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 adult and pediatric (12 years and older) patients with Stage IIB, IIC, or III melanoma 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 ≥ 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 ≥ 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.

KEYTRUDA is indicated for the treatment of patients with resectable Stage II, IIIA, or IIIB (T3-4N2) NSCLC in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment.

KEYTRUDA, as monotherapy, is indicated as adjuvant treatment following resection and platinum-based chemotherapy for adults patients with Stage IB (T2a ≥ 4 cm), II, or IIIA NSCLC.

Malignant Pleural Mesothelioma

KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of adult patients with unresectable non-epithelioid malignant pleural mesothelioma (MPM).

Head and Neck Cancer

KEYTRUDA is indicated for the treatment of adult patients with resectable locally advanced head and neck squamous cell carcinoma (HNSCC) whose tumours express PD-L1 with a CPS ≥ 1 as determined by a validated test, as neoadjuvant treatment, continued as adjuvant treatment in combination with radiotherapy (RT) with or without cisplatin and then as monotherapy.

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 HNSCC whose tumours express PD-L1 with a CPS ≥ 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, in combination with enfortumab vedotin, is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma.

KEYTRUDA, as monotherapy, 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) ≥ 10 as determined by a validated test, and who are not eligible for cisplatin-containing chemotherapy.

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

KEYTRUDA, in combination with enfortumab vedotin, as neoadjuvant treatment and then continued after radical cystectomy as adjuvant treatment, is indicated for the treatment of patients with resectable muscle invasive bladder cancer (MIBC).

Gastric Cancer

KEYTRUDA, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of patients with locally advanced unresectable or metastatic HER2-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma.

KEYTRUDA, in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of patients with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma, whose tumors express PD-L1 [Combined Positive Score (CPS) ≥ 1] as determined by a validated test.

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).

Hepatocellular Carcinoma

KEYTRUDA is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with an anti-angiogenic tyrosine kinase inhibitor (TKI).

Biliary Tract Carcinoma

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

Cervical Cancer

KEYTRUDA, in combination with chemoradiotherapy (CRT), is indicated for the treatment of patients with FIGO 2014 Stage III-IVA locally advanced 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 ≥ 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, in combination with lenvatinib, is indicated for the first-line treatment of patients with advanced 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)]*.

KEYTRUDA, in combination with belzutifan, is indicated for the adjuvant treatment of adult patients with RCC with a clear cell component (ccRCC) at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.

Endometrial Carcinoma

KEYTRUDA, in combination with carboplatin and paclitaxel, followed by KEYTRUDA as monotherapy, is indicated for the treatment of patients with primary advanced or recurrent endometrial carcinoma who are candidates for systemic therapy.

KEYTRUDA, in combination with lenvatinib, is indicated for the treatment of patients with advanced endometrial carcinoma who have disease progression following prior systemic therapy in any 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 ≥ 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 using a validated test *[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 or gastric cancer in combination with chemotherapy

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

- locally recurrent unresectable or metastatic TNBC.
- locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma.

For treatment of HNSCC in combination with radiotherapy, with or without chemotherapy

- Resectable locally advanced HNSCC, PD-L1 expression should be evaluated using a fully validated test.

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 MPM, HNSCC, cHL, urothelial carcinoma, gastric cancer, esophageal carcinoma, CRC, HCC, biliary tract carcinoma, cervical cancer, RCC, endometrial carcinoma, TNBC, previously untreated NSCLC, or for the adjuvant treatment of melanoma, NSCLC 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 urothelial carcinoma patients treated with KEYTRUDA in combination with enfortumab vedotin, administer KEYTRUDA after enfortumab vedotin when given on the same day.

For urothelial carcinoma patients treated with KEYTRUDA in combination with enfortumab vedotin, the recommended initial dose of enfortumab vedotin is 1.25 mg/kg (up to a maximum of 125 mg for patients ≥ 100 kg) as an intravenous solution on Days 1 and 8 of a 21-day cycle until disease progression or unacceptable toxicity.

For neoadjuvant and adjuvant treatment of cisplatin-eligible MIBC patients with KEYTRUDA in combination with enfortumab vedotin, the recommended dose of enfortumab vedotin is 1.25 mg/kg (up to a maximum of 125 mg for patients ≥ 100 kg). Enfortumab vedotin is administered as an intravenous solution as neoadjuvant treatment on Days 1 and 8 of each 21-day cycle for 4 cycles followed by adjuvant treatment on Days 1 and 8 of each 21-day cycle for 5 cycles.

For neoadjuvant and adjuvant treatment of cisplatin-ineligible MIBC patients with KEYTRUDA in combination with enfortumab vedotin, the recommended dose of enfortumab vedotin is 1.25 mg/kg (up to a maximum of 125 mg for patients ≥100 kg). Enfortumab vedotin is administered as an intravenous solution as neoadjuvant treatment on Days 1 and 8 of each 21-day cycle for 3 cycles followed by adjuvant treatment on Days 1 and 8 of each 21-day cycle for 6 cycles.

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 and RCC 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, NSCLC 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 resectable NSCLC, patients should be treated with neoadjuvant KEYTRUDA in combination with chemotherapy for 12 weeks or until disease progression that precludes definitive surgery or unacceptable toxicity, followed by adjuvant treatment with KEYTRUDA as monotherapy for 39 weeks or until disease recurrence or unacceptable toxicity.

For neoadjuvant and adjuvant treatment of cisplatin-eligible MIBC, patients should be treated with neoadjuvant KEYTRUDA 200 mg every 3 weeks for 4 doses or 400 mg every 6 weeks for 2 doses in combination with enfortumab vedotin or until disease progression that precludes radical cystectomy or unacceptable toxicity, followed by adjuvant treatment with KEYTRUDA 200 mg every 3 weeks for 13 doses or 400 mg every 6 weeks for 7 doses in combination with enfortumab vedotin or until disease recurrence or unacceptable toxicity.

For neoadjuvant and adjuvant treatment of cisplatin-ineligible MIBC, patients should be treated with neoadjuvant KEYTRUDA 200 mg every 3 weeks for 3 doses in combination with enfortumab vedotin or until disease progression that precludes radical cystectomy or unacceptable toxicity, followed by adjuvant treatment with KEYTRUDA 200 mg every 3 weeks for 14 doses or 400 mg every 6 weeks for 7 doses in combination with enfortumab vedotin 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.

Neoadjuvant treatment with KEYTRUDA for 2 doses of 200 mg every 3 weeks or 1 dose of 400 mg every 6 weeks or until disease progression that precludes definitive surgery or unacceptable toxicity, continued as adjuvant treatment in combination with RT with or without concomitant cisplatin for 3 doses of 200 mg every 3 weeks or 2 doses of 400 mg every 6 weeks followed by 12 doses of 200 mg every 3 weeks or 6 doses of 400 mg every 6 weeks as monotherapy or until disease recurrence or unacceptable toxicity.

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 ≥ 3 hyperglycemia (glucose >250 mg/dL or >13.9 mmol/L) or associated with ketoacidosis Hyperthyroidism Grade ≥ 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/non-HCC For liver enzyme elevations in RCC patients treated with combination therapy with axitinib, see dosing guidelines following this table.	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*
	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 ≥ 50% relative to baseline and lasts ≥ 1 week	Permanently discontinue
Immune-mediated hepatitis/HCC	AST or ALT with baseline <2 times ULN and increases to ≥ 5 times ULN; AST or ALT with baseline ≥ 2 times ULN and increases to >3 times baseline; or AST or ALT >500 U/L regardless of baseline levels	Withhold until adverse reactions recover to Grade 0-1*

	Total bilirubin with baseline levels <1.5 mg/dL and increases to >2 mg/dL; total bilirubin with baseline levels ≥ 1.5 mg/dL and increases to ≥ 2 times baseline; or total bilirubin >3.0 mg/dL regardless of baseline levels	
	ALT >20 times ULN; Child Pugh score ≥ 9 points; gastrointestinal bleeding suggestive of portal hypertension; ascites; or encephalopathy	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 or 4)	Permanently discontinue

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 or discontinue lenvatinib to manage adverse reactions as appropriate. For recommendations for management of adverse reactions of lenvatinib, refer to the prescribing information for lenvatinib. No dose reductions are recommended for KEYTRUDA.

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.
- Chemical and physical in-use stability has been demonstrated for up to 42 days at 2°C to 8°C or 23°C to 27°C.
- The product does not contain preservative. Aseptic handling should be ensured during the preparation of infusion. 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 up to 12 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 7 days. 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 melanoma and 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 or moderate hepatic impairment. KEYTRUDA has not been studied in patients with 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-mediated 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 ≤ 1 and corticosteroid dose has been reduced to ≤ 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 ≤ 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, encephalitis, sarcoidosis, myasthenic syndrome, myelitis, vasculitis, hypoparathyroidism, gastritis, hemolytic anemia, and pericarditis. The following were reported in other clinical studies with KEYTRUDA or in postmarketing use: myocarditis, sclerosing cholangitis, aplastic anaemia, exocrine pancreatic insufficiency, and myocarditis-myositis-myasthenia gravis overlap syndrome.

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 or MSI-H 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, anaemia, cough, and constipation.

Efficacy for pediatric patients with melanoma and 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-mediated 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.

Pembrolizumab in monotherapy (see section 2)

The safety of pembrolizumab as monotherapy has been evaluated in 7,631 patients across tumour types and across four doses (2 mg/kg bw every 3 weeks, 200 mg every 3 weeks, or 10 mg/kg bw every 2 or 3 weeks) in clinical studies. In this patient population, the median observation time was 8.5 months (range: 1 day to 39 months) and the most frequent adverse reactions with pembrolizumab were fatigue (31%), diarrhoea (22%), and nausea (20%). The majority of adverse reactions reported for monotherapy were of Grades 1 or 2 severity. The most serious adverse reactions were immune-mediated adverse reactions and severe infusion-related reactions *[See Warnings and Precautions (4)]*. The incidences of immune-mediated adverse reactions were 37% all Grades and 9% for Grades 3-5 for pembrolizumab monotherapy in the adjuvant setting and 25% all Grades and 6% for Grades 3-5 in the metastatic setting. No new immune-mediated adverse reactions were identified in the adjuvant setting.

Pembrolizumab in combination with chemotherapy, radiation therapy (RT) or chemoradiotherapy (CRT) (see section 2)

When pembrolizumab is administered in combination, refer to the prescribing information for the respective combination therapy components prior to initiation of treatment.

The safety of pembrolizumab in combination with chemotherapy, RT or CRT has been evaluated in 6 695 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 nausea (51%), anaemia (50%), diarrhoea (35%), fatigue (35%), constipation (32%), vomiting (27%), neutrophil count decreased (26%), and decreased appetite (26%). Incidences of Grades 3-5 adverse reactions in patients with NSCLC were 69% for pembrolizumab combination therapy and 61% for chemotherapy alone, in patients with HNSCC were 80% for pembrolizumab combination therapy (chemotherapy or RT with or without chemotherapy), and 79% for chemotherapy plus cetuximab or RT with or without chemotherapy, in patients with oesophageal 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, in patients with cervical cancer were 77% for pembrolizumab combination therapy (chemotherapy with or without bevacizumab or in combination with CRT) and 71% for chemotherapy with or without bevacizumab or CRT alone, in patients with gastric cancer were 74% for pembrolizumab combination therapy (chemotherapy with or without trastuzumab) and 68% for chemotherapy with or without trastuzumab,

in patients with biliary tract carcinoma were 85% for pembrolizumab combination therapy and 84% for chemotherapy alone, in patients with EC were 59% for pembrolizumab combination therapy and 46% for chemotherapy alone and in patients with malignant pleural mesothelioma were 44% for pembrolizumab combination therapy and 30% for chemotherapy alone.

Pembrolizumab in combination with tyrosine kinase inhibitor (TKI) (see section 2)

When pembrolizumab is administered in combination with axitinib or lenvatinib, refer to the prescribing information for axitinib or lenvatinib prior to initiation of treatment. For additional axitinib safety information for elevated liver enzymes see also section 4.

The safety of pembrolizumab in combination with axitinib or lenvatinib in advanced RCC, and in combination with lenvatinib in advanced EC has been evaluated in a total of 1,456 patients with advanced RCC or advanced EC receiving 200 mg pembrolizumab every 3 weeks with either axitinib 5 mg twice daily or lenvatinib 20 mg once daily in clinical studies, as appropriate. In these patient populations, the most frequent adverse reactions were diarrhoea (58%), hypertension (54%), hypothyroidism (46%), fatigue (41%), decreased appetite (40%), nausea (40%), arthralgia (30%), vomiting (28%), weight decreased (28%), dysphonia (28%), abdominal pain (28%), proteinuria (27%), palmar-plantar erythrodysaesthesia syndrome (26%), rash (26%), stomatitis (25%), constipation (25%), musculoskeletal pain (23%), headache (23%) and cough (21%). Grades 3-5 adverse reactions in patients with RCC were 80% for pembrolizumab in combination with either axitinib or lenvatinib and 71% for sunitinib alone. In patients with EC, Grades 3-5 adverse reactions were 89% for pembrolizumab in combination with lenvatinib and 73% for chemotherapy alone.

Tabulated summary of adverse reactions

Adverse reactions observed in clinical studies of pembrolizumab as monotherapy or in combination with chemotherapy, RT or CRT or other anti-tumour medicines or reported from post-marketing use of pembrolizumab are listed in Table 2. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 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. Adverse reactions known to occur with pembrolizumab or combination therapy components given alone may occur during treatment with these medicinal products in combination, even if these reactions were not reported in clinical studies with combination therapy.

For additional safety information when pembrolizumab is administered in combination, refer to the prescribing information for the respective combination therapy components.

Table 2: Adverse reactions in patients treated with pembrolizumab†

	Monotherapy	**In combination with chemotherapy, radiation therapy or chemoradiotherapy**	**In combination with axitinib or lenvatinib**
Infections and infestations			
Very common			urinary tract infection
Common	pneumonia	pneumonia	pneumonia
Blood and lymphatic system disorders			
Very common	anaemia	anaemia, neutropenia, thrombocytopenia	anaemia
Common	thrombocytopenia, neutropenia, lymphopenia	febrile neutropenia, leukopenia, lymphopenia	neutropenia, thrombocytopenia, lymphopenia, leukopenia
Uncommon	leukopenia, immune thrombocytopenia, eosinophilia	haemolytic anaemia*, eosinophilia	eosinophilia
Rare	haemolytic anaemia*, haemophagocytic lymphohistiocytosis, pure red cell aplasia	immune thrombocytopenia	

Immune system disorders			
Common	infusion-related reaction*	infusion-related reaction*	infusion-related reaction*
Uncommon	sarcoidosis*		
Rare		sarcoidosis	
Not known	solid organ transplant rejection		
Endocrine disorders			
Very common	hypothyroidism*	hypothyroidism*	hypothyroidism
Common	hyperthyroidism	adrenal insufficiency*, hyperthyroidism*, thyroiditis*	adrenal insufficiency*, hyperthyroidism, thyroiditis*
Uncommon	adrenal insufficiency*, hypophysitis*, thyroiditis*	hypophysitis*	hypophysitis*
Rare	hypoparathyroidism	hypoparathyroidism	hypoparathyroidism
Metabolism and nutrition disorders			
Very common	decreased appetite	hypokalaemia, decreased appetite	decreased appetite
Common	hyponatraemia, hypokalaemia, hypocalcaemia	hyponatraemia, hypocalcaemia	hyponatraemia, hypokalaemia, hypocalcaemia
Uncommon	type 1 diabetes mellitus*	type 1 diabetes mellitus*	type 1 diabetes mellitus*
Psychiatric disorders			
Very common		insomnia	
Common	insomnia		insomnia
Nervous system disorders			
Very common	headache	neuropathy peripheral, headache	headache, dysgeusia
Common	dizziness, neuropathy peripheral, lethargy, dysgeusia	dizziness, dysgeusia	dizziness, neuropathy peripheral, lethargy
Uncommon	myasthenic syndrome*, epilepsy	encephalitis*, epilepsy, lethargy	myasthenic syndrome*, encephalitis*
Rare	Guillain-Barré syndrome*, encephalitis*, myelitis*, optic neuritis, meningitis	myasthenic syndrome*, Guillain-Barré syndrome*, myelitis, optic neuritis,	optic neuritis

	(aseptic)*	meningitis (aseptic)	
Eye disorders			
Common	dry eye	dry eye	dry eye
Uncommon	uveitis*	uveitis*	uveitis*
Rare	Vogt-Koyanagi-Harada syndrome		Vogt-Koyanagi-Harada syndrome
Cardiac disorders			
Common	cardiac arrhythmia‡ (including atrial fibrillation)	cardiac arrhythmia‡ (including atrial fibrillation)	cardiac arrhythmia‡ (including atrial fibrillation)
Uncommon	myocarditis, pericarditis*, pericardial effusion	myocarditis*, pericarditis*, pericardial effusion	myocarditis, pericardial effusion
Vascular disorders			
Very common			hypertension
Common	hypertension	hypertension	
Uncommon		vasculitis*	vasculitis*
Rare	vasculitis*		
Respiratory, thoracic and mediastinal disorders			
Very common	dyspnoea, cough	dyspnoea, cough	dyspnoea, cough
Common	pneumonitis*	pneumonitis*	pneumonitis*
Gastrointestinal disorders			
Very common	diarrhoea, abdominal pain*, nausea, vomiting, constipation	diarrhoea, nausea, vomiting, abdominal pain*, constipation	diarrhoea, abdominal pain*, nausea, vomiting, constipation
Common	colitis*, dry mouth	colitis*, gastritis*, dry mouth	colitis*, pancreatitis*, gastritis*, dry mouth
Uncommon	pancreatitis*, gastritis*, gastrointestinal ulceration*	pancreatitis*, gastrointestinal ulceration*	gastrointestinal ulceration*
Rare	pancreatic exocrine insufficiency, small intestinal perforation, coeliac disease	pancreatic exocrine insufficiency, small intestinal perforation, coeliac disease	small intestinal perforation
Not known			pancreatic exocrine insufficiency, coeliac disease

Hepatobiliary disorders			
Common	hepatitis*	hepatitis*	hepatitis*
Rare	cholangitis sclerosing	cholangitis sclerosing*	
Skin and subcutaneous tissue disorders			
Very common	pruritus*, rash*	rash*, alopecia, pruritus*	rash*, pruritus*
Common	severe skin reactions*, erythema, dermatitis, dry skin, vitiligo*, eczema, alopecia, dermatitis acneiform	severe skin reactions*, erythema, dermatitis, dry skin, dermatitis acneiform, eczema	severe skin reactions*, dermatitis, dry skin, erythema, dermatitis acneiform, alopecia
Uncommon	psoriasis, lichenoid keratosis*, papule, hair colour changes	psoriasis, lichenoid keratosis*, vitiligo*, papule	eczema, lichenoid keratosis*, psoriasis, vitiligo*, papule, hair colour changes
Rare	Stevens-Johnson syndrome, erythema nodosum, toxic epidermal necrolysis	Stevens-Johnson syndrome, erythema nodosum, hair colour changes	toxic epidermal necrolysis, Stevens-Johnson syndrome
Musculoskeletal and connective tissue disorders			
Very common	musculoskeletal pain*, arthralgia	musculoskeletal pain*, arthralgia	arthralgia, musculoskeletal pain*, myositis*, pain in extremity
Common	myositis*, pain in extremity, arthritis*	myositis*, pain in extremity, arthritis*	arthritis*
Uncommon	tenosynovitis*	tenosynovitis*	tenosynovitis*
Rare	Sjogren's syndrome	Sjogren's syndrome	Sjogren's syndrome
Renal and urinary disorders			
Common		acute kidney injury	nephritis*
Uncommon	nephritis*	nephritis*, cystitis noninfective	
Rare	cystitis noninfective		cystitis noninfective
General disorders and administration site conditions			
Very common	fatigue, asthenia, oedema*, pyrexia	fatigue, asthenia, pyrexia, oedema*	fatigue, asthenia, oedema*, pyrexia

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

- haemolytic anaemia (autoimmune haemolytic anaemia and Coombs negative haemolytic anaemia)
- infusion-related reaction (drug hypersensitivity, anaphylactic reaction, anaphylactoid reaction, hypersensitivity, infusion-related hypersensitivity reaction, cytokine release syndrome and serum sickness)
- sarcoidosis (cutaneous sarcoidosis and pulmonary sarcoidosis)
- hypothyroidism (myxoedema, immune-mediated hypothyroidism and autoimmune hypothyroidism)
- adrenal insufficiency (Addison's disease, adrenocortical insufficiency acute, secondary adrenocortical insufficiency and primary adrenal insufficiency)

- thyroiditis (autoimmune thyroiditis, silent thyroiditis, thyroid disorder, thyroiditis acute and immune-mediated thyroiditis)
- hyperthyroidism (Graves' disease)
- hypophysitis (hypopituitarism and lymphocytic hypophysitis)
- type 1 diabetes mellitus (diabetic ketoacidosis)
- myasthenic syndrome (myasthenia gravis, including exacerbation)
- encephalitis (autoimmune encephalitis and noninfective encephalitis)
- Guillain-Barré syndrome (axonal neuropathy and demyelinating polyneuropathy)
- myelitis (including transverse myelitis)
- meningitis aseptic (meningitis and meningitis noninfective)
- uveitis (chorioretinitis, iritis and iridocyclitis)
- myocarditis (autoimmune myocarditis)
- pericarditis (autoimmune pericarditis, pleuropericarditis and myopericarditis)
- vasculitis (central nervous system vasculitis, aortitis and giant cell arteritis)
- pneumonitis (interstitial lung disease, organising pneumonia, immune-mediated pneumonitis, immune-mediated lung disease and autoimmune lung disease)
- abdominal pain (abdominal discomfort, abdominal pain upper and abdominal pain lower)
- colitis (colitis microscopic, enterocolitis, enterocolitis haemorrhagic, autoimmune colitis and immune-mediated enterocolitis)
- gastritis (gastritis erosive, gastritis haemorrhagic and immune-mediated gastritis)
- pancreatitis (autoimmune pancreatitis, pancreatitis acute and immune-mediated pancreatitis)
- gastrointestinal ulceration (gastric ulcer and duodenal ulcer)
- hepatitis (autoimmune hepatitis, immune-mediated hepatitis, drug induced liver injury and acute hepatitis)
- cholangitis sclerosing (immune-mediated cholangitis)
- pruritus (urticaria, urticaria papular and pruritus genital)
- rash (rash erythematous, rash follicular, rash macular, rash maculo-papular, rash papular, rash pruritic, rash vesicular and genital rash)
- severe skin reactions (exfoliative rash, pemphigus, and Grade ≥ 3 of the following: cutaneous vasculitis, 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)
- vitiligo (skin depigmentation, skin hypopigmentation and hypopigmentation of the eyelid)
- lichenoid keratosis (lichen planus and lichen sclerosus)

- musculoskeletal pain (musculoskeletal discomfort, back pain, musculoskeletal stiffness, musculoskeletal chest pain and torticollis)
- myositis (myalgia, myopathy, necrotising myositis, polymyalgia rheumatica and rhabdomyolysis)
- arthritis (joint swelling, polyarthritis, joint effusion, autoimmune arthritis and immune-mediated arthritis)
- tenosynovitis (tendonitis, synovitis and tendon pain)
- nephritis (autoimmune nephritis, immune-mediated nephritis, tubulointerstitial nephritis and renal failure, renal failure acute, or acute kidney injury with evidence of nephritis, nephrotic syndrome, glomerulonephritis, glomerulonephritis membranous and glomerulonephritis acute)
- oedema (oedema peripheral, generalised oedema, fluid overload, fluid retention, eyelid oedema and lip oedema, face oedema, localised oedema and periorbital oedema)

Pembrolizumab in combination with enfortumab vedotin

When pembrolizumab is administered in combination with enfortumab vedotin, refer to the prescribing information for enfortumab vedotin prior to initiation of treatment.

The safety of pembrolizumab in combination with enfortumab vedotin has been evaluated among 564 patients with unresectable or metastatic urothelial carcinoma receiving 200 mg pembrolizumab on Day 1 and enfortumab vedotin 1.25 mg/kg on Days 1 and 8 of each 21-day cycle.

Overall, the incidence of adverse reactions for pembrolizumab in combination with enfortumab vedotin was observed to be higher than for pembrolizumab monotherapy reflecting the contribution of enfortumab vedotin and the longer duration of treatment of the combination therapy.

Adverse reactions were generally similar to those observed in patients receiving pembrolizumab or enfortumab vedotin as monotherapy. The incidence of rash maculo-papular was 36% all Grades (10% Grades 3-4), which is higher than observed in pembrolizumab monotherapy.

Generally, adverse event frequencies were higher in patients ≥ 65 years of age compared to < 65 years of age, particularly for serious adverse events (56.3% and 35.3%, respectively) and ≥ Grade 3 events (80.3% and 64.2%, respectively), similar to observations with the chemotherapy comparator.

The safety of pembrolizumab in combination with enfortumab vedotin has been evaluated among 570 patients with MIBC receiving 200 mg pembrolizumab on Day 1 and enfortumab vedotin 1.25 mg/kg on Days 1 and 8 of each 21-day cycle as neoadjuvant treatment and continued after radical cystectomy as adjuvant treatment. Overall, the incidence of adverse reactions for

pembrolizumab in combination with enfortumab vedotin was observed to be higher than for pembrolizumab monotherapy reflecting the contribution of enfortumab vedotin. Adverse reactions were generally similar to those occurring in patients with unresectable or metastatic urothelial carcinoma treated with pembrolizumab in combination with enfortumab vedotin.

Description of selected adverse reactions

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

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

Immune-mediated pneumonitis

Pneumonitis occurred in 324 (4.2%) patients, including Grade 2, 3, 4 or 5 cases in 143 (1.9%), 81 (1.1%), 19 (0.2%) and 9 (0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of pneumonitis was 3.9 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 (3.9%). Pneumonitis led to discontinuation of pembrolizumab in 131 (1.7%) patients. Pneumonitis resolved in 196 patients, 6 with sequelae.

In patients with NSCLC, pneumonitis occurred in 230 (6.1%), including Grade 2, 3, 4 or 5 cases in 103 (2.7%), 63 (1.7%), 17 (0.4%) and 10 (0.3%), respectively. In patients with locally advanced or metastatic 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-mediated colitis

Colitis occurred in 158 (2.1%) patients, including Grade 2, 3 or 4 cases in 49 (0.6%), 82 (1.1%) and 6 (0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of colitis was 4.3 months (range 2 days to 24.3 months). The median duration was 1.1 month (range 1 day to 45.2 months). Colitis led to discontinuation of pembrolizumab in 48 (0.6%) patients. Colitis resolved in 132 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-mediated hepatitis

Hepatitis occurred in 80 (1.0%) patients, including Grade 2, 3 or 4 cases in 12 (0.2%), 55 (0.7%) and 8 (0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of hepatitis was 3.5 months (range 8 days to 26.3 months). The median duration was 1.3 months (range 1 day to 29.0+ months). Hepatitis led to discontinuation of pembrolizumab in 37 (0.5%) patients. Hepatitis resolved in 60 patients.

Immune-mediated nephritis

Nephritis occurred in 37 (0.5%) patients, including Grade 2, 3 or 4 cases in 11 (0.1%), 19 (0.2%) and 2 (< 0.1%) patients, respectively, receiving pembrolizumab as monotherapy. The median time to onset of nephritis was 4.2 months (range 12 days to 21.4 months). The median duration was 3.3 months (range 6 days to 28.2+ months). Nephritis led to discontinuation of pembrolizumab in 17 (0.2%) patients. Nephritis resolved in 25 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-mediated endocrinopathies

Adrenal insufficiency occurred in 74 (1.0%) patients, including Grade 2, 3 or 4 cases in 34 (0.4%), 31 (0.4%) and 4 (0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of adrenal insufficiency was 5.4 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 13 (0.2%) patients. Adrenal insufficiency resolved in 28 patients, 11 with sequelae.

Hypophysitis occurred in 52 (0.7%) patients, including Grade 2, 3 or 4 cases in 23 (0.3%), 24 (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 3.6 months (range 3 days to 48.1+ months). Hypophysitis led to discontinuation of pembrolizumab in 14 (0.2%) patients. Hypophysitis resolved in 23 patients, 8 with sequelae.

Hyperthyroidism occurred in 394 (5.2%) patients, including Grade 2 or 3 cases in 108 (1.4%) and 9 (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 4 (0.1%) patients. Hyperthyroidism resolved in 326 (82.7%) patients, 11 with sequelae. In patients with melanoma, NSCLC and RCC treated with pembrolizumab monotherapy in the adjuvant setting (n=2,060), the incidence of hyperthyroidism was 11.0%, the majority of which were Grade 1 or 2.

Hypothyroidism occurred in 939 (12.3%) patients, including Grade 2 or 3 cases in 687 (9.0%) 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 63.0+ months). Hypothyroidism led to discontinuation of pembrolizumab in 6 (0.1%) patients. Hypothyroidism resolved in 216 (23.0%) 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 recurrent or metastatic 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 recurrent or metastatic 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 resectable locally advanced HNSCC treated with pembrolizumab as neoadjuvant treatment and in combination with radiation therapy with or without concomitant cisplatin for adjuvant treatment (n=361), the incidence of hypothyroidism was 24.7%, all of which were Grade 1 or 2. In patients treated with pembrolizumab in combination with axitinib or lenvatinib (n=1 456), the incidence of hypothyroidism was 46.2% (all Grades) with 0.8% Grade 3 or 4. In patients with melanoma, NSCLC and RCC treated with pembrolizumab monotherapy in the adjuvant setting (n=2 060), the incidence of hypothyroidism was 18.5%, the majority of which were Grade 1 or 2.

Immune-mediated skin adverse reactions

Immune-mediated severe skin reactions occurred in 130 (1.7%) patients, including Grade 2, 3, 4 or 5 cases in 11 (0.1%), 103 (1.3%), 1 (< 0.1%) and 1 (< 0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of severe skin reactions was 2.8 months (range 2 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 18 (0.2%) patients. Severe skin reactions resolved in 95 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 cHL

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 ≥ 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, 7.3% for sodium decreased, 5.7% for haemoglobin decreased, 4.6% for glucose increased, 4.5% for phosphate decreased, 3.1% for ALT increased, 2.9% for AST increased, 2.6% for alkaline phosphatase increased, 2.2% for potassium decreased, 2.1% for neutrophils decreased, 1.7% for bilirubin increased, 1.7% for platelets decreased, 1.7% for potassium increased, 1.6% for calcium increased, 1.4% for albumin decreased, 1.3% for calcium decreased, 1.2% for creatinine increased, 0.8% for leukocytes decreased, 0.8% for magnesium increased, 0.6% for glucose decreased, 0.2% for magnesium decreased, and 0.2% for sodium increased.

In patients treated with pembrolizumab in combination with chemotherapy, RT or CRT, the proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 36.2% for neutrophils decreased, 31.9% for lymphocytes decreased, 23.7% for leukocytes decreased, 20.3% for haemoglobin decreased, 11.8% for platelets decreased, 9.6% for sodium

decreased, 7.8% for potassium decreased, 7.2% for phosphate decreased, 5.5% for glucose increased, 5.2% for ALT increased, 4.6% for AST increased, 3.4% for calcium decreased, 3.0% for bilirubin increased, 3.0% for potassium increased, 2.9% for creatinine increased, 2.4% for alkaline phosphatase increased, 2.2% for albumin decreased, 1.6% for calcium increased, 0.8% for glucose decreased and 0.4% for sodium increased.

In patients treated with pembrolizumab in combination with axitinib or lenvatinib, the proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 23.0% for lipase increased (not measured in patients treated with pembrolizumab and axitinib), 12.3% for lymphocyte decreased, 11.4% for sodium decreased, 11.2% for amylase increased, 11.2% for triglycerides increased, 10.4% for ALT increased, 8.9% for AST increased, 7.8% for glucose increased, 6.8% for phosphate decreased, 6.1% for potassium decreased, 5.1% for potassium increased, 4.5% for cholesterol increased, 4.4% for creatinine increased, 4.2% for haemoglobin decreased, 4.0% for neutrophils decreased, 3.1% for alkaline phosphatase increased, 3.0% for platelets decreased, 2.8% for bilirubin increased, 2.2% for calcium decreased, 2.2% for magnesium increased, 1.7% for leukocytes decreased, 1.5% for magnesium decreased, 1.5% for prothrombin INR increased, 1.4% for glucose decreased, 1.2% for albumin decreased, 1.0% for calcium increased, 0.4% for sodium increased, and 0.1% for haemoglobin increased.

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

Melanoma

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

The efficacy of KEYTRUDA was 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 ≥ 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 monthsᵖ	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

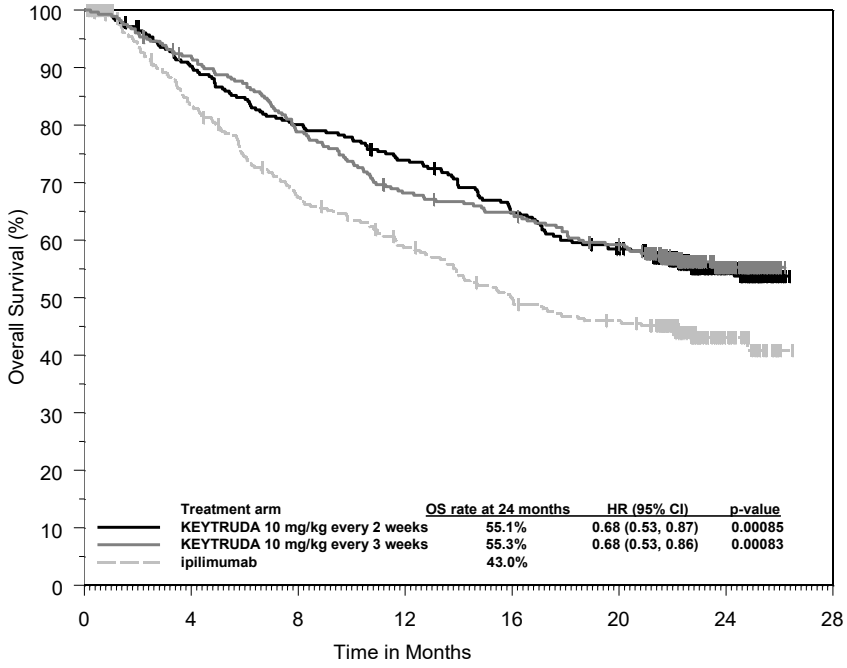
ᵖ Based on Kaplan-Meier estimates

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.

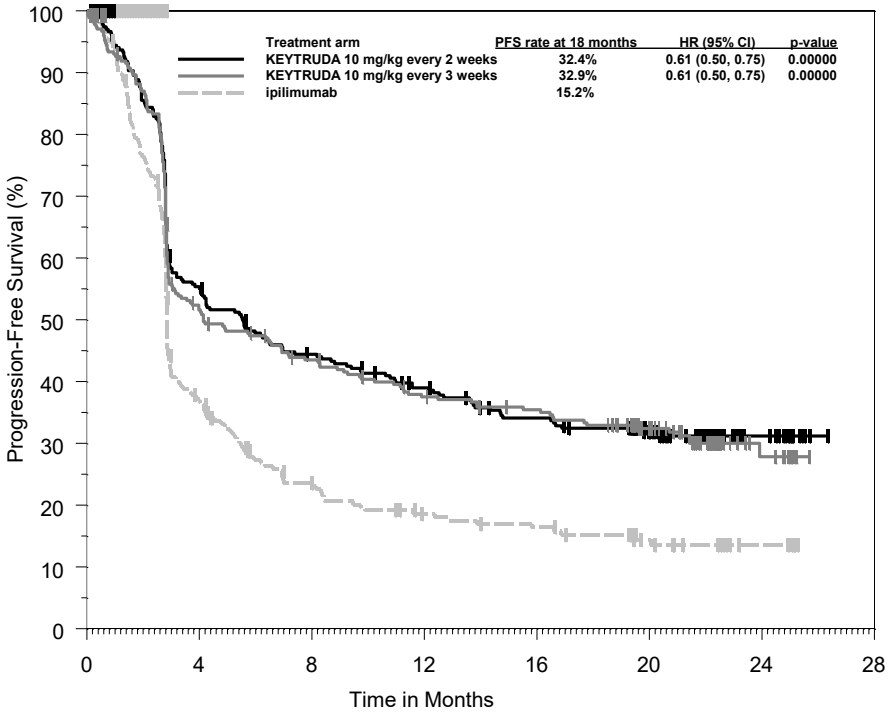
Figure 1: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-006 (Intent to Treat Population)



Number at Risk

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								
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 0.53 (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 efficacy of KEYTRUDA was 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	0.011è	---
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 INVÞ			
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 Durationß 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 monthsà	73%	79%	Not reachedð

* 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

Þ INV=Investigator assessment using RECIST 1.1

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

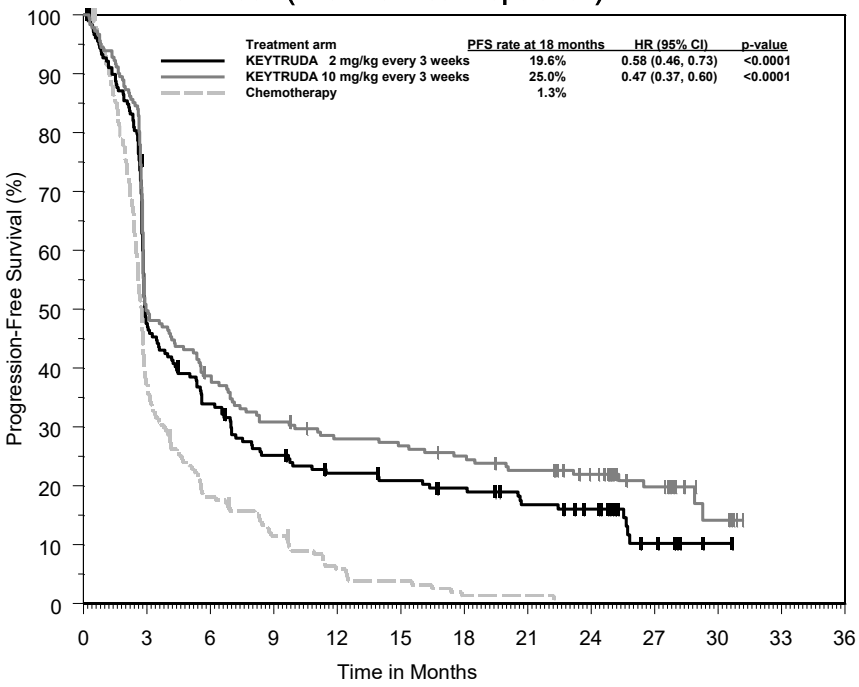
à Based on Kaplan-Meier estimates

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

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	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 ≥ 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 efficacy of KEYTRUDA was 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 ≥ 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 ≥ 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-716: Placebo-controlled trial for the adjuvant treatment of patients with completely resected Stage IIB or IIC melanoma

The efficacy of KEYTRUDA was investigated in KEYNOTE-716, a multicenter, randomized, double-blind, placebo-controlled trial in patients with completely resected stage IIB or IIC melanoma. A total of 976 patients were randomized (1:1) to receive KEYTRUDA 200 mg or the pediatric (≥ 12 years old) dose of KEYTRUDA 2 mg/kg intravenously (up to a maximum of 200 mg) every three weeks (n=487) or placebo (n=489) for up to one year, until disease recurrence, or until unacceptable toxicity. Randomization was stratified by American Joint Committee on Cancer 8th edition (AJCC) T stage. Patients must not have been previously treated for melanoma beyond complete surgical resection for their melanoma prior to study entry. Patients with active autoimmune disease or a medical condition that required immunosuppression or mucosal or ocular melanoma were ineligible. Patients underwent imaging every 6 months for 1 year from randomization, every 6 months from years 2 to 4, and then once in year 5 from randomization or until recurrence, whichever came first.

Among the 976 patients, the baseline characteristics were: median age of 61 years (range: 16 to 87), 39% age 65 or older; 2 adolescent patients [one per treatment arm]; 60% male; and 93% ECOG PS of 0 and 7% ECOG PS of 1. Sixty-four percent had stage IIB and 35% had stage IIC.

The primary efficacy outcome measure was investigator-assessed recurrence free survival (RFS) in the whole population, 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. OS was not formally assessed at the time of these analyses.

The trial initially demonstrated a statistically significant improvement in RFS and DMFS for patients randomized to the pembrolizumab arm compared with placebo. Results reported from the pre-specified interim analysis for RFS with a median follow-up of 14.3 months are summarized in Table 6. Results reported from the pre-specified interim analysis for DMFS with a median follow-up of 26.9 months are summarized in Table 6 and Figure 5.

Table 6: Efficacy Results in KEYNOTE-716

Endpoint	KEYTRUDA 200 mg every 3 weeks n=487	Placebo n=489
RFS		
Number (%) of patients with event	54 (11%)	82 (17%)
RFS rate at 18 months	85.8%	77%
Median in months (95% CI)	NR (22.6, NR)	NR (NR, NR)
Hazard ratio* (95% CI)	0.65 (0.46, 0.92)	
p-Value (stratified log-rank)	0.00658	
DMFS		
Number (%) of patients with event	63 (13%)	95 (19%)
DMFS rate at 24 months	88.1%	82.2%
Median in months (95% CI)	NR (NR, NR)	NR (NR, NR)
Hazard ratio* (95% CI)	0.64 (0.47, 0.88)	
p-Value (stratified log-rank)	0.00292	

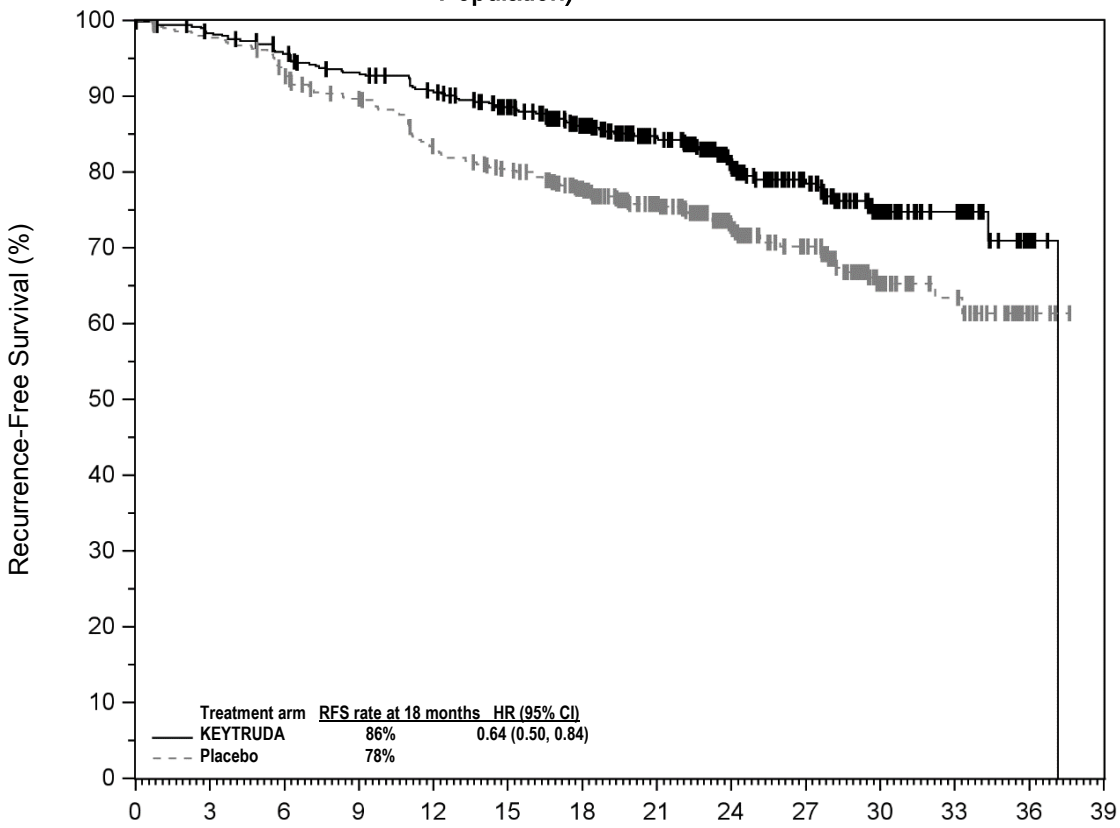
* Based on the stratified Cox proportional hazard model

NR=not reached

A pre-specified sensitivity analysis of RFS that included new primary melanomas was consistent with the primary RFS analysis, with an HR of 0.64 (95% CI: 0.46, 0.88).

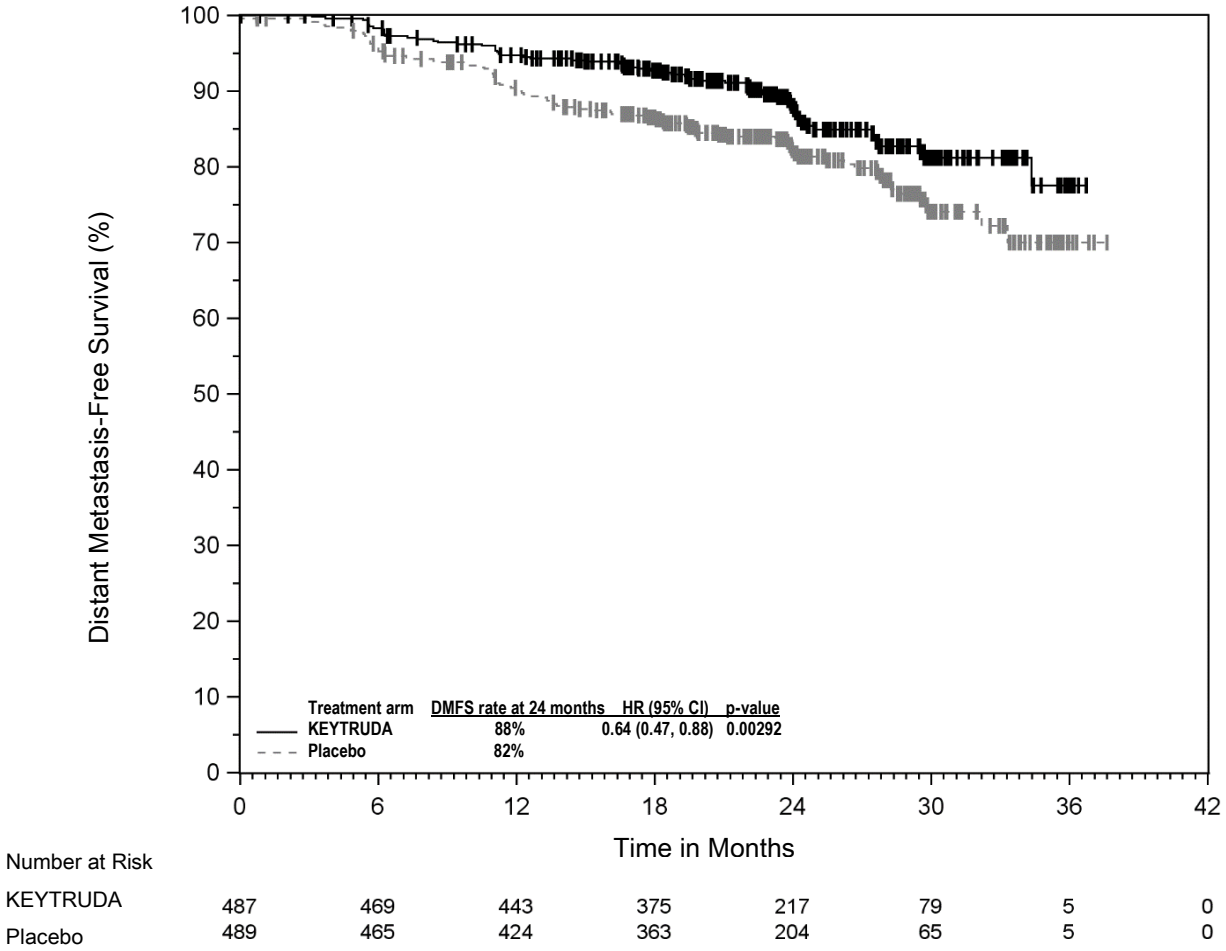
A pre-specified final analysis for RFS was performed with a median follow-up of 20.5 months (range: 4.6 to 32.7 months). At the time of this analysis, the hazard ratio in patients randomized to pembrolizumab versus patients randomized to placebo was 0.61 (95% CI: 0.45, 0.82) with 72/487 (14.8%) events and 115/489 (23.5%), respectively. Updated RFS results with a median follow-up of 26.9 months were consistent with the final analysis for RFS for patients randomized to the pembrolizumab arm compared with placebo (HR 0.64; 95% CI: 0.50, 0.84). These efficacy results are summarized in Figure 4.

Figure 4: Kaplan-Meier Curve for Recurrence-Free Survival in KEYNOTE-716 (Intent to Treat Population)



Number at Risk														
KEYTRUDA	487	472	456	440	424	401	351	300	204	148	73	33	5	0
Placebo	489	477	454	428	393	373	327	271	180	140	57	33	5	0

Figure 5: Kaplan-Meier Curve for Distant Metastasis-Free Survival in KEYNOTE-716 (Intent to Treat Population)



KEYNOTE-054: Placebo-controlled trial for the adjuvant treatment of patients with completely resected Stage III 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 until unacceptable toxicity. Randomization was stratified by AJCC 7th edition stage (IIIA vs. IIIB vs. IIIC 1-3 positive lymph nodes vs. IIIC ≥ 4 positive lymph nodes) and geographic region (North America, European countries, Australia, and other countries as designated). Patients must have undergone lymph node dissection and, if indicated, radiotherapy within 13 weeks prior to

starting treatment. 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 (≥ 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 ≥ 1%) according to an investigational use only (IUO) assay.

The primary efficacy outcome measures were investigator-assessed RFS in the whole population and in the population with PD-L1 positive tumors. The secondary outcome measures were 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. RFS efficacy results with a median follow-up time of 16.0 months are summarized in Table 7 and Figure 6. DMFS efficacy results with a median follow-up time of 45.5 months are summarized in Table 7 and Figure 7.

Table 7: 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 at 6 months	82%	73%
Median in months (95% CI)	NR (NR, 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 (49.6, 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

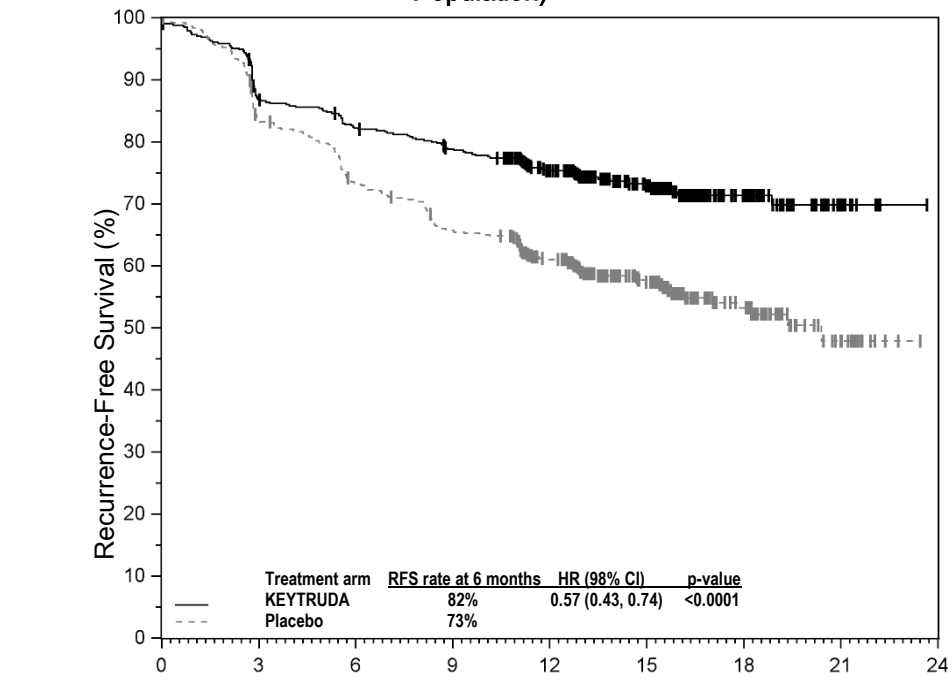
For patients in the whole population, the RFS rate at 42 months was 60% in the KEYTRUDA arm and 41% in the placebo arm (HR was 0.59 [95% CI: 0.49, 0.70]).

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.

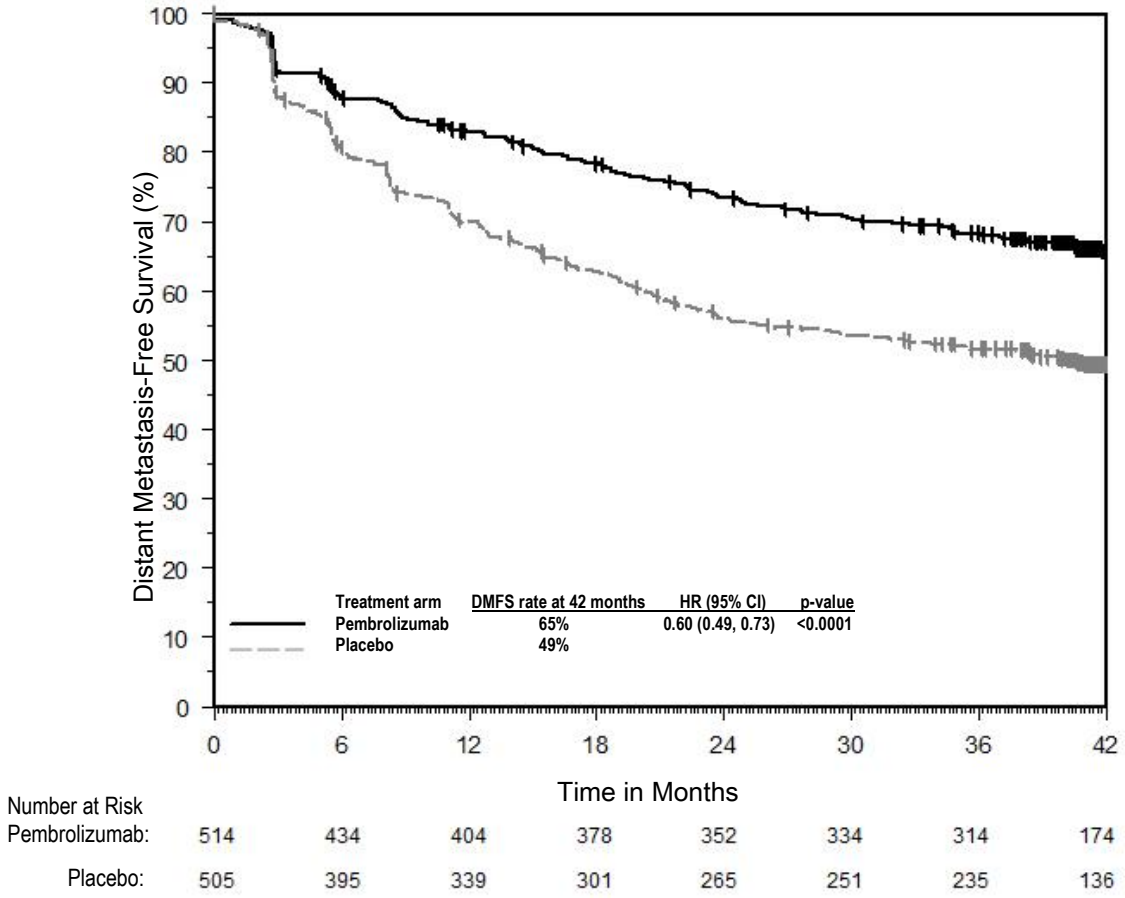
Figure 6: Kaplan-Meier Curve for Recurrence-Free Survival in KEYNOTE-054 (Intent to Treat Population)



Number at Risk

KEYTRUDA	514	438	413	392	313	182	73	15	0
Placebo	505	415	363	323	264	157	60	15	0

Figure 7: 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/m^2 and investigator's choice of cisplatin 75 mg/m^2 or carboplatin AUC 5 mg/mL/min intravenously every 3 weeks for 4 cycles followed by KEYTRUDA 200 mg and pemetrexed 500 mg/m^2 intravenously every 3 weeks.
- Placebo with pemetrexed 500 mg/m^2 and investigator's choice of cisplatin 75 mg/m^2 or carboplatin AUC 5 mg/mL/min intravenously every 3 weeks for 4 cycles followed by placebo and pemetrexed 500 mg/m^2 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 8 summarizes key efficacy measures.

Table 8: Response to KEYTRUDA, Pemetrexed, and Platinum Chemotherapy in Patients with Non-Squamous NSCLC in KEYNOTE-189

Endpoint	KEYTRUDA + Pemetrexed + Platinum Chemotherapy	Placebo + Pemetrexed + Platinum Chemotherapy

	n=410	n=206
OS		
Number (%) of patients with event	127 (31%)	108 (52%)
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

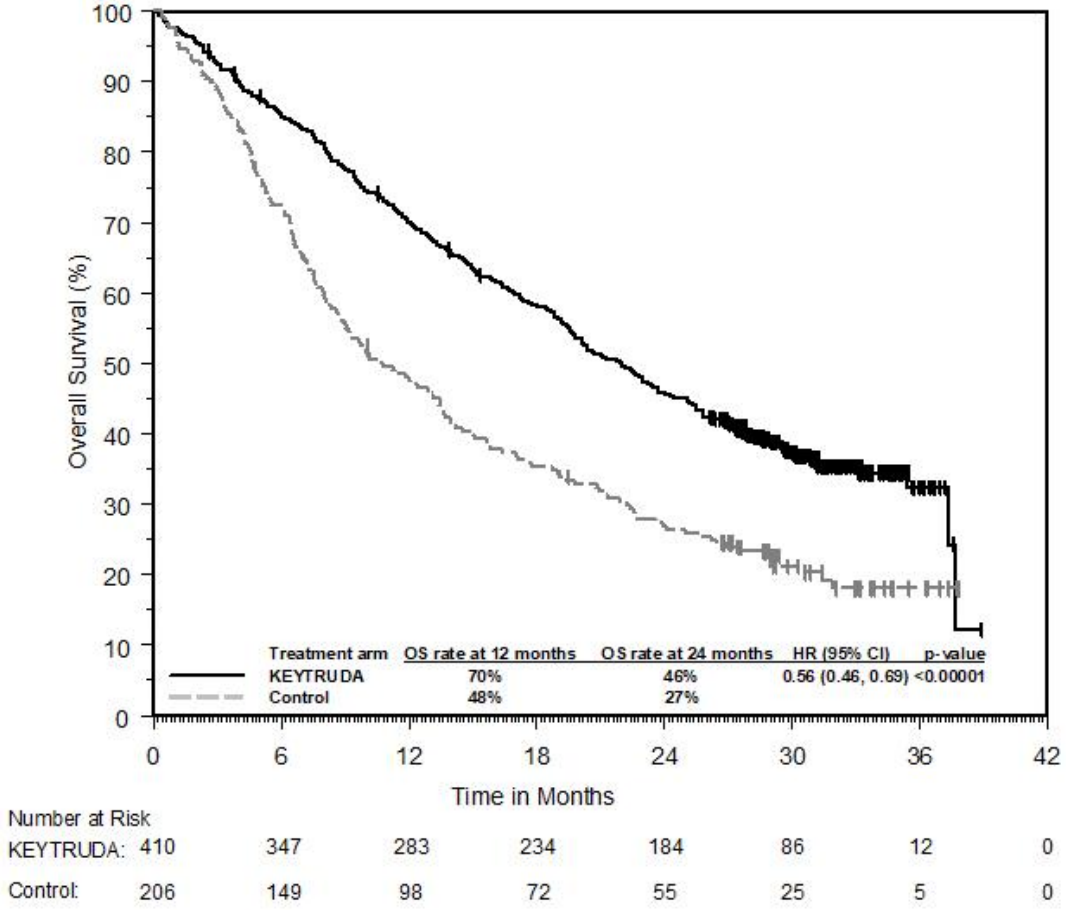
NA=not available

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 8 and 9.

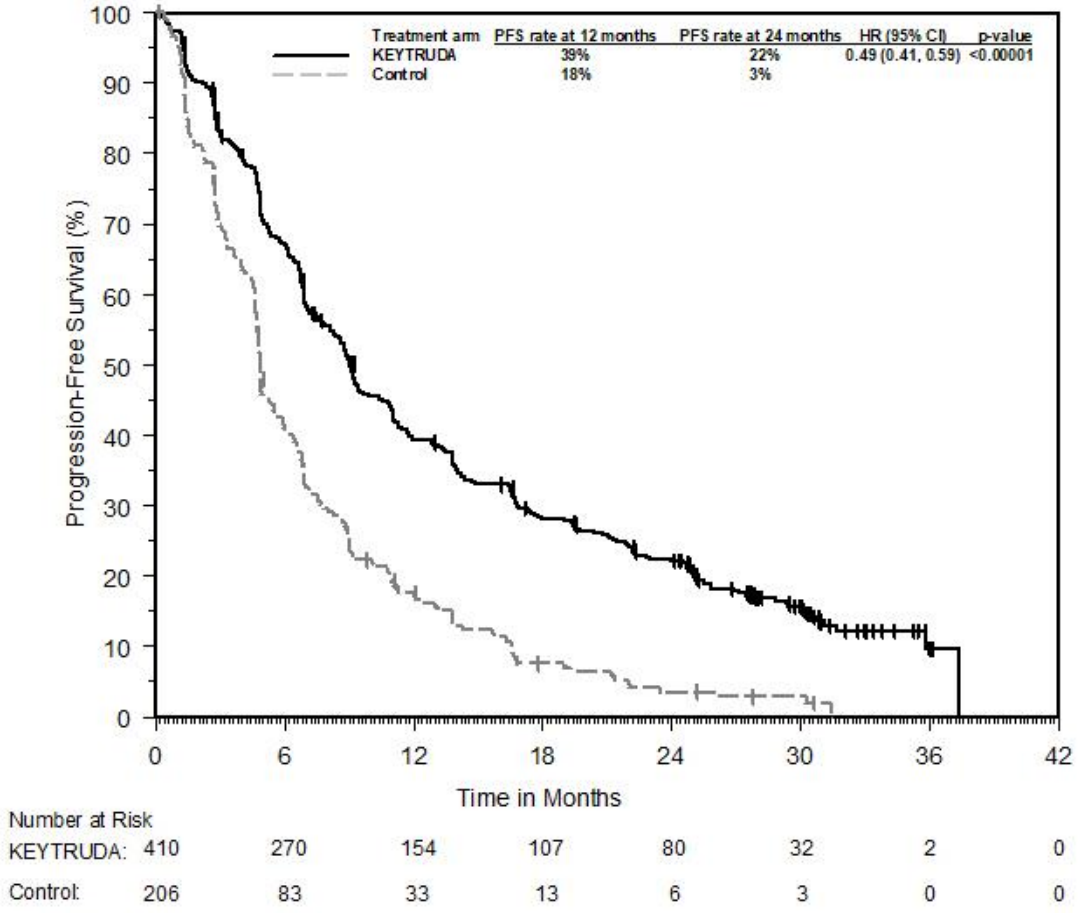
The ORR at the final analysis was 48% for the KEYTRUDA combination arm and 20% for the placebo plus chemotherapy arm. The median duration of response was 12.5 months (range 1.1+, 34.9+) for the KEYTRUDA combination arm and 7.1 months (range 2.4, 27.8+) for the placebo plus chemotherapy arm. The percentage 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 8: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-189 (Intent to Treat Population)



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

Figure 9: 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/m^2 on Day 1 of each 21-day cycle for 4 cycles or nab-paclitaxel 100 mg/m^2 on Days 1, 8 and 15 of each 21-day cycle for 4 cycles, followed by KEYTRUDA 200 mg every 3 weeks. KEYTRUDA was administered prior to chemotherapy on Day 1.
- Placebo and carboplatin AUC 6 mg/mL/min on Day 1 of each 21-day cycle for 4 cycles and paclitaxel 200 mg/m^2 on Day 1 of each 21-day cycle for 4 cycles or nab-paclitaxel 100 mg/m^2 on Days 1, 8 and 15 of each 21-day cycle for 4 cycles, followed by placebo every 3 weeks.

Treatment with KEYTRUDA 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 9).

Table 9: 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		
ORR†	58%	38%
(95% CI)	(52, 64)	(33, 44)
Response Duration		
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 10 and 11.

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 10: Kaplan-Meier Curve for Overall Survival in KEYNOTE-407

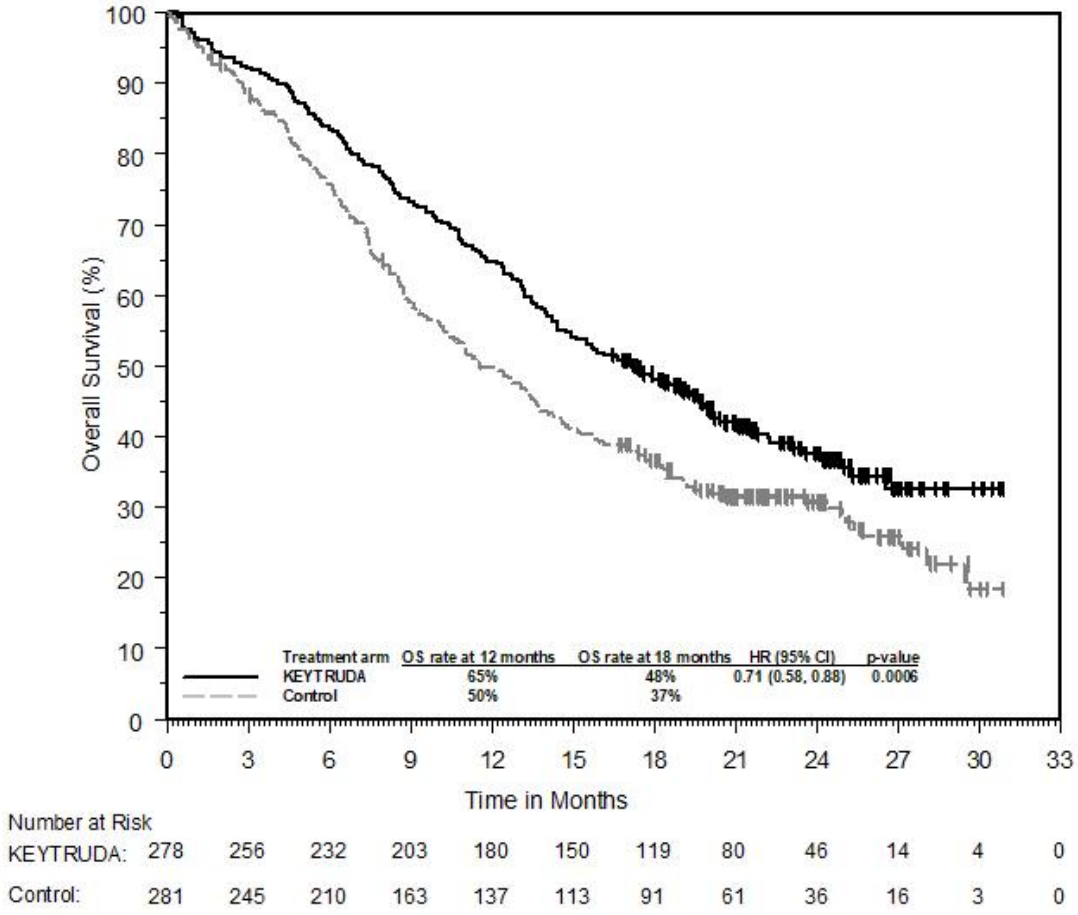
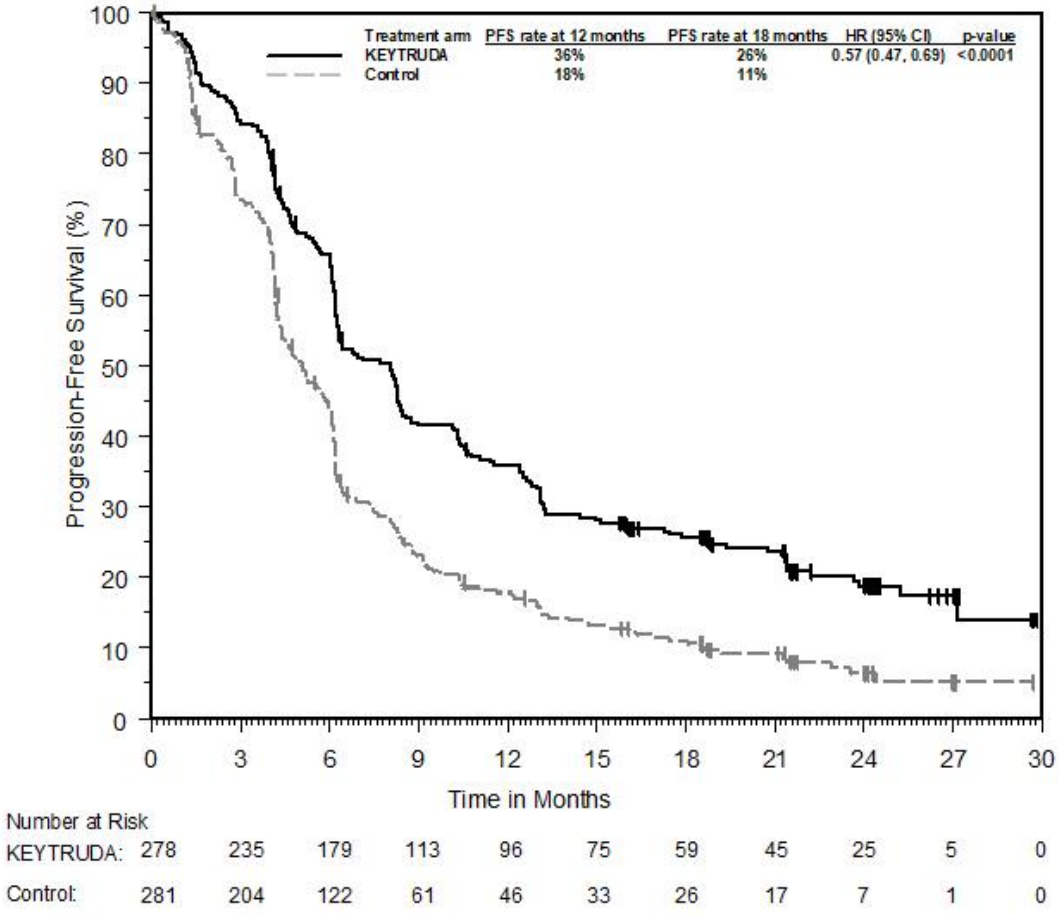


Figure 11: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-407



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 10 summarizes key efficacy measures for the entire ITT population.

Table 10: 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

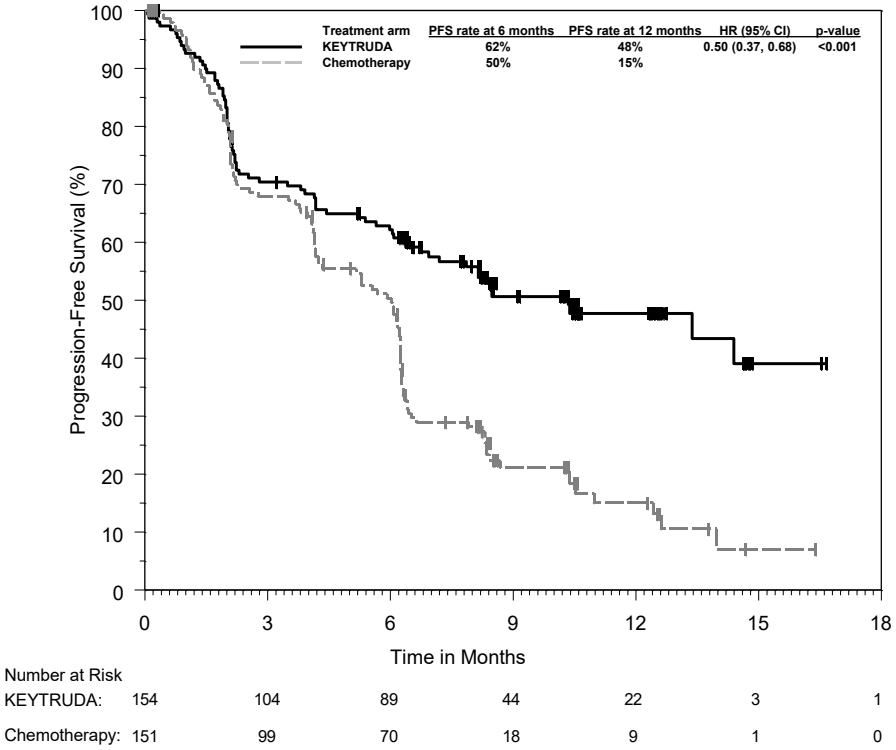
¶ Based on Kaplan-Meier estimates

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 13.

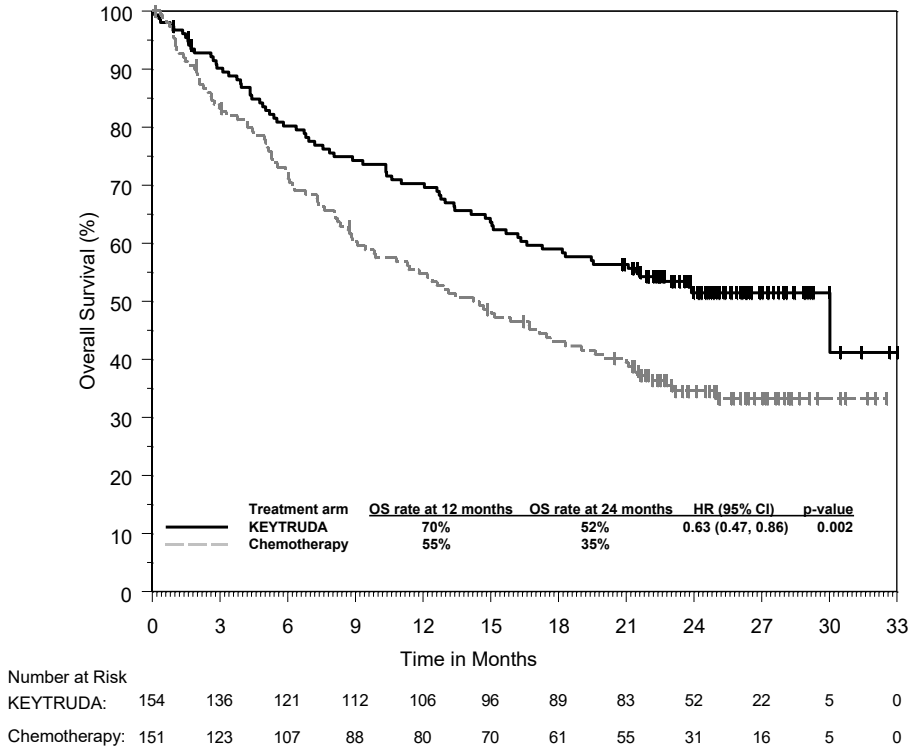
Figure 12: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-024 (Intent to Treat Population)



Number at Risk

KEYTRUDA:	154	104	89	44	22	3	1
Chemotherapy:	151	99	70	18	9	1	0

Figure 13: 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/m^2 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 11 summarizes key efficacy measures for the entire ITT population (TPS ≥ 1%) and for the subgroup of patients with TPS ≥ 50%. Kaplan-Meier curves for OS (TPS ≥ 1% and TPS ≥ 50%) are shown in Figures 14 and 15.

Table 11: 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/m² 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§,#,Þ			
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

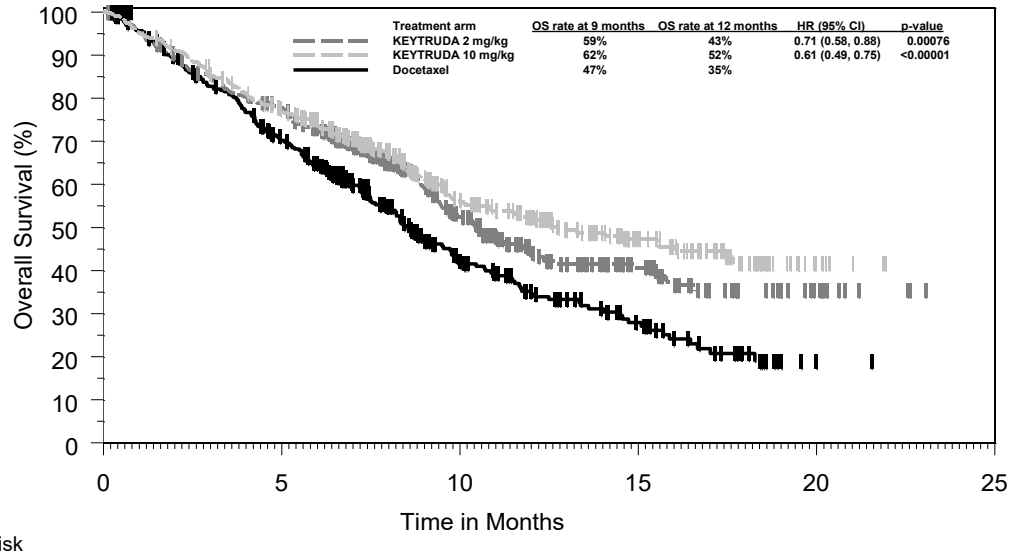
¶ All responses were partial responses

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

Þ 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

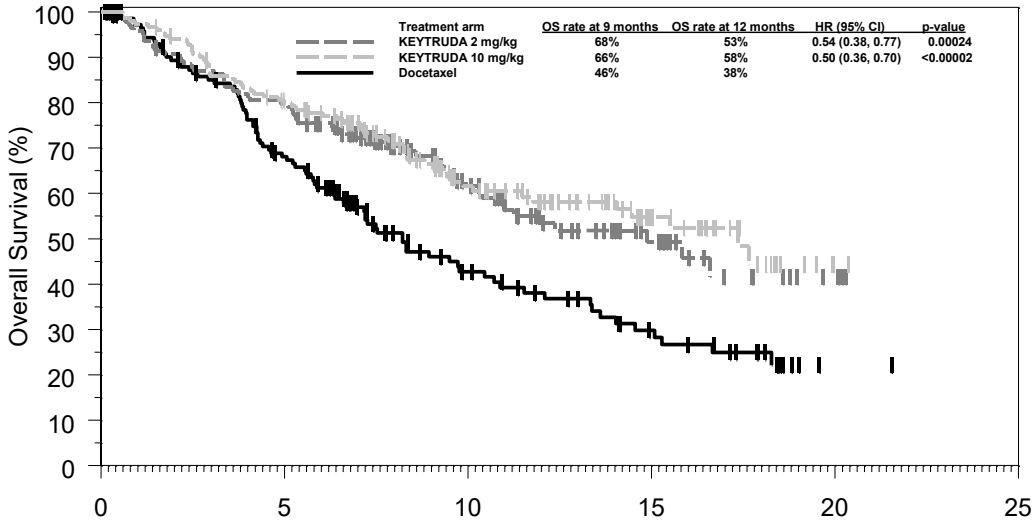
Figure 14: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-010 (TPS ≥ 1%, Intent to Treat Population)



Number at Risk

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

Figure 15: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-010 (TPS ≥ 50%, Intent to Treat Population)



Number at Risk

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 12.

Table 12: 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.

KEYNOTE-671: Controlled trial for the neoadjuvant and adjuvant treatment of patients with resectable NSCLC

The efficacy of KEYTRUDA in combination with platinum-containing chemotherapy given as neoadjuvant treatment and continued as monotherapy adjuvant treatment was investigated in KEYNOTE-671, a multicenter, randomized, double-blind, placebo-controlled trial. Key eligibility criteria were previously untreated and resectable Stage II, IIIA, or IIIB (N2) NSCLC by AJCC 8th edition, 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. Randomization was stratified by stage (II vs. III), tumor PD-L1 expression (TPS ≥ 50% or <50%), histology (squamous vs. non-squamous), and geographic region (East Asia vs. non-East Asia).

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

- Treatment Arm A: neoadjuvant KEYTRUDA 200 mg on Day 1 in combination with cisplatin 75 mg/m^2 and either pemetrexed 500 mg/m^2 on Day 1 or gemcitabine 1000 mg/m^2 on Days 1 and 8 of each 21-day cycle for up to 4 cycles. Following surgery, KEYTRUDA 200 mg was administered every 3 weeks for up to 13 cycles.
- Treatment Arm B: neoadjuvant placebo on Day 1 in combination with cisplatin 75 mg/m^2 and either pemetrexed 500 mg/m^2 on Day 1 or gemcitabine 1000 mg/m^2 on Days 1 and 8 of each 21-day cycle for up to 4 cycles. Following surgery, placebo was administered every 3 weeks for up to 13 cycles.

All study medications were administered via intravenous infusion. Treatment with KEYTRUDA or placebo continued until completion of the treatment (17 cycles), disease progression that precluded definitive surgery, disease recurrence in the adjuvant phase, disease progression for those who did not undergo surgery or had incomplete resection and entered the adjuvant phase, or unacceptable toxicity. Assessment of tumor status was performed at baseline, Week 7, and Week 13 in the neoadjuvant phase and within 4 weeks prior to the start of the adjuvant phase. Following the start of the adjuvant phase, assessment of tumor status was performed every 16 weeks through the end of Year 3, and then every 6 months thereafter.

The primary efficacy outcome measures were OS and investigator-assessed event-free survival (EFS). Secondary efficacy outcome measures were pathological complete response (pCR) rate and major pathological response (mPR) rate as assessed by blinded independent pathology review (BIPR).

A total of 797 patients in KEYNOTE-671 were randomized: 397 patients to the KEYTRUDA arm and 400 to the placebo arm. Baseline characteristics were: median age of 64 years (range: 26 to 83), 45% age 65 or older; 71% male; 61% White, 31% Asian, and 2.0% Black. Sixty-three percent and 37% had ECOG performance of 0 or 1, respectively; 30% had Stage II and 70% had Stage III disease; 33% had TPS ≥ 50% and 67% had TPS <50%; 43% had tumors with squamous histology and 57% had tumors with non-squamous histology; 31% were from the East Asian region.

Eighty-one percent of patients in the KEYTRUDA in combination with platinum-containing chemotherapy arm had definitive surgery compared to 76% of patients in the platinum-containing chemotherapy arm.

The trial demonstrated statistically significant improvements in OS and EFS for patients randomized to KEYTRUDA in combination with platinum-containing chemotherapy followed by KEYTRUDA monotherapy compared with patients randomized to placebo in combination with platinum-containing chemotherapy followed by placebo alone. OS efficacy results with a median follow-up time of 29.8 months (range: 0.4 to 62.0 months) are summarized in Table 13 and Figure 16. EFS, pCR, and mPR efficacy results with a median follow-up time of 21.4 months (range: 0.4 to 50.6 months) are summarized in Table 13.

Table 13: Efficacy Results in KEYNOTE-671

Endpoint	KEYTRUDA with chemotherapy/KEYTRUDA n=397	Placebo with chemotherapy/Placebo n=400
OS		
Number of patients with event (%)	110 (28%)	144 (36%)
Median in months* (95% CI)	NR (NR, NR)	52.4 (45.7, NR)
Hazard ratio† (95% CI)	0.72 (0.56, 0.93)	
p-Value‡	0.00517	
EFS		
Number of patients with event (%)	139 (35%)	205 (51%)
Median in months* (95% CI)	NR (34.1, NR)	17.0 (14.3, 22.0)
Hazard ratio† (95% CI)	0.58 (0.46, 0.72)	
p-Value‡	<0.0001	
pCR		
Number of patients with pCR	72	16
pCR Rate (%), (95% CI)	18.1 (14.5, 22.3)	4.0 (2.3, 6.4)
Treatment difference estimate (%), (95% CI)§	14.2 (10.1, 18.7)	
p-Value	<0.0001	
mPR		
Number of patients with mPR	120	44
mPR Rate (%), (95% CI)	30.2 (25.7, 35.0)	11.0 (8.1, 14.5)
Treatment difference estimate (%), (95% CI)§	19.2 (13.9, 24.7)	
p-Value	<0.0001	

* Based on Kaplan-Meier estimates

† Based on Cox regression model with treatment as a covariate stratified by stage, tumor PD-L1 expression, histology, and geographic region

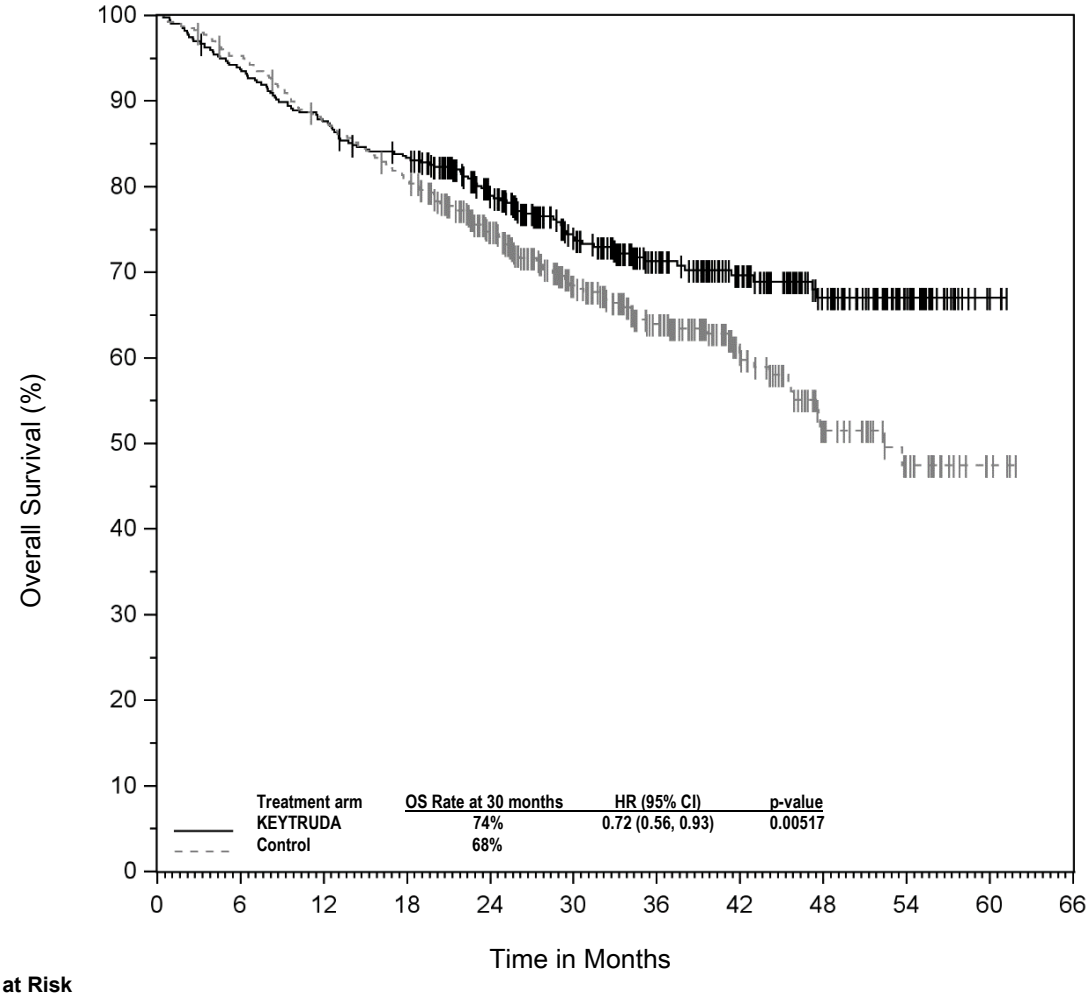
‡ Based on stratified log-rank test

§ Based on Miettinen and Nurminen method stratified by stage, tumor PD-L1 expression, histology, and geographic region

NR = not reached

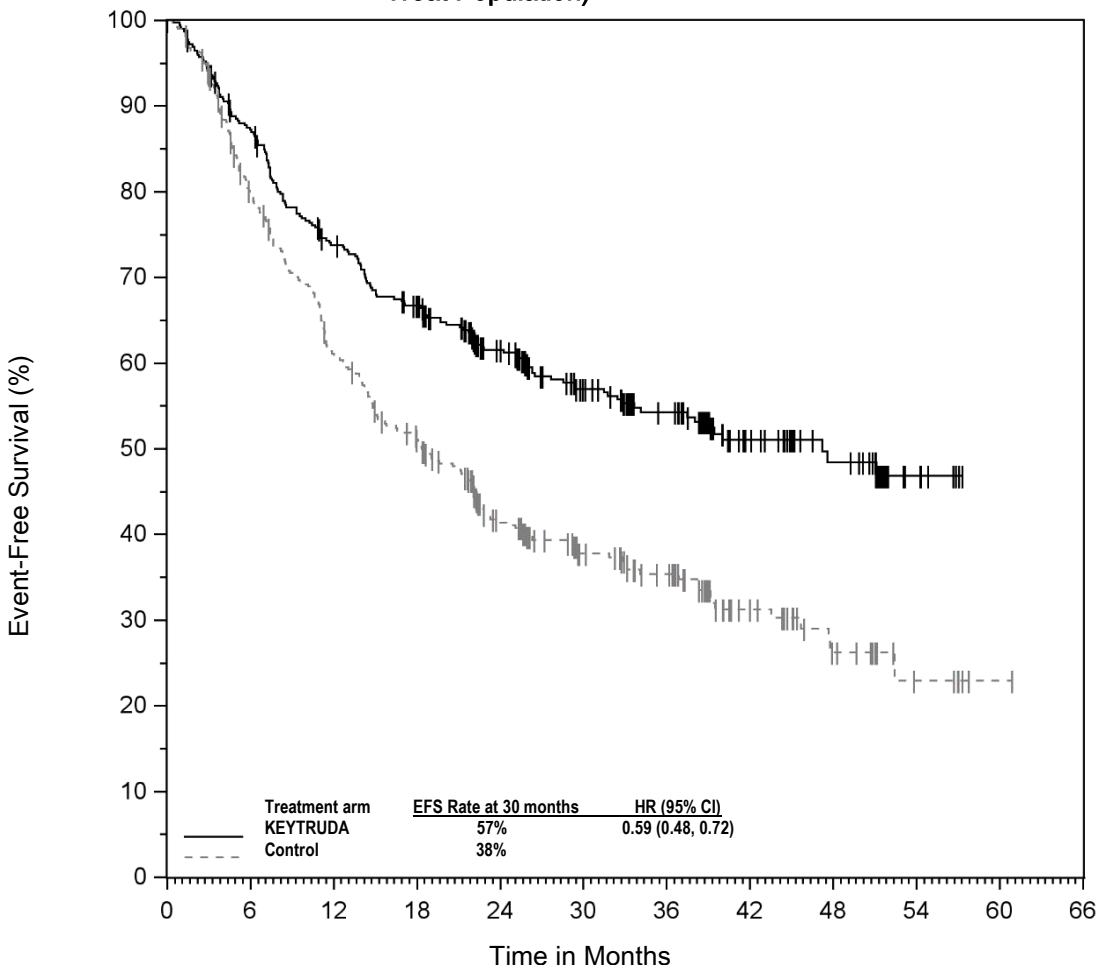
The final EFS analysis was performed at a median duration of follow-up of 29.8 months after 422 patient events (174 for the KEYTRUDA arm and 248 for the placebo arm). Median EFS was 47.2 months (95% CI: 32.9, NR) for the KEYTRUDA arm and 18.3 months (95% CI: 14.8, 22.1) for the placebo arm. The EFS HR was 0.59 (95% CI: 0.48, 0.72). See Figure 17.

Figure 16: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-671 (Intent to Treat Population)



Number at Risk												
KEYTRUDA	397	371	347	327	277	205	148	108	69	32	4	0
Control	400	379	347	319	256	176	125	77	39	20	4	0

Figure 17: Kaplan-Meier Curve for Event-Free Survival by Treatment Arm in KEYNOTE-671 (Intent to Treat Population)



KEYNOTE-091: Controlled trial for the adjuvant treatment of patients with resected NSCLC

The efficacy of KEYTRUDA was investigated in KEYNOTE-091, a multicenter, randomized, triple-blind, placebo-controlled trial. Key eligibility criteria were completely resected stage IB (T2a ≥ 4 cm), II, or IIIA NSCLC by AJCC 7th edition, regardless of tumor PD-L1 expression status, no prior neoadjuvant radiotherapy and/or neoadjuvant chemotherapy, and no prior or planned adjuvant radiotherapy for the current malignancy. Patients may or may not have received adjuvant chemotherapy. 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 4 cycles of adjuvant chemotherapy were ineligible. Randomization was stratified by stage (IB vs. II vs. IIIA), adjuvant chemotherapy (no adjuvant chemotherapy vs. adjuvant chemotherapy), PD-L1 status

(TPS <1% [negative] vs. TPS 1-49% vs. TPS ≥ 50%), and geographic region (Western Europe vs. Eastern Europe vs. Asia vs. Rest of World). Patients were randomized (1:1) to receive KEYTRUDA 200 mg or placebo intravenously every 3 weeks.

Treatment continued until RECIST 1.1-defined disease recurrence as determined by the investigator, unacceptable toxicity, or approximately one year (18 doses). Patients underwent imaging every 12 weeks after the first dose of KEYTRUDA for the first year, then every 6 months for years 2 to 3, and then annually up to the end of year 5. After year 5, imaging is performed as per local standard of care. The major efficacy outcome measure was investigator-assessed disease-free survival (DFS). An additional efficacy outcome measure was OS.

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

The trial met its primary endpoint, demonstrating a statistically significant improvement in DFS in the overall population [HR=0.76 (95% CI: 0.63, 0.91, p=0.00143)] for patients randomized to the KEYTRUDA arm compared to patients randomized to the placebo arm. In an exploratory subgroup analysis of the 167 patients (14%) who did not receive adjuvant chemotherapy, the DFS HR was 1.25 (95% CI: 0.76, 2.05). OS results were not mature with only 42% of pre-specified OS events in the overall population.

Table 14 and Figure 18 summarize the efficacy results for KEYNOTE-091 in patients who received adjuvant chemotherapy.

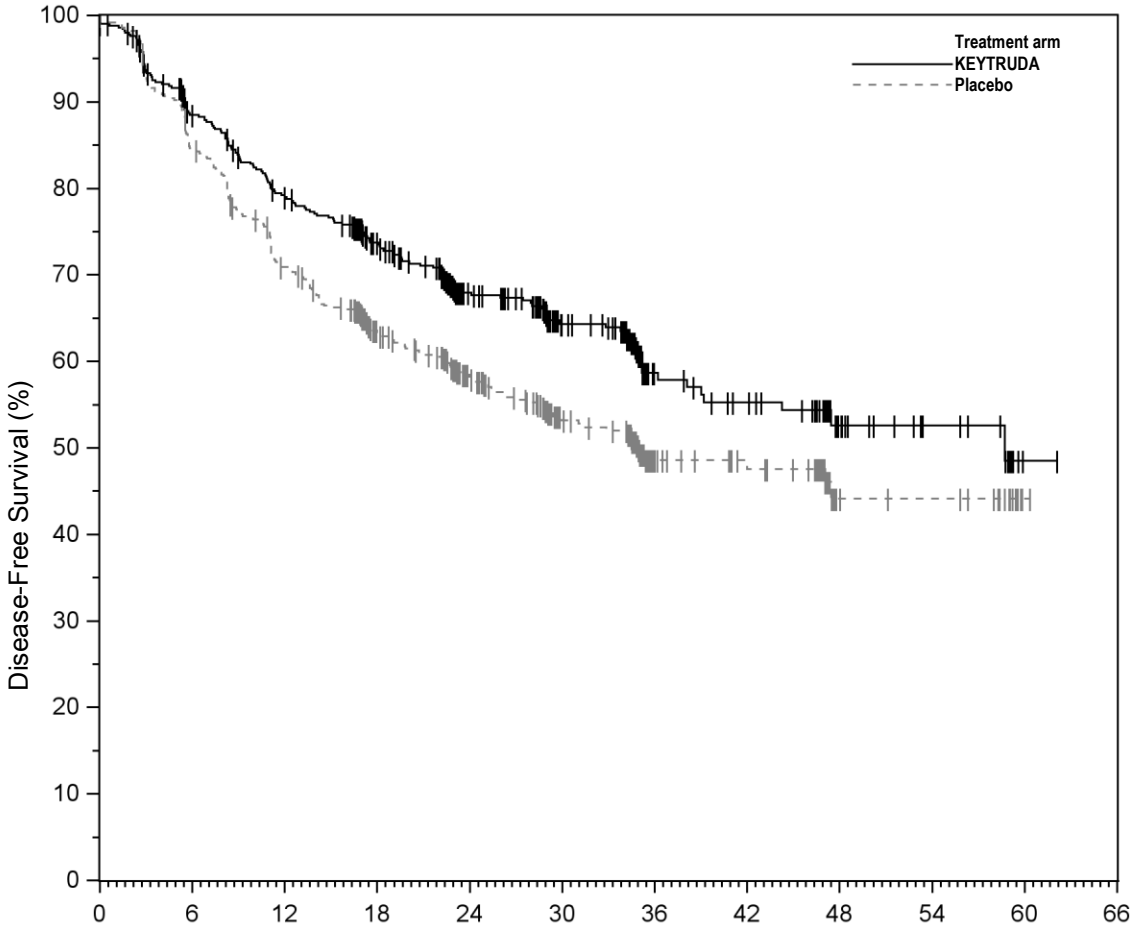
Table 14: Efficacy Results in KEYNOTE-091 for Patients who Received Adjuvant Chemotherapy

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

* Based on the unstratified univariate Cox regression model

NR = not reached

Figure 18: Kaplan-Meier Curve for Disease-Free Survival in KEYNOTE-091 for Patients Who Received Adjuvant Chemotherapy



Number at Risk												
KEYTRUDA	506	422	372	308	227	158	71	61	27	16	1	0
Placebo	504	422	349	272	206	134	58	47	17	15	1	0

Malignant Pleural Mesothelioma

KEYNOTE-483: Controlled trial of combination therapy in patients with untreated unresectable advanced or metastatic MPM

The efficacy of KEYTRUDA in combination with pemetrexed and platinum chemotherapy was investigated in a multicenter, randomized, open-label, active-controlled trial, KEYNOTE-483. Key eligibility criteria were unresectable advanced or metastatic MPM with no prior systemic therapy for advanced/metastatic disease. Patients were enrolled regardless of tumor PD-L1 expression. Patients with autoimmune disease that required systemic therapy within 3 years of treatment or a medical condition that required immunosuppression were ineligible. Randomization was stratified by histological subtype (epithelioid vs. non-epithelioid). Patients were randomized (1:1) to one of the following treatment arms; all study medications were administered via intravenous infusion:

- KEYTRUDA 200 mg with pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 or carboplatin AUC 5-6 mg/mL/min on Day 1 of each 21-day cycle for up to 6 cycles, followed by KEYTRUDA 200 mg every 3 weeks. KEYTRUDA was administered prior to chemotherapy on Day 1.
- Pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 or carboplatin AUC 5-6 mg/mL/min on Day 1 of each 21-day cycle for up to 6 cycles.

Treatment with KEYTRUDA continued until disease progression as determined by the investigator according to modified RECIST 1.1 for mesothelioma (mRECIST), unacceptable toxicity, or a maximum of 24 months. Assessment of tumor status was performed every 6 weeks for 18 weeks, followed by every 12 weeks thereafter.

Among the 440 patients in KEYNOTE-483 (222 patients in the KEYTRUDA combination arm and 218 in the chemotherapy arm), baseline characteristics were: median age of 70 years (77% age 65 or older); 76% male; 79% White, 21% not reported or unknown; 2% Hispanic or Latino; and 47% and 53% ECOG performance status of 0 or 1, respectively. Seventy-eight percent had epithelioid and 22% had non-epithelioid histology.

The primary efficacy outcome measure was OS. Additional efficacy outcome measures were PFS, ORR, and DoR, as assessed by BICR using mRECIST, and health-related quality of life as assessed using EORTC QLQ-C30 and EORTC QLQ-LC13. The trial demonstrated a statistically significant improvement in OS, PFS, and ORR in patients randomized to KEYTRUDA in combination with chemotherapy compared with patients randomized to chemotherapy alone. The median follow-up time was 17 months (range: 0.8 – 60.3 months). Table 15 and Figures 19 and 20 summarize key efficacy measures for KEYNOTE-483.

Table 15: Efficacy Results in KEYNOTE-483

Endpoint	KEYTRUDA 200 mg every 3 weeks + Pemetrexed + Platinum Chemotherapy (n=222)	Pemetrexed + Platinum Chemotherapy (n=218)
OS*		
Number (%) of patients with event	167 (75%)	175 (80%)
Hazard ratio† (95% CI)	0.79 (0.64, 0.98)	
p-Value‡	0.0162	
Median in months (95% CI)	17.3 (14.4, 21.3)	16.1 (13.1, 18.2)
PFS*,§		
Number (%) of patients with event	190 (86%)	166 (76%)
Hazard ratio† (95% CI)	0.80 (0.65, 0.99)	
p-Value‡	0.0194	
Median in months (95% CI)	7.1 (6.9, 8.1)	7.1 (6.8, 7.7)
Objective Response Rate§,¶		
ORR % (95% CI)	52% (45.5, 59.0)	29% (23.0, 35.4)
Number (%) of complete responses	1 (0.5%)	0 (0%)
Number (%) of partial responses	115 (52%)	63 (29%)
p-Value#	<0.00001	
Response Duration*,§,Þ		
Median in months (range)	6.9 (1.2+, 38.9+)	6.8 (1.4+, 25.1+)
% with duration ≥ 12 monthsß	23%	13%

* Based on the final analysis

† Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by histological subtype at randomization (epithelioid vs. other subtypes).

‡ Based on stratified log-rank test

§ Assessed by BICR using mRECIST

¶ Based on an interim analysis

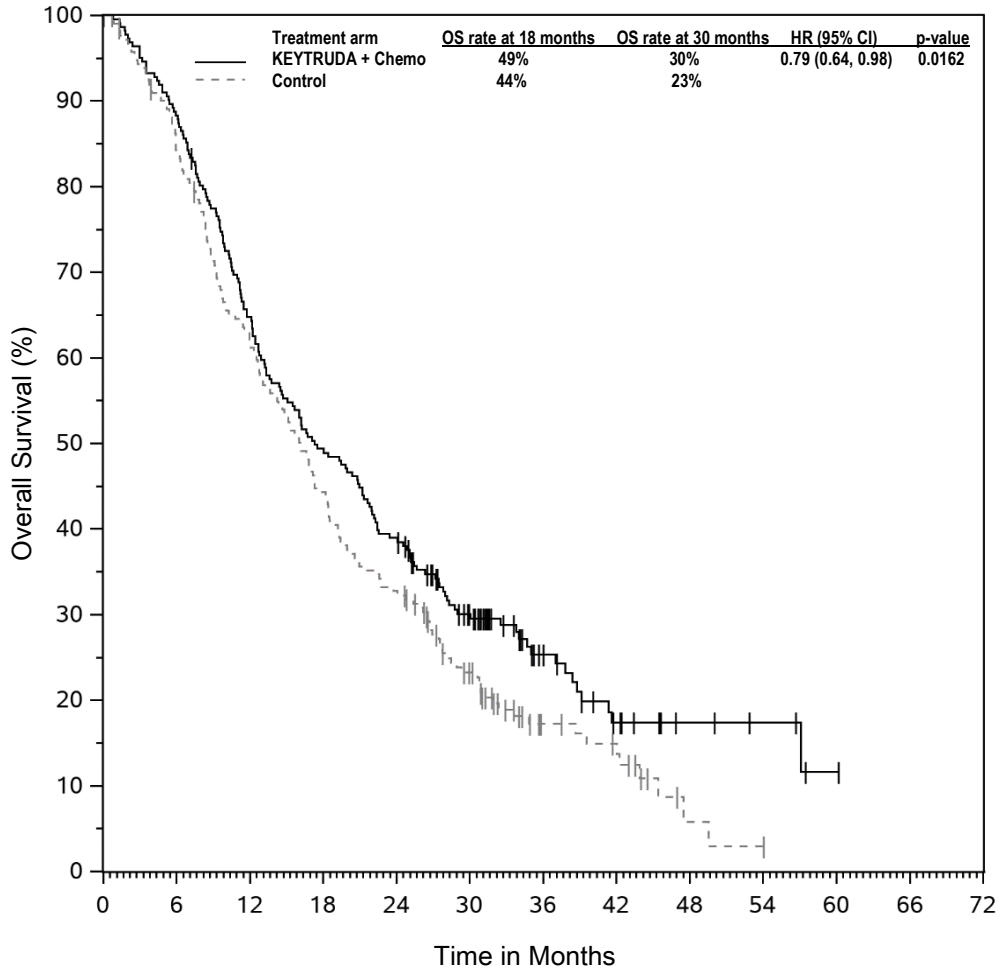
Based on Miettinen and Nurminen method stratified by histological subtype at randomization

(epithelioid vs. other subtypes).

Þ Based on patients with a best overall response as confirmed complete or partial response; n=117 for patients in the KEYTRUDA combination arm; n=64 for patients in the chemotherapy arm

β Based on Kaplan-Meier estimates

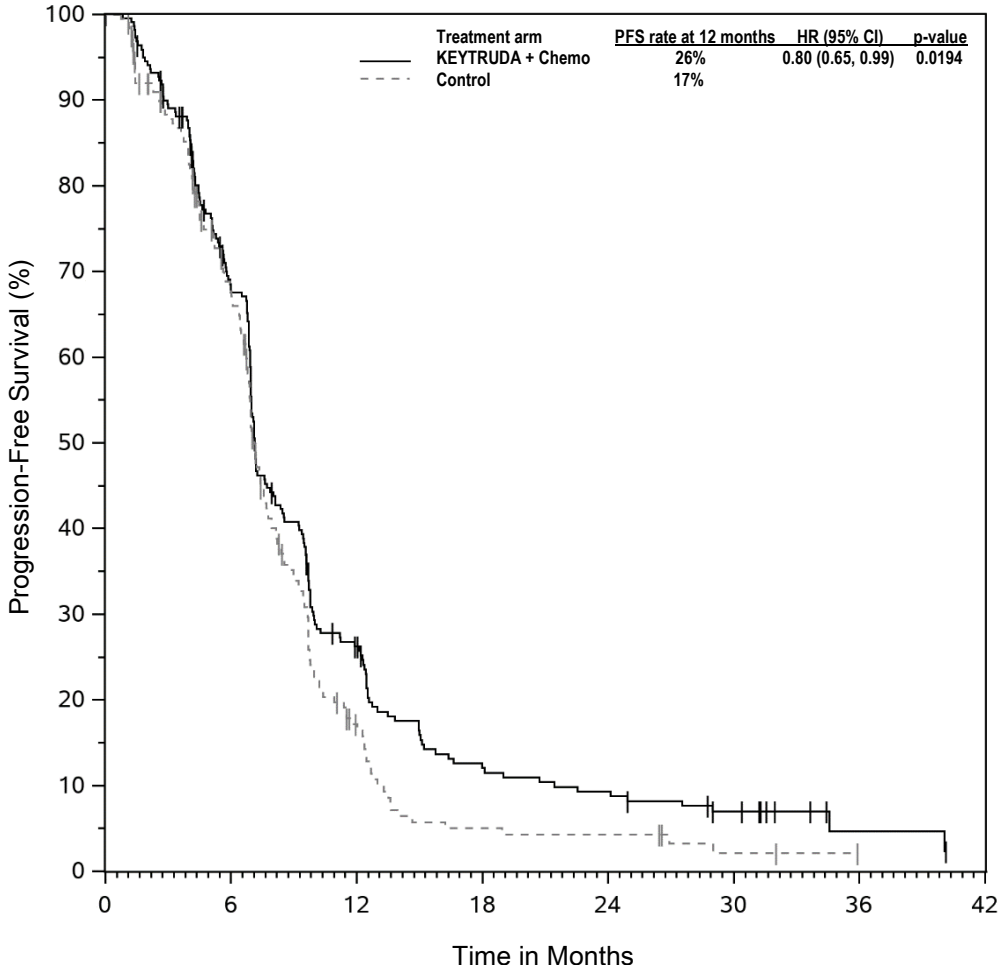
Figure 19: Kaplan-Meier Curve for Overall Survival in KEYNOTE-483



Number at Risk

KEYTRUDA + Chemo	222	196	143	109	86	54	25	13	6	4	1	0	0
Control	218	176	128	92	68	40	16	12	2	1	0	0	0

Figure 20: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-483



Number at Risk								
KEYTRUDA + Chemo	222	139	50	22	17	10	2	0
Control	218	121	24	7	6	2	0	0

In a pre-specified exploratory analysis based on histology, in the subgroup of patients with epithelioid histology (n=345), the hazard ratio (HR) for OS was 0.89 (95% CI: 0.70, 1.13), with median OS of 19.8 months in KEYTRUDA in combination with chemotherapy and 18.2 months in chemotherapy alone. In the subgroup of patients with non-epithelioid histology (n=95), the HR for OS was 0.57 (95% CI: 0.36, 0.89), with median OS of 12.3 months in KEYTRUDA in combination with chemotherapy and 8.2 months in chemotherapy alone.

Health-related QoL as evaluated by the EORTC QLQ-C30 (GHS/QoL, physical functioning, and dyspnea) and EORTC QLQ-LC13 (chest pain and cough) was generally maintained in patients receiving KEYTRUDA in combination with chemotherapy as compared to chemotherapy alone.

Head and Neck Cancer

KEYNOTE-689: Controlled trial for the neoadjuvant and adjuvant treatment of patients with resectable locally advanced HNSCC

The efficacy of KEYTRUDA was investigated in KEYNOTE-689, a randomized, multicenter, open label, active-controlled trial conducted in 714 patients with resectable locally advanced (Stage III-IVA) HNSCC. Patients with active autoimmune disease that required systemic therapy within two years of treatment or a medical condition that required immunosuppression were ineligible. Randomization was stratified by primary tumor site (oropharynx/oral cavity vs. larynx vs. hypopharynx), tumor stage (III vs. IVA) and PD-L1 status (TPS ≥ 50% vs. TPS < 50%) according to the PD-L1 IHC 22C3 pharmDx™ kit.

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

- Treatment Arm A: neoadjuvant KEYTRUDA 200 mg for 2 cycles prior to surgical resection. Within 6 weeks following surgery, KEYTRUDA 200 mg for 3 cycles in combination with either radiation + 3 cycles of cisplatin 100 mg/m^2 every 3 weeks for patients with high-risk pathological features after surgery or radiation alone for patients without high-risk pathological features after surgery. This was followed by KEYTRUDA 200 mg every 3 weeks for up to 12 cycles.
- Treatment Arm B: no neoadjuvant treatment prior to surgery. Within 6 weeks following surgery, either radiation + 3 cycles of cisplatin 100 mg/m^2 every 3 weeks for patients with high-risk pathological features after surgery or radiation alone for patients without high-risk pathological features after surgery.

On both treatment arms, patients received cisplatin with adjuvant RT if high-risk pathological features (i.e., positive margins <1 mm or extranodal extension) were present at surgery.

Treatment with KEYTRUDA continued until RECIST v1.1 defined progression of disease as assessed by BICR, until completion of the treatment (17 cycles), disease progression that precluded definitive surgery, disease recurrence in the adjuvant phase, disease progression for those who did not undergo surgery or had incomplete resection and entered the adjuvant phase, or unacceptable toxicity. Assessment of tumor status was performed prior to surgery at Week 6 in the neoadjuvant phase. Following the start of the adjuvant phase, assessment of tumor status was performed 12 weeks after end of RT ± cisplatin treatment and then every 3 months until the end of Year 3; then every 6 months thereafter up to the end of Year 5. In Arm A, 89% of patients had surgery, compared to 88% in Arm B. In Arm A, 29% of patients received cisplatin plus radiation and 46% received

radiation alone. In Arm B, 40% of patients received cisplatin plus radiation, and 39% received radiation alone.

The trial was not designed to isolate the effect of KEYTRUDA in each phase (neoadjuvant or adjuvant) of treatment.

The primary efficacy outcome measure was event-free survival (EFS) by BICR 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 disease progression or recurrence, or death due to any cause. Secondary primary malignancy was not considered an event. Additional efficacy outcome measures were major pathological response (mPR) rate as assessed by BIPR, overall survival (OS), and pathological complete response (pCR) rate as assessed by BIPR.

The study population characteristics in the 682 patients with PD-L1 expression of CPS ≥ 1 were: median age of 60 years (range: 22 to 87), 33% age 65 or older; 79% male; 78% White, 13% Asian and 2.5% Black; 14% were Hispanic or Latino; 43% had ECOG PS of 1, and 79% were former/current smokers. Four percent of patients' tumors were HPV-positive, and 26% had Stage III disease, 74% had Stage IVA disease. Sixty-eight percent of patients' tumors had PD-L1 expression of CPS ≥ 10.

The trial demonstrated a statistically significant improvement in EFS (HR 0.73; 95% CI: 0.58, 0.92; p-value 0.00411) for patients randomized to KEYTRUDA in combination with radiation with or without cisplatin compared to those randomized to radiation with or without cisplatin at the first pre-specified interim analysis in the overall population. OS at interim analysis was not formally tested. Table 16 summarizes key efficacy results for the pre-specified subgroup of patients whose tumours expressed PD-L1 with a CPS ≥ 1 at a median follow-up time of 27.0 months (range: 0.5 to 66.5 months). Figures 21 and 22 show the Kaplan-Meier curves for EFS and OS for patients whose tumours expressed PD-L1 with a CPS ≥ 1.

Table 16: Efficacy Results for Perioperative KEYTRUDA with adjuvant RT with or without cisplatin in Patients with HNSCC CPS ≥ 1 in KEYNOTE-689

Endpoint	KEYTRUDA 200 mg every 3 weeks with RT with or without cisplatin n=347	RT with or without cisplatin n=335
EFS		
Number of patients with event (%)	128 (37%)	156 (47%)
Median in months* (95% CI)	59.7 (37.9, NR)	29.6 (19.5, 41.9)
Hazard ratio† (95% CI)	0.70 (0.55, 0.89)	
p-Value‡	0.00140	
mPR		
Number of patients with mPR	34	0
mPR Rate (%), (95% CI)	9.8 (6.9, 13.4)	0.0 (0.0, 1.1)
mPR Rate difference estimate (%), (95% CI)§	9.8 (7.0, 13.3)	
p-Value‖	<0.00001	
OS		
Number (%) of patients with event	106 (31%)	128 (38%)
Median in months* (95% CI)	NR (NR, NR)	61.8 (49.2, NR)
Hazard ratio† (95% CI)	0.72 (0.56, 0.94)	

* From product-limit (Kaplan-Meier) method for censored data.

† Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by primary tumor site and tumor stage.

‡ One-sided p-value based on log-rank test stratified by primary tumor site and tumor stage. Compared to a one-sided p-value boundary of 0.0124.

§ Based on Miettinen & Nurminen method stratified by primary tumor site and tumor stage.

‖ Compared to a one-sided p-value boundary of 0.0005

NR = not reached

Figure 21: Kaplan-Meier Curve for Event-free Survival for KEYTRUDA in Patients with HNSCC CPS ≥ 1 in KEYNOTE-689

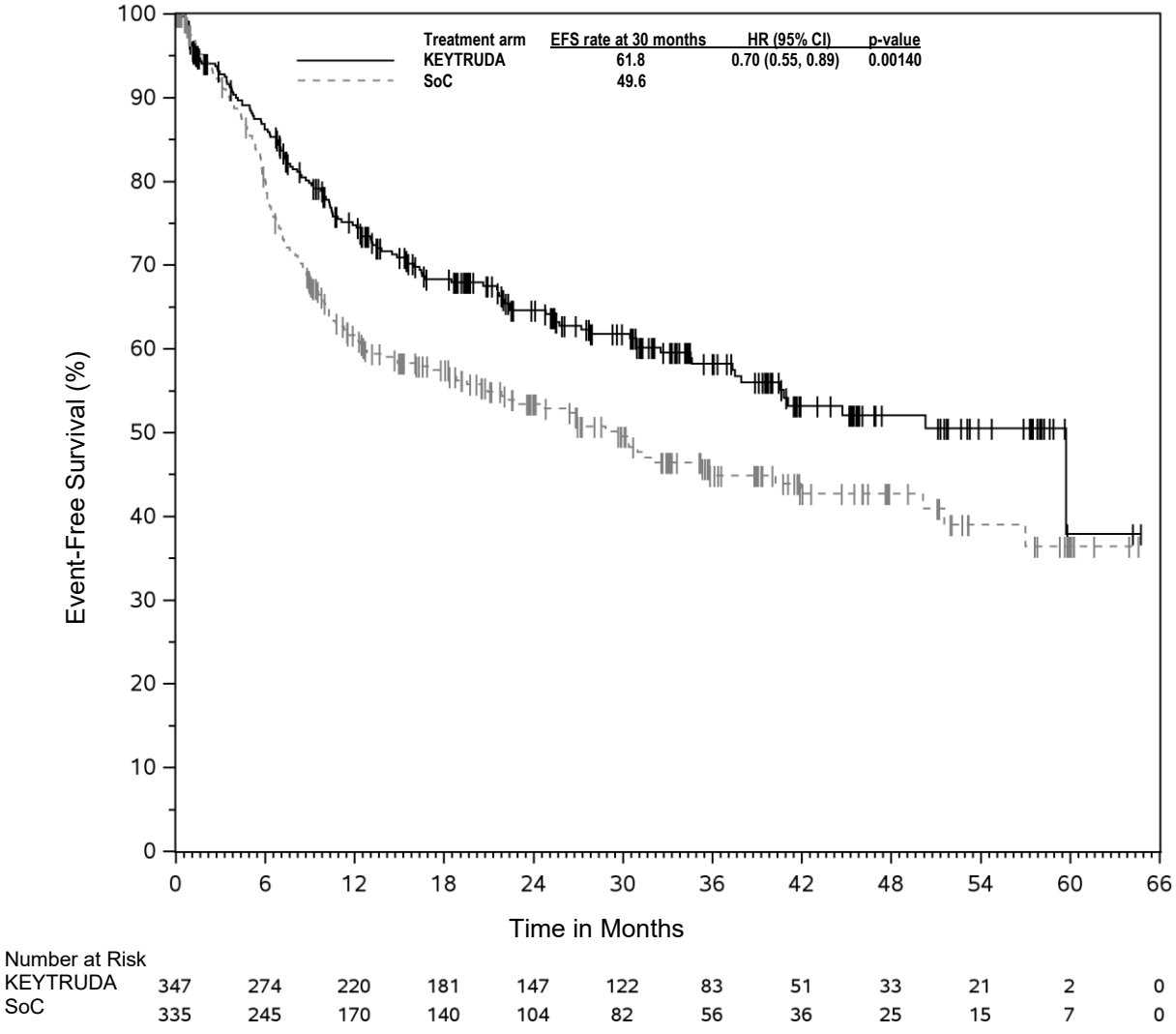
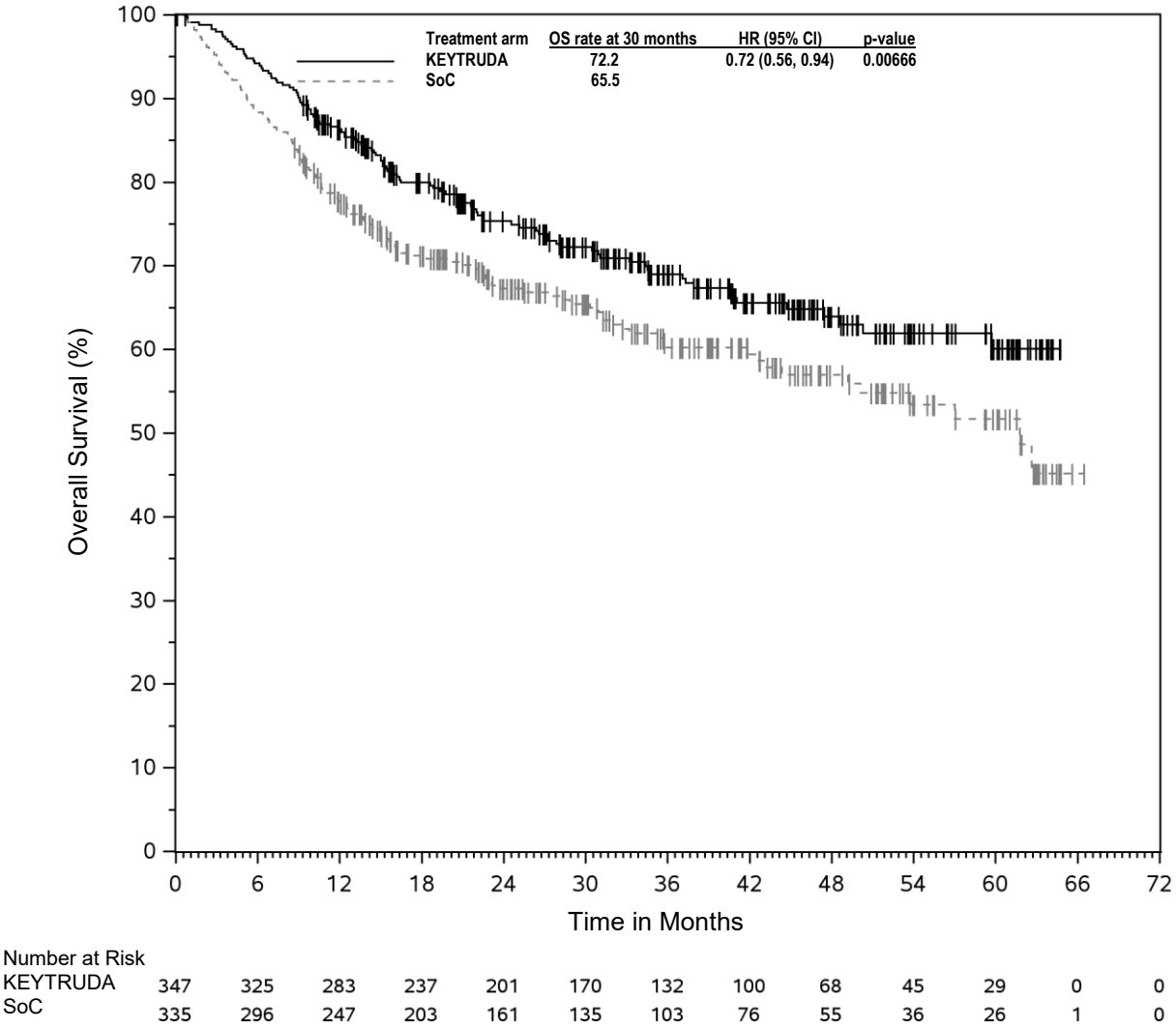


Figure 22: Kaplan-Meier Curve for Overall Survival for KEYTRUDA in Patients with HNSCC CPS ≥ 1 in KEYNOTE-689



Hypopharyngeal Tumours

In an exploratory subgroup analysis of patients with PD-L1 positive (CPS ≥ 1) hypopharyngeal tumours who were randomized (n=51), the EFS HR was 2.28 (95% CI: 0.79, 6.56). Among these patients, 23 patients in the KEYTRUDA arm received surgery, of which 17 patients (74%) had R0 resections. On the SOC arm, 23 patients received surgery, of which 20 (87%) had R0 resections.

Oral Cavity, Oropharyngeal and Laryngeal Tumors

In an exploratory subgroup analysis of patients with PD-L1 positive (CPS ≥ 1) oral cavity, oropharyngeal and laryngeal tumors who received surgery (n=555), 91% of patients on the KEYTRUDA arm had R0 resections while 85% of patients on the SOC arm had R0 resections.

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 ≥ 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/m^2 every 3 weeks, and 5-FU 1000 mg/m^2/d 4 days continuous every 3 weeks (maximum of 6 cycles of platinum and 5-FU)
- Cetuximab 400 mg/m^2 load then 250 mg/m^2 once weekly, carboplatin AUC 5 mg/mL/min every 3 weeks or cisplatin 100 mg/m^2 every 3 weeks, and 5-FU 1000 mg/m^2/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 ≥ 1, CPS ≥ 20, and TPS ≥ 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 17 and 19 and Figures 23 and 24 describe key efficacy results for KEYTRUDA in KEYNOTE-048.

Table 17: 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	
Objective Response Rate		
ORR§ (95% CI)	36% (30.3, 42.8)	36% (29.6, 42.2)
Complete response	7%	3%
Partial response	30%	33%
p-Value¶	0.4586	
Response Duration		
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 18: 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

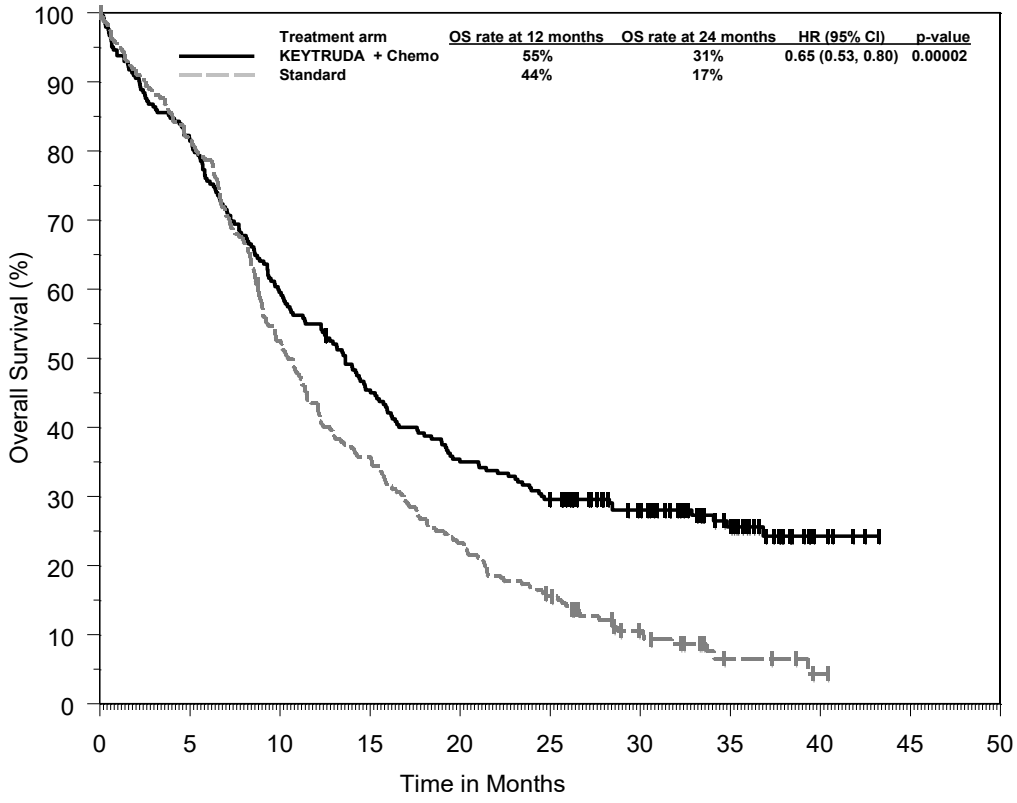
† Cetuximab, platinum, and 5-FU

‡ 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 23: Kaplan-Meier Curve for Overall Survival for KEYTRUDA plus Chemotherapy in KEYNOTE-048 (CPS≥ 1)*



Number at Risk

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 19: 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	
Objective Response Rate		
ORR¶ (95% CI)	19% (14.5, 24.4)	35% (29.1, 41.1)
Complete response	5%	3%
Partial response	14%	32%
p-Value#	1.0000	
Response Duration		
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

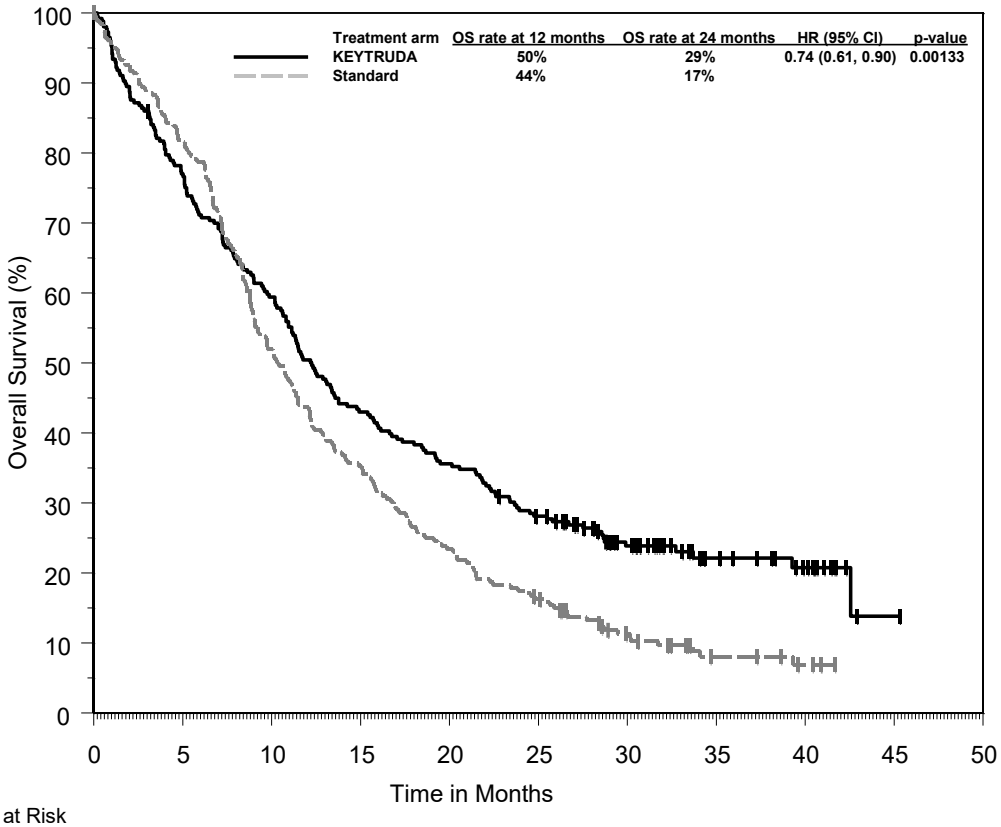
‡ Non-inferiority p-Value

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



Number at Risk

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

*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 20.

Table 20: 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 21.

Table 21: 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

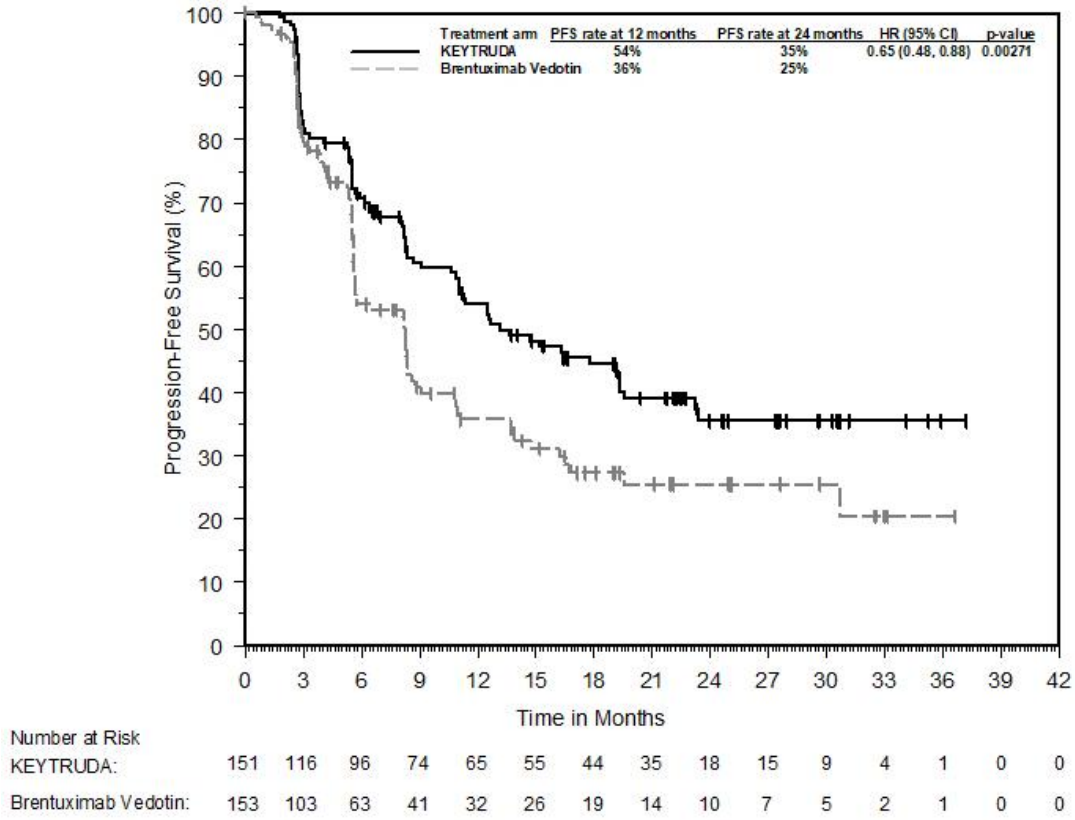
† Based on stratified log-rank test

‡ 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 25: 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 22.

Table 22: Efficacy Results in Patients with Refractory or Relapsed Classical Hodgkin Lymphoma

Endpoint	KEYNOTE-013	KEYNOTE-087
	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%Þ
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

[Þ] Based on Kaplan-Meier estimation; includes 60 patients with responses of 12 months or longer

Urothelial Carcinoma

KEYNOTE-A39: Controlled trial of combination therapy with enfortumab vedotin in urothelial carcinoma patients

The efficacy of KEYTRUDA in combination with enfortumab vedotin was investigated in KEYNOTE-A39, an open-label, multicenter, randomized, active-controlled trial that enrolled 886 platinum-eligible patients with locally advanced or metastatic urothelial carcinoma who received no prior systemic therapy for locally advanced or metastatic disease. The trial excluded patients with autoimmune disease or a medical condition that required immunosuppression, active CNS metastases, ongoing sensory or motor neuropathy Grade ≥ 2, or uncontrolled diabetes defined as hemoglobin A1C (HbA1c) ≥ 8% or HbA1c ≥ 7% with associated diabetes symptoms. Patients were considered cisplatin-ineligible if they had at least one of the following criteria: glomerular filtration rate 30-59 mL/min, ECOG PS ≥ 2, Grade ≥ 2 hearing loss, or NYHA Class III heart failure. Patients randomized to the gemcitabine and platinum-based chemotherapy arm were permitted to receive maintenance immunotherapy. Randomization was stratified by cisplatin eligibility (eligible or ineligible), PD-L1 expression [high (CPS ≥ 10) or low (CPS <10)], and liver metastases (present or absent). Patients were randomized (1:1) to one of the following treatment arms; all study medications were administered via intravenous infusion.

- KEYTRUDA 200 mg over 30 minutes on Day 1 and enfortumab vedotin 1.25 mg/kg on Days 1 and 8 of each 21-day cycle.
- Gemcitabine 1000 mg/m^2 on Days 1 and 8 and investigator's choice of cisplatin 70 mg/m^2 or carboplatin (AUC 4.5 or 5 mg/mL/min according to local guidelines) on Day 1 of each 21-day cycle.

Treatment with KEYTRUDA and enfortumab vedotin continued until RECIST v1.1-defined progression of disease, unacceptable toxicity or, for KEYTRUDA, a maximum of 35 cycles (up to approximately 2 years). Treatment was permitted beyond RECIST v1.1-defined disease progression if the treating investigator considered the patient to be deriving clinical benefit and the treatment was tolerated. Assessment of tumor status was performed every 9 weeks for 18 months and then every 12 weeks thereafter. The major efficacy outcome measures were PFS as assessed by BICR according to RECIST v1.1 and OS. Additional outcome measures were ORR and DoR as assessed by BICR according to RECIST v1.1 and time to pain progression (TTPP).

The study population characteristics were: median age of 69 years; 77% male; and 67% White. Ninety-five percent had M1 disease, and 5% had M0 disease. Seventy-three percent had a primary tumor in the lower tract, and 27% of patients had a primary tumor in the upper tract. Fifty-four percent were cisplatin-eligible, 58% had PD-L1 CPS≥ 10, and 72% of patients had visceral metastases, including 22% with liver metastases. Twenty percent had normal renal function, and 37%, 41% and 2% were characterized with mild, moderate, or severe renal impairment, respectively. Ninety-seven percent had ECOG PS of 0-1 and 3% had ECOG PS of 2. Eighty-five percent of patients had transitional cell carcinoma (TCC) histology, 2% had TCC with other histology, and 6% had TCC with squamous differentiation.

Thirty-two percent of patients receiving KEYTRUDA in combination with enfortumab vedotin went on to receive subsequent cancer-related therapies, compared to 70% in the gemcitabine and platinum-based chemotherapy arm. Thirty-two percent of patients in the gemcitabine and platinum-based chemotherapy arm received maintenance immunotherapy, and 26% received other PD-1/L1 inhibitor-containing therapy as first subsequent therapy after disease progression.

The trial demonstrated a statistically significant improvement in OS, PFS, and ORR in patients randomized to KEYTRUDA in combination with enfortumab vedotin compared with patients randomized to gemcitabine and platinum-based chemotherapy. Efficacy results were consistent across all pre-specified patient subgroups.

The median follow-up time for 442 patients treated with KEYTRUDA and enfortumab vedotin was 17.3 months (range: 0.3 to 37.2 months). Efficacy results are summarized in Table 23 and Figures 26 and 27.

Table 23: Efficacy Results in KEYNOTE-A39

Endpoint	KEYTRUDA 200 mg every 3 weeks in combination with enfortumab vedotin n=442	Gemcitabine + Platinum Chemotherapy with or without maintenance immunotherapy n=444
OS		
Number (%) of patients with event	133 (30%)	226 (51%)
Median in months (95% CI)	31.5 (25.4, NR)	16.1 (13.9, 18.3)
Hazard ratio* (95% CI)	0.47 (0.38, 0.58)	
p-Value†	<0.0001	
PFS		
Number (%) of patients with event	223 (50%)	307 (69%)
Median in months (95% CI)	12.5 (10.4, 16.6)	6.3 (6.2, 6.5)
Hazard ratio* (95% CI)	0.45 (0.38, 0.54)	
p-Value†	<0.0001	
Objective Response Rate‡		
ORR§ % (95% CI)	68% (63.1, 72.1)	44% (39.7, 49.2)
p-Value¶	<0.0001	
Complete response	29%	12%
Partial response	39%	32%
Stable Disease	19%	34%
Disease Control Rate#	86%	78%
Response Duration		
Median in months (range)	NR (2.0+, 28.3+)	7.0 (1.5+, 30.9+)
% with duration ≥ 6 monthsᵖ	86%	61%
% with duration ≥ 12 monthsᵖ	67%	35%
% with duration ≥ 18 monthsᵖ	60%	19%

* Based on the stratified Cox proportional hazard regression model

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

‡ Includes only patients with measurable disease at baseline

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

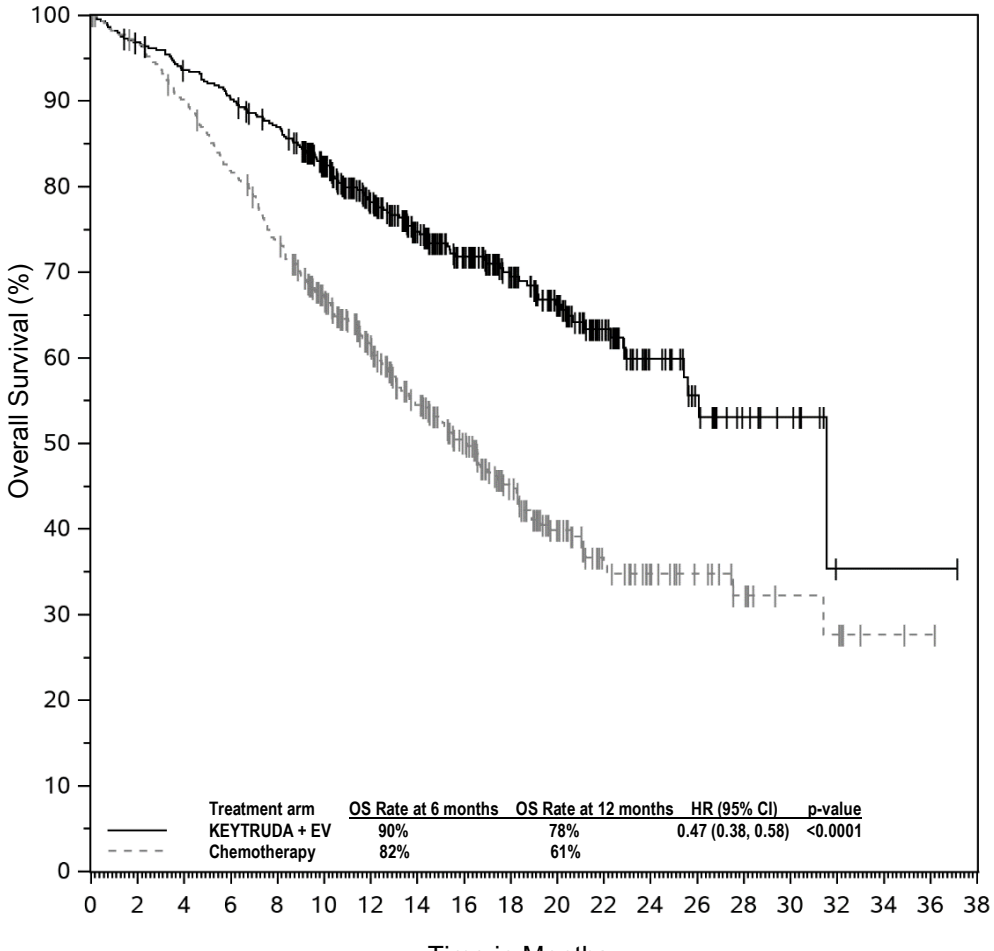
¶ Two-sided p-Value based on Cochran-Mantel-Haenszel test stratified by PD-L1 expression, cisplatin eligibility and liver metastases

Based on best response of stable disease or better

Þ Based on Kaplan-Meier estimation

NR = not reached

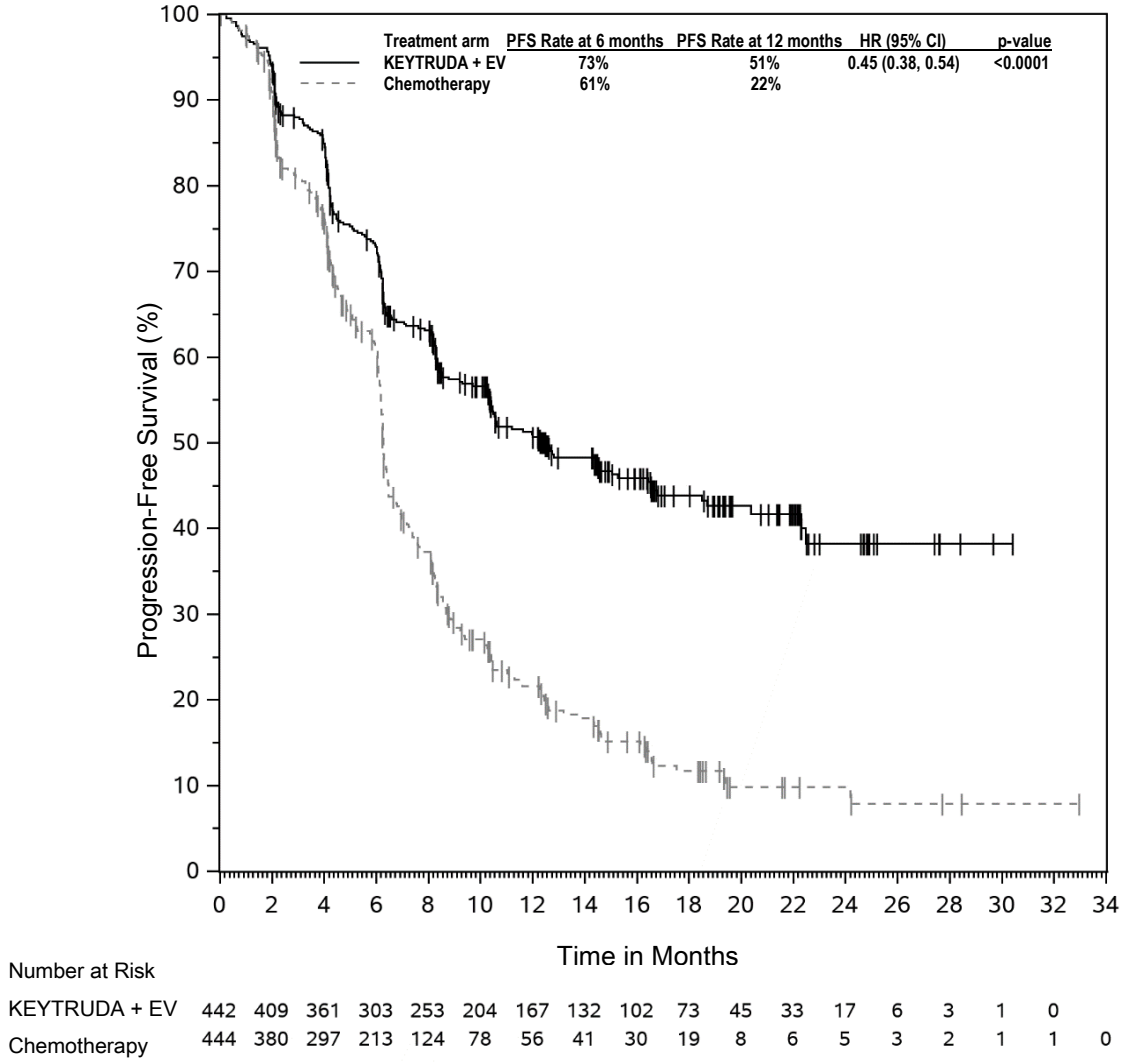
Figure 26: Kaplan-Meier Curve for Overall Survival in KEYNOTE-A39



Number at Risk

KEYTRUDA + EV	442	426	409	394	376	331	270	222	182	141	108	67	36	22	12	8	1	1	1	0
Chemotherapy	444	423	393	356	317	263	209	164	125	90	60	37	25	18	12	7	6	2	1	0

Figure 27: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-A39



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 24 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 24: 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 25).

Table 25: 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/m^2 (n=84), docetaxel 75 mg/m^2 (n=84), or vinflunine 320 mg/m^2 (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 ≥ 10 g/dL, could not have liver metastases, and must have received the last dose of their last prior chemotherapy regimen ≥ 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 26 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 28. 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 26: 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

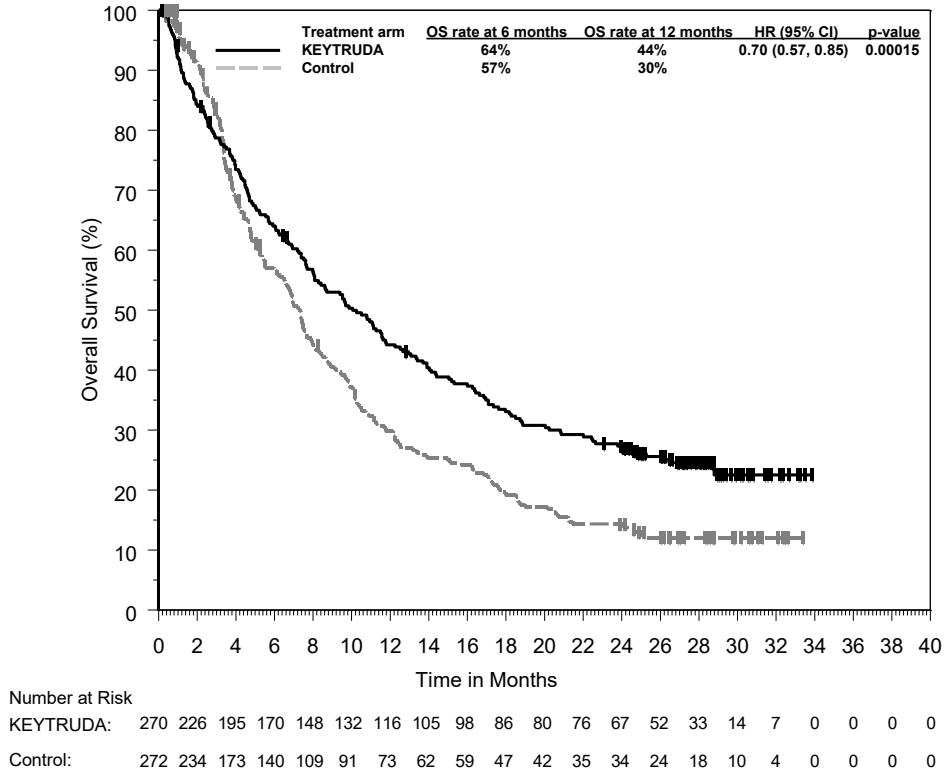
§ Based on method by Miettinen and Nurminen

¶ 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 28: 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 27).

Table 27: OS by PD-L1 Expression

PD-L1 Expression	Pembrolizumab	Chemotherapy	
	OS by PD-L1 Expression Number of Events (number of patients)*		Hazard 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.

KEYNOTE-B15: Controlled trial of combination with enfortumab vedotin for the neoadjuvant and adjuvant treatment of patients with MIBC who are eligible for cisplatin-containing chemotherapy

The efficacy of KEYTRUDA in combination with enfortumab vedotin as neoadjuvant treatment and continued after radical cystectomy as adjuvant treatment was investigated in KEYNOTE-B15, an open-label, randomized, multicenter, active-controlled trial in patients with MIBC. Key eligibility criteria were previously untreated Stage cT2-T4aN0M0 or cT1-T4aN1M0 muscle invasive bladder cancer in patients who were cisplatin-eligible and were eligible for radical cystectomy (RC) and pelvic lymph node dissection (PLND), regardless of PD-L1 status. Patients with active autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible.

Randomization was stratified by tumor stage (T2N0 vs. T3/T4aN0 vs. T1-T4aN1), PD-L1 combined positive score (CPS ≥ 10 vs. CPS <10), and geographic region (United States vs. European Union vs. Rest of the World). Patients were randomized (1:1) to one of the following treatment arms; all study medications were administered via intravenous infusion.

- KEYTRUDA in combination with enfortumab vedotin (n=405): Neoadjuvant KEYTRUDA 200 mg over 30 minutes on Day 1 and enfortumab vedotin 1.25 mg/kg on Days 1 and 8 of each 21-day cycle for 4 cycles. Following RC and PLND, adjuvant KEYTRUDA 200 mg over 30 minutes on Day 1 of each 21-day cycle for 13 cycles and adjuvant enfortumab vedotin 1.25 mg/kg on Days 1 and 8 of each 21-day cycle for 5 cycles.
- Gemcitabine and cisplatin based chemotherapy (n=403): Neoadjuvant gemcitabine 1000 mg/m^2 on Days 1 and 8 and cisplatin 70 mg/m^2 on Day 1 of each 21-day cycle for 4 cycles following RC and PLND, followed by observation.

Treatment continued until completion of study medications, disease progression that precluded RC and PLND, not undergoing or refusal of RC and PLND, disease recurrence in the adjuvant phase, or unacceptable toxicity. Assessment of tumor status was performed at baseline, within 5 weeks prior to RC and PLND, and at 6 weeks post-radical cystectomy. Following RC and PLND, assessment of tumor status was performed every 12 weeks up to 2 years, and every 24 weeks thereafter.

The major efficacy outcome measure was EFS as assessed by BICR. Additional efficacy outcome measures were pathological complete response (pCR) rate as assessed BICR and OS.

The study population characteristics were: median age of 66 years; 81% male; and 80% White; 57% were CPS ≥ 10 and 43% were CPS <10; 78% had ECOG PS of 0 and 22% had ECOG PS of 1; 19% were T2N0, 73% T3/T4aN0, and 8% T1-T4aN1. Eighty nine percent of patients had urothelial carcinoma histology; 4.8% had urothelial carcinoma with squamous differentiation, 2.6% had urothelial carcinoma with glandular differentiation, and 3.1% had urothelial carcinoma with other histologic variants.

A total of 351 (87%) patients in the KEYTRUDA in combination with enfortumab vedotin arm and 361 (90%) patients in the gemcitabine and cisplatin based chemotherapy arm underwent radical cystectomy.

The trial demonstrated a statistically significant and clinically meaningful improvement in EFS, OS, and pCR in patients treated with neoadjuvant and adjuvant KEYTRUDA in combination with enfortumab vedotin compared with patients treated with neoadjuvant chemotherapy. Efficacy results were consistent across all pre-specified patient subgroups. The median follow-up time for patients randomized to treatment with KEYTRUDA in combination with enfortumab was 31.3 months (range: 0.5 – 53.6 months). Table 28 and Figures 29 and 30 summarize key efficacy measures.

Table 28: Efficacy Results for Perioperative KEYTRUDA with Enfortumab vedotin in KEYNOTE-B15

Endpoint	KEYTRUDA 200 mg every 3 weeks in combination with enfortumab vedotin n=405	Gemcitabine with Cisplatin Chemotherapy n=403
EFS		
Number of patients with event (%)	87 (21%)	146 (36%)
Median in months* (95% CI)	NR (NR, NR)	48.5 (43.3, NR)
Hazard ratio† (95% CI)	0.53 (0.41, 0.70)	
p-Value‡	<0.0001	
12-month EFS rate (%), (95% CI)	86 (82, 89)	75 (71, 79)
24-month EFS rate (%), (95% CI)	79 (75, 83)	66 (61, 71)
OS		
Number of patients with event (%)	69 (17%)	99 (25%)
Median in months* (95% CI)	NR (NR, NR)	NR (NR, NR)
Hazard ratio† (95% CI)	0.65 (0.48, 0.89)	
p-Value‡	0.0029	
12-month OS rate (%), (95% CI)	93 (90, 95)	90 (86, 92)
24-month OS rate (%), (95% CI)	87 (83, 90)	81 (77, 85)
pCR		
Number of patients with pCR	226	131
pCR Rate (%), (95% CI)	55.8 (50.8, 60.7)	32.5 (28.0, 37.3)
Treatment difference estimate (%), (95% CI)§	23.4 (16.7, 29.8)	
p-Value	<0.0001	

* Based on Kaplan-Meier estimates

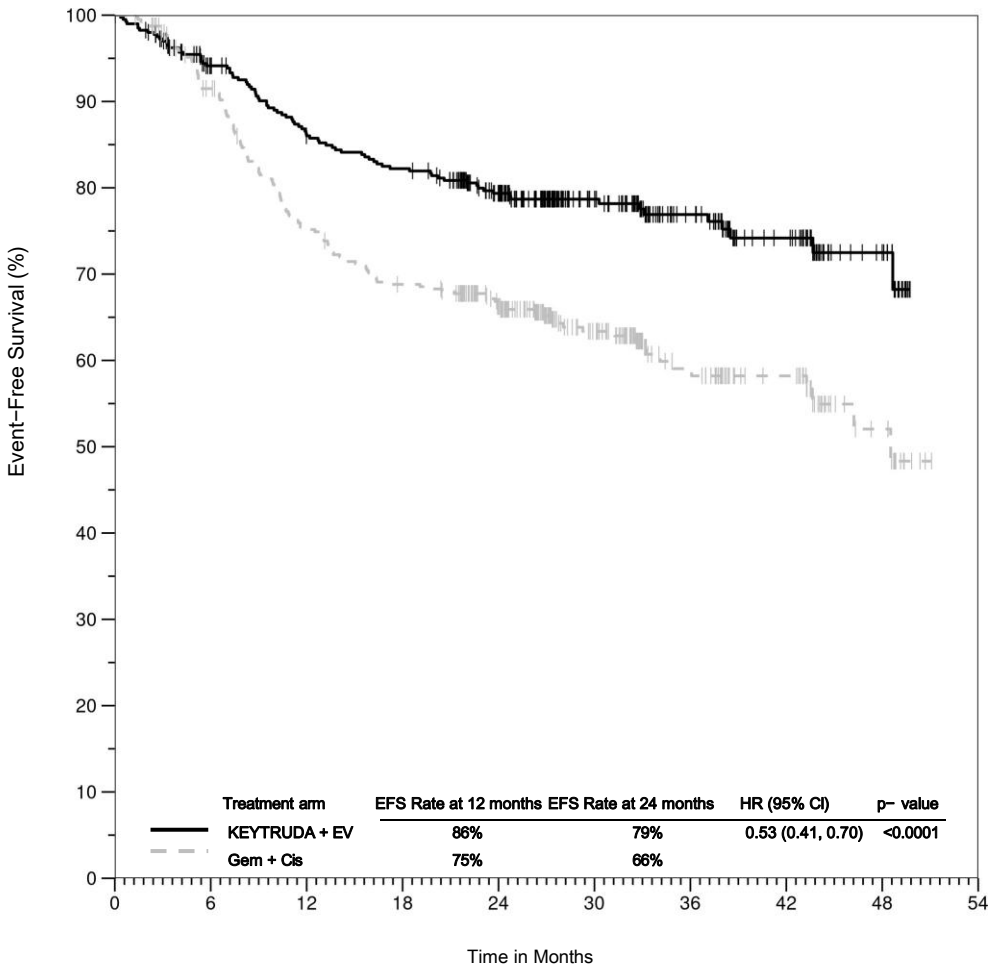
† Based on stratified Cox regression model with Efron's method of tie handling with treatment as a covariate

‡ Based on stratified log-rank test

§ Based on stratified Miettinen and Nurminen method

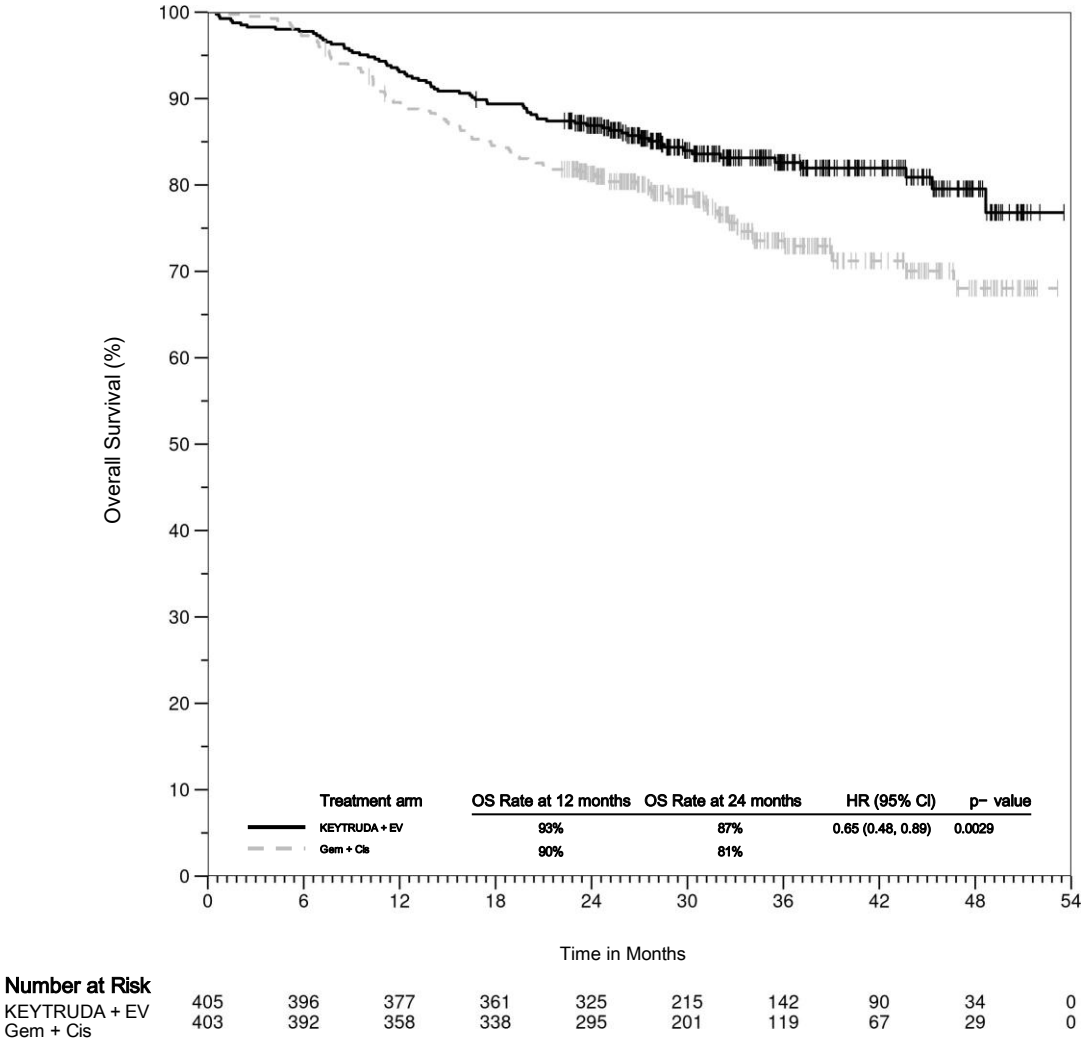
NR = not reached

Figure 29: Kaplan-Meier Curve for Event-Free Survival by Treatment Arm in KEYNOTE-B15



Number at Risk										
KEYTRUDA + EV	405	351	317	303	257	154	100	63	23	0
Gem + Cis	403	350	286	259	216	131	70	45	16	0

Figure 30: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-B15



The impact of the addition of KEYTRUDA to enfortumab vedotin on health-related quality of life was assessed using the EORTC QLQ-C30 and Bladder Cancer Index (BCI). In both treatment groups, participants generally maintained their global health status/QoL scores. No clinically meaningful differences were observed in definitive time to deterioration (TTD) in the global health status/QoL score and mean change from baseline to post-surgery Week 42 in the EORTC QLQ-C30 and BCI scores between the perioperative enfortumab vedotin plus pembrolizumab group and the cisplatin plus gemcitabine group.

KEYNOTE-905: Controlled trial of combination with enfortumab vedotin for neoadjuvant and adjuvant treatment of patients with MIBC who are ineligible for cisplatin-containing chemotherapy

The efficacy of KEYTRUDA in combination with enfortumab vedotin as neoadjuvant treatment and continued after radical cystectomy as adjuvant treatment was investigated in KEYNOTE-905, an open-label, randomized, multicenter, active-controlled trial in patients with MIBC. Key eligibility criteria were previously untreated cT2-T4aN0M0 or cT1-T4aN1M0 MIBC in patients who were ineligible for or declined cisplatin-based chemotherapy and were eligible for radical cystectomy (RC) and pelvic lymph node dissection (PLND), regardless of PD-L1 status. Patients with active autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Patients were randomized 1:1:1 to receive neoadjuvant and adjuvant KEYTRUDA in combination with enfortumab vedotin, neoadjuvant and adjuvant KEYTRUDA monotherapy, or RC and PLND alone. Randomization was stratified by tumor stage (T2N0 vs. T3/T4aN0 vs. T1-T4aN1), cisplatin eligibility (cisplatin-ineligible vs. cisplatin-eligible but declined), and geographic region (United States vs. European Union vs. Rest of the World). The study population characteristics and evaluation of efficacy was based on the following treatment arms; all study medications were administered via intravenous infusion.

- KEYTRUDA in combination with enfortumab vedotin (n=170): Neoadjuvant KEYTRUDA 200 mg over 30 minutes on Day 1 and enfortumab vedotin 1.25 mg/kg on Days 1 and 8 of each 21-day cycle for 3 cycles. Following RC and PLND, adjuvant KEYTRUDA 200 mg over 30 minutes on Day 1 of each 21-day cycle for 14 cycles and adjuvant enfortumab vedotin 1.25 mg/kg on Days 1 and 8 of each 21-day cycle for 6 cycles.
- RC and PLND alone (n=174).

Treatment continued until completion of study medications, disease progression that precluded RC and PLND, not undergoing or refusal of RC and PLND, disease recurrence in the adjuvant phase, or unacceptable toxicity. Assessment of tumor status was performed at baseline, within 5 weeks prior to RC and PLND, and at 6 weeks post-radical cystectomy. Following RC and PLND, assessment of tumor status was performed every 12 weeks up to 2 years, and every 24 weeks thereafter.

The major efficacy outcome measure was EFS as assessed by BICR. Additional efficacy outcome measures were pathological complete response (pCR) rate as assessed by BICR and OS.

The study population characteristics were: median age of 73 years; 78% male; and 78% White; 47% were CPS ≥ 10 and 51% were CPS <10; 86% had ECOG PS of 0-1 and 14% had ECOG PS of 2; 18% were T2N0, 77% T3/T4aN0, and 5% T1-T4aN1. Forty-one percent of patients had baseline creatinine clearance of ≥ 60 mL/min, 59% had <60 mL/min but ≥ 30 mL/min, and 0.3% had <30 mL/min, respectively. Ninety-one percent of patients had urothelial carcinoma histology; 4% had

urothelial carcinoma with squamous differentiation, 3% had urothelial carcinoma with glandular differentiation, and 2% had urothelial carcinoma with other variant histology.

A total of 149 (88%) patients in the KEYTRUDA in combination with enfortumab vedotin arm and 156 (90%) patients in the RC and PLND alone arm underwent radical cystectomy.

The trial demonstrated a statistically significant and clinically meaningful improvement in EFS, OS, and pCR in patients treated with neoadjuvant and adjuvant KEYTRUDA in combination with enfortumab vedotin compared with RC and PLND alone. Efficacy results were consistent across all stratified patient subgroups. The median follow-up time for patients randomized to treatment with KEYTRUDA in combination with enfortumab vedotin was 20.4 months (range: 1.4 – 52.6 months). Table 29 and Figures 31 and 32 summarize key efficacy measures.

Table 29: Efficacy Results for Perioperative KEYTRUDA with Enfortumab Vedotin in KEYNOTE-905

Endpoint	KEYTRUDA 200 mg every 3 weeks in combination with enfortumab vedotin n=170	RC and PLND alone n=174
EFS		
Number of patients with event (%)	48 (28%)	95 (55%)
Median in months* (95% CI)	NR (37.3, NR)	15.7 (10.3, 20.5)
Hazard ratio† (95% CI)	0.40 (0.28, 0.57)	
p-Value‡	<0.0001	
12-month EFS rate (%), (95% CI)	78 (70, 84)	55 (47, 62)
24-month EFS rate (%), (95% CI)	75 (67, 81)	39 (31, 48)
OS		
Number of patients with event (%)	38 (22%)	68 (39%)
Median in months* (95% CI)	NR (NR, NR)	41.7 (31.8, NR)
Hazard ratio† (95% CI)	0.50 (0.33, 0.74)	
p-Value‡	0.0002	
12-month OS rate (%), (95% CI)	86 (80, 91)	76 (69, 81)
24-month OS rate (%), (95% CI)	80 (72, 85)	63 (55, 70)
pCR		
Number of patients with pCR	97	15
pCR Rate (%), (95% CI)	57.1 (49.3, 64.6)	8.6 (4.9, 13.8)
Treatment difference estimate (%), (95% CI)§	48.3 (39.5, 56.5)	
p-Value	<0.0001	

* Based on Kaplan-Meier estimates

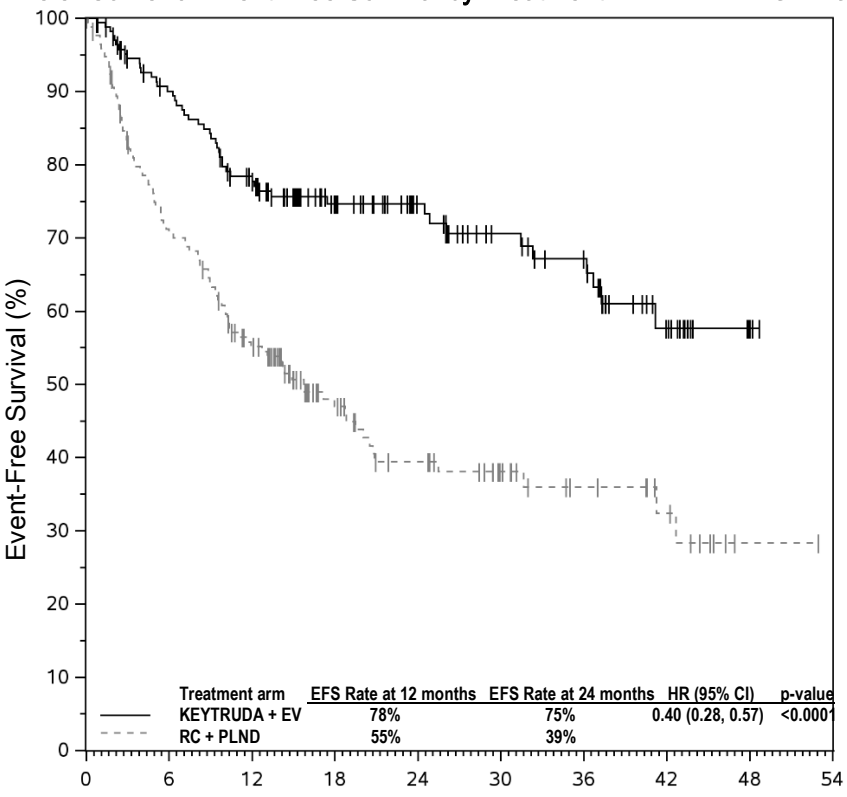
† Based on stratified Cox regression model with Efron's method of tie handling with treatment as a covariate

‡ Based on stratified log-rank test

§ Based on stratified Miettinen and Nurminen method

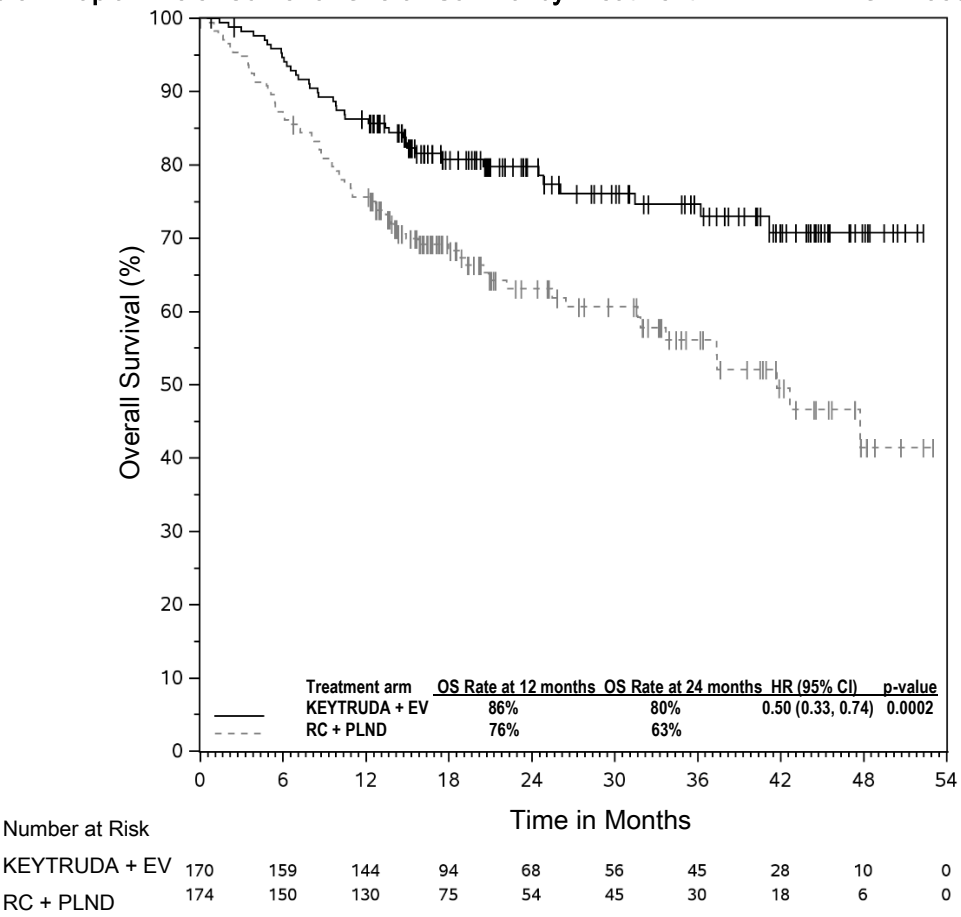
NR = not reached.

Figure 31: Kaplan-Meier Curve for Event-Free Survival by Treatment Arm in KEYNOTE-905



Number at Risk										
KEYTRUDA + EV	170	140	116	73	56	42	35	16	3	0
RC + PLND	174	116	84	48	33	22	14	9	1	0

Figure 32: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-905



Health-related QoL as evaluated by the Functional Assessment of Cancer Therapy-Bladder-Cystectomy (FACT-BI-Cys) and EQ-5D-5L was generally maintained from baseline to week 18 post-radical cystectomy in patients receiving neoadjuvant and adjuvant treatment with KEYTRUDA in combination with enfortumab vedotin.

Gastric Cancer

KEYNOTE-859: Controlled trial of combination therapy in HER2-negative gastric cancer patients naïve to treatment

The efficacy of KEYTRUDA in combination with fluoropyrimidine and platinum chemotherapy was investigated in KEYNOTE-859, a multicenter, randomized, double-blind, placebo-controlled trial that enrolled 1579 patients with HER2-negative advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma regardless of PD-L1 expression status, who had not previously received systemic therapy for metastatic disease. Patients with an autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible.

Randomization was stratified by PD-L1 expression (CPS ≥ 1 or <1), chemotherapy regimen (5-FU plus cisplatin [FP] or capecitabine plus oxaliplatin [CAPOX]), and geographic region (Europe/ Israel/ North America/ Australia, Asia or Rest of the World). Patients were randomized (1:1) to one of the following treatment arms; all study medications, except oral capecitabine, were administered as an intravenous infusion for every 3-week cycle:

- KEYTRUDA 200 mg, investigator's choice of combination chemotherapy of cisplatin 80 mg/m^2 and 5-FU 800 mg/m^2/day for 5 days (FP) or oxaliplatin 130 mg/m^2 and capecitabine 1000 mg/m^2 bid for 14 days (CAPOX) for up to 35 cycles. KEYTRUDA was administered prior to chemotherapy on Day 1 of each cycle.
- Placebo, investigator's choice of combination chemotherapy of cisplatin 80 mg/m^2 and 5-FU 800 mg/m^2/day for 5 days (FP) or oxaliplatin 130 mg/m^2 and capecitabine 1000 mg/m^2 bid for 14 days (CAPOX) for up to 35 cycles. Placebo was administered prior to chemotherapy on Day 1 of each cycle.

Treatment with KEYTRUDA and chemotherapy or placebo and chemotherapy continued until RECIST v1.1-defined progression of disease as determined by BICR, unacceptable toxicity, or a maximum of 24 months. Treatment was permitted beyond RECIST-defined disease progression if the patient was clinically stable and deriving clinical benefit as determined by the investigator. Assessment of tumor status was performed every 6 weeks. The primary efficacy outcome measure was OS. Additional secondary efficacy outcome measures included PFS, ORR, and DOR as assessed by BICR using RECIST v1.1.

The population characteristics were: median age of 62 years (range: 21 to 86), 39% age 65 or older; 68% male; 55% White and 34% Asian; 37% ECOG PS of 0 and 63% ECOG PS of 1. Ninety-seven percent of patients had metastatic disease (stage IV) and 3% had locally advanced unresectable disease. Seventy-eight percent had tumors that expressed PD-L1 with a CPS ≥ 1 and 5% (n=74) of patients had tumors that were MSI-H. Eighty-six percent of patients received CAPOX.

A statistically significant improvement in OS, PFS and ORR was demonstrated in patients randomized to KEYTRUDA in combination with chemotherapy compared with placebo in combination with chemotherapy. Efficacy results are summarized in Table 30.

Table 30: Efficacy Results for KEYNOTE-859

Endpoint	KEYTRUDA 200 mg every 3 weeks FP or CAPOX n=790	Placebo FP or CAPOX n=789
OS		
Number (%) of patients with event	603 (76)	666 (84)
Median in months* (95% CI)	12.9 (11.9,14.0)	11.5 (10.6,12.1)
Hazard ratio† (95% CI)	0.78 (0.70, 0.87)	
p-Value (stratified log-rank)‡	<0.0001	
PFS		
Number (%) of patients with event	572 (72)	608 (77)
Median in months* (95% CI)	6.9 (6.3, 7.2)	5.6 (5.5, 5.7)
Hazard ratio† (95% CI)	0.76 (0.67, 0.85)	
p-Value (stratified log-rank)‡	<0.0001	
Objective Response Rate		
ORR§ (95% CI)	51% (47.7, 54.8)	42% (38.5, 45.5)
Complete response rate	9%	6%
Partial response rate	42%	36%
Difference (95% CI)	9% (4.4, 14.1)	
p-Value¶	0.00009	
Response Duration	n=405	n=331
Median in months (range)	8.0 (1.2+ - 41.5+)	5.7 (1.3+ - 34.7+)
% with duration ≥ 12 months*	39%	26%
% with duration ≥ 24 months*	27%	13%

* Based on Kaplan-Meier estimation

† Based on the stratified Cox proportional hazard model

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

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

¶ One-sided p-Value based on stratified Miettinen and Nurminen method

Figure 33: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-859

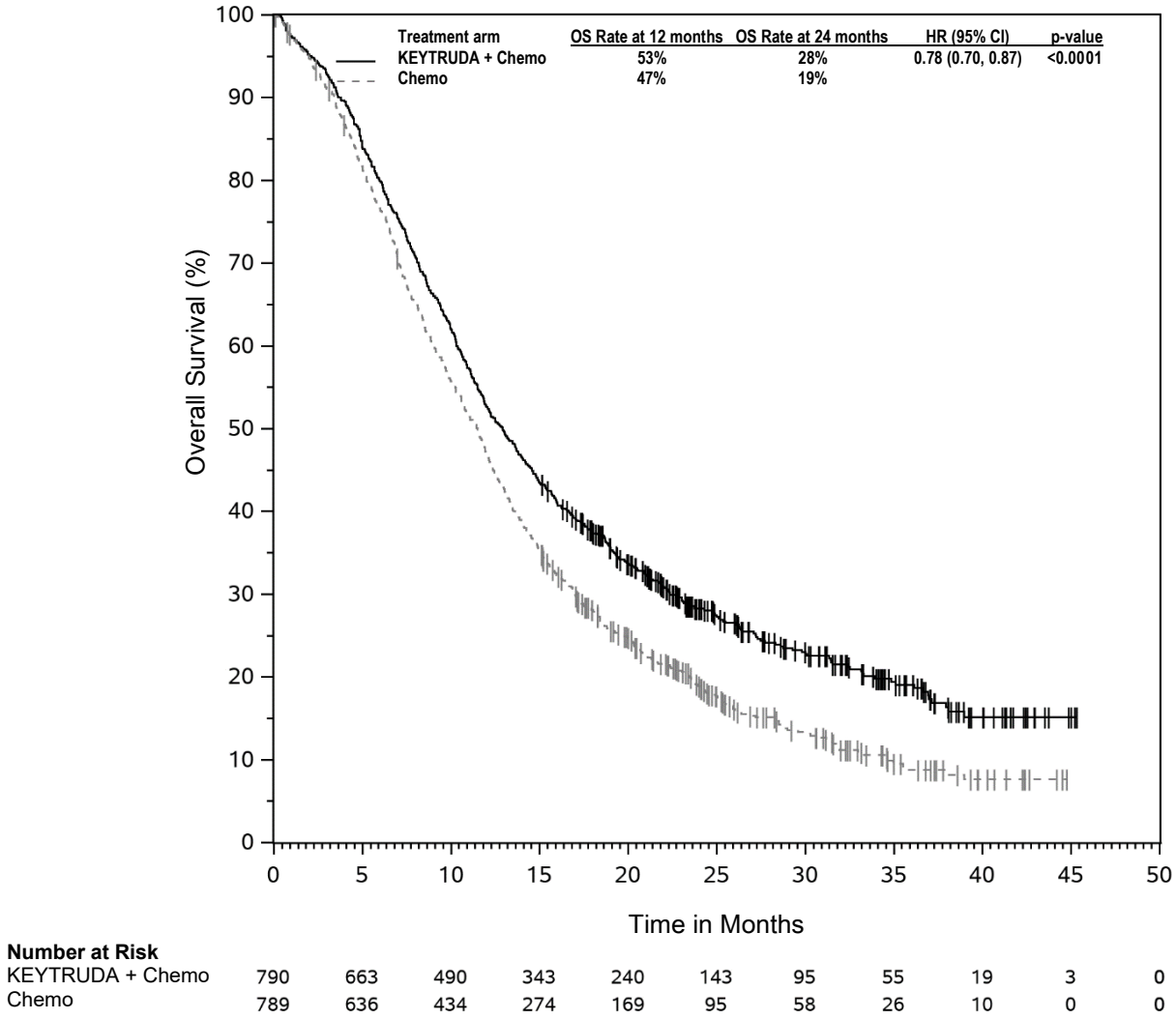
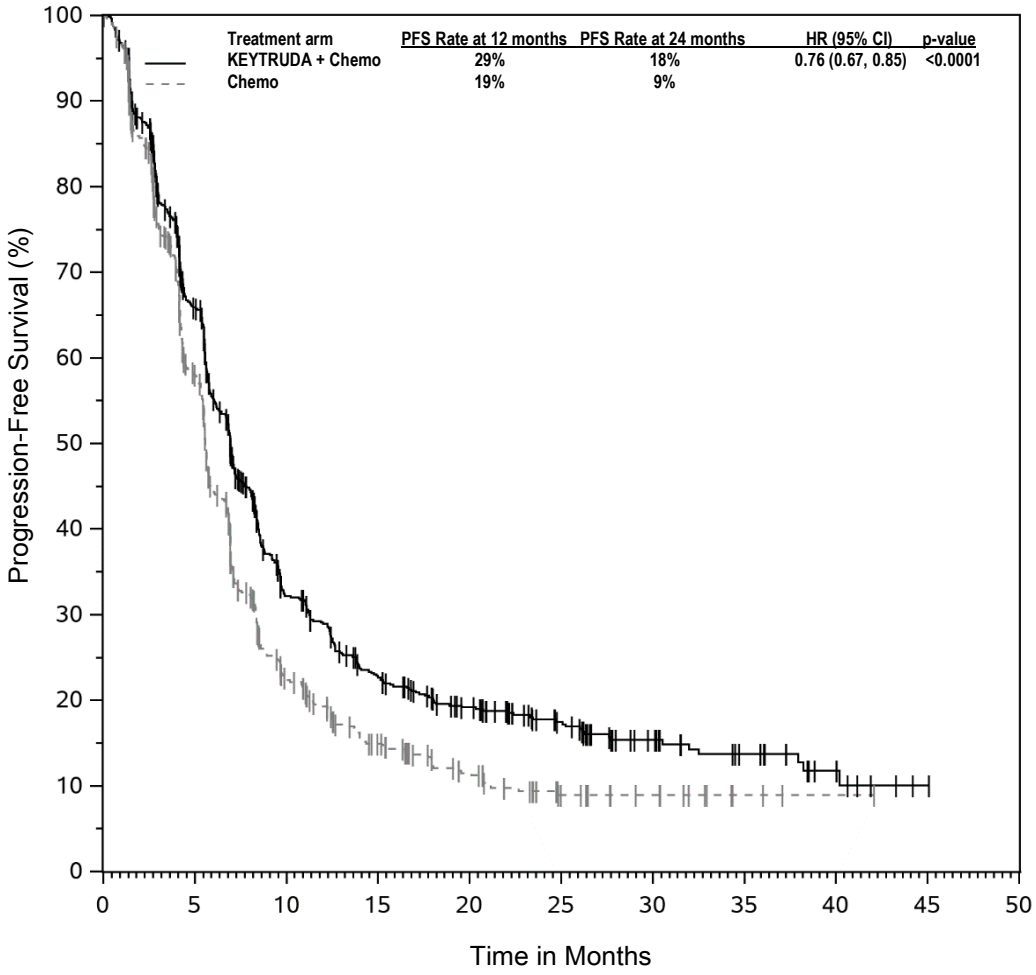


Figure 34: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-859



KEYNOTE-811: First-line treatment of locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma

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

to one of the following treatment arms; all study medications, except oral capecitabine, were administered as an intravenous infusion for every 3-week cycle:

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

Treatment with KEYTRUDA, trastuzumab and chemotherapy or placebo, trastuzumab and chemotherapy continued until RECIST v1.1-defined progression of disease as determined by BICR, unacceptable toxicity, or a maximum of 24 months. Treatment was permitted beyond RECIST-defined disease progression if the patient was clinically stable and deriving clinical benefit as determined by the investigator. Assessment of tumor status was performed every 6 weeks.

Among the 698 patients randomized in KEYNOTE-811, 594 (85%) had tumors that expressed PD-L1 with a CPS ≥ 1. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx™ kit. The population characteristics of these 594 patients were: median age of 63 years (range: 19 to 85), 43% age 65 or older; 80% male; 63% White, 33% Asian, and 0.7% Black; 42% ECOG PS of 0 and 58% ECOG PS of 1. Ninety-eight percent of patients had metastatic disease (stage IV) and 2% had locally advanced unresectable disease. Ninety-five percent (n=562) had tumors that were not MSI-H, 1% (n=8) had tumors that were MSI-H, and in 4% (n=24) the status was not known. Eighty-five percent of patients received CAPOX.

The primary efficacy outcome measures were PFS, based on BICR using RECIST 1.1, and OS. Secondary efficacy outcome measures included ORR and DoR, based on BICR using RECIST 1.1.

In the overall population, a statistically significant improvement in OS (HR 0.80; 95% CI: 0.67, 0.94; p-Value=0.004), at final analysis, and PFS (HR 0.72; 95% CI: 0.60, 0.87; p-Value=0.0002), at a pre-specified interim analysis, was demonstrated in patients randomized to KEYTRUDA in combination with trastuzumab and chemotherapy compared with placebo in combination with trastuzumab and chemotherapy.

At a pre-specified interim analysis, conducted on the first 264 patients randomized in the overall population (133 patients in the KEYTRUDA arm and 131 in the placebo arm), a statistically significant improvement in the objective response rate (74.4% vs. 51.9%, representing a 22.7% difference; 95% CI (11.2, 33.7); p-Value<0.0001) was demonstrated in patients randomized to KEYTRUDA in combination with trastuzumab and chemotherapy compared with placebo in combination with trastuzumab and chemotherapy.

A pre-specified subgroup analysis indicated that adding KEYTRUDA to trastuzumab and chemotherapy demonstrated a greater benefit in the population of patients whose tumors express PD-L1 with a CPS of ≥ 1.

Efficacy results at the final analysis for the pre-specified subgroup of patients whose tumors expressed PD-L1 with a CPS ≥ 1 are summarized in Table 31 and Figures 35 and 36.

Table 31: Efficacy Results for KEYNOTE-811 with PD-L1 Expression CPS ≥ 1

Endpoint	KEYTRUDA 200 mg every 3 weeks Trastuzumab Fluoropyrimidine and Platinum Chemotherapy n=298	Placebo Trastuzumab Fluoropyrimidine and Platinum Chemotherapy n=296
OS		
Number (%) of patients with event	226 (76%)	244 (82%)
Median in months (95% CI)	20.1 (17.9, 22.9)	15.7 (13.5, 18.5)
Hazard ratio* (95% CI)	0.79 (0.66, 0.95)	
p-Value†	0.0062	
PFS		
Number (%) of patients with event	221 (74%)	226 (76%)
Median in months (95% CI)	10.9 (8.5, 12.5)	7.3 (6.8, 8.4)
Hazard ratio* (95% CI)	0.72 (0.60, 0.87)	
p-Value†	0.0003	
Objective Response Rate		
ORR‡ (95% CI)	73% (67.7, 78.1)	58% (52.6, 64.1)
Complete response rate	17%	10%
Partial response rate	56%	48%
Difference (95% CI)§	15% (7.1, 22.2)	
p-Value§	<0.0001	
Response Duration	n=218	n=173
Median in months (range)	11.3 (1.1+, 60.8+)	9.6 (1.4+, 60.5+)
% with duration ≥ 6 months¶	75%	68%
% with duration ≥ 12 months¶	49%	42%

* Based on the unstratified Cox proportional hazard model

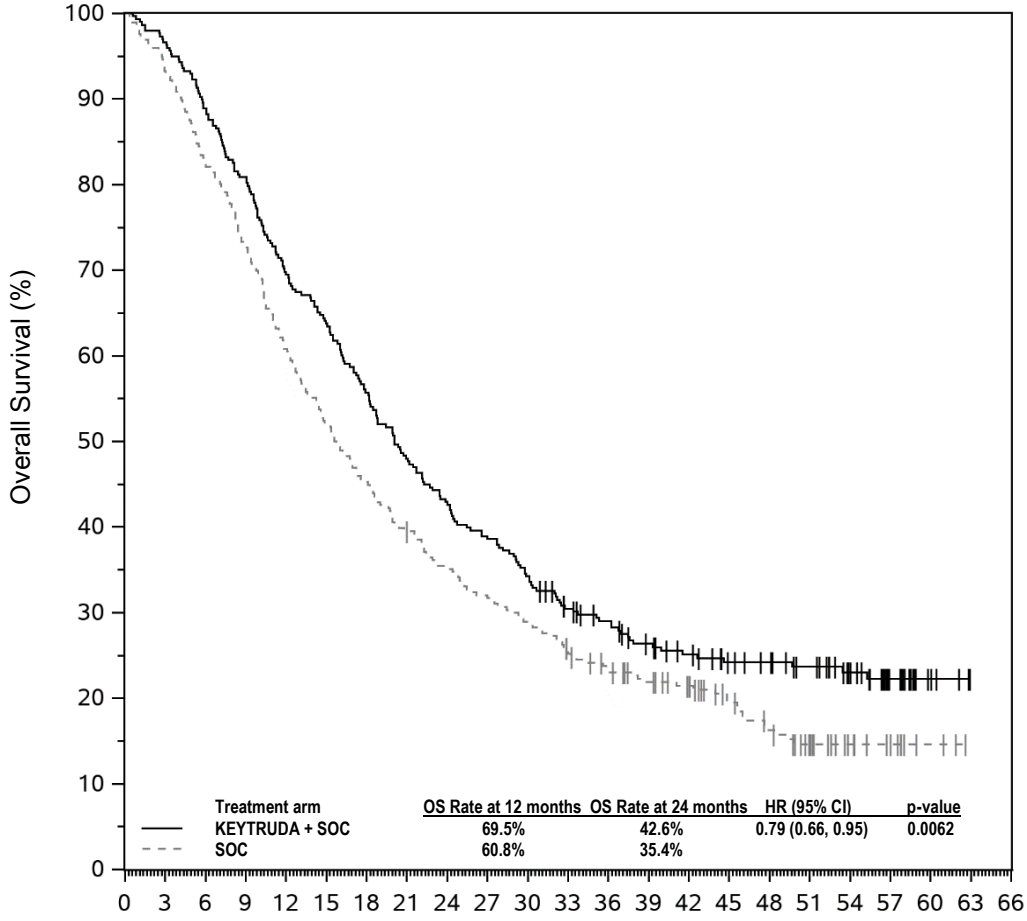
† Based on unstratified log-rank test; p-value is nominal p-value

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

§ Based on unstratified Miettinen and Nurminen method; p-value is nominal p-value

¶ Based on Kaplan-Meier estimation

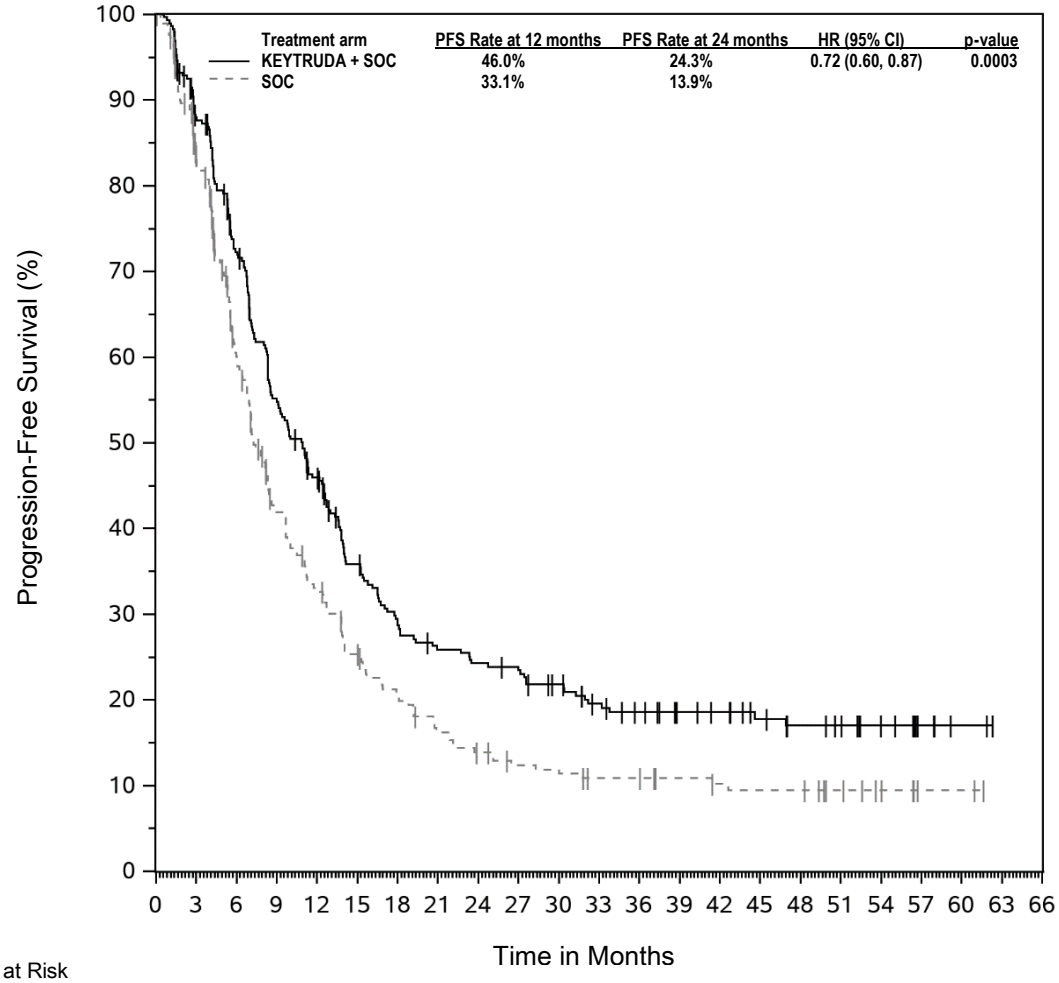
Figure 35: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-811 (CPS ≥ 1)



Number at Risk																					
KEYTRUDA + SOC	298	288	265	241	207	190	166	143	127	115	102	86	78	67	59	51	48	42	32	18	5	0	0
SOC	296	276	244	215	180	154	135	117	104	93	85	73	63	56	50	38	30	21	13	9	3	0	0

*Based on the pre-specified final analysis

Figure 36: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-811 (CPS ≥ 1)



Number at Risk

KEYTRUDA + SOC	298	250	200	151	123	91	73	64	60	57	50	41	36	30	28	23	19	17	12	5	2	0	0
SOC	296	231	152	100	78	58	45	35	29	24	23	19	19	16	14	13	13	9	6	2	2	0	0

*Based on the pre-specified final analysis

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/m^2 IV on Day 1 of each three-week cycle for up to six cycles and 5-FU 800 mg/m^2 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/m^2 IV on Day 1 of each three-week cycle for up to six cycles and 5-FU 800 mg/m^2 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 ≥ 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 32 summarizes the key efficacy measures for KEYNOTE-590. The Kaplan-Meier curves for OS and PFS are shown in Figures 37 and 38.

Table 32: 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%

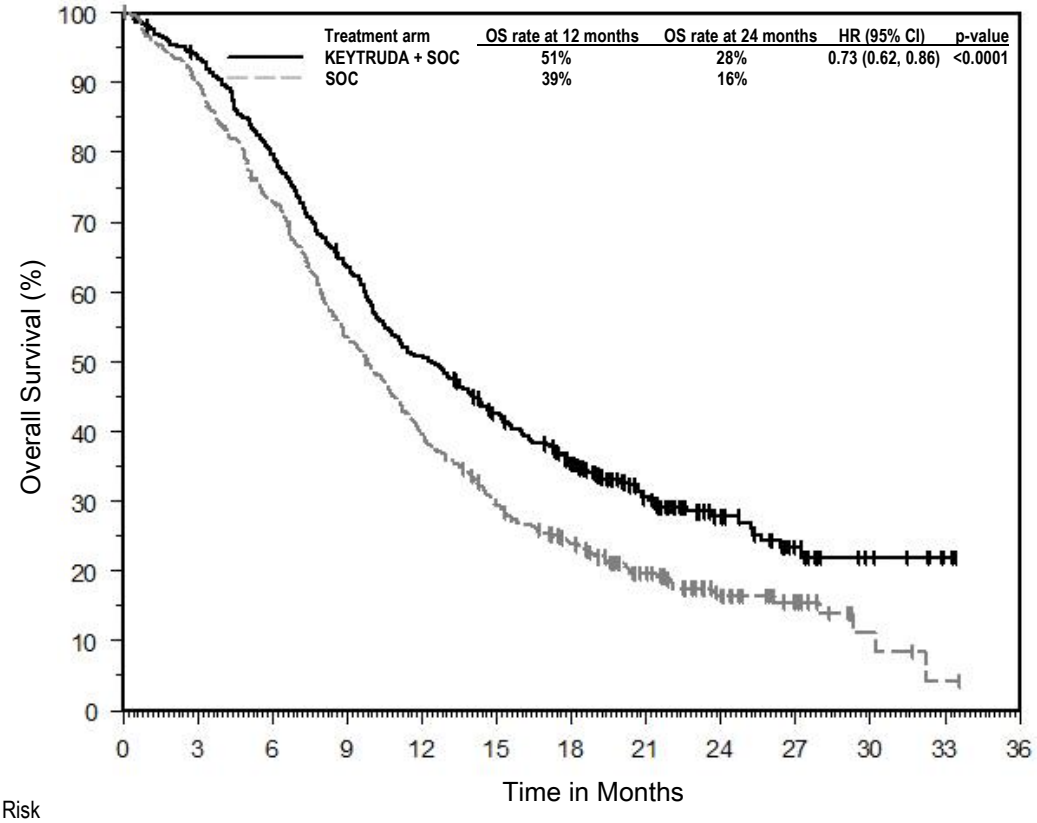
* Based on Kaplan-Meier estimation

† 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

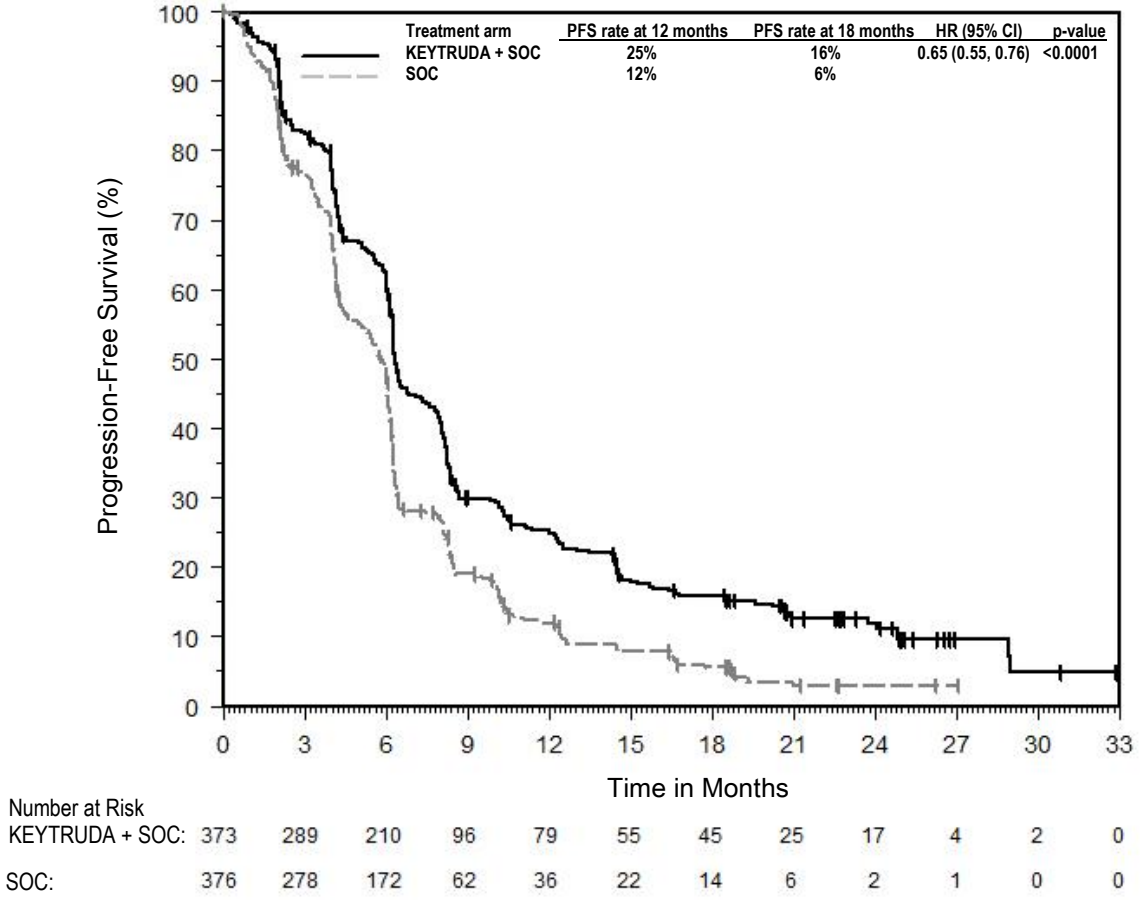
Figure 37: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-590



Number at Risk

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

Treatment with KEYTRUDA or chemotherapy continued until RECIST v1.1-defined progression of disease as determined by the investigator or unacceptable toxicity. Patients treated with KEYTRUDA without disease progression could be treated for up to 24 months. Assessment of tumor status was performed every 9 weeks. Patients randomized to chemotherapy were offered KEYTRUDA at the time of disease progression. The primary efficacy outcome measures were PFS assessed by BICR according to RECIST v1.1 and OS. 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 at the pre-specified final analysis for PFS. There was no statistically significant difference between KEYTRUDA and chemotherapy in the final OS analysis, with an additional 12 months of follow-up, in which 60% of the patients who had been randomized to receive chemotherapy had crossed over to receive subsequent anti-PD-1/PD-L1 therapies including KEYTRUDA. The median follow-up time was 38.1 months (range: 0.2 to 58.7 months). Table 33 and Figures 39 and 40 summarize the key efficacy measures for KEYNOTE-177.

Table 33: 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	
OS‡		
Number (%) of patients with event	62 (41%)	78 (51%)
Median in months (95% CI)	NR (49.2, NR)	36.7 (27.6, NR)
Hazard ratio* (95% CI)	0.74 (0.53, 1.03)	
p-Value§	0.0359	
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 final analysis

§ Not statistically significant after adjustment for multiplicity

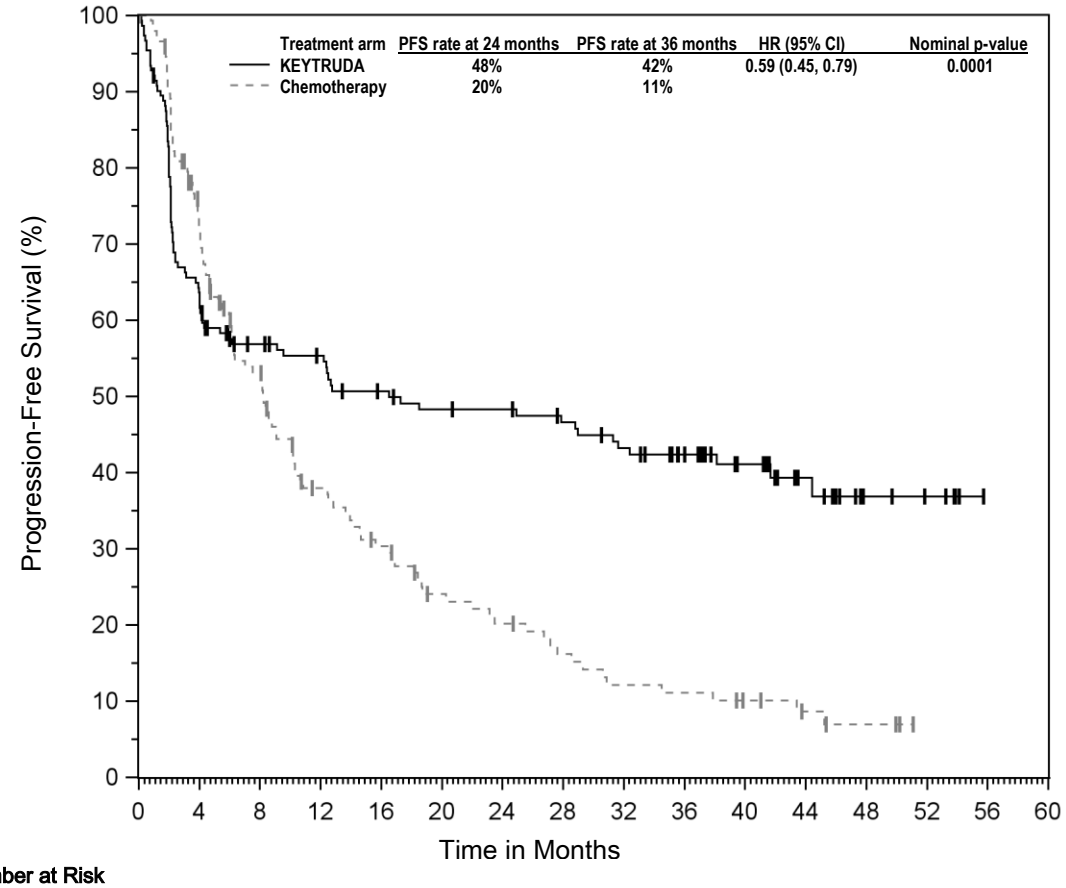
¶ Based on Kaplan-Meier estimation

NR=not reached

At the final analysis, there were a total of 203 PFS events (86 for KEYTRUDA; 117 for chemotherapy). The median PFS was 16.5 months (95% CI: 5.4, 38.1) for the KEYTRUDA arm and 8.2 months (95% CI: 6.1, 10.2) for the chemotherapy arm. The PFS HR vs. chemotherapy was 0.59 (95% CI:

0.45, 0.79, nominal p=0.0001) (Figure 39). The ORR at the final analysis was 45% for the KEYTRUDA arm and 33% for the chemotherapy arm. The median duration of response was not reached (range: 2.3+, 53.5+) for the KEYTRUDA arm and 10.6 months (range: 2.8, 48.3+) for the chemotherapy arm. The percentage of patients with ongoing responses based on Kaplan-Meier estimation was 84% at 24 months or longer in the KEYTRUDA arm vs. 34% in the chemotherapy arm.

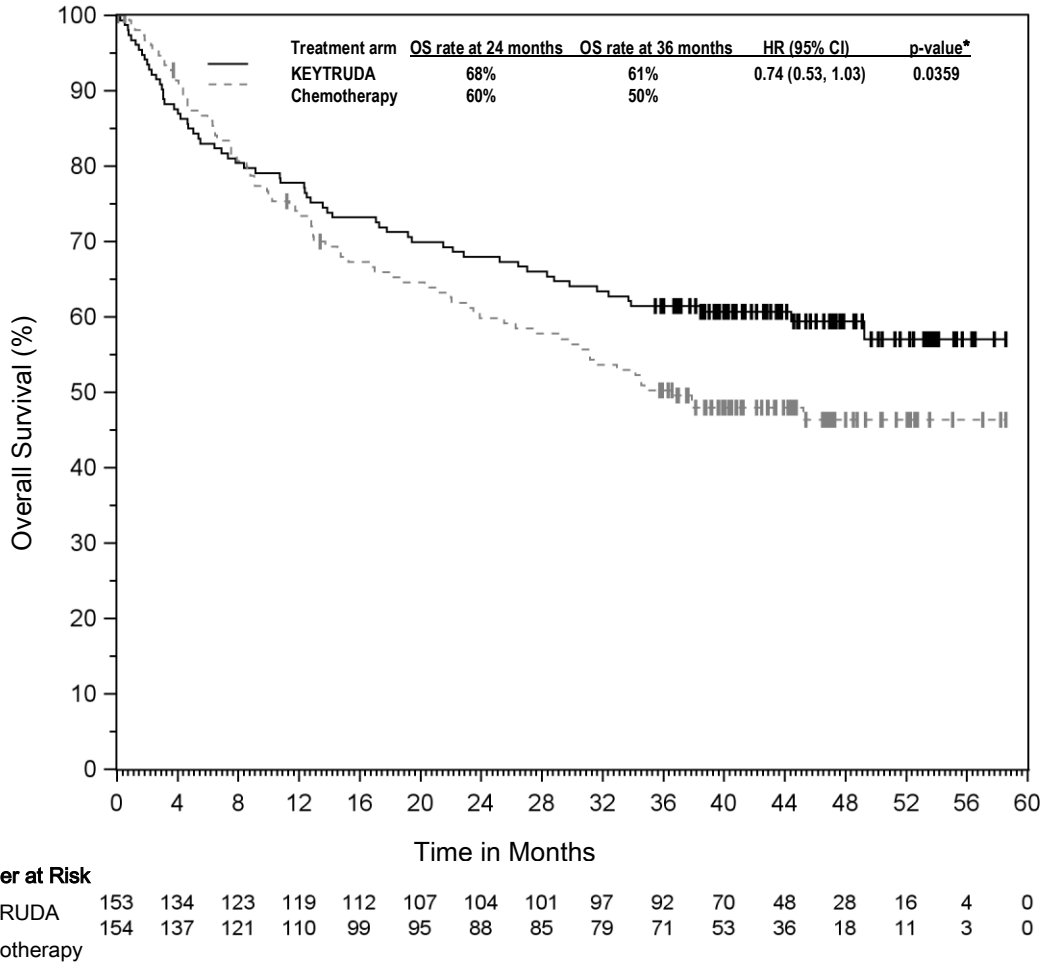
Figure 39: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-177 (Intent to Treat Population)



Number at Risk

KEYTRUDA	153	96	77	72	64	60	59	55	50	42	28	16	7	5	0	0
Chemotherapy	154	101	69	45	35	25	21	16	12	11	8	5	3	0	0	0

Figure 40: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-177 (Intent to Treat Population)



Number at Risk

KEYTRUDA	153	134	123	119	112	107	104	101	97	92	70	48	28	16	4	0
Chemotherapy	154	137	121	110	99	95	88	85	79	71	53	36	18	11	3	0

* Not statistically significant after adjustment for multiplicity.

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.

Hepatocellular Carcinoma

KEYNOTE-394: Controlled trial in patients with HCC, previously treated with sorafenib, an anti-angiogenic TKI or oxaliplatin-based chemotherapy

The efficacy of KEYTRUDA was investigated in KEYNOTE-394, a multicenter, randomized, placebo-controlled, double-blind trial in 453 patients with HCC, who were previously treated with sorafenib or oxaliplatin-based chemotherapy. Patients with an autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible.

Randomization was stratified by prior treatment: sorafenib vs. oxaliplatin-based chemotherapy, macrovascular invasion, etiology (HBV vs. others (HCV, non-infected)). Patients were randomized (2:1) to receive pembrolizumab 200 mg intravenously every 3 weeks or placebo.

Treatment with KEYTRUDA continued until RECIST v1.1-defined progression of disease as determined by BICR, unacceptable toxicity, or a maximum of 24 months. Administration of KEYTRUDA was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Assessment of tumor status was performed every 6 weeks. The primary efficacy outcome measure was OS and the secondary efficacy outcome measures were PFS, ORR, and DoR, as assessed by BICR using RECIST v1.1.

The study population characteristics were: median age of 54 years (range: 22 to 82), 22% age 65 or older; 85% male; 100% Asian; 41% ECOG PS of 0 and 59% ECOG PS of 1;100% Child-Pugh Class A; 80% of patients were hepatitis B active positive, 1.3% were hepatitis C active positive, and 0.4% had HBV/HCV co-infection; 91% received prior sorafenib and 9% received prior oxaliplatin-based chemotherapy. Patient characteristics also included extrahepatic disease (78%); macrovascular invasion (11%), BCLC stage C (93%) and B (7%), and baseline AFP ≥ 200 ng/mL (55%).

Efficacy results are summarized in Table 34 and Figure 41 and 42.

Table 34: Efficacy Results in Patients with Hepatocellular Carcinoma in KEYNOTE-394

Endpoint	KEYTRUDA 200 mg every 3 weeks n=300	Placebo n=153
OS*		
Number (%) of patients with event	222 (74)	128 (84)
Median in months (95% CI)	14.6 (12.6, 18)	13 (10.5, 15.1)
Hazard ratio† (95% CI)	0.79 (0.63, 0.99)	
p-Value‡	0.0180	
PFS§		
Number (%) of patients with event	237 (79)	134 (88)
Median in months (95% CI)	2.6 (1.5, 2.8)	2.3 (1.4, 2.8)
Hazard ratio† (95% CI)	0.74 (0.60, 0.92)	
p-Value‡	0.0032	
Objective Response Rate§		
ORR¶ (95% CI)	13% (9, 17)	1.3% (0.2, 4.6)
Number (%) of complete responses	6 (2)	1 (0.7)
Number (%) of partial responses	32 (11)	1 (0.7)
p-Value#	0.00004	
Response Duration*	n=41	n=2
Median in monthsᵖ (range)	23.9 (2.6+, 44.4+)	5.6 (3.0+, 5.6)
% with duration ≥ 12 monthsᵖ	65%	0%
% with duration ≥ 24 monthsᵖ	48	0

* Results at the pre-specified final OS analysis

† Based on the stratified Cox proportional hazard model

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

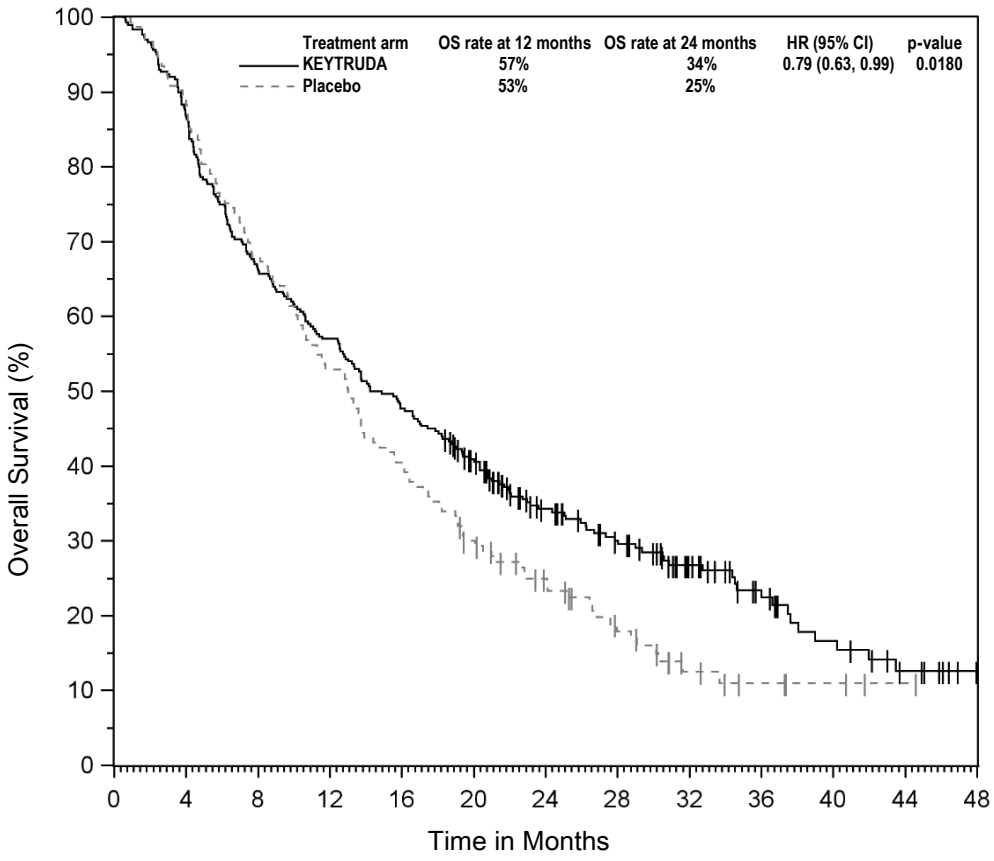
§ Results at pre-specified interim OS analysis

¶ Confirmed complete response or partial response

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

ᵖ Based on Kaplan-Meier estimation

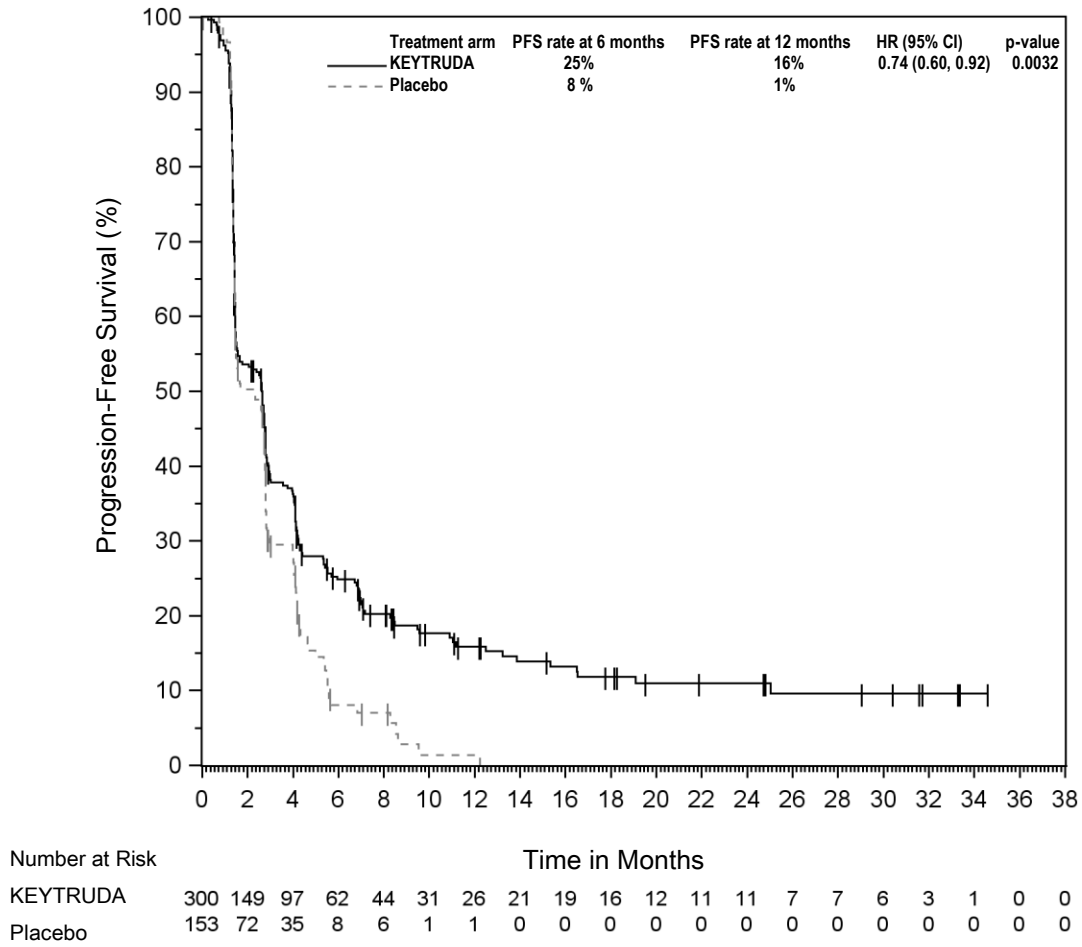
Figure 41: Kaplan-Meier Curve for Overall Survival in KEYNOTE-394*



Number at Risk													
KEYTRUDA	300	260	199	171	143	115	78	61	39	24	14	7	0
Placebo	153	135	104	81	62	44	31	19	9	5	3	1	0

*Based on the pre-specified final OS analysis

Figure 42: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-394*



*Based on the pre-specified OS interim analysis data cut-off

Pre-specified exploratory analysis of patient-reported outcome (PRO) endpoints using the EORTC QLQ-C30 indicated a smaller decline in global health status/quality of life (GHS/QoL) score from baseline to Week 12 for patients treated with KEYTRUDA compared to placebo (difference in Least Square (LS) means =4.43; 95% CI: 0.47, 8.40). Time to deterioration in the GHS/QoL score was similar for patients treated with KEYTRUDA compared to placebo (HR 0.85; 95% CI: 0.58, 1.25).

Biliary Tract Carcinoma

KEYNOTE-966: Controlled trial of combination therapy in patients with locally advanced unresectable or metastatic biliary tract carcinoma

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

Patients were randomized (1:1) to one of the two treatment groups:

- KEYTRUDA 200 mg on Day 1 plus gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2 on Day 1 and Day 8 every 3 weeks.
- Placebo on Day 1 plus gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2 on Day 1 and Day 8 every 3 weeks

All study medications were administered via intravenous infusion. Treatment was continued until unacceptable toxicity or disease progression. For pembrolizumab, treatment was continued for a maximum of 35 cycles, or approximately 24 months. For cisplatin, treatment could be administered for a maximum of 8 cycles and for gemcitabine, treatment could be continued beyond 8 cycles.

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

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

The primary efficacy outcome measure was OS and the secondary efficacy measures were PFS, ORR and DOR as assessed by BICR according to RECIST v1.1. The trial demonstrated a statistically significant improvement in OS at final analysis for patients randomized to KEYTRUDA in combination with chemotherapy compared to placebo in combination with chemotherapy.

Table 35 and Figures 43 and 44 summarize the efficacy results for KEYNOTE-966.

Table 35: Efficacy Results in Patients with BTC in KEYNOTE-966

Endpoint	KEYTRUDA 200 mg every 3 weeks with gemcitabine/cisplatin n=533	Placebo with gemcitabine/cisplatin n=536
OS*		
Number (%) of patients with event	414 (78%)	443 (83%)
Median in months (95% CI)	12.7 (11.5, 13.6)	10.9 (9.9, 11.6)
Hazard ratio† (95% CI)	0.83 (0.72, 0.95)	
p-Value‡	0.0034	
PFS§		
Number (%) of patients with event	361 (68%)	391 (73%)
Median in months (95% CI)	6.5 (5.7, 6.9)	5.6 (5.1, 6.6)
Hazard ratio† (95% CI)	0.86 (0.75, 1.00)	
p-Value‡	NS	
Objective Response Rate§		
ORR¶ (95% CI)	28.7% (24.9, 32.8)	28.5% (24.8, 32.6)
Number (%) of complete responses	11 (2.1%)	7 (1.3%)
Number (%) of partial responses	142 (26.6%)	146 (27.2%)
p-Value#	NS	
Duration of Response*, Þ	n=156	n=152
Median in months (range)	8.3 (1.2+ - 33.0+)	6.8 (1.1+ - 30.0+)
% with duration ≥ 6 months	65%	55%
% with duration ≥ 12 months	38%	27%
% with duration ≥ 24 months	18%	6%

* Results at the pre-specified final OS analysis

† Based on the stratified Cox proportional hazard model

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

§ Results at pre-specified interim analysis

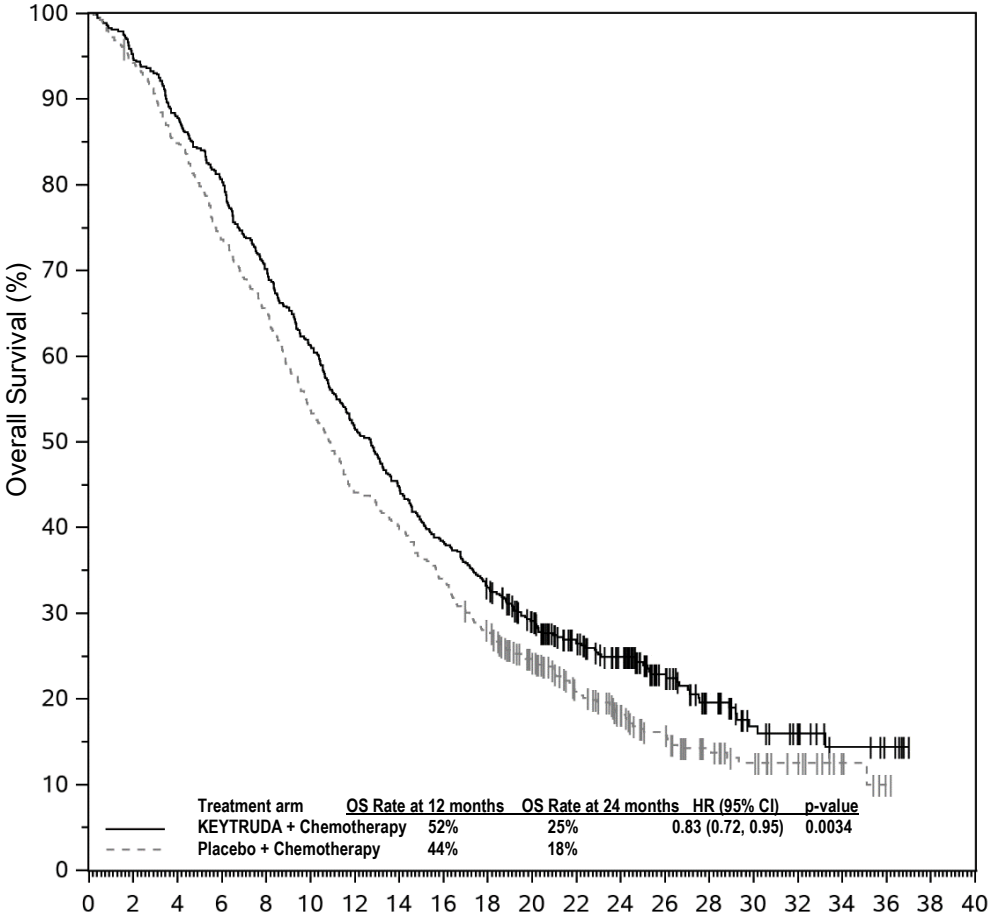
¶ Confirmed complete response or partial response

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

[Þ] Based on Kaplan-Meier estimate

NS = not significant

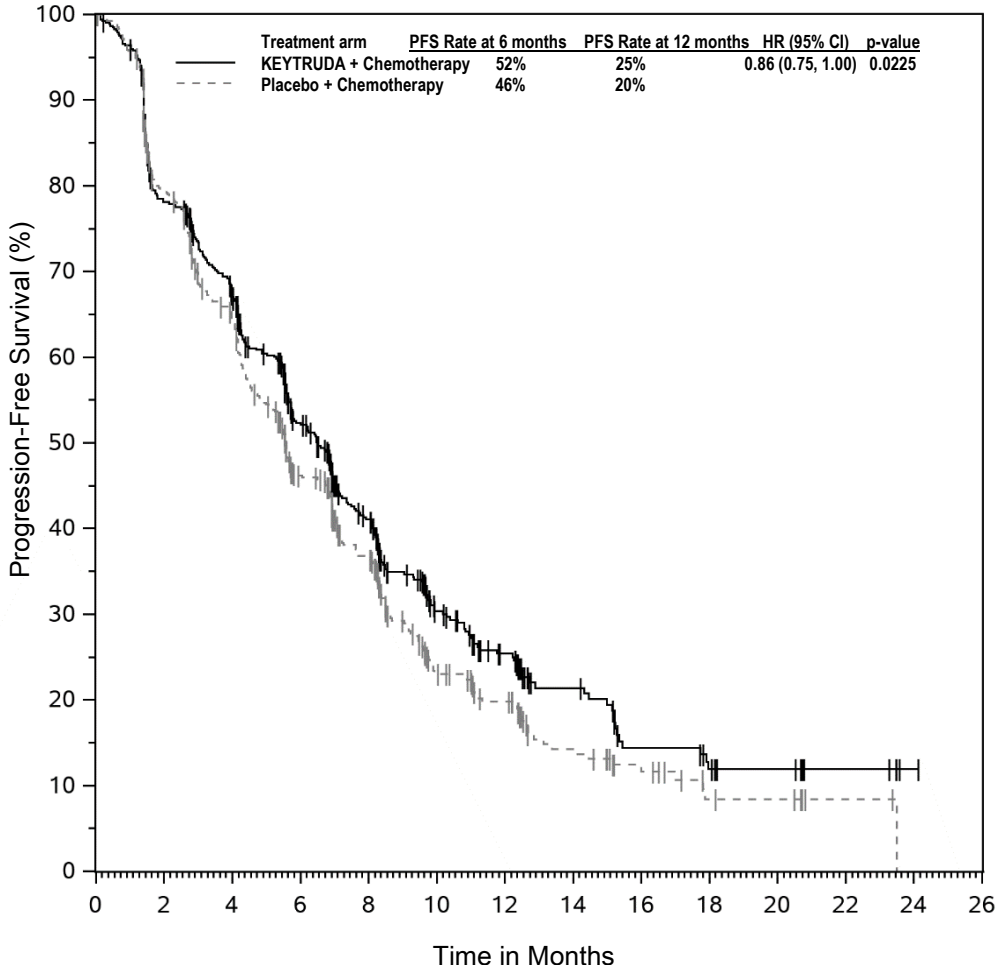
Figure 43: Kaplan-Meier Curve for Overall Survival in KEYNOTE-966*



Number at Risk																				
KEYTRUDA + Chemotherapy	533	505	469	430	374	326	275	238	204	175	142	108	88	56	35	21	16	8	5	0	0
Placebo + Chemotherapy	536	504	454	394	349	287	236	213	181	148	115	81	59	43	28	20	14	7	1	0	0

*Based on the pre-specified final OS analysis

Figure 44: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-966*



Number at Risk

KEYTRUDA + Chemotherapy	533	403	336	238	163	91	62	33	19	14	10	5	1	0
Placebo + Chemotherapy	536	411	323	211	147	70	51	25	16	7	6	2	0	0

*Based on the pre-specified interim analysis data cut-off

From baseline to Week 18, pre-specified exploratory patient-reported outcomes (PROs) using the EORTC QLQ-C30 (global health status/quality of life, physical functioning, role functioning), EORTC QLQ-BIL21 (pain and jaundice scores), and EQ-5D-5L visual analog scale (VAS) for patients receiving KEYTRUDA in combination with gemcitabine/cisplatin were similar to those treated with placebo and gemcitabine/cisplatin. From baseline to Week 18, health-related quality of life (HRQoL) was maintained when KEYTRUDA was added to gemcitabine/cisplatin.

Cervical Cancer

KEYNOTE-A18: Controlled trial of combination therapy with chemoradiotherapy in patients with locally advanced cervical cancer

The efficacy of KEYTRUDA in combination with cisplatin and external beam radiation therapy (EBRT) followed by brachytherapy (BT) was investigated in KEYNOTE-A18, a multicenter, randomized, double-blind, placebo-controlled trial that enrolled 1060 patients with locally advanced cervical cancer who had not previously received any definitive surgery, radiation, or systemic therapy for cervical cancer. There were 601 patients with FIGO 2014 Stage III-IVA (tumor involvement of the lower vagina with or without extension onto pelvic sidewall or hydronephrosis/non-functioning kidney or has spread to adjacent pelvic organs) with either node-positive or node-negative disease and 459 patients with FIGO 2014 Stage IB2-IIB (tumor lesions > 4 cm or clinically visible lesions that have spread beyond the uterus but have not extended onto the pelvic wall or to the lower third of vagina) with node-positive disease. 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 planned type of EBRT (Intensity-modulated radiation therapy [IMRT] or volumetric modulated arc therapy [VMAT] vs. non-IMRT and non-VMAT), stage at screening of cervical cancer (FIGO 2014 Stage IB2-IIB vs. Stage III-IVA), and planned total radiotherapy dose ([EBRT + BT dose] of <70 Gy vs. ≥ 70 Gy as per equivalent dose [EQD2]). Patients were randomized (1:1) to one of two treatment arms:

- KEYTRUDA 200 mg IV every 3 weeks (5 cycles) concurrent with cisplatin 40 mg/m^2 IV weekly (5 cycles, an optional sixth infusion could be administered per local practice) and radiotherapy (EBRT followed by BT), followed by KEYTRUDA 400 mg IV every 6 weeks (15 cycles)
- Placebo IV every 3 weeks (5 cycles) concurrent with cisplatin 40 mg/m^2 IV weekly (5 cycles, an optional sixth infusion could be administered per local practice), and radiotherapy (EBRT followed by BT), followed by placebo IV every 6 weeks (15 cycles)

Treatment continued until RECIST v1.1-defined progression of disease as determined by investigator or unacceptable toxicity. Assessment of tumor status was performed every 12 weeks for the first two years, every 24 weeks in year 3, and then annually. The primary efficacy outcomes were PFS as assessed by investigator according to RECIST v1.1, or histopathologic confirmation, and OS.

Among the 601 patients with FIGO 2014 Stage III-IVA disease enrolled in KEYNOTE-A18, the baseline characteristics were: median age of 51 years (range: 22 to 87), 16% age 65 or older; 36% White, 1% Black, 34% Asian, 38% Hispanic or Latino; 68% ECOG performance status of 0 and 32% ECOG performance status of 1; 93% with CPS ≥ 1; 71% had positive pelvic and/or positive

para-aortic lymph node(s), 29% had neither positive pelvic nor para-aortic lymph node, 86% IMRT or VMAT EBRT, 90% ≥ 70 Gy (EQD2). Eighty-four percent had squamous cell carcinoma and 16% had non-squamous histology.

The trial demonstrated statistically significant improvements in PFS [HR 0.70 (95% CI: 0.55, 0.89; p=0.0020)] from the first pre-specified interim analysis and OS [HR 0.67 (95% CI: 0.50, 0.90; p=0.0040)] from the second pre-specified interim analysis in the overall population for patients randomized to KEYTRUDA with CRT compared to placebo with CRT. Table 36 summarizes key efficacy measures from the second pre-specified interim analysis in patients with FIGO 2014 Stage III-IVA disease with median follow-up time of 26.6 months (range: 0.9 to 41.7 months).

Table 36: Efficacy Results for Patients with FIGO 2014 Stage III-IVA Cervical Cancer in KEYNOTE-A18

Endpoint	Pembrolizumab 200 mg every 3 weeks and 400 mg every 6 weeks with CRT n=296	Placebo with CRT n=305
OS		
Number (%) of patients with event	43 (15%)	73 (24%)
Median in months (95% CI)	NR (NR, NR)	NR (NR, NR)
Hazard ratio* (95% CI)	0.57 (0.39, 0.83)	
PFS by Investigator		
Number (%) of patients with event	79 (27%)	125 (41%)
Median in months (95% CI)	NR (NR, NR)	NR (26.3, NR)
Hazard ratio* (95% CI)	0.57 (0.43, 0.76)	

* Based on the stratified Cox proportional hazard model

CRT = Chemoradiotherapy

NR = Not reached

Figure 45: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-A18 for Patients with FIGO 2014 Stage III-IVA Cervical Cancer

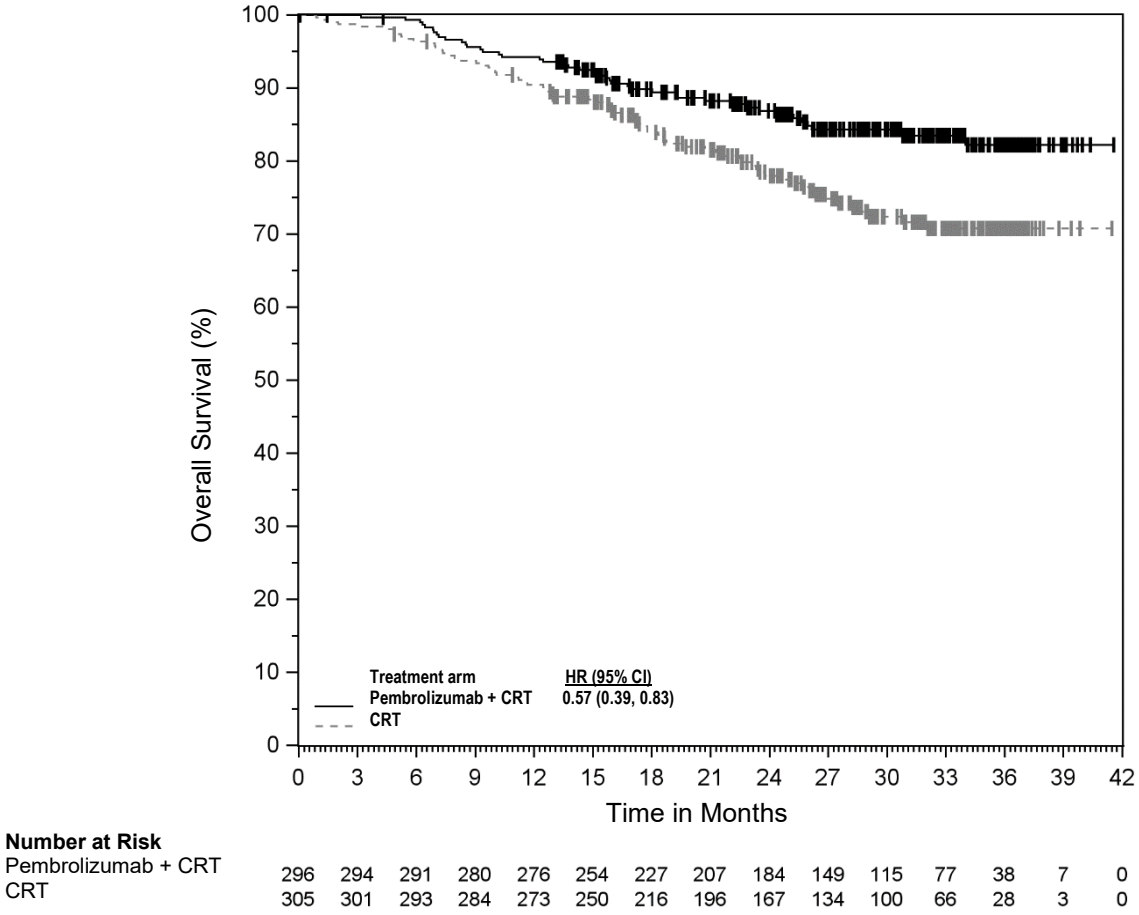
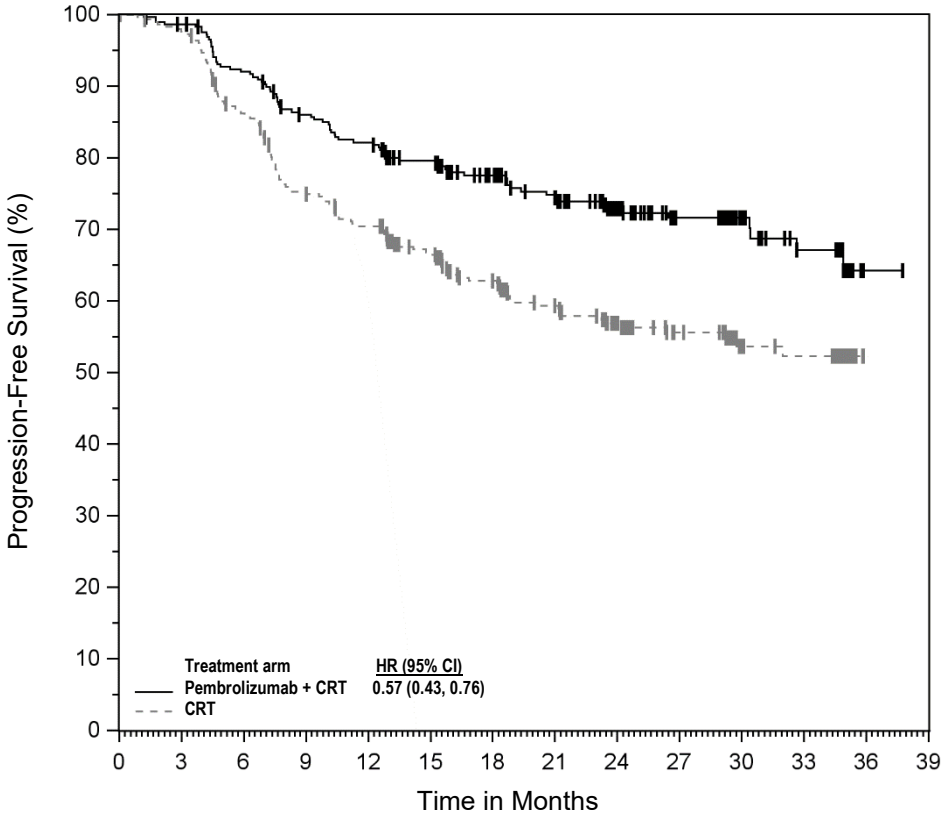


Figure 46: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-A18 for Patients with FIGO 2014 Stage III-IVA Cervical Cancer



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/m^2 + cisplatin 50 mg/m^2
2. Paclitaxel 175 mg/m^2 + cisplatin 50 mg/m^2 + bevacizumab 15 mg/kg
3. Paclitaxel 175 mg/m^2 + carboplatin AUC 5 mg/mL/min
4. Paclitaxel 175 mg/m^2 + 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 that expressed PD-L1 with a CPS ≥ 1 in KEYNOTE-826 are summarized in Table 37.

Table 37: Efficacy Results in KEYNOTE-826 for Patients with PD-L1 Expression (CPS ≥ 1)

Endpoint	KEYTRUDA 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

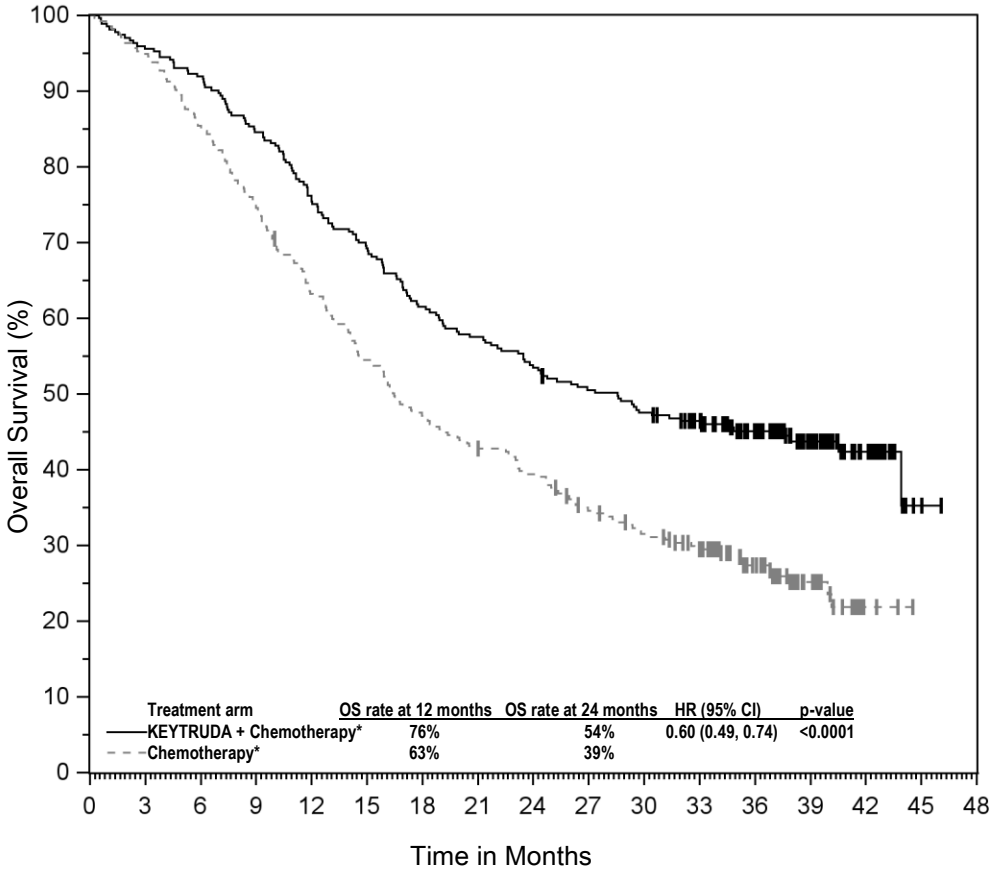
NR = not reached

The final OS analysis for patients with tumors that expressed PD-L1 with a CPS ≥ 1 was performed at a median duration of follow-up of 21.3 months after 354 patient events (153 for KEYTRUDA and

201 for placebo, both in combination with chemotherapy with or without bevacizumab). The median OS was 28.6 months (95% CI: 22.1, 38.0) for KEYTRUDA and 16.5 months (95% CI: 14.5, 20.0) for placebo, both in combination with chemotherapy with or without bevacizumab. The OS HR was 0.60 (95% CI: 0.49, 0.74; p<0.0001). The final PFS analysis for patients with tumors that expressed PD-L1 with a CPS ≥ 1 was performed based on 391 patient events (171 for KEYTRUDA and 220 for placebo, both in combination with chemotherapy with or without bevacizumab). The median PFS was 10.5 months (95% CI: 9.7, 12.3) for KEYTRUDA and 8.2 months (95% CI: 6.3, 8.5) for placebo, both in combination with chemotherapy with or without bevacizumab. The PFS HR was 0.58 (95% CI: 0.47, 0.71; p<0.0001). See Figures 47 and 48.

The ORR at the final analysis for patients with tumors that expressed PD-L1 with a CPS ≥ 1 was 69% for KEYTRUDA and 51% for placebo, both in combination with chemotherapy with or without bevacizumab. The median duration of response was 19.2 months (range 1.3+, 40.9+) for KEYTRUDA and 10.4 months (1.5+, 40.7+) for placebo, both in combination with chemotherapy with or without bevacizumab. The percentage of patients with ongoing responses based on Kaplan-Meier estimation was 48% at 24 months or longer, in patients who received KEYTRUDA, vs. 30% in patients who received placebo, both in combination with chemotherapy with or without bevacizumab.

Figure 47: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-826 Patients with PD-L1 Expression (CPS ≥ 1)

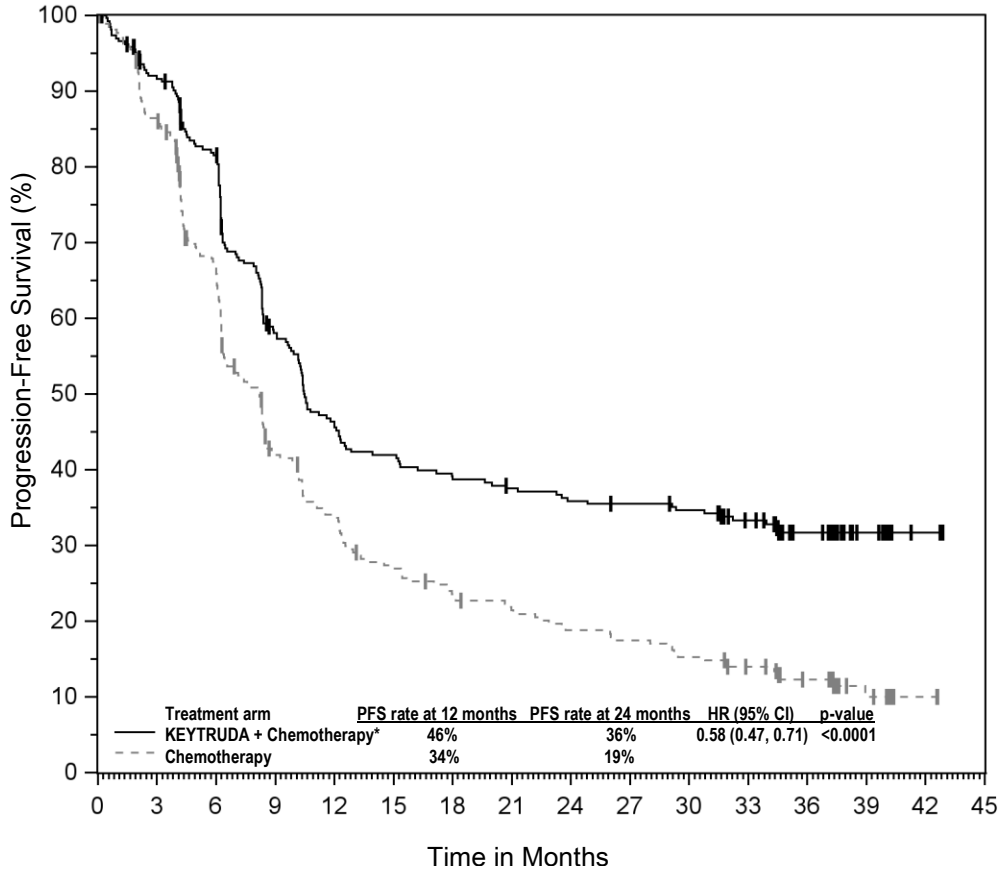


Number at Risk

KEYTRUDA + Chemotherapy*	273	261	251	231	206	189	168	157	146	136	128	116	90	52	22	2	0
Chemotherapy*	275	261	235	207	173	149	129	117	107	91	81	68	45	24	3	0	0

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

Figure 48: Kaplan-Meier Curve for Progression Free Survival by Treatment Arm in KEYNOTE-826 Patients with PD-L1 Expression (CPS ≥ 1)



Number at Risk

KEYTRUDA + Chemotherapy*	273	238	208	144	113	104	97	92	88	86	83	70	46	25	6	0
Chemotherapy*	275	229	170	103	81	64	55	49	43	40	35	28	18	7	2	0

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

Patient-reported outcomes (PROs) for patients with tumors that expressed PD-L1 with a CPS ≥ 1 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 with axitinib for first-line treatment of patients with advanced RCC

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 ≤ 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 ≥ 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 38 summarizes key efficacy measures. Consistent results were observed across pre-specified subgroups, IMDC risk categories and PD-L1 tumor expression status.

Table 38: 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	
Response Duration		
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

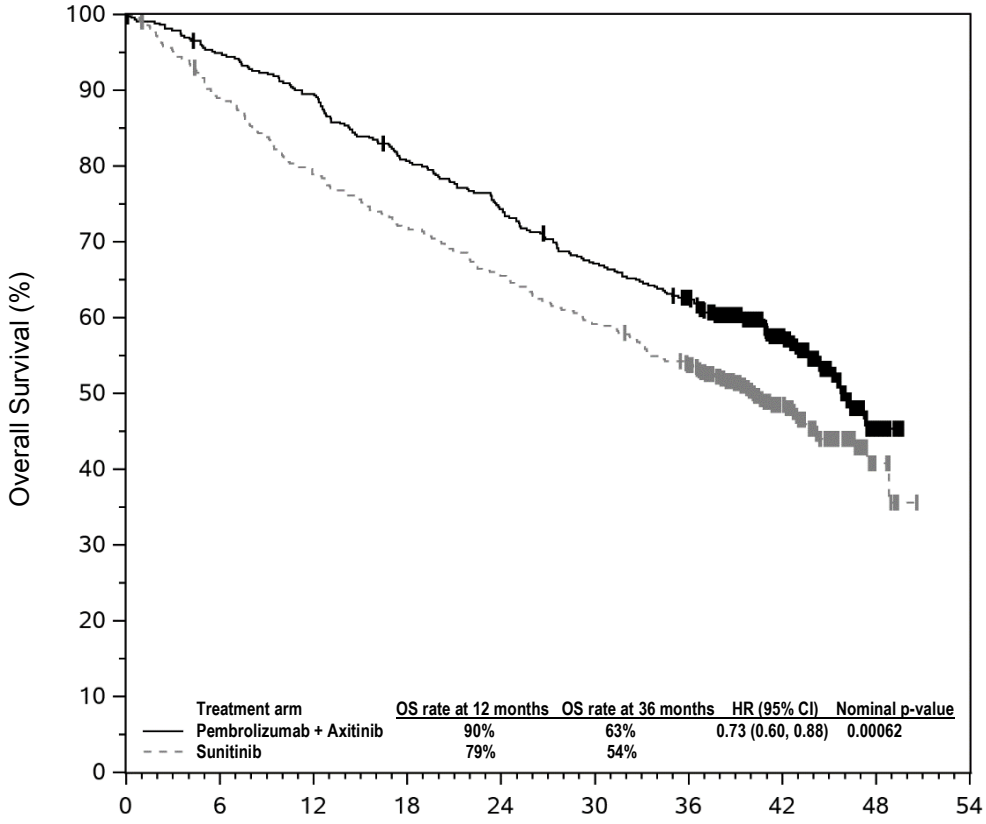
¶ Based on Kaplan-Meier estimation

NA=not available

The protocol-specified final OS analysis was performed at a median duration of follow-up of 37.7 months after 418 patient events (193 in the KEYTRUDA and axitinib arm and 225 in the sunitinib arm). Median OS was 45.7 months (95% CI: 43.6, NA) in the KEYTRUDA and axitinib arm and 40.1 months (95% CI: 34.3, 44.2) in the sunitinib arm. The OS HR was 0.73 (95% CI: 0.60, 0.88). The 12-month OS rates were 90% in the KEYTRUDA and axitinib arm and 79% in the sunitinib arm. The 36-month OS rates were 63% in the KEYTRUDA and axitinib arm and 54% in the sunitinib arm. At final analysis, a PFS analysis was performed based on 587 patient events (286 in the KEYTRUDA and axitinib arm and 301 in the sunitinib arm). The median PFS was 15.7 months (95% CI: 13.6, 20.2) in the KEYTRUDA and axitinib arm and 11.1 months (95% CI: 8.9, 12.5) in the sunitinib arm. The PFS HR was 0.68 (95% CI: 0.58, 0.80).

The ORR at the final analysis was 60% in the KEYTRUDA and axitinib arm and 40% in the sunitinib arm. The median duration of response was 23.6 months (range: 1.4+ to 43.4+) in the KEYTRUDA and axitinib arm and 15.3 months (range: 2.3 to 42.8+) in the sunitinib arm. The percentage of patients with ongoing responses based on Kaplan-Meier estimation were 45% at 30 months in patients with confirmed response in the KEYTRUDA and axitinib arm, vs. 32% in patients with confirmed response in the sunitinib arm.

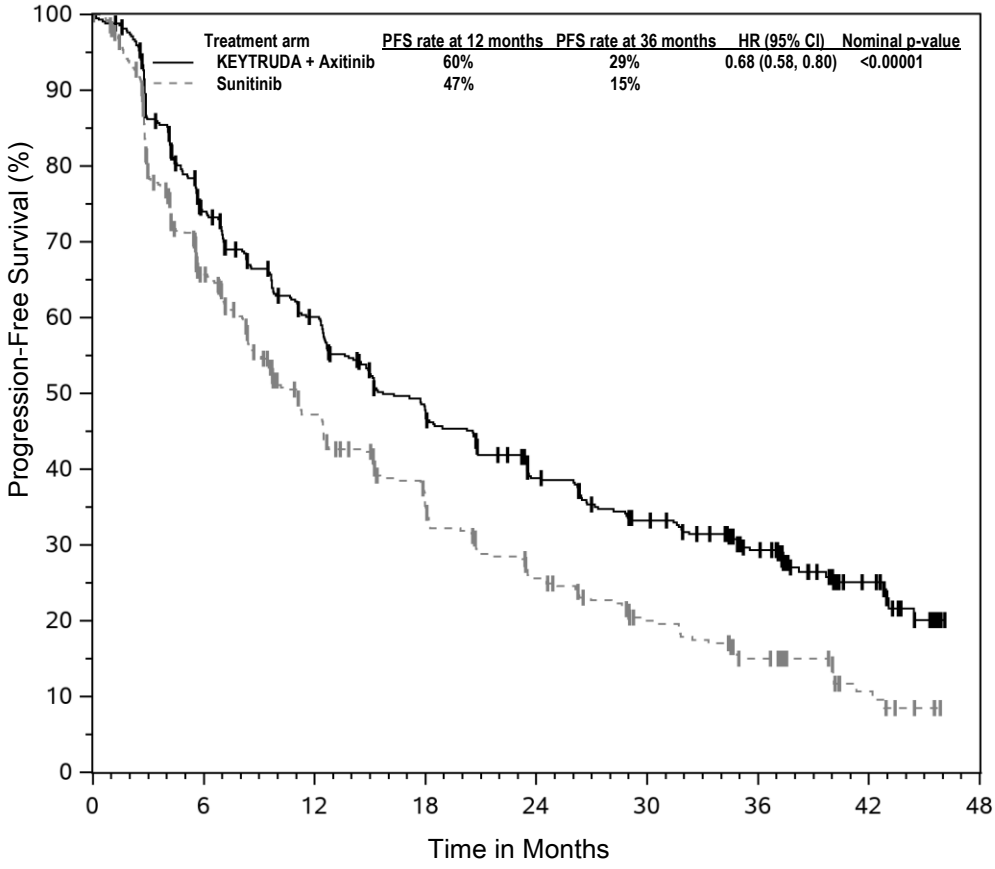
Figure 49: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-426 (Intent to Treat Population)



Number at Risk

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

Figure 50: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-426 (Intent to Treat Population)



Number at Risk

KEYTRUDA + Axitinib	432	298	233	180	136	110	80	28	0
Sunitinib	429	244	155	107	72	47	28	10	0

KEYNOTE-581: Controlled trial of combination therapy with lenvatinib for first-line treatment of patients with advanced RCC

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

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

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

Treatment continued until unacceptable toxicity or disease progression as determined by the investigator and confirmed by BICR using RECIST 1.1. Administration of KEYTRUDA with lenvatinib was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered by the investigator to be deriving clinical benefit. KEYTRUDA was continued for a maximum of 24 months; however, treatment with lenvatinib could be continued beyond 24 months. Assessment of tumor status was performed at baseline and then every 8 weeks.

Among the 1069 patients in KEYNOTE-581 (355 patients in the KEYTRUDA with lenvatinib arm, 357 patients in the lenvatinib with everolimus arm, and 357 patients in the sunitinib arm), the study population characteristics were: median age of 62 years (range: 29 to 88 years); 42% age 65 or older; 75% male; 74% White, 21% Asian, 1% Black, and 2% other races; 18% and 82% of patients had a baseline KPS of 70 to 80 and 90 to 100, respectively; patient distribution by IMDC risk categories was 33% favorable, 56% intermediate and 10% poor, and by MSKCC risk categories was 27% favorable, 64% intermediate and 9% poor. Common sites of metastases in patients were lung (68%), lymph node (45%), and bone (25%).

The primary efficacy outcome measure was PFS based on BICR using RECIST 1.1. Key secondary efficacy outcome measures included OS and ORR. The trial demonstrated statistically significant improvements in PFS, OS, and ORR in patients randomized to KEYTRUDA in combination with lenvatinib compared with sunitinib. The median overall survival follow-up time was 26.6 months. Pre-specified interim analysis efficacy results for KEYNOTE-581 are summarized in Table 39. Consistent results were observed across pre-specified subgroups, MSKCC prognostic groups and PD-L1 tumor expression status.

Table 39: Efficacy Results in KEYNOTE-581

Endpoint	KEYTRUDA 200 mg every 3 weeks and Lenvatinib n=355	Sunitinib n=357
PFS		
Number of patients with event (%)	160 (45%)	205 (57%)
Median in months (95% CI)	23.9 (20.8, 27.7)	9.2 (6.0, 11.0)
Hazard ratio* (95% CI)	0.39 (0.32, 0.49)	
p-Value†	<0.0001	
OS		
Number of patients with event (%)	80 (23%)	101 (28%)
Median in months (95% CI)	NR (33.6, NR)	NR (NR, NR)
Hazard ratio* (95% CI)	0.66 (0.49, 0.88)	
p-Value†	0.0049	
12-month OS rate (95% CI)	91% (88, 94)	80% (76, 84)
18-month OS rate (95% CI)	87% (83, 90)	74% (69, 79)
24-month OS rate (95% CI)	79% (74, 83)	70% (65, 75)
Objective Response Rate		
ORR‡ (95% CI)	71% (66, 76)	36% (31, 41)
Complete response rate	16%	4%
Partial response rate	55%	32%
p-Value§	<0.0001	
Response Duration¶		
Median in months (range)	26 (1.6+, 36.8+)	15 (1.6+, 33.2+)

* Based on the stratified Cox proportional hazard model

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

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

§ Nominal p-Value. At the earlier pre-specified final analysis of ORR (median follow-up time of 17.3 months), statistically significant superiority was achieved for ORR comparing KEYTRUDA plus lenvatinib with sunitinib, (odds ratio: 3.84 (95% CI: 2.81, 5.26), p-Value <0.0001)

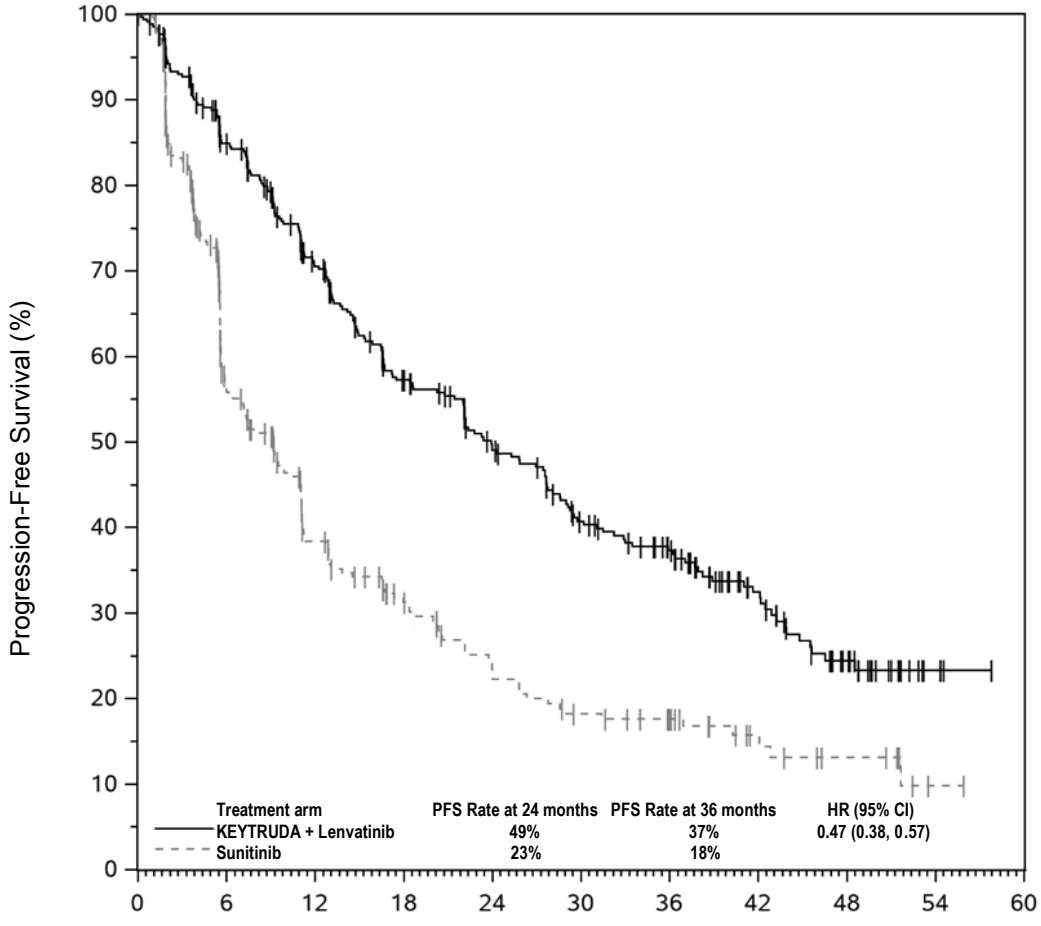
¶ Based on Kaplan-Meier estimates

NR = not reached

At the protocol-specified final analysis, median follow-up was 49.4 months. The PFS analysis was performed with 207 patient events for KEYTRUDA in combination with lenvatinib and 214 patient events for sunitinib. The median PFS was 23.9 months (95% CI: 20.8, 27.7) for KEYTRUDA in combination with lenvatinib and 9.2 months (95% CI: 6.0, 11.0) for sunitinib. The PFS HR was 0.47 (95% CI: 0.38, 0.57, nominal $p<0.0001$). At the final OS analysis there were 149 patients events for KEYTRUDA in combination with lenvatinib and 159 patients events for sunitinib. Median OS was 53.7 months (95% CI: 48.7, NE) for KEYTRUDA in combination with lenvatinib and 54.3 months (95% CI: 40.9, NE) for sunitinib. The OS HR was 0.79 (95% CI: 0.63, 0.99; nominal $p<0.0424$). The OS analysis was not adjusted to account for subsequent therapies, in which 195/357 (54.6%) patients in the sunitinib arm and 56/355 (15.8%) patients in the pembrolizumab plus lenvatinib arm received subsequent systemic anti-PD-1/PD-L1 therapy. OS may be confounded by the difference in subsequent therapies. See Figures 51 and 52.

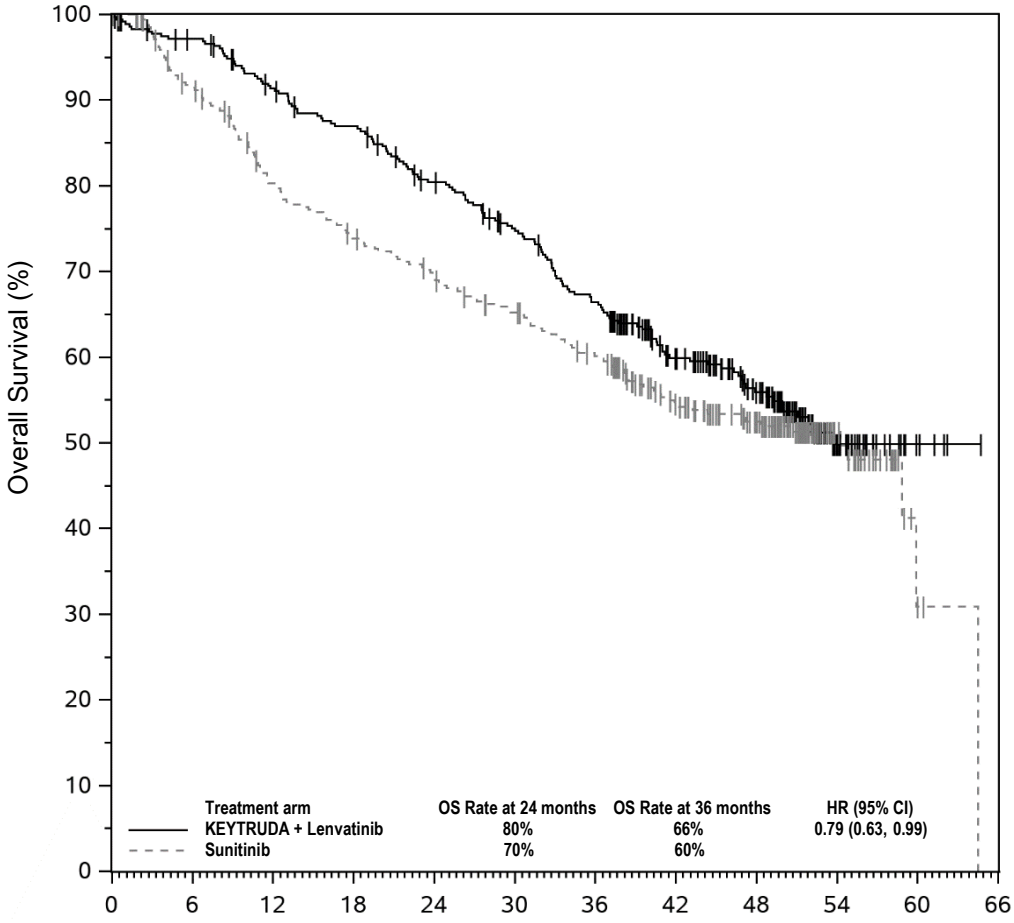
The ORR was 71% for KEYTRUDA in combination with lenvatinib and 37% for sunitinib. The complete response rates were 18% for KEYTRUDA in combination with lenvatinib and 5% for sunitinib. The median duration of response was 26.7 months (range: 1.64+, 55.92+) for KEYTRUDA in combination with lenvatinib and 14.7 months (range: 1.64+, 54.08+) for sunitinib. The percentage of patients with ongoing responses based on Kaplan-Meier estimation were 56% and 41% at 24 and 36 months or longer in patients who received KEYTRUDA in combination with lenvatinib vs. 32% and 24% in patients who received sunitinib.

Figure 51: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-581



Number at Risk											
KEYTRUDA + Lenvatinib	355	276	213	161	128	99	81	49	25	4	0
Sunitinib	357	145	85	59	41	30	23	12	7	1	0

Figure 52: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-581



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

Patient-reported outcomes (PROs) were assessed using the European Organization for the Research and Treatment of Cancer (EORTC) QLQ-30 and Kidney Cancer Symptom Index (FKSI-DRS). From baseline to a mean follow-up time of 46 weeks, patients treated with pembrolizumab in combination with lenvatinib had better physical functioning, fatigue, dyspnea, and constipation scores compared to the sunitinib group. Compared to sunitinib, pembrolizumab in combination with lenvatinib showed a more than 12 week delay in median time to worsening in global health status (GHS), physical functioning and patient reported symptoms with no subsequent recovery: EORTC QLQ-C30 GHS (114 vs. 75 weeks, HR=0.6 [95% CI: 0.47, 0.77]), physical functioning (134 vs. 78 weeks, HR=0.52 [95% CI: 0.41, 0.67]), fatigue (110 vs. 59 weeks, HR=0.54 [95% CI: 0.43, 0.67]), insomnia (156 vs. 126 weeks, HR=0.63 [95% CI: 0.47. 0.85]), dyspnea (153 vs. 126 weeks, HR=0.56 [95% CI: 0.41, 0.76]), nausea and vomiting (147 vs. 131 weeks, HR=0.53 [95% CI: 0.39, 0.74]), pain (119 vs.

105 weeks, HR=0.68 [95% CI: 0.53, 0.87]) and FKSI-DRS (134 vs. 117 weeks, HR=0.7 [95% CI: 0.53, 0.92]). These results should be interpreted in the context of the open-label study design and therefore taken cautiously.

KEYNOTE-B61: Open-label trial of combination therapy with lenvatinib in patients with advanced/metastatic non-clear cell RCC in the first-line setting

The efficacy of KEYTRUDA in combination with lenvatinib was investigated in KEYNOTE-B61, a multicenter, open-label, single-arm trial that enrolled 160 patients with advanced/metastatic non-clear cell RCC in the first-line setting. Patients were enrolled regardless of PD-L1 tumor expression status. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible.

Patients received KEYTRUDA 400 mg every 6 weeks up to 24 months in combination with lenvatinib 20 mg orally once daily. Treatment continued until unacceptable toxicity or disease progression. Administration of KEYTRUDA with lenvatinib was permitted beyond RECIST-defined disease progression if the patient was considered by the investigator to be deriving clinical benefit. KEYTRUDA was continued for a maximum of 24 months; however, lenvatinib could be continued beyond 24 months.

Among the 158 treated patients, the baseline characteristics were: median age of 60 years (range: 24 to 87 years), 71% male; 86% White, 8% Asian, and 3% Black; 22% and 78% of patients had a baseline KPS of 70 to 80 and 90 to 100 respectively; histologic subtypes were 59% papillary, 18% chromophobe, 4% translocation, 1% medullary, 13% unclassified, and 6% other; patient distribution by IMDC risk categories was 35% favorable, 54% intermediate and 10% poor; Common sites of metastases in patients were lymph node (65%), lung (35%), bone (30%), and liver (21%).

The primary efficacy outcome measure was ORR as assessed by BICR using RECIST 1.1. Secondary efficacy outcome measures included DOR and PFS (as assessed by BICR using RECIST 1.1), and OS. Efficacy results are summarized in Table 40. Clinical activity was observed regardless of the histological subtype.

Table 40: Efficacy Results in KEYNOTE-B61

Endpoint	KEYTRUDA 400 mg every 6 weeks and Lenvatinib n=158
Objective Response Rate*	
ORR† , (95% CI)	51% (43, 59)
Complete response	8%
Partial response	42%
Stable disease	32%
Disease control rate	82%
Response Duration*,‡	
Median in months (range)	19.5 (1.5+, 23.5+)
% with duration ≥ 6 months	89%
% with duration ≥ 12 months	76%
% with duration ≥ 18 months	51%
Time to Response	
Median in months (range)	2.8 (2.5, 15.2)
PFS*	
Median in months (95% CI)	17.9 (15.1, 22.1)
12-month PFS rate (95% CI)	64% (56, 71)
18-month PFS rate (95% CI)	48% (39, 56)
OS	
Median in months (95% CI)	NR (NR, NR)
12-month OS rate (95% CI)	82% (75, 87)
18-month OS rate (95% CI)	73% (65, 79)

* Assessed by BICR using RECIST 1.1

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

‡ Based on Kaplan-Meier estimates

NR = not reached

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 ≥ 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 until 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 DFS. The key secondary outcome measure was OS. The study demonstrated statistically significant improvements in DFS and OS for patients randomized to the KEYTRUDA arm compared with placebo. Generally consistent results were observed across pre-specified subgroups. Efficacy results are summarized in Table 41 and Figures 53 and 54.

Table 41: 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, NR)	NR (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)
24-month DFS rate (95% CI)	77% (73, 81)	68% (64, 72)
OS†		
Number (%) of patients with event	55 (11%)	86 (17%)
Median in months (95% CI)	NR (NR, NR)	NR (NR, NR)
Hazard ratio (95% CI)‡	0.62 (0.44, 0.87)	
p-Value	0.0024§	
12-month OS rate (95% CI)	99% (97, 99)	98% (96, 99)
24-month OS rate (95% CI)	96% (94, 98)	94% (91, 96)
36-month OS rate (95% CI)	94% (91, 96)	90% (86, 92)
48-month OS rate (95% CI)	91% (88, 93)	86% (83, 89)

* Median follow-up time was 23.9 months (range: 2.5 to 41.5 months).

† Median follow-up time was 55.8 months (range: 2.5 to 74.5 months).

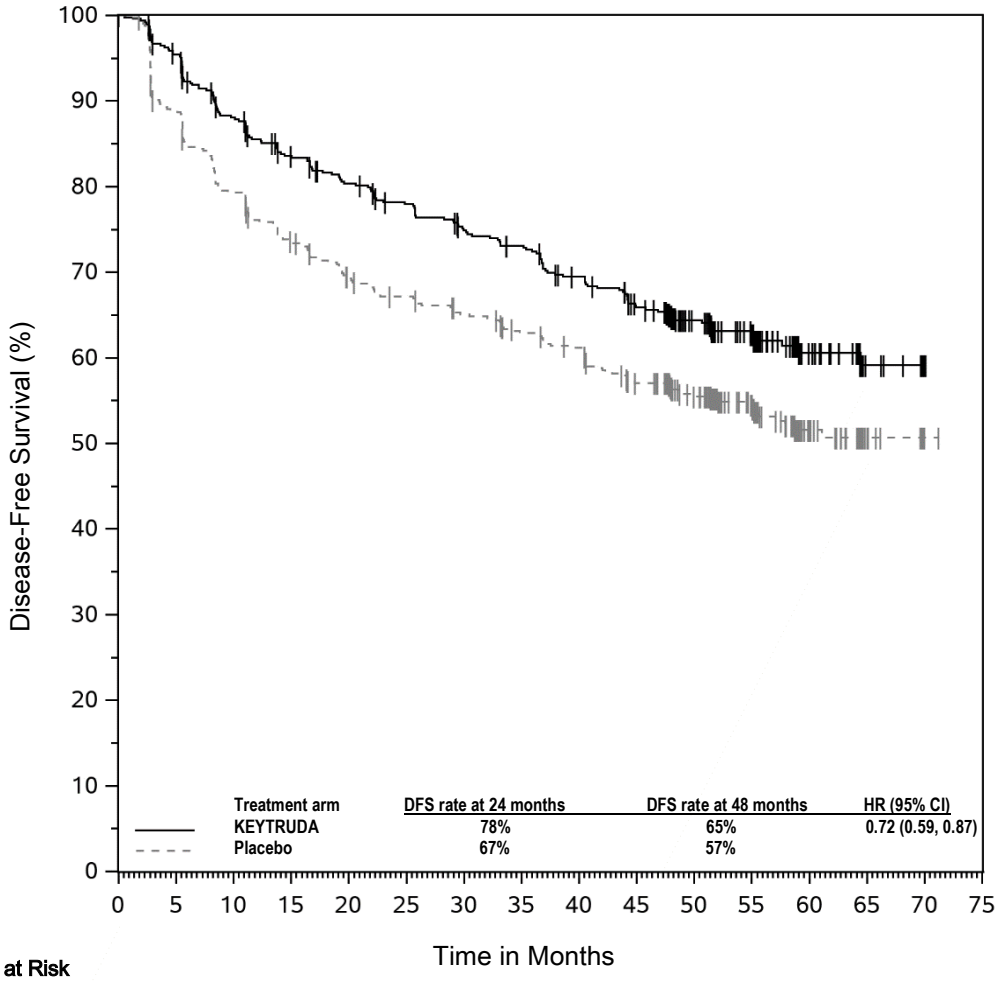
‡ Based on the stratified Cox proportional hazard model

§ Based on stratified log-rank test

NR = not reached

At a pre-specified interim analysis (median follow-up time was 55.8 months (range: 2.5 to 74.5 months)), the updated DFS HR was 0.72 (95% CI: 0.59, 0.87). The updated 12-month DFS rates were 86% (95% CI: 82, 88) in the KEYTRUDA arm and 76% (95% CI: 72, 80) in the placebo arm. The updated 24-month DFS rates were 78% (95% CI: 74, 82) in the KEYTRUDA arm and 67% (95% CI: 63, 71) in the placebo arm. The 36-month DFS rates were 72% (95% CI: 68, 76) in the KEYTRUDA arm and 63% (95% CI: 58, 67) in the placebo arm. The 48-month DFS rates were 65% (95% CI: 60, 69) in the KEYTRUDA arm and 57% (95% CI: 52, 61) in the placebo arm.

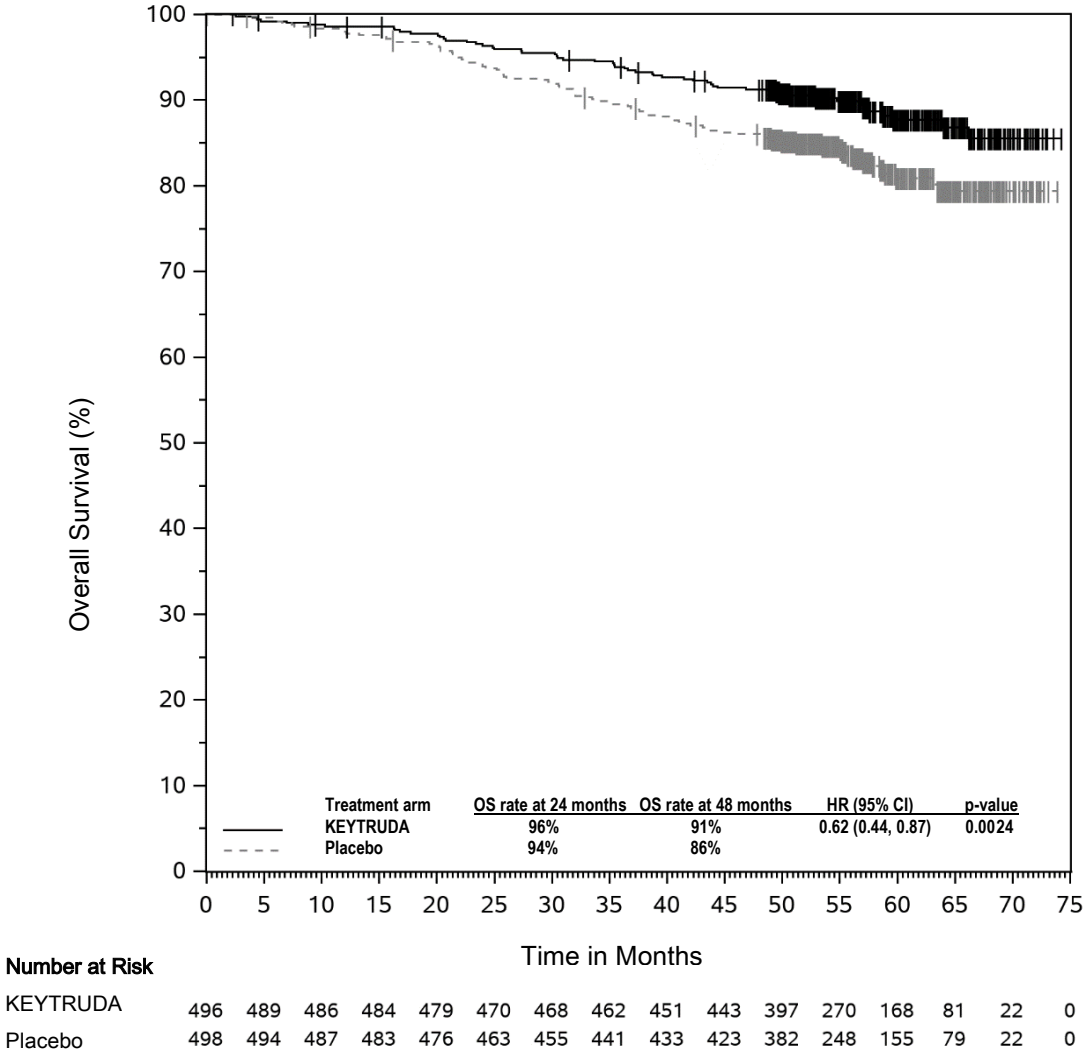
Figure 53: Kaplan-Meier Curve for Disease-Free Survival by Treatment Arm in KEYNOTE-564



Number at Risk

KEYTRUDA	496	458	416	388	370	355	337	327	307	284	221	160	65	19	5	0
Placebo	498	438	390	357	333	320	307	292	282	254	210	139	62	16	2	0

Figure 54: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-564



LITESPARK-022: Controlled study of combination therapy with belzutifan for the adjuvant treatment of patients with resected RCC

The efficacy of KEYTRUDA in combination with belzutifan was investigated as adjuvant therapy for RCC with a clear cell component in LITESPARK-022, a multicenter, randomized, double-blind, controlled study in 1,841 patients with intermediate-high risk or high risk of recurrence of RCC, or M1 NED. The intermediate-high risk category included: pT2 with Grade 4 or sarcomatoid features without nodal involvement (N0) or distant metastases (M0); pT3, any Grade N0 and 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 complete resection of

the primary tumor (partial or radical nephrectomy) and complete resection of solid, isolated, soft tissue metastatic lesion(s) in M1 NED participants. Patients were randomized (1:1) to receive KEYTRUDA 400 mg every 6 weeks plus belzutifan 120 mg by oral administration daily (n=921), or KEYTRUDA 400 mg every 6 weeks plus oral placebo daily (n=920). Randomization was stratified by risk of recurrence (intermediate-high risk, high risk, M1 NED) and tumor grade (1 or 2 versus 3 or 4).

Patients were evaluated radiologically every 12 weeks for the first 2 years from randomization, every 16 weeks from year 3 to 5, and every 24 weeks thereafter.

Among the 1,841 patients in LITESPARK-022, the baseline characteristics were: median age 60 years (range: 20-91 years), 32% age 65 or older; 71% male; 63% White; 29% Asian; 0.7% Black or African American; 85% ECOG PS of 0 and 15% ECOG PS of 1. Ninety-six percent were N0; 10% had sarcomatoid features; 85% were pT2 with Grade 4 or sarcomatoid features or pT3; 6% were pT4 or with nodal involvement; and 9% were M1 NED.

The primary efficacy outcome measure was investigator-assessed disease-free survival (DFS). The key secondary outcome measure was OS. The trial demonstrated a statistically significant improvement in DFS at the pre-specified interim analysis in patients randomized to KEYTRUDA plus belzutifan compared with KEYTRUDA plus placebo. At the time of analysis, OS results were not yet mature with 38 deaths out of 921 patients in the KEYTRUDA plus belzutifan arm and 49 deaths out of 920 patients in the KEYTRUDA plus placebo arm.

The efficacy results for LITESPARK-022 are summarized in Table 42 and Figure 55.

Table 42: Efficacy Results in LITESPARK-022

Efficacy Outcome Measure	KEYTRUDA plus Belzutifan n=921	KEYTRUDA plus Placebo n=920
DFS*		
Number (%) of patients with event	186 (20%)	246 (27%)
Median in months (95% CI)	NR (36.9, NR)	NR (NR, NR)
Hazard ratio† (95% CI)	0.72 (0.59, 0.87)	
p-Value	0.0003‡	
12-month DFS rate (95% CI)	92% (90, 94)	85% (83, 87)
18-month DFS rate (95% CI)	86% (84, 88)	79% (76, 81)
24-month DFS rate (95% CI)	81% (78, 83)	74% (71, 77)

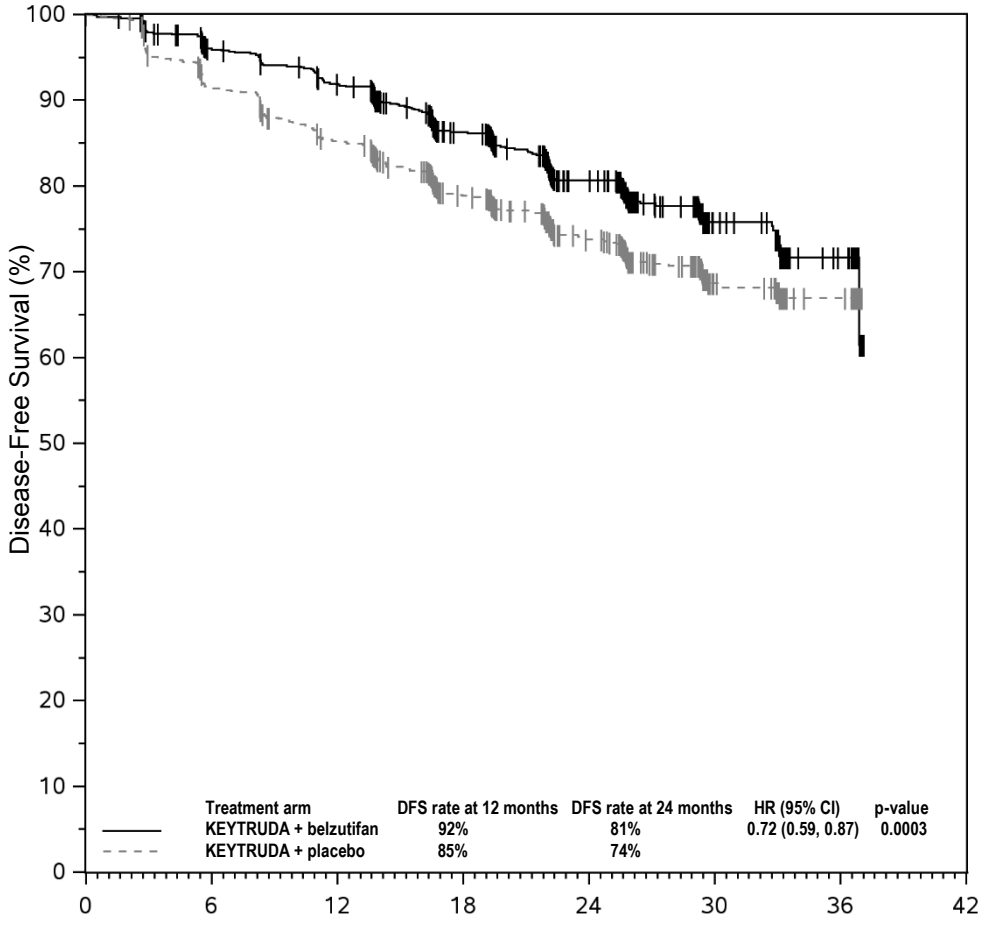
* Median follow-up time was 28 months (range: 0.5 to 40.1 months).

† Based on the stratified Cox proportional hazard model

‡ Based on stratified log-rank test

NR = not reached

Figure 55: Kaplan-Meier Curve for Disease-Free Survival by Treatment Arm in LITESPARK-022



Number at Risk								
KEYTRUDA + belzutifan	921	850	805	669	451	153	35	0
KEYTRUDA + placebo	920	823	759	619	417	140	38	0

Endometrial Carcinoma

KEYNOTE-868/NRG-GY018: Controlled trial of combination therapy for treatment of patients with primary advanced or recurrent endometrial carcinoma

The efficacy of KEYTRUDA in combination with paclitaxel and carboplatin was investigated in KEYNOTE-868, a multicenter, randomized, double-blind, placebo-controlled trial in 810 patients with advanced or recurrent endometrial carcinoma including those with dMMR and pMMR tumors. Patients had not received prior systemic therapy or had received prior chemotherapy in the adjuvant setting. Patients who had received prior adjuvant chemotherapy were eligible if their chemotherapy-free interval was at least 12 months. Patients with endometrial sarcoma, including carcinosarcoma, or patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible.

Randomization was stratified according to MMR status, ECOG PS (0 or 1 vs. 2), and prior adjuvant chemotherapy. Patients were randomized (1:1) to one of the following treatment arms:

- KEYTRUDA 200 mg every 3 weeks, paclitaxel 175 mg/m^2 and carboplatin AUC 5 mg/mL/min for 6 cycles, followed by KEYTRUDA 400 mg every 6 weeks for up to 14 cycles.
- Placebo every 3 weeks, paclitaxel 175 mg/m^2 and carboplatin AUC 5 mg/mL/min for 6 cycles, followed by placebo every 6 weeks for up to 14 cycles.

All study medications were administered as an intravenous infusion on Day 1 of each treatment cycle. Treatment continued until disease progression, unacceptable toxicity, or a maximum of 20 cycles (up to approximately 24 months). Patients with measurable disease who had RECIST-defined stable disease or partial response at the completion of cycle 6 were permitted to continue receiving paclitaxel and carboplatin with KEYTRUDA or placebo for up to 10 cycles as determined by the investigator. Assessment of tumor status was performed every 9 weeks for the first 9 months and then every 12 weeks thereafter.

Among the 810 randomized patients, 222 (27%) had dMMR tumor status and 588 (73%) had pMMR tumor status.

The dMMR population characteristics were: median age of 66 years (range: 37 to 86), 55% age 65 or older; 79% White, 9% Black, and 3% Asian; 5% Hispanic or Latino; 64% ECOG PS of 0, 33% ECOG PS of 1, and 3% ECOG PS of 2; 61% had recurrent disease and 39% had primary or persistent disease; 5% received prior adjuvant chemotherapy and 43% received prior radiotherapy. The histologic subtypes were endometrioid carcinoma (24% grade 1, 43% grade 2, 14% grade 3), adenocarcinoma NOS (11%), and other (8% including dedifferentiated/undifferentiated, serous, and mixed epithelial).

The pMMR population characteristics were: median age of 66 years (range: 29 to 94), 54% age 65 or older; 72% White, 16% Black, and 5% Asian; 6% Hispanic or Latino; 67% ECOG PS of 0, 30% ECOG PS of 1, and 3% ECOG PS of 2; 56% had recurrent disease and 44% had primary or persistent disease; 26% received prior adjuvant chemotherapy and 41% received prior radiotherapy. The histologic subtypes were endometrioid carcinoma (17% grade 1, 19% grade 2, 16% grade 3), serous (26%), adenocarcinoma NOS (10%), clear cell carcinoma (7%), and other (5% including mixed epithelial and dedifferentiated/undifferentiated).

The primary efficacy outcome measure was PFS as assessed by the investigator according to RECIST 1.1 in the dMMR and pMMR populations. Secondary efficacy outcome measures included OS, ORR, and DoR in the dMMR and pMMR populations. The trial demonstrated statistically significant improvements in PFS for patients randomized to KEYTRUDA in combination with chemotherapy compared to placebo in combination with chemotherapy in both the dMMR and pMMR populations. The median follow-up time was 13.6 months (range: 0.6 to 39.4 months) and 8.7 months (range: 0.1 to 37.2 months) in the dMMR and pMMR populations, respectively. OS endpoint was not formally assessed within multiplicity control. OS maturity was 12.2% in the dMMR population and 16.8% in the pMMR population. Among the patients who had been randomized to receive placebo in combination with chemotherapy and discontinued from the study, 55% from the dMMR population and 45% from the pMMR population subsequently received post-study therapies that incorporated anti-PD-1/PD-L1 therapy. Table 43 and Figures 56 and 57 summarize the efficacy results for KEYNOTE-868 by MMR status.

Table 43: Efficacy Results in KEYNOTE-868

Endpoint	dMMR Population		pMMR Population	
	KEYTRUDA with chemotherapy* n=110	Placebo with chemotherapy* n=112	KEYTRUDA with chemotherapy* n=294	Placebo with chemotherapy* n=294
PFS				
Number (%) of patients with event	29 (26%)	60 (54%)	95 (32%)	138 (47%)
Median in months (95% CI)	NR (30.7, NR)	8.3 (6.5, 12.3)	13.1 (10.6, 19.5)	8.7 (8.4, 11.0)
Hazard ratio† (95% CI)	0.34 (0.22, 0.53)		0.57 (0.44, 0.74)	
p-Value‡	<0.0001		<0.0001	
OS				
Number (%) of patients with event	10 (9%)	17 (15%)	45 (15%)	54 (18%)
Median in months (95% CI)	NR (NR, NR)	NR (NR, NR)	28.0 (21.4, NR)	27.4 (19.5, NR)
Hazard ratio† (95% CI)	0.55 (0.25, 1.19)		0.79 (0.53, 1.17)	
p-Value§	0.0617		0.1157	

* Chemotherapy (paclitaxel and carboplatin)

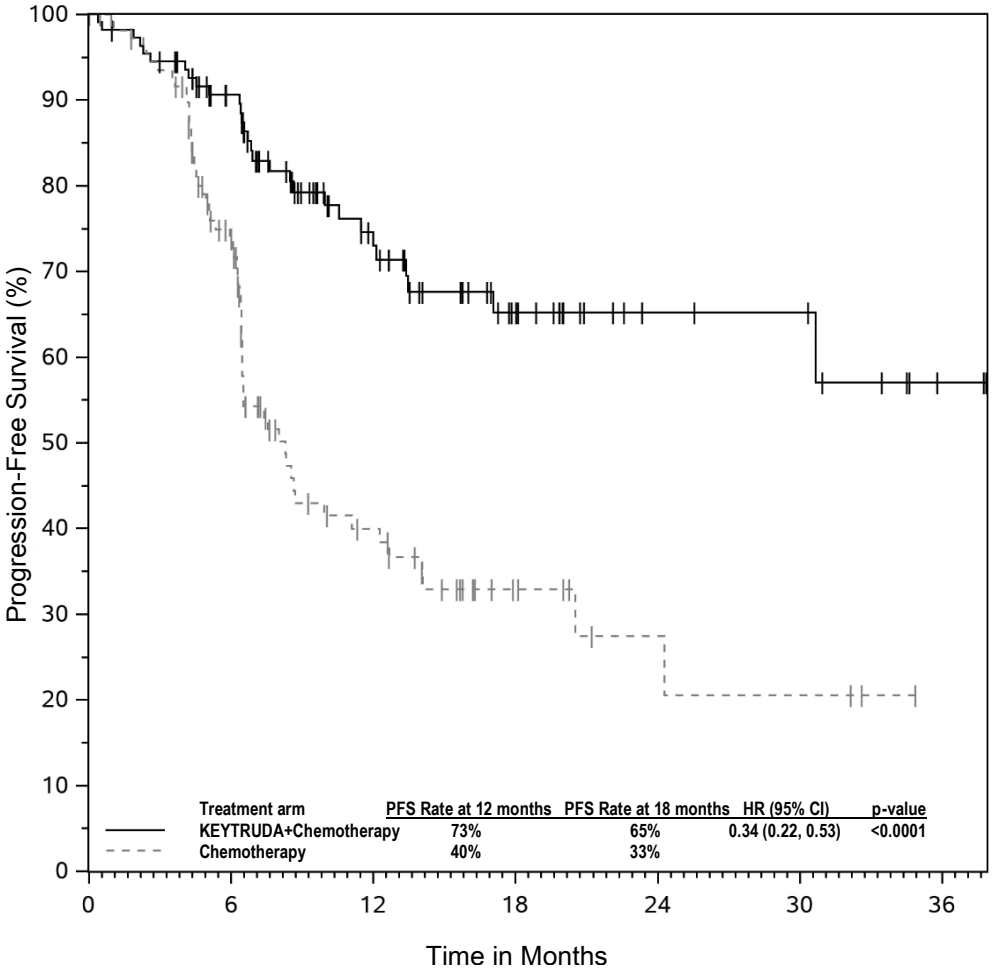
† Based on the stratified Cox proportional hazard model

‡ Based on stratified log-rank test (compared to an alpha boundary of 0.00207 for dMMR and 0.00116 for pMMR)

§ Nominal p-Value; no multiplicity adjustment

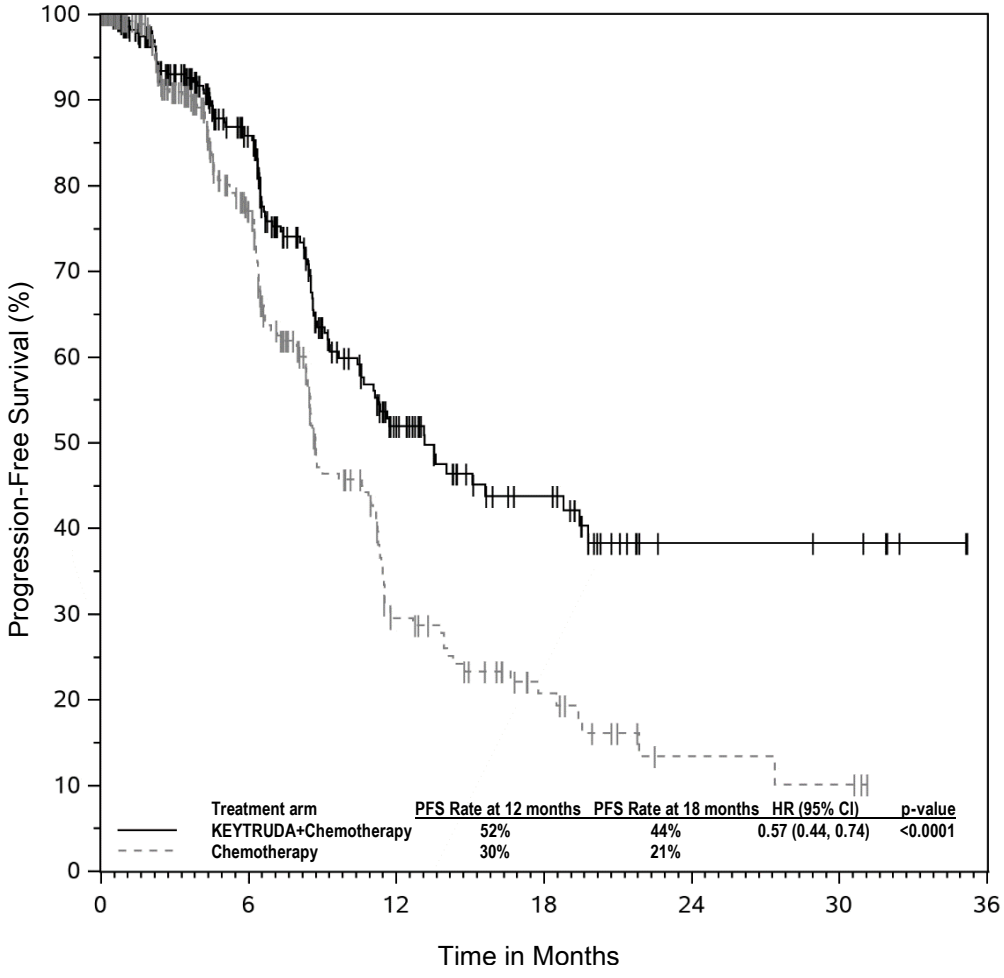
NR=not reached

Figure 56: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-868 (dMMR Population)



Number at Risk							
KEYTRUDA+Chemotherapy	110	85	45	24	10	9	2
Chemotherapy	112	69	25	9	4	3	0

Figure 57: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-868 (pMMR Population)



Number at Risk							
KEYTRUDA+Chemotherapy	294	162	57	29	7	6	0
Chemotherapy	294	144	36	15	4	3	0

KEYNOTE-775: Controlled trial of combination therapy in advanced endometrial carcinoma patients previously treated with systemic therapy

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

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

Treatment with KEYTRUDA and lenvatinib continued until RECIST 1.1-defined progression of disease as verified by BICR, unacceptable toxicity, or for KEYTRUDA, a maximum of 24 months. Treatment was permitted beyond RECIST 1.1-defined disease progression if the treating investigator considered the patient to be deriving clinical benefit and the treatment was tolerated. Assessment of tumor status was performed every 8 weeks.

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

The primary efficacy outcome measures were OS and PFS as assessed by BICR according to RECIST 1.1. Secondary efficacy outcome measures included ORR, as assessed by BICR using RECIST 1.1. The median follow-up time for this trial was 11.4 months (range: 0.3 to 26.9 months). Pre-specified interim analysis efficacy measures are summarized in Table 44. Improvements in OS,

PFS, and ORR were consistently demonstrated across pre-specified subgroups, including histology, prior therapies, MMR status, and ECOG performance status.

Table 44: Efficacy Results in Patients with Advanced Endometrial Carcinoma in KEYNOTE-775

Endpoint	KEYTRUDA 200 mg every 3 weeks + lenvatinib n=411	Doxorubicin or paclitaxel n=416
OS		
Number (%) of patients with event	188 (46%)	245 (59%)
Median in months (95% CI)	18.3 (15.2, 20.5)	11.4 (10.5, 12.9)
Hazard ratio* (95% CI)	0.62 (0.51, 0.75)	
p-Value†	<0.0001	
PFS		
Number (%) of patients with event	281 (68%)	286 (69%)
Median in months (95% CI)	7.2 (5.7, 7.6)	3.8 (3.6, 4.2)
Hazard ratio* (95% CI)	0.56 (0.47, 0.66)	
p-Value†	<0.0001	
Objective Response Rate		
ORR‡ (95% CI)	32% (27, 37)	15% (11, 18)
p-Value§	<0.0001	
Complete response	7%	3%
Partial response	25%	12%
Stable disease	47%	40%
Disease control rate¶	72%	47%
Response Duration#	n=131	n=61
Median in months (range)	14.4 (1.6+, 23.7+)	5.7 (0.0+, 24.2+)
% with duration ≥ 6 months	72%	43%
% with duration ≥ 12 months	51%	35%

* Based on the stratified Cox regression 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 MMR Status, ECOG performance status, geographic region, and history of pelvic radiation

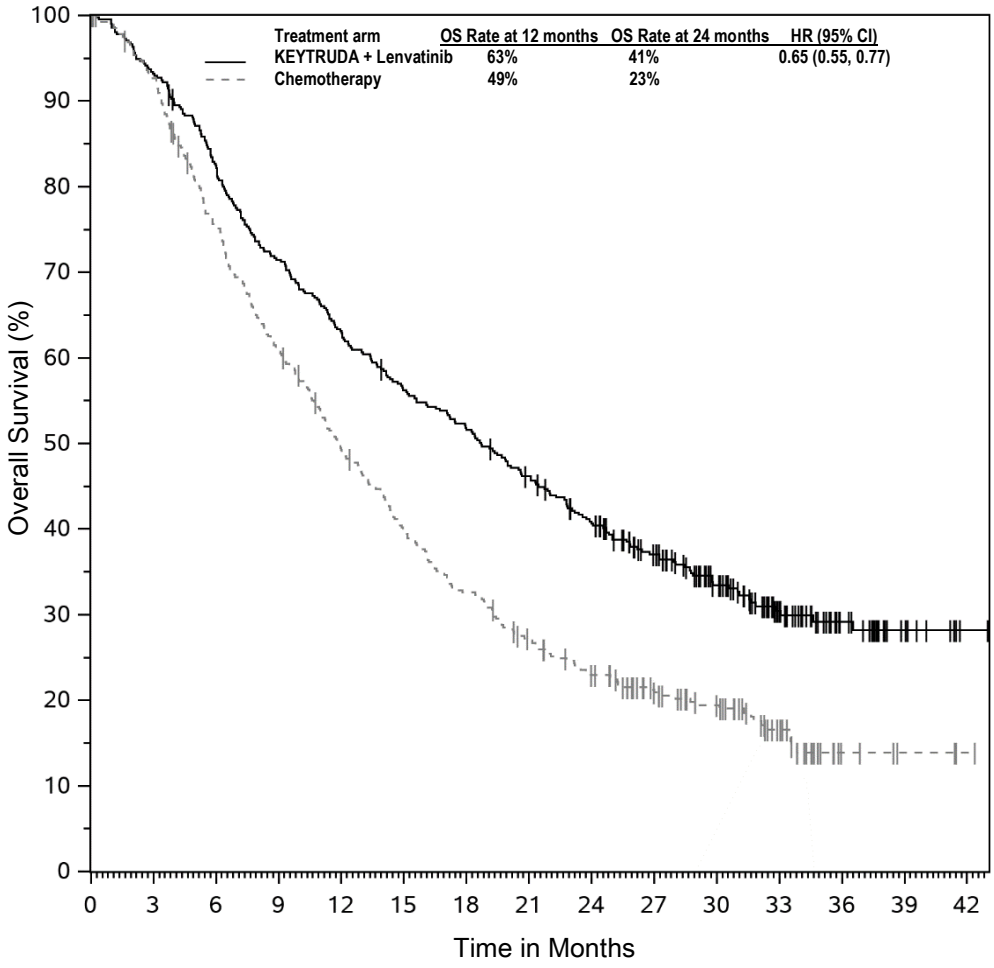
¶ Based on best response of stable disease or better

\# Based on Kaplan-Meier estimation

At the protocol-specified final OS analysis with approximately 16 months of additional follow-up duration from the interim analysis (overall median follow-up time of 14.7 months [range: 0.3 to 43.0 months]) there were 276 patient events for KEYTRUDA in combination with lenvatinib and 329 patient events for doxorubicin or paclitaxel. Median OS was 18.7 months (95% CI: 15.6, 21.3) for KEYTRUDA in combination with lenvatinib and 11.9 months (95% CI: 10.7, 13.3) for doxorubicin or paclitaxel. The OS HR was 0.65 (95% CI: 0.55, 0.77; nominal $p<0.0001$). At the time of the protocol-specified final OS analysis, an updated PFS analysis was performed with 320 patient events for KEYTRUDA in combination with lenvatinib and 298 patient events for doxorubicin or paclitaxel. The median PFS was 7.3 months (95% CI: 5.7, 7.6) for KEYTRUDA in combination with lenvatinib and 3.8 months (95% CI: 3.6, 4.2) for doxorubicin or paclitaxel. The PFS HR was 0.56 (95% CI: 0.48, 0.66, nominal $p<0.0001$). See Figures 58 and 59.

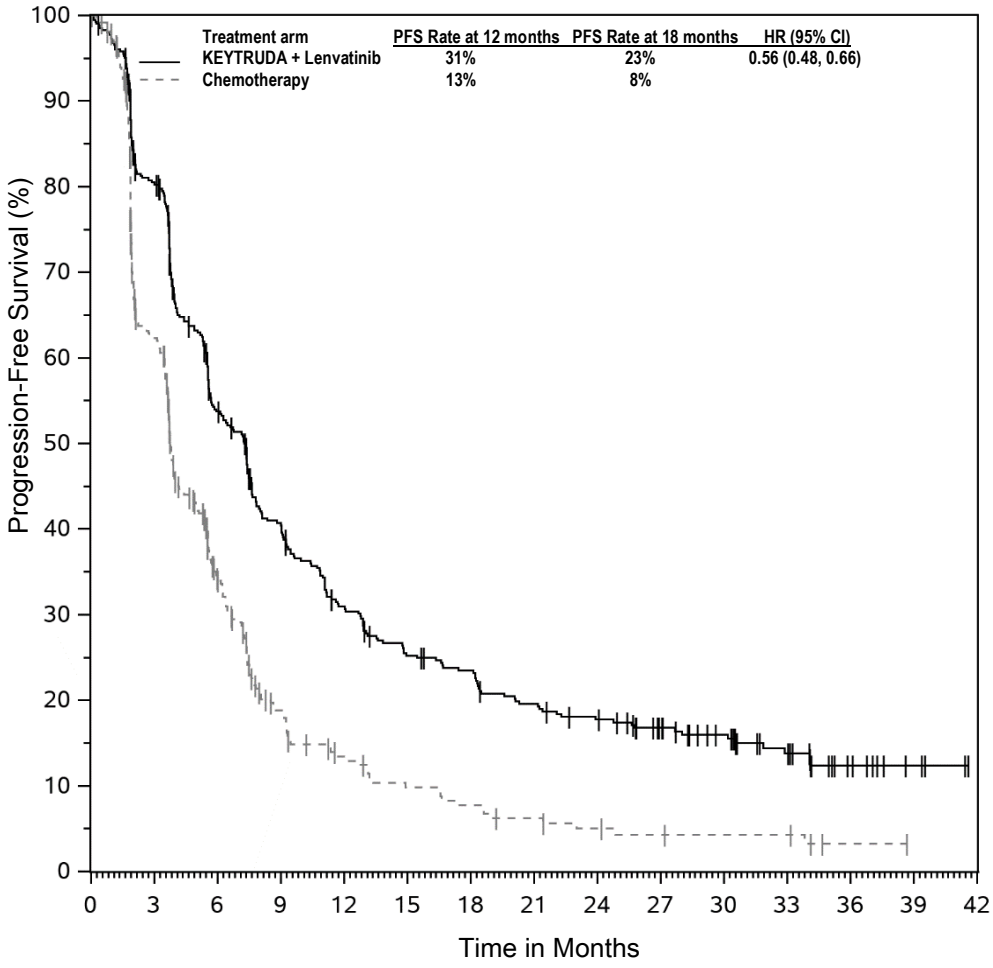
At the time of the protocol-specified final OS analysis, an updated ORR analysis demonstrated ORR of 34% for KEYTRUDA in combination with lenvatinib and 15% for doxorubicin or paclitaxel. The median duration of response was 12.9 months (range: 1.6+, 39.5+) for KEYTRUDA in combination with lenvatinib and 5.7 months (range: 0.0+, 37.1+) for doxorubicin or paclitaxel. The percentage of patients with ongoing responses based on Kaplan-Meier estimation was 52% at 12 months, in patients who received KEYTRUDA in combination with lenvatinib, vs. 29% in patients who received doxorubicin or paclitaxel.

Figure 58: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-775 (Intent to Treat Population)



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

Figure 59: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-775 (Intent to Treat Population)



Number at Risk														
KEYTRUDA + Lenvatinib	411	317	203	148	109	87	79	65	57	45	35	23	10	4	0
Chemotherapy	416	214	95	43	27	19	15	11	8	6	5	5	1	0	0

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 45.

Table 45: 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/m^2 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/m^2 or epirubicin 90 mg/m^2 every 3 weeks on Day 1 of cycles 5-8 of treatment regimen and
    - Cyclophosphamide 600 mg/m^2 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/m^2 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/m^2 **or** epirubicin 90 mg/m^2 every 3 weeks on Day 1 of cycles 5-8 of treatment regimen **and**
- Cyclophosphamide 600 mg/m^2 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 pCR rate and EFS. pCR was defined as absence of invasive cancer in the breast and lymph nodes (ypT0/Tis ypN0) and was assessed by the blinded local pathologist at the time of definitive surgery. EFS was defined as the time from randomization to the first occurrence of any of the following events: progression of disease that precludes definitive surgery, local or distant recurrence, second primary malignancy, or death due to any cause. An additional efficacy outcome 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, EFS, and OS at pre-specified analyses 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. Efficacy results are summarized in Table 46 and Figures 60 and 61.

Table 46: 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)	88 (85, 90)	81 (77, 85)
Hazard ratio (95% CI)§	0.63 (0.48, 0.82)	
p-Value¶	0.00031	
OS#	**n=784**	**n=390**
Number of patients with event (%)	115 (15%)	85 (22%)
36-month OS rate (%), (95% CI)	90 (87, 91)	87 (83, 90)
60-month OS rate (%), (95% CI)	87 (84, 89)	82 (77, 85)
Hazard ratio (95% CI)§	0.66 (0.50, 0.87)	
p-Value¶	0.00150	

* 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) with a median follow-up time of 37.8 months (range: 2.7 to 48 months)

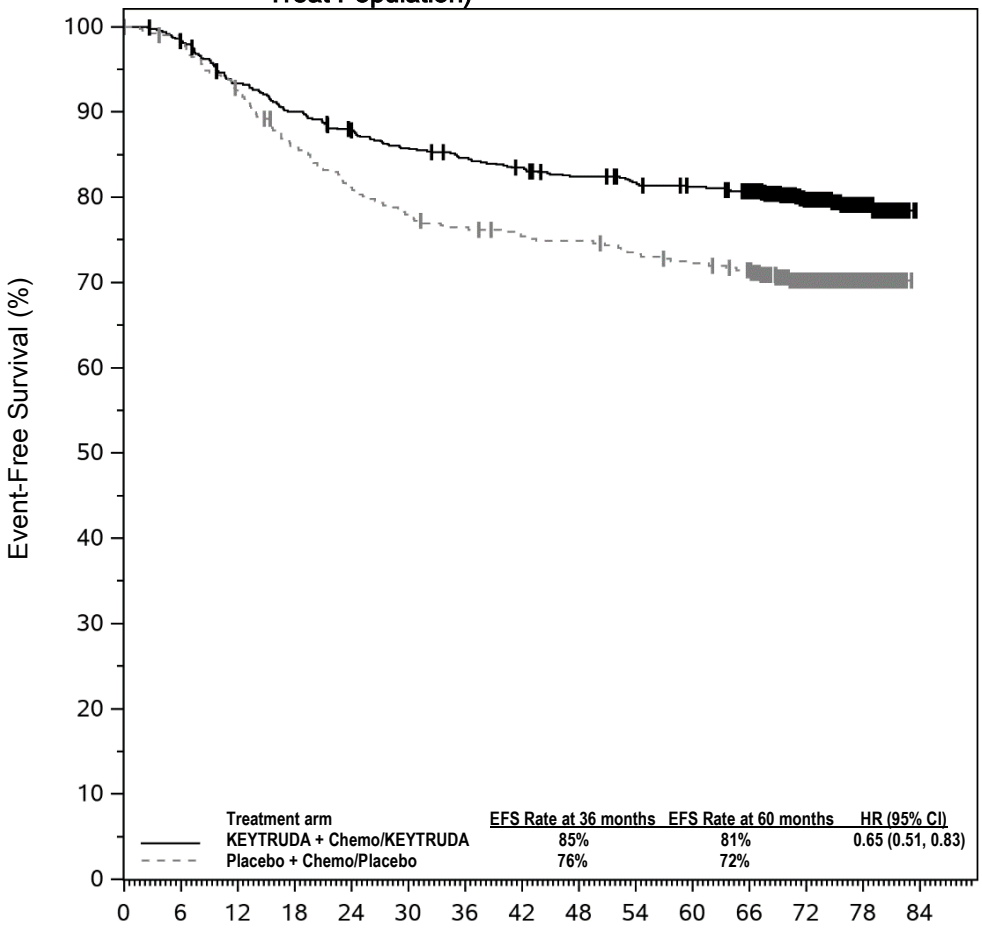
§ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by nodal status, tumor size, and choice of carboplatin

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

Based on a pre-specified OS interim analysis (compared to a significance level of 0.0050) with a median follow-up time was 73.1 months (range: 2.7 to 83.9 months)

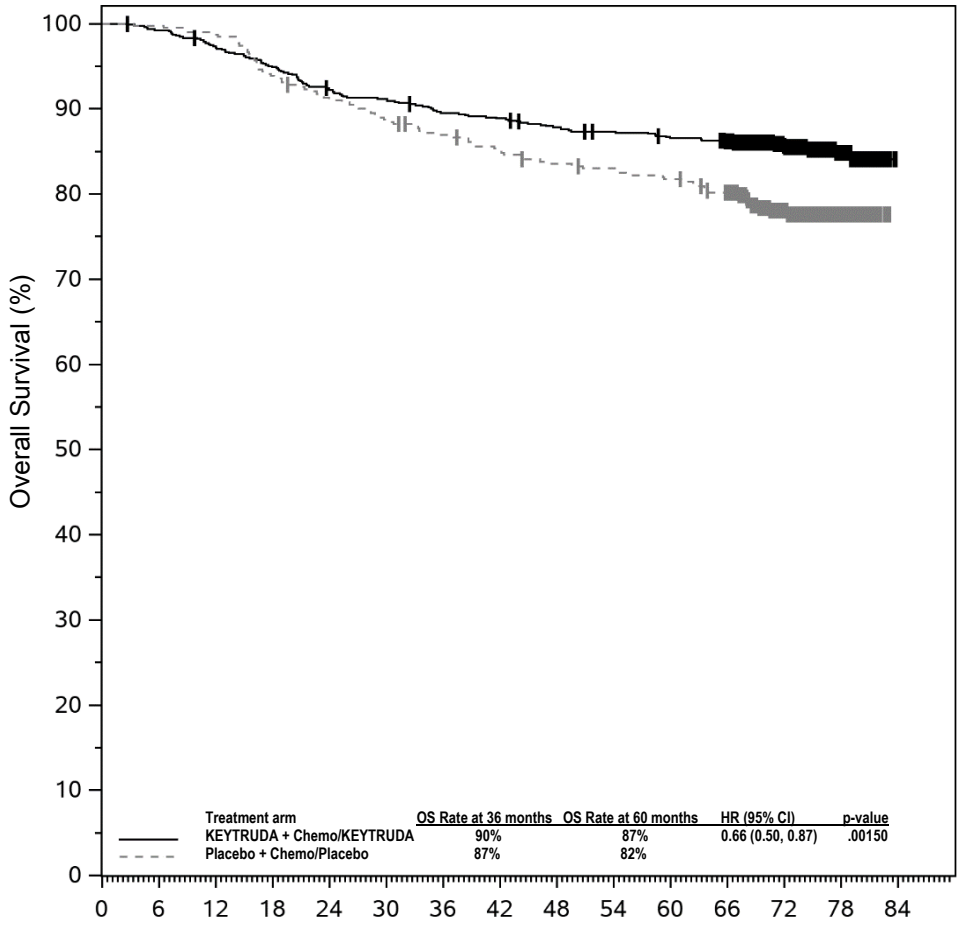
In a pre-specified interim analysis (median follow-up time was 73.1 months (range: 2.7 to 83.9 months)), the EFS HR was 0.65 (95% CI: 0.51, 0.83). The 36-month EFS rates were 85% (95% CI: 82, 87) in the KEYTRUDA arm and 76% (95% CI: 72, 80) in the placebo arm. The 60-month EFS rates were 81% (95% CI: 78, 84) in the KEYTRUDA arm and 72% (95% CI: 67, 76) in the placebo arm.

Figure 60: Kaplan-Meier Curve for Event-Free Survival by Treatment Arm in KEYNOTE-522 (Intent to Treat Population)



Number at Risk															
KEYTRUDA + Chemo/KEYTRUDA	784	769	728	702	681	665	654	644	633	625	618	602	409	164	0
Placebo + Chemo/Placebo	390	382	358	330	312	300	293	287	285	278	273	264	178	76	0

Figure 61: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-522 (Intent to Treat Population)



Number at Risk															
KEYTRUDA + Chemo/KEYTRUDA	784	777	760	742	720	712	698	693	683	677	670	656	448	176	0
Placebo + Chemo/Placebo	390	389	385	366	354	345	336	328	321	318	313	300	199	82	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

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

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 ≥ 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 ≥ 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 ≥ 1 and 38% had tumor PD-L1 expression CPS ≥ 10.

In KEYNOTE-355, there was a statistically significant improvement in OS and PFS in patients with tumor PD-L1 expression CPS ≥ 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 47 and Figures 62 and 63.

Table 47: 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 rateÞ	65%	54%
Response Duration¶,#		
Median in months (95% CI)	19.3 (9.9, 29.8)	7.3 (5.3, 15.8)
% with duration ≥ 6 monthsβ	83%	58%
% with duration ≥ 12 monthsβ	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

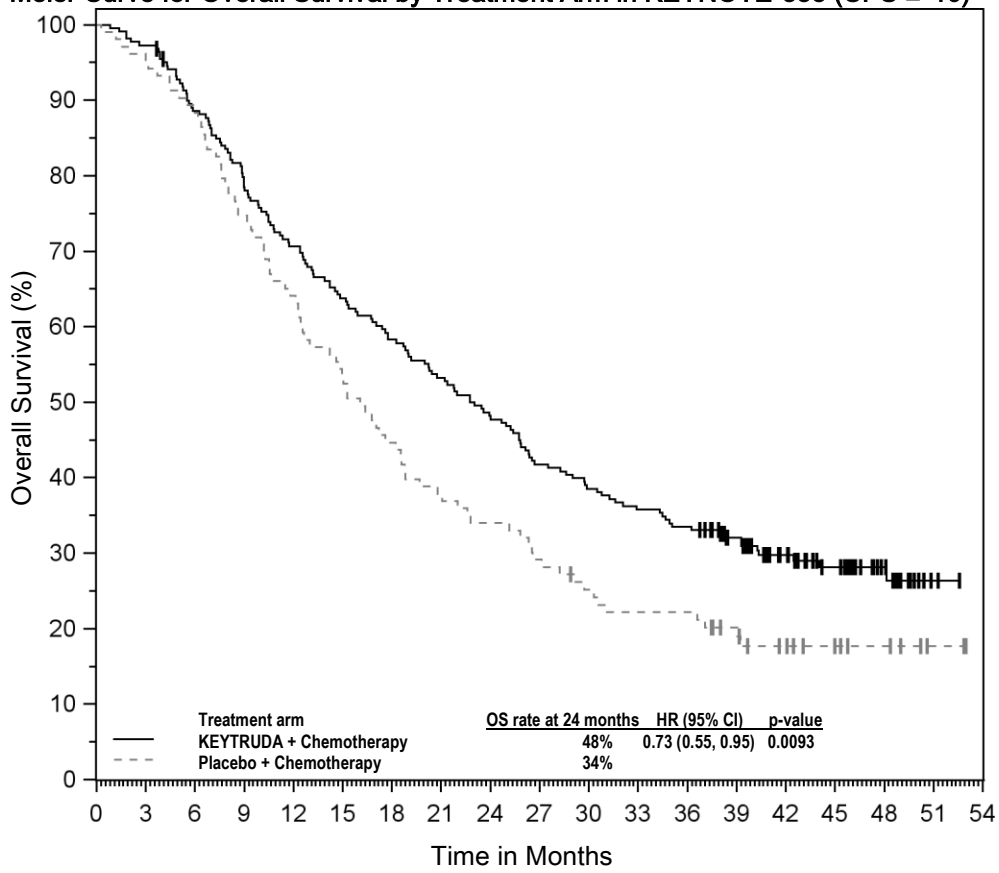
Based on a pre-specified interim analysis

Þ Based on stable disease for at least 24 weeks, or complete response, or partial response

ß From product-limit (Kaplan-Meier) method for censored data

At final analysis, the ORR was 53% in the KEYTRUDA with chemotherapy arm and 41% in the placebo with chemotherapy arm. The complete and partial response rates were 17% and 35%, respectively in the KEYTRUDA with chemotherapy arm and 14% and 27%, respectively in the placebo with chemotherapy arm. The median duration of response was 12.8 months (95% CI: 9.9, 25.9) in the KEYTRUDA with chemotherapy arm and 7.3 months (95% CI: 5.5, 15.4) in the placebo with chemotherapy arm. The percentage of patients with ongoing responses based on Kaplan-Meier estimation were 82% and 56% at 6 months and 12 months respectively, in patients in the KEYTRUDA with chemotherapy arm and 60% and 38% at 6 months and 12 months, respectively in patients in the placebo with chemotherapy arm.

Figure 62: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-355 (CPS ≥ 10)*

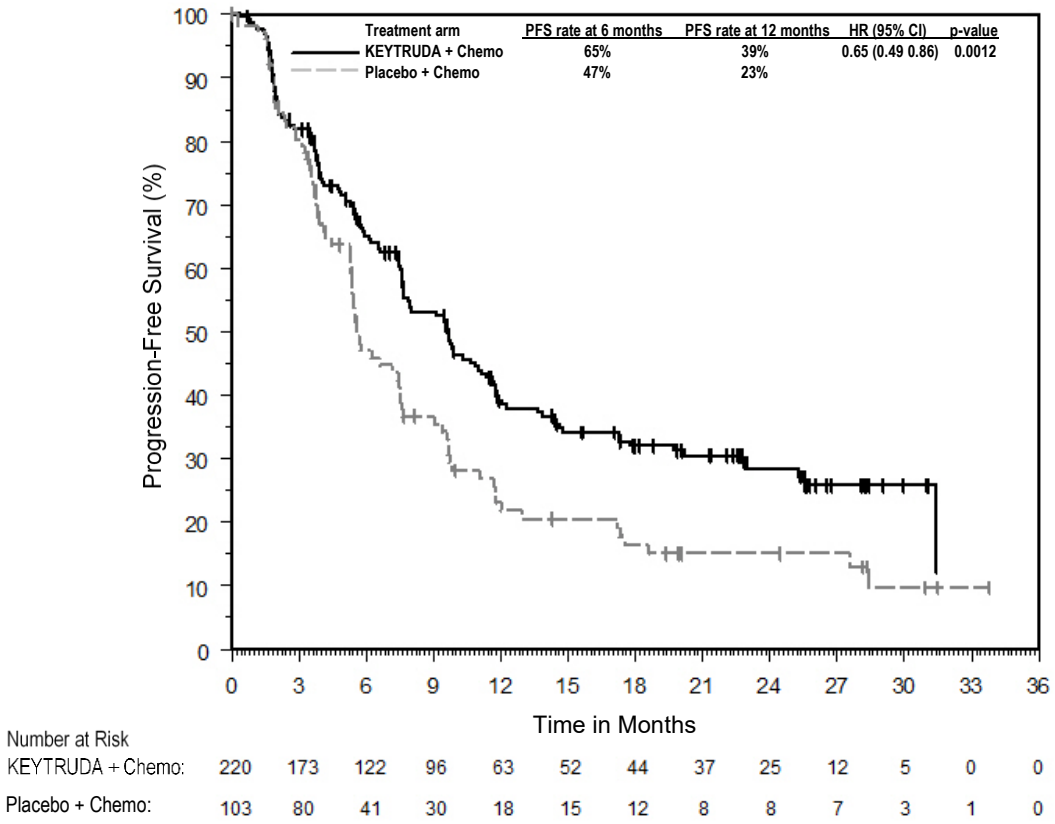


Number at Risk

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 63: 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.

In preclinical murine models, combinations of an anti-mouse PD-1 antibody plus a TKI have demonstrated enhanced anti-tumor activity compared to either agent alone.

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 (t½) 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 or moderate 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 m^2) or moderate (GFR <60 and ≥ 30 mL/min/1.73 m^2) renal impairment compared to patients with normal

(GFR ≥ 90 mL/min/1.73 m^2) 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 m^2) 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 and moderate hepatic impairment (total bilirubin (TB) 1.0 to 1.5 x ULN or AST >ULN and TB >1.5 to 3 x ULN and any AST, respectively, as defined using the National Cancer Institute criteria of hepatic dysfunction) compared to patients with normal hepatic function (TB and AST ≤ ULN). No clinically important differences in the clearance of pembrolizumab were found between patients with mild and moderate hepatic impairment and normal hepatic function. KEYTRUDA has not been studied in patients with 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

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USA

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MSD

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