

KEYTRUDA® (pembrolizumab)

Solution for Infusion

25 mg/mL

1. INDICATIONS AND USAGE

Melanoma

KEYTRUDA (pembrolizumab) is indicated for the treatment of patients with unresectable or metastatic melanoma.

KEYTRUDA is indicated for the adjuvant treatment of patients with melanoma with lymph node involvement who have undergone complete resection.

Non-Small Cell Lung Carcinoma

KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of patients with metastatic non-squamous non-small cell lung carcinoma (NSCLC), with no EGFR or ALK genomic tumor aberrations.

KEYTRUDA, in combination with carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of patients with metastatic squamous NSCLC.

KEYTRUDA as monotherapy is indicated for the first-line treatment of patients with metastatic NSCLC whose tumors express PD-L1 with a $\geq 50\%$ tumor proportion score (TPS) as determined by a validated test, with no EGFR or ALK genomic tumor aberrations.

KEYTRUDA as monotherapy is indicated for the treatment of patients with locally advanced or metastatic NSCLC whose tumors express PD-L1 with a $\geq 1\%$ TPS as determined by a validated test and who have received platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have received prior therapy for these aberrations prior to receiving KEYTRUDA.

Head and Neck Cancer

KEYTRUDA, as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, is indicated for the first line treatment of patients with metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) whose tumours express PD-L1 with a CPS \geq 1.

Classical Hodgkin Lymphoma

KEYTRUDA is indicated for the treatment of adult and pediatric patients aged 3 years and above, with relapsed or refractory classical Hodgkin lymphoma (cHL), who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option.

Urothelial Carcinoma

KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma whose tumours express PD-L1 with a combined positive score (CPS) \geq 10 as determined by a validated test, and who are not eligible for cisplatin-containing chemotherapy.

KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have received prior platinum-containing chemotherapy.

Esophageal Cancer

KEYTRUDA, in combination with platinum and fluoropyrimidine based chemotherapy, is indicated for the first-line treatment of patients with locally advanced or metastatic carcinoma of the esophagus or HER2 negative gastroesophageal junction (GEJ) adenocarcinoma (tumors with epicenter 1 to 5 centimeters above the GEJ) that is not amenable to surgical resection or definitive chemoradiation.

Colorectal Cancer

KEYTRUDA is indicated for the first-line treatment of patients with metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer (CRC).

Cervical Cancer

KEYTRUDA, in combination with chemotherapy with or without bevacizumab, is indicated for the treatment of patients with persistent, recurrent, or metastatic cervical cancer whose tumours express PD-L1 with a CPS \geq 1 [see *Clinical Studies (9)*].

Renal Cell Carcinoma

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

KEYTRUDA, as monotherapy, is indicated for the adjuvant treatment of patients with RCC at increased risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions [see *Clinical Studies (9)*].

Endometrial Carcinoma

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

Triple-Negative Breast Cancer

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

KEYTRUDA, in combination with chemotherapy, is indicated for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 (CPS \geq 10) as determined by a validated test and who have not received prior chemotherapy for metastatic disease [see *Clinical Studies (9)*].

2. DOSAGE AND ADMINISTRATION

2.1 General

Patient Selection

For single-agent treatment of Non-Small Cell Lung Carcinoma, Urothelial Carcinoma, or Colorectal Cancer.

Select patients for treatment with KEYTRUDA based on the presence of positive PD-L1 expression [see *Clinical Studies (9)*] in:

- locally advanced or metastatic NSCLC.
- locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy.

Select patients for treatment with KEYTRUDA based on microsatellite instability-high cancer (MSI-H) or mismatch repair deficient (dMMR) tumor status [see *Clinical Studies (9)*] in:

- metastatic CRC.

For treatment of TNBC in combination with chemotherapy

Select patients for treatment with KEYTRUDA based on the presence of positive PD-L1 expression [see *Clinical Studies (9)*] in:

- locally recurrent unresectable or metastatic TNBC.

For treatment of cervical cancer in combination with chemotherapy, with or without bevacizumab

Select patients for treatment with KEYTRUDA based on the presence of positive PD-L1 expression [see *Clinical Studies (9)*] in:

- persistent, recurrent, or metastatic cervical cancer.

Recommended Dosing

KEYTRUDA is administered as an intravenous infusion over 30 minutes.

The recommended dose of KEYTRUDA in adults with HNSCC, cHL, urothelial carcinoma, esophageal carcinoma, CRC, cervical cancer, RCC, endometrial carcinoma, TNBC, previously untreated NSCLC, or for the adjuvant treatment of melanoma or RCC is either:

- 200 mg every 3 weeks or
- 400 mg every 6 weeks.

The recommended dose of KEYTRUDA in adults with previously treated NSCLC or for unresectable or metastatic melanoma is 2 mg/kg every 3 weeks.

For use in combination, see the prescribing information for the concomitant therapies. When administering KEYTRUDA as part of a combination with intravenous chemotherapy, KEYTRUDA should be administered first.

For RCC patients treated with KEYTRUDA in combination with axitinib, see the prescribing information regarding dosing of axitinib. When used in combination with KEYTRUDA, dose escalation of axitinib above the initial 5 mg dose may be considered at intervals of six weeks or longer [see *Clinical Studies (9)*].

For endometrial carcinoma patients treated with KEYTRUDA in combination with lenvatinib, the recommended initial dose of lenvatinib is 20 mg orally once daily until disease progression or unacceptable toxicity.

Patients should be treated with KEYTRUDA until disease progression or unacceptable toxicity. Atypical responses (i.e., an initial transient increase in tumor size or small new lesions within the first few months followed by tumor shrinkage) have been observed. Clinically stable patients with initial evidence of disease progression should remain on treatment until disease progression is confirmed.

For the adjuvant treatment of melanoma or RCC, KEYTRUDA should be administered for up to one year or until disease recurrence or unacceptable toxicity.

For the neoadjuvant and adjuvant treatment of high-risk early-stage TNBC, patients should be treated with neoadjuvant KEYTRUDA in combination with chemotherapy for 8 doses of 200 mg every 3 weeks or 4 doses of 400 mg every 6 weeks or until disease progression that precludes definitive surgery or unacceptable toxicity, followed by adjuvant treatment with KEYTRUDA as monotherapy for 9 doses of 200 mg every 3 weeks or 5 doses of 400 mg every 6 weeks or until disease recurrence or unacceptable toxicity. Patients who experience disease progression that precludes definitive surgery or unacceptable toxicity related to KEYTRUDA as neoadjuvant treatment in combination with chemotherapy should not receive KEYTRUDA monotherapy as adjuvant treatment.

Dose modifications

No dose reductions of KEYTRUDA are recommended. Withhold or discontinue KEYTRUDA to manage adverse reactions as described in Table 1.

Table 1: Recommended Dose Modifications [see Warnings and Precautions (4)]

Adverse reactions	Severity	Dose modification
Immune-mediated pneumonitis	Moderate (Grade 2)	Withhold until adverse reactions recover to Grades 0-1*
	Severe or life-threatening (Grades 3 or 4) or recurrent moderate (Grade 2)	Permanently discontinue
Immune-mediated colitis	Moderate or severe (Grades 2 or 3)	Withhold until adverse reactions recover to Grades 0-1*
	Life-threatening (Grade 4) or recurrent severe (Grade 3)	Permanently discontinue
Immune-mediated nephritis	Moderate (Grade 2)	Withhold until adverse reactions recover to Grades 0-1*
	Severe or life-threatening (Grades 3 or 4)	Permanently discontinue

Immune-mediated endocrinopathies	Adrenal insufficiency Symptomatic hypophysitis Type 1 diabetes associated with Grade \geq 3 hyperglycemia (glucose $>$ 250 mg/dL or $>$ 13.9 mmol/L) or associated with ketoacidosis Hyperthyroidism Grade \geq 3	Withhold until adverse reactions recover to Grades 0-1* For patients with severe (Grade 3) or life-threatening (Grade 4) endocrinopathy that improves to Grade 2 or lower and is controlled with hormone replacement, continuation of KEYTRUDA may be considered
Immune-mediated hepatitis	Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) $>$ 3 to 5 times upper limit of normal (ULN) or total bilirubin $>$ 1.5 to 3 times ULN	Withhold until adverse reactions recover to Grades 0-1*
For liver enzyme elevations in RCC patients treated with combination therapy, see dosing guidelines following this table.	AST or ALT $>$ 5 times ULN or total bilirubin $>$ 3 times ULN	Permanently discontinue
	For patients with liver metastases who begin treatment with moderate (Grade 2) elevation of AST or ALT, if AST or ALT increases \geq 50% relative to baseline and lasts \geq 1 week	Permanently discontinue
Immune-mediated skin reactions or Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Severe skin reactions (Grade 3) or suspected SJS or TEN	Withhold until adverse reactions recover to Grades 0-1*
	Severe skin reactions (Grade 4) or confirmed SJS or TEN	Permanently discontinue
Other immune-mediated adverse reactions	Based on severity and type of reaction (Grade 2 or Grade 3)	Withhold until adverse reactions recover to Grades 0-1*
	Severe or life-threatening (Grades 3 or 4) myocarditis, encephalitis, or Guillain-Barré syndrome	Permanently discontinue
	Life-threatening (Grade 4) or recurrent severe (Grade 3)	Permanently discontinue
Infusion-related reactions	Severe or life-threatening (Grades 3	Permanently discontinue

	or 4)	
--	-------	--

Note: toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI CTCAE v.4)

* If corticosteroid dosing cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks or a treatment-related toxicity does not resolve to Grades 0-1 within 12 weeks after last dose of KEYTRUDA, then KEYTRUDA should be permanently discontinued.

In patients with cHL with Grade 4 hematological toxicity, KEYTRUDA should be withheld until adverse reactions recover to Grades 0-1.

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

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

When administering KEYTRUDA in combination with lenvatinib, interrupt one or both or dose reduce lenvatinib to manage adverse reactions as appropriate. For recommendations for management of adverse reactions of lenvatinib, refer to the prescribing information for lenvatinib.

Preparation and administration

- Protect from light. Do not freeze. Do not shake.
- Equilibrate the vial of KEYTRUDA to room temperature.
- Prior to dilution, the vial of liquid can be out of refrigeration (temperatures at or below 25°C) for up to 24 hours.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. KEYTRUDA is a clear to slightly opalescent, colorless to slightly yellow solution. Discard the vial if visible particles are observed.
- Withdraw the required volume up to 4 mL (100 mg) of KEYTRUDA and transfer into an intravenous bag containing 0.9% sodium chloride or 5% glucose (dextrose) to prepare a diluted solution with a final concentration ranging from 1 to 10 mg/mL. Mix diluted solution by gentle inversion.
- Do not freeze the infusion solution.

- The product does not contain preservative. The diluted product should be used immediately. If not used immediately, diluted solutions of KEYTRUDA may be stored at room temperature (at or below 25°C) for a cumulative time of up to 6 hours. Diluted solutions of KEYTRUDA may also be stored under refrigeration at 2°C to 8°C; however, the total time from dilution of KEYTRUDA to completion of infusion should not exceed 96 hours. If refrigerated, allow the vials and/or IV bags to come to room temperature prior to use.
- Translucent to white proteinaceous particles may be seen in the diluted solution. Administer infusion solution intravenously over 30 minutes using a sterile, non-pyrogenic, low-protein binding 0.2 to 5 µm in-line or add-on filter.
- Do not co-administer other drugs through the same infusion line.
- Discard any unused portion left in the vial.

2.2 Pediatric Patients

In cHL, the recommended dose of KEYTRUDA in pediatric patients is 2 mg/kg (up to a maximum of 200 mg), administered as an intravenous infusion over 30 minutes every 3 weeks.

2.3 Geriatric Patients

No overall differences in safety or efficacy were reported between elderly patients (65 years and over) and younger patients (less than 65 years). No dose adjustment is necessary in this population.

2.4 Renal Impairment

No dose adjustment is needed for patients with mild or moderate renal impairment. KEYTRUDA has not been studied in patients with severe renal impairment.

2.5 Hepatic Impairment

No dose adjustment is needed for patients with mild hepatic impairment. KEYTRUDA has not been studied in patients with moderate or severe hepatic impairment.

3. CONTRAINDICATIONS

KEYTRUDA is contraindicated in patients with hypersensitivity to pembrolizumab or any of the inactive ingredients.

4. WARNINGS AND PRECAUTIONS

Immune-mediated adverse reactions

Immune-mediated adverse reactions, including severe and fatal cases, have occurred in patients receiving KEYTRUDA. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of KEYTRUDA, administration of corticosteroids and/or supportive care. Immune-related adverse reactions have also occurred after the last dose of KEYTRUDA. Immune-mediated adverse reactions affecting more than one body system can occur simultaneously.

For suspected immune-mediated adverse reactions, ensure adequate evaluation to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, withhold KEYTRUDA and consider administration of corticosteroids. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Based on limited data from clinical studies in patients whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered. KEYTRUDA may be restarted within 12 weeks after last dose of KEYTRUDA if the adverse reaction remains at Grade \leq 1 and corticosteroid dose has been reduced to \leq 10 mg prednisone or equivalent per day. If another episode of a severe adverse reaction occurs, permanently discontinue KEYTRUDA. *[See Dosage and Administration (2.1) and Adverse Reactions (7).]*

Immune-mediated pneumonitis

Pneumonitis (including fatal cases) has been reported in patients receiving KEYTRUDA *[see Adverse Reactions (7)]*. Monitor patients for signs and symptoms of pneumonitis. If pneumonitis is suspected, evaluate with radiographic imaging and exclude other causes. Administer corticosteroids for Grade 2 or greater events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper), withhold KEYTRUDA for moderate (Grade 2) pneumonitis, and permanently discontinue KEYTRUDA for severe (Grade 3), life-threatening (Grade 4) or recurrent moderate (Grade 2) pneumonitis. *[See Dosage and Administration (2.1) and Immune-mediated adverse reactions above.]*

Immune-mediated colitis

Colitis has been reported in patients receiving KEYTRUDA *[see Adverse Reactions (7)]*. Monitor patients for signs and symptoms of colitis and exclude other causes. Administer corticosteroids for Grade 2 or greater events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper), withhold KEYTRUDA for moderate (Grade 2) or severe (Grade 3) colitis, and permanently

discontinue KEYTRUDA for life-threatening (Grade 4) colitis. *[See Dosage and Administration (2.1) and Immune-mediated adverse reactions above.]*

Immune-mediated hepatitis

Hepatitis has been reported in patients receiving KEYTRUDA *[see Adverse Reactions (7)]*. Monitor patients for changes in liver function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and symptoms of hepatitis and exclude other causes. Administer corticosteroids (initial dose of 0.5-1 mg/kg/day [for Grade 2 events] and 1-2 mg/kg/day [for Grade 3 or greater events] prednisone or equivalent followed by a taper) and, based on severity of liver enzyme elevations, withhold or discontinue KEYTRUDA. *[See Dosage and Administration (2.1) and Immune-mediated adverse reactions above.]*

Immune-mediated nephritis

Nephritis has been reported in patients receiving KEYTRUDA *[see Adverse Reactions (7)]*. Monitor patients for changes in renal function and exclude other causes. Administer corticosteroids for Grade 2 or greater events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper), withhold KEYTRUDA for moderate (Grade 2), and permanently discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) nephritis. *[See Dosage and Administration (2.1) and Immune-mediated adverse reactions above.]*

Immune-mediated endocrinopathies

Adrenal insufficiency (primary and secondary) has been reported in patients receiving KEYTRUDA. Hypophysitis has also been reported in patients receiving KEYTRUDA. *[See Adverse Reactions (7).]* Monitor patients for signs and symptoms of adrenal insufficiency and hypophysitis (including hypopituitarism) and exclude other causes. Administer corticosteroids to treat adrenal insufficiency and other hormone replacement as clinically indicated, withhold KEYTRUDA for adrenal insufficiency or symptomatic hypophysitis until the event is controlled with hormone replacement. Continuation with KEYTRUDA may be considered, after corticosteroid taper, if needed. *[See Dosage and Administration (2.1) and Immune-mediated adverse reactions above.]* Pituitary function and hormone levels should be monitored to ensure appropriate hormone replacement.

Type 1 diabetes mellitus, including diabetic ketoacidosis, has been reported in patients receiving KEYTRUDA *[see Adverse Reactions (7)]*. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Administer insulin for type 1 diabetes, and withhold KEYTRUDA in cases of severe hyperglycemia until metabolic control is achieved.

Thyroid disorders, including hypothyroidism, hyperthyroidism and thyroiditis, have been reported in patients receiving KEYTRUDA and can occur at any time during treatment; therefore, monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and clinical signs and symptoms of thyroid disorders. Hypothyroidism may be managed with replacement therapy without treatment interruption and without corticosteroids. Hyperthyroidism may be managed symptomatically. Withhold KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) hyperthyroidism until recovery to Grade \leq 1 hyperthyroidism. For patients with Grade 3 or Grade 4 hyperthyroidism that improved to Grade 2 or lower, continuation of KEYTRUDA may be considered, after corticosteroid taper, if needed. *[See Dosage and Administration (2.1), Adverse Reactions (7), and Immune-mediated adverse reactions above.]* Thyroid function and hormone levels should be monitored to ensure appropriate hormone replacement.

For patients with severe (Grade 3) or life-threatening (Grade 4) endocrinopathy that improves to Grade 2 or lower and is controlled with hormone replacement, continuation of KEYTRUDA may be considered.

Severe skin reactions

Immune-mediated severe skin reactions have been reported in patients treated with KEYTRUDA. Monitor patients for suspected severe skin reactions and exclude other causes. Based on the severity of the adverse reaction, withhold or permanently discontinue KEYTRUDA and administer corticosteroids *[see Dosage and Administration (2.1)].*

Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some with fatal outcome, have been reported in patients treated with KEYTRUDA. For signs or symptoms of SJS or TEN, withhold KEYTRUDA and refer the patient for specialized care for assessment and treatment. If SJS or TEN is confirmed, permanently discontinue KEYTRUDA. *[See Dosage and Administration (2.1).]*

Other immune-mediated adverse reactions

The following additional clinically significant, immune-mediated adverse reactions were reported in less than 1% (unless otherwise indicated) of patients treated with KEYTRUDA: uveitis, arthritis (1.5%), myositis, Guillain-Barré syndrome, pancreatitis, myasthenic syndrome, haemolytic anaemia, sarcoidosis, encephalitis, myelitis, vasculitis, and hypoparathyroidism. The following was reported in other clinical studies with KEYTRUDA or in postmarketing use: myocarditis and cholangitis sclerosing.

Cases of these immune-mediated adverse reactions, some of which were severe, have been reported in clinical trials or in postmarketing use.

Transplant-related adverse reactions

Solid organ transplant rejection has been reported in the postmarketing setting in patients treated with KEYTRUDA. Treatment with KEYTRUDA may increase the risk of rejection in solid organ transplant recipients. Consider the benefit of treatment with KEYTRUDA versus the risk of possible organ rejection in these patients.

Complications of allogeneic haematopoietic stem cell transplantation (HSCT)

Allogeneic HSCT after treatment with KEYTRUDA

Cases of graft-versus-host disease (GVHD) and hepatic veno-occlusive disease (VOD) have been observed in patients with classical Hodgkin lymphoma undergoing allogeneic HSCT after previous exposure to KEYTRUDA. Until further data become available, careful consideration to the potential benefits of HSCT and the possible increased risk of transplant-related complications should be made case by case [*see Adverse Reactions (7)*].

Allogeneic HSCT prior to treatment with KEYTRUDA

Acute graft-versus-host-disease (GVHD), including fatal GVHD, after treatment with KEYTRUDA has been reported in patients with a history of allogeneic hematopoietic stem cell transplant (HSCT). Patients who experienced GVHD after their transplant procedure may be at increased risk for GVHD after treatment with KEYTRUDA. Consider the benefit of treatment with KEYTRUDA versus the risk of possible GVHD in patients with a history of allogeneic HSCT.

Elevated liver enzymes when KEYTRUDA is given in combination with axitinib for RCC

When KEYTRUDA is given with axitinib, higher than expected frequencies of Grades 3 and 4 ALT and AST elevations have been reported in patients with advanced RCC [*see Adverse Reactions (7)*]. Monitor liver enzymes before initiation of and periodically throughout treatment. Consider more frequent monitoring of liver enzymes as compared to when the drugs are used in monotherapy. Follow medical management guidelines for both drugs. [*See Dosage and Administration (2.1) and the prescribing information for axitinib.*]

Increased mortality in patients with multiple myeloma when KEYTRUDA is added to a thalidomide analogue and dexamethasone

In two randomized clinical trials in patients with multiple myeloma, the addition of KEYTRUDA to a thalidomide analogue plus dexamethasone, a use for which no PD-1 or PD-L1 blocking antibody is

indicated, resulted in increased mortality. Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

Infusion-related reactions

Severe or life-threatening infusion-related reactions, including hypersensitivity and anaphylaxis, have been reported in 6 (0.2%) of 2799 patients receiving KEYTRUDA in KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, and KEYNOTE-010. For severe infusion reactions, stop infusion and permanently discontinue KEYTRUDA [see *Dosage and Administration (2.1)*]. Patients with mild or moderate infusion reaction may continue to receive KEYTRUDA with close monitoring; premedication with antipyretic and antihistamine may be considered.

5. DRUG INTERACTIONS AND OTHER FORMS OF INTERACTIONS

No formal pharmacokinetic drug interaction studies have been conducted with KEYTRUDA. Since pembrolizumab is cleared from the circulation through catabolism, no metabolic drug-drug interactions are expected.

The use of systemic corticosteroids or immunosuppressants before starting KEYTRUDA should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of KEYTRUDA. However, systemic corticosteroids or other immunosuppressants can be used after starting KEYTRUDA to treat immune-mediated adverse reactions. [See *Warnings and Precautions (4)*.] Corticosteroids can also be used as premedication, when KEYTRUDA is used in combination with chemotherapy, as antiemetic prophylaxis and/or to alleviate chemotherapy-related adverse reactions.

6. USE IN SPECIFIC POPULATIONS

6.1 Pregnancy

There are no data on the use of pembrolizumab in pregnant women. Animal reproduction studies have not been conducted with pembrolizumab; however, 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. These results indicate a potential risk, based on its mechanism of action, that administration of KEYTRUDA during pregnancy could cause fetal harm, including increased rates of abortion or stillbirth. Human IgG4 (immunoglobulin) is known to cross the placental barrier and pembrolizumab is an IgG4; therefore, pembrolizumab has the potential to be transmitted from the mother to the developing fetus. KEYTRUDA is not recommended during pregnancy unless the clinical benefit outweighs the potential risk to the fetus. Women of childbearing potential should use effective contraception during treatment with KEYTRUDA and for at least 4 months after the last dose of KEYTRUDA.

6.2 Nursing Mothers

It is unknown whether KEYTRUDA is secreted in human milk. Since it is known that antibodies can be secreted in human milk, a risk to the newborns/infants cannot be excluded. A decision should be made whether to discontinue breast-feeding or to discontinue KEYTRUDA, taking into account the benefit of breast-feeding for the child and the benefit of KEYTRUDA therapy for the woman.

6.3 Pediatric Use

In KEYNOTE-051, 161 pediatric patients (62 children ages 6 months to less than 12 years and 99 adolescents ages 12 years to 17 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 4 doses (range 1-35 doses), with 138 patients (86%) 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. The most common adverse reactions (reported in at least 20% of pediatric patients) were pyrexia, vomiting, headache, abdominal pain, anemia, cough, and constipation.

Efficacy for pediatric patients with cHL is extrapolated from the results in the respective adult populations [*see Clinical Studies (9)*].

7. ADVERSE REACTIONS

Summary of the safety profile

Pembrolizumab is most commonly associated with immune-related adverse reactions. Most of these, including severe reactions, resolved following initiation of appropriate medical therapy or withdrawal of pembrolizumab (see “Description of selected adverse reactions” below). The frequencies included below and in Table 2 are based on all reported adverse drug reactions, regardless of the investigator assessment of causality.

The safety of pembrolizumab as monotherapy has been evaluated in 7,148 patients with advanced melanoma, resected Stage III melanoma (adjuvant therapy), NSCLC, cHL, urothelial carcinoma, HNSCC, CRC, endometrial, gastric, small intestine, biliary, pancreatic cancer or adjuvant therapy of RCC across four doses (2 mg/kg every 3 weeks, 200 mg every 3 weeks, or 10 mg/kg every 2 or 3 weeks) in clinical studies. In this patient population, the median observation time was 7.9 months (range: 1 day to 39 months) and the most frequent adverse reactions with pembrolizumab were fatigue (31%), diarrhoea (22%), and nausea (21%). The majority of adverse reactions reported for monotherapy were of Grades 1 or 2 severity. The most serious adverse reactions were immune-related adverse reactions and severe infusion-related reactions [*See Warnings and Precautions (4)*]. The incidences of immune-related adverse reactions were 36.1% all Grades and 8.9% for Grades 3-5 for pembrolizumab monotherapy in the adjuvant setting (n=1,480) and 24.2% all Grades and 6.4% for Grades 3-5 in the metastatic setting (n=5,375). No new immune-related adverse reactions were identified in the adjuvant setting.

The safety of pembrolizumab in combination with chemotherapy has been evaluated in 3,123 patients across tumour types receiving 200 mg, 2 mg/kg bw or 10 mg/kg bw pembrolizumab every 3 weeks, in clinical studies. In this patient population, the most frequent adverse reactions were anaemia (55%), nausea (54%), fatigue (38%), neutropenia (36%), constipation (35%), alopecia (35%), diarrhoea (34%), vomiting (28%), and decreased appetite (27%). Incidences of Grades 3-5 adverse reactions in patients with NSCLC were 67% for pembrolizumab combination therapy and 66% for chemotherapy alone, in patients with HNSCC were 85% for pembrolizumab combination therapy and 84% for chemotherapy plus cetuximab, in patients with esophageal carcinoma were 86% for pembrolizumab combination therapy and 83% for chemotherapy alone, in patients with TNBC were 80% for pembrolizumab combination therapy and 77% for chemotherapy alone, and in patients with cervical cancer were 82% for pembrolizumab combination and 75% for chemotherapy alone.

The safety of pembrolizumab in combination with axitinib has been evaluated in a clinical study of 429 patients with advanced RCC receiving 200 mg pembrolizumab every 3 weeks and 5 mg axitinib twice daily. In this patient population, the most frequent adverse reactions were diarrhoea (54%),

hypertension (45%), fatigue (38%), hypothyroidism (35%), decreased appetite (30%), palmar-plantar erythrodysesthesia syndrome (28%), nausea (28%), ALT increased (27%), AST increased (26%), dysphonia (25%), cough (21%), and constipation (21%). Incidences of Grades 3-5 adverse reactions were 76% for pembrolizumab combination therapy and 71% for sunitinib alone.

Tabulated list of adverse reactions

Adverse reactions observed in clinical studies of pembrolizumab as monotherapy or in combination with chemotherapy or other anti-tumour medicines or reported from post-marketing use of pembrolizumab are listed in Table 2. Adverse reactions known to occur with pembrolizumab or chemotherapies given alone may occur during treatment with these medicinal products in combination, even if these reactions were not reported in clinical trials with combination therapy. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$), and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 2: Adverse reactions in patients treated with pembrolizumab*

	Monotherapy	Combination with chemotherapy	Combination with axitinib
Infections and infestations			
Common	pneumonia	pneumonia	pneumonia
Blood and lymphatic system disorders			
Very common	anaemia	neutropaenia, anaemia, thrombocytopaenia, leukopaenia	
Common	thrombocytopaenia, neutropaenia, lymphopaenia	febrile neutropaenia, lymphopaenia	anaemia, neutropaenia, leukopaenia, thrombocytopaenia
Uncommon	leukopaenia, eosinophilia	eosinophilia	lymphopaenia, eosinophilia
Rare	immune thrombocytopaenic purpura, haemolytic anaemia, pure red cell aplasia, haemophagocytic lymphohistiocytosis	haemolytic anaemia, immune thrombocytopaenia	

Immune system disorders			
Common	infusion-related reaction ^a	infusion-related reaction ^a	infusion-related reaction ^a
Uncommon	sarcoidosis		
Rare		sarcoidosis	
Not known	solid organ transplant rejection		
Endocrine disorders			
Very common	hypothyroidism ^b	hypothyroidism ^b	hyperthyroidism, hypothyroidism ^b
Common	hyperthyroidism	adrenal insufficiency ^c , thyroiditis ^d , hyperthyroidism ^e	hypophysitis ^f , thyroiditis ^d , adrenal insufficiency ^c
Uncommon	adrenal insufficiency ^c , hypophysitis ^f , thyroiditis ^d	hypophysitis ^f	hypoparathyroidism
Rare	hypoparathyroidism	hypoparathyroidism	
Metabolism and nutrition disorders			
Very common	decreased appetite	hypokalaemia, decreased appetite	decreased appetite
Common	hyponatraemia, hypokalaemia, hypocalcaemia	hyponatraemia, hypocalcaemia	hypokalaemia, hyponatraemia, hypocalcaemia
Uncommon	type 1 diabetes mellitus ^g	type 1 diabetes mellitus ^g	type 1 diabetes mellitus ^g
Psychiatric disorders			
Very common		insomnia	
Common	insomnia		insomnia
Nervous system disorders			
Very common	headache	neuropathy peripheral, headache, dizziness, dysgeusia	headache, dysgeusia
Common	dizziness, neuropathy peripheral, lethargy, dysgeusia	lethargy	dizziness, lethargy, neuropathy peripheral
Uncommon	epilepsy	encephalitis, epilepsy	myasthenic syndrome ^h
Rare	Guillain-Barré syndrome ⁱ , encephalitis ⁱ , myelitis ^k , myasthenic syndrome ^h ,	Guillain-Barré syndrome ⁱ , myasthenic syndrome	

	meningitis (aseptic), optic neuritis		
Eye disorders			
Common	dry eye	dry eye	dry eye
Uncommon	uveitis ^m		uveitis ^m
Rare	Vogt-Koyanagi-Harada syndrome	uveitis ^m	
Cardiac disorders			
Common	cardiac arrhythmia ^t (including atrial fibrillation)	cardiac arrhythmia ^t (including atrial fibrillation)	cardiac arrhythmia ^t (including atrial fibrillation)
Uncommon	myocarditis, pericardial effusion, pericarditis	myocarditis ⁿ , pericardial effusion, pericarditis	myocarditis
Vascular disorders			
Very common			hypertension
Common	hypertension	hypertension	
Uncommon		vasculitis ^o	
Rare	vasculitis ^o		
Respiratory, thoracic and mediastinal disorders			
Very common	dyspnoea, cough	dyspnoea, cough	dyspnoea, cough, dysphonia
Common	pneumonitis ^p	pneumonitis ^p	pneumonitis ^p
Gastrointestinal disorders			
Very common	diarrhoea, abdominal pain ^q , nausea, vomiting, constipation	nausea, diarrhoea, vomiting, abdominal pain ^q , constipation	diarrhoea, abdominal pain ^q , nausea, vomiting, constipation
Common	colitis ^r , dry mouth	colitis ^r , gastritis, dry mouth	colitis ^r , dry mouth, gastritis
Uncommon	pancreatitis ^s , gastritis, gastrointestinal ulceration ^t	pancreatitis ^s , gastrointestinal ulceration ^t	pancreatitis ^s , gastrointestinal ulceration ^t
Rare	small intestinal perforation	small intestinal perforation	
Hepatobiliary disorders			
Common		hepatitis ^u	hepatitis ^u
Uncommon	hepatitis ^u		

Rare	cholangitis sclerosing	cholangitis sclerosing ^v	
Skin and subcutaneous tissue disorders			
Very common	pruritus ^w , rash ^x	alopecia, rash ^x , pruritus ^w	palmar-plantar erythrodysaesthesia syndrome, rash ^x , pruritus ^w
Common	severe skin reactions ^y , erythema, dermatitis, dry skin, vitiligo ^z , alopecia, eczema, dermatitis acneiform	severe skin reactions ^y , erythema, dermatitis acneiform, dermatitis, dry skin, eczema	severe skin reactions ^y , dermatitis acneiform, dermatitis, dry skin, alopecia, eczema, erythema
Uncommon	psoriasis, lichenoid keratosis ^{aa} , papule, hair colour changes	psoriasis, lichenoid keratosis ^{aa} , vitiligo ^z , papule	hair colour changes, lichenoid keratosis, papule, psoriasis, vitiligo ^z
Rare	Stevens-Johnson syndrome, erythema nodosum, toxic epidermal necrolysis	Stevens-Johnson syndrome, erythema nodosum, hair colour changes	
Musculoskeletal and connective tissue disorders			
Very common	musculoskeletal pain ^{bb} , arthralgia	arthralgia, musculoskeletal pain ^{bb} , myositis ^{cc}	musculoskeletal pain ^{bb} , arthralgia, pain in extremity
Common	pain in extremity, myositis ^{cc} , arthritis ^{dd}	pain in extremity, arthritis ^{dd}	myositis ^{cc} , arthritis ^{dd} , tenosynovitis ^{ee}
Uncommon	tenosynovitis ^{ee}	tenosynovitis ^{ee}	Sjogren's syndrome
Rare	Sjogren's syndrome	Sjogren's syndrome	
Renal and urinary disorders			
Common		acute kidney injury	acute kidney injury, nephritis ^{ff}
Uncommon	nephritis ^{ff}	nephritis ^{ff} , cystitis noninfective	
Rare	cystitis noninfective		
General disorders and administration site conditions			
Very common	fatigue, asthenia, oedema ^{gg} , pyrexia	fatigue, asthenia, pyrexia, oedema ^{gg}	fatigue, asthenia, pyrexia

Common	influenza-like illness, chills	influenza-like illness, chills	oedema ⁹⁹ , influenza-like illness, chills
Investigations			
Very common		alanine aminotransferase increased, aspartate aminotransferase increased	alanine aminotransferase increased, aspartate aminotransferase increased, blood creatinine increased
Common	alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, hypercalcaemia, blood bilirubin increased, blood creatinine increased	blood creatinine increased, blood alkaline phosphatase increased, hypercalcaemia, blood bilirubin increased	blood alkaline phosphatase increased, hypercalcaemia, blood bilirubin increased
Uncommon	amylase increased	amylase increased	amylase increased

*Adverse reaction frequencies presented in Table 2 may not be fully attributable to pembrolizumab alone but may contain contributions from the underlying disease or from other medicinal products used in a combination.

† Based upon a standard query including bradyarrhythmias and tachyarrhythmias.

The following terms represent a group of related events that describe a medical condition rather than a single event:

- a. infusion-related reaction (drug hypersensitivity, anaphylactic reaction, anaphylactoid reaction, hypersensitivity, infusion-related hypersensitivity reaction, cytokine release syndrome, and serum sickness)
- b. hypothyroidism (myxoedema and immune-mediated hypothyroidism)
- c. adrenal insufficiency (Addison's disease, adrenocortical insufficiency acute, secondary adrenocortical insufficiency)
- d. thyroiditis (autoimmune thyroiditis, thyroid disorder, and thyroiditis acute)
- e. hyperthyroidism (Basedow's disease)
- f. hypophysitis (hypopituitarism, lymphocytic hypophysitis)
- g. type 1 diabetes mellitus (diabetic ketoacidosis)
- h. myasthenic syndrome (myasthenia gravis, including exacerbation)

- i. encephalitis (autoimmune encephalitis, noninfective encephalitis)
- j. Guillain-Barré syndrome (axonal neuropathy and demyelinating polyneuropathy)
- k. myelitis (including transverse myelitis)
- l. meningitis aseptic (meningitis, meningitis non-infective)
- m. uveitis (chorioretinitis, iritis and iridocyclitis)
- n. myocarditis (autoimmune myocarditis)
- o. vasculitis (central nervous system vasculitis, aortitis, giant cell arteritis)
- p. pneumonitis (interstitial lung disease, organising pneumonia, immune-mediated pneumonitis, and immune-mediated lung disease)
- q. abdominal pain (abdominal discomfort, abdominal pain upper and abdominal pain lower)
- r. colitis (colitis microscopic, enterocolitis, enterocolitis haemorrhagic, autoimmune colitis, and immune-mediated enterocolitis)
- s. pancreatitis (autoimmune pancreatitis, pancreatitis acute and immune-mediated pancreatitis)
- t. gastrointestinal ulceration (gastric ulcer and duodenal ulcer)
- u. hepatitis (autoimmune hepatitis, immune-mediated hepatitis, drug induced liver injury and acute hepatitis)
- v. cholangitis sclerosing (immune-mediated cholangitis)
- w. pruritus (urticaria, urticaria papular and pruritus genital)
- x. rash (rash erythematous, rash follicular, rash macular, rash maculo-papular, rash papular, rash pruritic, rash vesicular and genital rash)
- y. severe skin reactions (exfoliative rash, pemphigus, and Grade ≥ 3 of the following: dermatitis bullous, dermatitis exfoliative, dermatitis exfoliative generalised, erythema multiforme, lichen planus, oral lichen planus, pemphigoid, pruritus, pruritus genital, rash, rash erythematous, rash maculo-papular, rash pruritic, rash pustular, skin necrosis and toxic skin eruption)
- z. vitiligo (skin depigmentation, skin hypopigmentation and hypopigmentation of the eyelid)
- aa. lichenoid keratosis (lichen planus and lichen sclerosus)
- bb. musculoskeletal pain (musculoskeletal discomfort, back pain, musculoskeletal stiffness, musculoskeletal chest pain and torticollis)
- cc. myositis (myalgia, myopathy, necrotising myositis, polymyalgia rheumatica and rhabdomyolysis)
- dd. arthritis (joint swelling, polyarthritis and joint effusion)
- ee. tenosynovitis (tendonitis, synovitis and tendon pain)
- ff. nephritis (autoimmune nephritis, tubulointerstitial nephritis and renal failure, renal failure acute, or acute kidney injury with evidence of nephritis, nephrotic syndrome, glomerulonephritis and glomerulonephritis membranous)

gg. oedema (oedema peripheral, generalised oedema, fluid overload, fluid retention, eyelid oedema and lip oedema, face oedema, localised oedema and periorbital oedema)

The safety of pembrolizumab in combination with lenvatinib has been evaluated in 94 patients with endometrial carcinoma receiving 200 mg pembrolizumab every 3 weeks and lenvatinib 20 mg orally once daily until unacceptable toxicity or disease progression as determined by the investigator. In this patient population, the most frequent adverse events were hypertension (64%), diarrhea (63%), fatigue (54%), decreased appetite (51%), hypothyroidism (49%), nausea (48%), vomiting (39%), stomatitis (36%), decreased weight (36%), arthralgia (33%), headache (33%), constipation (32%), dysphonia (29%), urinary tract infection (29%), abdominal pain (27%), hypomagnesemia (27%), palmar-plantar erythrodysesthesia (26%), dyspnea (25%), cough (21%), myalgia (21%), and back pain (20%). Of these most commonly reported adverse events, the following were reported with Grades 3-4 in greater than 2% of patients: hypertension, fatigue, abdominal pain, nausea, diarrhea, urinary tract infection, decreased weight, hypomagnesemia, palmar-plantar erythrodysesthesia, and dyspnea.

Description of selected adverse reactions

Data for the following immune related adverse reactions are based on patients who received pembrolizumab across four doses (2 mg/kg every 3 weeks, 200 mg every 3 weeks, or 10 mg/kg every 2 or 3 weeks) in clinical studies [see *Clinical Studies (9)*]. The management guidelines for these adverse reactions are described in section 4.

Immune related adverse reactions [See Warnings and Precautions (4)]

Immune-related pneumonitis

Pneumonitis occurred in 314 (4.1%) patients, including Grade 2, 3, 4 or 5 cases in 138 (1.9%), 80 (1.1%), 19 (0.3%) and 9 (0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of pneumonitis was 3.7 months (range 2 days to 27.2 months). The median duration was 2.0 months (range 1 day to 51.0+ months). Pneumonitis occurred more frequently in patients with a history of prior thoracic radiation (8.1%) than in patients who did not receive prior thoracic radiation (4.1%). Pneumonitis led to discontinuation of pembrolizumab in 129 (1.8%) patients. Pneumonitis resolved in 188 patients, 6 with sequelae.

In patients with NSCLC, pneumonitis occurred in 160 (5.7%), including Grade 2, 3, 4 or 5 cases in 62 (2.2%), 47 (1.7%), 14 (0.5%) and 10 (0.4%), respectively. In patients with NSCLC, pneumonitis occurred in 8.9% with a history of prior thoracic radiation. In patients with cHL, the incidence of

pneumonitis (all Grades) ranged from 5.2% to 10.8% for cHL patients in KEYNOTE-087 (n=210) and KEYNOTE-204 (n=148), respectively.

Immune-related colitis

Colitis occurred in 140 (2.0%) patients, including Grade 2, 3 or 4 cases in 42 (0.6%), 74 (1.0%) and 6 (0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of colitis was 4.5 months (range 2 days to 24.3 months). The median duration was 1.0 month (range 1 day to 8.7+ months). Colitis led to discontinuation of pembrolizumab in 29 (0.5%) patients. Colitis resolved in 84 patients, 2 with sequelae. In patients with CRC treated with pembrolizumab as monotherapy (n=153), the incidence of colitis was 6.5% (all Grades) with 2.0% Grade 3 and 1.3% Grade 4.

Immune-related hepatitis

Hepatitis occurred in 70 (1.0%) patients, including Grade 2, 3 or 4 cases in 11 (0.2%), 47 (0.7%) and 8 (0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of hepatitis was 3.9 months (range 8 days to 26.3 months). The median duration was 1.2 months (range 1 day to 22.5+ months). Hepatitis led to discontinuation of pembrolizumab in 29 (0.4%) patients. Hepatitis resolved in 54 patients.

Immune-related nephritis

Nephritis occurred in 30 (0.4%) patients, including Grade 2, 3 or 4 cases in 8 (0.1%), 16 (0.2%) and 2 (<0.1%) patients, respectively, receiving pembrolizumab as monotherapy. The median time to onset of nephritis was 4.6 months (range 12 days to 21.4 months). The median duration was 6.9 months (range 6 days to 28.2+ months). Nephritis led to discontinuation of pembrolizumab in 13 (0.2%) patients. Nephritis resolved in 18 patients, 5 with sequelae. In patients with non-squamous NSCLC treated with pembrolizumab in combination with pemetrexed and platinum chemotherapy (n=488), the incidence of nephritis was 1.4% (all Grades) with 0.8% Grade 3 and 0.4% Grade 4.

Immune-related endocrinopathies

Adrenal insufficiency occurred in 62 (0.9%) patients, including Grade 2, 3 or 4 cases in 27 (0.4%), 27 (0.4%) and 4 (0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of adrenal insufficiency was 5.5 months (range 1 day to 23.7 months). The median duration was not reached (range 3 days to 40.1+ months). Adrenal insufficiency led to discontinuation of pembrolizumab in 10 (0.1%) patients. Adrenal insufficiency resolved in 24 patients, 10 with sequelae.

Hypophysitis occurred in 40 (0.6%) patients, including Grade 2, 3 or 4 cases in 15 (0.2%), 21 (0.3%) and 1 (<0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of

hypophysitis was 5.9 months (range 1 day to 17.7 months). The median duration was 3.3 months (range 3 days to 48.1+ months). Hypophysitis led to discontinuation of pembrolizumab in 10 (0.1%) patients. Hypophysitis resolved in 19 patients, 8 with sequelae.

Hyperthyroidism occurred in 344 (4.8%) patients, including Grade 2 or 3 cases in 93 (1.3%) and 8 (0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of hyperthyroidism was 1.4 months (range 1 day to 23.2 months). The median duration was 1.6 months (range 4 days to 43.1+ months). Hyperthyroidism led to discontinuation of pembrolizumab in 3 (<0.1%) patients. Hyperthyroidism resolved in 282 (82.0%) patients, 11 with sequelae. In patients with RCC and melanoma treated with pembrolizumab monotherapy in the adjuvant setting (n=1,480), the incidence of hyperthyroidism was 10.9%, the majority of which were Grade 1 or 2.

Hypothyroidism occurred in 856 (12.0%) patients, including Grades 2 or 3 cases in 630 (8.8%) and 8 (0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of hypothyroidism was 3.4 months (range 1 day to 25.9 months). The median duration was not reached (range 2 days to 62.9+ months). Four patients (0.1%) discontinued pembrolizumab due to hypothyroidism. Hypothyroidism resolved in 199 (23.2%) patients, 16 with sequelae. In patients with cHL (n=389) the incidence of hypothyroidism was 17%, all of which were Grade 1 or 2. In patients with HNSCC treated with pembrolizumab as monotherapy (n=909), the incidence of hypothyroidism was 16.1% (all grades) with 0.3% Grade 3. In patients with HNSCC treated with pembrolizumab in combination with platinum and 5-FU chemotherapy (n=276), the incidence of hypothyroidism was 15.2%, all of which were Grade 1 or 2. In patients with RCC and melanoma treated with pembrolizumab monotherapy in the adjuvant setting (n=1,480), the incidence of hypothyroidism was 17.7%, the majority of which were Grade 1 or 2.

Immune-related skin adverse reactions

Immune-related severe skin reactions occurred in 116 (1.6%) patients, including Grade 2, 3 or 5 cases in 11 (0.2%), 91 (1.3%) and 1 (<0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of severe skin reactions was 3.3 months (range 3 days to 25.5 months). The median duration was 1.9 months (range 1 day to 47.1+ months). Severe skin reactions led to discontinuation of pembrolizumab in 15 (0.2%) patients. Severe skin reactions resolved in 83 patients, 2 with sequelae.

Rare cases of SJS and TEN, some of them with fatal outcome, have been observed [*See Dosage and Administration (2.1) and Warnings and Precautions (4)*].

Complications of allogeneic HSCT in classical Hodgkin lymphoma

Of 14 patients in KEYNOTE-013 who proceeded to allogeneic HSCT after treatment with pembrolizumab, 6 patients reported acute GVHD and 1 patient reported chronic GVHD, none of which were fatal. Two patients experienced hepatic VOD, one of which was fatal. One patient experienced engraftment syndrome post-transplant.

Of 32 patients in KEYNOTE-087 who proceeded to allogeneic HSCT after treatment with pembrolizumab, 16 patients reported acute GVHD and 7 patients reported chronic GVHD, two of which were fatal. No patients experienced hepatic VOD. No patients experienced engraftment syndrome post-transplant.

Of 14 patients in KEYNOTE-204 who proceeded to allogeneic HSCT after treatment with pembrolizumab, 8 patients reported acute GVHD and 3 patients reported chronic GVHD, none of which were fatal. No patients experienced hepatic VOD. One patient experienced engraftment syndrome post-transplant.

Elevated liver enzymes when pembrolizumab is combined with axitinib in RCC

In a clinical study of previously untreated patients with RCC receiving pembrolizumab in combination with axitinib, a higher than expected incidence of Grades 3 and 4 ALT increased (20%) and AST increased (13%) were observed. The median time to onset of ALT increased was 2.3 months (range: 7 days to 19.8 months). In patients with ALT \geq 3 times ULN (Grades 2-4, n=116), ALT resolved to Grades 0-1 in 94%. Fifty-nine percent of the patients with increased ALT received systemic corticosteroids. Of the patients who recovered, 92 (84%) were rechallenged with either pembrolizumab (3%) or axitinib (31%) monotherapy or with both (50%). Of these patients, 55% had no recurrence of ALT > 3 times ULN, and of those patients with recurrence of ALT > 3 times ULN, all recovered. There were no Grade 5 hepatic events.

Laboratory abnormalities

In patients treated with pembrolizumab monotherapy, the proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 9.9% for lymphocytes decreased, 7.9% for sodium decreased, 6.2% for haemoglobin decreased, 5.5% for glucose increased, 5.4% for phosphate decreased, 3.3% for ALT increased, 3.2% for AST increased, 2.7% for alkaline phosphatase increased, 2.4% for potassium decreased, 2.1% for potassium increased, 2.0% for neutrophils decreased, 1.9% for platelets decreased, 1.9% for calcium increased, 1.8% for bilirubin increased, 1.5% for albumin decreased, 1.5% for calcium decreased, 1.4% for creatinine increased, 1.0% for glucose decreased, 0.9% for leucocytes decreased, 0.8% for magnesium

increased, 0.5% for haemoglobin increased, 0.5% for sodium increased, and 0.2% for magnesium decreased.

In patients treated with pembrolizumab in combination with chemotherapy, the proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 44.0% for neutrophils decreased, 29.4% for leucocytes decreased, 26.9% for lymphocytes decreased, 22.1% for haemoglobin decreased, 13.2% for platelets decreased, 11.0% for sodium decreased, 7.7% for phosphate decreased, 6.8% for ALT increased, 6.8% for potassium decreased, 6.1% for glucose increased, 5.6% for AST increased, 3.5% for calcium decreased, 3.2% for potassium increased, 2.9% for creatinine increased, 2.2% for albumin decreased, 2.1% for alkaline phosphatase increased, 2.0% for bilirubin increased, 2.0% for calcium increased, 1.3% for prothrombin INR increased, 1.2% for glucose decreased and 0.5% for sodium increased.

In patients treated with pembrolizumab in combination with axitinib, the proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 20.1% for ALT increased, 13.2% for AST increased, 10.8% for lymphocytes decreased, 8.9% for glucose increased, 7.8% for sodium decreased, 6.4% for phosphate decreased, 6.2% for potassium increased, 4.3% for creatinine increased, 3.6% for potassium decreased, 2.1% for bilirubin increased, 2.1% for haemoglobin decreased, 1.7% for alkaline phosphatase increased, 1.5% for prothrombin INR increased, 1.4% for leukocytes decreased, 1.4% for platelets decreased, 1.2% for activated partial thromboplastin time prolonged, 1.2% for neutrophils decreased, 1.2% for sodium increased, 0.7% for calcium decreased, 0.7% for calcium increased, 0.5% for albumin decreased, and 0.2% for glucose decreased.

8. OVERDOSAGE

There is no information on overdosage with KEYTRUDA. The maximum tolerated dose of KEYTRUDA has not been determined.

In case of overdose, patients must be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted.

9. CLINICAL STUDIES

Clinical efficacy and safety

Melanoma

KEYNOTE-006: Controlled trial in melanoma patients naïve to treatment with ipilimumab

The safety and efficacy of KEYTRUDA were investigated in KEYNOTE-006, a multicenter, controlled, Phase III study for the treatment of unresectable or metastatic melanoma in patients who were naïve to ipilimumab and who received no or one prior systemic therapy. Patients were randomized (1:1:1) to receive KEYTRUDA at a dose of 10 mg/kg every 2 (n=279) or 3 weeks (n=277) or ipilimumab (n=278). Randomization was stratified by line of therapy, ECOG performance status, and PD-L1 expression status. The study excluded patients with autoimmune disease or those receiving immunosuppression; previous severe hypersensitivity to other monoclonal antibodies; and HIV, hepatitis B or hepatitis C infection. Patients with BRAF V600E mutant melanoma were not required to have received prior BRAF inhibitor therapy.

Patients were treated with KEYTRUDA until disease progression or unacceptable toxicity. Clinically stable patients with initial evidence of disease progression were permitted to remain on treatment until disease progression was confirmed. Assessment of tumor status was performed at 12 weeks, then every 6 weeks through Week 48, followed by every 12 weeks thereafter.

Of the 834 patients in KEYNOTE-006, 60% were male, 44% were ≥ 65 years (median age was 62 years [range 18-89]) and 98% were white. Sixty-six percent had no prior systemic therapies and thus received study therapy as first-line treatment whereas 34% had one prior therapy and thus received study therapy as second-line treatment. Thirty-one percent had an ECOG PS of 1 and 69% had an ECOG PS of 0. Eighty percent of patients were PD-L1 positive (PD-L1 membrane expression in $\geq 1\%$ of tumor and associated immune cells as assessed prospectively by an immunohistochemistry assay with the 22C3 anti-PD-L1 antibody) and 18% were PD-L1 negative. Sixty-five percent of patients had M1c stage, 32% had elevated LDH and 9% had brain metastases. BRAF mutations were reported in 302 (36%) patients. Among patients with BRAF mutant tumors, 139 (46%) were previously treated with a BRAF inhibitor. Baseline characteristics were well-balanced across treatment arms.

The primary efficacy outcome measures were overall survival (OS) and progression-free survival (PFS; as assessed by Integrated Radiology and Oncology Assessment [IRO] review using Response

Evaluation Criteria in Solid Tumors [RECIST 1.1]). Secondary efficacy outcome measures were overall response rate (ORR) and response duration. Table 3 summarizes key efficacy measures.

Table 3: Response to KEYTRUDA 10 mg/kg Every 2 or 3 Weeks in Patients with Ipilimumab-Naïve Advanced Melanoma in KEYNOTE-006

Endpoint	KEYTRUDA 10 mg/kg every 3 weeks n=277	KEYTRUDA 10 mg/kg every 2 weeks n=279	Ipilimumab n=278
OS*			
Number (%) of patients with event	92 (33%)	85 (30%)	112 (40%)
Hazard ratio† (95% CI)	0.69 (0.52, 0.90)	0.63 (0.47, 0.83)	---
p-Value‡	0.00358	0.00052	---
Median in months (95% CI)	Not reached (NA, NA)	Not reached (NA, NA)	Not reached (13, NA)
PFS§ by IRO¶			
Number (%) of patients with event	157 (57%)	157 (56%)	188 (68%)
Hazard ratio† (95% CI)	0.58 (0.47, 0.72)	0.58 (0.46, 0.72)	---
p-Value‡	<0.00001	<0.00001	---
Median in months (95% CI)	4.1 (2.9, 6.9)	5.5 (3.4, 6.9)	2.8 (2.8, 2.9)
Best Overall Response§ by IRO¶			
ORR % (95% CI)	33% (27, 39)	34% (28, 40)	12% (8, 16)
Complete response %	6%	5%	1%
Partial response %	27%	29%	10%
Response Duration# by IRO¶			
Median in months (range)	Not reached (2.0+, 22.8+)	Not reached (1.8+, 22.8)	Not reached (1.1+, 23.8+)
% ongoing at 12 months ^p	79%	75%	79%

* Based on second interim analysis

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

‡ Based on stratified log-rank test

§ Based on first interim analysis

¶ IRO=Independent radiology plus oncologist review using RECIST 1.1

Based on patients with a best overall response as confirmed complete or partial response from the final analysis

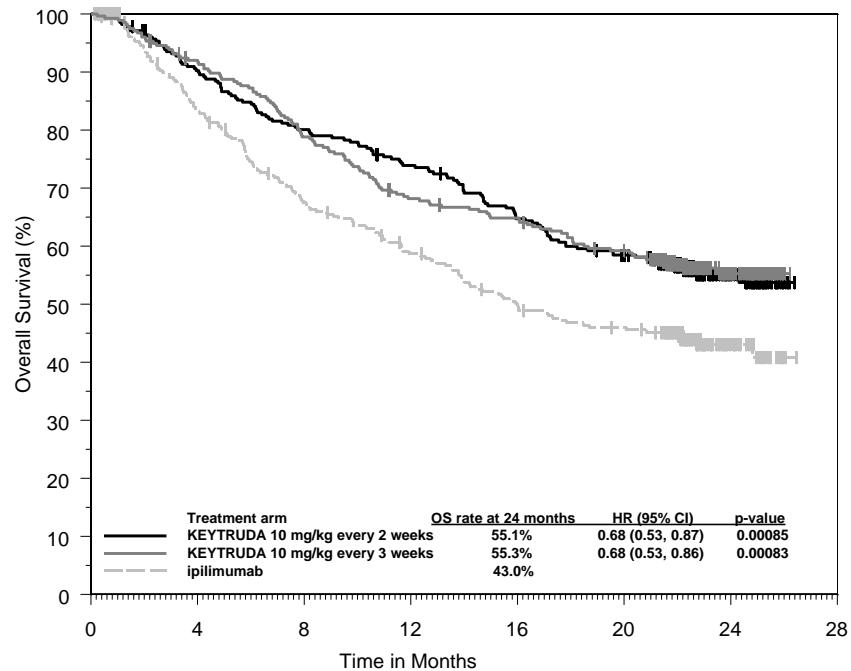
^p Based on Kaplan-Meier estimates

NA=not available

The final analysis was performed after all patients had at least 21 months of follow-up. The final OS analysis was performed after 383 patient events (119 for KEYTRUDA 10 mg/kg every 3 weeks, 122

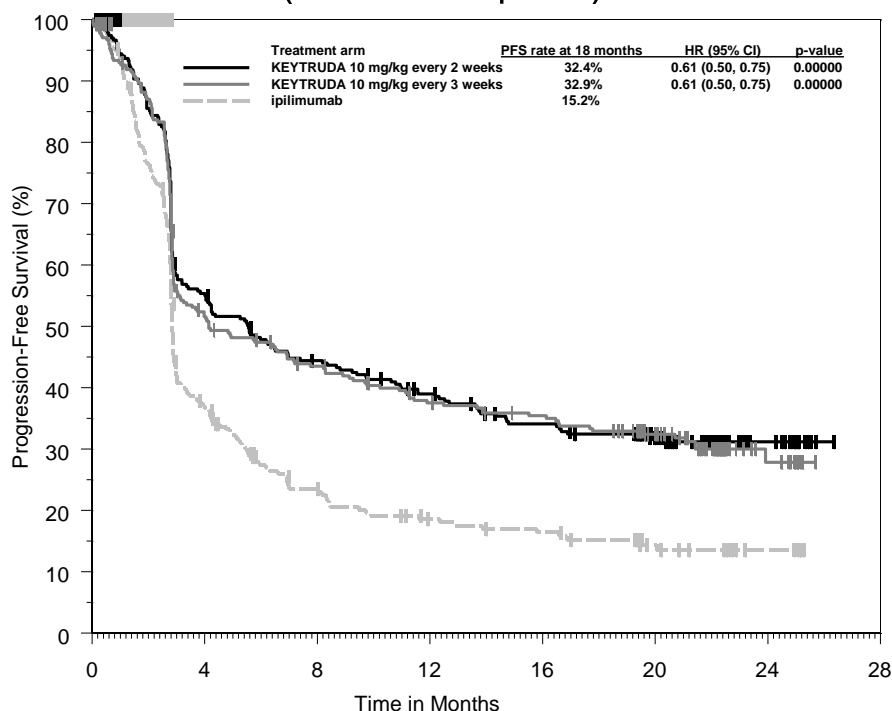
for KEYTRUDA 10 mg/kg every 2 weeks and 142 for ipilimumab). The OS HRs vs. ipilimumab were 0.68 (95% CI: 0.53, 0.86; $p < 0.001$) for patients treated with KEYTRUDA 10 mg/kg every 3 weeks and 0.68 (95% CI: 0.53, 0.87; $p < 0.001$) for patients treated with KEYTRUDA 10 mg/kg every 2 weeks. The OS rate at 18 months and 24 months were 62% and 55% respectively for KEYTRUDA 10 mg/kg every 3 weeks, 60% and 55% respectively for KEYTRUDA 10 mg/kg every 2 weeks, and 47% and 43% respectively for ipilimumab. At the final analysis, a long-term PFS analysis was performed based on 566 patient events (183 for KEYTRUDA 10 mg/kg every 3 weeks, 181 for KEYTRUDA 10 mg/kg every 2 weeks and 202 for ipilimumab). The PFS HRs vs. ipilimumab were 0.61 (95% CI: 0.50, 0.75) for patients treated with KEYTRUDA 10 mg/kg every 3 weeks and 0.61 (95% CI: 0.50, 0.75) for patients treated with KEYTRUDA 10 mg/kg every 2 weeks. (See Figures 1 and 2.) The percentage of responders with an ongoing response at 18 months was 68% for KEYTRUDA 10 mg/kg every 3 weeks, 71% for KEYTRUDA 10 mg/kg every 2 weeks and 70% for ipilimumab.

Figure 1: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-006 (Intent to Treat Population)



Number at Risk	0	4	8	12	16	20	24	28
KEYTRUDA 10 mg/kg every 2 weeks:	279	249	221	202	176	156	44	0
KEYTRUDA 10 mg/kg every 3 weeks:	277	251	215	184	174	156	43	0
ipilimumab:	278	213	170	145	122	110	28	0

Figure 2: Kaplan-Meier Curve for Progression-Free Survival (Based on IRO) by Treatment Arm in KEYNOTE-006 (Intent to Treat Population)



Number at Risk	0	4	8	12	16	20	24	28
KEYTRUDA 10 mg/kg every 2 weeks:	279	148	116	98	82	52	16	0
KEYTRUDA 10 mg/kg every 3 weeks:	277	136	111	91	84	60	13	0
ipilimumab:	278	88	48	34	29	16	5	0

Sub-population analysis by BRAF mutation status

A subgroup analysis was performed as part of the final analysis of KEYNOTE-006 in patients who were BRAF wild type, BRAF mutant without prior BRAF treatment and BRAF mutant with prior BRAF treatment. The PFS hazard ratios (HRs) (pooled KEYTRUDA [10 mg/kg every 2 or 3 weeks] vs. ipilimumab) were 0.61 (95% CI: 0.49, 0.76) for BRAF wild type, 0.52 (95% CI: 0.35, 0.78) for BRAF mutant without prior BRAF treatment, and 0.76 (95% CI: 0.51, 1.14) for BRAF mutant with prior BRAF treatment. The OS HRs for pooled KEYTRUDA vs. ipilimumab were 0.68 (95% CI: 0.52, 0.88) for BRAF wild type, 0.70 (95% CI: 0.40, 1.22) for BRAF mutant without prior BRAF treatment, and 0.66 (95% CI: 0.41, 1.04) for BRAF mutant with prior BRAF treatment. ORR for pooled KEYTRUDA vs. ipilimumab was 38% vs. 14% for BRAF wild type, 41% vs. 15% for BRAF mutant without prior BRAF treatment, and 24% vs. 10% for BRAF mutant with prior BRAF treatment.

Sub-population analysis by PD-L1 status

A subgroup analysis was performed as part of the final analysis of KEYNOTE-006 in patients who were PD-L1 positive vs. PD-L1 negative. The PFS HRs (pooled KEYTRUDA [10 mg/kg every 2 or 3 weeks] vs. ipilimumab) were 0.61 (95% CI: 0.50, 0.75) for PD-L1 positive and 0.61 (95% CI: 0.50, 0.75) for PD-L1 negative.

3 weeks] vs. ipilimumab) were 0.53 (95% CI: 0.44, 0.65) for PD-L1 positive patients and 0.87 (95% CI: 0.58, 1.30) for PD-L1 negative patients. The OS HRs for pooled KEYTRUDA vs. ipilimumab were 0.63 (95% CI: 0.50, 0.80) for PD-L1 positive patients and 0.76 (95% CI: 0.48, 1.19) for PD-L1 negative patients.

KEYNOTE-002: Controlled trial in melanoma patients previously treated with ipilimumab

The safety and efficacy of KEYTRUDA were investigated in KEYNOTE-002, a multicenter, controlled study for the treatment of unresectable or metastatic melanoma in patients previously treated with ipilimumab and if BRAF V600 mutation-positive, a BRAF or MEK inhibitor. Patients were randomized (1:1:1) to receive KEYTRUDA at a dose of 2 (n=180) or 10 mg/kg (n=181) every 3 weeks or chemotherapy (n=179; including dacarbazine, temozolomide, carboplatin, paclitaxel, or carboplatin+paclitaxel). The study excluded patients with autoimmune disease or those receiving immunosuppression; a history of severe or life-threatening immune-mediated adverse reactions from treatment with ipilimumab, defined as any Grade 4 toxicity or Grade 3 toxicity requiring corticosteroid treatment (greater than 10 mg/day prednisone or equivalent dose) for greater than 12 weeks; previous severe hypersensitivity to other monoclonal antibodies; a history of pneumonitis or interstitial lung disease; HIV, hepatitis B or hepatitis C infection.

Patients were treated with KEYTRUDA until disease progression or unacceptable toxicity. Clinically stable patients with initial evidence of disease progression were permitted to remain on treatment until disease progression was confirmed. Assessment of tumor status was performed at 12 weeks, then every 6 weeks through Week 48, followed by every 12 weeks thereafter. Patients on chemotherapy who experienced independently-verified progression of disease after the first scheduled disease assessment were able to crossover and receive 2 mg/kg or 10 mg/kg of KEYTRUDA every 3 weeks in a double-blind fashion.

Of the 540 patients in KEYNOTE-002, 61% were male, 43% were ≥ 65 years (median age was 62 years [range 15-89]) and 98% were white. Eighty-two percent of patients had M1c stage, 73% had at least two and 32% had three or more prior systemic therapies for advanced melanoma. Forty-five percent had an ECOG PS of 1, 40% had elevated LDH and 23% had a BRAF mutated tumor. Baseline characteristics were well-balanced across treatment arms.

The primary efficacy outcome measures were PFS (as assessed by IRO review using RECIST 1.1) and OS. Secondary efficacy outcome measures were PFS (as assessed by Investigator using RECIST 1.1), ORR and response duration. Table 4 summarizes key efficacy measures in patients previously treated with ipilimumab. There was no statistically significant difference between

KEYTRUDA and chemotherapy in the final OS analysis that was not adjusted for the potentially confounding effects of crossover. Of the patients randomized to the chemotherapy arm, 55% crossed over and subsequently received treatment with KEYTRUDA.

Table 4: Response to KEYTRUDA 2 mg/kg or 10 mg/kg Every 3 Weeks in Patients with Unresectable or Metastatic Melanoma in KEYNOTE-002

Endpoint	KEYTRUDA 2 mg/kg every 3 weeks n=180	KEYTRUDA 10 mg/kg every 3 weeks n=181	Chemotherapy n=179
OS*			
Number (%) of patients with event	123 (68%)	117 (65%)	128 (72%)
Hazard ratio [†] (95% CI)	0.86 (0.67, 1.10)	0.74 (0.57, 0.96)	---
p-Value [‡]	0.117	0.011 ^e	---
Median in months (95% CI)	13.4 (11.0, 16.4)	14.7 (11.3, 19.5)	11.0 (8.9, 13.8)
PFS[§] by IRO[¶]			
Number (%) of patients with event	129 (72%)	126 (70%)	155 (87%)
Hazard ratio [†] (95% CI)	0.57 (0.45, 0.73)	0.50 (0.39, 0.64)	---
p-Value [‡]	<0.0001	<0.0001	---
Median in months (95% CI)	2.9 (2.8, 3.8)	2.9 (2.8, 4.7)	2.7 (2.5, 2.8)
Mean in months (95% CI) [#]	5.4 (4.7, 6.0)	5.8 (5.1, 6.4)	3.6 (3.2, 4.1)
PFS[§] by INV[Ⓟ]			
Number (%) of patients with event	122 (68%)	112 (62%)	157 (88%)
Hazard ratio [†] (95% CI)	0.49 (0.38, 0.62)	0.41 (0.32, 0.52)	---
p-Value [‡]	<0.0001	<0.0001	---
Median in months (95% CI)	3.7 (2.9, 5.4)	5.4 (3.8, 6.8)	2.6 (2.4, 2.8)
Mean in months (95% CI) [#]	5.8 (5.2, 6.4)	6.5 (5.8, 7.1)	3.7 (3.2, 4.1)
Best Overall Response[§] by IRO[¶]			
ORR % (95% CI)	21% (15, 28)	25% (19, 32)	4% (2, 9)
Complete response %	2%	3%	0%
Partial response %	19%	23%	4%
Response Duration[§] by IRO[¶]			
Median in months (range)	22.8 (1.4+, 25.3+)	Not reached (1.1+, 28.3+)	6.8 (2.8, 11.3)
% ongoing at 12 months ^a	73%	79%	Not reached ^o

* Based on final analysis

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

‡ Based on stratified log-rank test

§ Based on second interim analysis

¶ IRO=Independent radiology plus oncologist review using RECIST 1.1

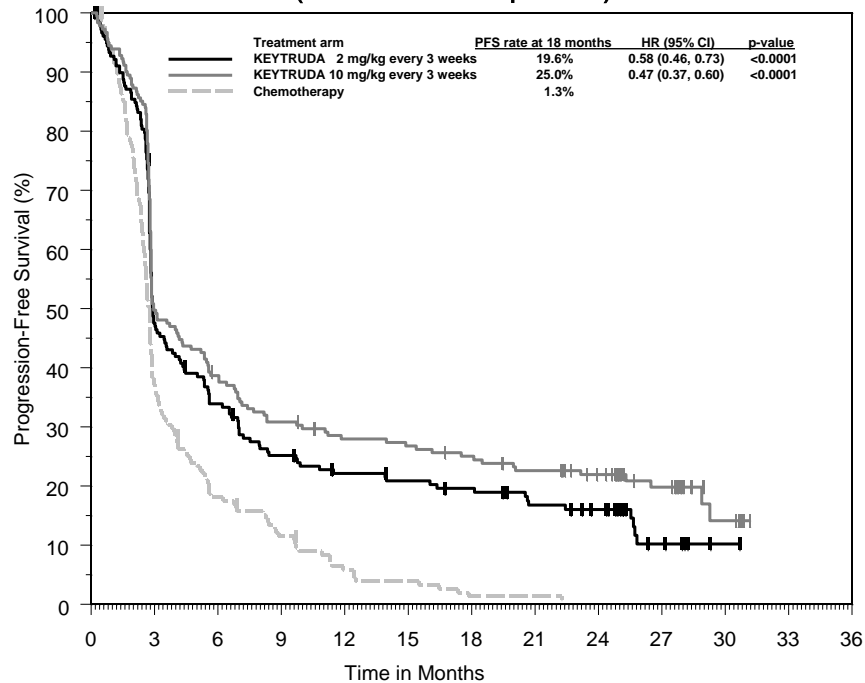
Restricted mean progression-free survival time based on follow-up of 12 months

Ⓟ INV=Investigator assessment using RECIST 1.1

- β Based on patients with a best overall response as confirmed complete or partial response from the final analysis
- à Based on Kaplan-Meier estimates
- è Not statistically significant after adjustment for multiplicity
- ð The maximum follow-up for ongoing patients in the chemotherapy arm is 11.3 months; patients continue to be followed

At the final analysis, a long-term PFS analysis was performed based on 466 PFS events (150 for KEYTRUDA 2 mg/kg every 3 weeks; 144 for KEYTRUDA 10 mg/kg every 3 weeks and 172 for chemotherapy). The PFS HRs vs. chemotherapy were 0.58 (95% CI: 0.46, 0.73) for patients treated with KEYTRUDA 2 mg/kg every 3 weeks and 0.47 (95% CI: 0.37, 0.60) for patients treated with KEYTRUDA 10 mg/kg every 3 weeks (Figure 3).

Figure 3: Kaplan-Meier Curve for Progression-Free Survival (Based on IRO) by Treatment Arm in KEYNOTE-002 (Intent to Treat Population)



Number at Risk	0	3	6	9	12	15	18	21	24	27	30	33	36
KEYTRUDA 2 mg/kg every 3 weeks:	180	59	36	29	19	1	0						
KEYTRUDA 10 mg/kg every 3 weeks:	181	69	48	42	30	5	0						
Chemotherapy:	179	31	9	2	1	0							

A subgroup analysis was performed as part of the final analysis in patients who were BRAF wild type (n=414; 77%) or BRAF mutant with prior BRAF treatment (n=126; 23%). The PFS HRs (pooled pembrolizumab [2 mg/kg or 10 mg/kg every 3 weeks] vs. chemotherapy) were 0.49 (95% CI: 0.39, 0.61) for BRAF wild type and 0.62 (95% CI: 0.41, 0.92) for BRAF mutant with prior BRAF treatment. The PFS HRs for pembrolizumab 2 mg/kg every 3 weeks vs. chemotherapy were 0.50 (95% CI: 0.39,

0.66) for BRAF wild type and 0.79 (95% CI: 0.50, 1.25) for BRAF mutant with prior BRAF treatment. The OS HRs for pooled pembrolizumab vs. chemotherapy were 0.77 (95% CI: 0.60, 0.99) for BRAF wild type and 0.86 (95% CI: 0.55, 1.34) for BRAF mutant with prior BRAF treatment. The OS HRs for pembrolizumab 2 mg/kg every 3 weeks vs. chemotherapy were 0.78 (95% CI: 0.58, 1.04) for BRAF wild type and 1.07 (95% CI: 0.64, 1.78) for BRAF mutant with prior BRAF treatment. ORR for pooled pembrolizumab and pembrolizumab 2 mg/kg every 3 weeks vs. chemotherapy was 29% and 26% vs. 6% for BRAF wild type and 13% and 9% vs. 0% for BRAF mutant with prior BRAF treatment.

A subgroup analysis was performed as part of the final analysis in patients who were PD-L1 positive (PD-L1 expression in $\geq 1\%$ of tumour and associated immune cells) vs. PD-L1 negative. PD-L1 expression was tested retrospectively by immunohistochemistry assay with the 22C3 anti-PD-L1 antibody. Among patients who were evaluable for PD-L1 expression (79%), 69% (n=294) were PD-L1 positive and 31% (n=134) were PD-L1 negative. The PFS HRs (pooled pembrolizumab [2 mg/kg or 10 mg/kg every 3 weeks] vs. chemotherapy) were 0.50 (95% CI: 0.38, 0.65) for PD-L1 positive patients and 0.57 (95% CI: 0.38, 0.87) for PD-L1 negative patients. The PFS HRs for pembrolizumab 2 mg/kg every 3 weeks vs. chemotherapy were 0.55 (95% CI: 0.40, 0.76) for PD-L1 positive patients and 0.81 (95% CI: 0.50, 1.31) for PD-L1 negative patients. The OS HRs for pooled pembrolizumab vs. chemotherapy were 0.81 (95% CI: 0.59, 1.10) for PD-L1 positive patients and 0.86 (95% CI: 0.55, 1.34) for PD-L1 negative patients. The OS HRs for pembrolizumab 2 mg/kg every 3 weeks vs. chemotherapy were 0.90 (95% CI: 0.63, 1.28) for PD-L1 positive patients and 1.18 (95% CI: 0.70, 1.99) for PD-L1 negative patients. ORR for pooled pembrolizumab and pembrolizumab 2 mg/kg every 3 weeks vs. chemotherapy was 28% and 25% vs. 4% for PD-L1 positive patients and 17% and 10% vs. 8% for PD-L1 negative patients.

KEYNOTE-001: Open-label study in melanoma patients

The safety and efficacy of KEYTRUDA were also investigated in an uncontrolled, open-label study for the treatment of unresectable or metastatic melanoma. Efficacy was evaluated for 276 patients from two defined cohorts of KEYNOTE-001, one which included patients previously treated with ipilimumab (and if BRAF V600 mutation-positive, a BRAF or MEK inhibitor) and another which included patients naïve to treatment with ipilimumab. Patients were randomized to receive KEYTRUDA at a dose of 2 mg/kg every 3 weeks or 10 mg/kg every 3 weeks. Patients were treated with KEYTRUDA until disease progression or unacceptable toxicity. Clinically stable patients with initial evidence of disease progression were permitted to remain on treatment until disease progression was confirmed. Exclusion criteria were similar to those of KEYNOTE-002.

Of the 89 patients receiving 2 mg/kg of KEYTRUDA who were previously treated with ipilimumab, 53% were male, 33% were \geq 65 years of age and the median age was 59 years (range 18-88). All but two patients were white. Eighty-four percent of patients had M1c stage and 8% had a history of brain metastases. Seventy-eight percent of patients had at least two and 35% had three or more prior systemic therapies for advanced melanoma. BRAF mutations were reported in 13% of the study population.

Of the 51 patients receiving 2 mg/kg of KEYTRUDA who were naïve to treatment with ipilimumab, 63% were male, 35% were \geq 65 years of age and the median age was 60 years (range 35-80). All but one patient was white. Sixty-three percent of patients had M1c stage and 2% had a history of brain metastases. Forty-five percent had no prior therapies for advanced melanoma. BRAF mutations were reported in 39% of the study population.

The primary efficacy outcome measure was ORR as assessed by independent review using confirmed responses and RECIST 1.1. Secondary efficacy outcome measures were disease control rate (DCR; including complete response, partial response and stable disease), response duration, PFS, and OS. Tumor response was assessed at 12-week intervals. Table 5 summarizes key efficacy measures in patients, previously treated or naïve to treatment with ipilimumab, receiving KEYTRUDA at a dose of 2 mg/kg based on a minimum follow-up time of 30 months for all patients.

Table 5: Response to KEYTRUDA 2 mg/kg Every 3 Weeks in Patients with Unresectable or Metastatic Melanoma in KEYNOTE-001

Endpoint	KEYTRUDA 2 mg/kg every 3 weeks in patients previously treated with ipilimumab n=89	KEYTRUDA 2 mg/kg every 3 weeks in patients naïve to treatment with ipilimumab n=51
Best Overall Response* by IRO†		
ORR %, (95% CI)	26% (17, 36)	35% (22, 50)
Disease control rate %‡	48%	49%
Complete response	7%	12%
Partial response	19%	24%
Stable disease	20%	14%
Response Duration§		
Median in months (range)	30.5 (2.8+, 30.6+)	27.4 (1.6+, 31.8+)
% ongoing at 24 months¶	75%	71%
PFS		
Median in months (95% CI)	4.9 (2.8, 8.3)	4.7 (2.8, 13.8)
PFS rate at 12 months	34%	38%
OS		
Median in months (95% CI)	18.9 (11, not available)	28.0 (14, not available)
OS rate at 24 months	44%	56%

* Includes patients without measurable disease at baseline by independent radiology

† IRO=Independent radiology plus oncologist review using RECIST 1.1

‡ Based on best response of stable disease or better

§ Based on patients with a confirmed response by independent review, starting from the date the response was first recorded; n=23 for patients previously treated with ipilimumab; n=18 for patients naïve to treatment with ipilimumab

¶ Based on Kaplan-Meier estimation

Results for patients previously treated with ipilimumab (n=84) and naïve to treatment with ipilimumab (n=52) who received 10 mg/kg of KEYTRUDA every 3 weeks were similar to those seen in patients who received 2 mg/kg of KEYTRUDA every 3 weeks.

KEYNOTE-054: Placebo-controlled trial for the adjuvant treatment of patients with completely resected melanoma

The efficacy of KEYTRUDA was evaluated in KEYNOTE-054, a multicenter, randomized double-blind, placebo-controlled trial in patients with completely resected stage IIIA (>1 mm lymph node metastasis), IIIB or IIIC melanoma. A total of 1019 patients were randomized (1:1) to receive KEYTRUDA 200 mg every 3 weeks (n=514) or placebo (n=505), for up to one year until disease recurrence or unacceptable toxicity. Randomization was stratified by American Joint Committee on Cancer 7th edition (AJCC) stage (IIIA vs. IIIB vs. IIIC 1-3 positive lymph nodes vs. IIIC \geq 4 positive lymph nodes) and geographic region (North America, European countries, Australia, and other countries as designated). Patients must have undergone lymph node dissection and, if indicated, radiotherapy within 13 weeks prior to starting treatment. Patients with active autoimmune disease or a medical condition that required immunosuppression or mucosal or ocular melanoma were ineligible. Patients underwent imaging every 12 weeks after the first dose of KEYTRUDA for the first two years, then every 6 months from year 3 to 5, and then annually.

Among the 1019 patients, the baseline characteristics were: median age of 54 years (25% age 65 or older); 62% male; ECOG PS of 0 (94%) and 1 (6%). Sixteen percent had stage IIIA; 46% had stage IIIB; 18% had stage IIIC (1-3 positive lymph nodes), and 20% had stage IIIC (\geq 4 positive lymph nodes); 50% were BRAF V600 mutation positive and 44% were BRAF wild type; 84% had PD-L1 positive melanoma with tumor proportion score (TPS \geq 1%) according to an investigational use only (IUO) assay.

The primary efficacy outcome measures were investigator-assessed recurrence-free survival (RFS) in the whole population and in the population with PD-L1 positive tumors where RFS was defined as the time between the date of randomization and the date of first recurrence (local, regional, or distant metastasis) or death, whichever occurred first. The secondary outcome measures were distant metastasis-free survival (DMFS) and OS in the whole population and in the population with PD-L1 positive tumours. OS was not formally assessed at the time of these analyses. The trial initially demonstrated a statistically significant improvement in RFS (HR 0.57; 98.4% CI 0.43, 0.74; p-Value < 0.0001) for patients randomized to the KEYTRUDA arm compared with placebo at its pre-specified interim analysis. Updated efficacy results with a median follow-up time of 45.5 months are summarized in Table 6 and Figures 4 and 5.

Table 6: Efficacy Results in KEYNOTE-054

Endpoint	KEYTRUDA 200 mg every 3 weeks n=514	Placebo n=505
RFS		
Number (%) of patients with event	135 (26%)	216 (43%)
RFS rate	82%	73%
Median in months (95% CI)	NR	20.4 (16.2, NR)
Hazard ratio* (98% CI)	0.57 (0.43, 0.74)	
p-Value (stratified log-rank)	<0.0001	
DMFS		
Number (%) of patients with event	173 (34%)	245 (49%)
DMFS rate at 42 months	65%	49%
Median in months (95% CI)	NR	40.0 (27.7, NR)
Hazard ratio* (95% CI)	0.60 (0.49, 0.73)	
p-Value (stratified log-rank)	<0.0001	

* Based on the stratified Cox proportional hazard model

NR=not reached

For patients in the whole population, the RFS rate at 42 months was 60% in the KEYTRUDA arm and 41% in the placebo arm (HR was 0.59 [95% CI: 0.49, 0.70]).

For patients with PD-L1 positive tumors, the RFS rate at 42 months was 61% in the KEYTRUDA arm and 44% in the placebo arm (HR was 0.59 (95% CI: 0.49, 0.73)). Additionally, pre-defined subgroup analyses were performed in patients whose tumors were PD-L1 negative, BRAF mutation positive, or BRAF mutation negative. The RFS benefit for KEYTRUDA compared to placebo was observed regardless of tumor PD-L1 expression or BRAF mutation status. The RFS HR for KEYTRUDA was 0.46 (95% CI: 0.27, 0.77) for patients with PD-L1 negative tumors. The RFS HR was 0.52 (95% CI: 0.40, 0.66) for patients with BRAF mutation positive tumors, and 0.67 (95% CI: 0.51, 0.88) for patients with BRAF mutation negative tumors.

For patients with PD-L1 positive tumors, the DMFS rate at 42 months was 67% in the KEYTRUDA arm and 52% in the placebo arm (HR was 0.61 (95% CI: 0.49, 0.76); p <0.0001). Additionally, pre-

defined subgroup analyses were performed in patients whose tumors were PD-L1 negative, BRAF mutation positive, or BRAF mutation negative. The DMFS benefit for KEYTRUDA compared to placebo was observed regardless of tumor PD-L1 expression or BRAF mutation status. The DMFS HR for KEYTRUDA was 0.49 (95% CI: 0.28, 0.83) for patients with PD-L1 negative tumors. The DMFS HR was 0.51 (95% CI: 0.39, 0.68) for patients with BRAF mutation positive tumors, and 0.73 (95% CI: 0.55, 0.98) for patients with BRAF mutation negative tumors.

Figure 4: Kaplan-Meier Curve for Recurrence-Free Survival in KEYNOTE-054 (Intent to Treat Population)

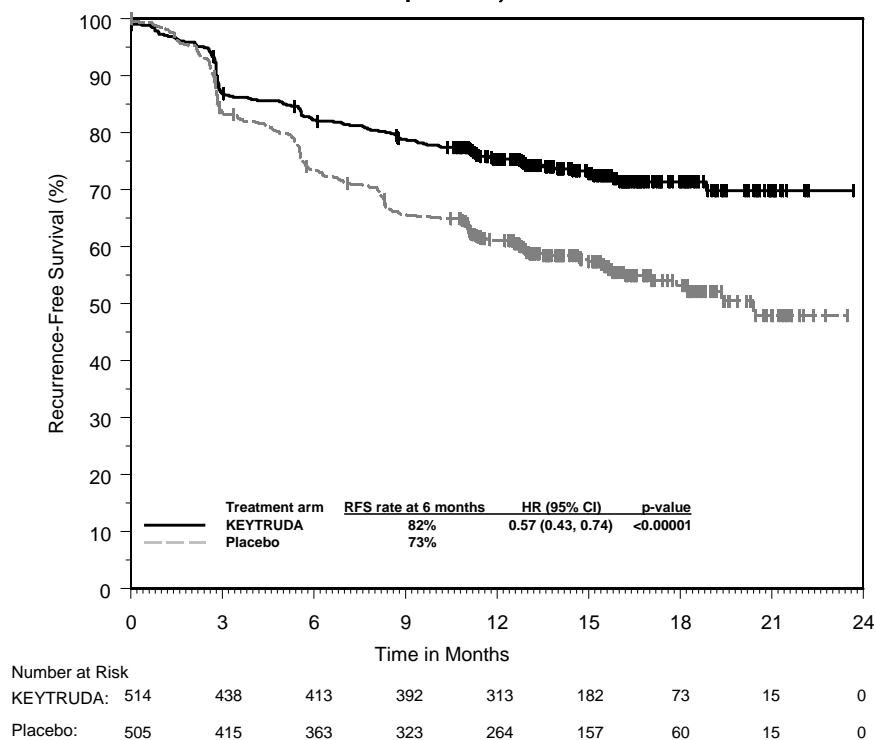
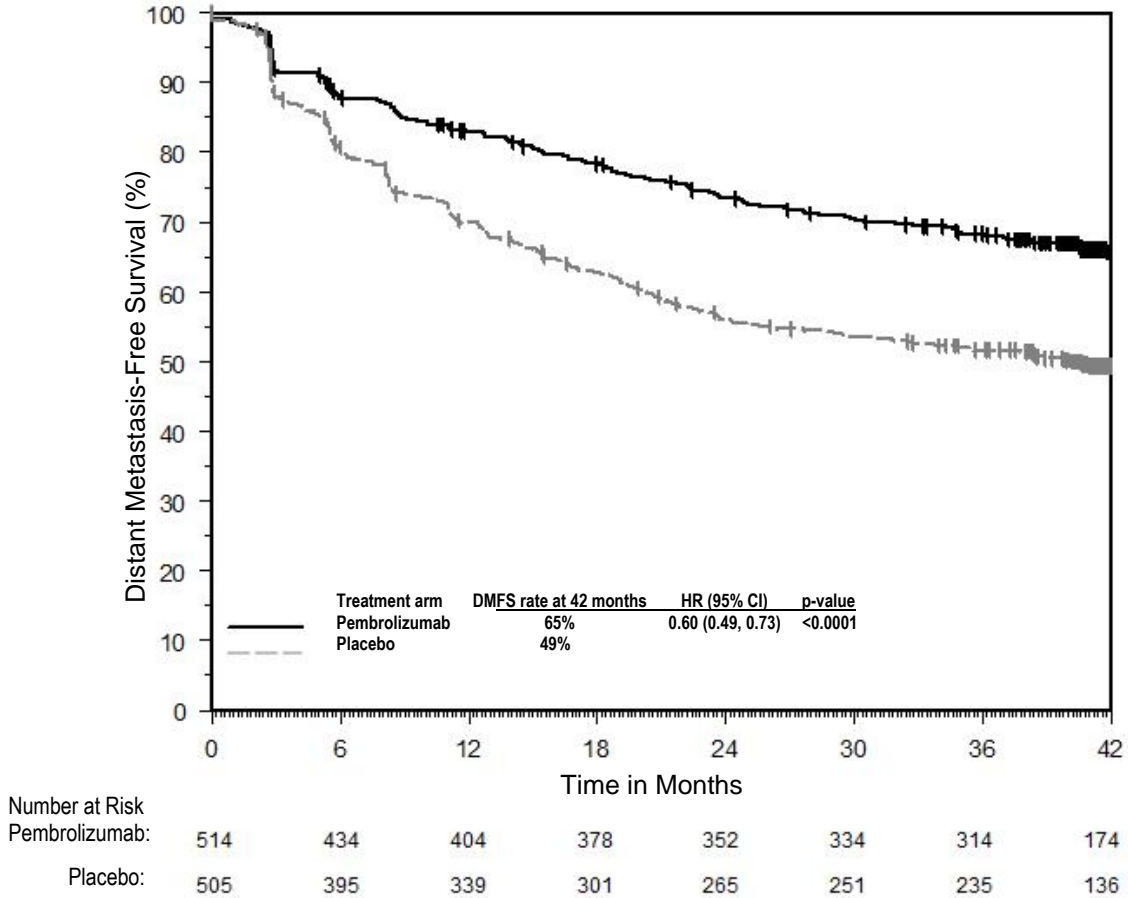


Figure 5: Kaplan-Meier Curve for Distant Metastasis-Free Survival in KEYNOTE-054 (Intent to Treat Population)



Non-Small Cell Lung Carcinoma

KEYNOTE-189: Controlled trial of combination therapy in non-squamous NSCLC patients naïve to treatment

The efficacy of KEYTRUDA in combination with pemetrexed and platinum chemotherapy was investigated in a multicenter, randomized, active-controlled, double-blind trial, KEYNOTE-189. Key eligibility criteria were metastatic non-squamous NSCLC, no prior systemic treatment for metastatic NSCLC, and no EGFR or ALK genomic tumor aberrations. Patients with autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Patients were randomized (2:1) to receive one of the following regimens:

- KEYTRUDA 200 mg with pemetrexed 500 mg/m² and investigator’s choice of cisplatin 75 mg/m² or carboplatin AUC 5 mg/mL/min intravenously every 3 weeks for 4 cycles followed by KEYTRUDA 200 mg and pemetrexed 500 mg/m² intravenously every 3 weeks.

- Placebo with pemetrexed 500 mg/m² and investigator's choice of cisplatin 75 mg/m² or carboplatin AUC 5 mg/mL/min intravenously every 3 weeks for 4 cycles followed by placebo and pemetrexed 500 mg/m² intravenously every 3 weeks.

Treatment with KEYTRUDA continued until RECIST 1.1-defined progression of disease as determined by the investigator, unacceptable toxicity, or a maximum of 24 months. Administration of KEYTRUDA was permitted beyond RECIST-defined disease progression by BICR or beyond discontinuation of pemetrexed if the patient was clinically stable and deriving clinical benefit as determined by the investigator. For patients who completed 24 months of therapy or had a complete response, treatment with KEYTRUDA could be reinitiated for disease progression and administered for up to 1 additional year. Assessment of tumor status was performed at Week 6 and Week 12, followed by every 9 weeks thereafter. Patients receiving placebo plus chemotherapy who experienced independently-verified progression of disease were offered KEYTRUDA as monotherapy.

Among the 616 patients in KEYNOTE-189 (410 patients in the KEYTRUDA combination arm and 206 in the placebo plus chemotherapy arm), baseline characteristics were: median age of 64 years (49% age 65 or older); 59% male; 94% White and 3% Asian; 43% and 56% ECOG performance status of 0 or 1 respectively; 31% with PD-L1 TPS <1%; and 18% with treated or untreated brain metastases at baseline. A total of 67 patients in the placebo plus chemotherapy arm crossed over to receive monotherapy KEYTRUDA at the time of disease progression and 18 additional patients received a checkpoint inhibitor as subsequent therapy.

The primary efficacy outcome measures were OS and PFS (as assessed by BICR using RECIST 1.1). Secondary efficacy outcome measures were ORR and response duration, as assessed by BICR using RECIST 1.1. The median follow-up time was 10.5 months (range: 0.2 – 20.4 months). Table 7 summarizes key efficacy measures.

Table 7: Response to KEYTRUDA, Pemetrexed, and Platinum Chemotherapy in Patients with Non-Squamous NSCLC in KEYNOTE-189

Endpoint	KEYTRUDA + Pemetrexed + Platinum Chemotherapy n=410	Placebo + Pemetrexed + Platinum Chemotherapy n=206
OS		
Number (%) of patients with	127 (31%)	108 (52%)

event		
Hazard ratio* (95% CI)	0.49 (0.38, 0.64)	
p-Value†	<0.00001	
Median in months (95% CI)	Not reached (NA, NA)	11.3 (8.7, 15.1)
PFS		
Number (%) of patients with event	245 (60%)	166 (81%)
Hazard ratio* (95% CI)	0.52 (0.43, 0.64)	
p-Value†	<0.00001	
Median in months (95% CI)	8.8 (7.6, 9.2)	4.9 (4.7, 5.5)
Objective Response Rate		
ORR‡ % (95% CI)	48% (43, 53)	19% (14, 25)
Complete response %	0.5%	0.5%
Partial response %	47%	18%
p-Value§	<0.0001	
Response Duration		
Median in months (range)	11.2 (1.1+, 18.0+)	7.8 (2.1+, 16.4+)
% with duration ≥ 6 months¶	81%	63%
% with duration ≥ 9 months¶	59%	44%

* Based on the stratified Cox proportional hazard model

† Based on stratified log-rank test

‡ Based on patients with a best overall response as confirmed complete or partial response

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

¶ Based on Kaplan-Meier estimation

NA=not available

The final OS analysis was performed at a median duration of follow-up of 18.8 months after 421 patient events (258 for the KEYTRUDA combination arm and 163 for the placebo plus chemotherapy arm). Median OS was 22.0 months (95% CI: 19.5, 24.5) for the KEYTRUDA combination arm and 10.6 months (95% CI: 8.7, 13.6) for the placebo plus chemotherapy arm. The OS HR was 0.56 (95% CI: 0.46, 0.69; p<0.00001). At final analysis, a PFS analysis was performed

based on 534 patient events (337 for the KEYTRUDA combination arm and 197 for the placebo plus chemotherapy arm). The median PFS was 9.0 months (95% CI: 8.1, 10.4) for the KEYTRUDA combination arm and 4.9 months (95% CI: 4.7, 5.5) for the placebo plus chemotherapy arm. The PFS HR was 0.49 (95% CI: 0.41, 0.59, $p < 0.00001$). See Figures 6 and 7.

The ORR at the final analysis was 48% for the KEYTRUDA combination arm and 20% for the placebo plus chemotherapy arm. The median duration of response was 12.5 months (range 1.1+, 34.9+) for the KEYTRUDA combination arm and 7.1 months (range 2.4, 27.8+) for the placebo plus chemotherapy arm. The percentage of patients with ongoing responses based on Kaplan-Meier estimation was 53% at 12 months or longer, in patients who received KEYTRUDA combination therapy, vs. 27% in patients who received placebo plus chemotherapy.

Figure 6: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-189 (Intent to Treat Population)

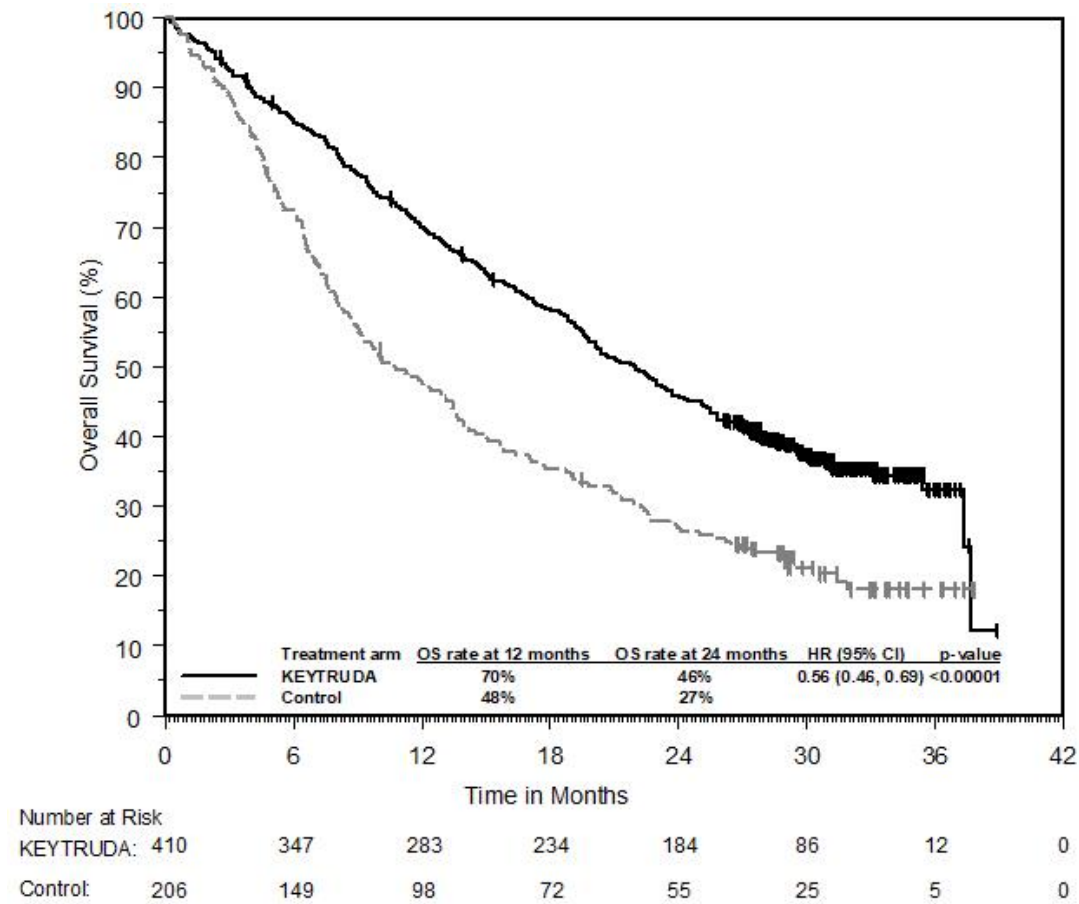
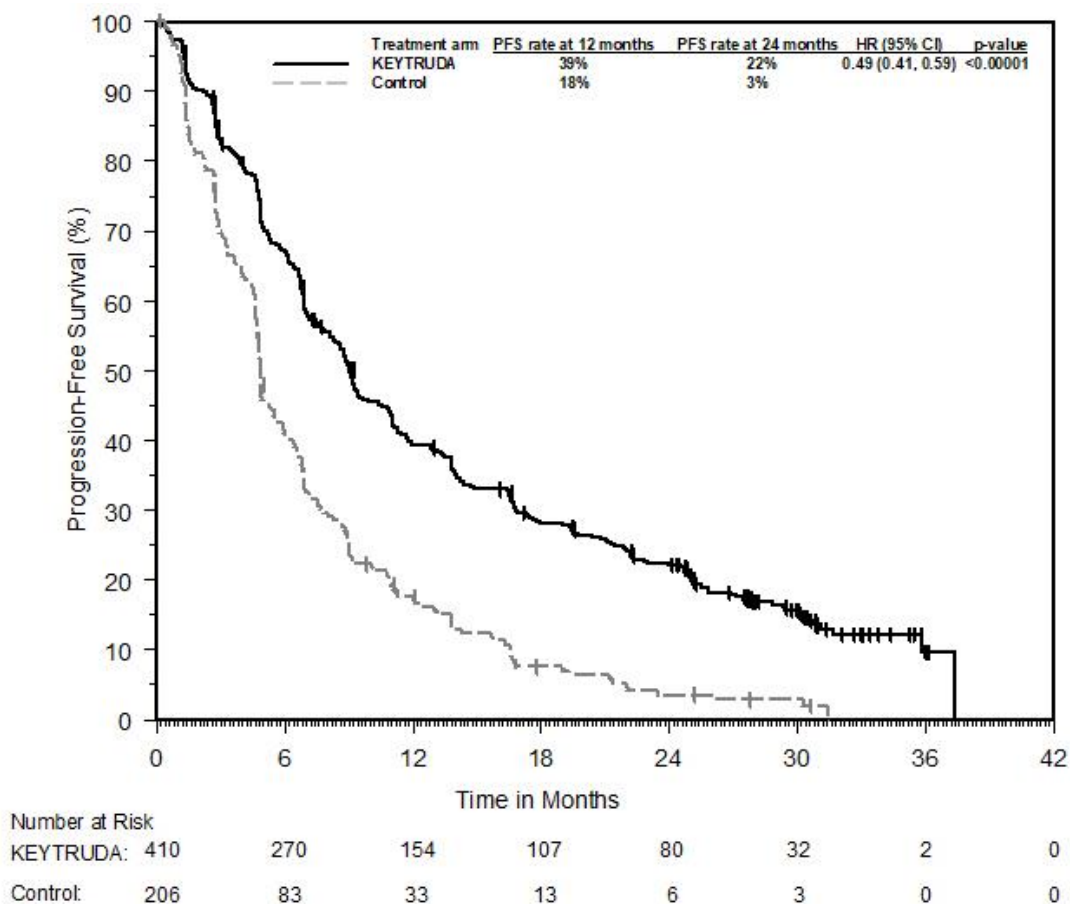


Figure 7: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-189 (Intent to Treat Population)



Patient-reported outcomes were assessed using the EORTC QLQ-C30 and EORTC QLQ-LC13. Exploratory analyses of patients receiving pembrolizumab combination therapy showed stable EORTC QLQ-C30 Global Health Status/QoL at Week 12 and Week 21 vs. declines in patients receiving placebo plus chemotherapy. There was a trend toward a prolonged time to deterioration in the EORTC QLQ-LC13/QLQ-C30 endpoint of cough, dyspnea or chest pain observed for patients receiving pembrolizumab combination therapy.

KEYNOTE-407: Controlled trial of combination therapy in squamous NSCLC patients naïve to treatment

The efficacy of KEYTRUDA in combination with carboplatin and either paclitaxel or nab-paclitaxel was investigated in Study KEYNOTE-407, a randomized, double-blind, multicenter, placebo-controlled study. The key eligibility criteria for this study were metastatic squamous 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 tumor PD-L1 expression (TPS <1% [negative] vs. TPS ≥ 1%), investigator's choice of paclitaxel or nab-paclitaxel, and geographic region (East Asia vs. non-East Asia). Patients were randomized (1:1) to one of the following treatment arms; all study medications were administered via intravenous infusion.

- KEYTRUDA 200 mg and carboplatin AUC 6 mg/mL/min on Day 1 of each 21-day cycle for 4 cycles, and paclitaxel 200 mg/m² on Day 1 of each 21-day cycle for 4 cycles or nab-paclitaxel 100 mg/m² on Days 1, 8 and 15 of each 21-day cycle for 4 cycles, followed by KEYTRUDA 200 mg every 3 weeks. KEYTRUDA was administered prior to chemotherapy on Day 1.
- Placebo and carboplatin AUC 6 mg/mL/min on Day 1 of each 21-day cycle for 4 cycles and paclitaxel 200 mg/m² on Day 1 of each 21-day cycle for 4 cycles or nab-paclitaxel 100 mg/m² on Days 1, 8 and 15 of each 21-day cycle for 4 cycles, followed by placebo every 3 weeks.

Treatment with KEYTRUDA or placebo 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. Treatment with KEYTRUDA could be reinitiated for subsequent disease progression and administered for up to 1 additional year.

Patients in the placebo arm were offered KEYTRUDA as monotherapy at the time of disease progression.

Assessment of tumor status was performed every 6 weeks through Week 18, every 9 weeks through Week 45 and every 12 weeks thereafter. The major efficacy outcome measures were progression-free survival and objective response rate (ORR) as assessed by BICR using RECIST 1.1 and overall survival. An additional efficacy outcome measure was duration of response as assessed by BICR using RECIST 1.1.

A total of 559 patients were randomized: 278 patients to the KEYTRUDA arm and 281 to the placebo arm. The study population characteristics were: median age of 65 years (range: 29 to 88); 55% age 65 or older; 81% male; 77% White; ECOG performance status of 0 (29%) and 1 (71%); and 8% with treated brain metastases at baseline. Thirty-five percent had tumor PD-L1 expression TPS <1% [negative]; 19% were from the East Asian region; and 60% received paclitaxel.

In KEYNOTE-407, there was a statistically significant improvement in OS, PFS and ORR in patients randomized to KEYTRUDA in combination with carboplatin and either paclitaxel or nab-paclitaxel compared with patients randomized to placebo with carboplatin and either paclitaxel or nab-paclitaxel (see Table 8).

Table 8: Efficacy Results in KEYNOTE-407

Endpoint	KEYTRUDA Carboplatin Paclitaxel/Nab-paclitaxel n=278	Placebo Carboplatin Paclitaxel/Nab-paclitaxel n=281
OS		
Number of events (%)	85 (31%)	120 (43%)
Median in months (95% CI)	15.9 (13.2, NA)	11.3 (9.5, 14.8)
Hazard ratio* (95% CI)	0.64 (0.49, 0.85)	
p-Value (stratified log-rank)	0.0008	
PFS		
Number of events (%)	152 (55%)	197 (70%)
Median in months (95% CI)	6.4 (6.2, 8.3)	4.8 (4.2, 5.7)
Hazard ratio* (95% CI)	0.56 (0.45, 0.70)	
p-Value (stratified log-rank)	<0.0001	
Overall Response Rate		
Overall response rate [†]	58%	38%
(95% CI)	(52, 64)	(33, 44)
Duration of Response		
Median duration of response in months (range)	7.7 (1.1+, 14.7+)	4.8 (1.3+, 15.8+)
% with duration ≥ 6 months [‡]	62%	40%

* Based on the stratified Cox proportional hazard model

† At the initial interim analysis (n=101 for KEYTRUDA combination therapy, n=102 for placebo), a statistically significant difference was observed; ORR was 58% [95% CI (48, 68)] and 35% [95% CI (26, 45)] for placebo, p=0.0004

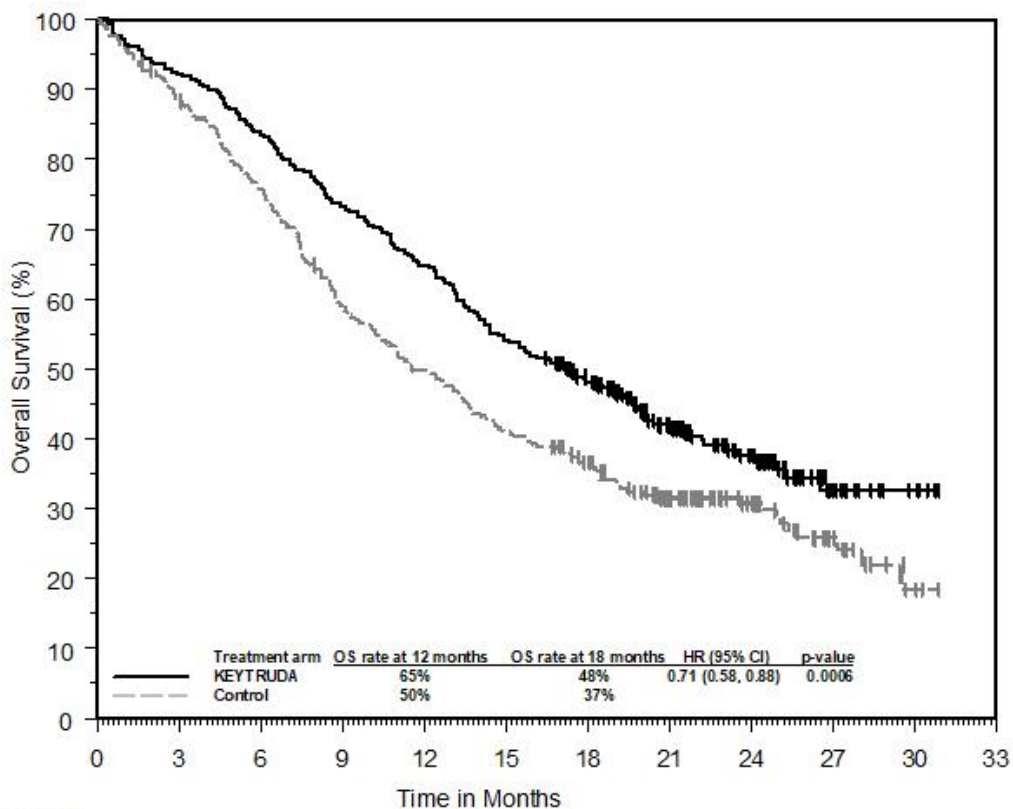
‡ Based on Kaplan-Meier estimation

NA=not available

The final OS analysis was performed at a median duration of follow-up of 14.3 months after 365 patient events (168 for the KEYTRUDA combination arm and 197 for the placebo plus chemotherapy arm). Median OS was 17.1 months (95% CI: 14.4, 19.9) for the KEYTRUDA combination arm and 11.6 months (95% CI: 10.1, 13.7) for the placebo plus chemotherapy arm. The OS HR was 0.71 (95% CI: 0.58, 0.88; $p=0.0006$). At final analysis, a PFS analysis was performed based on 469 patient events (217 for the KEYTRUDA combination arm and 252 for the placebo plus chemotherapy arm). The median PFS was 8.0 months (95% CI: 6.3, 8.4) for the KEYTRUDA combination arm and 5.1 months (95% CI: 4.3, 6.0) for the placebo plus chemotherapy arm. The PFS HR was 0.57 (95% CI: 0.47, 0.69, $p<0.0001$). See Figures 8 and 9.

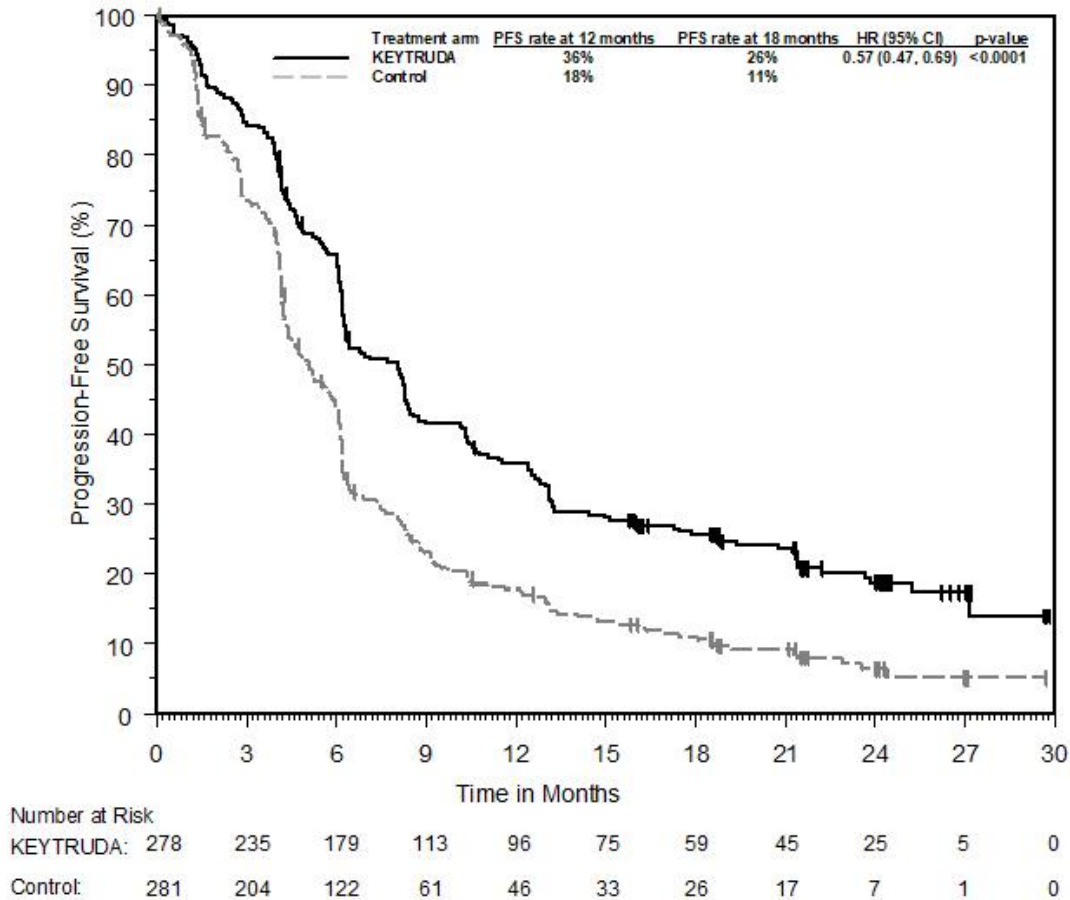
The ORR at the final analysis was 63% for the KEYTRUDA combination arm and 38% for the placebo plus chemotherapy arm. The median duration of response was 8.8 months (range 1.3+, 28.4+) for the KEYTRUDA combination arm and 4.9 months (range 1.3+, 28.3+) for the placebo plus chemotherapy arm. The percentage of patients with ongoing responses based on Kaplan-Meier estimation were 64% and 38% at 6 and 12 months or longer, in patients who received KEYTRUDA combination therapy, vs. 44% and 25% in patients who received placebo plus chemotherapy.

Figure 8: Kaplan-Meier Curve for Overall Survival in KEYNOTE-407



Number at Risk	0	3	6	9	12	15	18	21	24	27	30	33
KEYTRUDA:	278	256	232	203	180	150	119	80	46	14	4	0
Control:	281	245	210	163	137	113	91	61	36	16	3	0

Figure 9: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-407



KEYNOTE-024: Controlled trial of NSCLC patients naïve to treatment

The efficacy of KEYTRUDA was investigated in KEYNOTE-024, a multicenter, randomized, controlled trial. Key eligibility criteria were metastatic NSCLC, PD-L1 expression tumor proportion score (TPS) of 50% or greater by an immunohistochemistry assay using the PD-L1 IHC 22C3 pharmDx™ Kit, and no 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 thoracic radiation within the prior 26 weeks were ineligible. Patients were randomized (1:1) to receive KEYTRUDA 200 mg every 3 weeks (n=154) or investigator’s choice platinum-containing chemotherapy (n=151; including pemetrexed+carboplatin, pemetrexed+cisplatin, gemcitabine+cisplatin, gemcitabine+carboplatin, or paclitaxel+carboplatin. Non-squamous patients could receive pemetrexed maintenance). Patients were treated with KEYTRUDA until unacceptable toxicity or disease progression. Treatment could continue beyond disease progression if the patient

was clinically stable and was considered to be deriving clinical benefit by the investigator. Patients without disease progression could be treated for up to 24 months. Treatment with KEYTRUDA could be reinitiated for subsequent disease progression and administered for up to 1 additional year. Assessment of tumor status was performed every 9 weeks. Patients on chemotherapy who experienced independently-verified progression of disease were able to crossover and receive KEYTRUDA.

Among the 305 patients in KEYNOTE-024, baseline characteristics were: median age 65 years (54% age 65 or older); 61% male; 82% White and 15% Asian; and 35% and 65% with an ECOG performance status 0 and 1, respectively. Disease characteristics were squamous (18%) and non-squamous (82%); M1 (99%); and brain metastases (9%).

The primary efficacy outcome measure was PFS as assessed by blinded independent central review (BICR) using RECIST 1.1. Secondary efficacy outcome measures were OS and ORR (as assessed by BICR using RECIST 1.1). Table 9 summarizes key efficacy measures for the entire ITT population.

Table 9: 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%)
Hazard ratio† (95% CI)	0.50 (0.37, 0.68)	---
p-Value‡	<0.001	---
Median in months (95% CI)	10.3 (6.7, NA)	6.0 (4.2, 6.2)
OS		
Number (%) of patients with event	44 (29%)	64 (42%)
Hazard ratio† (95% CI)	0.60 (0.41, 0.89)	---
p-Value‡	0.005	---
Median in months (95% CI)	Not reached (NA, NA)	Not reached (9.4, NA)
Objective Response Rate*		
ORR % (95% CI)	45% (37, 53)	28% (21, 36)
Complete response %	4%	1%
Partial response %	41%	27%
Response Duration§,¶		
Median in months (range)	Not reached (1.9+, 14.5+)	6.3 (2.1+, 12.6+)
% with duration ≥ 6 months	88%	59%

* Assessed by BICR using RECIST 1.1

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

‡ Based on stratified log-rank test

§ Based on patients with a best overall response as confirmed complete or partial response

¶ Based on Kaplan-Meier estimates

NA=not available

The final OS analysis was performed at a median follow-up of 25 months after 169 patient events (73 for KEYTRUDA and 96 for chemotherapy). Median OS was 30.0 months (95% CI: 18.3, NA) for

KEYTRUDA and 14.2 months (95% CI: 9.8, 19.0) for chemotherapy. The OS HR was 0.63 (95% CI: 0.47, 0.86; p=0.002). See Figure 11.

Figure 10: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-024 (Intent to Treat Population)

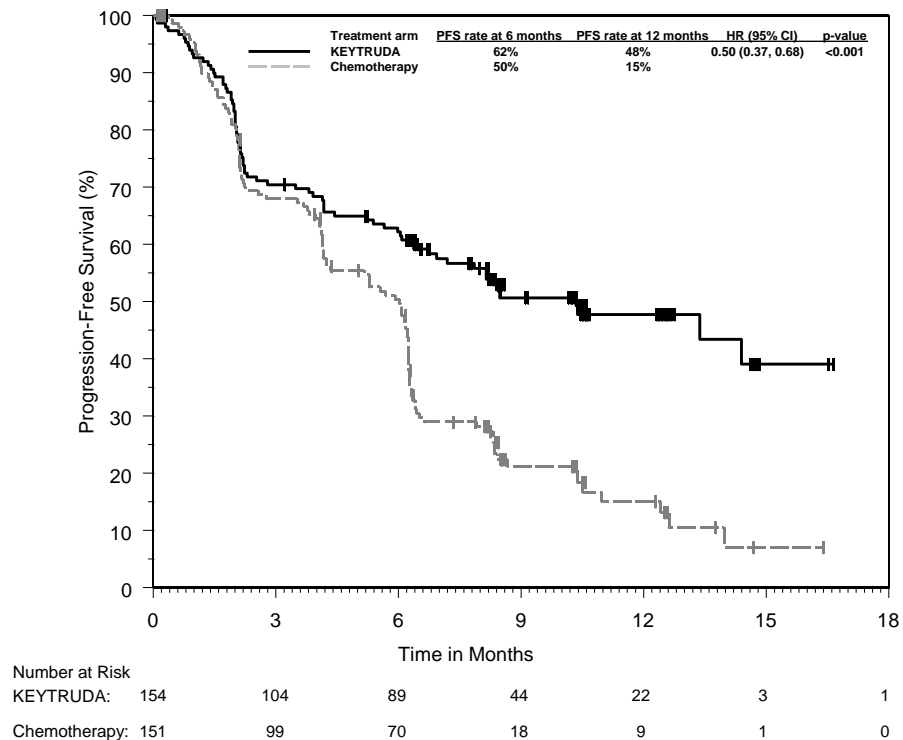
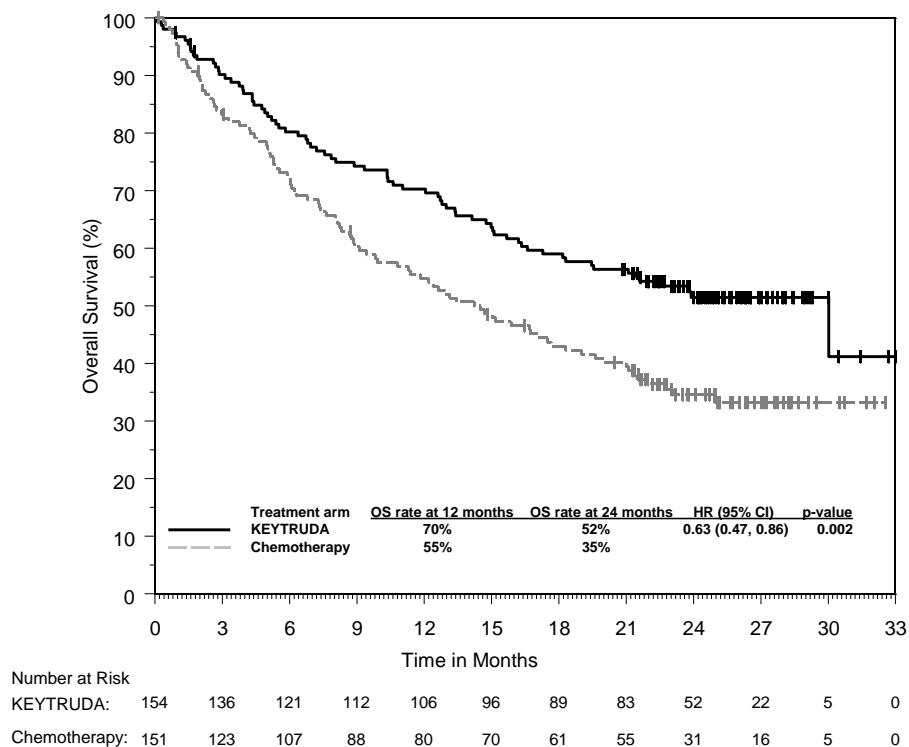


Figure 11: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-024 (Intent to Treat Population)



The improved benefit as assessed by PFS, OS, ORR, and response duration for KEYTRUDA as compared to chemotherapy in the population studied was associated with improvements in health-related quality of life (HRQoL). The change from baseline to Week 15 showed a meaningful improvement in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) C30 global health status/QoL score for patients receiving KEYTRUDA compared to chemotherapy (difference in LS means=7.82; 95% CI: 2.85, 12.79; two-sided p=0.002). The time to deterioration in the EORTC QLQ-LC13 composite endpoint of cough, dyspnea, and chest pain was prolonged for patients receiving KEYTRUDA compared to chemotherapy (HR=0.66; 95% CI: 0.44, 0.97; two-sided p=0.029), where deterioration is defined as a confirmed 10-point or greater score decrease from baseline in any one of these three symptoms.

KEYNOTE-010: Controlled trial of NSCLC patients previously treated with chemotherapy

The efficacy of KEYTRUDA was investigated in KEYNOTE-010, a multicenter, randomized, controlled trial. Key eligibility criteria were advanced NSCLC that had progressed following platinum-containing chemotherapy, and if appropriate, targeted therapy for ALK or EGFR mutations, and PD-L1 expression TPS of 1% or greater by a clinical trial assay version of 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. Patients were randomized (1:1:1) to receive 2 mg/kg (n=344) or 10 mg/kg (n=346) of KEYTRUDA every 3 weeks or 75 mg/m² of docetaxel every 3 weeks (n=343). Patients were treated with KEYTRUDA until disease progression or unacceptable toxicity. Assessment of tumor status was performed every 9 weeks.

Among the 1033 patients in KEYNOTE-010, baseline characteristics were: median age 63 years (42% age 65 or older); 61% male; 72% White and 21% Asian; and 34% and 66% with an ECOG performance status 0 and 1, respectively. Disease characteristics were squamous (21%) and non-squamous (70%); M1 (91%); brain metastases (15%); and the incidence of genomic aberrations was EGFR (8%) or ALK (1%). Prior therapy included platinum-doublet regimen (100%); patients received one (69%), or two or more (29%) prior therapies.

The primary efficacy outcome measures were OS and PFS as assessed by an independent review committee using RECIST 1.1. Secondary efficacy outcome measures were ORR and response duration. Table 10 summarizes key efficacy measures for the entire ITT population (TPS \geq 1%) and for the subgroup of patients with TPS \geq 50%. Kaplan-Meier curves for OS (TPS \geq 1% and TPS \geq 50%) are shown in Figures 12 and 13.

Table 10: Response to KEYTRUDA 2 or 10 mg/kg Every 3 Weeks in Previously Treated Patients with NSCLC in KEYNOTE-010

Endpoint	KEYTRUDA 2 mg/kg every 3 weeks	KEYTRUDA 10 mg/kg every 3 weeks	Docetaxel 75 mg/m ² every 3 weeks
TPS ≥ 1%			
Number of patients	344	346	343
OS			
Number (%) of patients with event	172 (50%)	156 (45%)	193 (56%)
Hazard ratio* (95% CI)	0.71 (0.58, 0.88)	0.61 (0.49, 0.75)	---
p-Value†	<0.001‡	<0.001‡	---
Median in months (95% CI)	10.4 (9.4, 11.9)	12.7 (10.0, 17.3)	8.5 (7.5, 9.8)
PFS§			
Number (%) of patients with event	266 (77%)	255 (74%)	257 (75%)
Hazard ratio* (95% CI)	0.88 (0.73, 1.04)	0.79 (0.66, 0.94)	---
p-Value†	0.068	0.005	---
Median in months (95% CI)	3.9 (3.1, 4.1)	4.0 (2.6, 4.3)	4.0 (3.1, 4.2)
Overall Response Rate§			
ORR %¶ (95% CI)	18% (14, 23)	18% (15, 23)	9% (7, 13)
Response Duration§,¶,Ⓟ			
Median in months (range)	Not reached (0.7+, 20.1+)	Not reached (2.1+, 17.8+)	6.2 (1.4+, 8.8+)
% ongoing	73%	72%	34%
TPS ≥ 50%			
Number of patients	139	151	152
OS			
Number (%) of patients with event	58 (42%)	60 (40%)	86 (57%)
Hazard ratio* (95% CI)	0.54 (0.38, 0.77)	0.50 (0.36, 0.70)	---
p-Value†	<0.001‡	<0.001‡	---
Median in months (95% CI)	14.9 (10.4, NA)	17.3 (11.8, NA)	8.2 (6.4, 10.7)
PFS§			
Number (%) of patients with event	89 (64%)	97 (64%)	118 (78%)
Hazard ratio* (95% CI)	0.58 (0.43, 0.77)	0.59 (0.45, 0.78)	---
p-Value†	<0.001‡	<0.001‡	---
Median in months (95% CI)	5.2 (4.0, 6.5)	5.2 (4.1, 8.1)	4.1 (3.6, 4.3)

Overall Response Rate[§]			
ORR % [†] (95% CI)	30% (23, 39)	29% (22, 37)	8% (4, 13)
Response Duration^{§, #, β}			
Median in months (range)	Not reached (0.7+, 16.8+)	Not reached (2.1+, 17.8+)	8.1 (2.1+, 8.8+)
% ongoing	76%	75%	33%

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

† Based on stratified log-rank test

‡ Statistically significant based on a pre-specified α level adjusted for multiplicity

§ Assessed by blinded independent central review (BICR) using RECIST 1.1

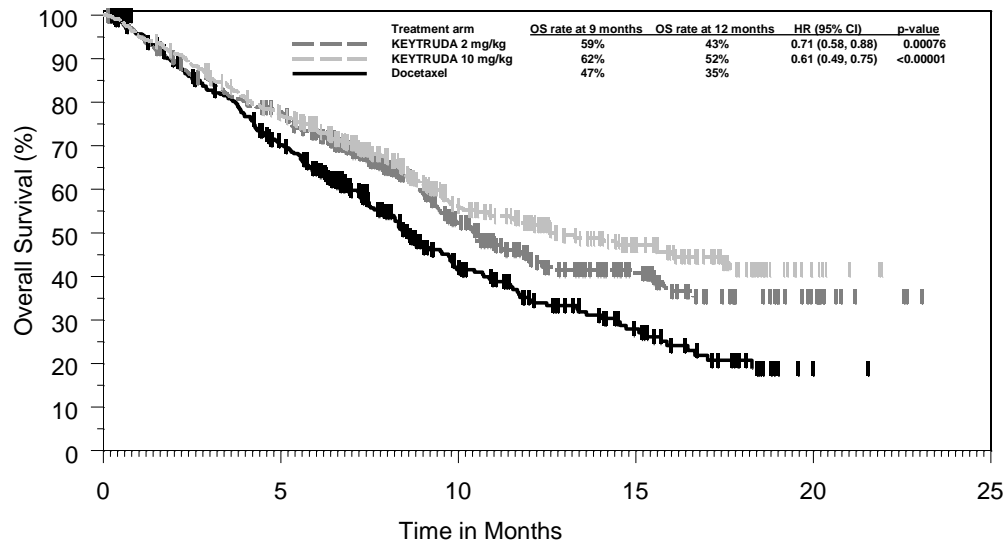
¶ All responses were partial responses

Based on patients with a best overall response as confirmed complete or partial response

▷ Includes 30, 31, and 2 patients with ongoing responses of 6 months or longer in the KEYTRUDA 2 mg/kg, KEYTRUDA 10 mg/kg, and docetaxel groups respectively

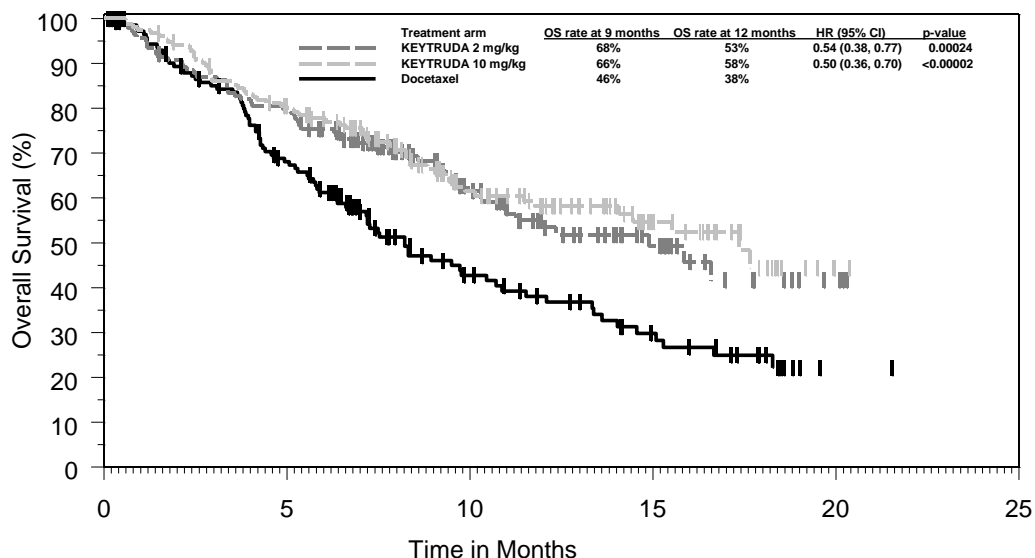
β Includes 22, 24, and 1 patients with ongoing responses of 6 months or longer in the KEYTRUDA 2 mg/kg, KEYTRUDA 10 mg/kg, and docetaxel groups respectively

Figure 12: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-010 (TPS \geq 1%, Intent to Treat Population)



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

Figure 13: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-010 (TPS ≥ 50%, Intent to Treat Population)



Number at Risk							
	0	5	10	15	20	25	
KEYTRUDA 2 mg/kg:	139	110	51	20	3	0	
KEYTRUDA 10 mg/kg:	151	115	60	25	1	0	
Docetaxel:	152	90	38	19	1	0	

Efficacy results were similar for the 2 mg/kg and 10 mg/kg KEYTRUDA arms. Efficacy results for OS were consistent regardless of the age of tumor specimen (new versus archival).

KEYNOTE-001: Open-label study in NSCLC patients previously treated with chemotherapy

The efficacy of KEYTRUDA was also investigated in a multicenter, open-label, randomized, dose-comparative cohort of KEYNOTE-001. Patients had advanced NSCLC that was PD-L1 positive, with progression of disease following treatment with platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations had disease progression on approved therapy for these aberrations prior to receiving KEYTRUDA. The trial excluded 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. Patients were randomized to receive 10 mg/kg of KEYTRUDA every 2 (n=69) or 3 (n=87) weeks until disease progression or unacceptable toxicity. Assessment of tumor status was performed every 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.

The prevalence of patients with a PD-L1 expression TPS greater than or equal to 50% among screened patients with NSCLC as ascertained retrospectively by the companion diagnostic PD-L1

IHC 22C3 pharmDx™ kit was 26%. Among the randomized patients with tumor samples evaluable for PD-L1 expression, 61 had TPS greater than or equal to 50%. The baseline characteristics for this population included: median age 60 years (34% age 65 or older); 61% male; 79% White; and 34% and 64% with an ECOG performance status 0 and 1, respectively. Disease characteristics were squamous and non-squamous (21% and 75%, respectively); M1 (98%); brain metastases (11%); and one (25%), two (31%), or three or more (44%) prior therapies. The mutation status among patients was EGFR (10%), ALK (0%), or Kras (16%).

Efficacy results for NSCLC patients treated with 10 mg/kg every 2 or 3 weeks in KEYNOTE-001 are summarized in Table 11.

Table 11: Response to KEYTRUDA 10 mg/kg Every 2 or 3 Weeks in Previously Treated NSCLC Patients with PD-L1 Expression TPS ≥ 50% (n=61)

Endpoint	
Best Overall Response*	
ORR %, (95% CI)	43% (30, 56)
Complete response	2%
Partial response	41%
Response Duration†	
Median in months (range)	Not reached (2.1+, 13.4+)
% ongoing	65%‡
Time to Response‡	
Median in months (range)	2.1 (1.4, 6.2)
PFS§	
Median in months (95% CI)	6.3 (2.1, 10.7)
6-month PFS rate	53%
OS§	
12-month OS rate	60%

* Based on all patients treated (n=61), with assessment by independent review and RECIST 1.1

† Based on patients (n=26) with a confirmed response by independent review

‡ Includes 17 patients with ongoing responses of 6 months or longer

§ Based on all treated patients (n=61)

Similar ORR results were observed in another group of patients (n=25) with TPS greater than or equal to 50% receiving KEYTRUDA at a dose of 2 mg/kg every 3 weeks in KEYNOTE-001.

Head and Neck Cancer

KEYNOTE-048: Controlled trial of first-line monotherapy or combination therapy in HNSCC patients naïve to treatment in the recurrent or metastatic setting

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

- KEYTRUDA 200 mg every 3 weeks
- KEYTRUDA 200 mg every 3 weeks, carboplatin AUC 5 mg/mL/min every 3 weeks or cisplatin 100 mg/m² every 3 weeks, and 5-FU 1000 mg/m²/d 4 days continuous every 3 weeks (maximum of 6 cycles of platinum and 5-FU)
- Cetuximab 400 mg/m² load then 250 mg/m² once weekly, carboplatin AUC 5 mg/mL/min every 3 weeks or cisplatin 100 mg/m² every 3 weeks, and 5-FU 1000 mg/m²/d 4 days continuous every 3 weeks (maximum of 6 cycles of platinum and 5-FU)

Treatment with KEYTRUDA continued until RECIST 1.1-defined progression of disease as determined by the investigator, unacceptable toxicity, or a maximum of 24 months. Administration of KEYTRUDA was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Assessment of tumor status was performed at Week 9 and then every 6 weeks for the first year, followed by every 9 weeks through 24 months.

A total of 882 patients were randomized; 301 patients to the KEYTRUDA monotherapy arm, 281 patients to the KEYTRUDA plus chemotherapy arm, and 300 patients to the standard treatment arm. The study population characteristics were: median age of 61 years (range: 20 to 94); 36% age 65 or older; 83% male; 73% White and 20% Asian; 61% ECOG PS of 1; and 79% were former/current smokers. Disease characteristics were: 22% HPV positive, 85%, 43%, and 23% had

PD-L1 expression defined as CPS \geq 1, CPS \geq 20, and TPS \geq 50%, respectively, and 95% had Stage IV disease (Stage IVa 19%, Stage IVb 6%, and Stage IVc 70%).

The primary efficacy outcome measures were OS and PFS (assessed by BICR according to RECIST 1.1). ORR, as assessed by BICR according to RECIST 1.1, was a secondary outcome measure. The trial demonstrated a statistically significant improvement in OS for patients randomized to KEYTRUDA in combination with chemotherapy compared to standard treatment. OS for patients randomized to KEYTRUDA monotherapy was non-inferior compared to standard treatment. Tables 12 and 14 and Figures 14 and 15 describe key efficacy results for KEYTRUDA in KEYNOTE-048.

Table 12: Efficacy Results for KEYTRUDA plus Chemotherapy in KEYNOTE-048 (CPS≥ 1)

Endpoint	KEYTRUDA Platinum Chemotherapy 5-FU n=242	Standard Treatment* n=235
OS		
Number (%) of patients with event	177 (73%)	213 (91%)
Median in months (95% CI)	13.6 (10.7, 15.5)	10.4 (9.1, 11.7)
Hazard ratio† (95% CI)	0.65 (0.53, 0.80)	
p-Value‡	0.00002	
PFS		
Number of patients with event (%)	212 (88%)	221 (94%)
Median in months (95% CI)	5.1 (4.7, 6.2)	5.0 (4.8, 6.0)
Hazard ratio† (95% CI)	0.84 (0.69, 1.02)	
p-Value‡	0.0369	
ORR		
Objective response rate§ (95% CI)	36% (30.3, 42.8)	36% (29.6, 42.2)
Complete response	7%	3%
Partial response	30%	33%
p-Value¶	0.4586	
Duration of Response		
Median in months (range)	6.7 (1.6+, 39.0+)	4.3 (1.2+, 31.5+)
% with duration ≥ 6 months	54%	34%

* Cetuximab, platinum, and 5-FU

† Based on the stratified Cox proportional hazard model

‡ Based on stratified log-rank test

§ Response: Best objective response as confirmed complete response or partial response

¶ Based on Miettinen and Nurminen method stratified by ECOG (0 vs. 1), HPV status (positive vs. negative), and PD-L1 status (strongly positive vs. not strongly positive)

Table 13: OS by PD-L1 Expression*

	CPS ≥ 1		CPS ≥ 20	
	KEYTRUDA Platinum Chemotherapy 5-FU n=242	Standard Treatment† n=235	KEYTRUDA Platinum Chemotherapy 5-FU n=126	Standard Treatment† n=110
Number of events (%)	164 (68%)	190 (81%)	79 (63%)	85 (77%)
Median in months (95% CI)	13.6 (10.7, 15.5)	10.4 (9.1, 11.7)	14.7 (10.3, 19.3)	11.0 (9.2, 13.0)
Hazard ratio‡ (95% CI)	0.71 (0.57, 0.88)		0.69 (0.51, 0.94)	
p-Value§	0.0007		0.0098	

* Results at a pre-specified interim analysis

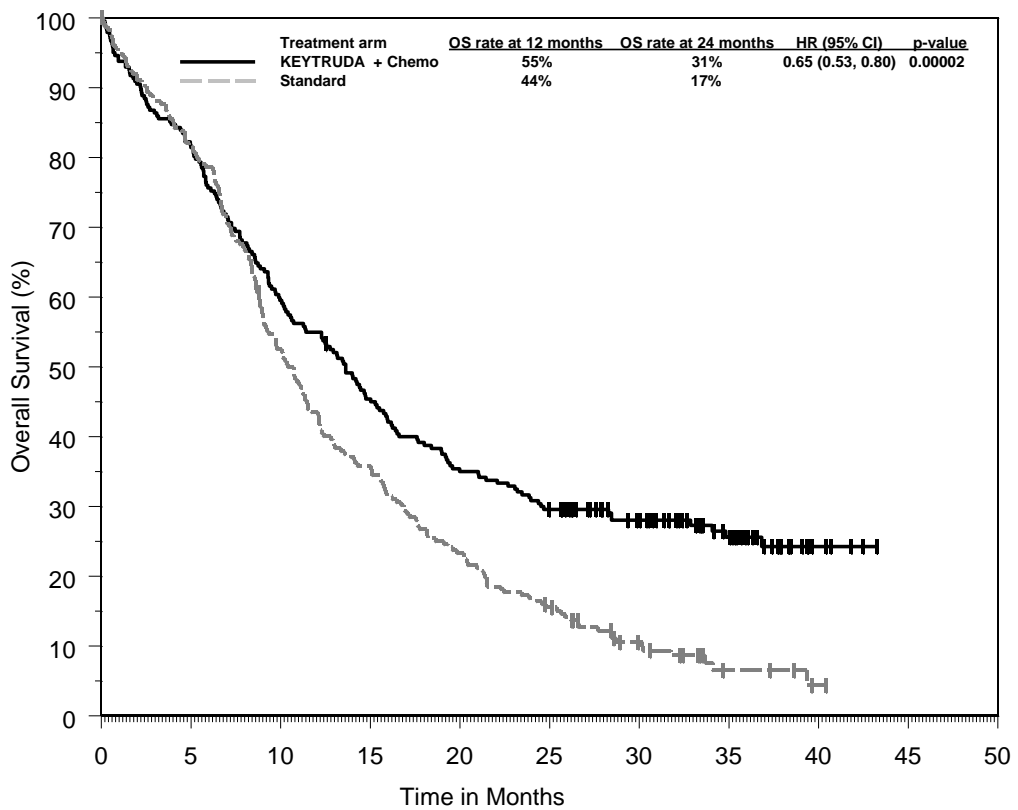
† Cetuximab, platinum, and 5-FU

‡ Hazard ratio (compared to standard treatment) based on the stratified Cox proportional hazard model

§ Based on stratified log-rank test

The OS HRs at final analysis with a median follow-up of 11.4 months were similar to those obtained at the pre-specified interim analysis and in addition, demonstrated a statistically significant improvement in OS for the subgroup of patients with PD-L1 CPS ≥ 1 and CPS ≥ 20: ITT (0.72, 95% CI: 0.60, 0.87), CPS ≥ 1 (0.65, 95% CI: 0.53, 0.80), CPS ≥ 20 (0.60, 95% CI: 0.45, 0.82).

Figure 14: Kaplan-Meier Curve for Overall Survival for KEYTRUDA plus Chemotherapy in KEYNOTE-048 (CPS \geq 1)*



Number at Risk	0	5	10	15	20	25	30	35	40	45	50
KEYTRUDA + Chemo:	242	197	144	109	84	70	52	29	5	0	0
Standard:	235	191	122	83	54	35	17	5	1	0	0

*Median follow-up of 11.5 months at protocol-specified final analysis.

Table 14: Efficacy Results for KEYTRUDA as Monotherapy in KEYNOTE-048 (CPS≥ 1)

Endpoint	KEYTRUDA n=257	Standard Treatment* n=255
OS		
Number (%) of patients with event	197 (77%)	229 (90%)
Median in months (95% CI)	12.3 (10.8, 14.3)	10.3 (9.0, 11.5)
Hazard ratio† (95% CI)	0.74 (0.61, 0.90)	
p-Value‡	0.00133	
PFS		
Number of patients with event (%)	228 (89%)	237 (93%)
Median in months (95% CI)	3.2 (2.2, 3.4)	5.0 (4.8, 6.0)
Hazard ratio† (95% CI)	1.13 (0.94, 1.36)	
p-Value§	0.8958	
ORR		
Objective response rate¶ (95% CI)	19% (14.5, 24.4)	35% (29.1, 41.1)
Complete response	5%	3%
Partial response	14%	32%
p-Value#	1.0000	
Duration of Response		
Median in months (range)	23.4 (1.5+, 43.0+)	4.5 (1.2+, 38.7+)
% with duration ≥ 6 months	81%	36%

* Cetuximab, platinum, and 5-FU

† Based on the stratified Cox proportional hazard model

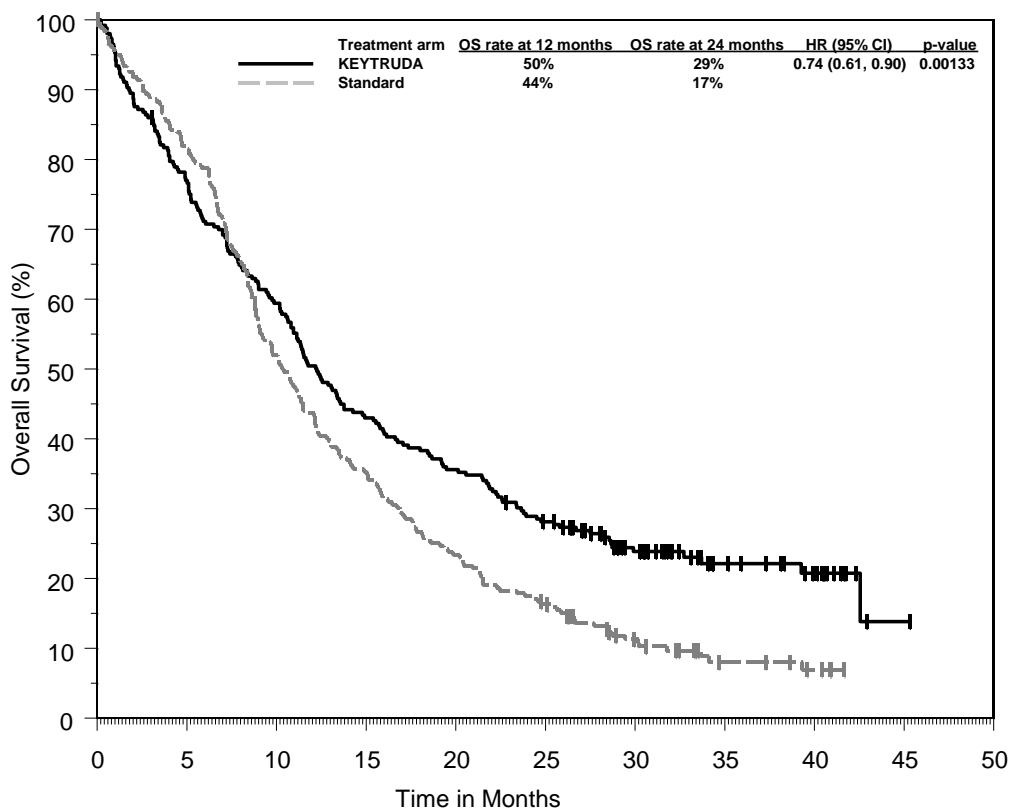
‡ Non-inferiority p-Value

§ Based on stratified log-rank test

¶ Response: Best objective response as confirmed complete response or partial response

Based on Miettinen and Nurminen method stratified by ECOG (0 vs. 1), HPV status (positive vs. negative), and PD-L1 status (strongly positive vs. not strongly positive)

Figure 15: Kaplan-Meier Curve for Overall Survival for KEYTRUDA as Monotherapy in KEYNOTE-048 (CPS ≥ 1)*



Number at Risk	0	5	10	15	20	25	30	35	40	45	
KEYTRUDA:	257	197	152	110	91	70	43	21	13	1	0
Standard:	255	207	131	89	59	40	21	9	5	0	0

*Median follow-up of 11.4 months at protocol-specified final analysis.

Additional OS analyses based on PD-L1 expression (CPS ≥ 1 and CPS ≥ 20) were performed in KEYNOTE-048. The trial demonstrated a statistically significant improvement in OS for patients randomized to KEYTRUDA monotherapy compared to standard treatment for PD-L1 expression CPS ≥ 1 and CPS ≥ 20. OS for patients who had PD-L1 CPS ≥ 1 or CPS ≥ 20 for KEYTRUDA monotherapy compared to standard treatment is summarized in Table 15.

Table 15: OS by PD-L1 Expression

	CPS ≥ 1		CPS ≥ 20	
	KEYTRUDA n=257	Standard Treatment* n=255	KEYTRUDA n=133	Standard Treatment* n=122

Number of events (%)	177 (69%)	206 (81%)	82 (62%)	95 (78%)
Median in months (95% CI)	12.3 (10.8, 14.9)	10.3 (9.0, 11.5)	14.9 (11.6, 21.5)	10.7 (8.8, 12.8)
Hazard ratio [†] (95% CI)	0.78 (0.64, 0.96)		0.61 (0.45, 0.83)	
p-Value [‡]	0.0085		0.0007	

* Cetuximab, platinum, and 5-FU

† Hazard ratio (compared to standard treatment) based on the stratified Cox proportional hazard model

‡ Based on stratified log-rank test

The final OS analysis was performed for patients with CPS ≥ 1 with a median follow-up of 11.4 months from the pre-specified interim analysis. Median OS was 12.3 months (95% CI: 10.8, 14.3) for KEYTRUDA as a single agent and 10.3 months (95% CI: 9.0, 11.5) for cetuximab in combination with chemotherapy, with an HR of 0.74 (95% CI: 0.61, 0.90).

The final OS analysis was performed for patients with CPS ≥ 20 with a median follow-up of 12.2 months from the pre-specified interim analysis. Median OS was 14.8 months (95% CI: 11.5, 20.6) for KEYTRUDA as a single agent and 10.7 months (95% CI: 8.8, 12.8) for cetuximab in combination with chemotherapy, with an HR of 0.58 (95% CI: 0.44, 0.78).

In an exploratory subgroup analysis for patients with CPS 1-19 HNSCC, the median OS was 10.8 months (95% CI: 9.0, 12.6) for KEYTRUDA as a single agent and 10.1 months (95% CI: 8.7, 12.1) for cetuximab in combination with chemotherapy, with an HR of 0.90 (95% CI: 0.68, 1.18). The final OS analysis was performed for patients with CPS 1-19 with a median follow-up of 10.3 months. At the final analysis, the median OS was 10.8 months (95% CI: 9.0, 12.6) for KEYTRUDA as a single agent and 10.1 months (95% CI: 8.7, 12.1) for cetuximab in combination with chemotherapy, with an HR of 0.86 (95% CI: 0.66, 1.12).

Classical Hodgkin Lymphoma

KEYNOTE-204: Controlled study in patients with relapsed or refractory classical Hodgkin Lymphoma (cHL)

KEYNOTE-204 was a randomized, open-label, active-controlled trial conducted in 304 patients with relapsed or refractory cHL. Patients with active, non-infectious pneumonitis, an allogeneic HSCT within the past 5 years (or >5 years but with symptoms of GVHD), active autoimmune disease, a medical condition that required immunosuppression, or an active infection requiring systemic therapy were ineligible for the trial. Randomization was stratified by prior auto-SCT (yes vs. no) and disease

status after frontline therapy (primary refractory vs. relapse less than 12 months after completion vs. relapse 12 months or more after completion). Patients were randomized (1:1) to one of the following treatment arms:

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

Patients received KEYTRUDA 200 mg intravenously every 3 weeks until unacceptable toxicity or documented disease progression. Disease assessment was performed every 12 weeks. The major efficacy outcome measures were PFS and ORR as assessed by BICR according to the 2007 revised International Working Group (IWG) criteria.

Among KEYNOTE-204 patients, the baseline characteristics were median age 35 years (16% age 65 or older); 57% male; 77% White; and 61% and 38% had an ECOG performance status 0 and 1, respectively. The median number of prior lines of therapy administered for the treatment of cHL was 2 (range 1 to 11). Forty-two percent were refractory to the last prior therapy and 29% had primary refractory disease. Thirty-seven percent had undergone prior auto-HSCT, 5% had received prior BV, and 39% had prior radiation therapy.

The median follow-up time for 151 patients treated with KEYTRUDA was 24.9 months (range: 1.8 to 42.0 months). Efficacy results are summarized in Table 16.

Table 16: Efficacy Results in Patients with Refractory or Relapsed Classical Hodgkin Lymphoma

Endpoint	KEYTRUDA 200 mg every 3 weeks n=151	Brentuximab vedotin 1.8 mg/kg every 3 weeks n=153
PFS		
Number of patients with event (%)	81 (54%)	88 (58%)
Median in months (95% CI)	13.2 (10.9, 19.4)	8.3 (5.7, 8.8)
Hazard ratio* (95% CI)	0.65 (0.48, 0.88)	
p-Value†	0.0027	
Objective Response Rate		
ORR‡ (95% CI)	66% (57.4, 73.1)	54% (46.0, 62.3)
Complete response	25%	24%
Partial response	41%	30%
p-Value§	0.0225	
Response Duration		
Median in months (range)	20.7 (0.0+, 33.2+)	13.8 (0.0+, 33.9+)
Number (%¶) of patients with duration ≥ 6 months	66 (80%)	34 (60%)
Number (%¶) of patients with duration ≥ 12 months	48 (62%)	23 (50%)
Number (%¶) of patients with duration ≥ 24 months	11 (47%)	7 (43%)

* Based on the stratified Cox proportional hazard model

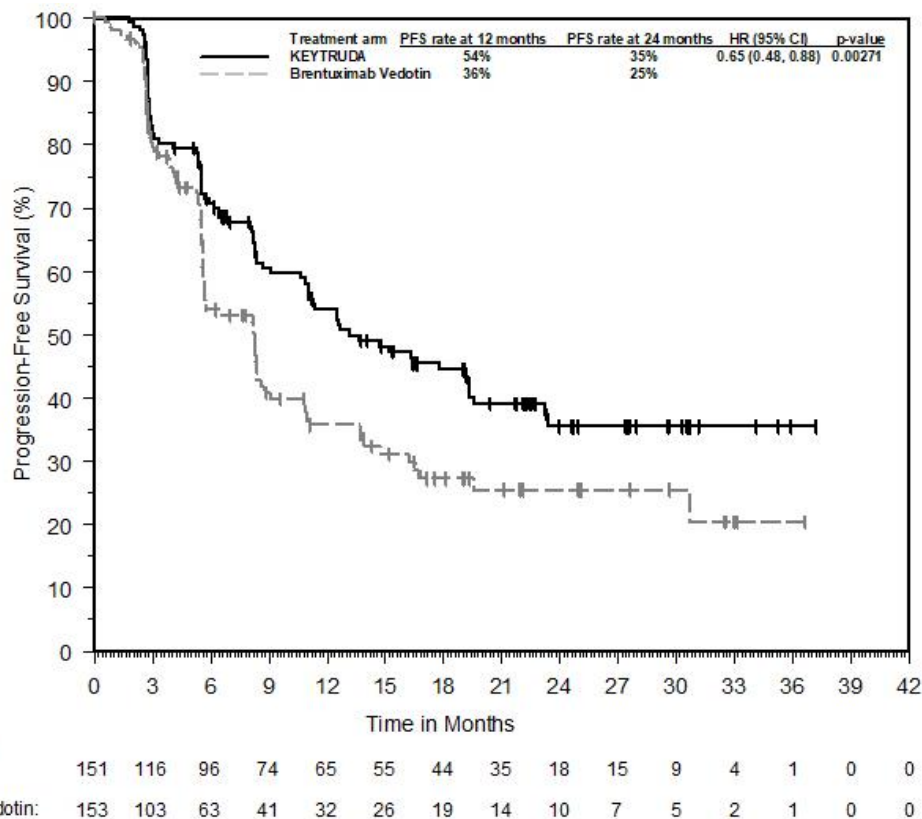
† Based on stratified log-rank test

‡ Based on patients with best overall response as complete response or partial response

§ Based on Miettinen and Nurminen method stratified by prior auto-SCT and disease status

¶ Based on Kaplan-Meier estimation

Figure 16: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-204



Patient-reported outcomes (PROs) were assessed using EORTC QLQ-C30. A prolonged time to deterioration in EORTC QLQ C30 global health status/QoL was observed for patients treated with pembrolizumab compared to BV (HR 0.40; 95% CI: 0.22-0.74). Over 24 weeks of follow-up, patients treated with pembrolizumab had an improvement in global health status/QoL compared to BV which showed a decline (difference in Least Square (LS) means=8.60; 95% CI: 3.89, 13.31; nominal two-sided $p=0.0004$). These results should be interpreted in the context of the open-label study design and therefore taken cautiously.

KEYNOTE-013 and KEYNOTE-087: Open-label studies in patients with refractory classical Hodgkin Lymphoma, or those who have relapsed after greater than or equal to 3 prior lines of therapy

The efficacy of KEYTRUDA was investigated in 241 patients with refractory classical Hodgkin Lymphoma, or who have relapsed after 3 or more prior lines of therapy, enrolled in two multicenter, non-randomized, open-label studies (KEYNOTE-013 and KEYNOTE-087). Both studies included patients regardless of PD-L1 expression. Patients with active, non-infectious pneumonitis, an allogeneic hematopoietic stem cell transplant within the past 5 years (or greater than 5 years but with GVHD), active autoimmune disease or a medical condition that required immunosuppression were

ineligible for either trial. Patients received KEYTRUDA 10 mg/kg every 2 weeks (n=31) or 200 mg every 3 weeks (n=210) until unacceptable toxicity or documented disease progression. Response was assessed using the revised lymphoma criteria by PET CT scans, with the first planned post-baseline assessment at Week 12. 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. Secondary efficacy outcome measures were PFS and OS.

Among KEYNOTE-013 patients, the baseline characteristics were median age 32 years (6% age 65 or older); 58% male; 94% White; and 45% and 55% had an ECOG performance status 0 and 1, respectively. The median number of prior lines of therapy administered for the treatment of cHL was 5 (range 2 to 15). Eighty-seven percent were refractory to at least one prior therapy, including 39% who were refractory to first-line therapy. Seventy-four percent of patients had received Auto-SCT, 26% were transplant ineligible; and 42% of patients had prior radiation therapy. Disease subtypes were 97% nodular sclerosis and 3% mixed cellularity.

Among KEYNOTE-087 patients, the baseline characteristics were median age 35 years (9% age 65 or older); 54% male; 88% White; and 49% and 51% had an ECOG performance status 0 and 1, respectively. The median number of prior lines of therapy administered for the treatment of cHL was 4 (range 1 to 12). Eighty-one percent were refractory to at least one prior therapy, including 34% who were refractory to first-line therapy. Sixty-one percent of patients had received Auto-SCT, 38% were transplant ineligible; 17% had no prior brentuximab vedotin use; and 37% of patients had prior radiation therapy. Disease subtypes were 80% nodular sclerosis, 11% mixed cellularity, 4% lymphocyte-rich and 2% lymphocyte-depleted.

Efficacy results are summarized in Table 17.

Table 17: Efficacy Results in Patients with Refractory or Relapsed Classical Hodgkin

Lymphoma

	KEYNOTE-013	KEYNOTE-087
Endpoint	n=31	n=210
Objective Response Rate*		
ORR %, (95% CI)	58% (39.1, 75.5)	71% (64, 77)
Complete remission	19%	28%
Partial remission	39%	43%
Response Duration*		
Median in months (range)	Not reached (0.0+, 26.1+)†	16.6 (0.0+, 39.1+)‡
% with duration ≥ 6-months	80%§	74%¶
% with duration ≥ 12-months	70%#	59% ^p
Time to Response		
Median in months (range)	2.8 (2.4, 8.6) †	2.8 (2.1, 16.5) ‡
PFS*		
Median in months (95% CI)	11.4 (4.9, 27.8)	13.6 (11.1, 16.7)
6-month PFS rate	66%	72%
9-month PFS rate	---	61%
12-month PFS rate	48%	52%
OS		
6-month OS rate	100%	99.5%
12-month OS rate	87.1%	96.1%

* Assessed by blinded independent central review according to the 2007 revised International Working Group (IWG) criteria

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

‡ Based on patients (n=149) with a response by independent review

§ Based on Kaplan-Meier estimation; includes 9 patients with responses of 6 months or longer

¶ Based on Kaplan-Meier estimation; includes 84 patients with responses of 6 months or longer

- # Based on Kaplan-Meier estimation; includes 7 patients with responses of 12 months or longer
- ▷ Based on Kaplan-Meier estimation; includes 60 patients with responses of 12 months or longer

Urothelial Carcinoma

KEYNOTE-052: Open-label trial in urothelial carcinoma patients ineligible for cisplatin-containing chemotherapy

The safety and efficacy of pembrolizumab were investigated in KEYNOTE-052, a multicenter, open-label study for the treatment of locally advanced or metastatic urothelial carcinoma in patients who were not eligible for cisplatin-containing chemotherapy. Patients received pembrolizumab at a dose of 200 mg every 3 weeks until unacceptable toxicity or disease progression. Treatment could continue beyond progression if the patient was clinically stable and was considered to be deriving clinical benefit by the investigator. Patients without disease progression could be treated for up to 24 months. The study excluded patients with autoimmune disease or a medical condition that required immunosuppression. Assessment of tumour status was performed at 9 weeks after the first dose, then every 6 weeks through the first year, followed by every 12 weeks thereafter.

Among 370 patients with urothelial carcinoma who were not eligible for cisplatin-containing chemotherapy, baseline characteristics were: median age 74 years (82% age 65 or older); 77% male; and 89% White and 7% Asian. Eighty-eight percent had M1 disease and 12% had M0 disease. Eighty-five percent of patients had visceral metastases, including 21% with liver metastases. Reasons for cisplatin ineligibility included: baseline creatinine clearance of <60 mL/min (50%), ECOG performance status of 2 (32%), ECOG performance status of 2 and baseline creatinine clearance of <60 mL/min (9%), and other (Class III heart failure, Grade 2 or greater peripheral neuropathy, and Grade 2 or greater hearing loss; 9%). Ninety percent of patients were treatment naïve, and 10% received prior adjuvant or neoadjuvant platinum-based chemotherapy. Eighty-one percent had a primary tumour in the lower tract, and 19% of patients had a primary tumour in the upper tract.

Among the 370 patients, 30% (n=110) had tumors that expressed PD-L1 with a combined positive score (CPS) of greater than or equal to 10. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx™ Kit. The baseline characteristics of these 110 patients were: median age 73 years, 68% male, and 87% White. Eighty-two percent had M1 disease, and 18% had M0 disease. Eighty-one percent had a primary tumor in the lower tract, and 18% of patients had a primary tumor in the upper tract. Seventy-six percent of patients had visceral metastases, including 11% with liver metastases. Reasons for cisplatin ineligibility included: 45% with baseline creatinine clearance of <60 mL/min,

37% with ECOG performance status of 2, 10% with ECOG 2 and baseline creatinine clearance of <60 mL/min, and 8% with other reasons (Class III heart failure, Grade 2 or greater peripheral neuropathy, and Grade 2 or greater hearing loss). Ninety percent of patients were treatment naïve, and 10% received prior adjuvant or neoadjuvant platinum-based chemotherapy.

The primary efficacy outcome measure was ORR as assessed by BICR using RECIST 1.1. Secondary efficacy outcome measures were duration of response, PFS, and OS. Table 18 summarises the key efficacy measures for the study population at the final analysis based on a median follow-up time of 11.4 months (range: 0.1, 41.2 months) for all patients.

Table 18: Response to Pembrolizumab 200 mg every 3 Weeks in Patients with Urothelial Carcinoma Ineligible for Cisplatin-Containing Chemotherapy in KEYNOTE-052

Endpoint	n=370
Objective Response Rate*	
ORR %, (95% CI)	29% (24, 34)
Disease control rate [†]	47%
Complete response	9%
Partial response	20%
Stable disease	18%
Response Duration	
Median in months (range)	30.1 (1.4+, 35.9+)
% with duration ≥ 6- months	81% [‡]
Time to Response	
Median in months (range)	2.1 (1.3, 9.0)
PFS*	
Median in months (95% CI)	2.2 (2.1, 3.4)
6-month PFS rate	33%
12-month PFS rate	22%
OS*	
Median in months (95% CI)	11.3 (9.7, 13.1)

6-month OS rate	67%
12-month OS rate	47%

- * Assessed by BICR using RECIST 1.1
- † Based on best response of stable disease or better
- ‡ Based on Kaplan-Meier estimates; includes 84 patients with response of 6 months or longer

An analysis was performed in KEYNOTE-052 in patients who had tumors that expressed PD-L1 with a CPS < 10 (n=251; 68%) or ≥ 10 (n=110; 30%) based on the PD-L1 IHC 22C3 pharmDx™ Kit (see Table 19).

Table 19: ORR and OS by PD-L1 Expression

Endpoint	CPS < 10 N=251	CPS ≥ 10 N=110
Objective Response Rate*		
ORR %, (95% CI)	20% (16, 26)	47% (38, 57)
OS		
Median in months (95% CI)	10 (8, 12)	19 (12, 29)
12-month OS rate	41%	61%

* BICR using RECIST 1.1

KEYNOTE-045: Controlled trial in urothelial carcinoma patients previously treated with platinum-containing chemotherapy

The safety and efficacy of pembrolizumab were evaluated in KEYNOTE-045, a multicenter, randomized (1:1), controlled study for the treatment of locally advanced or metastatic urothelial carcinoma in patients with disease progression on or after platinum-containing chemotherapy. Patients must have received first line platinum-containing regimen for locally advanced/metastatic disease or as neoadjuvant/adjuvant treatment, with recurrence/progression ≤ 12 months following completion of therapy. Patients were randomized (1:1) 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/m² (n=84), docetaxel 75 mg/m² (n=84), or vinflunine 320 mg/m² (n=87). Patients were treated with pembrolizumab until unacceptable toxicity or disease progression. Treatment could continue beyond progression if the patient was clinically stable and was considered to be deriving clinical benefit by the investigator. Patients without disease progression could be treated for up to 24 months. The study excluded patients with autoimmune

disease, a medical condition that required immunosuppression and patients with more than 2 prior lines of systemic chemotherapy for metastatic urothelial cancer. Patients with an ECOG performance status of 2 had to have a hemoglobin \geq 10 g/dL, could not have liver metastases, and must have received the last dose of their last prior chemotherapy regimen \geq 3 months prior to enrollment. Assessment of tumour status was performed at 9 weeks after the first dose, then every 6 weeks through the first year, followed by every 12 weeks thereafter.

Among the 542 randomized patients in KEYNOTE-045, baseline characteristics were: median age 66 years (range: 26 to 88); 58% age 65 or older; 74% male; 72% White and 23% Asian; 56% ECOG performance status of 1 and 1% ECOG performance status of 2; 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 tumour in the lower tract and 14% had a primary tumour 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 prior systemic regimens in the metastatic setting. Seventy-six percent of patients received prior cisplatin, 23% had prior carboplatin, and 1% was treated with other platinum-based regimens.

The primary efficacy outcomes were OS and PFS as assessed by BICR using RECIST v1.1. Secondary outcome measures were ORR (as assessed by BICR using RECIST v1.1) and duration of response. Table 20 summarises the key efficacy measures for the ITT population at the final analysis. The Kaplan-Meier curve based on the final analysis for OS is shown in Figure 17. The study demonstrated statistically significant improvements in OS and ORR for patients randomized to pembrolizumab as compared to chemotherapy. There was no statistically significant difference between pembrolizumab and chemotherapy with respect to PFS.

Table 20: Response to Pembrolizumab 200 mg every 3 Weeks in Patients with Urothelial Carcinoma Previously Treated with Chemotherapy in KEYNOTE-045

Endpoint	Pembrolizumab 200 mg every 3 weeks n=270	Chemotherapy n=272
OS		
Number (%) of patients with event	200 (74%)	219 (81%)
Hazard ratio* (95% CI)	0.70 (0.57, 0.85)	
p-Value†	<0.001	
Median in months (95% CI)	10.1 (8.0, 12.3)	7.3 (6.1, 8.1)
PFS‡		

Number (%) of patients with event	233 (86%)	237 (87%)
Hazard ratio* (95% CI)	0.96 (0.79, 1.16)	
p-Value†	0.313	
Median in months (95% CI)	2.1 (2.0, 2.2)	3.3 (2.4, 3.6)
Objective Response Rate‡		
ORR % (95% CI)	21% (16, 27)	11% (8, 15)
Complete response	9%	3%
Partial response	12%	8%
Stable disease	17%	34%
p-Value§	<0.001	
Response Duration¶ ·¶		
Median in months (range)	Not reached (1.6+, 30.0+)	4.4 (1.4+, 29.9+)
Number (%#) of patients with duration ≥ 6 months	46 (84%)	8 (47%)
Number (%#) of patients with duration ≥ 12 months	35 (68%)	5 (35%)

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

† Based on stratified log-rank test

‡ Assessed by BICR using RECIST 1.1

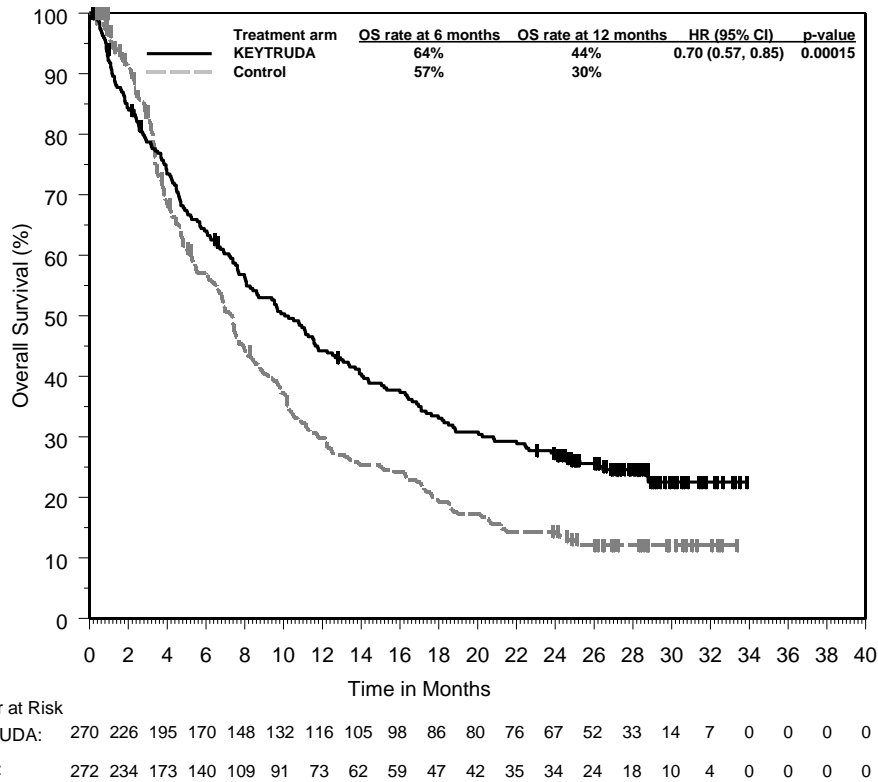
§ Based on method by Miettinen and Nurminen

¶ Based on patients with a best overall response as confirmed complete or partial response

Based on Kaplan-Meier estimation

In the first 2 months, a higher number of deaths was observed in the pembrolizumab arm (43 deaths) compared to the chemotherapy arm (24 deaths).

Figure 17: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-045 (Intent to Treat Population)



An analysis was performed in KEYNOTE-045 in patients who had PD-L1 Combined Positive Score (CPS) < 10 [pembrolizumab: n=186 (69%) vs. chemotherapy: n= 176 (65%)] or ≥ 10 [pembrolizumab: n=74 (27%) vs. chemotherapy: n= 90 (33%)] in both pembrolizumab- and chemotherapy-treated arms (see Table 21).

Table 21: OS by PD-L1 Expression

PD-L1 Expression	Pembrolizumab	Chemotherapy	
	OS by PD-L1 Expression		Hazard
	Number of Events (number of patients)*		Ratio† (95% CI)
CPS < 10	140 (186)	144 (176)	0.75 (0.59, 0.95)
CPS ≥ 10	53 (74)	72 (90)	0.55 (0.37, 0.81)

* Based on final analysis

† Hazard ratio (pembrolizumab compared to chemotherapy) based on the stratified Cox proportional hazard model

Patient-reported outcomes (PROs) were assessed using EORTC QLQ-C30. A prolonged time to deterioration in EORTC QLQ-C30 global health status/QoL was observed for patients treated with pembrolizumab compared to investigator's choice chemotherapy (HR 0.70; 95% CI 0.55-0.90). Over

15 weeks of follow-up, patients treated with pembrolizumab had stable global health status/QoL, while those treated with investigator's choice chemotherapy had a decline in global health status/QoL. These results should be interpreted in the context of the open-label study design and therefore taken cautiously.

Esophageal Cancer

KEYNOTE-590: First-line treatment of locally advanced unresectable or metastatic Esophageal Cancer/Gastroesophageal Junction

The efficacy of KEYTRUDA was investigated in KEYNOTE-590, a multicenter, randomized, placebo-controlled trial that enrolled 749 patients as a first-line treatment in patients with locally advanced unresectable or metastatic carcinoma of the esophagus and gastroesophageal junction (Siewert type I). All patients were required to have tumor specimens for PD-L1 testing at a central laboratory; PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx™ kit. Patients with active autoimmune disease, a medical condition that required immunosuppression, or known HER-2 positive GEJ adenocarcinoma patients were ineligible. Randomization was stratified by tumor histology (squamous cell carcinoma vs. adenocarcinoma), geographic region (Asia vs. ex-Asia), and ECOG performance status (0 vs. 1).

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

- KEYTRUDA 200 mg on Day 1 of each three-week cycle in combination with cisplatin 80 mg/m² IV on Day 1 of each three-week cycle for up to six cycles and 5-FU 800 mg/m² IV per day on Day 1 to Day 5 of each three-week cycle, or per local standard for 5-FU administration, for up to 24 months.
- Placebo on Day 1 of each three-week cycle in combination with cisplatin 80 mg/m² IV on Day 1 of each three-week cycle for up to six cycles and 5-FU 800 mg/m² IV per day on Day 1 to Day 5 of each three-week cycle, or per local standard for 5-FU administration, for up to 24 months.

Treatment with KEYTRUDA or chemotherapy continued until unacceptable toxicity or disease progression. Patients randomized to KEYTRUDA were permitted to continue beyond the first RECIST v1.1-defined disease progression if clinically stable until the first radiographic evidence of disease progression was confirmed at least 4 weeks later with repeat imaging. Patients treated with KEYTRUDA without disease progression could be treated for up to 24 months. Assessment of tumor status was performed every 9 weeks. The major efficacy outcome measures were OS and PFS as

assessed by the investigator according to RECIST v1.1. Secondary efficacy outcome measures were ORR and DoR, according to RECIST v1.1, as assessed by the investigator.

The baseline characteristics were: median age of 63 years (range: 27 to 94), 43% age 65 or older; 83% male; 37% White and 53% Asian; 40% had an ECOG PS of 0 and 60% had an ECOG PS of 1. Ninety-one percent had M1 disease and 9% had M0 disease. Seventy-three percent had a tumor histology of squamous cell carcinoma, and 27% had adenocarcinoma; 51% had tumors that expressed PD-L1 with a CPS \geq 10 and 46% had CPS <10. Three percent of patient's tumors were either not evaluable or missing PD-L1 status.

KEYTRUDA, in combination with chemotherapy, demonstrated a statistically significant and clinically meaningful improvement in OS and PFS when compared to chemotherapy (cisplatin and 5-FU) in previously untreated participants with locally advanced unresectable or metastatic carcinoma of the esophagus or gastroesophageal junction. The investigator-assessed results were consistent with BICR.

Table 22 summarizes the key efficacy measures for KEYNOTE-590. The Kaplan-Meier curves for OS and PFS are shown in Figures 18 and 19.

Table 22: Efficacy Results in Patients with Locally Advanced Unresectable or Metastatic Esophageal Cancer in KEYNOTE-590

Endpoint	KEYTRUDA 200 mg every 3 weeks Cisplatin 5-FU n=373	Placebo Cisplatin 5-FU n=376
OS		
Number (%) of patients with event	262 (70%)	309 (82%)
Median in months* (95% CI)	12.4 (10.5, 14.0)	9.8 (8.8, 10.8)
Hazard ratio† (95% CI)	0.73 (0.62, 0.86)	
p-Value (stratified log-rank)	<0.0001	
PFS‡		
Number (%) of patients with event	297 (79.6%)	333 (88.6%)
Median in months* (95% CI)	6.3 (6.2, 6.9)	5.8 (5.0, 6.0)
Hazard ratio† (95% CI)	0.65 (0.55, 0.76)	
p-Value (stratified log-rank)	<0.0001	
Objective Response Rate‡		
ORR % (95% CI)	45% (39.9, 50.2)	29.3% (24.7, 34.1)
Complete response rate	6.4%	2.4%
Partial response rate	38.6%	26.9%
p-Value (Miettinen-Nurminen)	<0.0001	
Response Duration‡ .§		
Median duration of response in months (range)	8.3 (1.2+, 31.0+)	6.0 (1.5+, 25.0+)
% of patients with duration ≥ 6 months*	73.5%	50.4%
% of patients with duration ≥ 12 months*	38.6%	17.8%
% of patients with duration ≥ 18 months*	29.4%	7.7%

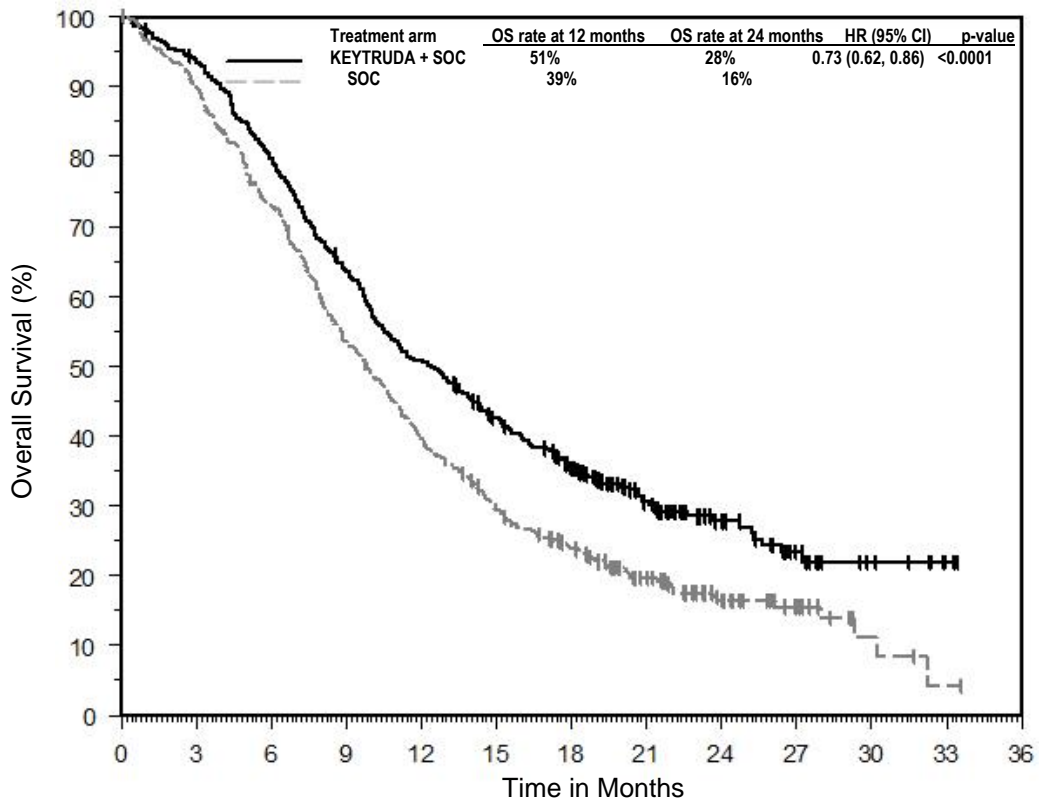
* Based on Kaplan-Meier estimation

† Based on the stratified Cox proportional hazard model

‡ Assessed by investigator using RECIST 1.1

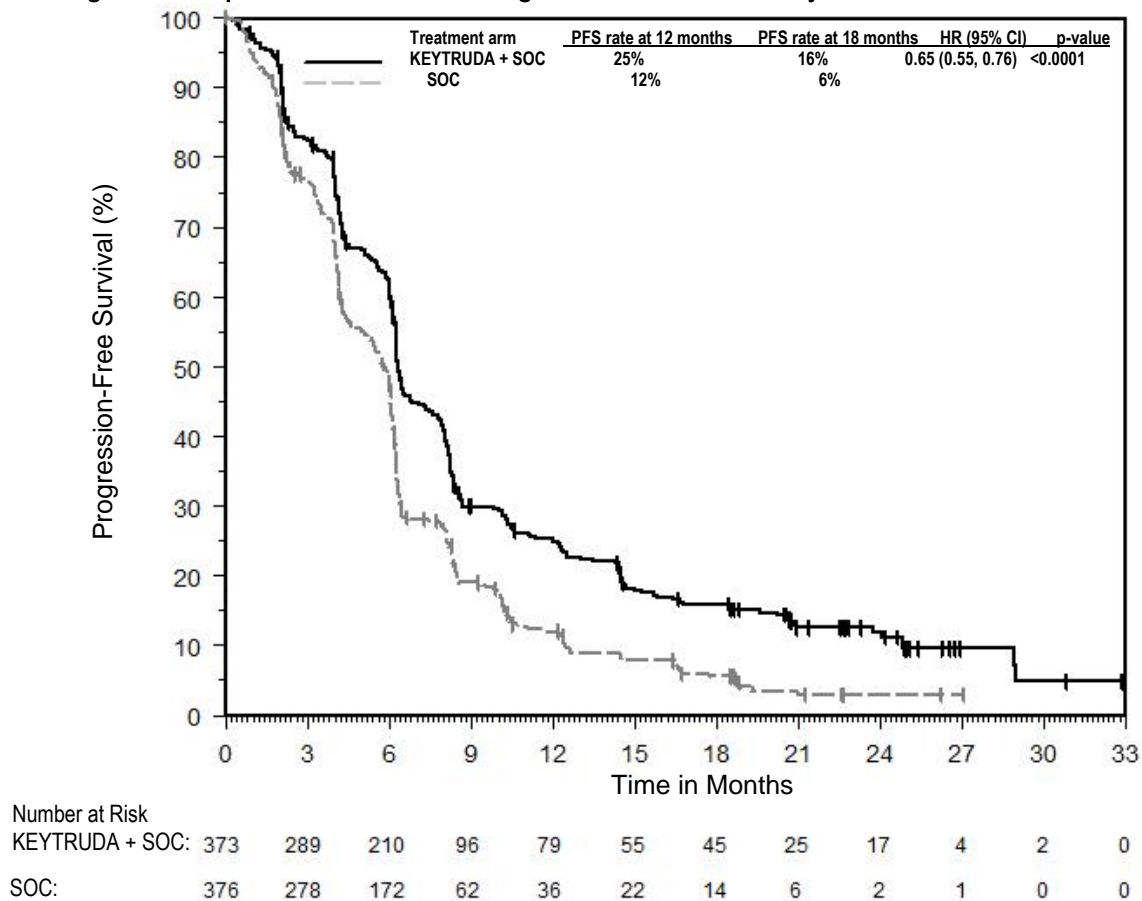
§ Based on patients with a best overall response as confirmed complete or partial response

Figure 18: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-590



Number at Risk	0	3	6	9	12	15	18	21	24	27	30	33	36
KEYTRUDA + SOC:	373	348	295	235	187	151	118	68	36	17	7	2	0
SOC:	376	338	274	200	147	108	82	51	28	15	4	1	0

Figure 19: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-590



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

Colorectal Cancer

KEYNOTE-177: Controlled trial for first-line treatment of patients with MSI-H or dMMR CRC

The efficacy of KEYTRUDA was investigated in KEYNOTE-177, a multicenter, randomized, open-label, active-controlled trial that enrolled 307 patients with previously untreated metastatic MSI-H or dMMR CRC. MSI or MMR tumor status was determined locally using polymerase chain reaction

(PCR) or immunohistochemistry (IHC), respectively. Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible.

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

- mFOLFOX6 (oxaliplatin, leucovorin, and FU) or mFOLFOX6 in combination with either bevacizumab or cetuximab: Oxaliplatin 85 mg/m², leucovorin 400 mg/m² (or levoleucovorin 200 mg/m²), and FU 400 mg/m² bolus on Day 1, then FU 2400 mg/m² over 46-48 hours. Bevacizumab 5 mg/kg on Day 1 or cetuximab 400 mg/m² on first infusion, then 250 mg/m² weekly.
- FOLFIRI (irinotecan, leucovorin, and FU) or FOLFIRI in combination with either bevacizumab or cetuximab: Irinotecan 180 mg/m², leucovorin 400 mg/m² (or levoleucovorin 200 mg/m²), and FU 400 mg/m² bolus on Day 1, then FU 2400 mg/m² over 46-48 hours. Bevacizumab 5 mg/kg on Day 1 or cetuximab 400 mg/m² on first infusion, then 250 mg/m² weekly.

Treatment with KEYTRUDA or chemotherapy continued until RECIST v1.1-defined progression of disease as determined by the investigator or unacceptable toxicity. Patients treated with KEYTRUDA without disease progression could be treated for up to 24 months. Assessment of tumor status was performed every 9 weeks. Patients randomized to chemotherapy were offered KEYTRUDA at the time of disease progression. The primary efficacy outcome measures included PFS assessed by BICR according to RECIST v1.1. Secondary outcome measures were ORR and DoR.

A total of 307 patients were enrolled and randomized to KEYTRUDA (n=153) or chemotherapy (n=154). The baseline characteristics of these 307 patients were: median age of 63 years (range: 24 to 93), 47% age 65 or older; 50% male; 75% White and 16% Asian; 52% had an ECOG PS of 0 and 48% had an ECOG PS of 1. Mutation status: 25% BRAF V600E, 24% KRAS/NRAS. For 143 patients treated with chemotherapy, 56% received mFOLFOX6 with or without bevacizumab or cetuximab and 44% received FOLFIRI with or without bevacizumab or cetuximab.

The trial demonstrated a statistically significant improvement in PFS for patients randomized to KEYTRUDA compared with chemotherapy. The median follow-up time was 27.6 months (range: 0.2 to 48.3 months). Table 23 and Figure 20 summarize the key efficacy measures for KEYNOTE-177.

Table 23: Efficacy Results for First-line Treatment in Patients with MSI-H CRC in KEYNOTE-177

Endpoint	KEYTRUDA 200 mg every 3 weeks n=153	Chemotherapy n=154
PFS		
Number (%) of patients with event	82 (54%)	113 (73%)
Median in months (95% CI)	16.5 (5.4, 32.4)	8.2 (6.1, 10.2)
Hazard ratio* (95% CI)	0.60 (0.45, 0.80)	
p-Value†	0.0002	
Objective Response Rate		
ORR (95% CI)	44% (35.8, 52.0)	33% (25.8, 41.1)
Complete response rate	11%	4%
Partial response rate	33%	29%
Response Duration		
Median in months (range)	NR (2.3+ - 41.4+)	10.6 (2.8 - 37.5+)
% of patients with duration ≥ 6 months‡	97%	88%
% of patients with duration ≥ 12 months‡	85%	44%
% of patients with duration ≥ 24 months‡	83%	35%

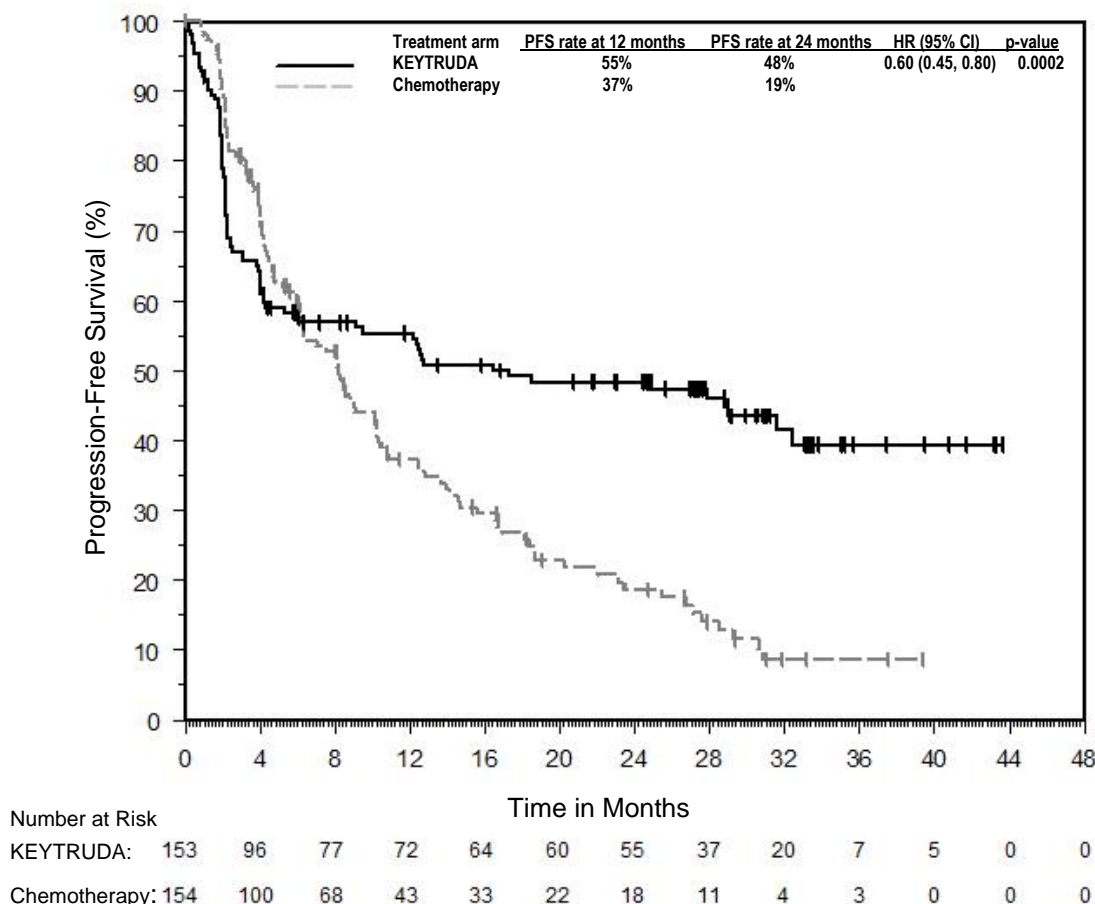
* Based on Cox regression model

† Based on log-rank test

‡ Based on Kaplan-Meier estimation

NR=not reached

Figure 20: Kaplan-Meier Curve for Progression-free Survival by Treatment Arm in KEYNOTE-177 (intent to treat population)



Exploratory analyses of patient-reported outcomes (PROs) using EORTC QLQ-C30 show improvement in global health status/quality of life, functioning (i.e., physical, role, social) and fatigue in patients treated with KEYTRUDA compared to a decline for patients treated with chemotherapy at pre-specified Week 18. Improvements from baseline in global health status/quality of life continued through Week 45 for patients treated with KEYTRUDA. In addition, a prolonged time to deterioration in global health status/QoL (HR 0.61; 95% CI 0.38-0.98), physical (HR 0.50; 95% CI 0.32-0.81) and social functioning (HR 0.53; 95% CI 0.32-0.87), and fatigue (HR 0.48; 95% CI 0.33-0.69) was observed for patients treated with KEYTRUDA compared to chemotherapy. These results should be interpreted in the context of the open-label study design and therefore taken cautiously.

Cervical Cancer

KEYNOTE-826: Controlled trial of combination therapy in patients with persistent, recurrent, or metastatic cervical cancer

The efficacy of KEYTRUDA in combination with paclitaxel and cisplatin or paclitaxel and carboplatin, with or without bevacizumab, was investigated in KEYNOTE-826, a multicenter, randomized, double-blind, placebo-controlled trial that enrolled 617 patients with persistent, recurrent, or first-line metastatic cervical cancer who had not been treated with chemotherapy except when used concurrently as a radio-sensitizing agent. Patients were enrolled regardless of tumor PD-L1 expression status. Patients with autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Randomization was stratified by metastatic status at initial diagnosis, investigator decision to use bevacizumab, and PD-L1 status (CPS <1 vs. CPS 1 to <10 vs. CPS ≥ 10). PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx™ Kit. Patients were randomized (1:1) to one of the two treatment groups:

- Treatment Group 1: KEYTRUDA 200 mg plus chemotherapy
- Treatment Group 2: Placebo plus chemotherapy

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

1. Paclitaxel 175 mg/m² + cisplatin 50 mg/m²
2. Paclitaxel 175 mg/m² + cisplatin 50 mg/m² + bevacizumab 15 mg/kg
3. Paclitaxel 175 mg/m² + carboplatin AUC 5 mg/mL/min
4. Paclitaxel 175 mg/m² + carboplatin AUC 5 mg/mL/min + bevacizumab 15 mg/kg

All study medications were administered as an intravenous infusion. All study treatments were administered on Day 1 of each 3-week treatment cycle. Cisplatin could be administered on Day 2 of each 3-week treatment cycle. The option to use bevacizumab was by investigator choice prior to randomization. Treatment with KEYTRUDA continued until RECIST v1.1-defined progression of disease, unacceptable toxicity, or a maximum of 24 months. Administration of KEYTRUDA was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Assessment of tumor status was performed at Week 9 and then every 9 weeks for the first year, followed by every 12 weeks thereafter. The primary efficacy outcome measures were OS and PFS as assessed by investigator according to RECIST v1.1. Secondary efficacy outcome measures were ORR and DoR, according to RECIST v1.1, as assessed by investigator.

Of the 617 enrolled patients, 548 patients (89%) had tumors expressing PD-L1 with a CPS ≥ 1. Among these 548 enrolled patients with tumors expressing PD-L1, 273 patients were randomized to KEYTRUDA in combination with chemotherapy with or without bevacizumab, and 275 patients were

randomized to placebo in combination with chemotherapy with or without bevacizumab. The baseline characteristics of these 548 patients were: median age of 51 years (range: 22 to 82), 16% age 65 or older; 59% White, 18% Asian, and 1% Black; 37% Hispanic or Latino; 56% and 43% ECOG performance status of 0 or 1, respectively; 63% received bevacizumab as study treatment; 21% with adenocarcinoma and 5% with adenosquamous histology; for patients with persistent or recurrent disease with or without distant metastases, 39% had received prior chemoradiation only and 17% had received prior chemoradiation plus surgery.

The study demonstrated statistically significant improvements in OS and PFS for patients randomized to KEYTRUDA in combination with chemotherapy with or without bevacizumab compared to placebo in combination with chemotherapy with or without bevacizumab at a pre-specified interim analysis in the overall population. The median follow-up time was 17.2 months (range: 0.3 to 29.4 months).

Efficacy results for patients with tumors expressed PD-L1 with a CPS \geq 1 in KEYNOTE-826 are summarized in Table 24, Figure 21, and Figure 22.

Table 24: Efficacy Results in KEYNOTE-826 for Patients with PD-L1 Expression (CPS ≥ 1)

Endpoint	Pembrolizumab 200 mg every 3 weeks plus Chemotherapy* with or without bevacizumab n=273	Placebo plus Chemotherapy* with or without bevacizumab n=275
OS		
Number of patients with event (%)	118 (43)	154 (56)
Median in months (95% CI)	NR (19.8, NR)	16.3 (14.5, 19.4)
Hazard ratio [†] (95% CI)	0.64 (0.50, 0.81)	
p-Value [‡]	0.0001	
PFS		
Number of patients with event (%)	157 (58)	198 (72)
Median in months (95% CI)	10.4 (9.7, 12.3)	8.2 (6.3, 8.5)
Hazard ratio [†] (95% CI)	0.62 (0.50, 0.77)	
p-Value [§]	< 0.0001	
Objective response rate		
ORR [¶] (95% CI)	68% (62, 74)	50% (44, 56)
Complete response	23%	13%
Partial response	45%	37%
Duration of response		
Median in months (range)	18.0 (1.3+, 24.2+)	10.4 (1.5+, 22.0+)
% with duration ≥ 12 months [#]	56	46
% with duration ≥ 18 months [#]	50	35

* Chemotherapy (paclitaxel and cisplatin or paclitaxel and carboplatin)

† Based on the stratified Cox proportional hazard model

‡ Based on stratified log-rank test (compared to an alpha boundary of 0.00549)

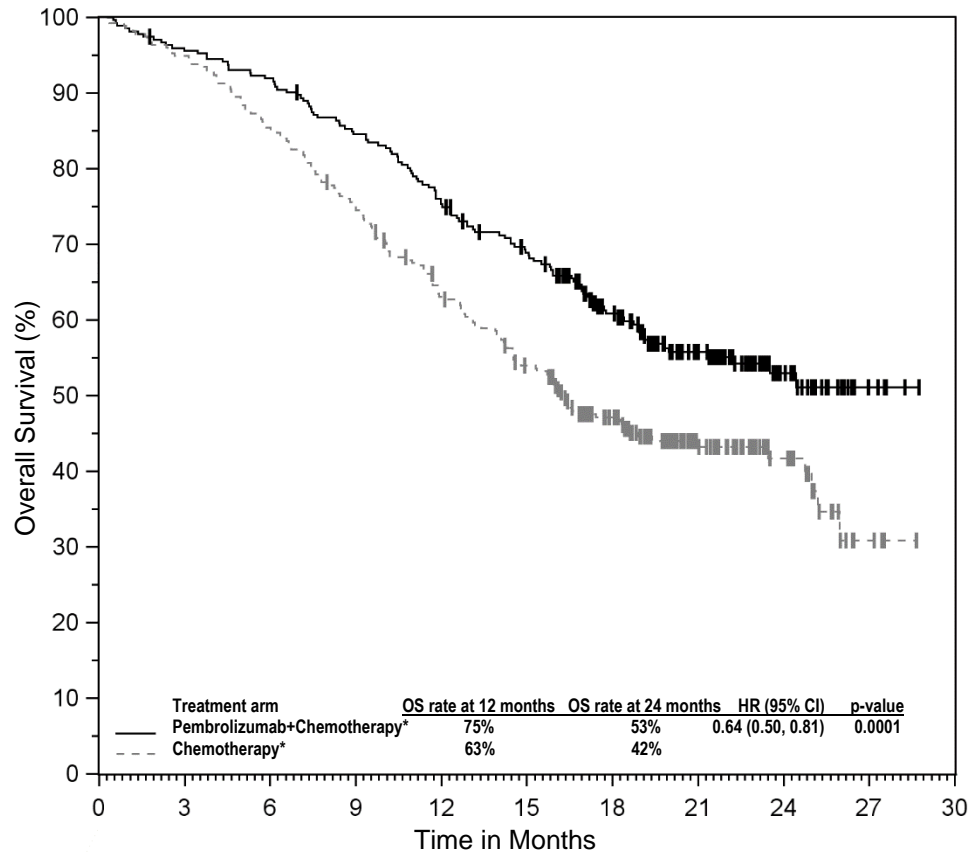
§ Based on stratified log-rank test (compared to an alpha boundary of 0.00144)

¶ Response: Best objective response as confirmed complete response or partial response

Based on Kaplan-Meier estimation

NR = not reached

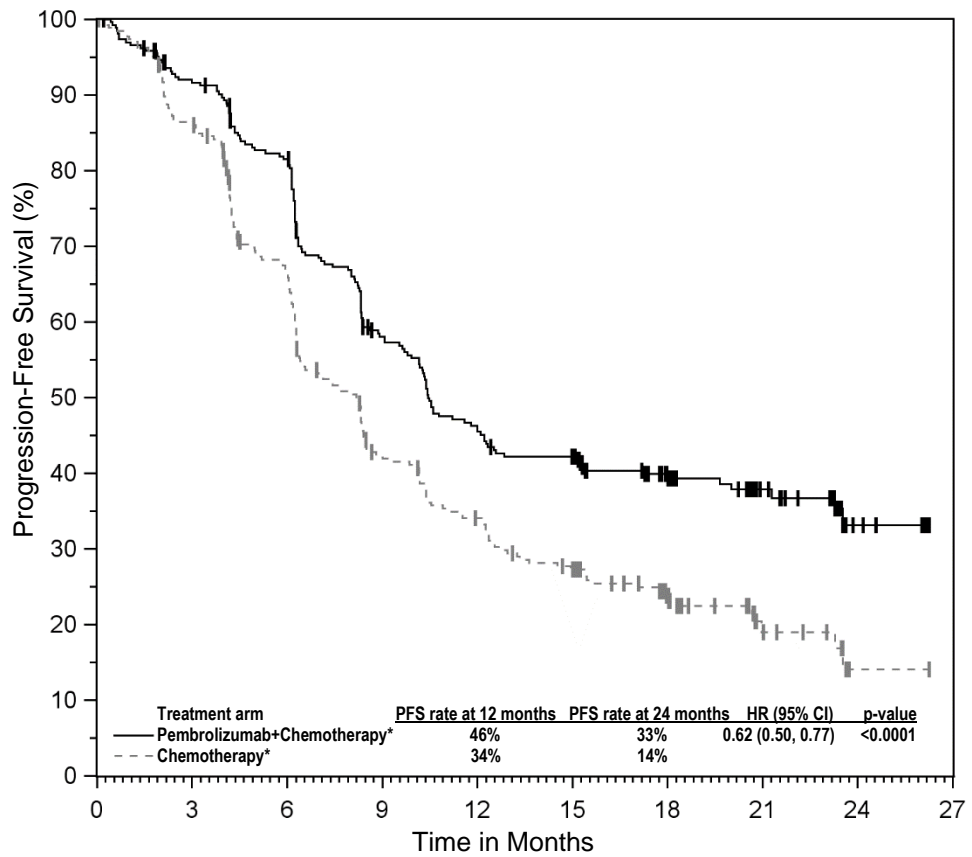
Figure 21: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-826 patients with PD-L1 Expression (CPS ≥ 1)



Number at Risk	0	3	6	9	12	15	18	21	24	27	30
Pembrolizumab+Chemotherapy*	273	260	250	229	204	181	132	82	34	6	0
Chemotherapy*	275	261	235	206	168	140	100	55	25	4	0

* Chemotherapy (paclitaxel and cisplatin or paclitaxel and carboplatin) with or without bevacizumab

Figure 22: Kaplan-Meier Curve for Progression Free Survival by Treatment Arm in KEYNOTE-826 patients with PD-L1 Expression (CPS ≥ 1)



Number at Risk	0	3	6	9	12	15	18	21	24	27
Pembrolizumab+Chemotherapy*	273	238	208	143	112	101	66	34	10	0
Chemotherapy*	275	229	170	103	81	63	38	13	1	0

*Chemotherapy (paclitaxel and cisplatin or paclitaxel and carboplatin) with or without bevacizumab

Patient-reported outcomes (PROs) were assessed using EQ-5D-5L. A prolonged time to deterioration in EQ-5D-5L was observed for patients treated with pembrolizumab plus chemotherapy compared to placebo plus chemotherapy (HR 0.80; 95% CI 0.61-1.04). Over 30 weeks of follow-up, more patients treated with pembrolizumab plus chemotherapy had improved or stable health status/QoL (78.1% vs. 70.5%).

Renal Cell Carcinoma

KEYNOTE-426: Controlled trial of combination therapy in advanced RCC patients naïve to treatment

The efficacy of KEYTRUDA in combination with axitinib was investigated in a randomized, multicenter, open-label, active-controlled trial KEYNOTE-426, conducted in patients with advanced RCC with clear cell component, regardless of PD-L1 tumor status and International Metastatic RCC Database

Consortium (IMDC) risk group categories. The trial excluded patients with autoimmune disease or a medical condition that required immunosuppression. Randomization was stratified by risk categories (favorable versus intermediate versus poor) and geographic region (North America versus Western Europe versus “Rest of the World”). Patients were randomized (1:1) to one of the following treatment arms:

- KEYTRUDA 200 mg intravenously every 3 weeks in combination with axitinib 5 mg orally, twice daily. Patients who tolerated axitinib 5 mg twice daily for 2 consecutive treatment cycles (i.e., 6 weeks) with no >Grade 2 treatment-related adverse events to axitinib and with blood pressure well controlled to \leq 150/90 mm Hg were permitted dose escalation of axitinib to 7 mg twice daily. Dose escalation of axitinib to 10 mg twice daily was permitted using the same criteria. Axitinib could be interrupted or reduced to 3 mg twice daily and subsequently to 2 mg twice daily to manage toxicity.
- Sunitinib 50 mg orally, once daily for 4 weeks and then off treatment for 2 weeks.

Treatment with KEYTRUDA and axitinib continued until RECIST 1.1-defined progression of disease as verified by BICR or confirmed by the investigator, unacceptable toxicity, or for KEYTRUDA, a maximum of 24 months. Administration of KEYTRUDA and axitinib was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Assessment of tumor status was performed at baseline, after randomization at Week 12, then every 6 weeks thereafter until Week 54, and then every 12 weeks thereafter. Chemistry and hematology laboratory tests were performed at each cycle.

Among the 861 patients in KEYNOTE-426 (432 patients in the KEYTRUDA combination arm and 429 in the sunitinib arm), baseline characteristics were: median age of 62 years (range: 26 to 90); 38% age 65 or older; 73% male; 79% White and 16% Asian; 99.9% had a Karnofsky Performance Score (KPS) of \geq 70%; patient distribution by IMDC risk categories was 31% favorable, 56% intermediate and 13% poor.

The primary efficacy outcome measures were OS and PFS (as assessed by BICR according to RECIST 1.1). Secondary efficacy outcome measures were ORR and response duration, as assessed by BICR using RECIST 1.1. The median follow-up time for 432 patients treated with KEYTRUDA and axitinib was 13.2 months (range: 0.1 – 21.5 months). Table 25 summarizes key efficacy measures. Consistent results were observed across pre-specified subgroups, IMDC risk categories and PD-L1 tumor expression status.

Table 25: Response to KEYTRUDA and Axitinib in Patients with Advanced RCC in KEYNOTE-426

Endpoint	KEYTRUDA with axitinib n=432	Sunitinib n=429
OS		
Number of patients with event (%)	59 (14%)	97 (23%)
Median in months (95% CI)	Not reached (NA, NA)	Not reached (NA, NA)
Hazard ratio* (95% CI)	0.53 (0.38, 0.74)	
p-Value†	0.00005	
12-month OS rate (95% CI)	90% (86, 92)	78% (74, 82)
18-month OS rate (95% CI)	82% (77, 86)	72% (66, 77)
PFS		
Number of patients with event (%)	183 (42%)	213 (50%)
Median in months (95% CI)	15.1 (12.6, 17.7)	11.0 (8.7, 12.5)
Hazard ratio* (95% CI)	0.69 (0.56, 0.84)	
p-Value†	0.00012	
ORR		
Overall response rate‡ (95% CI)	59% (54, 64)	36% (31, 40)
Complete response	6%	2%
Partial response	53%	34%
p-Value§	<0.0001	
Duration of Response		
Median in months (range)	Not reached (1.4+, 18.2+)	15.2 (1.1+, 15.4+)
Number (%¶) of patients with duration ≥ 6 months	161 (88%)	84 (81%)
Number (%¶) of patients with duration ≥ 12 months	58 (71%)	26 (62%)

* Based on the stratified Cox proportional hazard model

† Based on stratified log-rank test

‡ Based on patients with a best overall response as confirmed complete or

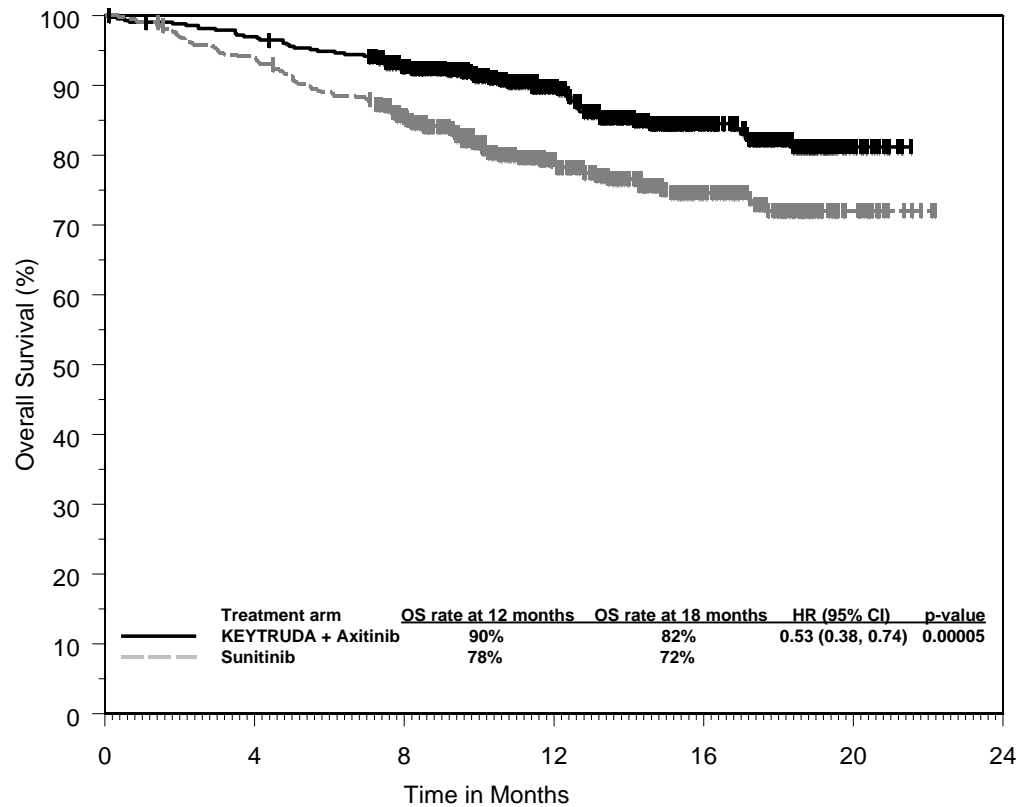
partial response

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

¶ Based on Kaplan-Meier estimation

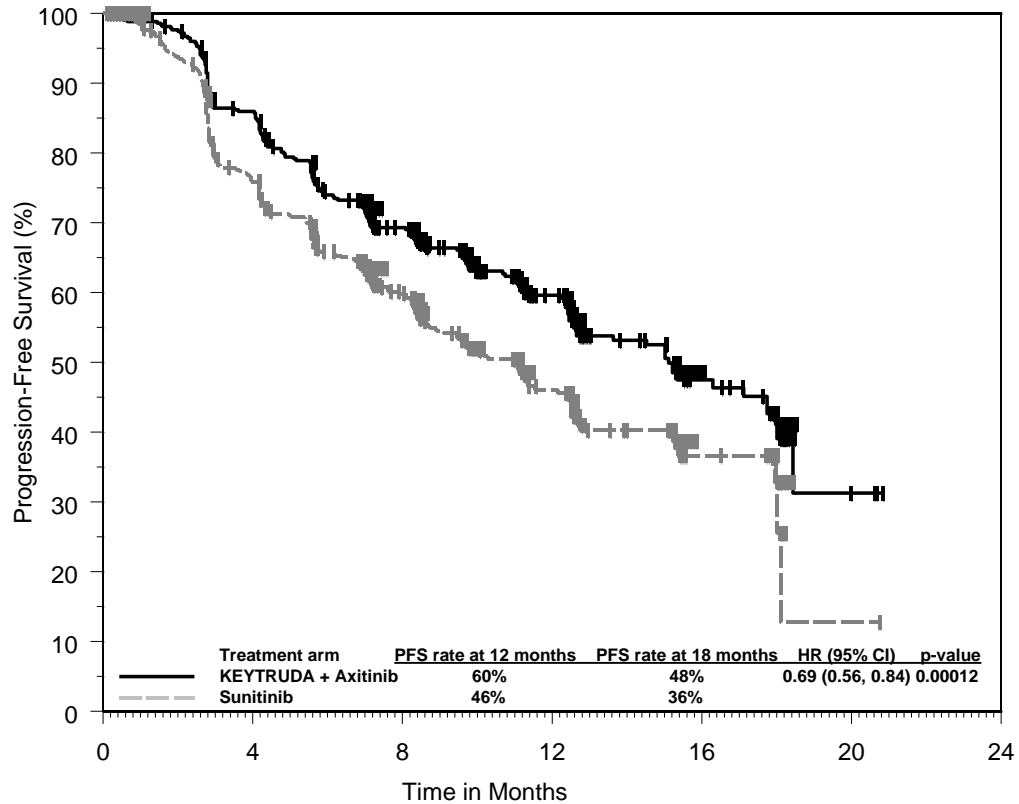
NA=not available

Figure 23: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-426 (Intent to Treat Population)



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

Figure 24: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-426 (Intent to Treat Population)



Number at Risk	0	4	8	12	16	20	24
KEYTRUDA + Axitinib:	432	357	251	140	42	3	0
Sunitinib:	429	302	193	89	29	1	0

An updated analysis was conducted after a median follow-up time of 27.0 months. At the time of this analysis, the median OS was not reached (95% CI: NR, NR) for KEYTRUDA in combination with axitinib and 35.7 months (95% CI: 33.3, NR) for sunitinib. The OS HR was 0.68 (95% CI: 0.55, 0.85). The 12-month OS rates were 90% (95% CI: 86, 92) in the combination arm and 79% (95% CI: 75, 83) in the sunitinib arm. The PFS HR (95% CI) was 0.71 (0.60, 0.84). The ORR (95% CI) was 60% (55, 65) in the combination arm and 40% (35, 45) in the sunitinib arm, and the CRR was 9% and 3%, respectively.

KEYNOTE-564: Placebo-controlled study for the adjuvant treatment of patients with resected RCC

The efficacy of KEYTRUDA was investigated as adjuvant therapy for RCC in KEYNOTE-564, a multicenter, randomized, double-blind, placebo-controlled study in 994 patients with increased risk of recurrence defined as intermediate-high or high risk of recurrence of RCC, or M1 no evidence of disease (NED). The intermediate high-risk category included: pT2 with Grade 4 or sarcomatoid features; pT3, any Grade without nodal involvement (N0) or distant metastases (M0). The high-risk

category included: pT4, any Grade N0 and M0; any pT, any Grade with nodal involvement and M0. The M1 NED category included patients with metastatic disease who had undergone complete resection of primary and metastatic lesions. Patients must have undergone a partial nephroprotective or radical complete nephrectomy (and complete resection of solid, isolated, soft tissue metastatic lesion(s) in M1 NED participants) with negative surgical margins \geq 4 weeks prior to the time of screening. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible. Patients were randomized (1:1) to receive KEYTRUDA 200 mg every 3 weeks (n=496) or placebo (n=498) for up to 1 year until disease recurrence or unacceptable toxicity. Randomization was stratified by metastasis status (M0, M1 NED), within M0 group, further stratified by ECOG PS (0,1), and geographic region (US, non-US). Patients underwent imaging every 12 weeks for the first 2 years from randomization, then every 16 weeks from year 3 to 5, and then every 24 weeks annually.

Among the 994 patients, the baseline characteristics were: median age of 60 years (range: 25 to 84), 33% age 65 or older; 71% male; and 85% ECOG PS of 0 and 15% ECOG PS of 1. Ninety-four percent were N0; 84% had no sarcomatoid features; 86% were pT2 with Grade 4 or sarcomatoid features or pT3; 8% were pT4 or with nodal involvement; and 6% were M1 NED. Baseline characteristics and demographics were generally comparable between the KEYTRUDA and placebo arms.

The primary efficacy outcome measure was investigator-assessed disease-free survival (DFS). The key secondary outcome measure was OS. The study demonstrated a statistically significant improvement in DFS for patients randomized to the KEYTRUDA arm compared with placebo. Consistent results were observed across pre-specified subgroups. At the time of analysis, OS results were not yet mature with 18 deaths out of 496 patients in the KEYTRUDA arm and 33 deaths out of 498 patients in the placebo arm. The median follow-up time was 23.9 months (range 2.5 to 41.5 months). Efficacy results are summarized in Table 26 and Figure 25.

Table 26: Efficacy Results in KEYNOTE-564

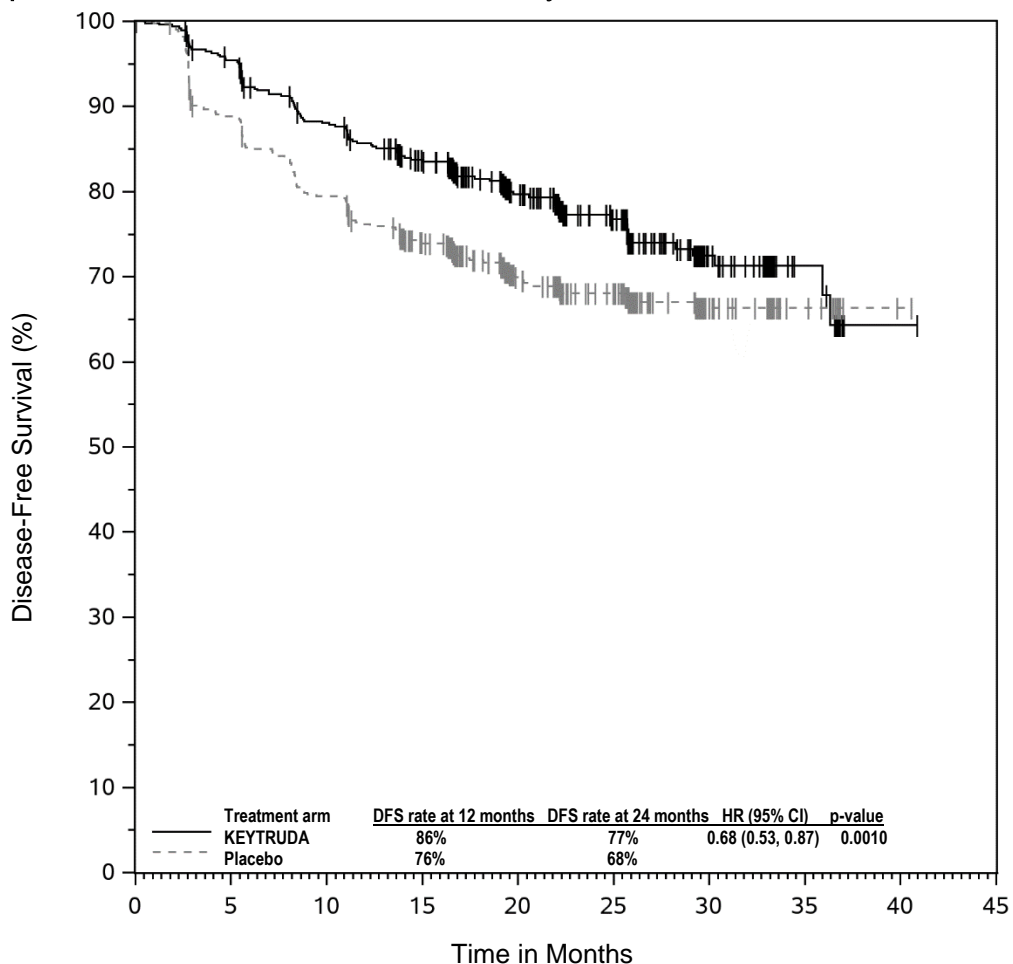
Endpoint	KEYTRUDA 200 mg every 3 weeks n=496	Placebo n=498
DFS		
Number (%) of patients with event	109 (22%)	151 (30%)
Median in months (95% CI)	NR	NR
Hazard ratio* (95% CI)	0.68 (0.53, 0.87)	
p-Value	0.0010†	
12-month DFS rate (95% CI)	86% (82, 89)	76% (72, 80)
18-month DFS rate (95% CI)	82% (78, 85)	72% (68, 76)
24-month DFS rate (95% CI)	77% (73, 81)	68% (64, 72)

* Based on the stratified Cox proportional hazard model

† Based on stratified log-rank test

NR = not reached

Figure 25: Kaplan-Meier Curve for Disease-Free Survival by Treatment Arm in KEYNOTE-564



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

Endometrial Carcinoma

KEYNOTE-146: Open-label study of combination therapy in patients with endometrial carcinoma

The efficacy of KEYTRUDA in combination with lenvatinib was investigated in a non-randomized, multicenter, open-label, multi-cohort trial KEYNOTE-146, conducted in 108 patients with metastatic endometrial carcinoma that had progressed following at least one prior systemic therapy in any setting. The trial excluded patients with active autoimmune disease or medical conditions that required immunosuppression.

Patients received KEYTRUDA at a dose of 200 mg intravenously every 3 weeks in combination with lenvatinib 20 mg orally once daily until unacceptable toxicity or disease progression as determined by the investigator. Clinically stable patients who were considered by the investigator to be deriving

clinical benefit were permitted to remain on treatment beyond RECIST-defined disease progression. Patients could be treated with KEYTRUDA for up to 24 months; however, treatment with lenvatinib could be continued beyond 24 months. Assessment of tumor status was performed at baseline and then every 6 weeks until Week 24, followed by every 9 weeks thereafter. The major efficacy outcome measures were ORR and duration of response, as assessed by blinded independent central review (BICR) using RECIST 1.1.

Among the 108 patients, 87% (n=94) had tumors that were not MSI-H or dMMR, 10% (n=11) had tumors that were MSI-H or dMMR, and in 3% (n=3) the status was not known. The baseline characteristics of the 94 patients with tumors that were not MSI-H or dMMR were: median age of 66 years with 62% age 65 or older; 86% White, 6% Black, 4% Asian, 3% other races; and ECOG PS of 0 (52%) or 1 (48%). All 94 of these patients received prior systemic therapy for endometrial carcinoma: 51% had one, 38% had two, and 11% had three or more prior systemic therapies.

Efficacy results are summarized in Table 27.

Table 27: Efficacy Results in Patients with Endometrial Carcinoma that is Not MSI-H or dMMR

Endpoint	KEYTRUDA with lenvatinib n=94*
Objective Response Rate (ORR)	
ORR (95% CI)	38.3% (29, 49)
Complete response, n (%)	10 (10.6%)
Partial response, n (%)	26 (27.7%)
Duration of Response	
Median in months (range)	NR (1.2+, 33.1+) [†]
Duration of response ≥ 6 months, n (%)	25 (69%)

Tumour assessments were based on RECIST 1.1 per independent radiologic review committee (IRC). All responses were confirmed.

* Median follow-up time of 18.7 months

[†] Based on patients (n=36) with a response by independent review

+ Censored at data cutoff

CI=confidence interval; NR=Not reached

Triple-Negative Breast Cancer

KEYNOTE-522: Controlled study of neoadjuvant and adjuvant treatment of patients with high-risk early-stage TNBC

The efficacy of KEYTRUDA in combination with carboplatin and paclitaxel followed by doxorubicin or epirubicin and cyclophosphamide, given as a neoadjuvant treatment and continued as monotherapy adjuvant treatment was investigated in Study KEYNOTE-522, a randomized, double-blind, multicenter, placebo-controlled study. The key eligibility criteria for this study were newly diagnosed previously untreated high-risk early-stage TNBC (tumor size >1 cm but ≤ 2 cm in diameter with nodal involvement or tumor size >2 cm in diameter regardless of nodal involvement), regardless of tumor PD-L1 expression. Patients with active autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible for the study. Randomization was stratified by nodal status (positive vs. negative), tumor size (T1/T2 vs. T3/T4), and choice of carboplatin (dosed every 3 weeks vs. weekly).

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

- **Arm 1:**

- Four cycles of preoperative KEYTRUDA 200 mg every 3 weeks on Day 1 of cycles 1-4 of treatment regimen in combination with:
 - Carboplatin
 - AUC 5 mg/mL/min every 3 weeks on Day 1 of cycles 1-4 of treatment regimen
 - or AUC 1.5 mg/mL/min every week on Day 1, 8, and 15 of cycles 1-4 of treatment regimen **and**
 - Paclitaxel 80 mg/m² every week on Day 1, 8, and 15 of cycles 1-4 of treatment regimen
- Followed by four additional cycles of preoperative KEYTRUDA 200 mg every 3 weeks on Day 1 of cycles 5-8 of treatment regimen in combination with:
 - Doxorubicin 60 mg/m² or epirubicin 90 mg/m² every 3 weeks on Day 1 of cycles 5-8 of treatment regimen **and**
 - Cyclophosphamide 600 mg/m² every 3 weeks on Day 1 of cycles 5-8 of treatment regimen
- Following surgery, 9 cycles of KEYTRUDA 200 mg every 3 weeks were administered.

- **Arm 2:**

- Four cycles of preoperative placebo every 3 weeks on Day 1 of cycles 1-4 of treatment regimen in combination with:
 - Carboplatin
 - AUC 5 mg/mL/min every 3 weeks on Day 1 of cycles 1-4 of treatment regimen
 - or AUC 1.5 mg/mL/min every week on Day 1, 8, and 15 of cycles 1-4 of treatment regimen **and**
 - Paclitaxel 80 mg/m² every week on Day 1, 8, and 15 of cycles 1-4 of treatment regimen
- Followed by four additional cycles of preoperative placebo every 3 weeks on Day 1 of cycles 5-8 of treatment regimen in combination with:

- Doxorubicin 60 mg/m² or epirubicin 90 mg/m² every 3 weeks on Day 1 of cycles 5-8 of treatment regimen **and**
- Cyclophosphamide 600 mg/m² every 3 weeks on Day 1 of cycles 5-8 of treatment regimen
- Following surgery, 9 cycles of placebo every 3 weeks were administered.

Treatment with KEYTRUDA or placebo continued until completion of the treatment (17 cycles), disease progression that precludes definitive surgery, disease recurrence in the adjuvant phase, or unacceptable toxicity.

The major efficacy outcome measures were pathological complete response (pCR) rate and event-free survival (EFS). pCR was defined as absence of invasive cancer in the breast and lymph nodes (ypT0/Tis ypN0) and was assessed by the blinded local pathologist at the time of definitive surgery. EFS was defined as the time from randomization to the first occurrence of any of the following events: progression of disease that precludes definitive surgery, local or distant recurrence, second primary malignancy, or death due to any cause. An additional efficacy outcome measure was OS.

A total of 1174 patients were randomized: 784 patients to the KEYTRUDA arm and 390 patients to the placebo arm. The study population characteristics were: median age of 49 years (range: 22 to 80), 11% age 65 or older; 99.9% female; 64% White, 20% Asian, 5% Black, and 2% American Indian or Alaska Native; 87% ECOG PS of 0 and 13% ECOG PS of 1; 56% were pre-menopausal status and 44% were post-menopausal status; 7% were primary Tumor 1 (T1), 68% T2, 19% T3, and 7% T4; 49% were nodal involvement 0 (N0), 40% N1, 11% N2, and 0.2% N3; 75% of patients were overall stage II and 25% were stage III.

The trial demonstrated a statistically significant improvement in pCR and EFS at a pre-specified analysis for patients randomized to KEYTRUDA in combination with chemotherapy followed by KEYTRUDA monotherapy compared with patients randomized to placebo in combination with chemotherapy followed by placebo alone. At the time of EFS analysis, OS results were not yet mature (45% of the required events for final analysis). However, the data showed an improvement in OS that favored the KEYTRUDA arm over the placebo arm. At a pre-specified interim analysis, the median follow-up time for 784 patients treated with KEYTRUDA was 37.8 months (range: 2.7-48 months). Efficacy results are summarized in Table 28 and Figure 26.

Table 28: Efficacy Results in Patients with High-Risk Early-Stage TNBC in KEYNOTE-522

Endpoint	KEYTRUDA with chemotherapy/KEYTRUDA	Placebo with chemotherapy/Placebo
pCR (ypT0/Tis ypN0)*	n=401	n=201
Number of patients with pCR	260	103
pCR Rate (%), (95% CI)	64.8 (59.9, 69.5)	51.2 (44.1, 58.3)
Treatment difference (%) estimate (95% CI)†	13.6 (5.4, 21.8)	
p-Value	0.00055	
EFS‡	n=784	n=390
Number of patients with event (%)	123 (16%)	93 (24%)
24 month EFS rate (95% CI)	87.8 (85.3, 89.9)	81.0 (76.8, 84.6)
Hazard ratio (95% CI)§	0.63 (0.48, 0.82)	
p-Value¶	0.00031	

* Based on a pre-specified pCR interim analysis (compared to a significance level of 0.003)

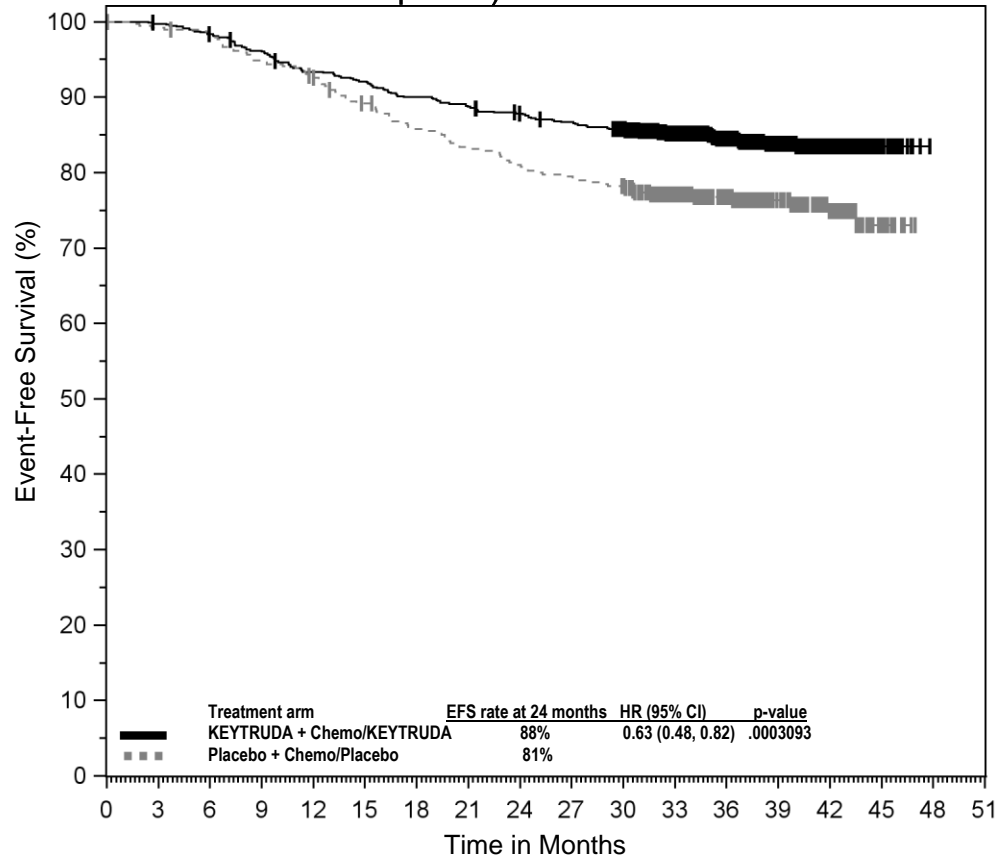
† Based on Miettinen and Nurminen method stratified by nodal status, tumor size, and choice of carboplatin

‡ Based on a pre-specified EFS interim analysis (compared to a significance level of 0.0052)

§ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by nodal status, tumor size, and choice of carboplatin

¶ Based on log-rank test stratified by nodal status, tumor size, and choice of carboplatin

Figure 26: Kaplan-Meier Curve for Event-Free Survival by Treatment Arm in KEYNOTE-522 (Intent to Treat Population)



Number at Risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51
KEYTRUDA + Chemo/KEYTRUDA:	784	781	769	751	728	718	702	692	681	671	652	551	433	303	165	28	0	0
Placebo + Chemo/Placebo:	390	386	382	368	358	342	328	319	310	304	297	250	195	140	83	17	0	0

The impact of the addition of KEYTRUDA to chemotherapy on health-related quality of life was assessed using the EORTC QLQ-C30. Over 21 weeks of follow up, the Least Square (LS) mean score change in the QLQ-C30 global health status/QoL scale was -11.24 (-12.82, -9.66) in patients treated with KEYTRUDA in combination with chemotherapy and -10.20 (-12.30, -8.10) in patients treated with placebo in combination with chemotherapy as neoadjuvant treatment [difference in LS means: -1.04; 95% CI: -3.46, 1.38]. Over 24 weeks of follow up, the LS mean score change in the global health status/QoL scale was 2.47 (1.05, 3.88) in patients treated with KEYTRUDA and 2.88 (1.05, 4.71) in patients treated with placebo as adjuvant treatment [difference in LS means: -0.41 (-2.60, 1.77)].

KEYNOTE-355: Controlled study of combination therapy in patients with locally recurrent unresectable or metastatic TNBC patients

The efficacy of KEYTRUDA in combination with paclitaxel, nab-paclitaxel, or gemcitabine and carboplatin was investigated in Study KEYNOTE-355, a randomized, double-blind, multicenter, placebo-controlled study. The key eligibility criteria for this study were locally recurrent unresectable or metastatic TNBC, regardless of tumor PD-L1 expression, and which had not been previously treated with chemotherapy. Patients with active autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible for the study. Randomization was stratified by chemotherapy treatment (paclitaxel or nab-paclitaxel vs. gemcitabine and carboplatin), tumor PD-L1 expression (CPS \geq 1 vs. CPS $<$ 1) based on the PD-L1 IHC 22C3 pharmDx™ kit, and prior treatment with the same class of chemotherapy in the neoadjuvant setting (yes vs. no).

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

- KEYTRUDA 200 mg on Day 1 every 3 weeks in combination with nab-paclitaxel 100 mg/m² on Days 1, 8 and 15 every 28 days, or paclitaxel 90 mg/m² on Days 1, 8, and 15 every 28 days, or gemcitabine 1000 mg/m² and carboplatin AUC 2 mg/mL/min on Days 1 and 8 every 21 days.
- Placebo on Day 1 every 3 weeks in combination with nab-paclitaxel 100 mg/m² on Days 1, 8 and 15 every 28 days, or paclitaxel 90 mg/m² on Days 1, 8, and 15 every 28 days, or gemcitabine 1000 mg/m² and carboplatin AUC 2 mg/mL/min on Days 1 and 8 every 21 days.

Treatment with KEYTRUDA or placebo continued until RECIST 1.1-defined progression of disease as determined by the investigator, unacceptable toxicity, or a maximum of 24 months. Administration of KEYTRUDA was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Assessment of tumor status was performed at Weeks 8, 16, and 24, then every 9 weeks for the first year, and every 12 weeks thereafter.

The major efficacy outcome measures were OS and PFS as assessed by BICR using RECIST 1.1, in patients with tumor PD-L1 expression CPS \geq 10. Additional efficacy outcome measures were ORR, DOR, and DCR (stable disease for at least 24 weeks, or complete response, or partial response) in patients with tumor PD-L1 expression CPS \geq 10 as assessed by BICR using RECIST 1.1.

A total of 847 patients were randomized: 566 patients to the KEYTRUDA arm and 281 patients to the placebo arm. The study population characteristics were: median age of 53 years (range: 22 to 85), 21% age 65 or older; 100% female; 68% White, 21% Asian, and 4% Black; 60% ECOG PS of 0 and 40% ECOG PS of 1; and 68% were post-menopausal status. Seventy-five percent of the patients had tumor PD-L1 expression defined as CPS \geq 1 and 38% had tumor PD-L1 expression CPS \geq 10.

In KEYNOTE-355, there was a statistically significant improvement in OS and PFS in patients with tumor PD-L1 expression CPS \geq 10 randomized to KEYTRUDA in combination with paclitaxel, nab-paclitaxel, or gemcitabine and carboplatin compared with patients randomized to placebo in combination with paclitaxel, nab-paclitaxel, or gemcitabine and carboplatin. The trial also demonstrated a clinically meaningful improvement in ORR and DoR.

Efficacy results are summarized in Table 29 and Figures 27 and 28.

Table 29: Efficacy Results in Patients with Locally Recurrent Unresectable or Metastatic TNBC with PD-L1 Expression CPS ≥ 10 in KEYNOTE-355

Endpoint	KEYTRUDA with chemotherapy* n=220	Placebo with chemotherapy* n=103
OS†		
Number of patients with event (%)	155 (70%)	84 (82%)
Median in months (95% CI)	23.0 (19.0, 26.3)	16.1 (12.6, 18.8)
Hazard ratio‡ (95% CI)	0.73 (0.55, 0.95)	
p-Value§	0.0093	
24-month OS rate (95% CI)	48.2 (41.4, 54.6)	34.0 (25.0, 43.1)
PFS‡,§		
Number of patients with event (%)	136 (62%)	79 (77%)
Median in months (95% CI)	9.7 (7.6, 11.3)	5.6 (5.3, 7.5)
Hazard ratio‡ (95% CI)	0.65 (0.49, 0.86)	
p-Value§	0.0012	
Objective Response Rate‡,§		
ORR, (95% CI)	53% (46, 60)	40% (30, 50)
Complete response	17%	13%
Partial response	36%	27%
Stable disease	28%	44%
Disease control rate ^p	65%	54%
Response Duration‡,§		
Median in months (95% CI)	19.3 (9.9, 29.8)	7.3 (5.3, 15.8)
% with duration ≥ 6 months ^β	83%	58%
% with duration ≥ 12 months ^β	56%	39%

* Chemotherapy: paclitaxel, nab-paclitaxel, or gemcitabine and carboplatin

† Based on the pre-specified final analysis

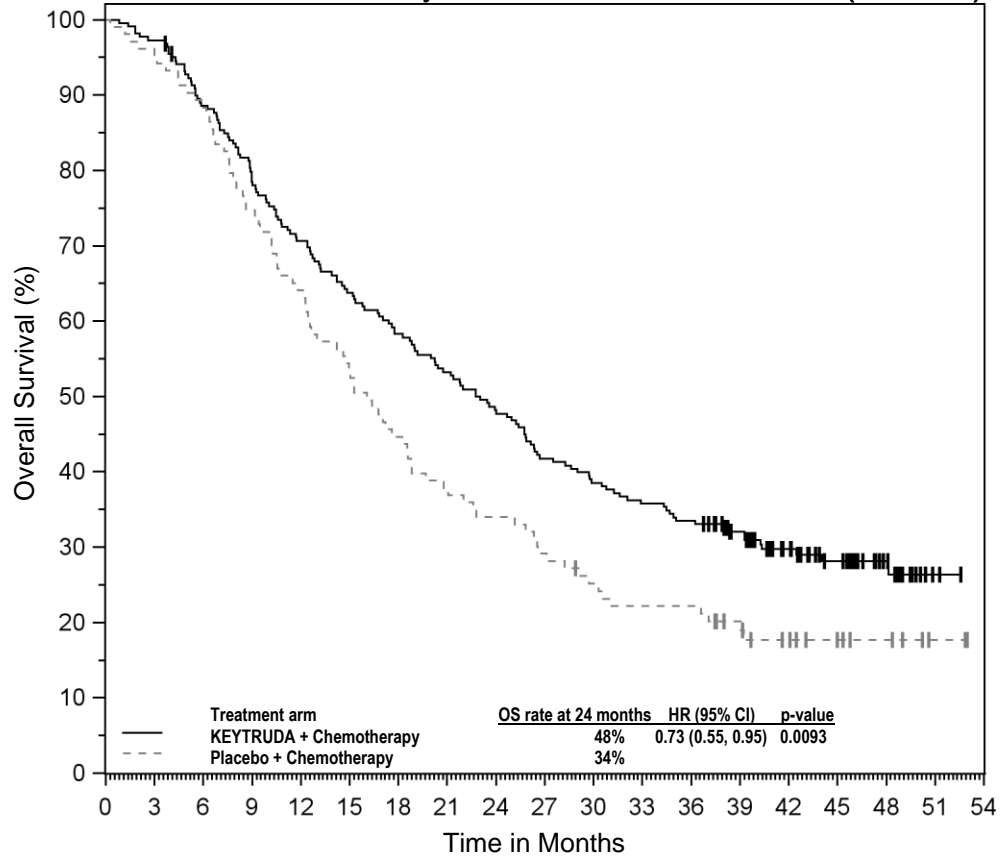
‡ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by chemotherapy on study (taxane vs. gemcitabine and carboplatin) and prior treatment with same class of chemotherapy in the neoadjuvant setting (yes vs. no)

§ One-sided p-Value based on log-rank test stratified by chemotherapy on

study (taxane vs. gemcitabine and carboplatin) and prior treatment with same class of chemotherapy in the neoadjuvant setting (yes vs. no)

- † Assessed by BICR using RECIST 1.1
- # Based on a pre-specified interim analysis
- ▷ Based on stable disease for at least 24 weeks, or complete response, or partial response
- β From product-limit (Kaplan-Meier) method for censored data

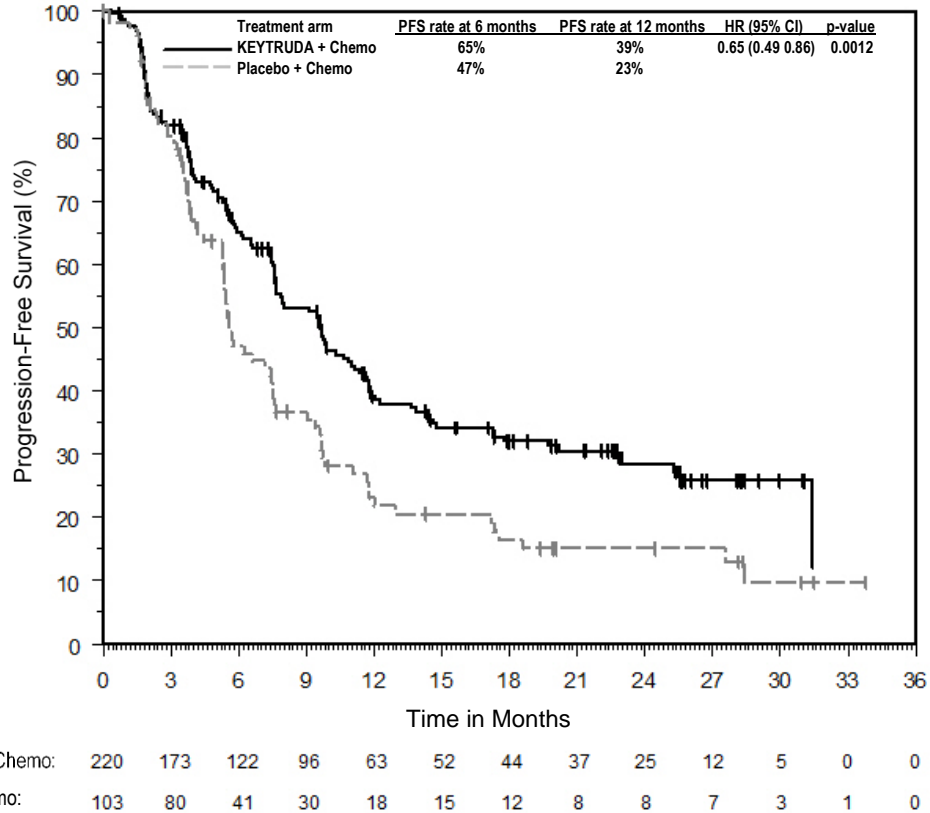
Figure 27: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-355 (CPS ≥ 10)*



Number at Risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
KEYTRUDA + Chemotherapy	220	214	193	171	154	139	127	116	105	91	84	78	73	59	43	31	17	2	0
Placebo + Chemotherapy	103	98	91	77	66	55	46	39	35	30	25	22	22	17	12	8	6	2	0

*Based on the pre-specified final analysis

Figure 28: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-355 (CPS ≥ 10)*



*Based on a pre-specified interim analysis

The impact of the addition of KEYTRUDA to chemotherapy on patient-reported outcomes were assessed using the EORTC QLQ-C30, EORTC QLQ-BR23 and EuroQol EQ-5D. Results from each measure showed that the addition of KEYTRUDA to chemotherapy did not result in a decrease in health-related quality of life through 15 weeks of follow-up.

Immunogenicity

In clinical studies in patients treated with pembrolizumab at a dose of 2 mg/kg every three weeks, 200 mg every three weeks, or 10 mg/kg every two or three weeks, 36 (1.8%) of 2034 evaluable patients tested positive for treatment-emergent antibodies against pembrolizumab, of which 9 (0.4%) patients had neutralizing antibodies against pembrolizumab. There was no evidence of an altered pharmacokinetic or safety profile with anti-pembrolizumab binding or neutralizing antibody development.

10. CLINICAL PHARMACOLOGY

10.1 Therapeutic Class

KEYTRUDA (pembrolizumab) is an antineoplastic agent, monoclonal antibody.

10.2 Mechanism of Action

PD-1 is an immune-checkpoint receptor that limits the activity of T lymphocytes in peripheral tissues. The PD-1 pathway is an immune control checkpoint that may be engaged by tumor cells to inhibit active T-cell immune surveillance. KEYTRUDA is a high affinity antibody against PD-1, which exerts dual ligand blockade of the PD-1 pathway, including PD-L1 and PD-L2, on antigen presenting or tumor cells. By inhibiting the PD-1 receptor from binding to its ligands, KEYTRUDA reactivates tumor-specific cytotoxic T lymphocytes in the tumor microenvironment and reactivates anti-tumor immunity.

10.3 Pharmacodynamics

Based on the modeling of dose/exposure relationships for efficacy and safety for pembrolizumab, there are no clinically significant difference in efficacy and safety between the doses of 200 mg or 2 mg/kg every 3 weeks or 400 mg every 6 weeks.

In peripheral blood of patients who received KEYTRUDA 2 mg/kg every 3 weeks or 10 mg/kg every 2 weeks or 3 weeks, an increased percentage of activated (i.e., HLA-DR+) CD4+ and CD8+ T-cells was observed after treatment at all doses and schedules without an increase in the circulating T-lymphocyte number.

10.4 Pharmacokinetics

The pharmacokinetics of pembrolizumab was studied in 2993 patients with various cancers who received doses in the range of 1 to 10 mg/kg every 2 weeks, 2 to 10 mg/kg every 3 weeks, or 200 mg every 3 weeks. There are no clinically meaningful differences in pharmacokinetics of pembrolizumab across indications.

Absorption

KEYTRUDA is dosed via the IV route and therefore is immediately and completely bioavailable.

Distribution

Consistent with a limited extravascular distribution, the volume of distribution of pembrolizumab at steady state is small (6.0 L; coefficient of variation [CV]: 20%). As expected for an antibody, pembrolizumab does not bind to plasma proteins in a specific manner.

Metabolism

Pembrolizumab is catabolized through non-specific pathways; metabolism does not contribute to its clearance.

Elimination

Pembrolizumab clearance (CV%) is approximately 23% lower [geometric mean, 195 mL/day (40%)] after achieving maximal change at steady state compared with the first dose (252 mL/day [CV%: 37%]); this decrease in clearance with time is not considered clinically important. The geometric mean value (CV%) for the 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.

Special Populations

The effects of various covariates on the pharmacokinetics of pembrolizumab were assessed in population pharmacokinetic analyses. The following factors had no clinically important effect on the clearance of pembrolizumab: age (range 15-94 years), gender, race, mild or moderate renal impairment, mild hepatic impairment, and tumor burden. The relationship between body weight and clearance supports the use of either fixed dose or body weight-based dosing to provide adequate and similar control of exposure. 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.

Renal Impairment

The effect of renal impairment on the clearance of pembrolizumab was evaluated by population pharmacokinetic analysis in patients with mild (GFR <90 and ≥ 60 mL/min/1.73 m²) or moderate (GFR <60 and ≥ 30 mL/min/1.73 m²) renal impairment compared to patients with normal (GFR ≥ 90 mL/min/1.73 m²) renal function. No clinically important differences in the clearance of pembrolizumab were found between patients with mild or moderate renal impairment and patients

with normal renal function. KEYTRUDA has not been studied in patients with severe (GFR <30 and ≥ 15 mL/min/1.73 m²) renal impairment. [See *Dosage and Administration* (2.4).]

Hepatic Impairment

The effect of hepatic impairment on the clearance of pembrolizumab was evaluated by population pharmacokinetic analysis in patients with mild hepatic impairment (total bilirubin (TB) 1.0 to 1.5 x ULN or AST >ULN as defined using the National Cancer Institute criteria of hepatic dysfunction) compared to patients with normal hepatic function (TB and AST \leq ULN). No clinically important differences in the clearance of pembrolizumab were found between patients with mild hepatic impairment and normal hepatic function. KEYTRUDA has not been studied in patients with moderate (TB >1.5 to 3 x ULN and any AST) or severe (TB >3 x ULN and any AST) hepatic impairment. [See *Dosage and Administration* (2.5).]

11. NAME OF THE DRUG

KEYTRUDA (pembrolizumab)

12. PHARMACEUTICAL FORM

Clear to slightly opalescent, colorless to slightly yellow solution.

13. PHARMACEUTICAL PARTICULARS

13.1 Chemistry

KEYTRUDA (pembrolizumab) is a selective humanized monoclonal antibody designed to block 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.

13.2 Composition

Active Ingredient

Pembrolizumab

Inactive Ingredients (List of excipients)

L-histidine

L-histidine hydrochloride monohydrate

Sucrose

Polysorbate 80

Water for injection

13.3 Storage

Store in a refrigerator (2°C to 8°C; 36°F to 46°F).

Protect from light. Do not freeze. Do not shake.

For storage conditions after dilution of the medicinal product, *see Dosage and Administration (2.1)*.

13.4 Shelf Life

Refer to outer carton.

13.5 Availability (a.k.a. Nature and Contents of Container)

Each single-use vial contains 100 mg/4 mL pembrolizumab.

Product Owner:

Merck Sharp & Dohme LLC

126 East Lincoln Ave.

P.O. Box 2000

Rahway, New Jersey 07065

USA

Date of revision: November 2022



Copyright © 2022 Merck & Co., Inc., Rahway, NJ, USA and its affiliates. All rights reserved.