhea (1.5%), and colitis (1.1%). Serious adverse reactions occurred in 39% of KEYTRUDA-treated patients. The most frequent serious adverse reactions ( $\geq 2\%$ ) in KEYTRUDA-treated patients were urinary tract infection, pneumonia, anemia, and pneumonitis. Tables 22 and 23 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-045.

**Table 22: Adverse Reactions Occurring in  $\geq 10\%$  of Patients Receiving KEYTRUDA in KEYNOTE-045**

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

\* Chemotherapy: paclitaxel, docetaxel, or vinflunine

<sup>†</sup> Graded per NCI CTCAE v4.0

<sup>‡</sup> Includes asthenia, fatigue, malaise, lethargy

<sup>§</sup> Includes back pain, myalgia, bone pain, musculoskeletal pain, pain in extremity, musculoskeletal chest pain, musculoskeletal discomfort, neck pain

<sup>¶</sup> 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

<sup>#</sup> Includes diarrhea, gastroenteritis, colitis, enterocolitis

<sup>‡</sup> Includes cough, productive cough

<sup>§</sup> Includes dyspnea, dyspnea exertional, wheezing

<sup>à</sup> Includes blood urine present, hematuria, chromaturia



**Table 23: Laboratory Abnormalities Worsened from Baseline Occurring in  $\geq 20\%$  of Urothelial Carcinoma Patients Receiving KEYTRUDA in KEYNOTE-045**

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks		Chemotherapy	
	All Grades <sup>†</sup> %	Grades 3-4 %	All Grades <sup>†</sup> %	Grades 3-4 %
<b>Chemistry</b>				
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 ( $\geq 2\%$ ) were diarrhea (4%) and urinary tract infection (2%). Serious adverse reactions occurred in 28% of KEYTRUDA-treated patients. The most frequent serious adverse reactions ( $\geq 2\%$ ) in KEYTRUDA-treated patients were pneumonia (3%), cardiac ischemia (2%), colitis (2%), pulmonary embolism (2%), sepsis (2%), and urinary tract infection (2%). Tables 24 and 25 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-057.

**Table 24: 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 (%)
<b>General</b>		
Fatigue <sup>†</sup>	29	0.7
Peripheral edema <sup>‡</sup>	11	0
<b>Gastrointestinal</b>		
Diarrhea <sup>§</sup>	24	2.0
Nausea	13	0
Constipation	12	0
<b>Skin and Subcutaneous Tissue</b>		
Rash <sup>¶</sup>	24	0.7
Pruritus	19	0.7
<b>Musculoskeletal and Connective Tissue</b>		
Musculoskeletal pain <sup>#</sup>	19	0
Arthralgia	14	1.4
<b>Renal and Urinary</b>		
Hematuria	19	1.4
<b>Respiratory, Thoracic, and Mediastinal</b>		
Cough <sup>Ⓟ</sup>	19	0
<b>Infections</b>		
Urinary tract infection	12	2.0
Nasopharyngitis	10	0
<b>Endocrine</b>		
Hypothyroidism	11	0

\* Graded per NCI CTCAE v4.03

<sup>†</sup> Includes asthenia, fatigue, malaise

<sup>‡</sup> Includes edema peripheral, peripheral swelling

<sup>§</sup> Includes diarrhea, gastroenteritis, colitis

<sup>¶</sup> Includes rash maculo-papular, rash, rash erythematous, rash pruritic, rash pustular, erythema, eczema, eczema asteatotic, lichenoid keratosis, urticaria, dermatitis

<sup>#</sup> Includes back pain, myalgia, musculoskeletal pain, pain in extremity, musculoskeletal chest pain, neck pain

<sup>Ⓟ</sup> Includes cough, productive cough

**Table 25: 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 <sup>†</sup> (%)	Grades 3-4 (%)
<b>Chemistry</b>		
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
<b>Hematology</b>		
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)

<sup>†</sup> Graded per NCI CTCAE v4.03

### 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 (14.8)*] treated with KEYTRUDA, the median duration of exposure to KEYTRUDA was 11.1 months (range: 1 day to

30.6 months). Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible. Adverse reactions occurring in patients with MSI-H or dMMR CRC were similar to those occurring in 2799 patients with melanoma or NSCLC treated with KEYTRUDA as a single agent.

### Gastric Cancer

#### *First-line Treatment of Locally Advanced Unresectable or Metastatic HER2-Positive Gastric or Gastroesophageal Junction Adenocarcinoma*

The safety of KEYTRUDA was evaluated in 433 patients with HER2-positive gastric or GEJ cancer enrolled in KEYNOTE-811, which included 217 patients treated with KEYTRUDA 200 mg, trastuzumab, and CAPOX (n=189) or FP (n=28) every 3 weeks, compared to 216 patients treated with placebo, trastuzumab, and CAPOX (n=187) or FP (n=29) every 3 weeks [see *Clinical Studies (14.9)*].

The median duration of exposure to KEYTRUDA was 5.8 months (range: 1 day to 17.7 months).

The study population characteristics were: median age of 63 years (range: 19 to 84), 43% age 65 or older; 81% male; 58% White, 35% Asian, and 0.9% Black; 44% ECOG PS of 0 and 56% ECOG PS of 1.

KEYTRUDA and placebo were discontinued due to adverse reactions in 6% of patients in each arm. The most common adverse reaction resulting in permanent discontinuation of KEYTRUDA was pneumonitis (1.4%). Adverse reactions leading to interruption of KEYTRUDA occurred in 58% of patients; the most common adverse reactions or laboratory abnormalities leading to interruption of KEYTRUDA ( $\geq 2\%$ ) were neutropenia (18%), thrombocytopenia (12%), diarrhea (6%), anemia (3.7%), hypokalemia (3.7%), fatigue/asthenia (3.2%), decreased appetite (3.2%), increased AST (2.8%), increased blood bilirubin (2.8%), pneumonia (2.8%), increased ALT (2.3%), and vomiting (2.3%).

In the KEYTRUDA arm versus placebo, there was a difference of  $\geq 5\%$  incidence between patients treated with KEYTRUDA versus standard of care for diarrhea (53% vs 44%), and nausea (49% vs 44%). There were no clinically meaningful differences in incidence of Grade 3-4 toxicity between arms.

There was a difference of  $\geq 5\%$  incidence between patients treated with KEYTRUDA versus standard of care for increased ALT (34% vs 29%), and increased creatinine (20% vs 10%). There were no clinically meaningful differences in incidence of Grade 3-4 toxicity between arms.

#### *First-line Treatment of Locally Advanced Unresectable or Metastatic HER2-Negative Gastric or Gastroesophageal Junction Adenocarcinoma*

The safety of KEYTRUDA was evaluated in 1572 patients with HER2-negative gastric or GEJ cancer enrolled in KEYNOTE-859, which included 785 patients treated with KEYTRUDA 200 mg and FP (n=106) or CAPOX (n=674) every 3 weeks, compared to 787 patients who received placebo and FP (n=107) or CAPOX (n=679) every 3 weeks [see *Clinical Studies (14.9)*].

The median duration of exposure to KEYTRUDA was 6.2 months (range: 1 day to 33.7 months).

Serious adverse reactions occurred in 45% of patients receiving KEYTRUDA. Serious adverse reactions in  $>2\%$  of patients included pneumonia (4.1%), diarrhea (3.9%), hemorrhage (3.9%), and vomiting (2.4%). Fatal adverse reactions occurred in 8% of patients who received KEYTRUDA, including infection (2.3%) and thromboembolism (1.3%).

Permanent discontinuation of KEYTRUDA due to adverse reactions occurred in 15% of patients. Adverse reaction resulting in permanent discontinuation of KEYTRUDA in  $\geq 1\%$  were infections (1.8%) and diarrhea (1.0%).

Dosage interruptions of KEYTRUDA due to an adverse reaction occurred in 65% of patients. Adverse reactions or laboratory abnormalities leading to interruption of KEYTRUDA ( $\geq 2\%$ ) were neutropenia (21%), thrombocytopenia (13%), diarrhea (5.5%), fatigue (4.8%), infection (4.8%), anemia (4.5%), increased AST (4.3%), increased ALT (3.8%), increased blood bilirubin (3.3%), white blood cell count decreased (2.2%), nausea (2%), palmar-plantar erythrodysesthesia syndrome (2%), and vomiting (2%).

Tables 26 and 27 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-859.

**Table 26: Adverse Reactions Occurring in ≥20% of Patients Receiving KEYTRUDA in KEYNOTE-859**

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks and FP or CAPOX n=785		Placebo and FP or CAPOX n=787	
	All Grades* (%)	Grades 3-4 (%)	All Grades* (%)	Grades 3-4 (%)
<b>Nervous System</b>				
Peripheral neuropathy†	47	5	48	6
<b>Gastrointestinal</b>				
Nausea	46	3.7	46	4.4
Diarrhea	36	6	32	5
Vomiting	34	5	27	5
Abdominal Pain‡	26	2.8	24	2.9
Constipation	22	0.5	21	0.8
<b>General</b>				
Fatigue§	40	8	39	9
<b>Metabolism and Nutrition</b>				
Decreased appetite	29	3.3	29	2.5
<b>Skin and Subcutaneous Tissue</b>				
Palmar-plantar erythrodysesthesia syndrome	25	3.1	22	1.8
<b>Investigations</b>				
Weight loss	20	2.8	19	2.7

\* Graded per NCI CTCAE v4.03

† Includes dysesthesia, hyperesthesia, hypoesthesia, neuralgia, neuropathy peripheral, paresthesia, peripheral sensory neuropathy, peripheral motor neuropathy, polyneuropathy

‡ Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal tenderness, abdominal pain upper, epigastric discomfort, gastrointestinal pain

§ Includes asthenia, fatigue

**Table 27: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients Receiving KEYTRUDA in KEYNOTE-859**

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks and FP or CAPOX		Placebo and FP or CAPOX	
	All Grades† %	Grades 3-4 %	All Grades† %	Grades 3-4 %
<b>Hematology</b>				
Anemia	65	15	69	13
Thrombocytopenia	64	12	62	10
Neutropenia	63	25	58	20
Leukopenia	59	7	56	6
Lymphopenia	57	20	51	16
<b>Chemistry</b>				
Increased AST	57	4.7	48	3.6
Hypoalbuminemia	55	4.1	52	2.9
Hyperglycemia	53	6	52	4.6
Hypocalcemia	49	3.6	45	3.3
Increased alkaline phosphatase	48	6	41	5
Hyponatremia	40	13	40	12
Increased ALT	40	4.2	29	2.9
Hypokalemia	35	10	27	9
Bilirubin increased	32	5	30	5
Hypophosphatemia	30	10	27	8
Hypomagnesemia	29	0.3	22	0.7
Increased creatinine	21	3.5	18	1.7
Hyperkalemia	20	3.7	18	2.9
Increased INR	20	1.4	22	0

\* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA/FP or CAPOX (range: 210 to 766 patients) and placebo/FP or CAPOX (range: 190 to 762 patients)

† Graded per NCI CTCAE v4.03

Esophageal Cancer

*First-line Treatment of Locally Advanced Unresectable or Metastatic Esophageal Cancer/Gastroesophageal Junction*

The safety of KEYTRUDA, in combination with cisplatin and FU chemotherapy was investigated in KEYNOTE-590, a multicenter, double-blind, randomized (1:1), placebo-controlled trial for the first-line treatment in patients with metastatic or locally advanced esophageal or gastroesophageal junction (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma who were not candidates for surgical resection or definitive chemoradiation [see *Clinical Studies (14.10)*]. A total of 740 patients received either KEYTRUDA 200 mg (n=370) or placebo (n=370) every 3 weeks for up to 35 cycles, both in combination with up to 6 cycles of cisplatin and up to 35 cycles of FU.

The median duration of exposure was 5.7 months (range: 1 day to 26 months) in the KEYTRUDA combination arm and 5.1 months (range: 3 days to 27 months) in the chemotherapy arm.

KEYTRUDA was discontinued for adverse reactions in 15% of patients. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA ( $\geq 1\%$ ) were pneumonitis (1.6%), acute kidney injury (1.1%), and pneumonia (1.1%). Adverse reactions leading to interruption of KEYTRUDA occurred in 67% of patients. The most common adverse reactions leading to interruption of KEYTRUDA ( $\geq 2\%$ ) were neutropenia (19%), fatigue/asthenia (8%), decreased white blood cell count (5%), pneumonia (5%), decreased appetite (4.3%), anemia (3.2%), increased blood creatinine (3.2%), stomatitis (3.2%), malaise (3.0%), thrombocytopenia (3%), pneumonitis (2.7%), diarrhea (2.4%), dysphagia (2.2%), and nausea (2.2%).

Tables 28 and 29 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-590.

**Table 28: Adverse Reactions Occurring in  $\geq 20\%$  of Patients Receiving KEYTRUDA in KEYNOTE-590**

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks Cisplatin FU n=370		Placebo Cisplatin FU n=370	
	All Grades* (%)	Grades 3-4 <sup>†</sup> (%)	All Grades* (%)	Grades 3-4 <sup>†</sup> (%)
<b>Gastrointestinal</b>				
Nausea	67	7	63	7
Constipation	40	0	40	0
Diarrhea	36	4.1	33	3
Vomiting	34	7	32	5
Stomatitis	27	6	26	3.8
<b>General</b>				
Fatigue <sup>‡</sup>	57	12	46	9
<b>Metabolism and Nutrition</b>				
Decreased appetite	44	4.1	38	5
<b>Investigations</b>				
Weight loss	24	3.0	24	5

\* Graded per NCI CTCAE v4.03

<sup>†</sup> One fatal event of diarrhea was reported in each arm.

<sup>‡</sup> Includes asthenia, fatigue

**Table 29: Laboratory Abnormalities Worsened from Baseline Occurring in  $\geq 20\%$  of Esophageal Cancer Patients Receiving KEYTRUDA in KEYNOTE-590**

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks Cisplatin FU		Chemotherapy (Cisplatin and FU)	
	All Grades <sup>†</sup> %	Grades 3-4 %	All Grades <sup>†</sup> %	Grades 3-4 %
<b>Hematology</b>				
Anemia	83	21	86	24
Neutropenia	74	43	71	41
Leukopenia	72	21	73	17
Lymphopenia	55	22	53	18
Thrombocytopenia	43	5	46	8
<b>Chemistry</b>				
Hyperglycemia	56	7	55	6
Hyponatremia	53	19	54	19
Hypoalbuminemia	52	2.8	52	2.3
Increased creatinine	45	2.5	42	2.5
Hypocalcemia	44	3.9	38	2
Hypophosphatemia	37	9	31	10
Hypokalemia	30	12	34	15
Increased alkaline phosphatase	29	1.9	29	1.7
Hyperkalemia	28	3.6	27	2.6
Increased AST	25	4.4	22	2.8
Increased ALT	23	3.6	18	1.7

\* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA/cisplatin/FU (range: 345 to 365 patients) and placebo/cisplatin/FU (range: 330 to 358 patients)

† Graded per NCI CTCAE v4.03

### *Previously Treated Recurrent Locally Advanced or Metastatic Esophageal Cancer*

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

### Cervical Cancer

#### *Persistent, Recurrent, or Metastatic Cervical Cancer*

The safety of KEYTRUDA in combination with paclitaxel and cisplatin or paclitaxel and carboplatin, with or without bevacizumab, was investigated in KEYNOTE-826, a multicenter, double-blind, randomized (1:1), placebo-controlled trial in patients with persistent, recurrent, or first-line metastatic cervical cancer who had not been treated with chemotherapy except when used concurrently as a radio-sensitizing agent [see *Clinical Studies (14.11)*]. A total of 616 patients, regardless of tumor PD-L1 expression, received KEYTRUDA 200 mg and chemotherapy with or without bevacizumab (n=307) every 3 weeks or placebo and chemotherapy with or without bevacizumab (n=309) every 3 weeks.

The median duration of exposure to KEYTRUDA was 9.9 months (range: 1 day to 26 months).

Fatal adverse reactions occurred in 4.6% of patients receiving KEYTRUDA in combination with chemotherapy with or without bevacizumab, including 3 cases of hemorrhage, 2 cases of sepsis, 2 cases due to unknown causes, and 1 case each of acute myocardial infarction, autoimmune encephalitis, cardiac arrest, cerebrovascular accident, femur fracture with perioperative pulmonary embolus, intestinal perforation, and pelvic infection.

Serious adverse reactions occurred in 50% of patients receiving KEYTRUDA in combination with chemotherapy with or without bevacizumab. Serious adverse reactions in  $\geq 3\%$  of patients included febrile neutropenia (6.8%), urinary tract infection (5.2%), anemia (4.6%), acute kidney injury (3.3%), and sepsis (3.3%).

KEYTRUDA was discontinued for adverse reactions in 15% of patients. The most common adverse reaction resulting in permanent discontinuation of KEYTRUDA ( $\geq 1\%$ ) was colitis (1%).

Adverse reactions leading to interruption of KEYTRUDA occurred in 66% of patients; the most common adverse reactions or laboratory abnormalities leading to interruption of KEYTRUDA ( $\geq 2\%$ ) were

thrombocytopenia (15%), neutropenia (14%), anemia (11%), increased ALT (6%), leukopenia (5%), fatigue/asthenia (4.2%), urinary tract infection (3.6%), increased AST (3.3%), pyrexia (3.3%), diarrhea (2.6%), acute kidney injury (2.6%), increased blood creatinine (2.6%), colitis (2.3%), decreased appetite (2%), and cough (2%).

For patients treated with KEYTRUDA, chemotherapy, and bevacizumab (n=196), the most common ( $\geq 20\%$ ) adverse reactions were peripheral neuropathy (62%), alopecia (58%), anemia (55%), fatigue/asthenia (53%), nausea (41%), neutropenia (41%), diarrhea (39%), hypertension (35%), thrombocytopenia (35%), constipation (31%), arthralgia (31%), vomiting (30%), urinary tract infection (27%), rash (26%), leukopenia (24%), hypothyroidism (22%), and decreased appetite (21%).

Table 30 and Table 31 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-826.

**Table 30: Adverse Reactions Occurring in  $\geq 20\%$  of Patients Receiving KEYTRUDA in KEYNOTE-826**

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks and chemotherapy* with or without bevacizumab n=307		Placebo and chemotherapy* with or without bevacizumab n=309	
	All Grades <sup>†</sup> (%)	Grades 3-4 (%)	All Grades <sup>†</sup> (%)	Grades 3-4 (%)
<b>Nervous System</b>				
Peripheral neuropathy <sup>‡</sup>	58	4.2	57	6
<b>Skin and Subcutaneous Tissue</b>				
Alopecia	56	0	58	0
Rash <sup>§</sup>	22	3.6	15	0.3
<b>General</b>				
Fatigue <sup>¶</sup>	47	7	46	6
<b>Gastrointestinal</b>				
Nausea	40	2	44	1.6
Diarrhea	36	2	30	2.6
Constipation	28	0.3	33	1
Vomiting	26	2.6	27	1.9
<b>Musculoskeletal and Connective Tissue</b>				
Arthralgia	27	0.7	26	1.3
<b>Vascular</b>				
Hypertension	24	9	23	11
<b>Infections</b>				
Urinary tract infection	24	9	26	8

\* Chemotherapy (paclitaxel and cisplatin or paclitaxel and carboplatin)

<sup>†</sup> Graded per NCI CTCAE v4.0

<sup>‡</sup> Includes neuropathy peripheral, peripheral sensory neuropathy, peripheral motor neuropathy, peripheral sensorimotor neuropathy, paresthesia

<sup>§</sup> Includes rash, rash maculo-papular, rash erythematous, rash macular, rash papular, rash pruritic, rash pustular

<sup>¶</sup> Includes fatigue, asthenia

**Table 31: Laboratory Abnormalities Worsened from Baseline Occurring in  $\geq 20\%$  of Patients Receiving KEYTRUDA in KEYNOTE-826**

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks and chemotherapy <sup>†</sup> with or without bevacizumab n=307		Placebo and chemotherapy <sup>†</sup> with or without bevacizumab n=309	
	All Grades <sup>‡</sup> (%)	Grades 3-4 (%)	All Grades <sup>‡</sup> (%)	Grades 3-4 (%)

<b>Hematology</b>				
Anemia	80	35	77	33
Leukopenia	76	27	69	19
Neutropenia	66	39	58	31
Lymphopenia	61	33	56	33
Thrombocytopenia	57	19	53	15
<b>Chemistry</b>				
Hyperglycemia	51	4.7	46	2.3
Hypoalbuminemia	46	1.3	38	5
Hyponatremia	40	14	38	11
Increased ALT	40	7	38	6
Increased AST	40	6	36	3.0
Increased alkaline phosphatase	38	3.4	40	2.3
Hypocalcemia	37	4.0	31	5
Increased creatinine	34	5	32	6
Hypokalemia	29	7	26	7
Hyperkalemia	23	3.7	27	4.7
Hypercalcemia	21	1.0	20	1.3

\* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA plus chemotherapy (range: 297 to 301 patients) and placebo plus chemotherapy (range: 299 to 302 patients)

† Chemotherapy (paclitaxel and cisplatin or paclitaxel and carboplatin)

‡ Graded per NCI CTCAE v4.0

### Previously Treated Recurrent or Metastatic Cervical Cancer

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

KEYTRUDA was discontinued due to adverse reactions in 8% of patients. Serious adverse reactions occurred in 39% of patients receiving KEYTRUDA. The most frequent serious adverse reactions reported included anemia (7%), fistula (4.1%), hemorrhage (4.1%), and infections [except UTIs] (4.1%). Tables 32 and 33 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-158.

**Table 32: 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 (%)
<b>General</b>		
Fatigue <sup>†</sup>	43	5
Pain <sup>‡</sup>	22	2.0
Pyrexia	19	1.0
Edema peripheral <sup>§</sup>	15	2.0
<b>Musculoskeletal and Connective Tissue</b>		
Musculoskeletal pain <sup>¶</sup>	27	5
<b>Gastrointestinal</b>		
Diarrhea <sup>#</sup>	23	2.0
Abdominal pain <sup>b</sup>	22	3.1
Nausea	19	0
Vomiting	19	1.0
Constipation	14	0
<b>Metabolism and Nutrition</b>		
Decreased appetite	21	0
<b>Vascular</b>		
Hemorrhage <sup>§</sup>	19	5
<b>Infections</b>		
UTI <sup>a</sup>	18	6
Infection (except UTI) <sup>§</sup>	16	4.1
<b>Skin and Subcutaneous Tissue</b>		
Rash <sup>o</sup>	17	2.0
<b>Endocrine</b>		



Hypothyroidism	11	0
<b>Nervous System</b>		
Headache	11	2.0
<b>Respiratory, Thoracic and Mediastinal</b>		
Dyspnea	10	1.0

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

**Table 33: 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 (%)
<b>Hematology</b>		
Anemia	54	24
Lymphopenia	47	9
<b>Chemistry</b>		
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).

### BTC

The safety of KEYTRUDA in combination with gemcitabine and cisplatin, was investigated in KEYNOTE-966, a multicenter, double-blind, randomized, placebo-controlled trial in patients with locally advanced unresectable or metastatic BTC who had not received prior systemic therapy in the advanced disease setting [see *Clinical Studies (14.12)*]. A total of 1063 patients received either KEYTRUDA 200 mg

plus gemcitabine and cisplatin chemotherapy (n=529) or placebo plus gemcitabine and cisplatin chemotherapy (n=534) every 3 weeks.

The median duration of exposure to KEYTRUDA was 6 months (range: 1 day to 28 months).

KEYTRUDA was discontinued for adverse reactions in 15% of patients. The most common adverse reaction resulting in permanent discontinuation of KEYTRUDA ( $\geq 1\%$ ) was pneumonitis (1.3%).

Adverse reactions leading to the interruption of KEYTRUDA occurred in 55% of patients. The most common adverse reactions or laboratory abnormalities leading to interruption of KEYTRUDA ( $\geq 2\%$ ) were decreased neutrophil count (18%), decreased platelet count (10%), anemia (6%), decreased white blood count (4%), pyrexia (3.8%), fatigue (3.0%), cholangitis (2.8%), increased ALT (2.6%), increased AST (2.5%), and biliary obstruction (2.3%).

In the KEYTRUDA plus chemotherapy versus placebo plus chemotherapy arms, there was a difference of  $\geq 5\%$  incidence in adverse reactions between patients treated with KEYTRUDA versus placebo for pyrexia (26% vs 20%), rash (21% vs 13%), pruritus (15% vs 10%), and hypothyroidism (9% vs. 2.6%). There were no clinically meaningful differences in incidence of Grade 3-4 toxicity between arms.

There was a difference of  $\geq 5\%$  incidence in laboratory abnormalities between patients treated with KEYTRUDA plus chemotherapy versus placebo plus chemotherapy for decreased lymphocytes (69% vs 61%). There were no clinically meaningful differences in incidence of Grade 3-4 toxicity between arms.

## MCC

Among the 105 patients with MCC enrolled in KEYNOTE-017 and KEYNOTE-913 [see *Clinical Studies (14.13)*], the median duration of exposure to KEYTRUDA was 6.3 months (range 1 day to 28 months). Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible. Adverse reactions occurring in patients with MCC were similar to those occurring in 2799 patients with melanoma or NSCLC treated with KEYTRUDA as a single agent. Laboratory abnormalities (Grades 3-4) that occurred at a higher incidence included increased lipase (17%).

## RCC

*In combination with axitinib in the first-line treatment of advanced RCC (KEYNOTE-426)*

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

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

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

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

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

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

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

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

Tables 34 and 35 summarize the adverse reactions and laboratory abnormalities, respectively, that occurred in at least 20% of patients treated with KEYTRUDA and axitinib in KEYNOTE-426.

**Table 34: 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 (%)
<b>Gastrointestinal</b>				
Diarrhea†	56	11	45	5
Nausea	28	0.9	32	0.9
Constipation	21	0	15	0.2
<b>General</b>				
Fatigue/Asthenia	52	5	51	10
<b>Vascular</b>				
Hypertension‡	48	24	48	20
<b>Hepatobiliary</b>				
Hepatotoxicity§	39	20	25	4.9
<b>Endocrine</b>				
Hypothyroidism	35	0.2	32	0.2
<b>Metabolism and Nutrition</b>				
Decreased appetite	30	2.8	29	0.7
<b>Skin and Subcutaneous Tissue</b>				
Palmar-plantar erythrodysesthesia syndrome	28	5	40	3.8
Stomatitis/Mucosal inflammation	27	1.6	41	4
Rash¶	25	1.4	21	0.7
<b>Respiratory, Thoracic and Mediastinal</b>				
Dysphonia	25	0.2	3.3	0
Cough	21	0.2	14	0.5

\*Graded per NCI CTCAE v4.03

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

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

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

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

Other clinically important adverse reactions occurring in patients receiving KEYTRUDA and axitinib were cardiac arrhythmias (5.8%) including atrial fibrillation (1.6%).

**Table 35: 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 <sup>†</sup> %	Grades 3-4 %	All Grades %	Grades 3-4 %
<b>Chemistry</b>				
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 <sup>‡</sup>	22	0.2	29	0.7
Blood bilirubin increased	22	2.1	21	1.9
Activated partial thromboplastin time prolonged <sup>§</sup>	22	1.2	14	0
<b>Hematology</b>				
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.

#### *In combination with lenvatinib in the first-line treatment of advanced RCC (KEYNOTE-581)*

The safety of KEYTRUDA was evaluated in KEYNOTE-581 [see *Clinical Studies 14.14*]. Patients received KEYTRUDA 200 mg intravenously every 3 weeks in combination with lenvatinib 20 mg orally once daily (n=352), or lenvatinib 18 mg orally once daily in combination with everolimus 5 mg orally once daily (n=355), or sunitinib 50 mg orally once daily for 4 weeks then off treatment for 2 weeks (n=340). The median duration of exposure to the combination therapy of KEYTRUDA and lenvatinib was 17 months (range: 0.1 to 39).

Fatal adverse reactions occurred in 4.3% of patients treated with KEYTRUDA in combination with lenvatinib, including cardio-respiratory arrest (0.9%), sepsis (0.9%), and one case (0.3%) each of arrhythmia, autoimmune hepatitis, dyspnea, hypertensive crisis, increased blood creatinine, multiple organ dysfunction syndrome, myasthenic syndrome, myocarditis, nephritis, pneumonitis, ruptured aneurysm, and subarachnoid hemorrhage.

Serious adverse reactions occurred in 51% of patients receiving KEYTRUDA and lenvatinib. Serious adverse reactions in  $\geq 2\%$  of patients were hemorrhagic events (5%), diarrhea (4%), hypertension (3%), myocardial infarction (3%), pneumonitis (3%), vomiting (3%), acute kidney injury (2%), adrenal insufficiency (2%), dyspnea (2%), and pneumonia (2%).

Permanent discontinuation of either of KEYTRUDA, lenvatinib or both due to an adverse reaction occurred in 37% of patients receiving KEYTRUDA in combination with lenvatinib; 29% KEYTRUDA only, 26% lenvatinib only, and 13% both. The most common adverse reactions ( $\geq 2\%$ ) resulting in permanent discontinuation of KEYTRUDA, lenvatinib, or the combination were pneumonitis (3%), myocardial infarction (3%), hepatotoxicity (3%), acute kidney injury (3%), rash (3%), and diarrhea (2%).

Dose interruptions of KEYTRUDA, lenvatinib, or both due to an adverse reaction occurred in 78% of patients receiving KEYTRUDA in combination with lenvatinib. KEYTRUDA was interrupted in 55% of patients and both drugs were interrupted in 39% of patients. The most common adverse reactions ( $\geq 3\%$ ) resulting in interruption of KEYTRUDA were diarrhea (10%), hepatotoxicity (8%), fatigue (7%), lipase increased (5%), amylase increased (4%), musculoskeletal pain (3%), hypertension (3%), rash (3%), acute kidney injury (3%), and decreased appetite (3%).

Fifteen percent (15%) of patients treated with KEYTRUDA in combination with lenvatinib received an oral prednisone equivalent to  $\geq 40$  mg daily for an immune-mediated adverse reaction.

Tables 36 and 37 summarize the adverse reactions and laboratory abnormalities, respectively, that occurred in  $\geq 20\%$  of patients treated with KEYTRUDA and lenvatinib in KEYNOTE-581.

**Table 36: Adverse Reactions Occurring in  $\geq 20\%$  of Patients Receiving KEYTRUDA with Lenvatinib in KEYNOTE-581**

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks with Lenvatinib N=352		Sunitinib 50 mg N=340	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
<b>General</b>				
Fatigue*	63	9	56	8
<b>Gastrointestinal</b>				
Diarrhea†	62	10	50	6
Stomatitis‡	43	2	43	2
Nausea	36	3	33	1
Abdominal pain§	27	2	18	1
Vomiting	26	3	20	1
Constipation	25	1	19	0
<b>Musculoskeletal and Connective Tissue</b>				
Musculoskeletal disorders¶	58	4	41	3
<b>Endocrine</b>				
Hypothyroidism#	57	1	32	0
<b>Vascular</b>				
Hypertension <sup>p</sup>	56	29	43	20
Hemorrhagic events <sup>§</sup>	27	5	26	4
<b>Metabolism</b>				
Decreased appetite <sup>a</sup>	41	4	31	1
<b>Skin and Subcutaneous Tissue</b>				
Rash <sup>§</sup>	37	5	17	1
Palmar-plantar erythrodysesthesia syndrome <sup>o</sup>	29	4	38	4
<b>Investigations</b>				
Weight loss	30	8	9	0.3
<b>Respiratory, Thoracic and Mediastinal</b>				
Dysphonia	30	0	4	0
<b>Renal and Urinary</b>				
Proteinuria <sup>p</sup>	30	8	13	3
Acute kidney injury <sup>y</sup>	21	5	16	2
<b>Hepatobiliary</b>				
Hepatotoxicity <sup>c</sup>	25	9	21	5
<b>Nervous System</b>				
Headache	23	1	16	1

\* Includes asthenia, fatigue, lethargy, malaise

† Includes diarrhea, gastroenteritis

‡ Includes aphthous ulcer, gingival pain, glossitis, glossodynia, mouth ulceration, mucosal inflammation, oral discomfort, oral mucosal blistering, oral pain, oropharyngeal pain, pharyngeal inflammation, stomatitis

§ Includes abdominal discomfort, abdominal pain, abdominal rigidity, abdominal tenderness, epigastric discomfort, lower abdominal pain, upper abdominal pain

¶ Includes arthralgia, arthritis, back pain, bone pain, breast pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, non-cardiac chest pain, pain in extremity, pain in jaw

# Includes hypothyroidism, increased blood thyroid stimulating hormone, secondary hypothyroidism

<sup>p</sup> Includes essential hypertension, increased blood pressure, increased diastolic blood pressure, hypertension, hypertensive crisis, hypertensive retinopathy, labile blood pressure

<sup>§</sup> Includes all hemorrhage terms. Hemorrhage terms that occurred in 1 or more subjects in either treatment group include Anal hemorrhage, aneurysm ruptured, blood blister, blood loss anemia, blood urine present, catheter site hematoma, cerebral microhemorrhage, conjunctival hemorrhage, contusion, diarrhea hemorrhagic, disseminated intravascular coagulation, ecchymosis, epistaxis, eye hemorrhage, gastric hemorrhage, gastritis hemorrhagic, gingival bleeding, hemorrhage urinary tract, hemothorax, hematemeses, hematoma, hematochezia, hematuria, hemoptysis, hemorrhoidal hemorrhage, increased tendency to bruise, injection site hematoma, injection site hemorrhage, intra-abdominal hemorrhage, lower gastrointestinal hemorrhage, Mallory-Weiss syndrome, melaena, petechiae, rectal hemorrhage, renal hemorrhage, retroperitoneal hemorrhage, small intestinal hemorrhage, splinter hemorrhages, subcutaneous hematoma, subdural hematoma, subarachnoid hemorrhage, thrombotic thrombocytopenic purpura, tumor hemorrhage, traumatic hematoma, upper gastrointestinal hemorrhage

<sup>a</sup> Includes decreased appetite, early satiety

- <sup>e</sup> Includes genital rash, infusion site rash, penile rash, perineal rash, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular
- <sup>d</sup> Includes palmar erythema, palmar-plantar erythrodysesthesia syndrome, plantar erythema
- <sup>o</sup> Includes hemoglobinuria, nephrotic syndrome, proteinuria
- <sup>y</sup> Includes acute kidney injury, azotemia, blood creatinine increased, creatinine renal clearance decreased, hypercreatininemia, renal failure, renal impairment, oliguria, glomerular filtration rate decreased, and nephropathy toxic
- <sup>z</sup> Includes alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, drug-induced liver injury, hepatic enzyme increased, hepatic failure, hepatic function abnormal, hepatocellular injury, hepatotoxicity, hyperbilirubinemia, hypertransaminasemia, immune-mediated hepatitis, liver function test increased, liver injury, transaminases increased, gamma-glutamyltransferase increased

Clinically relevant adverse reactions (<20%) that occurred in patients receiving KEYTRUDA with lenvatinib were myocardial infarction (3%) and angina pectoris (1%).

**Table 37: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% (All Grades)-of Patients Receiving KEYTRUDA with Lenvatinib in KEYNOTE-581**

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks with Lenvatinib		Sunitinib 50 mg	
	All Grades % <sup>†</sup>	Grade 3-4 % <sup>†</sup>	All Grades % <sup>†</sup>	Grade 3-4 % <sup>†</sup>
<b>Chemistry</b>				
Hypertriglyceridemia	80	15	71	15
Hypercholesterolemia	64	5	43	1
Increased lipase	61	34	59	28
Increased creatinine	61	5	61	2
Increased amylase	59	17	41	9
Increased AST	58	7	57	3
Hyperglycemia	55	7	48	3
Increased ALT	52	7	49	4
Hyperkalemia	44	9	28	6
Hypoglycemia	44	2	27	1
Hyponatremia	41	12	28	9
Decreased albumin	34	0.3	22	0
Increased alkaline phosphatase	32	4	32	1
Hypocalcemia	30	2	22	1
Hypophosphatemia	29	7	50	8
Hypomagnesemia	25	2	15	3
Increased creatine phosphokinase	24	6	36	5
Hypermagnesemia	23	2	22	3
Hypercalcemia	21	1	11	1
<b>Hematology</b>				
Lymphopenia	54	9	66	15
Thrombocytopenia	39	2	73	13
Anemia	38	3	66	8
Leukopenia	34	1	77	8
Neutropenia	31	4	72	16

\* With at least one Grade increase from baseline

<sup>†</sup> Laboratory abnormality percentage is based on the number of patients who had both baseline and at least one post-baseline laboratory measurement for each parameter: KEYTRUDA with lenvatinib (range: 343 to 349 patients) and sunitinib (range: 329 to 335 patients).

Grade 3 and 4 increased ALT or AST was seen in 9% of patients. Grade ≥2 increased ALT or AST was reported in 64 (18%) patients, of whom 20 (31%) received ≥40 mg daily oral prednisone equivalent. Recurrence of Grade ≥2 increased ALT or AST was observed on rechallenge in 10 patients receiving both KEYTRUDA and lenvatinib (n=38) and was not observed on rechallenge with KEYTRUDA alone (n=3).

## Adjuvant treatment of RCC

The safety of KEYTRUDA as a single agent was investigated in KEYNOTE-564, a randomized (1:1) double-blind placebo-controlled trial in which 984 patients who had undergone nephrectomy for RCC received 200 mg of KEYTRUDA by intravenous infusion every 3 weeks (n=488) or placebo (n=496) for up to one year [see *Clinical Studies (14.14)*]. The median duration of exposure to KEYTRUDA was 11.1 months (range: 1 day to 14.3 months). Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible.

Serious adverse reactions occurred in 20% of these patients receiving KEYTRUDA. Serious adverse reactions ( $\geq 1\%$ ) were acute kidney injury, adrenal insufficiency, pneumonia, colitis, and diabetic ketoacidosis (1% each). Fatal adverse reactions occurred in 0.2% of those treated with KEYTRUDA, including one case of pneumonia.

Discontinuation of KEYTRUDA due to an adverse reaction occurred in 21% of patients; the most common ( $\geq 1\%$ ) were increased ALT (1.6%), colitis (1%), and adrenal insufficiency (1%).

Dose interruptions of KEYTRUDA due to an adverse reaction occurred in 26% of patients; the most common ( $\geq 1\%$ ) were increased AST (2.3%), arthralgia (1.6%), hypothyroidism (1.6%), diarrhea (1.4%), increased ALT (1.4%), fatigue (1.4%), rash, decreased appetite, and vomiting (1% each). Tables 38 and 39 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-564.

**Table 38: Selected\* Adverse Reactions Occurring in  $\geq 10\%$  of Patients Receiving KEYTRUDA in KEYNOTE-564**

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks n=488		Placebo n=496	
	All Grades <sup>†</sup> (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
<b>Musculoskeletal and Connective Tissue</b>				
Musculoskeletal pain <sup>‡</sup>	41	1.2	36	0.6
<b>General</b>				
Fatigue <sup>§</sup>	40	1.2	31	0.2
<b>Skin and Subcutaneous Tissue</b>				
Rash <sup>¶</sup>	30	1.4	15	0.4
Pruritus	23	0.2	13	0
<b>Gastrointestinal</b>				
Diarrhea <sup>#</sup>	27	2.7	23	0.2
Nausea	16	0.4	10	0
Abdominal pain <sup>♯</sup>	11	0.4	13	0.2
<b>Endocrine</b>				
Hypothyroidism	21	0.2	3.6	0
Hyperthyroidism	12	0.2	0.2	0
<b>Respiratory, Thoracic and Mediastinal</b>				
Cough <sup>®</sup>	17	0	12	0
<b>Nervous System</b>				
Headache <sup>à</sup>	15	0.2	13	0
<b>Hepatobiliary</b>				
Hepatotoxicity <sup>é</sup>	14	3.7	7	0.6
<b>Renal and Urinary</b>				
Acute kidney injury <sup>ó</sup>	13	1.2	10	0.2

\* Adverse reactions occurring at same or higher incidence than in placebo arm

† Graded per NCI CTCAE v4.0

‡ Includes arthralgia, back pain, myalgia, arthritis, pain in extremity, neck pain, musculoskeletal pain, musculoskeletal stiffness, spinal pain, musculoskeletal chest pain, bone pain, musculoskeletal discomfort

§ Includes asthenia, fatigue

¶ Includes rash, rash maculo-papular, rash papular, skin exfoliation, lichen planus, rash erythematous, eczema, rash macular, dermatitis acneiform, dermatitis, rash pruritic, Stevens-Johnson Syndrome, eczema asteatotic, palmar-plantar erythrodysesthesia syndrome

# Includes diarrhea, colitis, enterocolitis, frequent bowel movements, enteritis

♯ Includes abdominal pain, abdominal pain lower, abdominal pain upper, abdominal discomfort, gastrointestinal pain

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

à Includes tension headache, headache, sinus headache, migraine with aura

é Includes alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, drug-induced liver injury, hepatic enzyme increased, hepatic function abnormal, hepatocellular injury, hepatotoxicity, hyperbilirubinemia, immune-mediated hepatitis, liver function test increased,

- transaminases increased, gamma-glutamyltransferase increased, bilirubin conjugated increased
- Includes acute kidney injury, blood creatinine increased, renal failure, renal impairment, oliguria, glomerular filtration rate decreased, nephropathy toxic

**Table 39: Selected\* Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients Receiving KEYTRUDA in KEYNOTE-564**

Laboratory Test†	KEYTRUDA 200 mg every 3 weeks		Placebo	
	All Grades‡ %	Grades 3-4 %	All Grades %	Grades 3-4 %
<b>Chemistry</b>				
Increased glucose	48	8	45	4.5
Increased creatinine	40	1.1	28	0.2
Increased INR	27	0.9	20	0.8
Hyponatremia	21	3.3	13	1.9
Increased ALT	20	3.8	11	0.2
<b>Hematology</b>				
Anemia	28	0.5	20	0.4

\* Laboratory abnormalities occurring at same or higher incidence than placebo

† Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (range: 440 to 449 patients) and placebo (range: 461 to 469 patients); increased INR: KEYTRUDA n=228 and placebo n=254.

‡ Graded per NCI CTCAE v4.03

### Endometrial Carcinoma

The safety of KEYTRUDA in combination with lenvatinib was investigated in KEYNOTE-775, a multicenter, open-label, randomized (1:1), active-controlled trial in 827 patients with advanced endometrial carcinoma previously treated with at least one prior platinum-based chemotherapy regimen in any setting, including in the neoadjuvant and adjuvant settings [see *Clinical Studies (14.15)*]. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible. Patients received KEYTRUDA 200 mg intravenously every 3 weeks with lenvatinib 20 mg orally once daily (n=406), or treatment of investigator's choice (n=388), consisting of 60 mg/m<sup>2</sup> doxorubicin every 3 weeks or 80 mg/m<sup>2</sup> paclitaxel given weekly, 3 weeks on/1 week off.

The median duration of study treatment was 7.6 months (range 1 day to 26.8 months). The median duration of exposure to KEYTRUDA was 6.9 months (range: 1 day to 25.8 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 5.7% of patients treated with KEYTRUDA and lenvatinib, including pneumonia, acute kidney injury, acute myocardial infarction, cerebrovascular accident, colitis, decreased appetite, intestinal perforation, lower gastrointestinal hemorrhage, malignant gastrointestinal obstruction, multiple organ dysfunction syndrome, myelodysplastic syndrome, pulmonary embolism, right ventricular dysfunction, urosepsis, and vaginal hemorrhage.

Serious adverse reactions occurred in 53% of patients receiving KEYTRUDA and lenvatinib. Serious adverse reactions with frequency ≥3% were hypertension (4.2%) and urinary tract infections (3.2%).

Discontinuation of KEYTRUDA, lenvatinib or both due to an adverse reaction (Grades 1-4) occurred in 30% of patients; 15% KEYTRUDA, and 11% both drugs. The most common adverse reactions leading to discontinuation of KEYTRUDA were diarrhea, increased ALT, and intestinal obstruction (each 1.0%). Refer to the lenvatinib prescribing information for lenvatinib discontinuation information.

Dose interruptions of KEYTRUDA, lenvatinib, or both due to an adverse reaction occurred in 69% of patients; KEYTRUDA was interrupted in 50%, and both drugs were interrupted in 31% of patients. The most common adverse reactions leading to interruption of KEYTRUDA (≥2%) were diarrhea (8%), increased ALT (3.9%), hypertension (3.4%), increased AST (3.2%), decreased appetite (2.2%), fatigue (2.2%), urinary tract infection (2.2%), proteinuria (2.0%), and asthenia (2.0%). Refer to the lenvatinib prescribing information for lenvatinib interruption information.

Tables 40 and 41 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in combination with lenvatinib in KEYNOTE-775.



**Table 40: Adverse Reactions Occurring in ≥20% of Patients with Endometrial Carcinoma in KEYNOTE-775**

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks and Lenvatinib n=406		Doxorubicin or Paclitaxel n=388	
	All Grades* (%)	Grades 3-4 (%)	All Grades* (%)	Grades 3-4 (%)
<b>Endocrine</b>				
Hypothyroidism <sup>†</sup>	69	1	1	0
<b>Vascular</b>				
Hypertension <sup>‡</sup>	65	38	6	2
Hemorrhagic events <sup>§</sup>	24	2	13	<1
<b>General</b>				
Fatigue <sup>¶</sup>	59	11	54	7
<b>Gastrointestinal</b>				
Diarrhea <sup>#</sup>	54	8	21	2
Nausea	50	3	46	1
Vomiting	37	3	21	2
Stomatitis <sup>ⓑ</sup>	35	3	25	1
Abdominal pain <sup>ⓑ</sup>	33	3	21	2
Constipation	26	<1	25	<1
<b>Musculoskeletal and Connective Tissue</b>				
Musculoskeletal disorders <sup>ⓐ</sup>	52	5	26	<1
<b>Metabolism</b>				
Decreased appetite <sup>ⓓ</sup>	45	8	21	<1
<b>Investigations</b>				
Weight loss	34	10	6	<1
<b>Renal and Urinary</b>				
Proteinuria <sup>ⓓ</sup>	30	5	3	<1
<b>Infections</b>				
Urinary tract infection <sup>ⓞ</sup>	29	5	12	1
<b>Nervous System</b>				
Headache	25	<1	9	<1
<b>Respiratory, Thoracic and Mediastinal</b>				
Dysphonia	23	0	<1	0
<b>Skin and Subcutaneous Tissue</b>				
Palmar-plantar erythrodysesthesia <sup>Ⓨ</sup>	22	3	1	0
Rash <sup>Ⓩ</sup>	20	2	4	0

\* Graded per NCI CTCAE v4.03

† Includes hypothyroidism, blood thyroid stimulating hormone increased, thyroiditis, primary hypothyroidism, secondary hypothyroidism

‡ Includes hypertension, blood pressure increased, hypertensive crisis, secondary hypertension, blood pressure abnormal, hypertensive encephalopathy, blood pressure fluctuation

§ Includes epistaxis, vaginal hemorrhage, hematuria, gingival bleeding, metrorrhagia, rectal hemorrhage, contusion, hematochezia, cerebral hemorrhage, conjunctival hemorrhage, gastrointestinal hemorrhage, hemoptysis, hemorrhage urinary tract, lower gastrointestinal hemorrhage, mouth hemorrhage, petechiae, uterine hemorrhage, anal hemorrhage, blood blister, eye hemorrhage, hematoma, hemorrhage intracranial, hemorrhagic stroke, injection site hemorrhage, melena, purpura, stoma site hemorrhage, upper gastrointestinal hemorrhage, wound hemorrhage, blood urine present, coital bleeding, ecchymosis, hematemesis, hemorrhage subcutaneous, hepatic hematoma, injection site bruising, intestinal hemorrhage, laryngeal hemorrhage, pulmonary hemorrhage, subdural hematoma, umbilical hemorrhage, vessel puncture site bruise

¶ Includes fatigue, asthenia, malaise, lethargy

# Includes diarrhea, gastroenteritis

ⓑ Includes stomatitis, mucosal inflammation, oropharyngeal pain, aphthous ulcer, mouth ulceration, cheilitis, oral mucosal erythema, tongue ulceration

ⓑ Includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, gastrointestinal pain, abdominal tenderness, epigastric discomfort

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

ⓓ Includes decreased appetite, early satiety

ⓓ Includes proteinuria, protein urine present, hemoglobinuria

ⓞ Includes urinary tract infection, cystitis, pyelonephritis

Ⓨ Includes palmar-plantar erythrodysesthesia syndrome, palmar erythema, plantar erythema, skin reaction

Ⓩ Includes rash, rash maculo-papular, rash pruritic, rash erythematous, rash macular, rash pustular, rash papular, rash vesicular, application site rash

**Table 41: Laboratory Abnormalities Worsened from Baseline\* Occurring in  $\geq 20\%$  (All Grades) or  $\geq 3\%$  (Grades 3-4) of Patients with Endometrial Carcinoma in KEYNOTE-775**

Laboratory Test <sup>†</sup>	KEYTRUDA 200 mg every 3 weeks and Lenvatinib		Doxorubicin or Paclitaxel	
	All Grades <sup>‡</sup> %	Grades 3-4 %	All Grades <sup>‡</sup> %	Grades 3-4 %
<b>Chemistry</b>				
Hypertriglyceridemia	69	7	43	2
Hypoalbuminemia	61	3	42	2
Increased aspartate aminotransferase	58	9	22	1
Hyperglycemia	57	8	45	4
Hypomagnesemia	54	7	33	4
Increased alanine aminotransferase	53	8	21	1
Hypercholesterolemia	53	3	22	<1
Hyponatremia	47	14	27	7
Increased alkaline phosphatase	43	4	19	1
Hypocalcemia	40	4	20	2
Increased lipase	35	14	12	4
Increased creatinine	35	4	17	2
Hypokalemia	34	11	23	5
Hypophosphatemia	25	8	18	4
Increased amylase	25	7	7	1
Hyperkalemia	24	2	13	2
Increased creatine kinase	20	3	6	0
Increased bilirubin	19	3	6	2
<b>Hematology</b>				
Lymphopenia	51	17	65	22
Thrombocytopenia	51	7	30	5
Anemia	50	8	84	16
Leukopenia	44	3	83	42
Neutropenia	33	6	75	57

\* With at least one grade increase from baseline

† Laboratory abnormality percentage is based on the number of patients who had both baseline and at least one post-baseline laboratory measurement for each parameter: KEYTRUDA/lenvatinib (range: 312 to 404 patients) and doxorubicin or paclitaxel (range: 280 to 380 patients).

‡ Graded per NCI CTCAE v4.03

### TMB-H Cancer

The safety of KEYTRUDA was investigated in 105 patients with TMB-H cancer enrolled in KEYNOTE-158 [see *Clinical Studies (14.16)*]. The median duration of exposure to KEYTRUDA was 4.9 months (range: 0.03 to 35.2 months). Adverse reactions occurring in patients with TMB-H cancer were similar to those occurring in patients with other solid tumors who received KEYTRUDA as a single agent.

### cSCC

Among the 159 patients with advanced cSCC (recurrent or metastatic or locally advanced disease) enrolled in KEYNOTE-629 [see *Clinical Studies (14.17)*], the median duration of exposure to KEYTRUDA was 6.9 months (range 1 day to 28.9 months). Patients with autoimmune disease or a medical condition that required systemic corticosteroids or other immunosuppressive medications were ineligible. Adverse reactions occurring in patients with recurrent or metastatic cSCC or locally advanced cSCC were similar to those occurring in 2799 patients with melanoma or NSCLC treated with KEYTRUDA as a single agent. Laboratory abnormalities (Grades 3-4) that occurred at a higher incidence included lymphopenia (10%) and decreased sodium (10%).

### TNBC

#### *Neoadjuvant and Adjuvant Treatment of High-Risk Early-Stage TNBC*

The safety of KEYTRUDA in combination with neoadjuvant chemotherapy (carboplatin and paclitaxel followed by doxorubicin or epirubicin and cyclophosphamide) followed by surgery and continued adjuvant treatment with KEYTRUDA as a single agent was investigated in KEYNOTE-522, a randomized (2:1),

multicenter, double-blind, placebo-controlled trial in patients with newly diagnosed, previously untreated, high-risk early-stage TNBC.

A total of 778 patients on the KEYTRUDA arm received at least 1 dose of KEYTRUDA in combination with neoadjuvant chemotherapy followed by KEYTRUDA as adjuvant treatment after surgery, compared to 389 patients who received at least 1 dose of placebo in combination with neoadjuvant chemotherapy followed by placebo as adjuvant treatment after surgery [see *Clinical Studies (14.18)*].

The median duration of exposure to KEYTRUDA 200 mg every 3 weeks was 13.3 months (range: 1 day to 21.9 months).

Fatal adverse reactions occurred in 0.9% of patients receiving KEYTRUDA, including 1 each of adrenal crisis, autoimmune encephalitis, hepatitis, pneumonia, pneumonitis, pulmonary embolism, and sepsis in association with multiple organ dysfunction syndrome and myocardial infarction.

Serious adverse reactions occurred in 44% of patients receiving KEYTRUDA. Serious adverse reactions in  $\geq 2\%$  of patients who received KEYTRUDA included febrile neutropenia (15%), pyrexia (3.7%), anemia (2.6%), and neutropenia (2.2%).

KEYTRUDA was discontinued for adverse reactions in 20% of patients. The most common adverse reactions ( $\geq 1\%$ ) resulting in permanent discontinuation of KEYTRUDA were increased ALT (2.7%), increased AST (1.5%), and rash (1%). Adverse reactions leading to the interruption of KEYTRUDA occurred in 57% of patients. The most common adverse reactions leading to interruption of KEYTRUDA ( $\geq 2\%$ ) were neutropenia (26%), thrombocytopenia (6%), increased ALT (6%), increased AST (3.7%), anemia (3.5%), rash (3.2%), febrile neutropenia (2.8%), leukopenia (2.8%), upper respiratory tract infection (2.6%), pyrexia (2.2%), and fatigue (2.1%).

Tables 42 and 43 summarize the adverse reactions and laboratory abnormalities, respectively, in patients treated with KEYTRUDA in KEYNOTE-522.

**Table 42: Adverse Reactions Occurring in  $\geq 20\%$  of Patients Receiving KEYTRUDA in KEYNOTE-522**

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks with chemotherapy*/KEYTRUDA n=778		Placebo with chemotherapy*/Placebo n=389	
	All Grades <sup>†</sup> (%)	Grades 3-4 (%)	All Grades <sup>†</sup> (%)	Grades 3-4 (%)

<b>General</b>				
Fatigue <sup>‡</sup>	70	8	66	3.9
Pyrexia	28	1.3	19	0.3
<b>Gastrointestinal</b>				
Nausea	67	3.7	66	1.8
Constipation	42	0	39	0.3
Diarrhea	41	3.2	34	1.8
Stomatitis <sup>§</sup>	34	2.7	29	1
Vomiting	31	2.7	28	1.5
Abdominal pain <sup>¶</sup>	24	0.5	23	0.8
<b>Skin and Subcutaneous Tissue</b>				
Alopecia	61	0	58	0
Rash <sup>#</sup>	52	5	41	0.5
<b>Nervous System</b>				
Peripheral neuropathy <sup>Ⓟ</sup>	41	3.3	42	2.3
Headache	30	0.5	29	1
<b>Musculoskeletal and Connective Tissue</b>				
Arthralgia	29	0.5	31	0.3
Myalgia	20	0.5	19	0
<b>Respiratory, Thoracic and Mediastinal</b>				
Cough <sup>Ⓠ</sup>	26	0.1	24	0
<b>Metabolism and Nutrition</b>				
Decreased appetite	23	0.9	17	0.3
<b>Psychiatric</b>				
Insomnia	21	0.5	19	0

\* Chemotherapy: carboplatin and paclitaxel followed by doxorubicin or epirubicin and cyclophosphamide

† Graded per NCI CTCAE v4.0

‡ Includes asthenia, fatigue

§ Includes aphthous ulcer, cheilitis, lip pain, lip ulceration, mouth ulceration, mucosal inflammation, oral mucosal eruption, oral pain, stomatitis, tongue blistering, tongue ulceration

¶ Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness

# Includes dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis bullous, dermatitis exfoliative generalized, drug eruption, eczema, incision site rash, injection site rash, rash, rash erythematous, rash follicular, rash macular, rash maculo-papular, rash morbilliform, rash papular, rash pruritic, rash pustular, rash rubelliform, skin exfoliation, skin toxicity, toxic skin eruption, urticaria, vasculitic rash, viral rash

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

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

**Table 43: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients Receiving KEYTRUDA in KEYNOTE-522**

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks with chemotherapy <sup>†</sup> /KEYTRUDA		Placebo with chemotherapy <sup>†</sup> /Placebo	
	All Grades <sup>‡</sup> %	Grades 3-4 %	All Grades <sup>‡</sup> %	Grades 3-4 %

<b>Hematology</b>				
Anemia	97	22	96	19
Leukopenia	93	41	91	32
Neutropenia	88	62	89	62
Lymphopenia	80	28	74	22
Thrombocytopenia	58	11	57	9
<b>Chemistry</b>				
Increased ALT	71	9	69	4.6
Increased AST	66	6	58	1.8
Hyperglycemia	65	5	62	2.8
Increased alkaline phosphatase	41	1	37	0.8
Hyponatremia	38	9	28	6
Hypoalbuminemia	36	1.2	30	1.5
Hypocalcemia	32	3.2	29	4.4
Hypokalemia	32	6	24	2.8
Hypophosphatemia	23	6	18	4.5
Hypercalcemia	21	3	24	3.4

\* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA in combination with chemotherapy followed by KEYTRUDA as a single agent (range: 759 to 777 patients) and placebo in combination with chemotherapy followed by placebo (range: 378 to 389 patients).

† Chemotherapy: carboplatin and paclitaxel followed by doxorubicin or epirubicin and cyclophosphamide

‡ Graded per NCI CTCAE v4.0

### *Locally Recurrent Unresectable or Metastatic TNBC*

The safety of KEYTRUDA in combination with paclitaxel, paclitaxel protein bound, or gemcitabine and carboplatin was investigated in KEYNOTE 355, a multicenter, double blind, randomized (2:1), placebo controlled trial in patients with locally recurrent unresectable or metastatic TNBC who had not been previously treated with chemotherapy in the metastatic setting [see *Clinical Studies (14.18)*]. A total of 596 patients (including 34 patients from a safety run-in) received KEYTRUDA 200 mg every 3 weeks in combination with paclitaxel, paclitaxel protein bound, or gemcitabine and carboplatin.

The median duration of exposure to KEYTRUDA was 5.7 months (range: 1 day to 33.0 months). Fatal adverse reactions occurred in 2.5% of patients receiving KEYTRUDA in combination with chemotherapy, including cardio-respiratory arrest (0.7%) and septic shock (0.3%).

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

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

Tables 44 and 45 summarize the adverse reactions and laboratory abnormalities in patients on KEYTRUDA in KEYNOTE-355.

**Table 44: 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 (%)
<b>General</b>				
Fatigue†	48	5	49	4.3
<b>Gastrointestinal</b>				
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
<b>Skin and Subcutaneous Tissue</b>				
Alopecia	34	0.8	35	1.1
Rash‡	26	2	16	0
<b>Respiratory, Thoracic and Mediastinal</b>				
Cough§	23	0	20	0.4
<b>Metabolism and Nutrition</b>				
Decreased appetite	21	0.8	14	0.4
<b>Nervous System</b>				
Headache¶	20	0.7	23	0.7

\* Graded per NCI CTCAE v4.03

† Includes fatigue and asthenia

‡ Includes rash, rash maculo-papular, rash pruritic, rash pustular, rash macular, rash papular, butterfly rash, rash erythematous, eyelid rash

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

¶ Includes headache, migraine, tension headache

**Table 45: 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 %
<b>Hematology</b>				
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
<b>Chemistry</b>				
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 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of KEYTRUDA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

*Gastrointestinal:* Exocrine pancreatic insufficiency

*Hepatobiliary:* sclerosing cholangitis

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form <https://sideeffects.health.gov.it>

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

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

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

#### Data

##### *Animal Data*

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

### 8.2 Lactation

#### Risk Summary

There are no data on the presence of pembrolizumab in either animal or human milk or its effects on the breastfed child or on milk production. Maternal IgG is known to be present in human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed child to KEYTRUDA are unknown. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with KEYTRUDA and for 4 months after the last dose.

### 8.3 Females and Males of Reproductive Potential

#### Pregnancy Testing

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

#### Contraception

KEYTRUDA can cause fetal harm when administered to a pregnant woman [*see Warnings and Precautions (5.5), Use in Specific Populations (8.1)*]. Advise females of reproductive potential to use effective contraception during treatment with KEYTRUDA and for 4 months after the last dose.

### 8.4 Pediatric Use

The safety and effectiveness of KEYTRUDA as a single agent have been established in pediatric patients with melanoma, cHL, PMBCL, MCC, MSI-H or dMMR cancer, and TMB-H cancer. Use of KEYTRUDA in pediatric patients for these indications is supported by evidence from adequate and well-controlled studies

in adults with additional pharmacokinetic and safety data in pediatric patients [see *Adverse Reactions* (6.1), *Clinical Pharmacology* (12.3), *Clinical Studies* (14.1, 14.4, 14.5, 14.7, 14.13, 14.16)].

In KEYNOTE-051, 173 pediatric patients (65 pediatric patients aged 6 months to younger than 12 years and 108 pediatric patients aged 12 to 17 years) with advanced melanoma, lymphoma, or PD-L1 positive or MSI-H solid tumors received KEYTRUDA 2 mg/kg every 3 weeks. The median duration of exposure was 2.1 months (range: 1 day to 25 months). Adverse reactions that occurred at a  $\geq 10\%$  higher rate in pediatric patients when compared to adults included pyrexia (33%), vomiting (29%), headache (25%), abdominal pain (23%), decreased lymphocyte count (13%), and decreased white blood cell count (11%). Laboratory abnormalities that occurred at a  $\geq 10\%$  higher rate in pediatric patients when compared to adults were leukopenia (31%), neutropenia (28%), thrombocytopenia (22%), and Grade 3 anemia (17%).

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

## 8.5 Geriatric Use

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

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

Of 506 adult patients with Stage IB (T2a  $\geq 4$  cm), II, or IIIA NSCLC following complete resection and platinum-based chemotherapy who were treated with KEYTRUDA in KEYNOTE-091, 242 (48%) were 65 years and over. No overall differences in safety or effectiveness were observed between elderly patients and younger patients.

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

Of 406 adult patients with endometrial carcinoma who were treated with KEYTRUDA in combination with lenvatinib in KEYNOTE-775, 201 (50%) were 65 years and over. No overall differences in safety or effectiveness were observed between elderly patients and younger patients.

Of the 432 patients randomized to KEYTRUDA in combination with axitinib in the KEYNOTE-426 trial, 40% were 65 years or older. No overall difference in safety or efficacy was reported between patients who were  $\geq 65$  years of age and younger.

## 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 100 mg/4 mL 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: sucrose (70 mg), L-histidine (1.55 mg), polysorbate 80 (0.2 mg), and Water for Injection, USP.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors.

Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor



immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.

In syngeneic mouse tumor models, combination treatment of a PD-1 blocking antibody and kinase inhibitor lenvatinib decreased tumor-associated macrophages, increased activated cytotoxic T cells, and reduced tumor growth compared to either treatment alone.

## 12.2 Pharmacodynamics

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

## 12.3 Pharmacokinetics

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

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

### Distribution

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

### Elimination

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

### Specific Populations

The following factors had no clinically important effect on the CL of pembrolizumab: age (range: 15 to 94 years), sex, race (89% White), renal impairment ( $eGFR \geq 15$  mL/min/1.73 m<sup>2</sup>), mild to moderate hepatic impairment (total bilirubin  $\leq 3$  times ULN and any AST), or tumor burden. The impact of severe hepatic impairment (total bilirubin  $>3$  times ULN and any AST) on the pharmacokinetics of pembrolizumab is unknown.

*Pediatric Patients:* Pembrolizumab concentrations with weight-based dosing at 2 mg/kg every 3 weeks in pediatric patients (10 months to 17 years) are comparable to those of adults at the same dose.

## 12.6 Immunogenicity

The observed incidence of anti-drug antibodies (ADA) is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of ADA in the studies described in this section with the incidence of ADA in other studies, including those of KEYTRUDA or of other pembrolizumab products.

Trough levels of pembrolizumab interfere with the electrochemiluminescent (ECL) assay results; therefore, a subset analysis was performed in the KEYTRUDA-treated patients with a pembrolizumab concentration below the drug tolerance level of the ADA assay.

In clinical studies in patients treated with KEYTRUDA at a dosage of 2 mg/kg every 3 weeks, 200 mg every 3 weeks, or 10 mg/kg every 2 or 3 weeks, 27 (2.1%) of 1,289 evaluable patients tested positive for treatment-emergent anti-pembrolizumab antibodies of whom 6 (0.5%) patients had neutralizing antibodies against pembrolizumab. There were no identified clinically significant effects of ADA on pembrolizumab pharmacokinetics or on the risk of infusion reactions. Because of the low occurrence of ADA, the effect of these ADA on the effectiveness of KEYTRUDA is unknown.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

### 13.2 Animal Toxicology and/or Pharmacology

In animal models, inhibition of PD-1/PD-L1 signaling increased the severity of some infections and enhanced inflammatory responses. *Mycobacterium tuberculosis*-infected PD-1 knockout mice exhibit markedly decreased survival compared with wild-type controls, which correlated with increased bacterial proliferation and inflammatory responses in these animals. PD-1 blockade using a primate anti-PD-1 antibody was also shown to exacerbate *M. tuberculosis* infection in rhesus macaques. PD-1 and PD-L1 knockout mice and mice receiving PD-L1-blocking antibody have also shown decreased survival following infection with lymphocytic choriomeningitis virus. Administration of pembrolizumab in chimpanzees with naturally occurring chronic hepatitis B infection resulted in two out of four animals with significantly increased levels of serum ALT, AST, and GGT, which persisted for at least 1 month after discontinuation of pembrolizumab.

## 14 CLINICAL STUDIES

### 14.1 Melanoma

#### Ipilimumab-Naive Melanoma

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

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

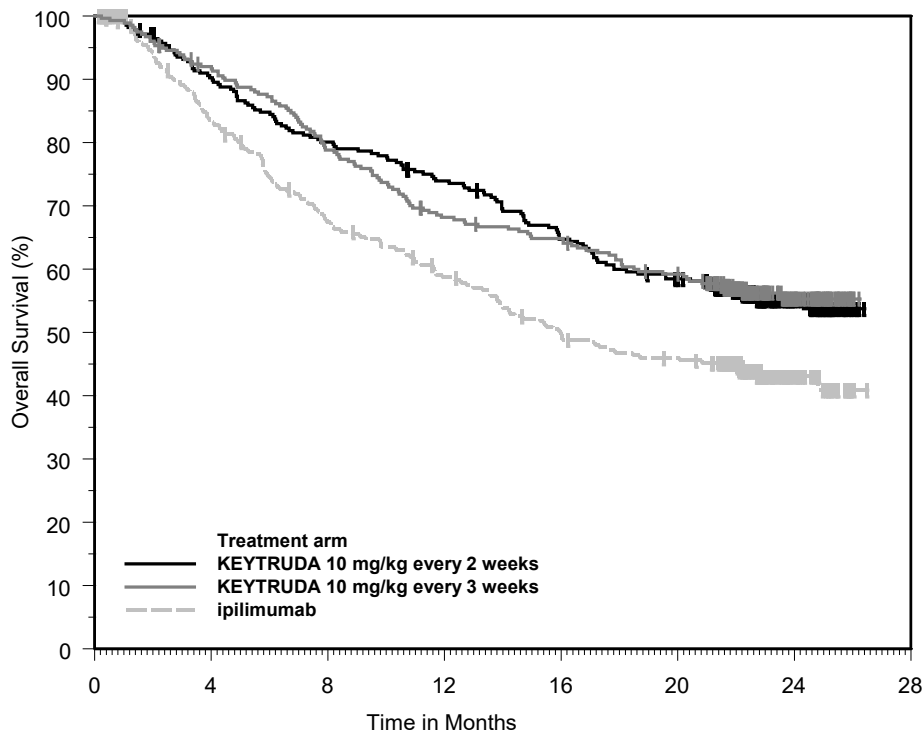
The study demonstrated statistically significant improvements in OS and PFS for patients randomized to KEYTRUDA as compared to ipilimumab. Among the 91 patients randomized to KEYTRUDA 10 mg/kg every 3 weeks with an objective response, response durations ranged from 1.4+ to 8.1+ months. Among the 94 patients randomized to KEYTRUDA 10 mg/kg every 2 weeks with an objective response, response durations ranged from 1.4+ to 8.2 months. Efficacy results are summarized in Table 46 and Figure 1.

**Table 46: 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
<b>OS</b>			
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	---
<b>PFS by BICR</b>			
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	---
<b>Best objective response by BICR</b>			
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	0	4	8	12	16	20	24	28
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<sup>2</sup> intravenously every 3 weeks (26%), temozolomide 200 mg/m<sup>2</sup> orally once daily for 5 days every 28 days (25%), carboplatin AUC 6 mg/mL/min intravenously plus paclitaxel 225 mg/m<sup>2</sup> intravenously every 3 weeks for four cycles then carboplatin AUC of 5 mg/mL/min plus paclitaxel 175 mg/m<sup>2</sup> every 3 weeks (25%), paclitaxel 175 mg/m<sup>2</sup> intravenously every 3 weeks (16%), or carboplatin AUC 5 or 6 mg/mL/min intravenously every 3 weeks (8%). Randomization was stratified by ECOG PS (0 vs. 1), LDH levels (normal vs. elevated [ $\geq 110\%$  ULN]) and BRAF V600 mutation status (wild-type [WT] or V600E). The trial included patients with unresectable or metastatic melanoma with progression of disease; refractory to two or more doses of ipilimumab (3 mg/kg or higher) and, if BRAF V600 mutation-positive, a BRAF or MEK inhibitor; and disease progression within 24 weeks following the last dose of ipilimumab. The trial excluded patients with uveal melanoma and active brain metastasis. Patients received KEYTRUDA until unacceptable toxicity; disease progression that was symptomatic, was rapidly progressive, required urgent intervention, occurred with a decline in performance status, or was confirmed at 4 to 6 weeks with repeat imaging; withdrawal of consent; or physician's decision to stop therapy for the patient. Assessment of tumor status was performed at 12 weeks after randomization, then every 6 weeks through week 48, followed by every 12 weeks thereafter. Patients on chemotherapy who experienced progression of disease were offered KEYTRUDA. The major efficacy outcomes were PFS as assessed by BICR per RECIST v1.1 modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, and OS. Additional efficacy outcome measures were confirmed ORR as assessed by BICR per RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, and DoR.

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

The study demonstrated a statistically significant improvement in PFS for patients randomized to KEYTRUDA as compared to control arm. There was no statistically significant difference between KEYTRUDA 2 mg/kg and chemotherapy or between KEYTRUDA 10 mg/kg and chemotherapy in the OS analysis in which 55% of the patients who had been randomized to receive chemotherapy had crossed over to receive KEYTRUDA. Among the 38 patients randomized to KEYTRUDA 2 mg/kg with an objective response, response durations ranged from 1.3+ to 11.5+ months. Among the 46 patients randomized to KEYTRUDA 10 mg/kg with an objective response, response durations ranged from 1.1+ to 11.1+ months. Efficacy results are summarized in Table 47 and Figure 2.

**Table 47: Efficacy Results in KEYNOTE 002**

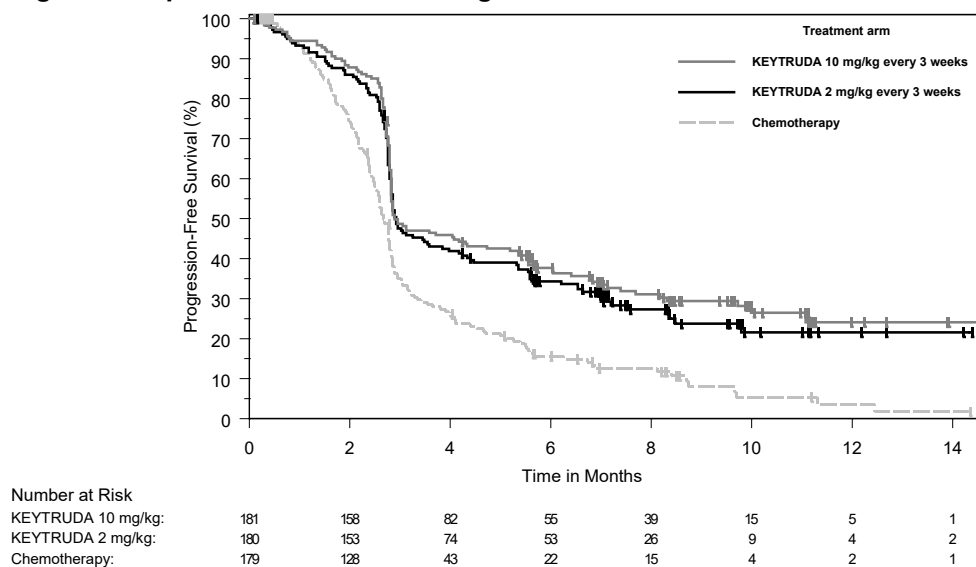
Endpoint	KEYTRUDA 2 mg/kg every 3 weeks n=180	KEYTRUDA 10 mg/kg every 3 weeks n=181	Chemotherapy  n=179
<b>PFS</b>			
Number of Events, n (%)	129 (72%)	126 (70%)	155 (87%)
Progression, n (%)	105 (58%)	107 (59%)	134 (75%)
Death, n (%)	24 (13%)	19 (10%)	21 (12%)
Median in months (95% CI)	2.9 (2.8, 3.8)	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)	---
<b>OS<sup>†</sup></b>			
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 <sup>‡</sup>	---
Median in months (95% CI)	13.4 (11.0, 16.4)	14.7 (11.3, 19.5)	11.0 (8.9, 13.8)
<b>Objective Response Rate</b>			
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

<sup>†</sup> With additional follow-up of 18 months after the PFS analysis

<sup>‡</sup> Not statistically significant compared to multiplicity adjusted significance level of 0.01

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



### Adjuvant Treatment of Resected Stage IIB or IIC Melanoma

The efficacy of KEYTRUDA was investigated in KEYNOTE-716 (NCT03553836), a multicenter, randomized (1:1), double-blind, placebo-controlled trial in patients with completely resected Stage IIB or IIC melanoma. Patients were randomized to KEYTRUDA 200 mg or the pediatric ( $\geq 12$  years old) dose of KEYTRUDA 2 mg/kg intravenously (up to a maximum of 200 mg) every three weeks or placebo for up to one year until disease recurrence or unacceptable toxicity. Randomization was stratified by AJCC 8<sup>th</sup> edition T Stage ( $>2.0$ - $4.0$  mm with ulceration vs.  $>4.0$  mm without ulceration vs.  $>4.0$  mm with ulceration). Patients must not have been previously treated for melanoma beyond complete surgical resection for their melanoma prior to study entry. The major efficacy outcome measure was investigator-assessed recurrence-free survival (RFS) (defined as the time between the date of randomization and the date of first recurrence [local, in-transit or regional lymph nodes or distant recurrence] or death, whichever occurred first). New primary melanomas were excluded from the definition of RFS. Distant metastasis-free survival (DMFS), defined as a spread of tumor to distant organs or distant lymph nodes, was an additional efficacy outcome measure. Patients

underwent imaging every six months for one year from randomization, every 6 months from years 2 to 4, and then once in year 5 from randomization or until recurrence, whichever came first.

The study population characteristics were: median age of 61 years (range: 16 to 87), 39% age 65 or older; 60% male; 98% White; and 93% ECOG PS of 0 and 7% ECOG PS of 1. Sixty-four percent had Stage IIB and 35% had Stage IIC.

The trial demonstrated a statistically significant improvement in RFS and DMFS for patients randomized to the KEYTRUDA arm compared with placebo. Efficacy results are summarized in Table 48 and Figure 3.

**Table 48: Efficacy Results in KEYNOTE-716**

Endpoint	KEYTRUDA 200 mg every 3 weeks n=487	Placebo n=489
<b>RFS</b>		
Number (%) of patients with event	54 (11%)	82 (17%)
Median in months (95% CI)	NR (22.6, NR)	NR (NR, NR)
Hazard ratio* <sup>†</sup> (95% CI)	0.65 (0.46, 0.92)	
p-Value <sup>†</sup>	0.0132 <sup>‡</sup>	
<b>DMFS</b>		
Number (%) of patients with event	63 (13%)	95 (19%)
Median in months (95% CI)	NR (NR, NR)	NR (NR, NR)
Hazard ratio* <sup>†</sup> (95% CI)	0.64 (0.47, 0.88)	
p-Value <sup>†</sup>	0.0058 <sup>§</sup>	

\* Based on the stratified Cox proportional hazard model

<sup>†</sup> Based on a log-rank test stratified by American Joint Committee on Cancer 8<sup>th</sup> edition (AJCC) stage

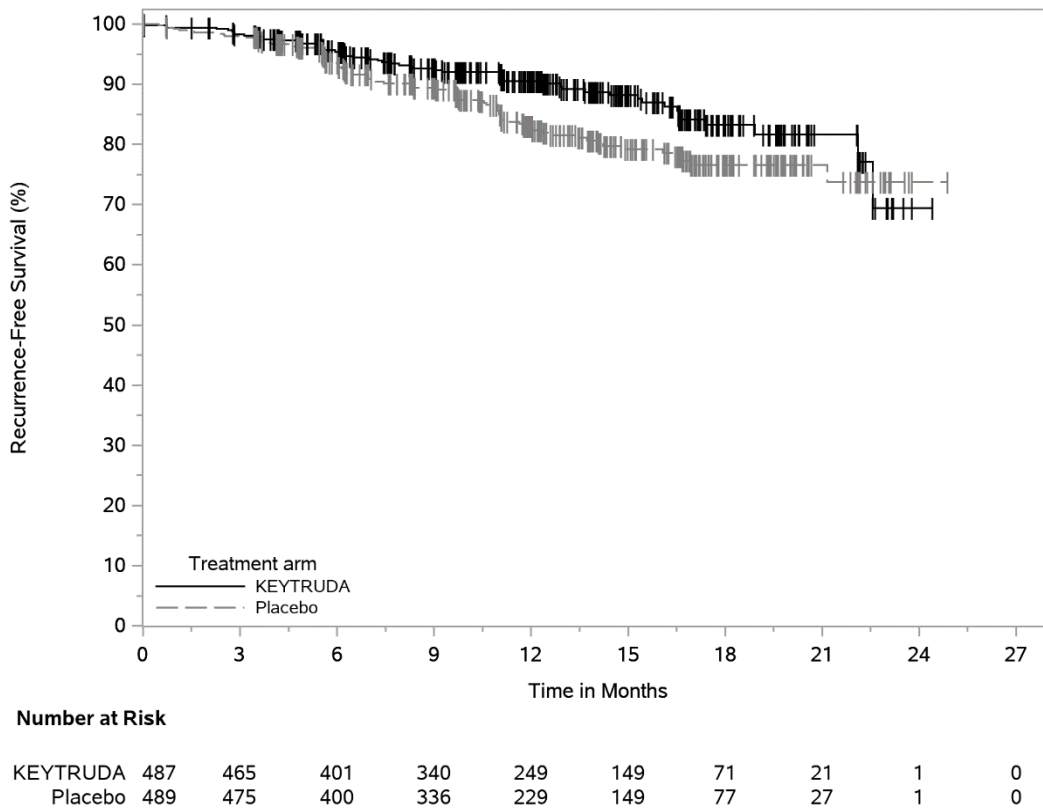
<sup>‡</sup> p-Value is compared with 0.0202 of the allocated alpha for this interim analysis.

<sup>§</sup> p-Value is compared with 0.0256 of the allocated alpha for this interim analysis.

NR = not reached

For patients with stage T3b melanoma, the RFS HR was 0.44 (95% CI: 0.24, 0.80). For patients with stage T4a melanoma, the RFS HR was 0.43 (95% CI: 0.18, 1.04). For patients with stage T4b melanoma, the RFS HR was 0.94 (95% CI: 0.56, 1.59). For patients with stage T3b melanoma, the DMFS HR was 0.71 (95% CI: 0.41, 1.22). For patients with stage T4a melanoma, the DMFS HR was 0.42 (95% CI: 0.19, 0.96). For patients with stage T4b melanoma, the DMFS HR was 0.70 (95% CI: 0.44, 1.13). The study was not powered to evaluate efficacy by individual T stage population, and the number of participants in these subgroups are limited.

**Figure 3: Kaplan-Meier Curve for Recurrence-Free Survival in KEYNOTE-716**



**Adjuvant Treatment of Stage III Resected Melanoma**

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

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

The trial demonstrated a statistically significant improvement in RFS and DMFS for patients randomized to the KEYTRUDA arm compared with placebo. Efficacy results are summarized in Table 49 and Figure 4.

**Table 49: 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* <sup>†</sup> (95% CI)	0.57 (0.46, 0.70)	
p-Value <sup>†</sup> (log-rank)	<0.001 <sup>‡</sup>	
<b>DMFS</b>		
Number (%) of patients with event	173 (34%)	245 (49%)
Median in months (95% CI)	NR (49.6, NR)	40.0 (27.7, NR)
Hazard ratio* <sup>†</sup> (95% CI)	0.60 (0.49, 0.73)	
p-Value <sup>†</sup> (log-rank)	<0.0001 <sup>§</sup>	

\* Based on the stratified Cox proportional hazard model

<sup>†</sup> Stratified by American Joint Committee on Cancer 7<sup>th</sup> edition (AJCC) stage

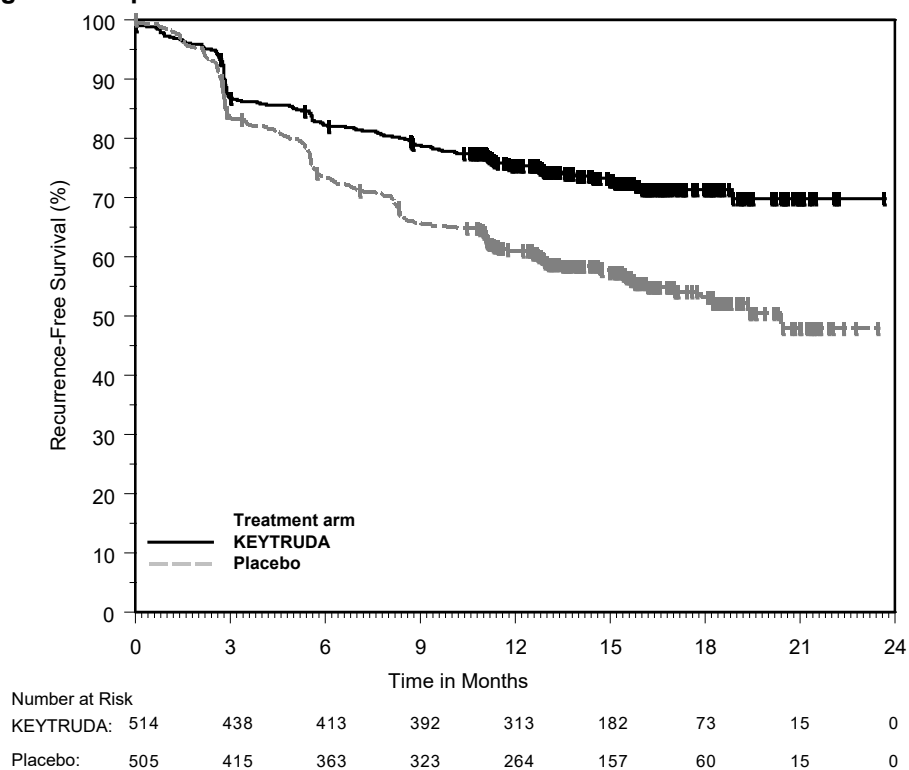
<sup>‡</sup> p-Value is compared with 0.016 of the allocated alpha for this interim analysis.

<sup>§</sup> p-Value is compared with 0.028 of the allocated alpha for this analysis.

NR = not reached

For patients with PD-L1 positive tumors, the RFS HR was 0.54 (95% CI: 0.42, 0.69); p<0.0001.  
 For patients with PD-L1 positive tumors, the DMFS HR was 0.61 (95% CI: 0.49, 0.76); p<0.0001.  
 The RFS and DMFS benefit for KEYTRUDA compared to placebo was observed regardless of tumor PD-L1 expression.

**Figure 4: Kaplan-Meier Curve for Recurrence-Free Survival in KEYNOTE-054**



## 14.2 Non-Small Cell Lung Cancer

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

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

- KEYTRUDA 200 mg, pemetrexed 500 mg/m<sup>2</sup>, and investigator's choice of cisplatin 75 mg/m<sup>2</sup> 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<sup>2</sup> intravenously every 3 weeks. KEYTRUDA was administered prior to chemotherapy on Day 1.

- Placebo, pemetrexed 500 mg/m<sup>2</sup>, and investigator's choice of cisplatin 75 mg/m<sup>2</sup> 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<sup>2</sup> intravenously every 3 weeks.

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

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

The trial demonstrated a statistically significant improvement in OS and PFS for patients randomized to KEYTRUDA in combination with pemetrexed and platinum chemotherapy compared with placebo, pemetrexed, and platinum chemotherapy. Table 50 and Figure 5 summarize the efficacy results for KEYNOTE-189.

**Table 50: Efficacy Results in KEYNOTE-189**

Endpoint	KEYTRUDA 200 mg every 3 weeks Pemetrexed Platinum Chemotherapy n=410	Placebo Pemetrexed Platinum Chemotherapy n=206
<b>OS</b>		
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 <sup>†</sup>	<0.0001	
<b>PFS</b>		
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 <sup>†</sup>	<0.0001	
<b>Objective Response Rate</b>		
ORR <sup>‡</sup> (95% CI)	48% (43, 53)	19% (14, 25)
Complete response	0.5%	0.5%
Partial response	47%	18%
p-Value <sup>§</sup>	<0.0001	
<b>Duration of Response</b>		
Median in months (range)	11.2 (1.1+, 18.0+)	7.8 (2.1+, 16.4+)

\* Based on the stratified Cox proportional hazard model

<sup>†</sup> Based on stratified log-rank test.

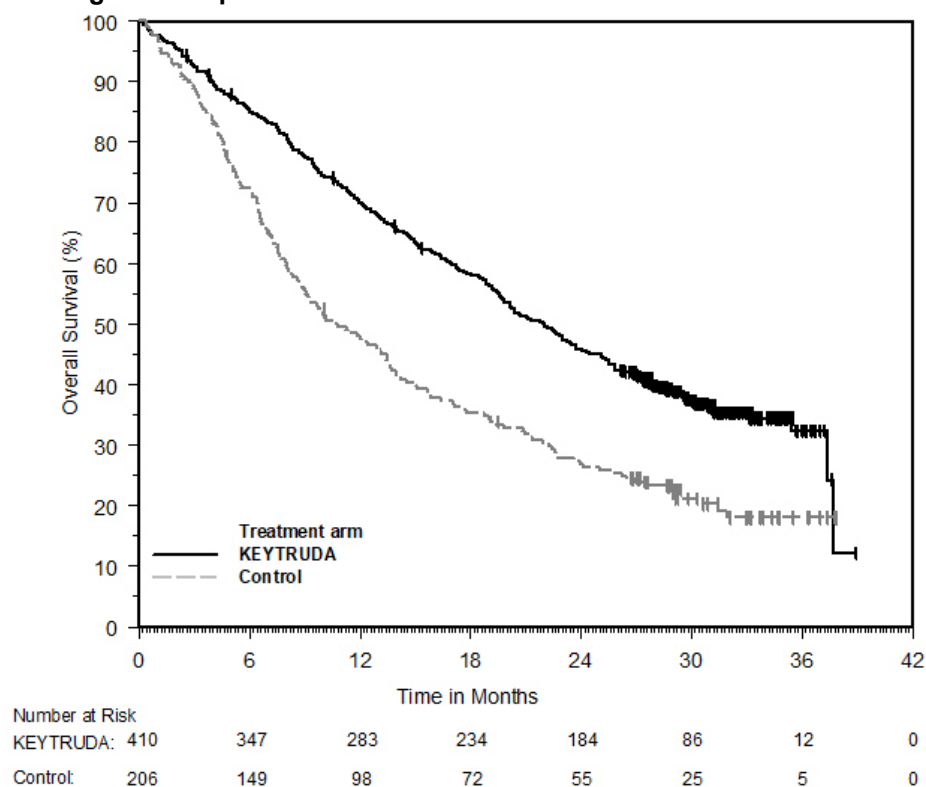
<sup>‡</sup> Response: Best objective response as confirmed complete response or partial response

<sup>§</sup> Based on Miettinen and Nurminen method stratified by PD-L1 status, platinum chemotherapy and smoking status

NR = not reached

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

**Figure 5: Kaplan-Meier Curve for Overall Survival in KEYNOTE-189\***



\*Based on the protocol-specified final OS analysis

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

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

- KEYTRUDA 200 mg and carboplatin AUC 6 mg/mL/min on Day 1 of each 21-day cycle for 4 cycles, and paclitaxel 200 mg/m<sup>2</sup> on Day 1 of each 21-day cycle for 4 cycles or paclitaxel protein-bound 100 mg/m<sup>2</sup> 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<sup>2</sup> on Day 1 of each 21-day cycle for 4 cycles or paclitaxel protein-bound 100 mg/m<sup>2</sup> 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 51 and Figure 6 summarize the efficacy results for KEYNOTE-407.

**Table 51: 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
<b>OS</b>		
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 <sup>†</sup>	0.0017	
<b>PFS</b>		
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 <sup>†</sup>	<0.0001	
	<b>n=101</b>	<b>n=103</b>
<b>Objective Response Rate<sup>‡</sup></b>		
ORR (95% CI)	58% (48, 68)	35% (26, 45)
Difference (95% CI)	23.6% (9.9, 36.4)	
p-Value <sup>§</sup>	0.0008	
<b>Duration of Response<sup>‡</sup></b>		
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

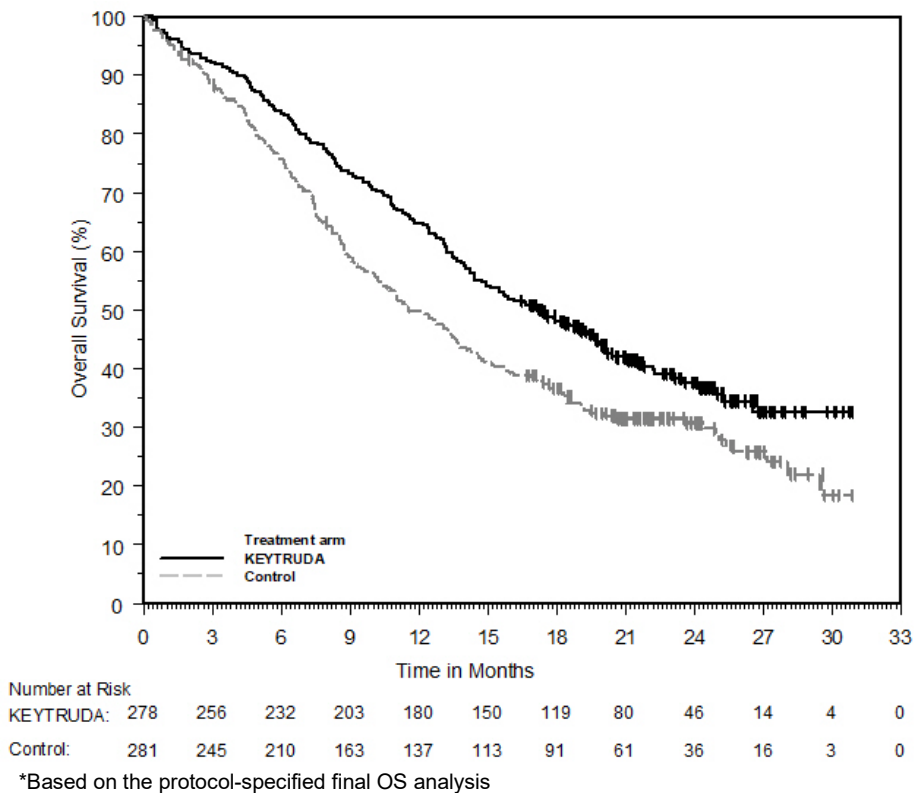
‡ ORR primary analysis and DoR analysis were conducted with the first 204 patients enrolled.

§ Based on a Miettinen-Nurminen test

NE = not estimable

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

**Figure 6: Kaplan-Meier Curve for Overall Survival in KEYNOTE-407\***



#### First-line treatment of metastatic NSCLC as a single agent

Study KEYNOTE 024 was a randomized, multicenter, open-label, active-controlled trial in 305 patients with metastatic NSCLC, whose tumors had high PD-L1 expression [tumor proportion score (TPS) of 50% or greater] by an immunohistochemistry assay using the PD-L1 IHC 22C3 pharmDx kit, and had not received prior systemic treatment for metastatic NSCLC. Patients with EGFR or ALK genomic tumor aberrations; autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of radiation in the thoracic region within the prior 26 weeks of initiation of study were ineligible. Randomization was stratified by ECOG performance status (0 vs. 1), histology (squamous vs. non-squamous), and geographic region (East Asia vs. non-East Asia). 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<sup>2</sup> 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<sup>2</sup> every 3 weeks for patients with non-squamous histologies;
- Pemetrexed 500 mg/m<sup>2</sup> every 3 weeks and cisplatin 75 mg/m<sup>2</sup> every 3 weeks on Day 1 for 4 to 6 cycles followed by optional pemetrexed 500 mg/m<sup>2</sup> every 3 weeks for patients with non-squamous histologies;
- Gemcitabine 1250 mg/m<sup>2</sup> on days 1 and 8 and cisplatin 75 mg/m<sup>2</sup> every 3 weeks on Day 1 for 4 to 6 cycles;
- Gemcitabine 1250 mg/m<sup>2</sup> 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<sup>2</sup> 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 non-squamous 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 as determined by an independent radiology committee, unacceptable toxicity, or for up to 24 months. Treatment could continue beyond disease progression if the patient was clinically stable and was considered to be deriving clinical benefit by the investigator. Patients randomized to chemotherapy were offered KEYTRUDA at the time of disease progression.

Assessment of tumor status was performed every 9 weeks. 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 the BICR according to RECIST v1.1 modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

The study population characteristics were: median age of 65 years (range: 33 to 90), 54% age 65 or older; 61% male; 82% White and 15% Asian; 65% with ECOG PS of 1; 18% with squamous and 82% with non-squamous 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 PFS for patients randomized to KEYTRUDA as compared with chemotherapy. Additionally, a pre-specified interim OS analysis at 108 events (64% of the events needed for final analysis) also demonstrated statistically significant improvement of OS for patients randomized to KEYTRUDA as compared with chemotherapy. Table 52 and Figure 7 summarizes the efficacy results for KEYNOTE 024.

**Table 52: Efficacy Results in KEYNOTE 024**

Endpoint	KEYTRUDA 200 mg every 3 weeks n=154	Chemotherapy  n=151
<b>PFS</b>		
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	
<b>OS</b>		
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	
<b>Objective Response Rate</b>		
ORR (95% CI)	45% (37, 53)	28% (21, 36)
Complete response rate	4%	1%
Partial response rate	41%	27%
p-Value (Miettinen-Nurminen)	0.001	
Median duration of response in months (range)	NR (1.9+, 14.5+)	6.3 (2.1+, 12.6+)

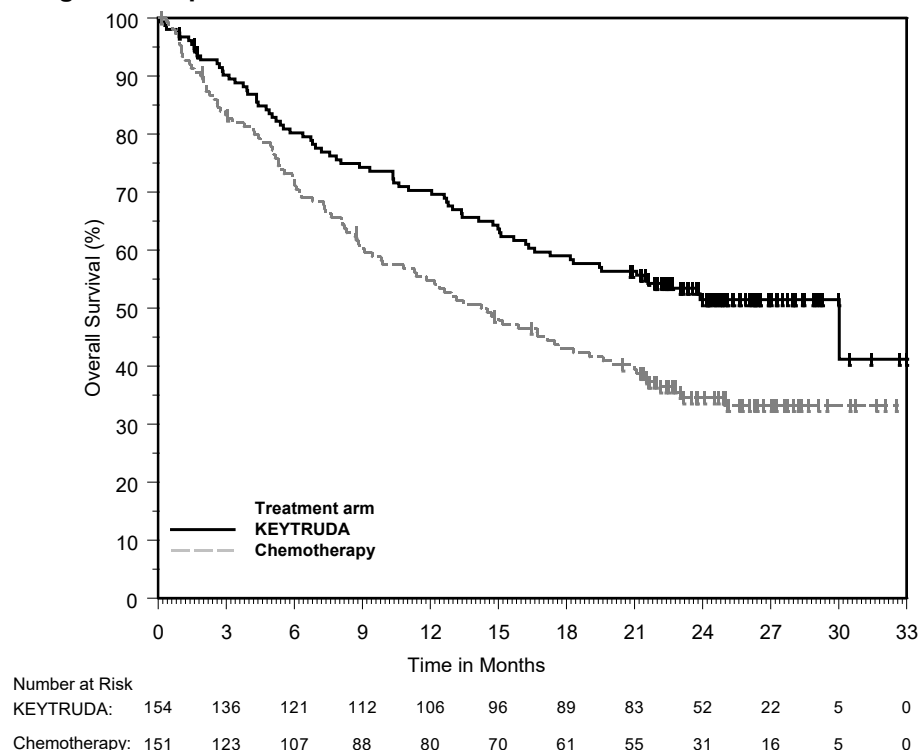
\*Based on the stratified Cox proportional hazard model for the interim analysis

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

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

NR = not reached

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



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

### Previously treated NSCLC

The efficacy of KEYTRUDA was investigated in KEYNOTE 010, (NCT01905657), a randomized, multicenter, open-label, active-controlled trial conducted in 1033 patients with metastatic NSCLC that had progressed following platinum-containing chemotherapy, and if appropriate, targeted therapy for EGFR or ALK genomic tumor aberrations. Eligible patients had PD-L1 expression TPS of 1% or greater by an immunohistochemistry assay using the PD-L1 IHC 22C3 pharmDx kit. Patients with autoimmune disease; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Randomization was stratified by tumor PD-L1 expression (PD-L1 expression TPS  $\geq 50\%$  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<sup>2</sup> 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  $\geq 50\%$  and the overall population with TPS  $\geq 1\%$ . Additional efficacy outcome measures were ORR and DoR in the subgroup of patients with TPS  $\geq 50\%$  and the overall population with TPS  $\geq 1\%$ .

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 non-squamous, and 8% with mixed, other or unknown histology; 91% metastatic (M1) disease; 15% with history of brain metastases; and 8% and 1% with EGFR and ALK genomic aberrations, respectively. All patients had received prior therapy with a platinum-doublet regimen, 29% received two or more prior therapies for their metastatic disease.

Tables 53 and 54 and Figure 8 summarize efficacy results in the subgroup with TPS  $\geq 50\%$  population and in all patients, respectively.

**Table 53: Efficacy Results of the Subgroup of Patients with TPS  $\geq 50\%$  in KEYNOTE 010**

Endpoint	KEYTRUDA 2 mg/kg every 3 weeks n=139	KEYTRUDA 10 mg/kg every 3 weeks n=151	Docetaxel 75 mg/m <sup>2</sup> every 3 weeks n=152
<b>OS</b>			
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	---
<b>PFS</b>			
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	---
<b>Objective Response Rate</b>			
ORR <sup>†</sup> (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 54: Efficacy Results of All Randomized Patients (TPS  $\geq 1\%$ ) in KEYNOTE 010**

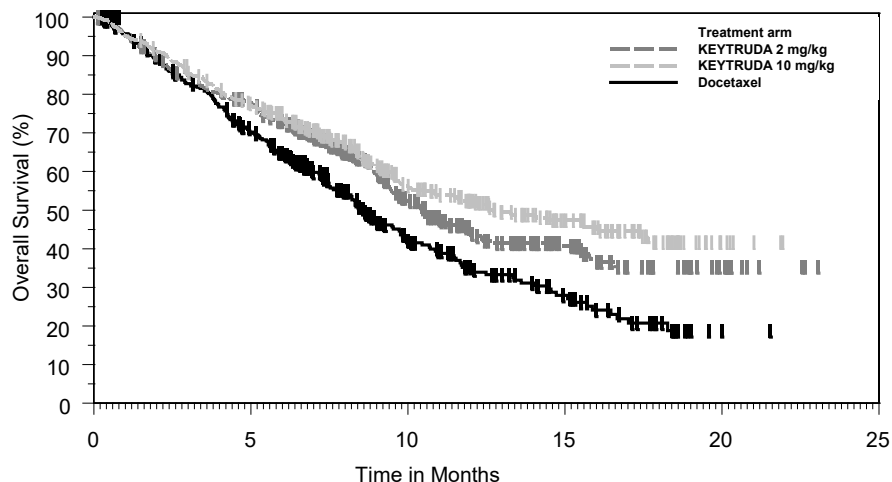
Endpoint	KEYTRUDA 2 mg/kg every 3 weeks n=344	KEYTRUDA 10 mg/kg every 3 weeks n=346	Docetaxel 75 mg/m <sup>2</sup> every 3 weeks n=343
<b>OS</b>			
Deaths (%)	172 (50%)	156 (45%)	193 (56%)
Median in months (95% CI)	10.4 (9.4, 11.9)	12.7 (10.0, 17.3)	8.5 (7.5, 9.8)
Hazard ratio* (95% CI)	0.71 (0.58, 0.88)	0.61 (0.49, 0.75)	---
p-Value (stratified log-rank)	<0.001	<0.001	---
<b>PFS</b>			
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	---
<b>Objective Response Rate</b>			
ORR <sup>†</sup> (95% CI)	18% (14, 23)	19% (15, 23)	9% (7, 13)
p-Value (Miettinen-Nurminen)	<0.001	<0.001	---
Median duration of response in months (range)	NR (0.7+, 20.1+)	NR (2.1+, 17.8+)	6.2 (1.4+, 8.8+)

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

† All responses were partial responses

NR = not reached

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



Number at Risk						
	0	5	10	15	20	25
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

Results of a post hoc analysis of patients with TPS 1% to 49% are shown in Table 55.

**Table 55: Efficacy Results of Patients with 1%  $\leq$  TPS  $\leq$  49% in KEYNOTE 010**

Endpoint	KEYTRUDA 2 mg/kg every 3 weeks n=205	KEYTRUDA 10 mg/kg every 3 weeks n=195	Docetaxel 75 mg/m <sup>2</sup> every 3 weeks n=191
<b>OS</b>			
Deaths (%)	114 (56%)	96 (49%)	107 (56%)
Median in months (95% CI)	9.4 (8.7, 10.5)	10.8 (8.9, 13.3)	8.6 (7.8, 9.9)
Hazard ratio* (95% CI)	0.79 (0.61, 1.04)	0.71 (0.53, 0.94)	---
p-Value (stratified log-rank)	0.044	0.007	---
<b>PFS</b>			
Events (%)	177 (86%)	158 (81%)	139 (73%)
Median in months (95% CI)	3.1 (2.1, 3.8)	2.3 (2.1, 4.0)	3.9 (2.5, 4.3)
Hazard ratio* (95% CI)	1.07 (0.85, 1.34)	0.99 (0.78, 1.25)	---
p-Value (stratified log-rank)	0.719	0.465	---
<b>Overall response rate</b>			
ORR % <sup>†</sup> (95% CI)	10% (6, 15)	10% (6, 15)	10% (7, 16)
p-Value (Miettinen-Nurminen)	0.572	0.490	---
Median duration of response in months (range)	10.6 (2.1+, 20.1+)	10.4 (3.0+, 17.1+)	6.0 (1.4+, 7.2)

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

<sup>†</sup> All responses were partial responses

### Adjuvant treatment of resected NSCLC

The efficacy of KEYTRUDA was investigated in KEYNOTE-091 (NCT02504372), a multicenter, randomized, triple-blind, placebo-controlled trial conducted in 1177 patients with completely resected Stage IB (T2a  $\geq$ 4 cm), II, or IIIA NSCLC by AJCC 7th edition. Patients had not received neoadjuvant radiotherapy or chemotherapy. Adjuvant chemotherapy up to 4 cycles was optional. Patients were ineligible if they had active autoimmune disease, were on chronic immunosuppressive agents or had a history of interstitial lung disease or pneumonitis. Randomization was stratified by stage (IB vs. II vs. IIIA), receipt of adjuvant chemotherapy (yes vs. no), PD-L1 status (TPS <1% [negative] vs. TPS 1-49% vs. TPS  $\geq$ 50%), and geographic region (Western Europe vs. Eastern Europe vs. Asia vs. Rest of World). Patients were randomized (1:1) to receive KEYTRUDA 200 mg or placebo intravenously every 3 weeks.

Treatment continued until RECIST v1.1-defined disease recurrence as determined by the investigator, unacceptable toxicity or up to one year. Tumor assessments were conducted every 12 weeks for the first



year, then every 6 months for years 2 to 3, and then annually through year 5. After year 5, imaging was performed as per local standard of care. The major efficacy outcome measure was investigator-assessed disease-free survival (DFS). An additional efficacy outcome measure was OS.

Of 1177 patients randomized, 1010 (86%) received adjuvant platinum-based chemotherapy following resection. Among these 1010 patients, the median age was 64 years (range: 35 to 84), 49% age 65 or older; 68% male; 77% White, 18% Asian; 86% current or former smokers; and 39% with ECOG PS of 1. Eleven percent had Stage IB, 57% had Stage II, and 31% had Stage IIIA disease. Thirty-nine percent had PD-L1 TPS <1% [negative], 33% had TPS 1-49%, and 28% had TPS ≥50%. Fifty-two percent were from Western Europe, 20% from Eastern Europe, 17% from Asia, and 11% from Rest of World.

The trial met its primary endpoint, demonstrating a statistically significant improvement in DFS in the overall population for patients randomized to the KEYTRUDA arm compared to patients randomized to the placebo arm. In an exploratory subgroup analysis of the 167 patients (14%) who did not receive adjuvant chemotherapy, the DFS HR was 1.25 (95% CI: 0.76, 2.05). OS results were not mature with only 42% of pre-specified OS events in the overall population.

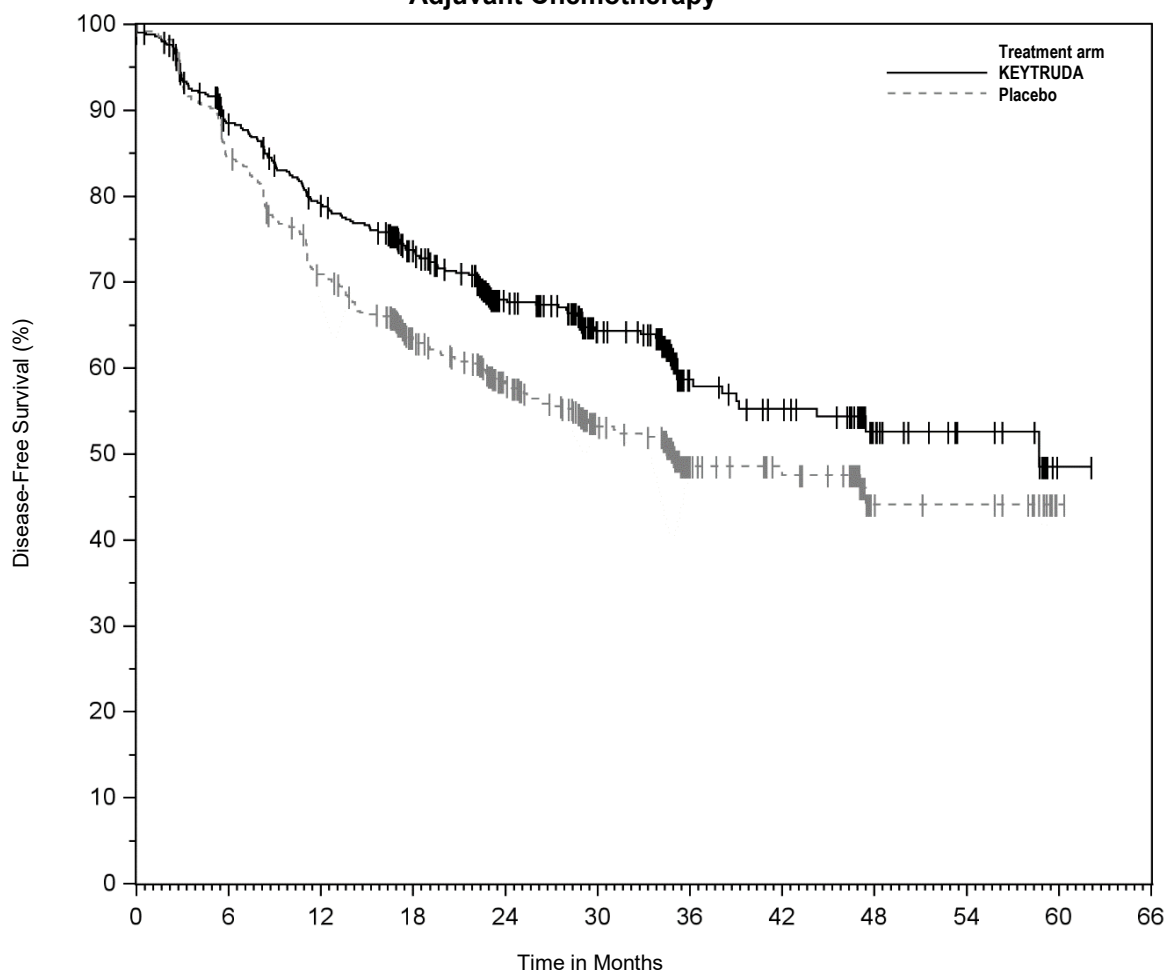
Table 56 and Figure 9 summarize the efficacy results for KEYNOTE-091 in patients who received adjuvant chemotherapy.

**Table 56: Efficacy Results in KEYNOTE-091 for Patients Who Received Adjuvant Chemotherapy**

Endpoint	KEYTRUDA 200 mg every 3 weeks n=506	Placebo n=504
<b>DFS</b>		
Number (%) of patients with event	177 (35%)	231 (46%)
Median in months (95% CI)	58.7 (39.2, NR)	34.9 (28.6, NR)
Hazard ratio* (95% CI)	0.73 (0.60, 0.89)	

\* Based on the unstratified univariate Cox regression model  
NR = not reached

**Figure 9: Kaplan-Meier Curve for Disease-Free Survival in KEYNOTE-091 for Patients Who Received Adjuvant Chemotherapy**



Number at Risk	0	6	12	18	24	30	36	42	48	54	60	66
KEYTRUDA	506	422	372	308	227	158	71	61	27	16	1	0
Placebo	504	422	349	272	206	134	58	47	17	15	1	0

At the time of the final analysis for DFS in patients who received adjuvant chemotherapy in the overall population, the following results, based on the multivariate Cox regression model, were observed: The HR for DFS was 0.76 (95% CI: 0.64, 0.91). The HRs for the subgroups of patients whose tumors had a TPS < 1%, TPS 1-49%, or TPS ≥ 50% were 0.75 (95% CI: 0.56, 0.99), 0.70 (95% CI: 0.51, 0.96), and 0.83 (95% CI: 0.57, 1.19), respectively. The HRs for patients with stage 1B, II, and IIIA were 0.66 (95% CI: 0.33, 1.33), 0.73 (95% CI: 0.57, 0.94), and 0.82 (95% CI: 0.61, 1.09), respectively. The HRs for the squamous and non-squamous cell histology were 0.85 (95% CI: 0.60, 1.20) and 0.72 (95% CI: 0.59, 0.89), respectively. The study was not powered to demonstrate efficacy in the subgroup populations; therefore, the results of these analyses should be interpreted with caution.

An exploratory analysis of OS suggested a trend in favor of KEYTRUDA compared to placebo with a HR of 0.79 (95% CI: 0.62, 1.01) in patients who received adjuvant chemotherapy.

### 14.3 Head and Neck Squamous Cell Cancer

#### First-line treatment of metastatic or unresectable, recurrent HNSCC

The efficacy of KEYTRUDA was investigated in KEYNOTE-048 (NCT02358031), a randomized, multicenter, open-label, active-controlled trial conducted in 882 patients with metastatic HNSCC who had not previously received systemic therapy for metastatic disease or with recurrent disease who were considered incurable by local therapies. Patients with active autoimmune disease that required systemic therapy within two years of

treatment or a medical condition that required immunosuppression were ineligible. Randomization was stratified by tumor PD-L1 expression (TPS  $\geq 50\%$  or  $< 50\%$ ) according to the PD-L1 IHC 22C3 pharmDx kit, HPV status according to p16 IHC (positive or negative), and ECOG PS (0 vs. 1). Patients were randomized 1:1:1 to one of the following treatment arms:

- KEYTRUDA 200 mg intravenously every 3 weeks
- KEYTRUDA 200 mg intravenously every 3 weeks, carboplatin AUC 5 mg/mL/min intravenously every 3 weeks or cisplatin 100 mg/m<sup>2</sup> intravenously every 3 weeks, and FU 1000 mg/m<sup>2</sup>/day as a continuous intravenous infusion over 96 hours every 3 weeks (maximum of 6 cycles of platinum and FU)
- Cetuximab 400 mg/m<sup>2</sup> intravenously as the initial dose then 250 mg/m<sup>2</sup> intravenously once weekly, carboplatin AUC 5 mg/mL/min intravenously every 3 weeks or cisplatin 100 mg/m<sup>2</sup> intravenously every 3 weeks, and FU 1000 mg/m<sup>2</sup>/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  $\geq 20$ , the subgroup of patients with CPS  $\geq 1$ , and the overall population.

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

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 57 and Figure 10 summarize efficacy results for KEYTRUDA in combination with chemotherapy.

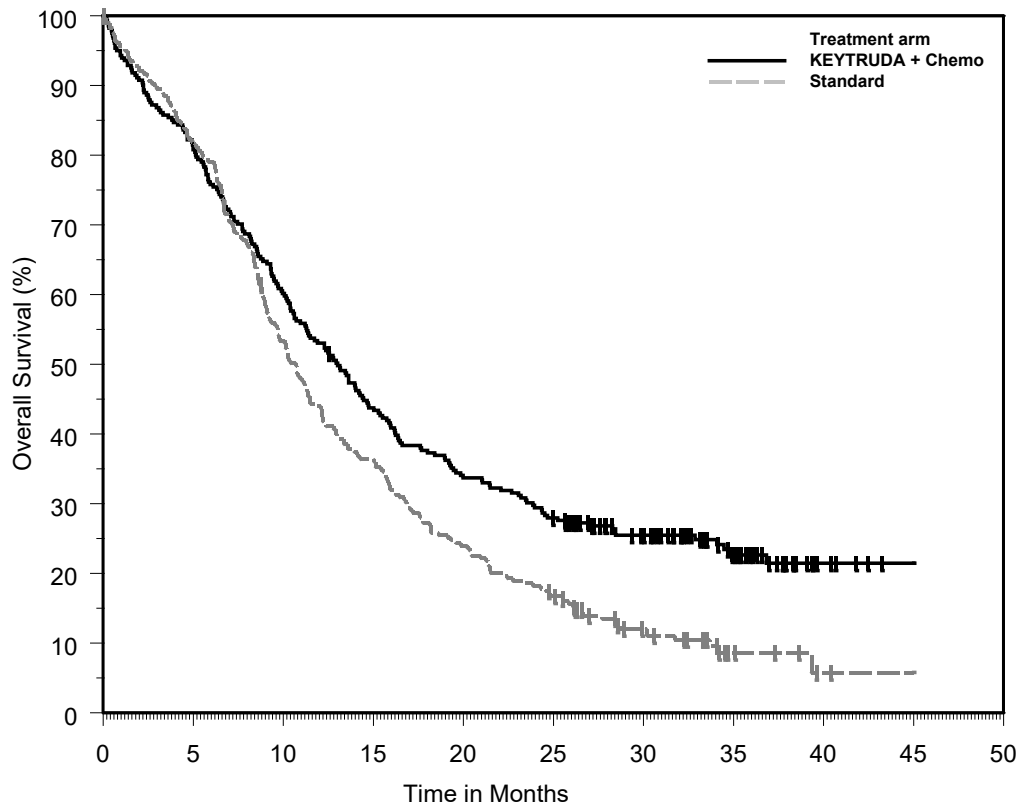
**Table 57: Efficacy Results\* for KEYTRUDA plus Platinum/Fluorouracil in KEYNOTE-048**

Endpoint	KEYTRUDA 200 mg every 3 weeks Platinum FU n=281	Cetuximab Platinum FU n=278
<b>OS</b>		
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 <sup>†</sup> (95% CI)	0.77 (0.63, 0.93)	
p-Value <sup>‡</sup>	0.0067	
<b>PFS</b>		
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 <sup>†</sup> (95% CI)	0.92 (0.77, 1.10)	
p-Value <sup>‡</sup>	0.3394	
<b>Objective Response Rate</b>		
ORR <sup>§</sup> (95% CI)	36% (30.0, 41.5)	36% (30.7, 42.3)
Complete response rate	6%	3%
Partial response rate	30%	33%
<b>Duration of Response</b>		
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  $\geq 1$  (HR=0.65, 95% CI: 0.53, 0.80) and CPS  $\geq 20$  (HR=0.60, 95% CI: 0.45, 0.82).

**Figure 10: Kaplan-Meier Curve for Overall Survival for KEYTRUDA plus Platinum/Fluorouracil in KEYNOTE-048\***



Number at Risk	0	5	10	15	20	25	30	35	40	45
KEYTRUDA + Chemo:	281	227	169	122	94	77	55	29	5	0
Standard:	278	227	147	100	66	45	23	6	1	0

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

The trial also demonstrated a statistically significant improvement in OS for the subgroup of patients with PD-L1 CPS  $\geq 1$  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 58 summarizes efficacy results for KEYTRUDA as a single agent in the subgroups of patients with CPS  $\geq 1$  HNSCC and CPS  $\geq 20$  HNSCC. Figure 11 summarizes the OS results in the subgroup of patients with CPS  $\geq 1$  HNSCC.

**Table 58: Efficacy Results\* for KEYTRUDA as a Single Agent in KEYNOTE-048 (CPS  $\geq 1$  and CPS  $\geq 20$ )**

Endpoint	CPS $\geq 1$		CPS $\geq 20$	
	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
<b>OS</b>				
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 <sup>†</sup> (95% CI)	0.78 (0.64, 0.96)		0.61 (0.45, 0.83)	
p-Value <sup>‡</sup>	0.0171		0.0015	
<b>PFS</b>				
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 <sup>†</sup> (95% CI)	1.15(0.95, 1.38)		0.97 (0.74, 1.27)	
<b>Objective Response Rate</b>				
ORR <sup>§</sup> (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%
<b>Duration of Response</b>				
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

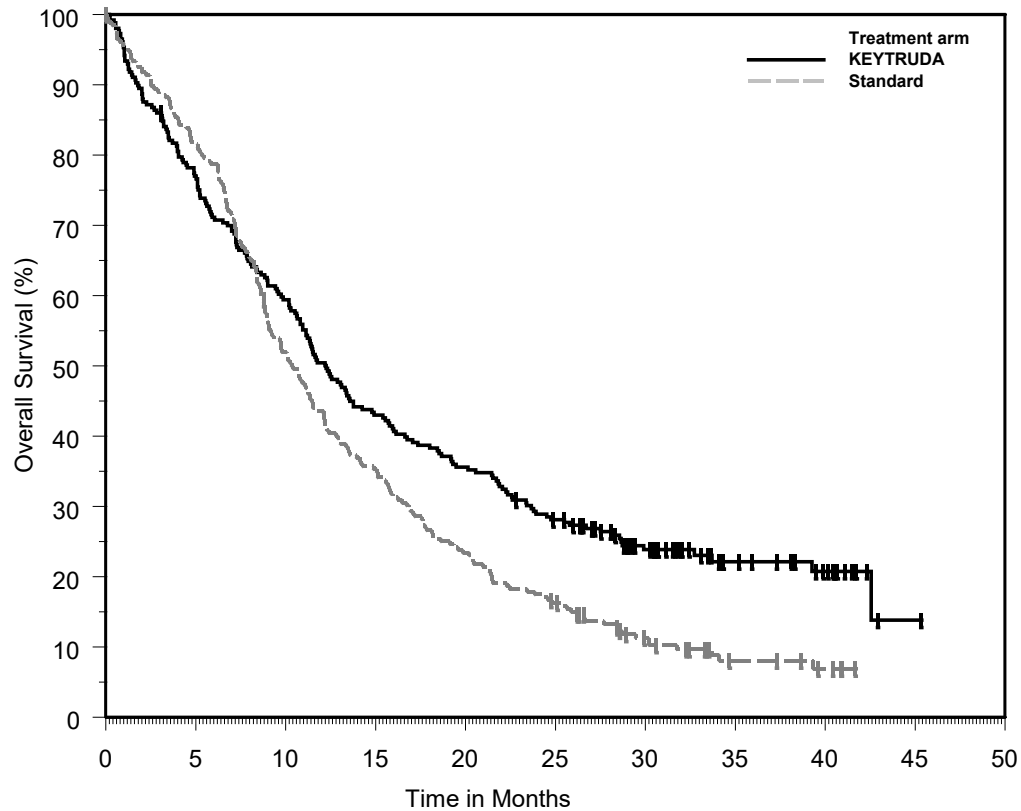
‡ Based on a stratified log-rank test

§ 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  $\geq 1$  was 0.74 (95% CI: 0.61, 0.90) and the hazard ratio for the subgroup of patients with CPS  $\geq 20$  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 11: 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.

#### 14.4 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 59 and Figure 12.

**Table 59: 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
<b>PFS</b>		
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	
<b>Objective Response Rate</b>		
ORR§ (95% CI)	66% (57, 73)	54% (46, 62)
Complete response	25%	24%
Partial response	41%	30%
<b>Duration of Response</b>		
Median in months (range)*	20.7 (0.0+, 33.2+)	13.8 (0.0+, 33.9+)

\* Based on Kaplan-Meier estimates.

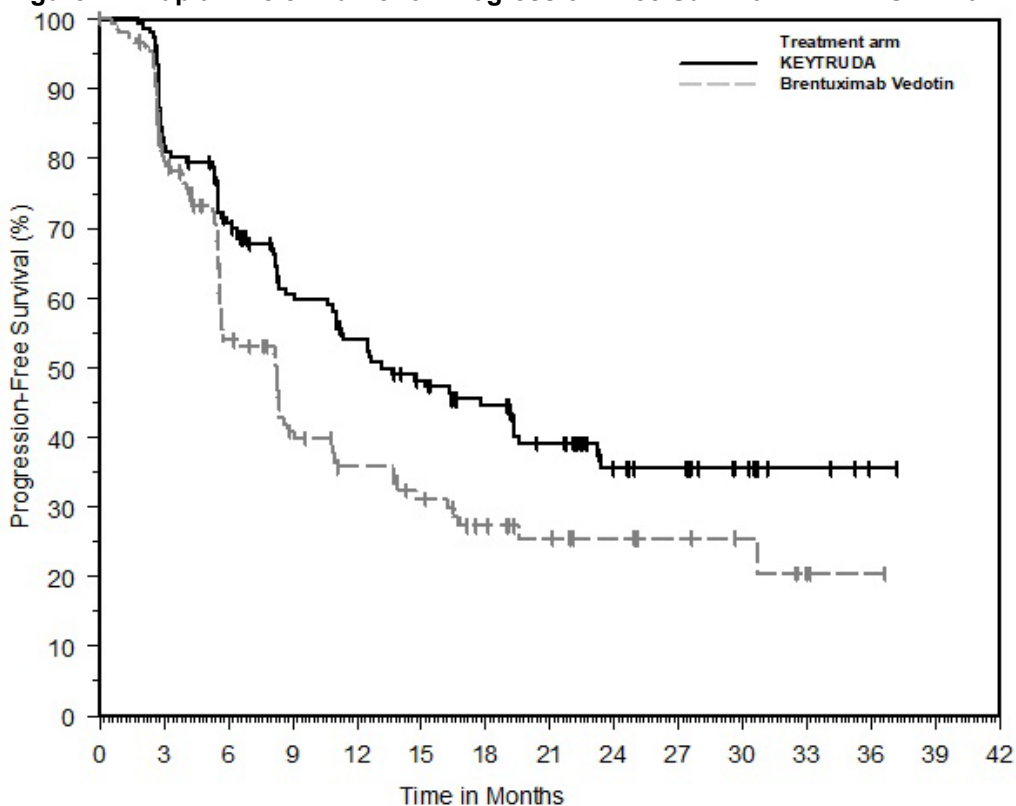
† Based on the stratified Cox proportional hazard model.

‡ Based on a stratified log-rank test. One-sided p-Value, with a prespecified boundary of 0.0043.

§ Difference in ORR is not statistically significant.

+ Denotes a censored value.

**Figure 12: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-204**



Number at Risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42
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 60.



**Table 60: Efficacy Results in Patients with cHL in KEYNOTE-087**

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

\* Median follow-up time of 9.4 months

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

#### 14.5 Primary Mediastinal Large B-Cell Lymphoma

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

The study population characteristics were: median age 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 61.

**Table 61: Efficacy Results in Patients with PMBCL in KEYNOTE-170**

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

\*Median follow-up time of 9.7 months

†Based on patients (n=24) with a response by independent review NR =not reached

#### 14.6 Urothelial Cancer

##### 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 11.4 months (range 0.1 to 63.8 months). Efficacy results are summarized in Table 62.

**Table 62: 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
<b>Objective Response Rate</b>			
ORR (95% CI)	29% (24, 34)	21% (16, 27)	47% (38, 57)
Complete response rate	10%	5%	21%
Partial response rate	20%	17%	26%
<b>Duration of Response</b>			
Median in months (range)	33.4 (1.4+, 60.7+)	25.9 (1.6+, 59.7+)	NR (1.4+, 60.7+)

\* Includes 9 subjects with unknown PD-L1 status

+ Denotes ongoing response

NR = not reached

#### Platinum Eligible Patients with Previously Untreated Urothelial Carcinoma

The efficacy of KEYTRUDA for the first-line treatment of platinum-eligible patients with locally advanced or metastatic urothelial carcinoma was investigated in KEYNOTE-361 (NCT02853305), a multicenter, randomized open-label, active-controlled study in 1010 previously untreated patients. The safety and efficacy of KEYTRUDA in combination with platinum-based chemotherapy for previously untreated patients with locally advanced or metastatic urothelial carcinoma has not been established. The study compared KEYTRUDA with or without platinum-based chemotherapy (i.e., cisplatin or carboplatin with gemcitabine) to platinum-based chemotherapy alone. Among the patients receiving KEYTRUDA plus platinum-based chemotherapy, 44% received cisplatin and 56% received carboplatin.

The study did not meet its major efficacy outcome measures of improved PFS or OS in the KEYTRUDA plus chemotherapy arm compared to the chemotherapy-alone arm. Additional efficacy endpoints, including improvement of OS in the KEYTRUDA monotherapy arm, could not be formally tested.

#### Previously Treated Urothelial Carcinoma

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

Patients were randomized to receive either KEYTRUDA 200 mg every 3 weeks (n=270) or investigator's choice of any of the following chemotherapy regimens all given intravenously every 3 weeks (n=272):

paclitaxel 175 mg/m<sup>2</sup> (n=90), docetaxel 75 mg/m<sup>2</sup> (n=92), or vinflunine 320 mg/m<sup>2</sup> (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 63 and Figure 13 summarize the efficacy results for KEYNOTE-045.

**Table 63: Efficacy Results in KEYNOTE-045**

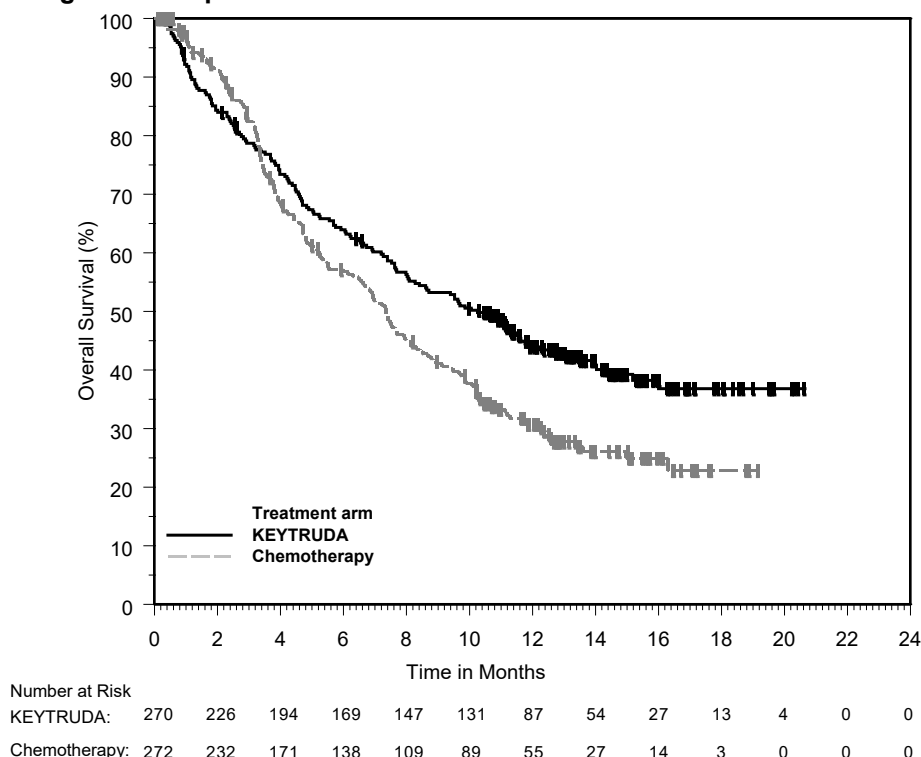
	<b>KEYTRUDA 200 mg every 3 weeks n=270</b>	<b>Chemotherapy n=272</b>
<b>OS</b>		
Deaths (%)	155 (57%)	179 (66%)
Median in months (95% CI)	10.3 (8.0, 11.8)	7.4 (6.1, 8.3)
Hazard ratio* (95% CI)	0.73 (0.59, 0.91)	
p-Value (stratified log-rank)	0.004	
<b>PFS by BICR</b>		
Events (%)	218 (81%)	219 (81%)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



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

The efficacy of KEYTRUDA was investigated in KEYNOTE-057 (NCT02625961), a multicenter, open-label, single-arm trial in 96 patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy. BCG-unresponsive high-risk NMIBC was defined as persistent disease despite adequate BCG therapy, disease recurrence after an initial tumor-free state following adequate BCG therapy, or T1 disease following a single induction course of BCG. Adequate BCG therapy was defined as administration of at least five of six doses of an initial induction course plus either of: at least two of three doses of maintenance therapy or at least two of six doses of a second induction course. Prior to treatment, all patients had undergone transurethral resection of bladder tumor (TURBT) to remove all resectable disease (Ta and T1 components). Residual CIS (Tis components) not amenable to complete resection was allowed. The trial excluded patients with muscle invasive (i.e., T2, T3, T4) locally advanced non-resectable or metastatic urothelial carcinoma, concurrent extra-vesical (i.e., urethra, ureter or renal pelvis) non-muscle invasive transitional cell carcinoma of the urothelium, or autoimmune disease or a medical condition that required immunosuppression.

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

The study population characteristics were: median age of 73 years (range: 44 to 92); 44% age  $\geq$ 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 64.

**Table 64: 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

**14.7 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. MSI-H trials are summarized in Table 65.

**Table 65: MSI-H Trials**

Study	Design and Patient Population	Number of patients	MSI-H/dMMR testing	Dose	Prior therapy
<b>KEYNOTE-016</b> NCT01876511	<ul style="list-style-type: none"> <li>prospective, investigator-initiated</li> <li>6 sites</li> <li>patients with CRC and other tumors</li> </ul>	28 CRC 30 non-CRC	local PCR or IHC	10 mg/kg every 2 weeks	<ul style="list-style-type: none"> <li>CRC: ≥ 2 prior regimens</li> <li>Non-CRC: ≥1 prior regimen</li> </ul>
<b>KEYNOTE-164</b> NCT02460198	<ul style="list-style-type: none"> <li>prospective international multi-center</li> <li>CRC</li> </ul>	61	local PCR or IHC	200 mg every 3 weeks	Prior fluoropyrimidine, oxaliplatin, and irinotecan +/- anti-VEGF/EGFR mAb
<b>KEYNOTE-012</b> NCT01848834	<ul style="list-style-type: none"> <li>retrospectively identified patients with PD-L1-positive gastric, bladder, or triple-negative breast cancer</li> </ul>	6	central PCR	10 mg/kg every 2 weeks	≥1 prior regimen
<b>KEYNOTE-028</b> NCT02054806	<ul style="list-style-type: none"> <li>retrospectively identified patients with PD-L1-positive esophageal, biliary, breast, endometrial, or CRC</li> </ul>	5	central PCR	10 mg/kg every 2 weeks	≥1 prior regimen
<b>KEYNOTE-158</b> NCT02628067	<ul style="list-style-type: none"> <li>prospective international multi-center enrollment of patients with MSI-H/dMMR non-CRC</li> <li>retrospectively identified patients who were enrolled in specific rare tumor non-CRC cohorts</li> </ul>	19	local PCR or IHC (central PCR for patients in rare tumor non-CRC cohorts)	200 mg every 3 weeks	≥1 prior regimen
<b>Total</b>		<b>149</b>			

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 Table 66 and 67.

**Table 66: Efficacy Results for Patients with MSI-H/dMMR Cancer**

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

NR = not reached

**Table 67: Response by Tumor Type**

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

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

#### 14.8 Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer (CRC)

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

400 mg/m<sup>2</sup> bolus on Day 1, then FU 2400 mg/m<sup>2</sup> over 46-48 hours. Bevacizumab 5 mg/kg on Day 1 or cetuximab 400 mg/m<sup>2</sup> on first infusion, then 250 mg/m<sup>2</sup> weekly.

Treatment with KEYTRUDA or chemotherapy continued until RECIST v1.1-defined progression of disease as determined by the investigator or unacceptable toxicity. Patients treated with KEYTRUDA without disease progression could be treated for up to 24 months. Assessment of tumor status was performed every 9 weeks. Patients randomized to chemotherapy were offered KEYTRUDA at the time of disease progression. The main efficacy outcome measures were PFS (as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ) and OS. Additional efficacy outcome measures were ORR and DoR.

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

The trial demonstrated a statistically significant improvement in PFS for patients randomized to KEYTRUDA compared with chemotherapy. There was no statistically significant difference between KEYTRUDA and chemotherapy in the final OS analysis. Sixty percent of the patients who had been randomized to receive chemotherapy had crossed over to receive subsequent anti-PD-1/PD-L1 therapies including KEYTRUDA. The median follow-up time at the final analysis was 38.1 months (range: 0.2 to 58.7 months). Table 68 and Figure 14 summarize the key efficacy measures for KEYNOTE-177.

**Table 68: 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
<b>PFS</b>		
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 <sup>†</sup>	0.0004	
<b>OS<sup>‡</sup></b>		
Number (%) of patients with event	62 (41%)	78 (51%)
Median in months (95% CI)	NR (49.2, NR)	36.7 (27.6, NR)
Hazard ratio* (95% CI)	0.74 (0.53, 1.03)	
p-Value <sup>§</sup>	0.0718	
<b>Objective Response Rate<sup>¶</sup></b>		
ORR (95% CI)	44% (35.8, 52.0)	33% (25.8, 41.1)
Complete response rate	11%	4%
Partial response rate	33%	29%
<b>Duration of Response<sup>¶,#</sup></b>		
Median in months (range)	NR (2.3+, 41.4+)	10.6 (2.8, 37.5+)
% with duration ≥12 months <sup>Ⓟ</sup>	75%	37%
% with duration ≥24 months <sup>Ⓟ</sup>	43%	18%

\* Based on Cox regression model

<sup>†</sup> Two-sided p-Value based on log-rank test (compared to a significance level of 0.0234)

<sup>‡</sup> Final OS analysis

<sup>§</sup> Two-sided p-Value based on log-rank test (compared to a significance level of 0.0492)

<sup>¶</sup> Based on confirmed response by BICR review

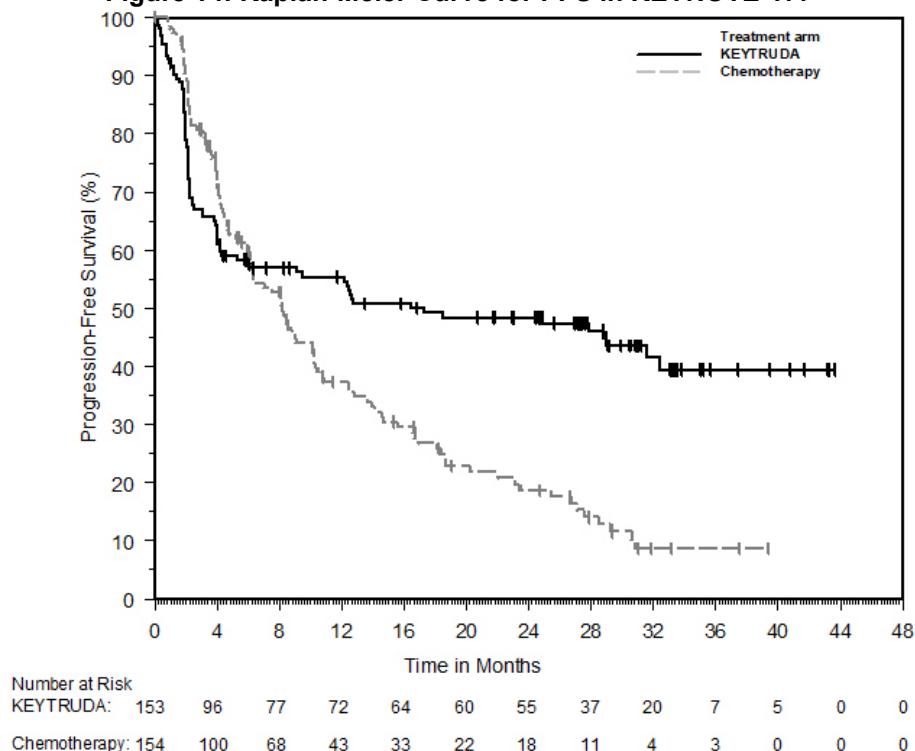
<sup>#</sup> Based on n=67 patients with a response in the KEYTRUDA arm and n=51 patients with a response in the chemotherapy arm

<sup>Ⓟ</sup> Based on observed duration of response

+ Denotes ongoing response

NR = not reached

**Figure 14: Kaplan-Meier Curve for PFS in KEYNOTE-177**



#### 14.9 Gastric Cancer

##### First-line Treatment of Locally Advanced Unresectable or Metastatic HER2-Positive Gastric or Gastroesophageal Junction Adenocarcinoma

The efficacy of KEYTRUDA in combination with trastuzumab plus fluoropyrimidine and platinum chemotherapy was investigated in KEYNOTE-811 (NCT03615326), a multicenter, randomized, double-blind, placebo-controlled trial that enrolled 698 patients with HER2-positive advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma who had not previously received systemic therapy for metastatic disease. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx™ kit. Patients with an autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Randomization was stratified by PD-L1 expression (CPS  $\geq 1$  or CPS  $< 1$ ), chemotherapy regimen (5-FU plus cisplatin [FP] or capecitabine plus oxaliplatin [CAPOX]), and geographic region (Europe/Israel/North America/Australia, Asia, or Rest of the World). Patients were randomized (1:1) to one of the following treatment arms.

- KEYTRUDA 200 mg, trastuzumab 8 mg/kg on first infusion and 6 mg/kg in subsequent cycles, followed by investigator's choice of combination chemotherapy of cisplatin 80 mg/m<sup>2</sup> for up to 6 cycles and 5-FU 800 mg/m<sup>2</sup>/day for 5 days (FP) or oxaliplatin 130 mg/m<sup>2</sup> up to 6-8 cycles and capecitabine 1000 mg/m<sup>2</sup> bid for 14 days (CAPOX). KEYTRUDA was administered prior to trastuzumab and chemotherapy on Day 1 of each cycle.
- Placebo, trastuzumab 8 mg/kg on first infusion and 6 mg/kg in subsequent cycles, followed by investigator's choice of combination chemotherapy of cisplatin 80 mg/m<sup>2</sup> for up to 6 cycles and 5-FU 800 mg/m<sup>2</sup>/day for 5 days (FP) or oxaliplatin 130 mg/m<sup>2</sup> up to 6-8 cycles and capecitabine 1000 mg/m<sup>2</sup> bid for 14 days (CAPOX).

All study medications, except oral capecitabine, were administered as an intravenous infusion every 3 week cycle. Treatment with KEYTRUDA continued until RECIST v1.1-defined progression of disease as determined by BICR, unacceptable toxicity, or a maximum of 24 months. In an interim efficacy analysis, the major outcome measures assessed were ORR and DoR by BICR using RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

At the time of the interim analysis, ORR and DoR were assessed in the first 264 patients randomized. Among the 264 patients, the population characteristics were: median age of 62 years (range: 19 to 84), 41% age 65 or older; 82% male; 63% White, 31% Asian, and 0.8% Black; 47% ECOG PS of 0 and 53% ECOG



PS of 1. Ninety-seven percent of patients had metastatic disease (Stage IV) and 3% had locally advanced unresectable disease. Ninety-one percent (n=240) had tumors that were not MSI-H, 1% (n=2) had tumors that were MSI-H, and in 8% (n=22) the status was not known. Eighty-seven percent of patients received CAPOX.

A statistically significant improvement in ORR was demonstrated in patients randomized to KEYTRUDA in combination with trastuzumab and chemotherapy compared with placebo in combination with trastuzumab and chemotherapy. Efficacy results are summarized in Table 69.

**Table 69: Efficacy Results for KEYNOTE-811**

Endpoint	KEYTRUDA 200 mg every 3 weeks Trastuzumab Fluoropyrimidine and Platinum Chemotherapy n=133	Placebo  Trastuzumab Fluoropyrimidine and Platinum Chemotherapy n=131
<b>Objective Response Rate</b>		
ORR* (95% CI)	74% (66, 82)	52% (43, 61)
Complete response rate	11%	3.1%
Partial response rate	63%	49%
p-Value <sup>†</sup>	<0.0001	
<b>Duration of Response</b>	n=99	n=68
Median in months (range)	10.6 (1.1+, 16.5+)	9.5 (1.4+, 15.4+)
% with duration ≥6 months <sup>‡</sup>	65%	53%

- \* Response: Best objective response as confirmed complete response or partial response
- † p-Value based on stratified Miettinen and Nurminen method (compared to an alpha boundary of 0.002)
- ‡ Based on observed duration of response
- + Denotes ongoing response

In a pre-specified subgroup analysis of ORR based on PD-L1 status, the ORR in patients with PD-L1-positive disease (CPS ≥1) was 76% (95% CI: 67, 83) in the pembrolizumab arm (n=117) versus 51% (95% CI: 41, 60) in the control arm (n=112). In patients with tumors that were PD-L1 CPS<1, the ORR was 63% (95% CI: 35, 85) in the pembrolizumab arm (n=16) versus 58% (95% CI: 34, 80) in the control arm (n=19).

In a subsequent interim analysis of pre-specified subgroups based on PD-L1 status in the full study population (n=698), the HR for PFS and OS in patients with PD-L1 CPS<1 (N=104) was 1.03 (95% CI: 0.65, 1.64) and 1.41 (95% CI: 0.90, 2.20), respectively.

#### First-line Treatment of Locally Unresectable or Metastatic HER2-Negative Gastric or Gastroesophageal Junction Adenocarcinoma

The efficacy of KEYTRUDA in combination with fluoropyrimidine- and platinum-containing chemotherapy was investigated in KEYNOTE-859 (NCT03675737), a multicenter, randomized, double-blind, placebo-controlled trial that enrolled 1579 patients with HER2-negative advanced gastric or GEJ adenocarcinoma who had not previously received systemic therapy for metastatic disease. Patients with an autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Randomization was stratified by PD-L1 expression (CPS ≥1 or CPS <1), chemotherapy regimen (FP or CAPOX), and geographic region (Europe/Israel/North America/Australia, Asia, or Rest of the World). Patients were randomized (1:1) to one of the following treatment arms; treatment was administered prior to chemotherapy on Day 1 of each cycle:

- KEYTRUDA 200 mg, investigator's choice of combination chemotherapy of cisplatin 80 mg/m<sup>2</sup> and 5-FU 800 mg/m<sup>2</sup>/day for 5 days (FP) or oxaliplatin 130 mg/m<sup>2</sup> and capecitabine 1000 mg/m<sup>2</sup> bid for 14 days (CAPOX).
- Placebo, investigator's choice of combination chemotherapy of cisplatin 80 mg/m<sup>2</sup> and 5-FU 800 mg/m<sup>2</sup>/day for 5 days (FP) or oxaliplatin 130 mg/m<sup>2</sup> and capecitabine 1000 mg/m<sup>2</sup> bid for 14 days (CAPOX).

All study medications, except oral capecitabine, were administered as an intravenous infusion every 3-week cycle. Platinum agents could be administered for 6 or more cycles following local guidelines. Treatment with KEYTRUDA continued until RECIST v1.1-defined progression of disease as determined by BICR, unacceptable toxicity, or a maximum of 24 months. The major efficacy outcome measure was OS. Additional

secondary efficacy outcome measures included PFS, ORR, and DoR as assessed by BICR using RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

The population characteristics were: median age of 62 years (range: 21 to 86), 39% age 65 or older; 68% male and 32% female; 55% White, 34% Asian, 4.6% Multiple, 4.2% American Indian or Alaskan Native, 1.3% Black, and 0.2% Native Hawaiian or other Pacific Islander; 76% Not Hispanic or Latino and 21% Hispanic or Latino; 37% ECOG PS of 0 and 63% ECOG PS of 1. Ninety-seven percent of patients had metastatic disease (Stage IV) and 3% had locally advanced unresectable disease. Seventy-eight percent had tumors that expressed PD-L1 with a CPS  $\geq$ 1 and 5% (n=74) had tumors that were MSI-H. Eighty-six percent of patients received CAPOX.

A statistically significant improvement in OS, PFS, and ORR was demonstrated in patients randomized to KEYTRUDA in combination with chemotherapy compared with placebo in combination with chemotherapy at the time of a pre-specified interim analysis of OS. Efficacy results are summarized in Table 70 and Figures 15 and 16.

**Table 70: Efficacy Results\* for KEYNOTE-859**

Endpoint	KEYTRUDA 200 mg every 3 weeks and FP or CAPOX n=790	Placebo  and FP or CAPOX n=789	KEYTRUDA 200 mg every 3 weeks and FP or CAPOX n=618	Placebo  and FP or CAPOX n=617	KEYTRUDA 200 mg every 3 weeks and FP or CAPOX n=279	Placebo  and FP or CAPOX n=272
	All Patients		CPS $\geq$ 1		CPS $\geq$ 10	
<b>OS</b>						
Number (%) of patients with event	603 (76)	666 (84)	464 (75)	526 (85)	188 (67)	226 (83)
Median in months (95% CI)	12.9 (11.9, 14.0)	11.5 (10.6, 12.1)	13.0 (11.6, 14.2)	11.4 (10.5, 12.0)	15.7 (13.8, 19.3)	11.8 (10.3, 12.7)
Hazard ratio <sup>†</sup> (95% CI)	0.78 (0.70, 0.87)		0.74 (0.65, 0.84)		0.65 (0.53, 0.79)	
p-Value (stratified log-rank) <sup>‡</sup>	<0.0001		<0.0001		<0.0001	
<b>PFS</b>						
Number (%) of patients with event	572 (72)	608 (77)	443 (72%)	483 (78%)	190 (68)	210 (77)
Median in months (95% CI)	6.9 (6.3, 7.2)	5.6 (5.5, 5.7)	6.9 (6.0, 7.2)	5.6 (5.4, 5.7)	8.1 (6.8, 8.5)	5.6 (5.4, 6.7)
Hazard ratio <sup>†</sup> (95% CI)	0.76 (0.67, 0.85)		0.72 (0.63, 0.82)		0.62 (0.51, 0.76)	
p-Value (stratified log-rank) <sup>‡</sup>	<0.0001		<0.0001		<0.0001	
<b>Objective Response Rate</b>						
ORR <sup>§</sup> (95% CI)	51% (48, 55)	42% (38, 45)	52% (48, 56)	43% (39, 47)	61% (55, 66)	43% (37, 49)
Complete response rate	9%	6%	10%	6%	13%	5%
Partial response rate	42%	36%	42%	37%	48%	38%
p-Value <sup>¶</sup>	<0.0001		0.0004		<0.0001	
<b>Duration of Response</b>	n=405	n=331	n=322	n=263	n=169	n=117
Median in months <sup>#</sup> (95% CI)	8.0 (7.0, 9.7)	5.7 (5.5, 6.9)	8.3 (7.0, 10.9)	5.6 (5.4, 6.9)	10.9 (8.0, 13.8)	5.8 (5.3, 7.0)
Range in months	1.2+, 41.5+	1.3+, 34.7+	1.2+, 41.5+	1.3+, 34.2+	1.2+, 41.5+	1.4+, 31.2+

\* Based on a pre-specified interim analysis

<sup>†</sup> Based on the stratified Cox proportional hazard model

<sup>‡</sup> One-sided p-Value based on stratified log-rank test

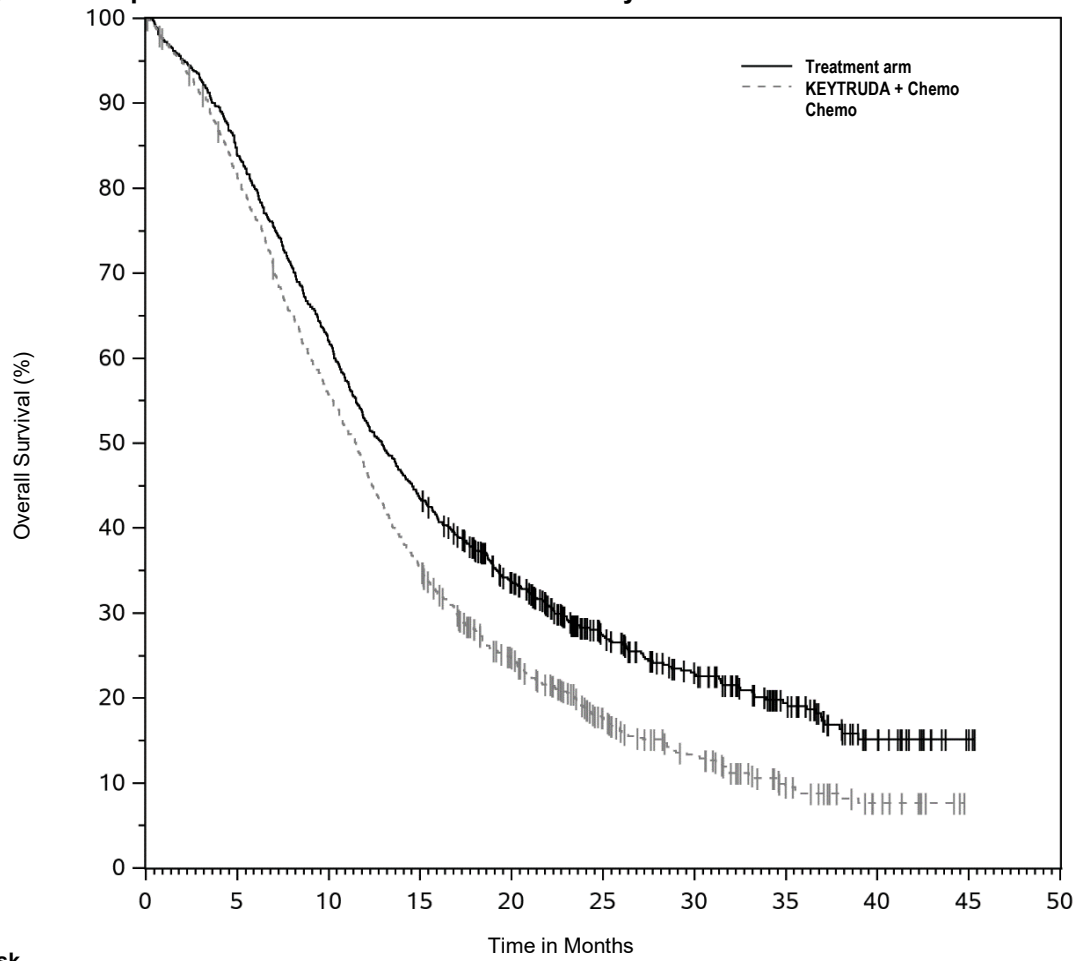
<sup>§</sup> Response: Best objective response as confirmed complete response or partial response

<sup>¶</sup> One-sided p-Value based on stratified Miettinen & Nurminen method

<sup>#</sup> Based on Kaplan-Meier estimates

<sup>+</sup> Denotes ongoing response

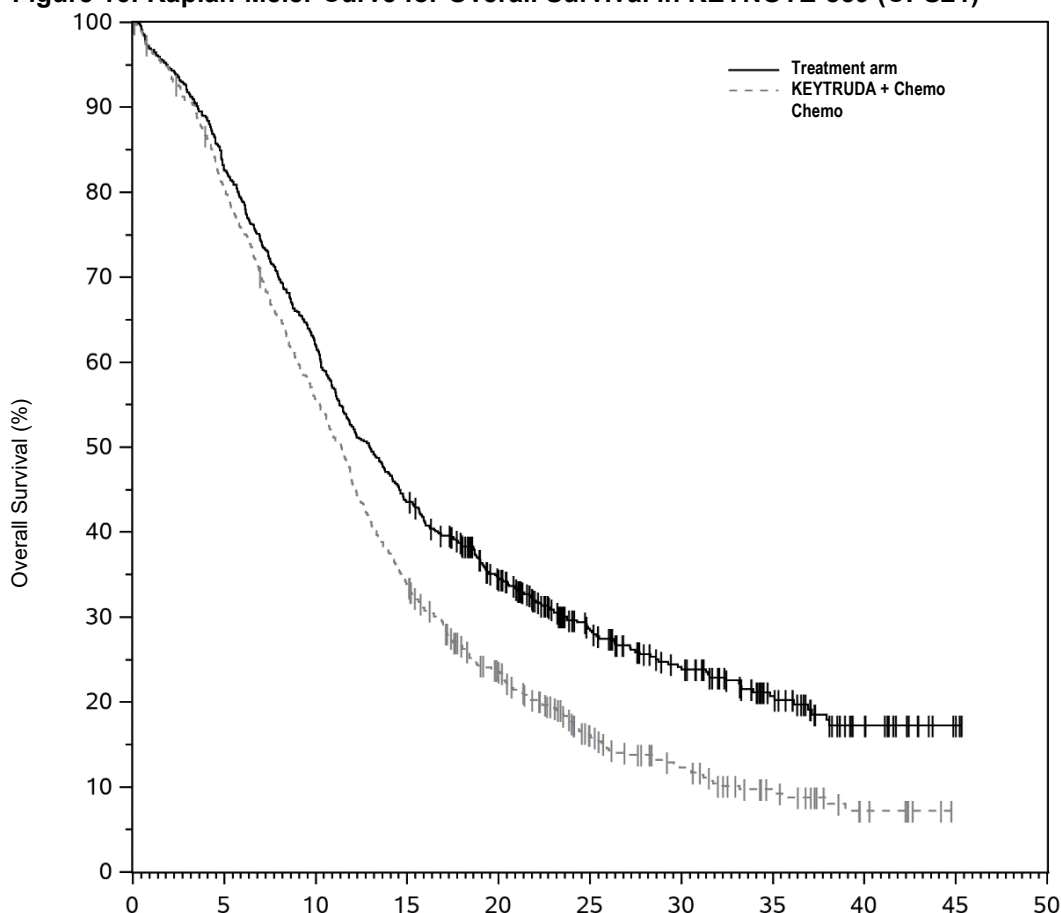
**Figure 15: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-859**



**Number at Risk**

	0	5	10	15	20	25	30	35	40	45	
KEYTRUDA + Chemo	790	663	490	343	240	143	95	55	19	3	0
Chemo	789	636	434	274	169	95	58	26	10	0	0

**Figure 16: Kaplan-Meier Curve for Overall Survival in KEYNOTE-859 (CPS≥1)**



Number at Risk	Time in Months										
	0	5	10	15	20	25	30	35	40	45	50
KEYTRUDA + Chemo	618	511	383	269	192	121	81	46	17	3	0
Chemo	617	493	339	206	126	66	41	20	7	0	0

In an exploratory subgroup analysis in patients with PD-L1 CPS<1 (n=344) at the time of the pre-specified interim analysis of OS, the median OS was 12.7 months (95% CI: 11.4, 15.0) for the KEYTRUDA arm and 12.2 months (95% CI: 9.5, 14.0) for the placebo arm, with a HR of 0.92 (95% CI: 0.73, 1.17).

#### 14.10 Esophageal Cancer

##### First-line Treatment of Locally Advanced Unresectable or Metastatic Esophageal /Gastroesophageal Junction Cancer

###### *KEYNOTE-590*

The efficacy of KEYTRUDA was investigated in KEYNOTE-590 (NCT03189719), a multicenter, randomized, placebo-controlled trial that enrolled 749 patients with metastatic or locally advanced esophageal or gastroesophageal junction (tumors with epicenter 1 to 5 centimeters above the GEJ) carcinoma who were not candidates for surgical resection or definitive chemoradiation. PD-L1 status was centrally determined in tumor specimens in all patients using the PD-L1 IHC 22C3 pharmDx kit. Patients with active autoimmune disease, a medical condition that required immunosuppression, or who received prior systemic therapy in the locally advanced or metastatic setting were ineligible. Randomization was stratified by tumor histology (squamous cell carcinoma vs. adenocarcinoma), geographic region (Asia vs. ex-Asia), and ECOG performance status (0 vs. 1).

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

- KEYTRUDA 200 mg on Day 1 of each three-week cycle in combination with cisplatin 80 mg/m<sup>2</sup> IV on Day 1 of each three-week cycle for up to six cycles and FU 800 mg/m<sup>2</sup> IV per day on Day 1 to Day 5 of each three-week cycle, or per local standard for FU administration, for up to 24 months.
- Placebo on Day 1 of each three-week cycle in combination with cisplatin 80 mg/m<sup>2</sup> IV on Day 1 of each three-week cycle for up to six cycles and FU 800 mg/m<sup>2</sup> IV per day on Day 1 to Day 5 of each three-week cycle, or per local standard for FU administration, for up to 24 months.

Treatment with KEYTRUDA or chemotherapy continued until unacceptable toxicity or disease progression. Patients could be treated with KEYTRUDA for up to 24 months in the absence of disease progression. The major efficacy outcome measures were OS and PFS as assessed by the investigator according to RECIST v1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ). The study pre-specified analyses of OS and PFS based on squamous cell histology, CPS ≥10, and in all patients. Additional efficacy outcome measures were ORR and DoR, according to modified RECIST v1.1, as assessed by the investigator.

The study population characteristics were: median age of 63 years (range: 27 to 94), 43% age 65 or older; 83% male; 37% White, 53% Asian, and 1% Black; 40% had an ECOG PS of 0 and 60% had an ECOG PS of 1. Ninety-one percent had M1 disease and 9% had M0 disease. Seventy-three percent had a tumor histology of squamous cell carcinoma, and 27% had adenocarcinoma.

The trial demonstrated a statistically significant improvement in OS and PFS for patients randomized to KEYTRUDA in combination with chemotherapy, compared to chemotherapy.

Table 71 and Figure 17 summarize the efficacy results for KEYNOTE-590 in all patients.

**Table 71: Efficacy Results in Patients with Locally Advanced Unresectable or Metastatic Esophageal Cancer in KEYNOTE-590**

Endpoint	KEYTRUDA 200 mg every 3 weeks Cisplatin FU n=373	Placebo Cisplatin FU n=376
<b>OS</b>		
Number (%) of events	262 (70)	309 (82)
Median in months (95% CI)	12.4 (10.5, 14.0)	9.8 (8.8, 10.8)
Hazard ratio* (95% CI)	0.73 (0.62, 0.86)	
p-Value <sup>†</sup>	<0.0001	
<b>PFS</b>		
Number of events (%)	297 (80)	333 (89)
Median in months (95% CI)	6.3 (6.2, 6.9)	5.8 (5.0, 6.0)
Hazard ratio* (95% CI)	0.65 (0.55, 0.76)	
p-Value <sup>†</sup>	<0.0001	
<b>Objective Response Rate</b>		
ORR, % <sup>‡</sup> (95% CI)	45 (40, 50)	29 (25, 34)
Number (%) of complete responses	24 (6)	9 (2.4)
Number (%) of partial responses	144 (39)	101 (27)
p-Value <sup>§</sup>	<0.0001	
<b>Duration of Response</b>		
Median in months (range)	8.3 (1.2+, 31.0+)	6.0 (1.5+, 25.0+)

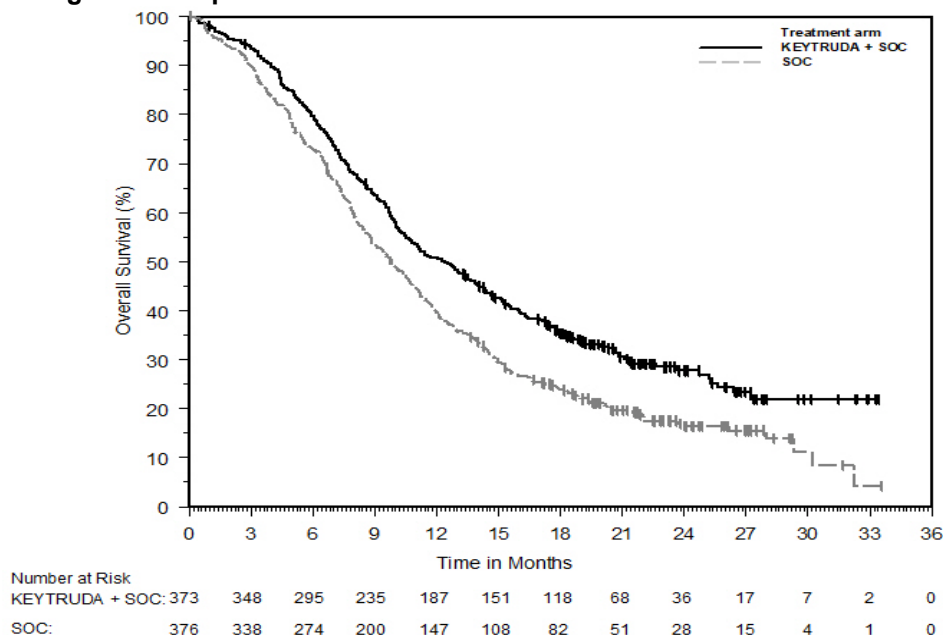
\* Based on the stratified Cox proportional hazard model

† Based on a stratified log-rank test

‡ Confirmed complete response or partial response

§ Based on the stratified Miettinen and Nurminen method

**Figure 17: Kaplan-Meier Curve for Overall Survival in KEYNOTE-590**



In a pre-specified formal test of OS in patients with PD-L1 CPS  $\geq 10$  (n=383), the median was 13.5 months (95% CI: 11.1, 15.6) for the KEYTRUDA arm and 9.4 months (95% CI: 8.0, 10.7) for the placebo arm, with a HR of 0.62 (95% CI: 0.49, 0.78; p-Value < 0.0001). In an exploratory analysis, in patients with PD-L1 CPS < 10 (n=347), the median OS was 10.5 months (95% CI: 9.7, 13.5) for the KEYTRUDA arm and 10.6 months (95% CI: 8.8, 12.0) for the placebo arm, with a HR of 0.86 (95% CI: 0.68, 1.10).

#### Previously Treated Recurrent Locally Advanced or Metastatic Esophageal Cancer

##### **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<sup>2</sup> on Days 1, 8, and 15 of every 4-week cycle, docetaxel 75 mg/m<sup>2</sup> every 3 weeks, or irinotecan 180 mg/m<sup>2</sup> 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  $\geq 10$ , 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  $\geq 10$ . 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.

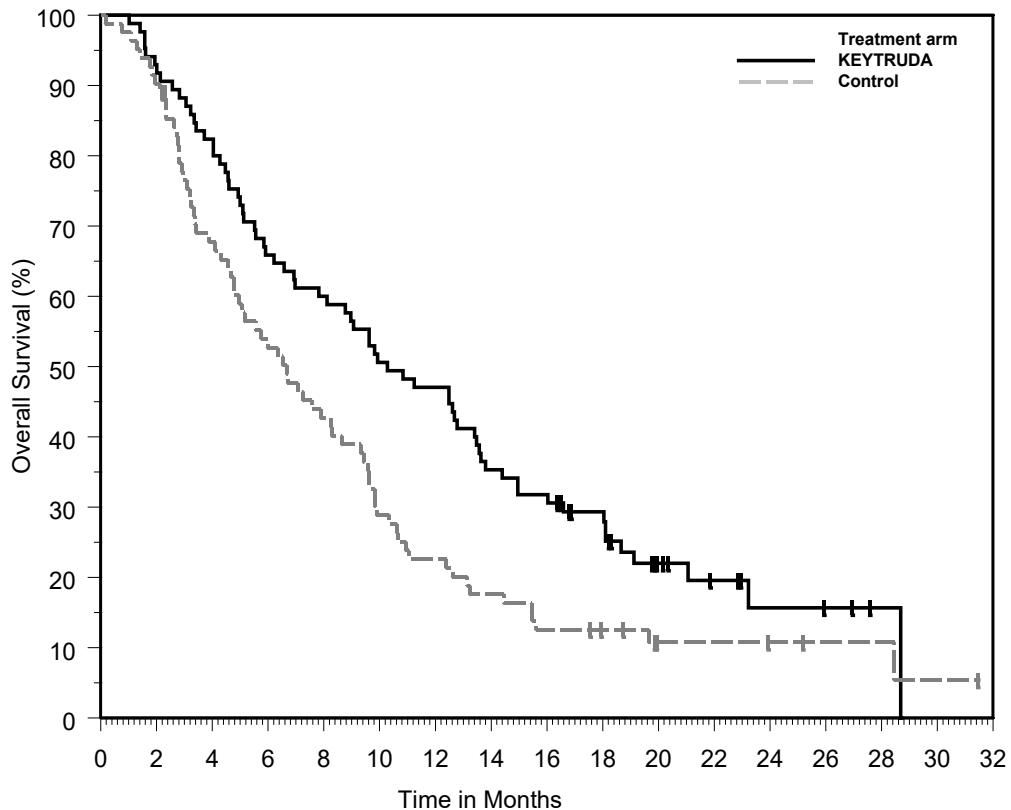
The observed OS hazard ratio was 0.77 (95% CI: 0.63, 0.96) in patients with ESCC, 0.70 (95% CI: 0.52, 0.94) in patients with tumors expressing PD-L1 CPS  $\geq 10$ , and 0.89 (95% CI: 0.75, 1.05) in all randomized patients. On further examination in patients whose ESCC tumors expressed PD-L1 (CPS  $\geq 10$ ), an improvement in OS was observed among patients randomized to KEYTRUDA as compared with chemotherapy. Table 72 and Figure 18 summarize the key efficacy measures for KEYNOTE-181 for patients with ESCC CPS  $\geq 10$ .

**Table 72 : 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
<b>OS</b>		
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)	
<b>PFS</b>		
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)	
<b>Objective Response Rate</b>		
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 18: Kaplan-Meier Curve for Overall Survival in KEYNOTE-181 (ESCC CPS ≥10)**



Number at Risk	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32
KEYTRUDA:	85	79	70	56	51	43	40	30	27	21	11	7	4	3	1	0	0
Control:	82	74	54	42	34	23	18	14	10	8	4	4	3	2	2	1	0

**KEYNOTE-180**

The efficacy of KEYTRUDA was investigated in KEYNOTE-180 (NCT02559687), a multicenter, non-randomized, open-label trial that enrolled 121 patients with locally advanced or metastatic esophageal cancer who progressed on or after at least 2 prior systemic treatments for advanced disease. With the exception of the number of prior lines of treatment, the eligibility criteria were similar to and the dosage regimen identical to KEYNOTE-181.

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



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

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

#### **14.11 Cervical Cancer**

##### **Persistent, Recurrent, or Metastatic Cervical Cancer**

The efficacy of KEYTRUDA in combination with paclitaxel and cisplatin or paclitaxel and carboplatin, with or without bevacizumab, was investigated in KEYNOTE-826 (NCT03635567), a multicenter, randomized, double-blind, placebo-controlled trial that enrolled 617 patients with persistent, recurrent, or first-line metastatic cervical cancer who had not been treated with chemotherapy except when used concurrently as a radio-sensitizing agent. Patients were enrolled regardless of tumor PD-L1 expression status. Patients with autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Randomization was stratified by metastatic status at initial diagnosis, investigator decision to use bevacizumab, and PD-L1 status (CPS  $< 1$  vs. CPS 1 to  $< 10$  vs. CPS  $\geq 10$ ). Patients were randomized (1:1) to one of the two treatment groups:

- Treatment Group 1: KEYTRUDA 200 mg plus chemotherapy with or without bevacizumab
- Treatment Group 2: Placebo plus chemotherapy with or without bevacizumab

The investigator selected one of the following four treatment regimens prior to randomization:

1. Paclitaxel 175 mg/m<sup>2</sup> + cisplatin 50 mg/m<sup>2</sup>
2. Paclitaxel 175 mg/m<sup>2</sup> + cisplatin 50 mg/m<sup>2</sup> + bevacizumab 15 mg/kg
3. Paclitaxel 175 mg/m<sup>2</sup> + carboplatin AUC 5 mg/mL/min
4. Paclitaxel 175 mg/m<sup>2</sup> + carboplatin AUC 5 mg/mL/min + bevacizumab 15 mg/kg

All study medications were administered as an intravenous infusion. All study treatments were administered on Day 1 of each 3-week treatment cycle. Cisplatin could be administered on Day 2 of each 3-week treatment cycle. Treatment with KEYTRUDA continued until RECIST v1.1-defined progression of disease, unacceptable toxicity, or a maximum of 24 months. Administration of KEYTRUDA was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Assessment of tumor status was performed every 9 weeks for the first year, followed by every 12 weeks thereafter. The main efficacy outcome measures were OS and PFS as assessed by investigator according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Additional efficacy outcome measures were ORR and DoR, according to RECIST v1.1, as assessed by investigator.

Of the 617 enrolled patients, 548 patients (89%) had tumors expressing PD-L1 with a CPS  $\geq 1$ . Among these 548 enrolled patients with tumors expressing PD-L1, 273 patients were randomized to KEYTRUDA in combination with chemotherapy with or without bevacizumab, and 275 patients were randomized to placebo in combination with chemotherapy with or without bevacizumab. Sixty-three percent of the 548 patients received bevacizumab as part of study treatment. The baseline characteristics of the 548 patients were: median age of 51 years (range: 22 to 82), 16% age 65 or older; 59% White, 18% Asian, 6% American Indian or Alaska Native, and 1% Black; 37% Hispanic or Latino; 56% ECOG performance status 0 and 43% ECOG performance status 1. Seventy-five percent had squamous cell carcinoma, 21% adenocarcinoma, and 5% adenosquamous histology, and 32% of patients had metastatic disease at diagnosis. At study entry, 21% of patients had metastatic disease only and 79% had persistent or recurrent disease with or without distant metastases, of whom 39% had received prior chemoradiation only and 17% had received prior chemoradiation plus surgery.

A statistically significant improvement in OS and PFS was demonstrated in patients randomized to receive KEYTRUDA compared with patients randomized to receive placebo. An updated OS analysis was conducted at the time of final analysis when 354 deaths in the CPS  $\geq 1$  population were observed.

Table 73 and Figure 19 summarize the key efficacy measures for KEYNOTE-826 for patients with tumors expressing PD-L1 (CPS ≥1).

**Table 73: Efficacy Results in Patients with Persistent, Recurrent, or Metastatic Cervical Cancer (CPS ≥1) in KEYNOTE-826**

Endpoint	KEYTRUDA 200 mg every 3 weeks and chemotherapy* with or without bevacizumab n=273	Placebo and chemotherapy* with or without bevacizumab n=275
<b>OS</b>		
Number of patients with event (%)	118 (43.2)	154 (56.0)
Median in months (95% CI)	NR (19.8, NR)	16.3 (14.5, 19.4)
Hazard ratio <sup>†</sup> (95% CI)	0.64 (0.50, 0.81)	
p-Value <sup>‡</sup>	0.0001	
<b>Updated OS</b>		
Number of patients with event (%)	153 (56.0%)	201 (73.1%)
Median in months (95% CI)	28.6 (22.1, 38.0)	16.5 (14.5, 20.0)
Hazard ratio <sup>†</sup> (95% CI)	0.60 (0.49, 0.74)	
<b>PFS</b>		
Number of patients with event (%)	157 (57.5)	198 (72.0)
Median in months (95% CI)	10.4 (9.7, 12.3)	8.2 (6.3, 8.5)
Hazard ratio <sup>†</sup> (95% CI)	0.62 (0.50, 0.77)	
p-Value <sup>§</sup>	< 0.0001	
<b>Objective Response Rate</b>		
ORR <sup>¶</sup> (95% CI)	68% (62, 74)	50% (44, 56)
Complete response rate	23%	13%
Partial response rate	45%	37%
<b>Duration of Response</b>		
Median in months (range)	18.0 (1.3+, 24.2+)	10.4 (1.5+, 22.0+)

\* Chemotherapy (paclitaxel and cisplatin or paclitaxel and carboplatin)

<sup>†</sup> Based on the stratified Cox proportional hazard model

<sup>‡</sup> p-Value (one-sided) is compared with the allocated alpha of 0.0055 for this interim analysis (with 72% of the planned number of events for final analysis)

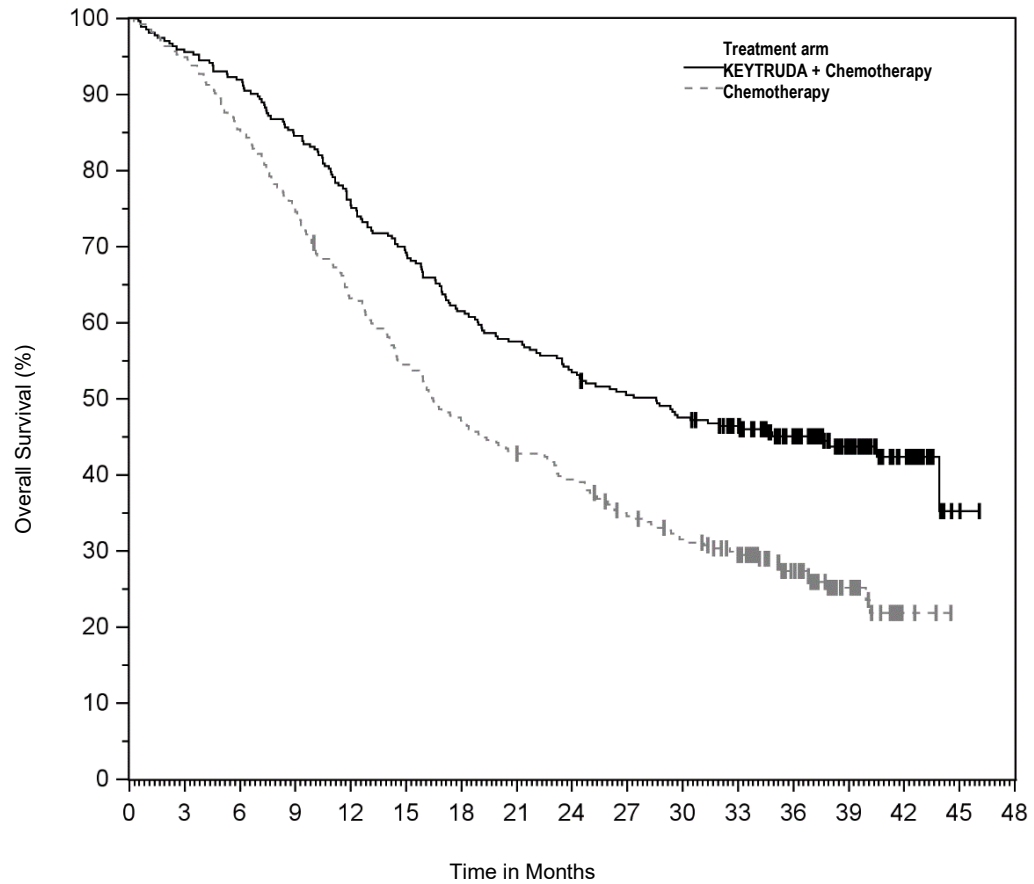
<sup>§</sup> p-Value (one-sided) is compared with the allocated alpha of 0.0014 for this interim analysis (with 82% of the planned number of events for final analysis)

<sup>¶</sup> Response: Best objective response as confirmed complete response or partial response

+ Denotes ongoing response

NR = not reached

**Figure 19: Kaplan-Meier Curve for Overall Survival in KEYNOTE-826 (CPS ≥1)\*, †**



\*Treatment arms include KEYTRUDA plus chemotherapy, with or without bevacizumab, versus placebo plus chemotherapy, with or without bevacizumab.

†Based on the protocol-specified final OS analysis

### Previously Treated Recurrent or Metastatic Cervical Cancer

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  $\geq 1$  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 74 for patients with PD-L1 expression (CPS ≥1).

**Table 74: Efficacy Results in Patients with Recurrent or Metastatic Cervical Cancer (CPS ≥1) in KEYNOTE-158**

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

\* Median follow-up time of 11.7 months (range 0.6 to 22.7 months)

<sup>†</sup> Based on patients (n=11) with a response by independent review

+ Denotes ongoing response

NR = not reached

#### 14.12 Biliary Tract Cancer

The efficacy of KEYTRUDA in combination with gemcitabine and cisplatin chemotherapy was investigated in KEYNOTE-966 (NCT04003636), a multicenter, randomized, double-blind, placebo-controlled trial that enrolled 1069 patients with locally advanced unresectable or metastatic BTC, who had not received prior systemic therapy in the advanced disease setting. Patients with autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Randomization was stratified by region (Asia vs. non-Asia), locally advanced versus metastatic, and site of origin (gallbladder, intrahepatic or extrahepatic cholangiocarcinoma).

Patients were randomized (1:1) to KEYTRUDA 200 mg on Day 1 plus gemcitabine 1000 mg/m<sup>2</sup> and cisplatin 25 mg/m<sup>2</sup> on Day 1 and Day 8 every 3 weeks, or placebo on Day 1 plus gemcitabine 1000 mg/m<sup>2</sup> and cisplatin 25 mg/m<sup>2</sup> on Day 1 and Day 8 every 3 weeks. Study medications were administered via intravenous infusion. Treatment continued until unacceptable toxicity or disease progression. For pembrolizumab, treatment continued for a maximum of 35 cycles, or approximately 24 months. For gemcitabine, treatment could be continued beyond 8 cycles while for cisplatin, treatment could be administered for a maximum of 8 cycles.

Administration of KEYTRUDA with chemotherapy was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered by the investigator to be deriving clinical benefit. Assessment of tumor status was performed at baseline and then every 6 weeks through 54 weeks, followed by every 12 weeks thereafter.

Study population characteristics were median age of 64 years (range: 23 to 85), 47% age 65 or older; 52% male; 49% White, 46% Asian, 1.3% Black or African American; 10% Hispanic or Latino; 46% ECOG PS of 0 and 54% ECOG PS of 1; 31% of patients had a history of hepatitis B infection, and 3% had a history of hepatitis C infection.

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

Table 75 and Figure 20 summarize the efficacy results for KEYNOTE-966.

**Table 75: Efficacy Results in KEYNOTE-966**

Endpoint	KEYTRUDA 200 mg every 3 weeks with gemcitabine/cisplatin n=533	Placebo with gemcitabine/cisplatin  n=536
<b>OS*</b>		
Number of patients with event (%)	414 (78%)	443 (83%)
Median in months (95% CI)	12.7 (11.5, 13.6)	10.9 (9.9, 11.6)
Hazard ratio <sup>†</sup> (95% CI)	0.83 (0.72, 0.95)	
p-Value <sup>‡</sup>	0.0034	
<b>PFS<sup>§</sup></b>		
Number (%) of patients with event	361 (68%)	391 (73%)
Median in months (95% CI)	6.5 (5.7, 6.9)	5.6 (5.1, 6.6)
Hazard ratio <sup>†</sup> (95% CI)	0.86 (0.75, 1.00)	
p-Value <sup>‡</sup>	NS	
<b>Objective Response Rate<sup>§</sup></b>		
ORR <sup>¶</sup> (95% CI)	29% (25, 33)	29% (25, 33)
Number (%) of complete responses	11 (2.1%)	7 (1.3%)
Number (%) of partial responses	142 (27%)	146 (27%)
p-Value <sup>#</sup>	NS	
<b>Duration of Response<sup>¶</sup></b>		
Median in months <sup>‡</sup> (95% CI)	n=156 8.3 (6.9, 10.2)	n=152 6.8 (5.7, 7.1)

\* Results at the pre-specified final OS analysis

† Based on the stratified Cox proportional hazard model

‡ One-sided p-Value based on a stratified log-rank test

§ Results at pre-specified final analysis of PFS and ORR

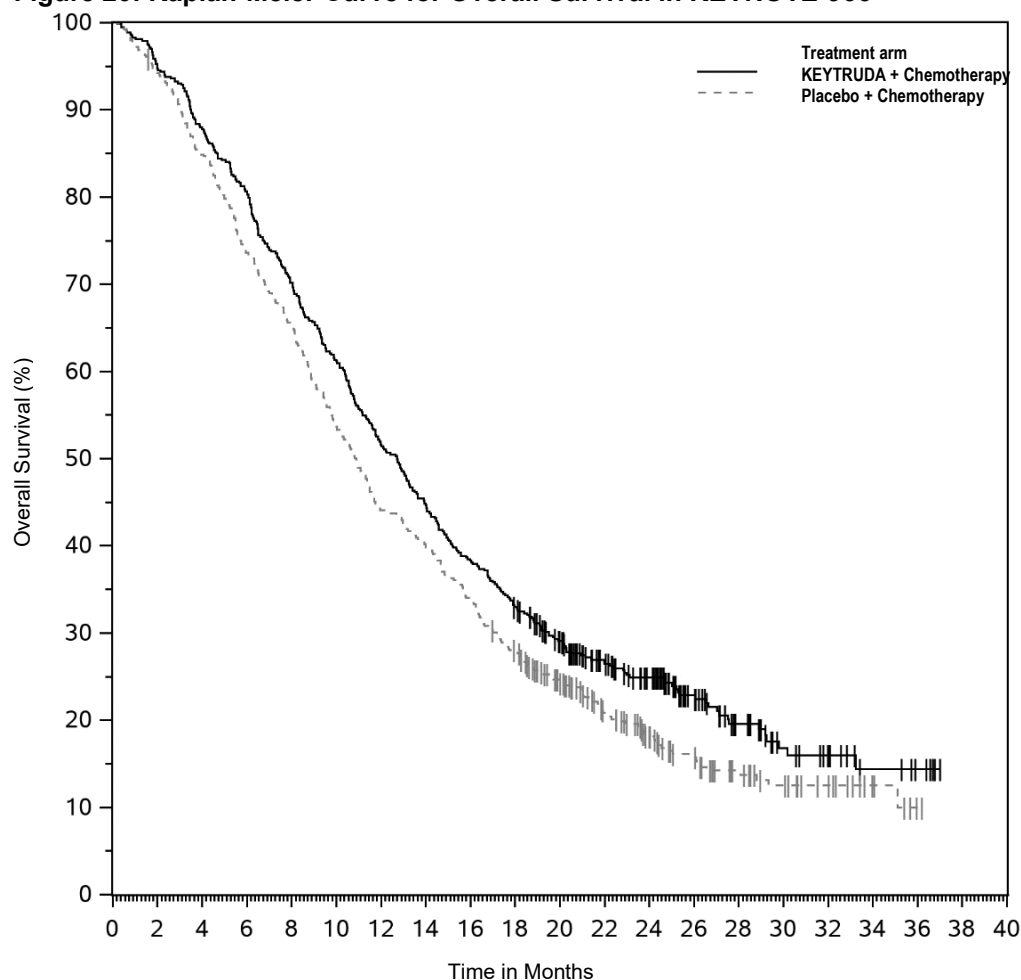
¶ Confirmed complete response or partial response

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

‡ Based on Kaplan-Meier estimate

NS = not significant

**Figure 20: Kaplan-Meier Curve for Overall Survival in KEYNOTE-966**



Number at Risk	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40
KEYTRUDA + Chemotherapy	533	505	469	430	374	326	275	238	204	175	142	108	88	56	35	21	16	8	5	0	0
Placebo + Chemotherapy	536	504	454	394	349	287	236	213	181	148	115	81	59	43	28	20	14	7	1	0	0

### 14.13 Merkel Cell Carcinoma

The efficacy of KEYTRUDA was investigated in KEYNOTE-017 (NCT02267603) and KEYNOTE-913 (NCT03783078), two multicenter, non-randomized, open-label trials that enrolled 105 patients with recurrent locally advanced or metastatic MCC who had not received prior systemic therapy for their advanced disease. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible.

Patients received KEYTRUDA 2 mg/kg (KEYNOTE-017) or 200 mg (KEYNOTE-913) every 3 weeks until unacceptable toxicity or disease progression that was symptomatic, rapidly progressive, required urgent intervention, occurred with a decline in performance status, or was confirmed at least 4 weeks later with repeat imaging. Patients without disease progression were treated for up to 24 months.

The major efficacy outcome measures were ORR and DoR as assessed by BICR per RECIST v1.1.

Among the 105 patients enrolled the median age was 73 years (range: 38 to 91), 79% were age 65 or older; 62% were male; 80% were White, race in 19% was unknown or missing, and 1% were Asian; 53% had ECOG PS of 0, and 47% had ECOG PS of 1. Thirteen percent had stage IIIB disease and 84% had stage IV. Seventy-six percent of patients had prior surgery and 51% had prior radiation therapy.

Efficacy results are summarized in Table 76.

**Table 76 : Efficacy Results in KEYNOTE-017 and KEYNOTE-913**

Endpoint	KEYNOTE-017 KEYTRUDA 2 mg/kg every 3 weeks n=50	KEYNOTE-913 KEYTRUDA 200 mg or 2 mg/kg every 3 weeks n=55
<b>Objective Response Rate</b>		
ORR (95% CI)	56% (41, 70)	49% (35, 63)
Complete responses, n (%)	12 (24%)	9 (16%)
Partial responses, n (%)	16 (32%)	18 (33%)
<b>Duration of Response</b>	<b>n=28</b>	<b>n=27</b>
Median DoR in months (range)	NR (5.9, 34.5+)	NR (4.8, 25.4+)
Patients with duration ≥6 months, n (%)	27 (96%)	25 (93%)
Patients with duration ≥12 months, n (%)	15 (54%)	19 (70%)

+ Denotes ongoing response  
NR = not reached

#### 14.14 Renal Cell Carcinoma

##### First-line treatment with axitinib

###### KEYNOTE-426

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

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

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

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

The study population characteristics were: median age of 62 years (range: 26 to 90), 38% age 65 or older; 73% male; 79% White and 16% Asian; 20% and 80% of patients had a baseline KPS of 70 to 80 and 90 to 100, respectively; and patient distribution by IMDC risk categories was 31% favorable, 56% intermediate, and 13% poor.

The main efficacy outcome measures were OS and PFS as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Additional efficacy outcome measures included ORR, as assessed by BICR. A statistically significant improvement in OS was demonstrated at the first pre-specified interim analysis in patients randomized to KEYTRUDA in combination with axitinib compared with sunitinib. The trial also demonstrated statistically significant improvements in PFS and ORR. An updated OS analysis was conducted when 418 deaths were observed based on the planned number of deaths for the pre-specified final analysis. Table 77 and Figure 21 summarize the efficacy results for KEYNOTE 426.

**Table 77: Efficacy Results in KEYNOTE-426**

Endpoint	KEYTRUDA 200 mg every 3 weeks and Axitinib n=432	Sunitinib n=429
<b>OS</b>		
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 <sup>†</sup>	<0.0001 <sup>‡</sup>	
<b>Updated OS</b>		
Number of patients with event (%)	193 (45%)	225 (52%)
Median in months (95% CI)	45.7 (43.6, NR)	40.1 (34.3, 44.2)
Hazard ratio* (95% CI)	0.73 (0.60, 0.88)	
<b>PFS</b>		
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 <sup>†</sup>	0.0001 <sup>§</sup>	
<b>Objective Response Rate</b>		
ORR <sup>¶</sup> (95% CI)	59% (54, 64)	36% (31, 40)
Complete response rate	6%	2%
Partial response rate	53%	34%
p-Value <sup>#</sup>	<0.0001	

\* Based on the stratified Cox proportional hazard model

<sup>†</sup> Based on stratified log-rank test

<sup>‡</sup> 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).

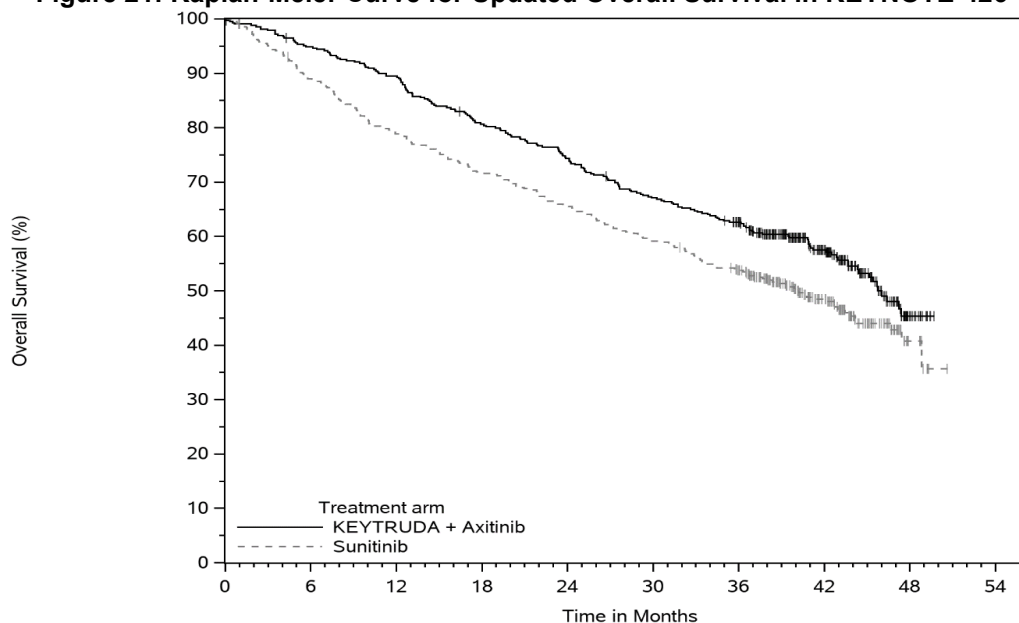
<sup>§</sup> p-Value (one-sided) is compared with the allocated alpha of 0.0013 for this interim analysis (with 81% of the planned number of events for final analysis).

<sup>¶</sup> Response: Best objective response as confirmed complete response or partial response

<sup>#</sup> Based on Miettinen and Nurminen method stratified by IMDC risk group and geographic region

NR = not reached

**Figure 21: Kaplan-Meier Curve for Updated Overall Survival in KEYNOTE-426**



Number at Risk

KEYTRUDA + Axitinib	432	407	384	345	318	286	259	141	16	0
Sunitinib	429	379	336	306	279	252	224	110	12	0

In an exploratory analysis, the updated analysis of OS in patients with IMDC favorable, intermediate, intermediate/poor, and poor risk demonstrated a HR of 1.17 (95% CI: 0.76, 1.80), 0.67 (95% CI: 0.52, 0.86), 0.64 (95% CI: 0.52, 0.80), and 0.51 (95% CI: 0.32, 0.81), respectively.



## First-line treatment with lenvatinib

### KEYNOTE-581

The efficacy of KEYTRUDA in combination with lenvatinib was investigated in KEYNOTE-581 (NCT02811861), a multicenter, open-label, randomized trial conducted in 1069 patients with advanced RCC in the first-line setting. Patients were enrolled regardless of PD-L1 tumor expression status. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible. Randomization was stratified by geographic region (North America versus Western Europe versus “Rest of the World”) and Memorial Sloan Kettering Cancer Center (MSKCC) prognostic groups (favorable versus intermediate versus poor risk).

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

- KEYTRUDA 200 mg intravenously every 3 weeks up to 24 months in combination with lenvatinib 20 mg orally once daily.
- Lenvatinib 18 mg orally once daily in combination with everolimus 5 mg orally once daily.
- Sunitinib 50 mg orally once daily for 4 weeks then off treatment for 2 weeks.

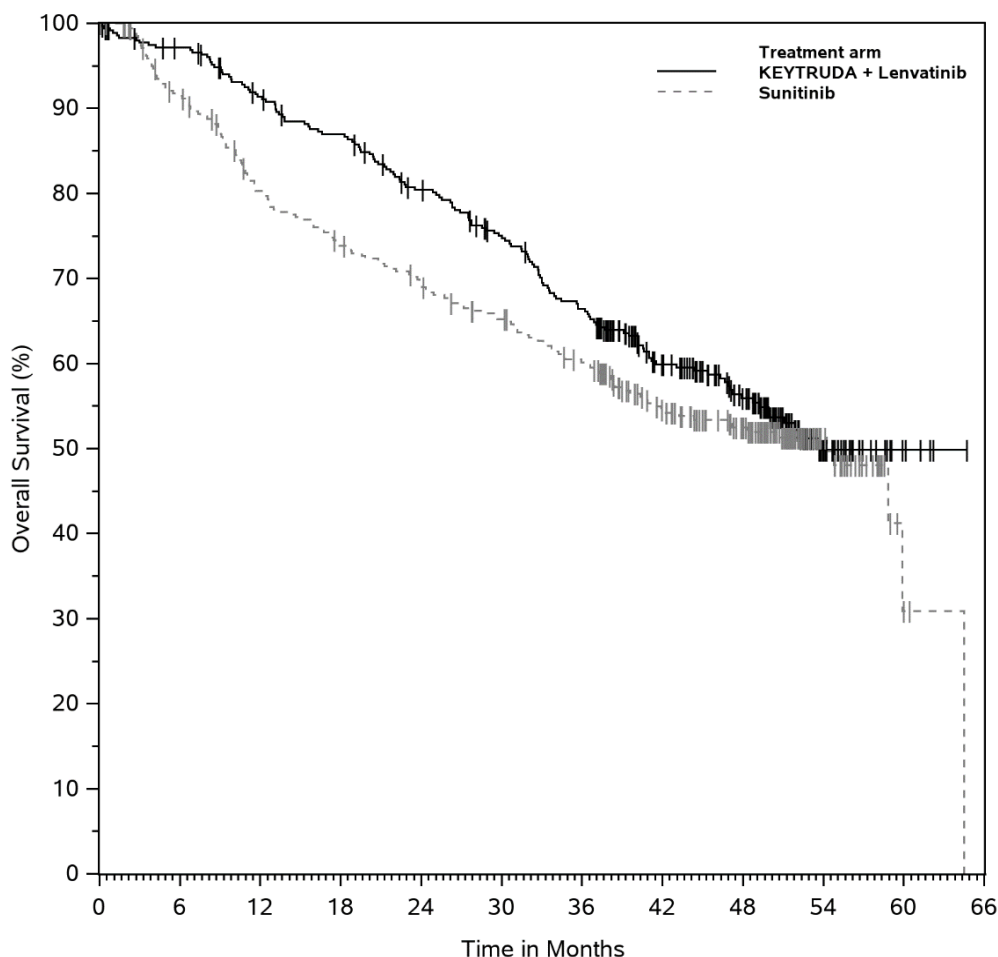
Treatment continued until unacceptable toxicity or disease progression. Administration of KEYTRUDA with lenvatinib was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered by the investigator to be deriving clinical benefit. KEYTRUDA was continued for a maximum of 24 months; however, treatment with lenvatinib could be continued beyond 24 months. Assessment of tumor status was performed at baseline and then every 8 weeks.

The study population characteristics were: median age of 62 years (range: 29 to 88 years), 42% age 65 or older; 75% male; 74% White, 21% Asian, 1% Black, and 2% other races; 18% and 82% of patients had a baseline KPS of 70 to 80 and 90 to 100, respectively; patient distribution by MSKCC risk categories was 27% favorable, 64% intermediate, and 9% poor. Common sites of metastases in patients were lung (68%), lymph node (45%), and bone (25%).

The major efficacy outcome measures were PFS, as assessed by independent radiologic review (IRC) according to RECIST v1.1, and OS. Additional efficacy outcome measures included confirmed ORR-as assessed by IRC. KEYTRUDA in combination with lenvatinib demonstrated statistically significant improvements in PFS, OS, and ORR compared with sunitinib. An updated OS analysis was conducted when 304 deaths were observed based on the planned number of deaths for the pre-specified final analysis. Table 78 and Figures 22 and 23 summarize the efficacy results for KEYNOTE-581.



**Figure 23: Kaplan-Meier Curve for Updated Overall Survival in KEYNOTE-581**



**Number at Risk**

KEYTRUDA + Lenvatinib	355	338	313	296	269	245	216	158	117	34	5	0
Sunitinib	357	308	264	242	226	208	188	145	108	33	3	0

**Adjuvant Treatment of RCC (KEYNOTE-564)**

The efficacy of KEYTRUDA was investigated as adjuvant therapy for RCC in KEYNOTE-564 (NCT03142334), a multicenter, randomized (1:1), double-blind, placebo-controlled trial in 994 patients with intermediate-high or high risk of recurrence of RCC, or M1 no evidence of disease (NED). The intermediate-high risk category included: pT2 with Grade 4 or sarcomatoid features; pT3, any Grade without nodal involvement (N0) or distant metastases (M0). The high risk category included: pT4, any Grade N0 and M0; any pT, any Grade with nodal involvement and M0. The M1 NED category included patients with metastatic disease who had undergone complete resection of primary and metastatic lesions at the time of or  $\leq 1$  year from nephrectomy. Patients must have undergone a partial nephroprotective or radical complete nephrectomy (and complete resection of solid, isolated, soft tissue metastatic lesion(s) in M1 NED participants) with negative surgical margins  $\geq 4$  weeks prior to the time of screening. Patients were excluded from the trial if they had received prior systemic therapy for advanced RCC. Patients with active autoimmune disease or a medical condition that required immunosuppression were also ineligible. Patients with RCC with clear cell component were randomized to KEYTRUDA 200 mg administered intravenously every 3 weeks or placebo for up to 1 year until disease recurrence or unacceptable toxicity. Randomization was stratified by

metastasis status (M0, M1 NED); M0 group was further stratified by ECOG PS (0,1) and geographic region (US, non-US).

The study population characteristics were: median age of 60 years (range: 25 to 84), 33% age 65 or older; 71% male; 75% White, 14% Asian, 9% Unknown, 1% Black or African American, 1% American Indian or Alaska Native, 1% Multiracial; 13% Hispanic or Latino, 78% Not Hispanic or Latino, 8% Unknown; and 85% ECOG PS of 0 and 15% ECOG PS of 1. Ninety-four percent of patients enrolled had N0 disease; 11% had sarcomatoid features; 86% were intermediate-high risk; 8% were high risk; and 6% were M1 NED. Ninety-two percent of patients had a radical nephrectomy, and 8% had a partial nephrectomy.

The major efficacy outcome measure was investigator-assessed disease-free survival (DFS), defined as time to recurrence, metastasis, or death. An additional outcome measure was OS. Statistically significant improvements in DFS and OS were demonstrated at pre-specified interim analyses in patients randomized to the KEYTRUDA arm compared with placebo. Efficacy results are summarized in Table 79 and Figures 24 and 25.

**Table 79: Efficacy Results in KEYNOTE-564**

Endpoint	KEYTRUDA 200 mg every 3 weeks n=496	Placebo n=498
<b>DFS</b>		
Number (%) of patients with event	109 (22%)	151 (30%)
Median in months (95% CI)	NR	NR
Hazard ratio* (95% CI)	0.68 (0.53, 0.87)	
p-Value <sup>†</sup>	0.0010 <sup>‡</sup>	
24-month DFS rate (95% CI)	77% (73, 81)	68% (64, 72)
<b>OS</b>		
Number (%) of patients with event	55 (11%)	86 (17%)
Median in months (95% CI)	NR (NR, NR)	NR (NR, NR)
Hazard ratio* (95% CI)	0.62 (0.44, 0.87)	
p-Value <sup>†</sup>	0.0024 <sup>§</sup>	
48-month OS rate (95% CI)	91% (88, 93)	86% (83, 89)

\* Based on the stratified Cox proportional hazard model

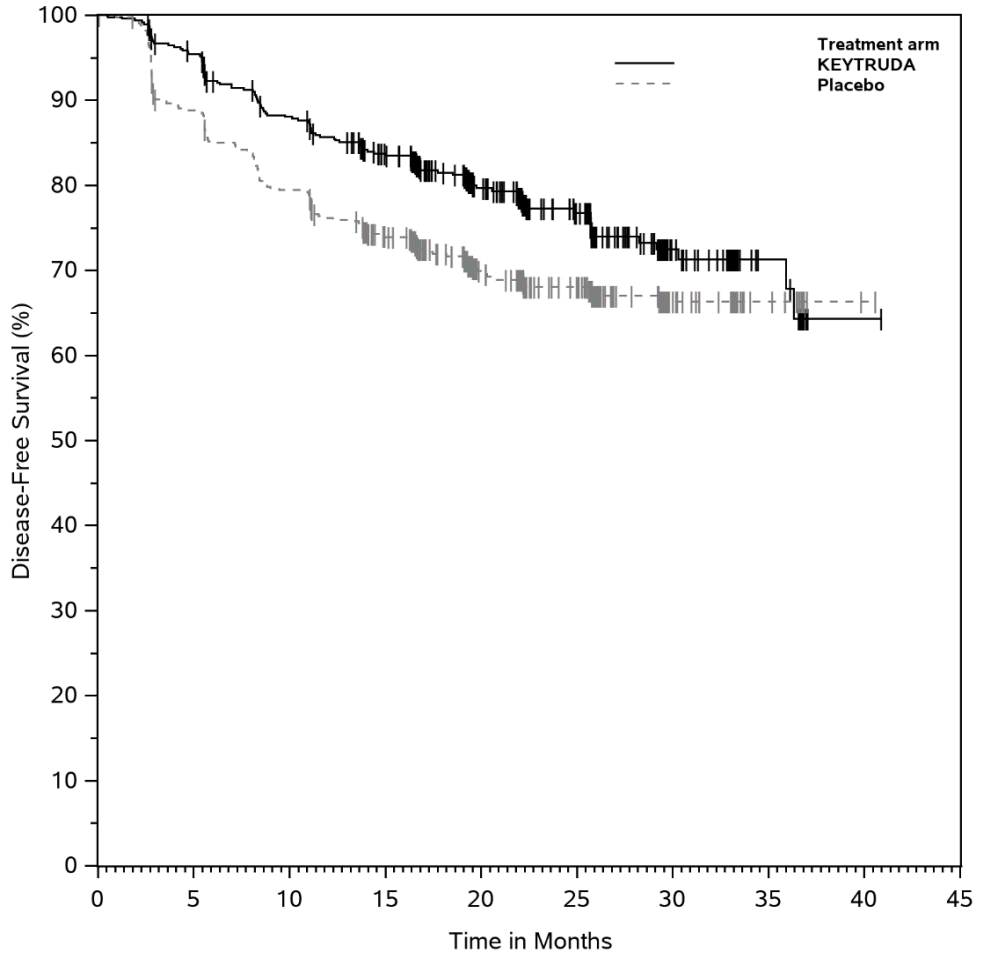
<sup>†</sup> Based on stratified log-rank test

<sup>‡</sup> p-Value (one-sided) is compared with a boundary of 0.0114.

<sup>§</sup> p-Value (one-sided) is compared with a boundary of 0.0072.

NR = not reached

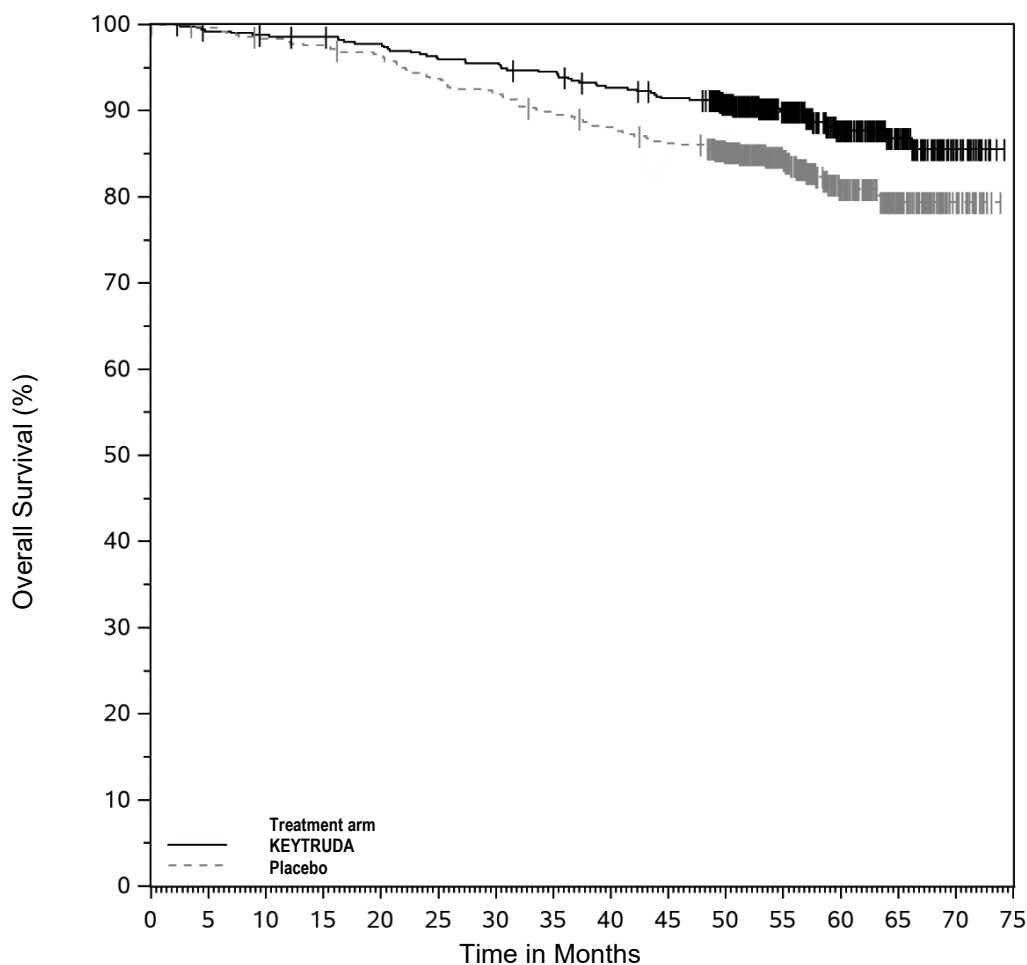
**Figure 24: Kaplan-Meier Curve for Disease-Free Survival in KEYNOTE-564**



**Number at Risk**

KEYTRUDA	496	457	414	371	233	151	61	21	1	0
Placebo	498	436	389	341	209	145	56	19	1	0

**Figure 25: Kaplan-Meier Curve for Overall Survival in KEYNOTE-564**



Number at Risk		0	5	10	15	20	25	30	35	40	45	50	55	60	65	70	75
KEYTRUDA		496	489	486	484	479	470	468	462	451	443	397	270	168	81	22	0
Placebo		498	494	487	483	476	463	455	441	433	423	382	248	155	79	22	0

#### 14.15 Endometrial Carcinoma

The efficacy of KEYTRUDA in combination with lenvatinib was investigated in KEYNOTE-775 (NCT03517449), a multicenter, open-label, randomized, active-controlled trial that enrolled 827 patients with advanced endometrial carcinoma who had been previously treated with at least one prior platinum-based chemotherapy regimen in any setting, including in the neoadjuvant and adjuvant settings. Patients with endometrial sarcoma, including carcinosarcoma, or patients who had active autoimmune disease or a medical condition that required immunosuppression were ineligible. Randomization was stratified according to MMR status (dMMR or pMMR [not dMMR]) using an IHC test. The pMMR stratum was further stratified by ECOG performance status, geographic region, and history of pelvic radiation. Patients were randomized (1:1) to one of the following treatment arms:

- KEYTRUDA 200 mg intravenously every 3 weeks in combination with lenvatinib 20 mg orally once daily.
- Investigator's choice, consisting of either doxorubicin 60 mg/m<sup>2</sup> every 3 weeks or paclitaxel 80 mg/m<sup>2</sup> given weekly, 3 weeks on/1 week off.

Treatment with KEYTRUDA and lenvatinib continued until RECIST v1.1-defined progression of disease as verified by BICR, unacceptable toxicity, or for KEYTRUDA, a maximum of 24 months. Treatment was permitted beyond RECIST v1.1-defined disease progression if the treating investigator considered the patient to be deriving clinical benefit, and the treatment was tolerated. Assessment of tumor status was performed every 8 weeks. The major efficacy outcome measures were OS and PFS as assessed by BICR

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

A total of 827 patients were enrolled and randomized to KEYTRUDA in combination with lenvatinib (n=411) or investigator's choice of doxorubicin (n=306) or paclitaxel (n=110). The study population characteristics were: median age of 65 years (range: 30 to 86), 50% age 65 or older; 61% White, 21% Asian, and 4% Black; 59% ECOG PS of 0 and 41% ECOG PS of 1; and 84% with pMMR tumor status. The histologic subtypes were endometrioid carcinoma (60%), serous (26%), clear cell carcinoma (6%), mixed (5%), and other (3%). All 827 of these patients received prior systemic therapy for endometrial carcinoma: 69% had one, 28% had two, and 3% had three or more prior systemic therapies. Thirty-seven percent of patients received only prior neoadjuvant or adjuvant therapy.

At the pre-specified interim analysis, with a median follow-up time of 11.4 months (range: 0.3 to 26.9 months), the trial demonstrated statistically significant superiority in OS and PFS. The pre-specified final OS analysis with approximately 16 months of additional follow-up duration from the interim analysis (overall median follow-up time of 14.7 months [range: 0.3 to 43.0 months]) was performed without multiplicity adjustment. The trial also demonstrated statistically significant superiority in ORR. PFS, ORR and response duration results at the interim analysis and OS results at final analysis are summarized in Table 80. Kaplan-Meier curves for final OS and interim PFS analyses are shown in Figures 26 and 27, respectively.

**Table 80: Efficacy Results in KEYNOTE-775**

Endpoint	KEYTRUDA 200 mg every 3 weeks and Lenvatinib n=411	Doxorubicin or Paclitaxel n=416
<b>OS</b>		
Number (%) of patients with event	276 (67%)	329 (79%)
Median in months (95% CI)	18.7 (15.6, 21.3)	11.9 (10.7, 13.3)
Hazard ratio* (95% CI)	0.65 (0.55, 0.77)	
p-Value†	<0.0001	
<b>PFS‡</b>		
Number (%) of patients with event	281 (68%)	286 (69%)
Median in months (95% CI)	7.2 (5.7, 7.6)	3.8 (3.6, 4.2)
Hazard ratio* (95% CI)	0.56 (0.47, 0.66)	
p-Value§	<0.0001	
<b>Objective Response Rate‡</b>		
ORR¶ (95% CI)	32% (27, 37)	15% (11, 18)
Complete response rate	7%	3%
Partial response rate	25%	12%
p-Value#	<0.0001	
<b>Duration of Response‡</b>	n=131	n=61
Median in months <sup>▷</sup> (range)	14.4 (1.6+, 23.7+)	5.7 (0.0+, 24.2+)

\* Based on the stratified Cox regression model

† One-sided nominal p-Value for final analysis based on stratified log-rank test. At the pre-specified interim analysis of OS with a median follow-up time of 11.4 months (range: 0.3 to 26.9 months), statistically significant superiority was achieved for OS comparing the combination of pembrolizumab and lenvatinib with chemotherapy (HR: 0.62 [95% CI: 0.51, 0.75] p-Value < 0.0001)

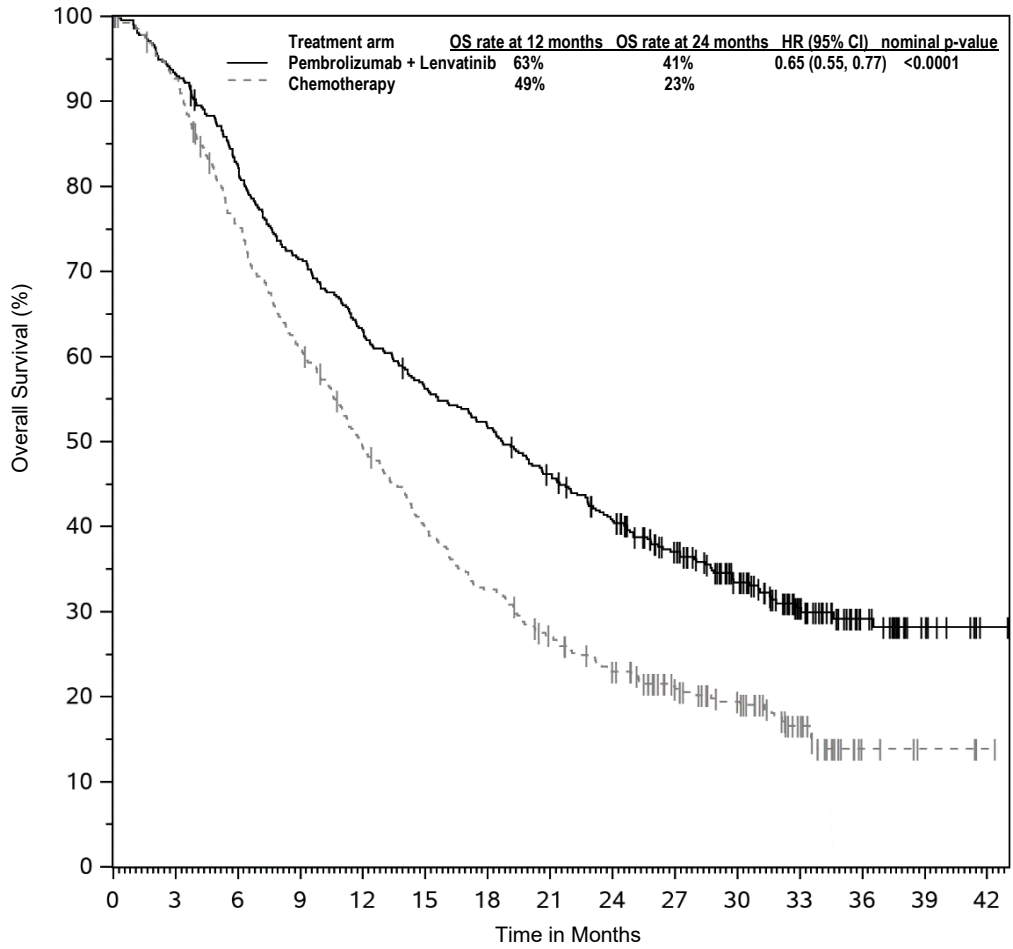
‡ At pre-specified interim analysis

§ One-sided p-Value based on stratified log-rank test¶ Response: Best objective response as confirmed complete response or partial response

# Based on Miettinen and Nurminen method stratified by MMR Status, ECOG performance status, geographic region, and history of pelvic radiation

▷ Based on Kaplan-Meier estimation

**Figure 26: Kaplan-Meier Curve for Overall Survival in KEYNOTE-775**

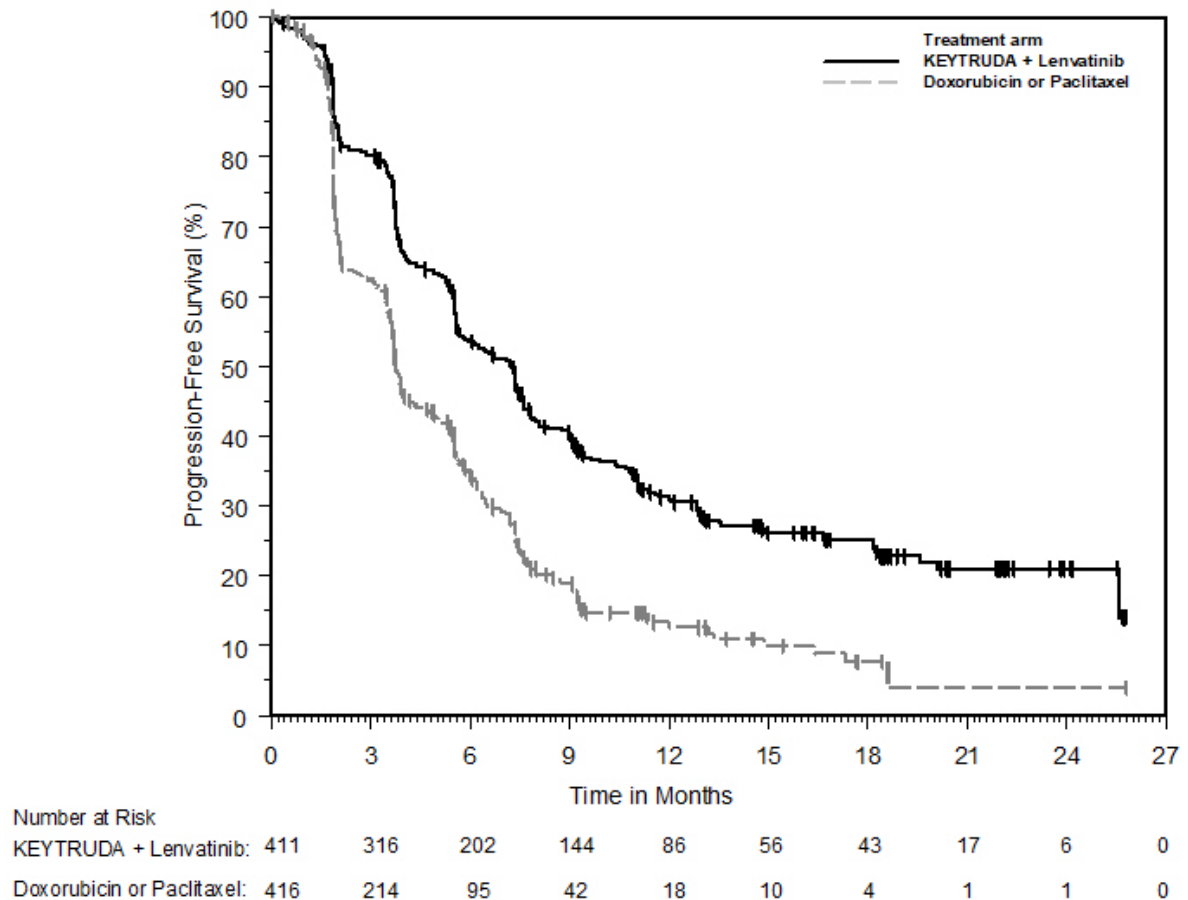


**Number at Risk**

Pembrolizumab + Lenvatinib	411	383	337	292	258	229	211	186	160	125	91	58	30	10	2
Chemotherapy	416	378	305	246	196	158	129	104	84	64	49	28	6	3	1



**Figure 27: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-775**



#### 14.16 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  $\geq 10$  and  $\geq 13$  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  $\geq 10$  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 81 and 82.

**Table 81 : 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
<b>Objective Response Rate</b>		
ORR (95% CI)	29% (21, 39)	37% (26, 50)
Complete response rate	4%	3%
Partial response rate	25%	34%
<b>Duration of Response</b>	n=30	n=26
Median in months (range) <sup>†</sup>	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

<sup>†</sup> From product-limit (Kaplan-Meier) method for censored data

+ Denotes ongoing response

NR = not reached

**Table 82: Response by Tumor Type (TMB ≥10 mut/Mb)**

	N	Objective Response Rate n (%)		95% CI	Duration of Response range (months)
<b>Overall*</b>	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.

#### 14.17 Cutaneous Squamous Cell Carcinoma

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

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

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

Among the 105 patients with recurrent or metastatic cSCC treated, the study population characteristics were: median age of 72 years (range: 29 to 95), 71% age 65 or older; 76% male; 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.

Among the 54 patients with locally advanced cSCC treated, the study population characteristics were: median age of 76 years (range: 35 to 95), 80% age 65 or older; 72% male; 83% White, 13% race unknown; 41% ECOG PS of 0 and 59% ECOG PS of 1. Twenty-two percent received one or more prior lines of therapy; 63% received prior radiation therapy.

Efficacy results are summarized in Table 83.

**Table 83: Efficacy Results in KEYNOTE-629**

Endpoint	KEYTRUDA Recurrent or Metastatic cSCC n=105	KEYTRUDA Locally Advanced cSCC n=54
<b>Objective Response Rate</b>		
ORR (95% CI)	35% (26, 45)	50% (36, 64)
Complete response rate	11%	17%
Partial response rate	25%	33%
<b>Duration of Response*</b>	n=37	n=27
Median in months (range)	NR (2.7, 30.4+)	NR (1.0+, 17.2+)
% with duration ≥6 months	76%	81%
% with duration ≥12 months	68%	37%

\* Median follow-up time: recurrent or metastatic cSCC: 23.8 months; locally advanced cSCC: 13.4 months

+ Denotes ongoing response

#### 14.18 Triple-Negative Breast Cancer

##### Neoadjuvant and Adjuvant Treatment of High-Risk Early-Stage TNBC

The efficacy of KEYTRUDA in combination with neoadjuvant chemotherapy followed by surgery and continued adjuvant treatment with KEYTRUDA as a single agent was investigated in KEYNOTE-522 (NCT03036488), a randomized (2:1), multicenter, double-blind, placebo-controlled trial conducted in 1174 patients with newly diagnosed previously untreated high-risk early-stage TNBC (tumor size >1 cm but ≤2 cm in diameter with nodal involvement or tumor size >2 cm in diameter regardless of nodal involvement). Patients were enrolled regardless of tumor PD-L1 expression. Patients with active autoimmune disease that required systemic therapy within two years of treatment or a medical condition that required immunosuppression were ineligible. Randomization was stratified by nodal status (positive vs. negative), tumor size (T1/T2 vs. T3/T4), and choice of carboplatin (dosed every 3 weeks vs. weekly).

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

- **Arm 1:**
  - Four cycles of preoperative KEYTRUDA 200 mg every 3 weeks on Day 1 of cycles 1-4 of treatment regimen in combination with:
    - Carboplatin
      - AUC 5 mg/mL/min every 3 weeks on Day 1 of cycles 1-4 of treatment regimen
      - or-**
      - AUC 1.5 mg/mL/min every week on Days 1, 8, and 15 of cycles 1-4 of treatment regimen
      - and-**
    - Paclitaxel 80 mg/m<sup>2</sup> every week on Days 1, 8, and 15 of cycles 1-4 of treatment regimen
  - Followed by four additional cycles of preoperative KEYTRUDA 200 mg every 3 weeks on Day 1 of cycles 5-8 of treatment regimen in combination with:

- Doxorubicin 60 mg/m<sup>2</sup> **-or-** epirubicin 90 mg/m<sup>2</sup> every 3 weeks on Day 1 of cycles 5-8 of treatment regimen **-and-**
  - Cyclophosphamide 600 mg/m<sup>2</sup> every 3 weeks on Day 1 of cycles 5-8 of treatment regimen
  - Following surgery, nine cycles of KEYTRUDA 200 mg every 3 weeks were administered.
- **Arm 2:**
    - Four cycles of preoperative placebo every 3 weeks on Day 1 of cycles 1-4 of treatment regimen in combination with:
      - Carboplatin
        - AUC 5 mg/mL/min every 3 weeks on Day 1 of cycles 1-4 of treatment regimen
        - or-**
        - AUC 1.5 mg/mL/min every week on Days 1, 8, and 15 of cycles 1-4 of treatment regimen
        - and-**
      - Paclitaxel 80 mg/m<sup>2</sup> every week on Days 1, 8, and 15 of cycles 1-4 of treatment regimen
    - Followed by four cycles of preoperative placebo every 3 weeks on Day 1 of cycles 5-8 of treatment regimen in combination with:
      - Doxorubicin 60 mg/m<sup>2</sup> **-or-** epirubicin 90 mg/m<sup>2</sup> every 3 weeks on Day 1 of cycles 5-8 of treatment regimen **-and-**
      - Cyclophosphamide 600 mg/m<sup>2</sup> every 3 weeks on Day 1 of cycles 5-8 of treatment regimen
    - Following surgery, nine cycles of placebo every 3 weeks were administered.

The main efficacy outcomes were pCR rate and EFS. pCR was defined as absence of invasive cancer in the breast and lymph nodes (ypT0/Tis ypN0) and was assessed by the blinded local pathologist at the time of definitive surgery. EFS was defined as the time from randomization to the first occurrence of any of the following events: progression of disease that precludes definitive surgery, local or distant recurrence, second primary malignancy, or death due to any cause. An additional efficacy outcome was overall survival (OS).

The study population characteristics were: median age of 49 years (range: 22 to 80), 11% age 65 or older; 99.9% female; 64% White, 20% Asian, 4.5% Black, and 1.8% American Indian or Alaska Native; 87% ECOG PS of 0 and 13% ECOG PS of 1; 56% were pre-menopausal status and 44% were post-menopausal status; 7% were primary Tumor 1 (T1), 68% T2, 19% T3, and 7% T4; 49% were nodal involvement 0 (N0), 40% N1, 11% N2, and 0.2% N3; 75% of patients were overall Stage II and 25% were Stage III.

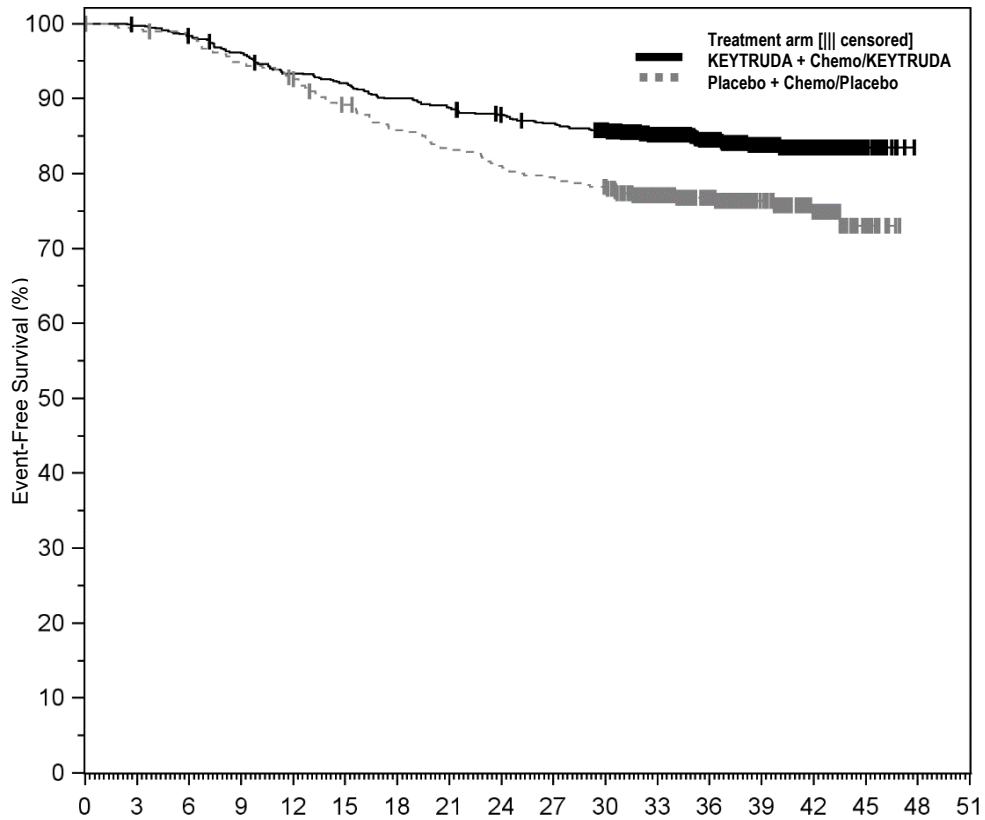
Table 84 and Figure 28 summarize the efficacy results for KEYNOTE-522. At the protocol pre-specified IA4 interim analysis of OS, OS data were not mature with 45% of the required events for the final analysis.

**Table 84: Efficacy Results in KEYNOTE-522**

Endpoint	KEYTRUDA 200 mg every 3 weeks with chemotherapy/KEYTRUDA n=784	Placebo with chemotherapy/Placebo n=390
<b>pCR (ypT0/Tis ypN0)*</b>		
Number of patients with pCR	494	217
pCR Rate (%), (95% CI)	63.0 (59.5, 66.4)	55.6 (50.6, 60.6)
Treatment difference (%) estimate (95% CI) <sup>†,‡</sup>	7.5 (1.6, 13.4)	
<b>EFS</b>		
Number of patients with event (%)	123 (16%)	93 (24%)
Hazard ratio (95% CI) <sup>§</sup>	0.63 (0.48, 0.82)	
p-Value <sup>¶,#</sup>	0.00031	

- \* Based on the entire intention-to-treat population n=1174 patients
- † Based on a pre-specified pCR interim analysis in n=602 patients, the pCR rate difference was statistically significant (p=0.00055 compared to a significance level of 0.003).
- ‡ Based on Miettinen and Nurminen method stratified by nodal status, tumor size, and choice of carboplatin
- § Based on stratified Cox regression model
- ¶ Based on a pre-specified EFS interim analysis (compared to a significance level of 0.0052)
- # Based on log-rank test stratified by nodal status, tumor size, and choice of carboplatin

**Figure 28: Kaplan-Meier Curve for Event-Free Survival in KEYNOTE-522**



Number at Risk	Time in Months																	
	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51
KEYTRUDA + Chemo/KEYTRUDA:	784	781	769	751	728	718	702	692	681	671	652	551	433	303	165	28	0	0
Placebo + Chemo/Placebo:	390	386	382	368	358	342	328	319	310	304	297	250	195	140	83	17	0	0

Locally Recurrent Unresectable or Metastatic TNBC

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

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

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

Assessment of tumor status was performed at Weeks 8, 16, and 24, then every 9 weeks for the first year, and every 12 weeks thereafter. The main efficacy outcome measures were OS and PFS as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ tested in the subgroup of patients with CPS  $\geq$ 10. Additional efficacy outcome measures were ORR and DoR as assessed by BICR.

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

Table 85 and Figures 29 and 30 summarize the efficacy results for KEYNOTE-355.

**Table 85: 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
<b>OS*</b>		
Number of patients with event (%)	155 (70%)	84 (82%)
Median in months (95% CI)	23 (19.0, 26.3)	16.1 (12.6, 18.8)
Hazard ratio† (95% CI)	0.73 (0.55, 0.95)	
p-Value‡	0.0093	
<b>PFS§</b>		
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	
<b>Objective Response Rate (Confirmed)*</b>		
ORR (95% CI)	53% (46,59)	41% (31, 51)
Complete response rate	17%	14%
Partial response rate	35%	27%
<b>Duration of Response*</b>		
	<b>n=116</b>	<b>n=42</b>
Median in months (95% CI)	12.8 (9.9, 25.9)	7.3 (5.5, 15.4)

\* Based on the pre-specified final analysis

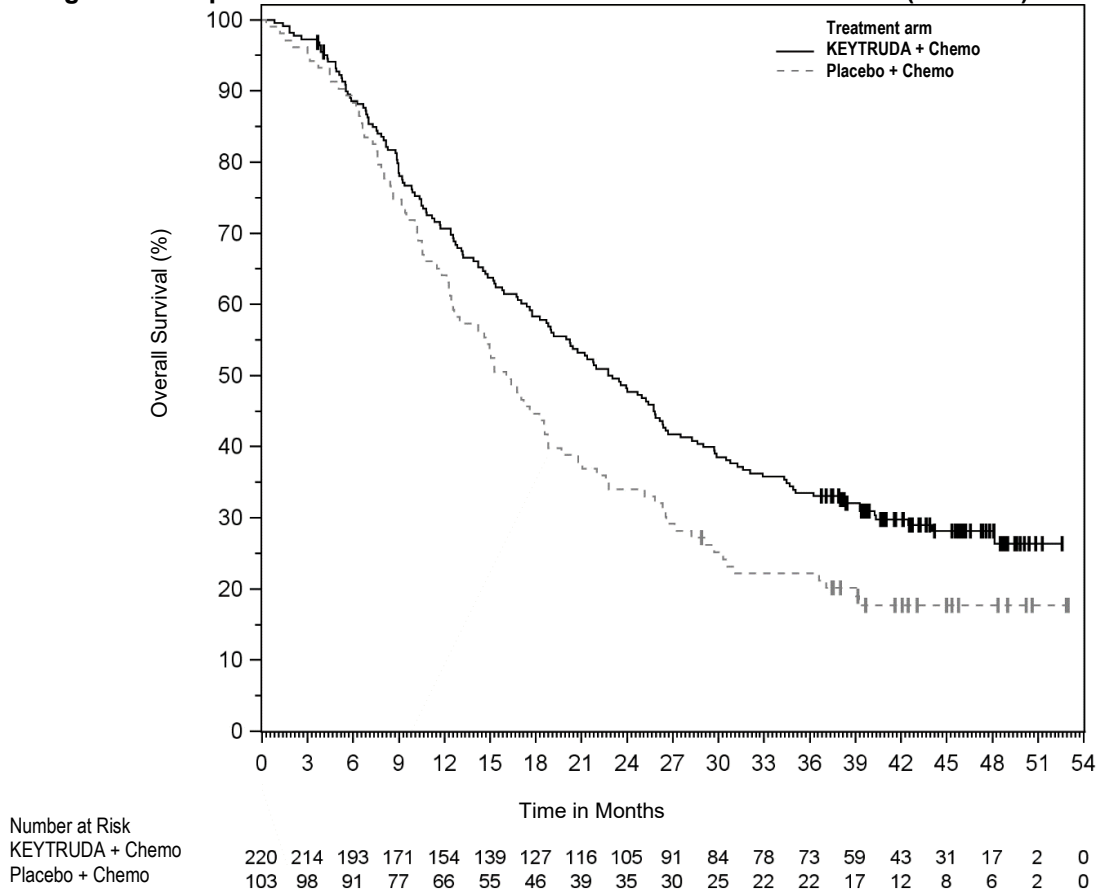
† Based on stratified Cox regression model

‡ One-sided p-Value based on stratified log-rank test (compared to a significance level of 0.0113)

§ Based on a pre-specified interim analysis

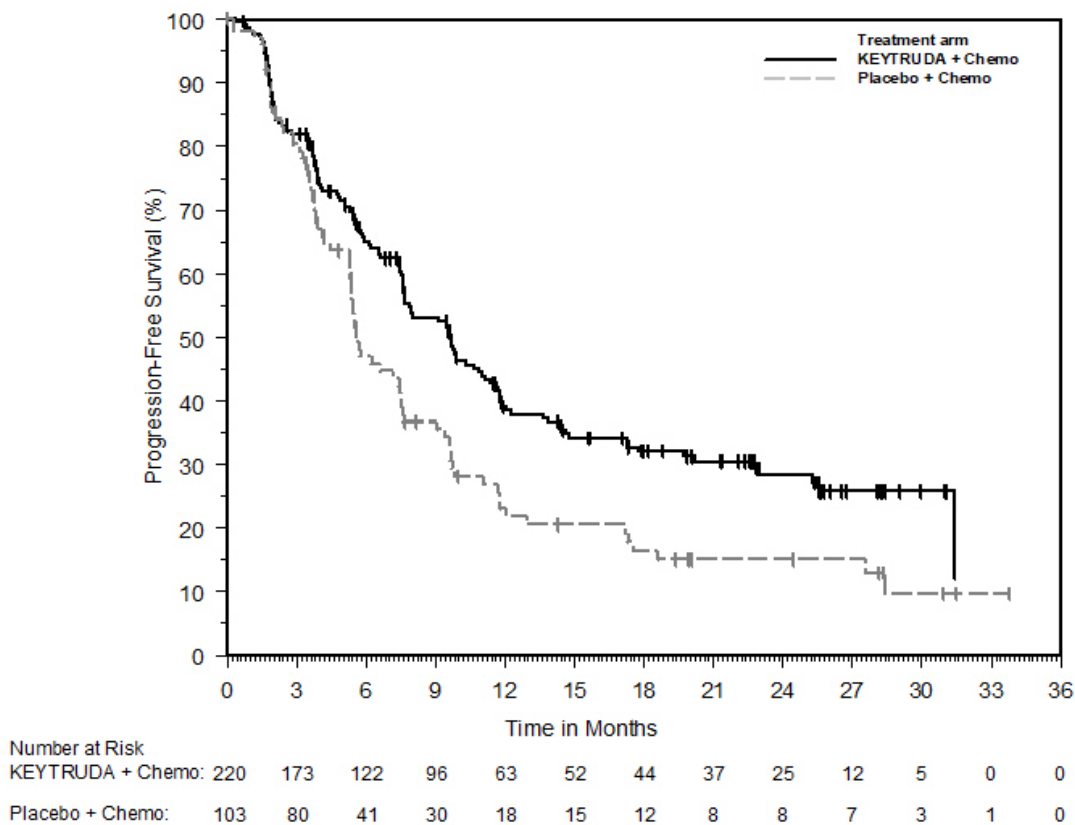
¶ One-sided p-Value based on stratified log-rank test (compared to a significance level of 0.00411)

**Figure 29: Kaplan-Meier Curve for Overall Survival in KEYNOTE-355 (CPS  $\geq 10$ )**



**Figure 30: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-355 (CPS  $\geq 10$ )**





A prespecified analysis was performed in KEYNOTE-355 in patients whose tumors expressed PD-L1 CPS  $\geq 10$ . The study was not powered to evaluate efficacy within each of the chemotherapy choices or formally compare efficacy between the 3 chemotherapy backbones, and the number of participants in these subgroups are too limited; therefore, the results of these subgroup analyses should be interpreted with caution. The median PFS was 9.9 months for KEYTRUDA in combination with paclitaxel protein-bound (n=63) and 5.5 months for placebo in combination with paclitaxel protein-bound (n=36), with an HR of 0.57 (95% CI: 0.34, 0.95). The median PFS was 9.6 months for KEYTRUDA in combination with paclitaxel (n=33) and 3.6 months for placebo in combination with paclitaxel (n=11), with an HR of 0.33 (95% CI: 0.14, 0.76). The median PFS was 8.0 months for KEYTRUDA in combination with gemcitabine and carboplatin (n=124) and 7.2 months for placebo in combination with gemcitabine and carboplatin (n=56), with an HR of 0.77 (95% CI: 0.53, 1.11).

## 16 HOW SUPPLIED/STORAGE AND HANDLING

carton containing one 100 mg/4 mL (25 mg/mL), single-dose vial.

Store vials under refrigeration at 2°C to 8°C in original carton to protect from light. Do not freeze. Do not shake.

The expiry date of the product is indicated on the packaging materials

## 17 LICENSE HOLDER AND IMPORTER

Merck Sharp & Dohme (Israel-1996) Company Ltd., 34 Ha'charash St., Hod-Hasharon.

## 18 REGISTRATION NUMBER

KEYTRUDA 100 mg/4 mL: 154.38.34448.00

Revised in November 2024 according to MoH's guidelines.