1.6 Urothelial Carcinoma

KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy *[see Clinical Studies (14.6)].*

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

KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy *[see Clinical Studies (14.6)].*

1.7 Microsatellite Instability-High Cancer

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

- solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or
- colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan *[see Clinical Studies (14.7)]*.

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

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 Gastric Cancer

KEYTRUDA is indicated for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test, with disease progression on or after two or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy *[see Clinical Studies (14.8)]*.

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

1.9 Cervical Cancer

KEYTRUDA is indicated for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test *[see Clinical Studies (14.9)]*.

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

cHL

Among the 210 patients with cHL enrolled in Study KEYNOTE-087 *[see Clinical Studies (14.4)]*, the median duration of exposure to KEYTRUDA was 8.4 months (range: 1 day to 15.2 months). KEYTRUDA was discontinued due to adverse reactions in 5% of patients, and treatment was interrupted due to adverse reactions in 26%. Fifteen percent (15%) of patients had an adverse reaction requiring systemic corticosteroid therapy. Serious adverse reactions occurred in 16% of patients. The most frequent serious adverse reactions (≥1%) included pneumonia, pneumonitis, pyrexia, dyspnea, graft versus host disease and herpes zoster. Two patients died from causes other than disease progression; one from GVHD after subsequent allogeneic HSCT and one from septic shock.

Table 9 summarizes the adverse reactions that occurred in at least 10% of patients treated with KEYTRUDA.

Table 9: Adverse Reactions in ≥10% of Patients with cHL in KEYNOTE-087

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

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

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

Table 10: Selected Laboratory Abnormalities Worsened from Baseline Occurring in ≥15% of cHL Patients Receiving KEYTRUDA in KEYNOTE-087

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

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

† Graded per NCI CTCAE v4.0

‡ Includes elevation of AST or ALT

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

PMBCL

Among the 53 patients with PMBCL treated in KEYNOTE-170 *[see Clinical Studies (14.5)],* the median duration of exposure to KEYTRUDA was 3.5 months (range: 1 day to 22.8 months). KEYTRUDA was discontinued due to adverse reactions in 8% of patients, and treatment was interrupted due to adverse reactions in 15%. Twenty-five percent of patients had an adverse reaction requiring systemic corticosteroid therapy. Serious adverse reactions occurred in 26% of patients, and included arrhythmia (4%), cardiac tamponade (2%), myocardial infarction (2%), pericardial effusion (2%), and pericarditis (2%). Six (11%) patients died within 30 days of start of treatment.

Table 11 summarizes the adverse reactions that occurred in at least 10% of patients treated with KEYTRUDA. Table 12 summarizes the incidence of laboratory abnormalities that occurred in at least 15% of patients receiving KEYTRUDA.

Table 11: Adverse Reactions in ≥10% of Patients with PMBCL in KEYNOTE-170

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

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

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

Table 12: Laboratory Abnormalities Worsened from Baseline Occurring in ≥15% of PMBCL Patients Receiving KEYTRUDA in KEYNOTE-170

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

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

Urothelial Carcinoma

Cisplatin Ineligible Patients with Urothelial Carcinoma

The safety of KEYTRUDA was investigated in Study 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. 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).

The most common adverse reactions (reported in at least 20% of patients) were fatigue, musculoskeletal pain, decreased appetite, constipation, rash and diarrhea. 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 13 summarizes the incidence of adverse reactions occurring in at least 10% of patients receiving KEYTRUDA.

Table 13: Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-052

	KEYTRUDA 200 mg every 3 weeks N=370	
Adverse Reaction	**All Grades* (%)**	**Grades 3 – 4 (%)**
All Adverse Reactions	96	49
Blood and Lymphatic System Disorders		
Anemia	17	7
Gastrointestinal Disorders		
Constipation	21	1.1
Diarrhea†	20	2.4
Nausea	18	1.1
Abdominal pain‡	18	2.7
Elevated LFTs§	13	3.5
Vomiting	12	0
General Disorders and Administration Site Conditions		
Fatigue¶	38	6
Pyrexia	11	0.5
Weight decreased	10	0
Infections and Infestations		
Urinary tract infection	19	9
Metabolism and Nutrition Disorders		
Decreased appetite	22	1.6
Hyponatremia	10	4.1
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain#	24	4.9
Arthralgia	10	1.1
Renal and Urinary Disorders		
Blood creatinine increased	11	1.1
Hematuria	13	3.0
Respiratory, Thoracic, and Mediastinal Disorders		
Cough	14	0
Dyspnea	11	0.5
Skin and Subcutaneous Tissue Disorders		
Rashᵖ	21	0.5
Pruritus	19	0.3
Edema peripheral	14	1.1

* Graded per NCI CTCAE v4.0

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

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

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

¶ Includes fatigue, asthenia

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

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

Previously Treated Urothelial Carcinoma

The safety of KEYTRUDA for the treatment of patients with locally advanced or metastatic urothelial carcinoma with disease progression following platinum-containing chemotherapy was investigated in

Study KEYNOTE-045. KEYNOTE-045 was a multicenter, open-label, randomized (1:1), active-controlled trial in which 266 patients received KEYTRUDA 200 mg every 3 weeks or investigator's choice of chemotherapy (n=255), consisting of paclitaxel (n=84), docetaxel (n=84) or vinflunine (n=87) *[see Clinical Studies (14.6)]*. Patients with autoimmune disease or a medical condition that required systemic corticosteroids or other immunosuppressive medications were ineligible. The median duration of exposure was 3.5 months (range: 1 day to 20 months) in patients who received KEYTRUDA and 1.5 months (range: 1 day to 14 months) in patients who received chemotherapy.

KEYTRUDA was discontinued due to adverse reactions in 8% of patients. The most common adverse reaction resulting in permanent discontinuation of KEYTRUDA was pneumonitis (1.9%). Adverse reactions leading to interruption of KEYTRUDA occurred in 20% of patients; the most common (≥1%) were urinary tract infection (1.5%), diarrhea (1.5%), and colitis (1.1%). The most common adverse reactions (occurring in at least 20% of patients who received KEYTRUDA) were fatigue, musculoskeletal pain, pruritus, decreased appetite, nausea and rash. Serious adverse reactions occurred in 39% of KEYTRUDA-treated patients. The most frequent serious adverse reactions (≥2%) in KEYTRUDA-treated patients were urinary tract infection, pneumonia, anemia, and pneumonitis.

Table 14 summarizes the incidence of adverse reactions occurring in at least 10% of patients receiving KEYTRUDA. Table 15 summarizes the incidence of laboratory abnormalities that occurred in at least 20% of patients receiving KEYTRUDA.

Table 14: Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-045

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

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

Table 15: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Urothelial Carcinoma Patients Receiving KEYTRUDA in KEYNOTE-045

	KEYTRUDA 200 mg every 3 weeks		Chemotherapy	
Laboratory Test*	**All Grades† %**	**Grades 3-4 %**	**All Grades† %**	**Grades 3-4 %**
Chemistry				
Glucose increased	52	8	60	7
Hemoglobin decreased	52	13	68	18
Lymphocytes decreased	45	15	53	25
Albumin decreased	43	1.7	50	3.8
Sodium decreased	37	9	47	13
Alkaline phosphatase increased	37	7	33	4.9
Creatinine increased	35	4.4	28	2.9
Phosphate decreased	29	8	34	14
Aspartate aminotransferase increased	28	4.1	20	2.5
Potassium increased	28	0.8	27	6
Calcium decreased	26	1.6	34	2.1

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

† Graded per NCI CTCAE v4.0

Gastric Cancer

Among the 259 patients with gastric cancer enrolled in Study KEYNOTE-059, the median duration of exposure to KEYTRUDA was 2.1 months (range: 1 day to 21.4 months). Patients with autoimmune disease or a medical condition that required immunosuppression or with clinical evidence of ascites by physical exam were ineligible.

Adverse reactions occurring in patients with gastric cancer were similar to those occurring in patients with melanoma or NSCLC.

Cervical Cancer

Among the 98 patients with cervical cancer enrolled in Cohort E of Study KEYNOTE-158, 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%).

Table 16 summarizes the adverse reactions occurring in at least 10% of patients receiving KEYTRUDA.

Table 16: Adverse Reactions Occurring in ≥10% of Patients with Cervical Cancer in KEYNOTE-158

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

* Graded per NCI CTCAE v4.0

† Includes asthenia, fatigue, lethargy, malaise

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

§ Includes edema peripheral, peripheral swelling

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

Includes colitis, diarrhea, gastroenteritis

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

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

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

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

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

Table 17 summarizes the laboratory abnormalities that occurred in at least 20% of patients receiving KEYTRUDA.

Table 17: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients with Cervical Cancer in KEYNOTE-158

	KEYTRUDA 200 mg every 3 weeks	
Laboratory Test*	All Grades† (%)	Grade 3-4 (%)
Chemistry		
Hypoalbuminemia	44	5
Alkaline phosphatase increased	42	2.6
Hyponatremia	38	13
Hyperglycemia	38	1.3
Aspartate aminotransferase increased	34	3.9
Creatinine increased	32	5
Hypocalcemia	27	0
Alanine aminotransferase increased	21	3.9
Hypokalemia	20	6
Hematology		
Anemia	54	24
Lymphocyte count decreased	47	9

* 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), INR increased (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).

6.2 Immunogenicity

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

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, KEYTRUDA can cause fetal harm when administered to a pregnant woman. 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. There are no available human data informing the risk of embryo-fetal toxicity. Apprise 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, but an assessment of the effects on reproduction was provided. 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

It is not known whether KEYTRUDA is excreted in human milk. No studies have been conducted to assess the impact of KEYTRUDA on milk production or its presence in breast milk. Because many drugs are excreted in human milk, instruct women to discontinue nursing during treatment with KEYTRUDA and for 4 months after the final dose.

8.3 Females and Males of Reproductive Potential

Contraception

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

8.4 Pediatric Use

There is limited experience with KEYTRUDA in pediatric patients. In a study, 40 pediatric patients (16 children ages 2 years to less than 12 years and 24 adolescents ages 12 years to 18 years) with advanced melanoma, lymphoma, or PD-L1 positive advanced, relapsed, or refractory solid tumors were administered KEYTRUDA 2 mg/kg every 3 weeks. Patients received KEYTRUDA for a median of 3 doses (range: 1-17 doses), with 34 patients (85%) receiving KEYTRUDA for 2 doses or more. The concentrations of pembrolizumab in pediatric patients were comparable to those observed in adult patients at the same dose regimen of 2 mg/kg every 3 weeks.

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

Efficacy for pediatric patients with cHL, PMBCL or MSI-H cancers is extrapolated from the results in the respective adult populations *[see Clinical Studies (14.4, 14.5, 14.7)].*

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

10 OVERDOSAGE

There is no information on overdosage with KEYTRUDA.

11 DESCRIPTION

Pembrolizumab is a humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab is an IgG4 kappa immunoglobulin with an approximate molecular weight of 149 kDa. Pembrolizumab is produced in recombinant Chinese hamster ovary (CHO) cells.

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

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

12 CLINICAL PHARMACOLOGY

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

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

12.3 Pharmacokinetics
The pharmacokinetics (PK) of pembrolizumab was characterized using a population PK analysis with concentration data collected from 2993 patients with various cancers who received pembrolizumab doses of 1 to 10 mg/kg every 2 weeks, 2 to 10 mg/kg every 3 weeks, or 200 mg every 3 weeks. 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 geometric mean value (CV%) for volume of distribution at steady state is 6.0 L (20%) and for terminal half-life ($t_{1/2}$) is 22 days (32%).

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.

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 greater than or equal to 15 mL/min/1.73 m^2), mild hepatic impairment (total bilirubin less than or equal to upper limit of normal (ULN) and AST greater than ULN or total bilirubin between 1 and 1.5 times ULN and any AST), or tumor burden. There is insufficient information to determine whether there are clinically important differences in the CL of pembrolizumab in patients with moderate or severe hepatic impairment. Pembrolizumab concentrations with weight-based dosing at 2 mg/kg every 3 weeks in pediatric patients (2 to 17 years) are comparable to those of adults at the same dose.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

13.2 Animal Toxicology and/or Pharmacology

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

14 CLINICAL STUDIES

14.1 Melanoma

Ipilimumab-Naive Melanoma

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

A total of 834 patients were randomized: 277 patients to the KEYTRUDA 10 mg/kg every 3 weeks arm, 279 to the KEYTRUDA 10 mg/kg every 2 weeks arm, and 278 to the ipilimumab arm. The study

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

The study demonstrated statistically significant improvements in OS and PFS for patients randomized to KEYTRUDA as compared to ipilimumab (Table 18 and Figure 1).

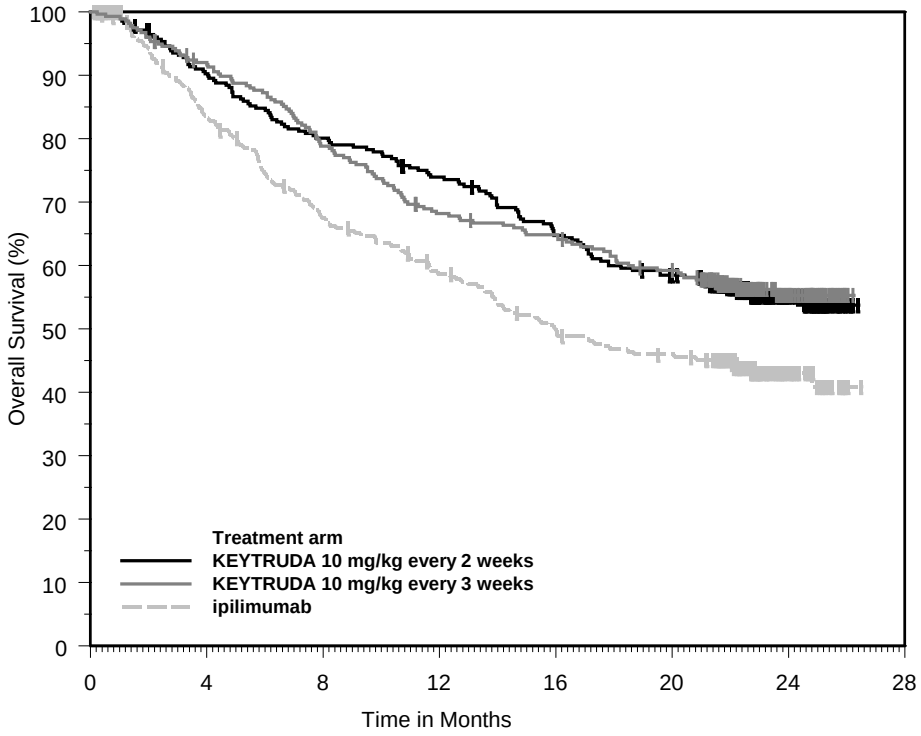
Table 18: Efficacy Results in KEYNOTE-006

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

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

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.

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



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

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

Ipilimumab-Refractory Melanoma

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

The treatment arms consisted of KEYTRUDA 2 mg/kg (n=180) or 10 mg/kg (n=181) every 3 weeks or investigator's choice chemotherapy (n=179). Among the 540 randomized patients, the median age was 62 years (range: 15 to 89 years), with 43% age 65 or older; 61% male; 98% White; and ECOG performance score was 0 (55%) and 1 (45%). Twenty-three percent of patients were BRAF V600 mutation positive, 40% had elevated LDH at baseline, 82% had M1c disease, and 73% had two or more prior therapies for advanced or metastatic disease.

The study demonstrated a statistically significant improvement in PFS for patients randomized to KEYTRUDA as compared to control arm (Table 19). 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.

Table 19: Efficacy Results in KEYNOTE-002

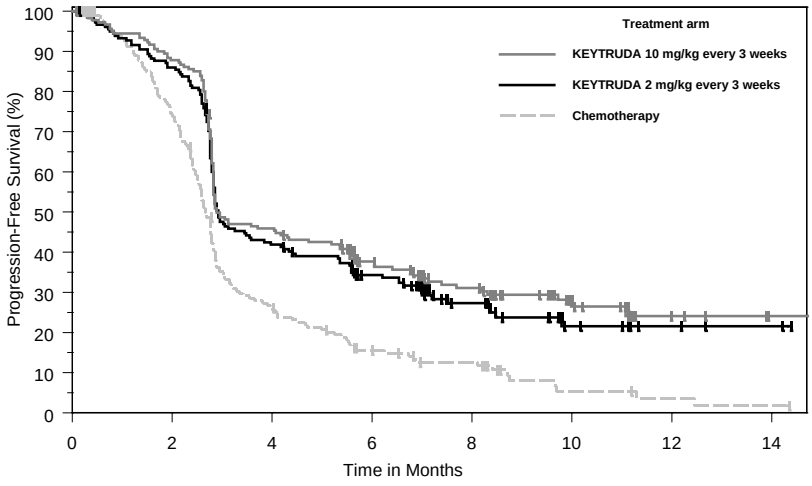
	KEYTRUDA 2 mg/kg every 3 weeks n=180	**KEYTRUDA 10 mg/kg every 3 weeks n=181**	**Chemotherapy n=179**
Progression-Free Survival			
Number of Events, n (%)	129 (72%)	126 (70%)	155 (87%)
Progression, n (%)	105 (58%)	107 (59%)	134 (75%)
Death, n (%)	24 (13%)	19 (10%)	21 (12%)
Median in months (95% CI)	2.9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

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

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

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

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



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

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.

14.2 Non-Small Cell Lung Cancer

First-line treatment of metastatic NSCLC as a single agent

Study KEYNOTE-024 (NCT02142738) was a randomized, multicenter, open-label, active-controlled trial in 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. nonsquamous), 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^2 every 3 weeks and carboplatin AUC 5 to 6 mg/mL/min every 3 weeks on Day 1 for 4 to 6 cycles followed by optional pemetrexed 500 mg/m^2 every 3 weeks for patients with nonsquamous histologies;
- Pemetrexed 500 mg/m^2 every 3 weeks and cisplatin 75 mg/m^2 every 3 weeks on Day 1 for 4 to 6 cycles followed by optional pemetrexed 500 mg/m^2 every 3 weeks for patients with nonsquamous histologies;
- Gemcitabine 1250 mg/m^2 on days 1 and 8 and cisplatin 75 mg/m^2 every 3 weeks on Day 1 for 4 to 6 cycles;
- Gemcitabine 1250 mg/m^2 on Days 1 and 8 and carboplatin AUC 5 to 6 mg/mL/min every 3 weeks on Day 1 for 4 to 6 cycles;
- Paclitaxel 200 mg/m^2 every 3 weeks and carboplatin AUC 5 to 6 mg/mL/min every 3 weeks on Day 1 for 4 to 6 cycles followed by optional pemetrexed maintenance (for nonsquamous histologies).

Treatment with KEYTRUDA continued until RECIST 1.1-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 a blinded independent central radiologists' (BICR) review according to RECIST 1.1. Additional efficacy outcome measures were OS and ORR as assessed by the BICR according to RECIST 1.1.

A total of 305 patients were randomized: 154 patients to the KEYTRUDA arm and 151 to the chemotherapy arm. 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% ECOG performance status of 1; 18% with squamous and 82% with nonsquamous histology and 9% with history of brain metastases. A total of 66 patients in the chemotherapy arm received KEYTRUDA at the time of disease progression.

The trial demonstrated a statistically significant improvement in 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 20 summarizes key efficacy measures for KEYNOTE-024.

Table 20: Efficacy Results in KEYNOTE-024

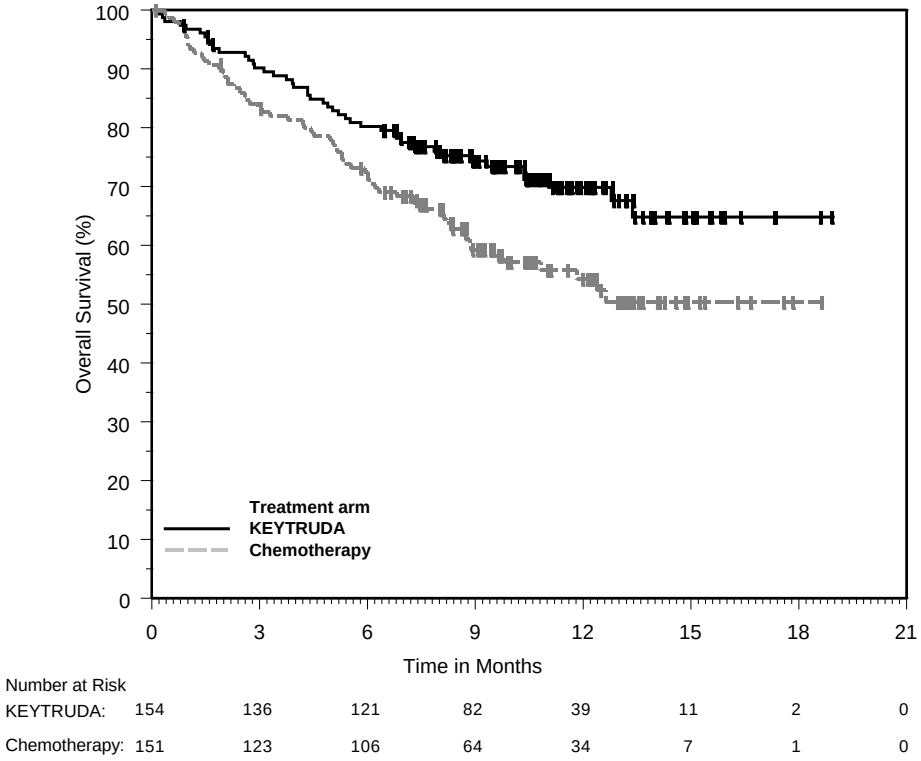
Endpoint	**KEYTRUDA 200 mg every 3 weeks n=154**	**Chemotherapy n=151**
PFS		
Number (%) of patients with event	73 (47%)	116 (77%)
Median in months (95% CI)	10.3 (6.7, NR)	6.0 (4.2, 6.2)
Hazard ratio* (95% CI)	0.50 (0.37, 0.68)	
p-Value (stratified log-rank)	<0.001	
OS		
Number (%) of patients with event	44 (29%)	64 (42%)
Median in months (95% CI)	NR (NR, NR)	NR (9.4, NR)
Hazard ratio* (95% CI)	0.60 (0.41, 0.89)	
p-Value (stratified log-rank)	0.005†	
Objective Response Rate		
ORR (95% CI)	45% (37, 53)	28% (21, 36)
Complete response rate	4%	1%
Partial response rate	41%	27%
p-Value (Miettinen-Nurminen)	0.001	
Median duration of response in months (range)	NR (1.9+, 14.5+)	6.3 (2.1+, 12.6+)

* Based on the stratified Cox proportional hazard model

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

NR = not reached

Figure 3: Kaplan-Meier Curve for Overall Survival in KEYNOTE-024



First-line treatment of metastatic nonsquamous NSCLC in combination with pemetrexed and carboplatin
The efficacy of KEYTRUDA was investigated in patients enrolled in an open-label, multicenter, multi-cohort study, Study KEYNOTE-021 (NCT02039674); the efficacy data are limited to patients with metastatic nonsquamous NSCLC randomized within a single cohort (Cohort G1). The key eligibility criteria for this cohort were locally advanced or metastatic nonsquamous NSCLC, regardless of tumor PD-L1 expression status, and no prior systemic treatment 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 PD-L1 tumor expression (TPS <1% vs. TPS ≥1%). Patients were randomized (1:1) to one of the following treatment arms:

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

At the investigator's discretion, maintenance pemetrexed 500 mg/m^2 every 3 weeks was permitted in both treatment arms.

Treatment with KEYTRUDA continued until RECIST 1.1-defined progression of disease as determined by blinded independent central review (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 on chemotherapy 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 and every 9 weeks thereafter. The major efficacy outcome measure was objective response rate (ORR) as assessed by

BICR using RECIST 1.1. Additional efficacy outcome measures were progression-free survival (PFS) as assessed by BICR using RECIST 1.1, duration of response, and overall survival (OS).

A total of 123 patients were randomized: 60 patients to the KEYTRUDA and chemotherapy arm and 63 to the chemotherapy arm. The study population characteristics were: median age of 64 years (range: 37 to 80); 48% age 65 or older; 39% male; 87% White and 8% Asian; ECOG performance status of 0 (41%) and 1 (56%); 97% had metastatic disease; and 12% had brain metastases. Thirty-six percent had tumor PD-L1 expression TPS <1%; no patients had sensitizing EGFR or ALK genomic aberrations. A total of 20 (32%) patients in the chemotherapy arm received KEYTRUDA at the time of disease progression and 12 (19%) additional patients received a checkpoint inhibitor as subsequent therapy.

In Cohort G1 of KEYNOTE-021, there was a statistically significant improvement in ORR in patients randomized to KEYTRUDA in combination with pemetrexed and carboplatin compared with pemetrexed and carboplatin alone (see Table 21).

Table 21: Efficacy Results in Cohort G1 of KEYNOTE-021

Endpoint	KEYTRUDA Pemetrexed Carboplatin n=60	Pemetrexed Carboplatin n=63
Overall Response Rate		
Overall response rate	55%	29%
(95% CI)	(42, 68)	(18, 41)
Complete response	0%	0%
Partial response	55%	29%
p-Value*	0.0032	
Duration of Response		
% with duration ≥ 6 months†	93%	81%
Range (months)	1.4+ to 13.0+	1.4+ to 15.2+
PFS		
Number of events (%)	23 (38%)	33 (52%)
Progressive disease	15 (25%)	27 (43%)
Death	8 (13%)	6 (10%)
Median in months (95% CI)	13.0 (8.3, NE)	8.9 (4.4, 10.3)
Hazard ratio‡ (95% CI)	0.53 (0.31, 0.91)	
p-Value§	0.0205	

* Based on Miettinen-Nurminen method stratified by PD-L1 status (TPS <1% vs. TPS ≥1%).
† Based on Kaplan-Meier estimation
‡ Based on the Cox proportional hazard model stratified by PD-L1 status (TPS <1% vs. TPS ≥1%).
§ Based on the log-rank test stratified by PD-L1 status (TPS <1% vs. TPS ≥1%).
NE = not estimable

Exploratory analyses for ORR were conducted in subgroups defined by the stratification variable, PD-L1 tumor expression (TPS <1% and TPS ≥1%). In the TPS <1% subgroup, the ORR was 57% in the KEYTRUDA-containing arm and 13.0% in the chemotherapy arm. In the TPS ≥1% subgroup, the ORR was 54% in the KEYTRUDA-containing arm and 38% in the chemotherapy arm.

Previously treated NSCLC
The efficacy of KEYTRUDA was investigated in Study KEYNOTE-010 (NCT01905657), a randomized, multicenter, open-label, active-controlled trial conducted in patients with metastatic NSCLC that had progressed following platinum-containing chemotherapy, and if appropriate, targeted therapy for EGFR or ALK genomic tumor aberrations. Eligible patients had PD-L1 expression TPS of 1% or greater by an immunohistochemistry assay using the PD-L1 IHC 22C3 pharmDx Kit. Patients with autoimmune disease; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Randomization was stratified by tumor PD-L1 expression (PD-L1 expression TPS ≥50% vs. PD-L1 expression TPS=1-49%), ECOG performance scale (0 vs. 1), and geographic region (East Asia vs. non-East Asia). Patients were randomized (1:1:1) to receive KEYTRUDA 2 mg/kg intravenously every 3 weeks, KEYTRUDA 10 mg/kg intravenously every 3 weeks or docetaxel intravenously 75 mg/m^2 every 3 weeks until unacceptable toxicity or disease progression. Patients randomized to KEYTRUDA were permitted to continue until disease progression that was symptomatic, rapidly progressive, required urgent intervention, occurred with a decline in performance status, or confirmation of progression at 4 to 6 weeks with repeat imaging or for up to 24 months without disease progression.

Assessment of tumor status was performed every 9 weeks. The main efficacy outcome measures were OS and PFS as assessed by the BICR according to RECIST 1.1 in the subgroup of patients with TPS ≥50% and the overall population with TPS ≥1%. Additional efficacy outcome measures were ORR and response duration in the subgroup of patients with TPS ≥50% and the overall population with TPS ≥1%.

A total of 1033 patients were randomized: 344 to the KEYTRUDA 2 mg/kg arm, 346 patients to the KEYTRUDA 10 mg/kg arm, and 343 patients to the docetaxel arm. The study population characteristics were: median age 63 years (range: 20 to 88), 42% age 65 or older; 61% male; 72% White and 21% Asian; 66% ECOG performance status 1; 43% with high PD-L1 tumor expression; 21% with squamous, 70% with nonsquamous, and 8% with mixed, other or unknown histology; 91% metastatic (M1) disease; 15% with history of brain metastases; and 8% and 1% with EGFR and ALK genomic aberrations, respectively. All patients had received prior therapy with a platinum-doublet regimen, 29% received two or more prior therapies for their metastatic disease.

Tables 22 and 23 summarize key efficacy measures in the subgroup with TPS ≥50% population and in all patients, respectively. The Kaplan-Meier curve for OS (TPS ≥1%) is shown in Figure 4.

Table 22: Efficacy Results of the Subgroup of Patients with TPS ≥50% in KEYNOTE-010

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

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

† All responses were partial responses

NR = not reached

Table 23: Efficacy Results of All Randomized Patients (TPS ≥1%) in KEYNOTE-010

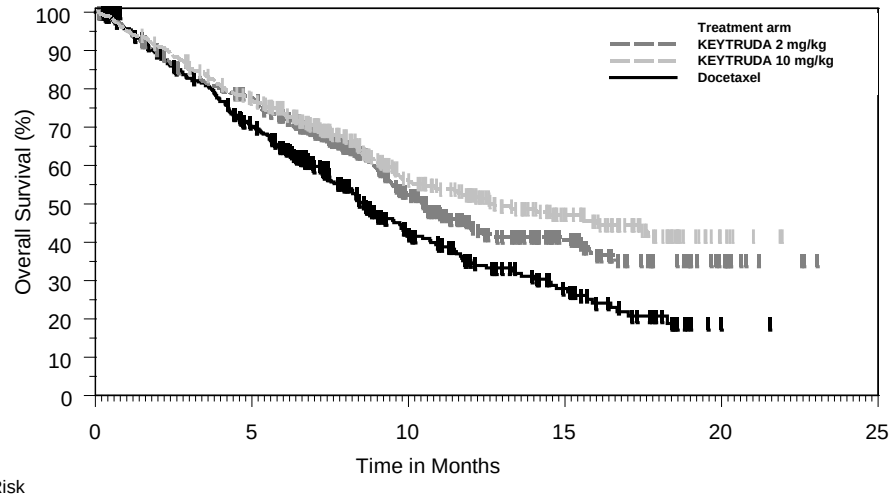
Endpoint	KEYTRUDA 2 mg/kg every 3 weeks n=344	KEYTRUDA 10 mg/kg every 3 weeks n=346	Docetaxel 75 mg/m^2 every 3 weeks n=343
OS			
Deaths (%)	172 (50%)	156 (45%)	193 (56%)
Median in months (95% CI)	10.4 (9.4, 11.9)	12.7 (10.0, 17.3)	8.5 (7.5, 9.8)
Hazard ratio* (95% CI)	0.71 (0.58, 0.88)	0.61 (0.49, 0.75)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

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

† All responses were partial responses

NR = not reached

Figure 4: Kaplan-Meier Curve for Overall Survival in all Randomized Patients in KEYNOTE-010 (TPS ≥1%)



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

14.3 Head and Neck Cancer

The efficacy of KEYTRUDA was investigated in Study 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 1.1, as assessed by blinded independent central review, and duration of response.

Among the 174 patients, the baseline characteristics were median age 60 years (32% age 65 or older); 82% male; 75% White, 16% Asian, and 6% Black; 87% had M1 disease; 33% had HPV positive tumors; 63% had prior cetuximab; 29% had an ECOG PS of 0 and 71% had an ECOG PS of 1; and the median number of prior lines of therapy administered for the treatment of HNSCC was 2.

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

14.4 Classical Hodgkin Lymphoma

The efficacy of KEYTRUDA was investigated in 210 patients with relapsed or refractory cHL, enrolled in a multicenter, non-randomized, open-label study (KEYNOTE-087; NCT02453594). Patients with active,

non-infectious pneumonitis, an allogeneic HSCT within the past 5 years (or greater than 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 at a dose of 200 mg every 3 weeks until unacceptable toxicity or documented disease progression, or for up to 24 months in patients who did not progress. Disease assessment was performed every 12 weeks. The major efficacy outcome measures (ORR, CRR, and duration of response) were assessed by blinded independent central review according to the 2007 revised International Working Group (IWG) criteria.

Among the 210 patients, the baseline characteristics were: median age of 35 years (range: 18 to 76), 9% age 65 or older; 54% male; 88% White; 49% had an ECOG performance status (PS) of 0 and 51% had an ECOG PS of 1. The median number of prior lines of therapy administered for the treatment of cHL was 4 (range: 1 to 12). Fifty-eight percent were refractory to the last prior therapy, including 35% with primary refractory disease and 14% whose disease was chemo-refractory to all prior regimens. Sixty-one percent of patients had undergone prior auto-HSCT, 83% had received prior brentuximab vedotin and 36% of patients had prior radiation therapy.

Efficacy results for KEYNOTE-087 are summarized in Table 24.

Table 24: Efficacy Results in KEYNOTE-087

	KEYNOTE-087*
Endpoint	N=210
Overall Response Rate	
ORR (95% CI)	69% (62, 75)
Complete response	22%
Partial response	47%
Response Duration	
Median in months (range)	11.1 (0.0+, 11.1)†

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

14.5 Primary Mediastinal Large B-Cell Lymphoma

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

Among the 53 patients accrued, the baseline characteristics were: median age 33 years (range: 20 to 61 years), 43% male; 92% White; 43% had an ECOG performance status (PS) of 0 and 57% had an ECOG PS of 1. The median number of prior lines of therapy administered for the treatment of PMBCL was 3 (range 2 to 8). Thirty-six percent had primary refractory disease, 49% had relapsed disease refractory to the last prior therapy, and 15% had untreated relapse. Twenty-six percent of patients had undergone prior autologous HSCT, and 32% of patients had prior radiation therapy. All patients had received rituximab as part of a prior line of therapy.

Efficacy was based on overall response rate (ORR) and duration of response. The efficacy results for KEYNOTE-170 are summarized in Table 25. 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).

Table 25: Efficacy Results in KEYNOTE-170

Endpoint	KEYNOTE-170*
	N=53
Overall Response Rate	
ORR (95% CI)	45% (32, 60)
Complete response	11%
Partial response	34%
Response Duration	
Median in months (range)	NR (1.1+, 19.2+)†

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

14.6 Urothelial Carcinoma

Cisplatin Ineligible Patients with Urothelial Carcinoma

The efficacy of KEYTRUDA was investigated in Study KEYNOTE-052 (NCT02335424), a multicenter, open-label, single-arm trial in 370 patients with locally advanced or metastatic urothelial carcinoma who were not eligible for cisplatin-containing chemotherapy. The trial excluded patients with autoimmune disease or a medical condition that required immunosuppression.

Patients received KEYTRUDA 200 mg every 3 weeks until unacceptable toxicity or disease progression. Patients with initial radiographic disease progression could receive additional doses of treatment during confirmation of progression unless disease progression was symptomatic, was rapidly progressive, required urgent intervention, or occurred with a decline in performance status. Patients without disease progression could be treated for up to 24 months. Tumor response assessments were performed at 9 weeks after the first dose, then every 6 weeks for the first year, and then every 12 weeks thereafter. The major efficacy outcome measures were ORR according to RECIST 1.1 as assessed by independent radiology review and duration of response.

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

The median follow-up time for 370 patients treated with KEYTRUDA was 7.8 months (range 0.1 to 20 months). Efficacy results are summarized in Table 26.

Table 26: Efficacy Results in KEYNOTE-052

Endpoint	KEYTRUDA 200 mg every 3 weeks n=370
Objective Response Rate	
ORR (95% CI)	29% (24, 34)
Complete response rate	7%
Partial response rate	22%
Duration of Response	
Median in months (range)	NR (1.4+, 17.8+)

\+ Denotes ongoing
NR = not reached

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

Patients were randomized to receive either KEYTRUDA 200 mg every 3 weeks (n=270) or investigator's choice of any of the following chemotherapy regimens all given intravenously every 3 weeks (n=272): paclitaxel 175 mg/m^2 (n=84), docetaxel 75 mg/m^2 (n=84), or vinflunine 320 mg/m^2 (n=87). 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 1.1. Additional efficacy outcome measures were ORR as assessed by BICR per RECIST 1.1 and duration of response.

Among the 542 randomized patients, the study population characteristics were: median age 66 years (range: 26 to 88), 58% age 65 or older; 74% male; 72% White and 23% Asian; 42% ECOG status of 0 and 56% ECOG performance status of 1; and 96% M1 disease and 4% M0 disease. Eighty-seven percent of patients had visceral metastases, including 34% with liver metastases. Eighty-six percent had a primary tumor in the lower tract and 14% had a primary tumor in the upper tract. Fifteen percent of patients had disease progression following prior platinum-containing neoadjuvant or adjuvant chemotherapy. Twenty-one percent had received 2 or more prior systemic regimens in the metastatic setting. Seventy-six percent of patients received prior cisplatin, 23% had prior carboplatin, and 1% were treated with other platinum-based regimens.

Table 27 and Figure 5 summarize the key efficacy measures for KEYNOTE-045. 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 27: Efficacy Results in KEYNOTE-045

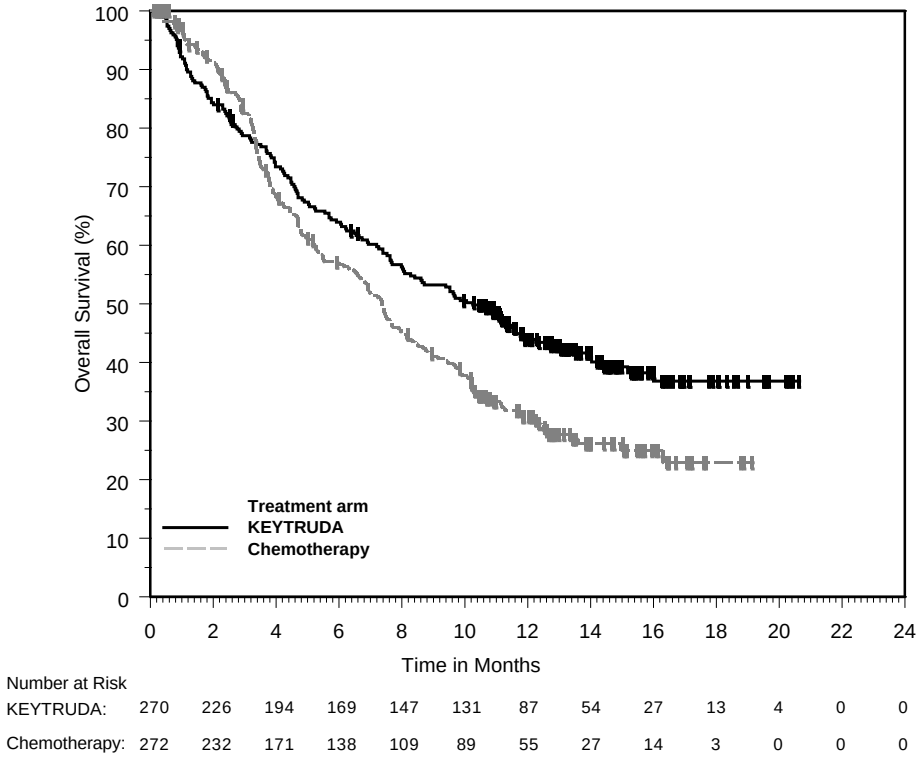
	KEYTRUDA 200 mg every 3 weeks n=270	Chemotherapy n=272
OS		
Deaths (%)	155 (57%)	179 (66%)
Median in months (95% CI)	10.3 (8.0, 11.8)	7.4 (6.1, 8.3)
Hazard ratio* (95% CI)	0.73 (0.59, 0.91)	
p-Value (stratified log-rank)	0.004	
PFS by BICR		
Events (%)	218 (81%)	219 (81%)
Median in months (95% CI)	2.1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

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

\+ Denotes ongoing

NR = not reached

Figure 5: Kaplan-Meier Curve for Overall Survival in KEYNOTE-045



14.7 Microsatellite Instability-High Cancer

The efficacy of KEYTRUDA was evaluated in patients with MSI-H or mismatch repair deficient (dMMR), solid tumors enrolled in one of five uncontrolled, open-label, multi-cohort, multi-center, single-arm trials.

Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible across the five trials. Patients received either KEYTRUDA 200 mg every 3 weeks or KEYTRUDA 10 mg/kg every 2 weeks. Treatment continued until unacceptable toxicity or disease progression that was either symptomatic, rapidly progressive, required urgent intervention, or occurred with a decline in performance status. A maximum of 24 months of treatment with KEYTRUDA was administered. For the purpose of assessment of anti-tumor activity across these 5 trials, the major efficacy outcome measures were ORR as assessed by blinded independent central radiologists' (BICR) review according to RECIST 1.1 and duration of response.

Table 28: MSI-H Trials

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

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

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

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

Efficacy results are summarized in Table 29.

Table 29: Efficacy Results for Patients with MSI-H/dMMR Cancer

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

NR = not reached

Table 30: Response by Tumor Type

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

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

14.8 Gastric Cancer

The efficacy of KEYTRUDA was investigated in Study KEYNOTE-059 (NCT02335411), a multicenter, non-randomized, open-label multi-cohort trial that enrolled 259 patients with gastric or gastroesophageal junction (GEJ) adenocarcinoma who progressed on at least 2 prior systemic treatments for advanced disease. Previous treatment must have included a fluoropyrimidine and platinum doublet. HER2/neu positive patients must have previously received treatment with approved HER2/neu-targeted therapy. Patients with active autoimmune disease or a medical condition that required immunosuppression or with clinical evidence of ascites by physical exam were ineligible.

Patients received KEYTRUDA 200 mg every 3 weeks until unacceptable toxicity or disease progression that was symptomatic, rapidly progressive, required urgent intervention, occurred with a decline in performance status, or was confirmed at least 4 weeks later with repeat imaging. Patients without disease progression were treated for up to 24 months. Assessment of tumor status was performed every 6 to 9 weeks. The major efficacy outcome measures were ORR according to RECIST 1.1, as assessed by blinded independent central review, and duration of response.

Among the 259 patients, 55% (n = 143) had tumors that expressed PD-L1 with a combined positive score (CPS) of greater than or equal to 1 and microsatellite stable (MSS) tumor status or undetermined MSI or MMR status. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx Kit. The baseline characteristics of these 143 patients were: median age 64 years (47% age 65 or older); 77% male;

82% White, 11% Asian; and ECOG PS of 0 (43%) and 1 (57%). Eighty-five percent had M1 disease and 7% had M0 disease. Fifty-one percent had two and 49% had three or more prior lines of therapy in the recurrent or metastatic setting.

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

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

14.9 Cervical Cancer

KEYTRUDA was investigated in 98 patients with recurrent or metastatic cervical cancer enrolled in a single cohort (Cohort E) in Study 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 were treated with KEYTRUDA intravenously at a dose of 200 mg 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 1.1, as assessed by blinded independent central review, and duration of response.

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

No responses were observed in patients whose tumors did not have PD-L1 expression (CPS <1). Efficacy results are summarized in Table 31.

Table 31: Efficacy Results in Patients with Recurrent or Metastatic Cervical Cancer (CPS ≥1) in KEYNOTE-158

Endpoint	n=77*
Objective response rate	
ORR (95% CI)	14.3% (7.4, 24.1)
Complete response rate	2.6%
Partial response rate	11.7%
Response duration	
Median in months (range)	NR (4.1, 18.6+)[†]
% with duration ≥6 months	91%

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

16 HOW SUPPLIED/STORAGE AND HANDLING

KEYTRUDA for injection (lyophilized powder): carton containing one 50 mg single-dose vial (NDC 0006-3029-02).

Store vials under refrigeration at 2°C to 8°C (36°F to 46°F).

KEYTRUDA injection (clear to slightly opalescent, colorless to slightly yellow solution): carton containing one 100 mg/4 mL (25 mg/mL), single-dose vial (NDC 0006-3026-02)

Store vials under refrigeration at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze. Do not shake.

17 PATIENT COUNSELING INFORMATION

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

- Inform patients of the risk of immune-mediated adverse reactions that may be severe or fatal, may occur after discontinuation of treatment, and may require corticosteroid treatment and interruption or discontinuation of KEYTRUDA. These reactions may include:
  - Pneumonitis: Advise patients to contact their healthcare provider immediately for new or worsening cough, chest pain, or shortness of breath *[see Warnings and Precautions (5.1)]*.
  - Colitis: Advise patients to contact their healthcare provider immediately for diarrhea or severe abdominal pain *[see Warnings and Precautions (5.2)]*.
  - Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, or easy bruising or bleeding *[see Warnings and Precautions (5.3)]*.
  - Hypophysitis: Advise patients to contact their healthcare provider immediately for persistent or unusual headache, extreme weakness, dizziness or fainting, or vision changes *[see Warnings and Precautions (5.4)]*.
  - Hyperthyroidism and Hypothyroidism: Advise patients to contact their healthcare provider immediately for signs or symptoms of hyperthyroidism and hypothyroidism *[see Warnings and Precautions (5.4)].*
  - Type 1 Diabetes Mellitus: Advise patients to contact their healthcare provider immediately for signs or symptoms of type 1 diabetes *[see Warnings and Precautions (5.4)].*
  - Nephritis: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis *[see Warnings and Precautions (5.5)]*.
  - Severe skin reactions: Advise patients to contact their healthcare provider immediately for any signs or symptoms of severe skin reactions, SJS or TEN *[see Warnings and Precautions (5.6)]*.
  - Other immune-mediated adverse reactions: Advise patients that immune-mediated adverse reactions can occur and may involve any organ system, and to contact their healthcare provider immediately for any new signs or symptoms *[see Warnings and Precautions (5.7)]*.
- Advise patients to contact their healthcare provider immediately for signs or symptoms of infusion-related reactions *[see Warnings and Precautions (5.8)]*.
- Advise patients of the risk of solid organ transplant rejection and to contact their healthcare provider immediately for signs or symptoms of organ transplant rejection *[see Warnings and Precautions (5.7)]*.
- Advise patients of the risk of post-allogeneic hematopoietic stem cell transplantation complications *[see Warnings and Precautions (5.9)].*
- Advise patients of the importance of keeping scheduled appointments for blood work or other laboratory tests *[see Warnings and Precautions (5.3, 5.4, 5.5)]*.
- Advise females that KEYTRUDA can cause fetal harm. Instruct females of reproductive potential to use highly effective contraception during and for 4 months after the last dose of KEYTRUDA *[see Warnings and Precautions (5.11) and Use in Specific Populations (8.1, 8.3)]*.
- Advise nursing mothers not to breastfeed while taking KEYTRUDA and for 4 months after the final dose *[see Use in Specific Populations (8.2)]*.

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

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

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

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

uspi-mk3475-iv-1806r016

MEDICATION GUIDE

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

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

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

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

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

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

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

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

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

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

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

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

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

Infusion (IV) reactions that can sometimes be severe and life-threatening. Signs and symptoms of infusion reactions may include:
- chills or shaking
- shortness of breath or wheezing
- itching or rash
- flushing
- dizziness
- fever
- feeling like passing out

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

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

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

What is KEYTRUDA?

KEYTRUDA is a prescription medicine used to treat:

- a kind of skin cancer called melanoma that has spread or cannot be removed by surgery (advanced melanoma).
- a kind of lung cancer called non-small cell lung cancer (NSCLC).
  - KEYTRUDA may be used alone when your lung cancer:
    - has spread (advanced NSCLC) **and,**
    - tests positive for “PD-L1” **and,**
      - as your first treatment if you have not received chemotherapy to treat your advanced NSCLC and your tumor does not have an abnormal “EGFR” or “ALK” gene,

      or
      - you have received chemotherapy that contains platinum to treat your advanced NSCLC, and it did not work or it is no longer working, **and**
      - if your tumor has an abnormal “EGFR” or “ALK” gene, you have also received an EGFR or ALK inhibitor medicine and it did not work or is no longer working.
  - KEYTRUDA may be used with the chemotherapy medicines pemetrexed and carboplatin as your first treatment when your lung cancer:
    - has spread (advanced NSCLC) **and**
    - is a type of lung cancer called “nonsquamous”.
- a kind of cancer called head and neck squamous cell cancer (HNSCC) that:
    - has returned or spread **and**
    - you have received chemotherapy that contains platinum and it did not work or is no longer working.
- a kind of cancer called classical Hodgkin lymphoma (cHL) in adults and children when:
    - you have tried a treatment and it did not work **or**
    - your cHL has returned after you received 3 or more types of treatment.
- a kind of cancer called primary mediastinal B-cell lymphoma (PMBCL) in adults and children when:
    - you have tried a treatment and it did not work **or**
    - your PMBCL has returned after you received 2 or more types of treatment.
- a kind of bladder and urinary tract cancer called urothelial carcinoma. KEYTRUDA may be used when your bladder or urinary tract cancer:
    - has spread or cannot be removed by surgery (advanced urothelial cancer) **and**,
    - you are not able to receive chemotherapy that contains a medicine called cisplatin, **or**

- you have received chemotherapy that contains platinum, and it did not work or is no longer working.

- a kind of cancer that is shown by a laboratory test to be a microsatellite instability-high (MSI-H) or a mismatch repair deficient (dMMR) solid tumor. KEYTRUDA may be used in adults and children to treat:
  - cancer that has spread or cannot be removed by surgery (advanced cancer), **and**
  - has progressed following treatment, and you have no satisfactory treatment options, **or**
  - you have colon or rectal cancer, and you have received chemotherapy with fluoropyrimidine, oxaliplatin, and irinotecan but it did not work or is no longer working.

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

What should I tell my doctor before receiving KEYTRUDA?

Before you receive KEYTRUDA, tell your doctor if you:

- have immune system problems such as Crohn's disease, ulcerative colitis, or lupus
- have received an organ transplant, such as a kidney or liver
- have received or plan to receive a stem cell transplant that uses donor stem cells (allogeneic)
- have lung or breathing problems
- have liver problems
- have any other medical problems
- are pregnant or plan to become pregnant
  - KEYTRUDA can harm your unborn baby.
  - Females who are able to become pregnant should use an effective method of birth control during and for at least 4 months after the final dose of KEYTRUDA. Talk to your doctor about birth control methods that you can use during this time.
  - Tell your doctor right away if you become pregnant during treatment with KEYTRUDA.
- are breastfeeding or plan to breastfeed.
  - It is not known if KEYTRUDA passes into your breast milk.
  - Do not breastfeed during treatment with KEYTRUDA and for 4 months after your final dose of KEYTRUDA.

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

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

How will I receive KEYTRUDA?

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

What are the possible side effects of KEYTRUDA?

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

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

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

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

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

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

General information about the safe and effective use of KEYTRUDA

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

What are the ingredients in KEYTRUDA?

Active ingredient: pembrolizumab

Inactive ingredients:

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

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

For KEYTRUDA for injection, at:
MSD International GmbH, County Cork, Ireland
For KEYTRUDA injection, at:
MSD Ireland (Carlow), County Carlow, Ireland
U.S. License No. 0002

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

usmg-mk3475-iv-1806r014

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: June 2018