NEW ZEALAND DATA SHEET

1. PRODUCT NAME

KEYTRUDA® 100 mg/4 mL (25 mg/mL) concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CAS No.: 1374853-91-4

One vial contains 100 mg of pembrolizumab in 4 mL of solution.

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. Pembrolizumab is produced in Chinese hamster ovary cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

KEYTRUDA concentrate for solution for infusion is a sterile, preservative-free, clear to slightly opalescent, colourless to slightly yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Melanoma

KEYTRUDA® (pembrolizumab) is indicated as monotherapy for the treatment of unresectable or metastatic melanoma in adults.

KEYTRUDA® is indicated for the adjuvant treatment of adult and paediatric (12 years and older) patients with Stage IIB, IIC, or III melanoma who have undergone complete resection.

Non-small cell lung cancer (NSCLC)

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 tumour 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 NSCLC expressing PD-L1 [tumour proportion score (TPS) ≥1%] as determined by a validated test, with no EGFR or ALK genomic tumour aberrations, and is

- stage III where patients are not candidates for surgical resection or definitive chemoradiation, or
- metastatic.

KEYTRUDA® as monotherapy is indicated for the treatment of patients with advanced NSCLC whose tumours 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

tumour 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 for the adjuvant treatment of patients with Stage IB (T2a ≥4 cm), II, or IIIA NSCLC who have undergone complete resection.

Malignant Pleural Mesothelioma

KEYTRUDA®, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of adult and paediatric (12 years and older) patients with unresectable advanced or metastatic malignant pleural mesothelioma (MPM).

Classical Hodgkin Lymphoma (cHL)

KEYTRUDA® is indicated for the treatment of adult and paediatric patients with relapsed or refractory classical Hodgkin Lymphoma (cHL).

Urothelial carcinoma

KEYTRUDA® is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by a validated test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.

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

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

Head and Neck Squamous Cell Cancer (HNSCC)

KEYTRUDA® is indicated for the treatment of 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 monotherapy as neoadjuvant treatment, continued as adjuvant treatment in combination with radiotherapy (RT) with or without cisplatin and then as monotherapy.

KEYTRUDA®, 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.

KEYTRUDA®, as monotherapy, is indicated for the first-line treatment of patients with metastatic or unresectable recurrent HNSCC, whose tumours express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by a validated test.

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

Microsatellite instability-high cancer

Colorectal

KEYTRUDA® is indicated in adult and paediatric patients for the treatment of unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. This indication was approved based on objective response rate and response duration in a single-arm trial.

Non-colorectal

KEYTRUDA® is indicated in adult and paediatric patients for the treatment of unresectable or metastatic, MSI-H or dMMR tumours that have progressed following prior treatment and when there are no satisfactory alternative treatment options. Sample sizes for individual tissue types were too small to provide data on clinical utility of the MSI-H/dMMR tests for each of the tissue types, individually. The assumption that MSI-H/dMMR-status is predictive of the treatment effect of KEYTRUDA for every tissue type has not been verified.

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

Colorectal Cancer

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

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).

Endometrial Carcinoma

KEYTRUDA®, in combination with carboplatin and paclitaxel, followed by KEYTRUDA as a single agent, is indicated for the treatment of adult patients with primary advanced or recurrent endometrial carcinoma.

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.

Cervical Cancer

KEYTRUDA®, in combination with chemoradiotherapy (CRT), is indicated for the treatment of patients with high-risk, locally advanced cervical cancer (FIGO 2014 Stage IB2-IIB and node-positive, or Stage III-IVA).

KEYTRUDA®, in combination with platinum chemotherapy and paclitaxel, with or without bevacizumab, is indicated for the treatment of patients with persistent, recurrent, or metastatic cervical cancer whose tumours express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by a validated test.

Cutaneous Squamous Cell Carcinoma

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

Merkel Cell Carcinoma (MCC)

KEYTRUDA®, as monotherapy, is indicated for the treatment of adult and paediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma (MCC).

Renal Cell Carcinoma

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

KEYTRUDA® (pembrolizumab), 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 intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.

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 tumours express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by a validated test.

Oesophageal Cancer

KEYTRUDA®, in combination with platinum and fluoropyrimidine based chemotherapy, is indicated for the first-line treatment of patients with locally advanced unresectable or metastatic carcinoma of the oesophagus or gastroesophageal junction.

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 tumours express PD-L1 (CPS ≥10) as determined by a validated test.

4.2 Dose and method of administration

Treatment must be initiated and supervised by healthcare professionals experienced in the treatment of cancer.

Patients receiving subcutaneous KEYTRUDA SC can switch to intravenous pembrolizumab at their next scheduled dose. Patients receiving intravenous pembrolizumab can switch to subcutaneous KEYTRUDA SC at their next scheduled dose

Patient Selection

If specified in the indication, select patients for treatment with KEYTRUDA based on the presence of positive PD-L1 expression or MSI-H or dMMR tumour status.

Determination of PD-L1 expression should be performed by laboratories with demonstrated proficiency in the *in-vitro* diagnostic technology being employed.

MSI or MMR tumour status should be evaluated using a validated test.

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

Recommended Dosing

KEYTRUDA is administered as an intravenous infusion over 30 minutes.

The recommended dose of KEYTRUDA in adults is either:

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

The recommended dose of KEYTRUDA in paediatric patients is 2 mg/kg (up to a maximum of 200 mg) every 3 weeks (see section 4.2, Paediatric Patients).

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

For RCC patients treated with KEYTRUDA in combination with axitinib, see the prescribing information regarding dosing of axitinib. When used in combination with KEYTRUDA, dose escalation of axitinib above the initial 5 mg dose may be considered at intervals of six weeks or longer (see section 5.1).

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 tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed. Clinically stable patients with initial evidence of disease progression can under some circumstances remain on treatment until disease progression is confirmed (see section 5.1 for a description of the circumstances where such continued treatment was allowed in the pivotal studies).

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 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.

For the neoadjuvant treatment of resectable locally advanced HNSCC, patients should be treated 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 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 Section 4.4]*

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	Severe or life-threatening (Grades 3 or 4)	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 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 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 haematological 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.

Paediatric Patients

The recommended dose of KEYTRUDA in paediatric patients is 2 mg/kg (up to a maximum of 200 mg), administered as an intravenous infusion over 30 minutes every 3 weeks [see Section 4.1 for paediatric indications and Section 4.8].

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.

Renal Insufficiency

No dose adjustment is needed for patients with mild or moderate renal impairment. KEYTRUDA has not been studied in patients with severe renal impairment [see section 5].

Hepatic Insufficiency

No dose adjustment is needed for patients with mild hepatic impairment. KEYTRUDA has not been studied in patients with moderate or severe hepatic impairment [see section 5].

Method of administration

It is important to check the vial label to ensure that the correct formulation (intravenous or subcutaneous) is being prepared and administered to the patient as prescribed, to reduce the risk of medication errors.

KEYTRUDA concentrate for solution for infusion is for intravenous use only. KEYTRUDA concentrate for solution for infusion is not intended for subcutaneous administration.

KEYTRUDA concentrate for solution for infusion must be administered by intravenous infusion over 30 minutes. KEYTRUDA concentrate for solution for infusion must not be administered as an intravenous push or bolus injection.

KEYTRUDA concentrate for solution for infusion should not be substituted for or with subcutaneous pembrolizumab because they have different recommended dosages and routes of administration.

For instructions on dilution of the medicine before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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 occurred during treatment, were reversible and managed with interruptions of KEYTRUDA, administration of corticosteroids and/or supportive care. Immune-related adverse reactions have also occurred after the last dose of KEYTRUDA. Immune-mediated adverse reactions affecting more than one body system can occur simultaneously.

For suspected immune-mediated adverse reactions, ensure adequate evaluation to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, withhold KEYTRUDA and consider administration of corticosteroids. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Based on limited data from clinical studies in patients whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered. Restart KEYTRUDA if the adverse reaction remains at Grade 1 or less following corticosteroid taper. If another episode of a severe adverse reaction occurs, permanently discontinue KEYTRUDA [see sections 4.2 and 4.8].

Immune-mediated pneumonitis

Pneumonitis (including fatal cases) has been reported in patients receiving KEYTRUDA [see section 4.8].

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 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 sections 4.2, 4.8 and Immune-mediated Adverse Reactions above].

Immune-mediated colitis

Colitis has been reported in patients receiving KEYTRUDA [see section 4.8]. 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 sections 4.2, 4.8 and Immune-mediated Adverse Reactions above].

Immune-mediated hepatitis

Hepatitis has been reported in patients receiving KEYTRUDA [see section 4.8]. 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 sections 4.2, 4.8 and Immune-mediated Adverse Reactions above].

Immune-mediated nephritis

Nephritis has been reported in patients receiving KEYTRUDA [see section 4.8]. 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 sections 4.2, 4.8 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 section 4.8.]

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 moderate (Grade 2), withhold or discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency or hypophysitis. [see sections 4.2, 4.8 and Immune-mediated Adverse Reactions above].

Type 1 diabetes mellitus, including diabetic ketoacidosis, has been reported in patients receiving KEYTRUDA [see section 4.8]. Monitor patients for hyperglycaemia or other signs and symptoms of diabetes. Administer insulin for type 1 diabetes, and withhold KEYTRUDA in cases of severe hyperglycaemia until metabolic control is achieved.

Thyroid disorders, including hyperthyroidism, hypothyroidism 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 or discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) hyperthyroidism [see sections 4.2, 4.8 and Immune-mediated Adverse Reactions above].

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 section 4.2].

Cases of Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and bullous pemphigoid, have been reported in patients treated with KEYTRUDA. Some cases of SJS and TEN have had a fatal outcome. 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 section 4.2.]

Other immune-mediated adverse reactions

The following additional clinically significant, immune-mediated adverse reactions were reported in less than 1% of patients treated with KEYTRUDA in KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, and KEYNOTE-010: uveitis, myositis, Guillain-Barré syndrome, pancreatitis, encephalitis, sarcoidosis, myasthenic syndrome/myasthenia gravis (including exacerbation), myelitis, vasculitis, hypoparathyroidism, gastritis, haemolytic anaemia, and pericarditis. The following were reported in other clinical studies with KEYTRUDA or in post-marketing use: myocarditis, sclerosing cholangitis, 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 post-marketing use.

Transplant-related adverse reactions

Solid organ transplant rejection has been reported in the post-marketing 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.

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 section 4.8). 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 section 4.2 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 randomised 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 infusion 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 section 4.2]. Patients with mild or moderate infusion reaction may continue to receive KEYTRUDA with close monitoring; premedication with antipyretic and antihistamine may be considered.

Patients excluded from clinical trials

Patients with HIV, HBV, HCV, other active infections requiring therapy; and patients with a history of severe immune-mediated adverse reactions with ipilimumab, defined as any Grade 4 toxicity requiring treatment with corticosteroids or Grade 3 toxicity requiring corticosteroid treatment (greater than 10 mg/day prednisone or equivalent dose) for greater than 12 weeks were excluded from the clinical trial. No clinical data is available. Caution should be used in these patient populations.

Patients who experienced less severe adverse reactions (including immune-mediated) on ipilimumab that resolved or improved to Grade 0-1 and ≤10 mg/day prednisone (or equivalent dose) for immune-mediated adverse events for at least two weeks prior to first dose of KEYTRUDA were included in the clinical trial. Caution should be used in this patient population.

Effect on Laboratory Tests

Thyroid and liver (hepatic transaminase and bilirubin levels) function tests should be performed at the start of treatment, periodically during treatment and as indicated based on clinical evaluation [see section 4.4 and 4.2].

4.5 Interaction with other medicines and other forms of interaction

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 section 4.4]. 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.

4.6 Fertility, pregnancy and lactation

Effects on Fertility

Fertility studies have not been conducted with pembrolizumab. There were no notable effects on male and female reproductive organs observed in general repeat-dose toxicity studies conducted with pembrolizumab in Cynomolgus monkeys, involving IV administration at doses up to 200 mg/kg once a week for 1 month or once every two weeks for 6 months [see section 5.3].

Use in Pregnancy (Category D)

There are no data on the use of pembrolizumab in pregnant women. Animal reproduction studies have not been conducted with pembrolizumab; however, blockade of the PD-L1 pathway has been shown in mouse models of pregnancy to disrupt tolerance to the foetus and to result in an increase in foetal loss. These results indicate a potential risk, based on its mechanism of action, that administration of KEYTRUDA during pregnancy could cause foetal 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 foetus. 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 following the last dose of KEYTRUDA.

Use in Lactation

It is unknown whether KEYTRUDA is secreted in human milk. Because many drugs are secreted in human milk, 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.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Based on its pharmacodynamic properties, KEYTRUDA is unlikely to affect this ability. Because of potential adverse reactions such as fatigue (see section 4.8), patients should be advised to use caution when driving or operating machinery until they are certain that KEYTRUDA does not adversely affect them.

4.8 Undesirable effects

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/

Clinical trials experience

The safety of KEYTRUDA was evaluated in 2799 patients in controlled and uncontrolled studies. The median treatment duration was 4.2 months (range 1 day to 30.4 months) including 1153 patients treated for greater than or equal to six months and 600 patients treated for greater than or equal to one year.

KEYTRUDA was discontinued for treatment-related adverse reactions in 5% of patients. Treatment-related serious adverse events (SAEs) reported up to 90 days after the last dose occurred in 10% of patients receiving KEYTRUDA. Of these treatment-related SAEs, the most common were: pneumonitis, colitis, diarrhoea, and pyrexia. The most common treatment-related adverse reactions (reported in > 10% of patients) were: fatigue, pruritus, rash, diarrhoea, and nausea. The safety profile was generally similar for patients with melanoma and NSCLC.

Immune-mediated adverse reactions [see section 4.4]

Immune-mediated adverse reactions are presented based on 2799 patients with melanoma and NSCLC. The safety profile was generally similar for patients with melanoma and NSCLC. Table 2 presents the incidence of immune-mediated adverse reactions by Grade that occurred in patients receiving KEYTRUDA.

Table 2: Immune-Mediated Adverse Reactions

	KEYTRUDA 2 mg/kg every 3 weeks or 10 mg/kg every 2 or 3 weeks n=2799				
Adverse Reaction	All Grades (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	Grade 5 (%)
Hypothyroidism*	8.5	6.2	0.1	0	0
Hyperthyroidism†	3.4	0.8	0.1	0	0
Pneumonitis‡	3.4	1.3	0.9	0.3	0.1
Colitis	1.7	0.4	1.1	<0.1	0
Adrenal Insufficiency	0.8	0.3	0.3	<0.1	0
Hepatitis	0.7	0.1	0.4	<0.1	0
Hypophysitis	0.6	0.2	0.3	<0.1	0
Nephritis§	0.3	0.1	0.1	<0.1	0
Type 1 Diabetes Mellitus	0.2	<0.1	0.1	0.1	0

* In patients with cHL (n=389) the incidence of hypothyroidism was 17%, all of which were Grade 1 or 2. In indiviual studies of patients with HNSCC treated with KEYTRUDA as monotherapy (n=909) the incidence of hypothyroidism was 16.1% (all Grades) with 0.3% Grade 3. In patients with HNSCC treated with KEYTRUDA in combination with platinum and 5-FU chemotherapy (n=276) the incidence of hypothyroidism was 15.2%, all of which were Grades 1 or 2. In the adjuvant study of patients with resected RCC treated with KEYTRUDA as monotherapy (n=488) the incidence of hypothyroidism was 21% (all Grades) with 0.2% Grade 3.

† In the adjuvant study of patients with resected RCC treated with KEYTRUDA as monotherapy (n=488) the incidence of hyperthyroidism was 12% (all Grades) with 0.2% Grade 3.

‡ In individual studies of patients with NSCLC treated with KEYTRUDA as monotherapy (total n=2602), the incidence of pneumonitis (all Grades) ranged from 3.8% to 8.3%. In cHL patients treated with KEYTRUDA as monotherapy, 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.

§ In patients with non-squamous NSCLC treated with KEYTRUDA 200 mg in combination with pemetrexed and platinum chemotherapy (n=405) the incidence of nephritis was 1.7% (all Grades) with 1.0% Grade 3 and 0.5% Grade 4.

Endocrinopathies: The median time to onset of adrenal insufficiency was 5.3 months (range 26 days to 16.6 months). The median duration was not reached (range 4 days to 1.9+ years). Adrenal insufficiency led to discontinuation of KEYTRUDA in 1 (<0.1%) patient. Adrenal insufficiency resolved in 5 patients. The median time to onset of hypophysitis was 3.7 months (range 1 day to 11.9 months). The median duration was 4.7 months (range 8+ days to 12.7+ months). Hypophysitis led to discontinuation of KEYTRUDA in 4 (0.1%) patients. Hypophysitis resolved in 7 patients. The median time to onset of hyperthyroidism was 1.4 months (range 1 day to 21.9 months). The median duration was 2.1 months (range 3 days to 15.0+ months). Hyperthyroidism led to discontinuation of KEYTRUDA in 2 (<0.1%) patients. Hyperthyroidism resolved in 71 patients. The median time to onset of hypothyroidism was 3.5 months (range 1 day to 18.9 months). The median duration was not reached (range 2 days to 27.7+ months). One (<0.1%) patient discontinued KEYTRUDA due to hypothyroidism.

Pneumonitis: The median time to onset of pneumonitis was 3.3 months (range 2 days to 19.3 months). The median duration was 1.5 months (range 1 day to 17.2+ months).

Pneumonitis led to discontinuation of KEYTRUDA in 36 (1.3%) patients. Pneumonitis resolved in 55 patients.

Colitis: The median time to onset of colitis was 3.5 months (range 10 days to 16.2 months). The median duration was 1.3 months (range 1 day to 8.7+ months). Colitis led to discontinuation of KEYTRUDA in 15 (0.5%) patients. Colitis resolved in 41 patients.

Hepatitis: The median time to onset of hepatitis was 1.3 months (range 8 days to 21.4 months). The median duration was 1.8 months (range 8 days to 20.9+ months). Hepatitis led to discontinuation of KEYTRUDA in 6 (0.2%) patients. Hepatitis resolved in 15 patients.

Nephritis: The median time to onset of nephritis was 5.1 months (range 12 days to 12.8 months). The median duration was 3.3 months (range 12 days to 8.9+ months). Nephritis led to discontinuation of KEYTRUDA in 3 (0.1%) patients. Nephritis resolved in 5 patients.

Other adverse events

Melanoma

Table 3 summarises the adverse events that occurred in at least 10% of patients with melanoma treated with KEYTRUDA in KEYNOTE-006. The most common adverse events (reported in at least 15% of patients) were arthralgia and cough.

Table 3: Adverse Events Occurring in ≥10% of Patients Treated with KEYTRUDA and at a Higher Incidence than in the Ipilimumab Arm (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grade 3]) (KEYNOTE-006)

	KEYTRUDA 10 mg/kg every 2 or 3 weeks n=555		**Ipilimumab 3 mg/kg every 3 weeks n=256**	
Adverse Events	**All Grades (%)**	**Grade 3* (%)**	**All Grades (%)**	**Grade 3* (%)**
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	18	0	10	1
Back pain	12	1	7	1
Respiratory, Thoracic and Mediastinal Disorders				
Cough	17	0	7	0
Skin And Subcutaneous Tissue Disorders				
Vitiligo	11	0	2	0

* Of these ≥10% adverse events, none was reported as Grade 4.

Table 4: Laboratory Abnormalities Worsened from Baseline in ≥20% of Patients with Unresectable or Metastatic Melanoma and at a Higher Incidence than in the Ipilimumab Arm (Between Arm Difference of ≥5% [All Grades]or ≥2% [Grades 3-4]) (KEYNOTE-006)

	KEYTRUDA 10 mg/kg every 2 or 3 weeks n=555		Ipilimumab n=256	
Laboratory Test	**All Grades %**	**Grades 3-4 %**	**All Grades %**	**Grades 3-4 %**
Haematology				
Lymphopenia	45	5	36	5
Chemistry				
Hypertriglyceridemia	40	2	33	1

Table 5 summarises the adverse events that occurred in at least 10% of patients with melanoma treated with KEYTRUDA in KEYNOTE-002. The most common adverse event (reported in at least 20% of patients) was pruritus.

Table 5: Adverse Events Occurring in ≥10% of Patients Treated with KEYTRUDA and at a Higher Incidence than in the Chemotherapy Arm (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-4]) (KEYNOTE-002)

	KEYTRUDA 2 mg/kg every 3 weeks n=178		Chemotherapy n=171	
Adverse Event	**All Grades (%)**	**Grades 3-4* (%)**	**All Grades (%)**	**Grades 3-4* (%)**
Gastrointestinal Disorders				
Abdominal pain	13	2	8	1
Skin And Subcutaneous Tissue Disorders				
Pruritus	25	0	8	0
Rash	13	0	8	0
Metabolism and Nutrition Disorders				
Hyponatremia	11	3	5	1
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	15	1	10	1

Of these ≥10% adverse events, none was reported as Grade 4 in patients receiving KEYTRUDA at 2 mg/kg. Hyponatremia was reported as Grade 4 in one patient receiving chemotherapy.

Table 6: Laboratory Abnormalities Worsened from Baseline in ≥20% of Patients with Unresectable or Metastatic Melanoma and at a Higher Incidence than in the Chemotherapy Arm (Between Arm Difference of ≥5% [All Grades]or ≥2% [Grades 3-4]) (KEYNOTE-002)

	KEYTRUDA 2 mg/kg every 3 weeks n=178		Chemotherapy n=171	
Laboratory Test	**All Grades %**	**Grades 3-4 %**	**All Grades %**	**Grades 3-4 %**
Chemistry				
Hyperglycemia	63	9	56	6
Hyponatremia	45	8	29	5
Hypoalbuminemia	43	4	39	1
Increased Aspartate Aminotransferase	26	2	17	1
Increased Alkaline Phosphatase	35	4	28	2
Haematology				
Anaemia	69	12	76	8

Overall, the safety profile was similar across all doses and between patients previously treated with ipilimumab and patients naïve to treatment with ipilimumab.

Resected Melanoma

Among the 969 patients with resected melanoma enrolled in KEYNOTE-716 and 1019 patients with resected melanoma enrolled in KEYNOTE-054, the adverse reactions were generally similar to those occurring in patients with unresectable or metastatic melanoma or NSCLC.

Non-Small Cell Lung Carcinoma

Combination Therapy

Table 7 summarises the adverse events that occurred in at least 20% of patients treated with KEYTRUDA, pemetrexed, and platinum chemotherapy in KEYNOTE-189. Adverse events occurring in previously untreated patients with NSCLC receiving KEYTRUDA in combination with carboplatin and either paclitaxel or nab-paclitaxel in KEYNOTE-407 were generally similar to those occurring in patients in KEYNOTE-189 with the exception of alopecia (46%) and arthralgia (21%).

Table 7: Adverse Events Occurring in ≥20% of Patients Receiving KEYTRUDA with Pemetrexed and Platinum Chemotherapy and at a Higher Incidence than in Patients Receiving Placebo with Pemetrexed and Platinum Chemotherapy (Between-Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-4]) (KEYNOTE-189)

	KEYTRUDA + Pemetrexed + Platinum Chemotherapy n=405		Placebo + Pemetrexed + Platinum Chemotherapy n=202	
Adverse Events	**All Grades* (%)**	**Grades 3-4 (%)**	**All Grades (%)**	**Grades 3-4 (%)**
General Disorders and Administration Site Conditions				
Fatigue	41	6	38	2.5
Asthenia	20	6	24	3.5
Gastrointestinal Disorders				
Diarrhoea	31	5	21	3.0
Blood and Lymphatic System Disorders				
Neutropenia	27	16	24	12
Skin and Subcutaneous Tissue Disorders				
Rash	20	1.7	11	1.5

* Graded per NCI CTCAE v4.03

Neoadjuvant and Adjuvant Therapy for Resectable NSCLC

Adverse events occurring in patients with resectable NSCLC receiving KEYTRUDA in combination with platinum-containing chemotherapy, given as neoadjuvant treatment and continued as monotherapy adjuvant treatment in KEYNOTE-671, were generally similar to those occurring in patients in other clinical trials across tumor types receiving KEYTRUDA in combination with chemotherapy.

Monotherapy

Table 8 summarises the adverse events that occurred in at least 10% of previously untreated patients with NSCLC receiving KEYTRUDA in KEYNOTE-042. The most common adverse events (reported in at least 15% of patients) were dyspnoea and cough. Adverse events occurring in previously untreated patients with NSCLC receiving KEYTRUDA in KEYNOTE-024 and previously treated patients in KEYNOTE-010 were generally similar to those occurring in patients in KEYNOTE-042.

Table 8: Adverse Events Occurring in ≥10% of NSCLC Patients Treated with KEYTRUDA and at a Higher Incidence than in the Chemotherapy Arm (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-5]) (KEYNOTE-042)

	KEYTRUDA 200 mg every 3 weeks n=636		Chemotherapy n=615	
Adverse Event	**All Grades* (%)**	**Grades 3-5 (%)**	**All Grades (%)**	**Grades 3-5 (%)**
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnoea	17	2.0	11	0.8
Cough	16	0.2	11	0.3
Endocrine Disorders				
Hypothyroidism	12	0.2	1.5	0

* Graded per NCI CTCAE v4.03

Adjuvant Therapy for Resected NSCLC

Among the 580 patients with resected NSCLC treated with KEYTRUDA in KEYNOTE-091, the adverse events were generally similar to those occurring in other patients with NSCLC receiving KEYTRUDA as monotherapy with the exception of hypothyroidism (21%) and hyperthyroidism (11%).

Other Cancers

Monotherapy

Adverse events occurring in patients with HNSCC, urothelial carcinoma, cHL, MSI-H/dMMR cancer, CRC, recurrent or metastatic cSCC or locally advanced cSCC, or adjuvant treatment of RCC were generally similar to those occurring in patients with melanoma or NSCLC.

Merkel Cell Carcinoma

Among the 105 patients with MCC enrolled in KEYNOTE-017 and KEYNOTE-913 [see Section 5.1], the median duration of exposure to KEYTRUDA was 6.3 months (range 1 day to 28 months). Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible. Adverse reactions occurring in patients with MCC were similar to those occurring in 2799 patients with melanoma or NSCLC treated with KEYTRUDA as a single agent. Laboratory abnormalities (Grades 3-4) that occurred at a higher incidence included increased lipase (17%).

Combination Therapy

Malignant Pleural Mesothelioma

Among the 241 patients with MPM treated with KEYTRUDA in combination with pemetrexed and platinum chemotherapy in KEYNOTE-483, the adverse events were generally similar to those occurring in other patients receiving KEYTRUDA in combination with pemetrexed and platinum chemotherapy.

Head and Neck Squamous Cell Cancer

In patients with HNSCC receiving KEYTRUDA as neoadjuvant treatment, continued as adjuvant treatment in combination with RT with or without cisplatin and then as monotherapy,

adverse events occurring in at least 20% of patients and at a higher incidence (≥2% difference) of Grades 3-4 severity for KEYTRUDA plus RT with or without cisplatin compared to RT with or without cisplatin was weight loss (14% vs. 10%),

In patients with HNSCC receiving KEYTRUDA plus chemotherapy (platinum and 5-FU), adverse events occurring at a greater severity (Grades 3-4) and at a higher incidence (≥2% difference) compared to cetuximab plus chemotherapy (platinum and 5-FU) were: fatigue (7% vs. 4.9%), mucosal inflammation (10% vs. 5%), and stomatitis (8% vs. 3.5%).

Gastric Cancer

In patients with gastric cancer receiving KEYTRUDA plus chemotherapy (fluoropyrimidine and platinum), adverse events occurring in at least 20% of patients and at a higher incidence (≥2% difference) of Grades 3-4 severity compared to placebo plus chemotherapy (fluoropyrimidine and platinum) were: anaemia (12% vs. 10%), platelet count decreased (7% vs. 5%).

In patients with gastric cancer receiving KEYTRUDA plus trastuzumab and chemotherapy (fluoropyrimidine and platinum), adverse events occurring in at least 20% of patients and at a higher incidence (≥2% difference) of Grades 3-4 severity compared to placebo plus trastuzumab and chemotherapy (fluoropyrimidine and platinum) were: vomiting (4.6% vs. 1.9%), anaemia (14% vs.12%), decreased platelet count (14% vs.10%), and lymphopenia (13% vs.9%).

Cervical Cancer

In patients with cervical cancer receiving KEYTRUDA plus CRT (cisplatin plus external beam radiation therapy [EBRT] followed by brachytherapy [BT]), adverse events occurring at a higher incidence (≥2% difference) of Grades 3-5 severity for KEYTRUDA plus CRT compared to placebo plus CRT was leukopenia (13% vs. 11%).

In patients with cervical cancer receiving KEYTRUDA plus chemotherapy (paclitaxel and cisplatin or paclitaxel and carboplatin) with or without bevacizumab, adverse events occurring at a higher incidence (≥2% difference) of Grades 3-5 severity for KEYTRUDA plus chemotherapy with or without bevacizumab compared to placebo plus chemotherapy with or without bevacizumab were: anaemia (30% vs. 27%), neutropenia (12% vs. 10%), thrombocytopenia (8% vs. 5%), asthenia (3.6% vs. 1.6%).

Renal Cell Carcinoma

In Combination with Axitinib (KEYNOTE-426)

The most common adverse events that occurred in at least 20% of previously untreated patients with RCC receiving KEYTRUDA and axitinib in KEYNOTE-426 were diarrhoea, hypertension, fatigue, hypothyroidism, decreased appetite, palmar-plantar erythrodysaesthesia syndrome, nausea, ALT increased, AST increased, dysphonia, cough and constipation.

In KEYNOTE-426, a higher than expected incidence of Grades 3 and 4 ALT increased (20%) and AST increased (13%) were observed in previously untreated patients with RCC receiving KEYTRUDA in combination with axitinib. 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 KEYTRUDA (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. (See section 4.2 and 4.4).

In Combination with Lenvatinib (KEYNOTE-581)

Table 9 summarises the adverse events that occurred in at least 20% of patients treated with KEYTRUDA and lenvatinib in KEYNOTE-581.

Table 9: Adverse Events Occurring in ≥20% of Patients Receiving KEYTRUDA with Lenvatinib and at a Higher Incidence than in Patients Receiving Sunitinib (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-4]) (KEYNOTE-581)

	KEYTRUDA + lenvatinib n=352		Sunitinib n=340	
Adverse Events	**All Grades* (%)**	**Grades 3-4 (%)**	**All Grades (%)**	**Grades 3-4 (%)**
Gastrointestinal Disorders				
Diarrhoea	61	10	49	5
Nausea	36	2.6	33	0.6
Vomiting	26	3.4	20	1.5
Constipation	25	0.9	19	0
Abdominal pain	21	2.0	8	0.9
Vascular Disorders				
Hypertension	55	28	41	19
Endocrine Disorders				
Hypothyroidism	47	1.4	26	0
Metabolism and Nutrition Disorders				
Decreased appetite	40	4.0	31	1.5
Respiratory, Thoracic and Mediastinal Disorders				
Dysphonia	30	0	4.1	0
Investigations				
Decreased weight	30	8	9	0.3
Renal and Urinary Disorders				
Proteinuria	30	8	13	2.9
Skin and Subcutaneous Tissue Disorders				
Rash	27	3.7	14	0.6
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	28	1.4	15	0.3
Nervous System Disorders				
Headache	23	0.6	16	0.9

* Graded per NCI CTCAE v4.03

Endometrial Carcinoma

In Combination with Chemotherapy (KEYNOTE-868/ NRG-GY018)

In patients with endometrial carcinoma receiving KEYTRUDA plus chemotherapy (paclitaxel and carboplatin), adverse events were generally similar to those observed with KEYTRUDA alone or chemotherapy alone with the exception of rash maculo-papular (13% all Grades; 2% Grades 3-4).

In Combination with Lenvatinib (KEYNOTE-775 and KEYNOTE-146)

Table 10 summarises the adverse events that occurred in at least 20% of patients treated with KEYTRUDA and lenvatinib in KEYNOTE-775. Adverse events occurring in patients with endometrial carcinoma receiving KEYTRUDA in combination with lenvatinib in KEYNOTE-146 were generally similar to those occurring in patients in KEYNOTE-775.

Table 10: Adverse Events Occurring in ≥20% of Patients Receiving KEYTRUDA with Lenvatinib and at a Higher Incidence than in Patients Receiving Doxorubicin or Paclitaxel (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-4]) (KEYNOTE-775)

	KEYTRUDA + lenvatinib n=406		Doxorubicin or paclitaxel n=388	
Adverse Events*	**All Grades† (%)**	**Grades 3-4 (%)**	**All Grades† (%)**	**Grades 3-4 (%)**
Vascular Disorders				
Hypertension	64	37.9	5.2	2.3
Endocrine Disorders				
Hypothyroidism	57	1.2	0.8	0
Gastrointestinal Disorders				
Diarrhoea	54	8	20	2.1
Nausea	50	3.4	46	1.3
Vomiting	37	2.7	21	2.3
Abdominal pain	20	2.5	14	1.3
Metabolism and Nutrition Disorders				
Decreased appetite	45	8‡	21	0.5
Investigations				
Decreased weight	34	10	6	0.3
Increased ALT	21	4.6	5	0.8
General Disorders and Administration Site Conditions				
Fatigue	33	5	28	3.1
Asthenia	24	6	24	3.9
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	31	1.7	8	0
Renal and Urinary Disorders				
Proteinuria	29	5	2.8	0.3
Infections				
Urinary tract infection	26	3.9	10	1.0
Nervous System Disorders				
Headache	25	0.5	9	0.3
Respiratory, Thoracic and Mediastinal Disorders				
Dysphonia	23	0	0.5	0
Skin and Subcutaneous Tissue Disorders				
Palmar-plantar erythrodysaesthesia syndrome	21	2.7	0.8	0

* The median duration of study treatment was 7.6 months (range: 1 day to 26.8 months). The median duration of exposure to KEYTRUDA was 6.9 months (range: 1 day to 25.8 months) compared to 3.4 months (range: 1 day to 25.8 months) for chemotherapy.

† Graded per NCI CTCAE v4.03

‡ There was one Grade 5 (0.2%) reported.

Discontinuation of KEYTRUDA, lenvatinib or both due to an adverse event (Grades 1-4) occurred in 30% of patients; 15% KEYTRUDA, and 11% both drugs. The most common adverse events leading to discontinuation of KEYTRUDA were diarrhoea, increased ALT, and

intestinal obstruction (each 1.0%). Refer to the lenvatinib prescribing information for lenvatinib discontinuation information.

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

Oesophageal Cancer

In patients with oesophageal cancer, adverse events occurring in at least 20% of patients and at a higher incidence (≥2% difference) of Grades 3-5 severity for KEYTRUDA in combination with chemotherapy (cisplatin and 5-FU) compared to placebo plus chemotherapy (cisplatin and 5-FU) were: vomiting (7% vs. 5%), stomatitis (6% vs. 3.8%), neutrophil count decreased (24.1% vs. 17.3%), and white blood cell count decreased (9.2% vs. 4.9%).

Triple-Negative Breast Cancer

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

In patients with high-risk early-stage TNBC receiving KEYTRUDA in combination with chemotherapy (carboplatin and paclitaxel followed by doxorubicin or epirubicin and cyclophosphamide), given as a neoadjuvant treatment and continued as monotherapy adjuvant treatment, adverse events occurring in at least 20% of the patients and at a higher incidence (≥5% difference) compared to patients with TNBC receiving placebo in combination with chemotherapy (carboplatin and paclitaxel followed by doxorubicin or epirubicin and cyclophosphamide), given as a neoadjuvant treatment and continued alone as adjuvant treatment were diarrhoea (41% vs. 34%), rash (30% vs. 24%), pyrexia (28% vs. 19%), and decreased appetite (23% vs. 17%). Of these adverse events, Grades 3-4 events were diarrhoea (3.2% vs. 1.8%), rash (1.8% vs. 0.3%), pyrexia (1.3% vs. 0.3%), and decreased appetite (0.9% vs. 0.3%).

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

In patients with TNBC receiving KEYTRUDA in combination with chemotherapy (paclitaxel, nab-paclitaxel, or gemcitabine and carboplatin), adverse events occurring in at least 20% of the patients and at a higher incidence (≥5% difference) compared to patients with TNBC receiving placebo in combination with chemotherapy (paclitaxel, nab-paclitaxel, or gemcitabine and carboplatin) were diarrhoea (28% vs. 23%), decreased appetite (21% vs. 14%), and rash (20% vs. 12%). Of these adverse events, Grades 3-4 events were diarrhoea (1.8% vs. 1.8%), decreased appetite (0.8% vs. 0.4%), and rash (0.8% vs. 0.0%).

Biliary Tract Carcinoma

In patients with BTC receiving KEYTRUDA plus chemotherapy (gemcitabine and cisplatin), adverse events occurring at a higher incidence (≥5%) compared to placebo plus chemotherapy were pyrexia (26% vs. 20%), rash (17% vs. 9%), pruritus (15% vs. 10%) and hypothyroidism (9% vs. 2.6%). Of these adverse events, Grades 3-4 events were pyrexia (2.3% vs. 0.9%), rash (0.6% vs. 0.4%), pruritus (0.0% vs. 0.0%) and hypothyroidism (0.2% vs.

0.0%).

Paediatric Patients

In KEYNOTE-051, 161 paediatric 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 tumours 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 paediatric 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 paediatric patients was similar to that seen in adults treated with pembrolizumab. The most common adverse reactions (reported in at least 20% of paediatric patients) were pyrexia, vomiting, headache, abdominal pain, anaemia, cough, and constipation.

Post-marketing Experience

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

Eye disorders: Vogt-Koyanagi-Harada syndrome
Immune system disorders: haemophagocytic lymphohistiocytosis
Musculoskeletal and connective tissue disorders: arthritis
Nervous system disorders: optic neuritis

4.9 Overdose

There is no information on overdosage with KEYTRUDA. The maximum tolerated dose of KEYTRUDA has not been determined. In clinical trials, patients received up to 10 mg/kg with a similar safety profile to that seen in patients receiving 2 mg/kg.

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

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies.

ATC code: L01XC18

Pharmacology and pharmacological actions

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 tumour 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 tumour cells. By inhibiting the PD-1 receptor from binding to its ligands, KEYTRUDA reactivates tumour-specific cytotoxic T lymphocytes in the tumour microenvironment and reactivates anti-tumour immunity.

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

Based on the modeling of dose/exposure relationships for efficacy and safety for pembrolizumab, there are no clinically significant differences 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.

Clinical efficacy and safety

Melanoma

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

The efficacy of KEYTRUDA was investigated in KEYNOTE-006, a multicentre, 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 randomised (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). Randomisation 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 tumour 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 tumour 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 tumours, 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 Tumours [RECIST 1.1]). Secondary efficacy outcome measures were overall response rate (ORR) and response duration. Table 11 summarises key efficacy measures.

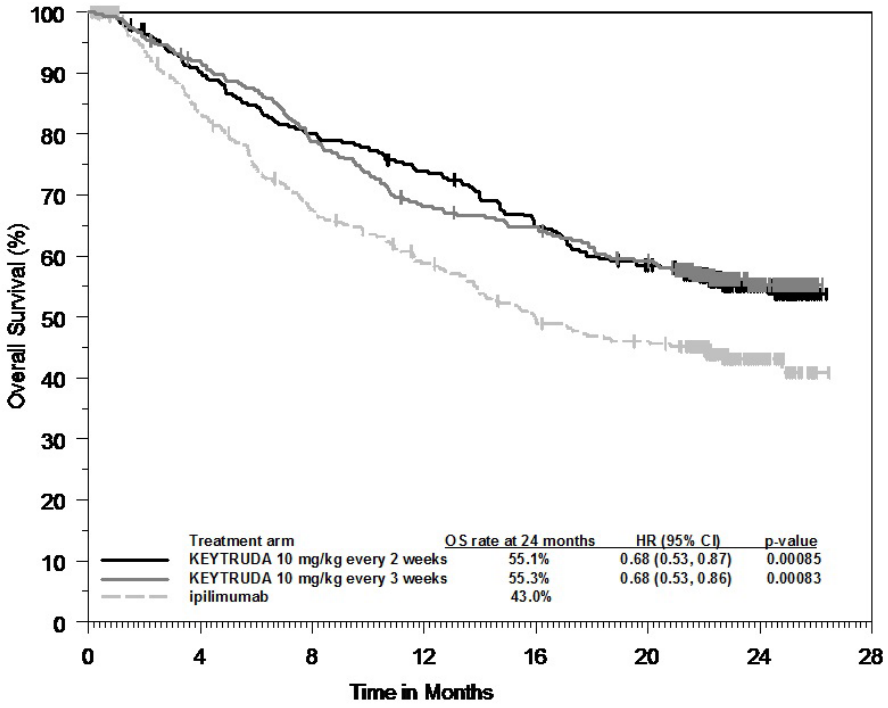
Table 11: Response to KEYTRUDA 10 mg/kg Every 2 or 3 Weeks in Patients with Ipilimumab-Naïve Advanced Melanoma in KEYNOTE-006

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 monthsÞ	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
Þ Based on Kaplan-Meier estimates
NA = not available

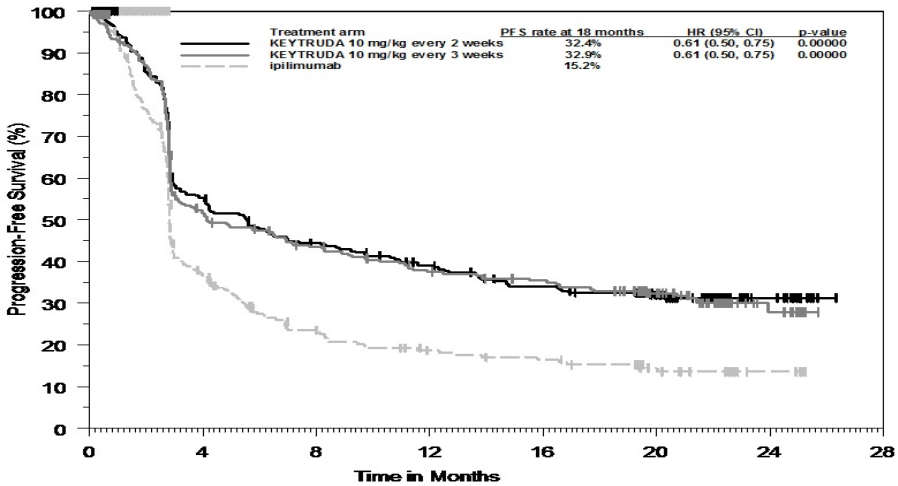
The final analysis was performed after all patients had at least 21 months of follow-up. The final OS analysis was performed after 383 patient events (119 for KEYTRUDA 10 mg/kg every 3 weeks, 122 for KEYTRUDA 10 mg/kg every 2 weeks and 142 for ipilimumab). The OS HRs vs. ipilimumab were 0.68 (95% CI: 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 multicentre, 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 randomised (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 tumour 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 tumour. 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 overall survival (OS). Secondary efficacy outcome measures were PFS as assessed by Investigator using RECIST 1.1, ORR and response duration. Table 12 summarises 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 randomised to the chemotherapy arm, 55% crossed over and subsequently received treatment with KEYTRUDA.

Table 12: 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

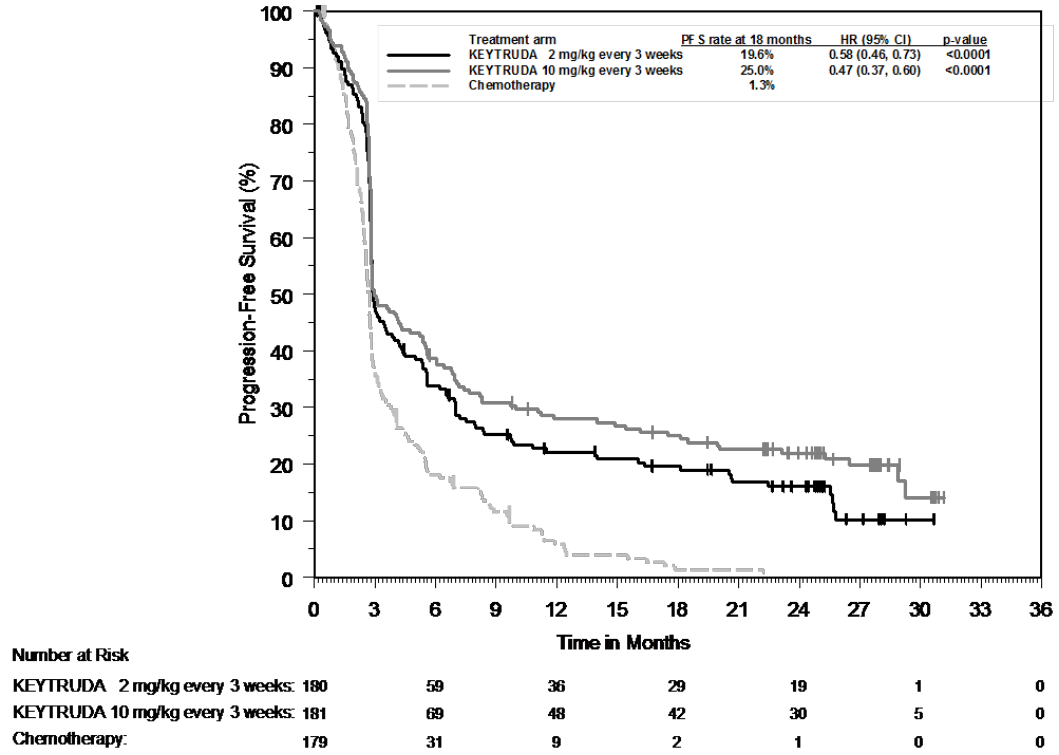
è Not statistically significant after adjustment for multiplicity

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)



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 randomised to receive KEYTRUDA at a dose of 2 mg/kg every 3 weeks or 10 mg/kg every 3 weeks. The study excluded patients with autoimmune disease; medical conditions that required immunosuppression; a history of severe immune-mediated adverse reactions with ipilimumab, defined as any Grade 4 toxicity requiring treatment with corticosteroids or Grade 3 toxicity requiring corticosteroid treatment (greater than 10 mg/day prednisone or equivalent dose) for greater than 12 weeks; medical conditions that required systemic corticosteroids or other immunosuppressive medication; a history of pneumonitis or interstitial lung disease; or any active infection requiring therapy, including HIV, HBV or HCV. Patients were treated with KEYTRUDA until disease progression that was symptomatic, was rapidly progressive, required urgent intervention, or occurred with a decline in performance status, at the discretion of the investigator, based on clinical judgment. Patients were also discontinued if disease progression was confirmed at 4 to 6 weeks with repeat imaging or unacceptable toxicity.

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% of patients had a history of brain metastases. Seventy-eight percent of patients had at least two and 35% of patients 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. Tumour response was assessed at 12-week intervals. Table 13 summarises 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 13: 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 multicentre, randomised, double-blind, placebo-controlled trial in patients with completely resected stage IIB or IIC melanoma. A total of 976 patients were randomised (1:1) to receive KEYTRUDA 200 mg or the paediatric (≥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. Randomisation 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 randomisation, every 6 months from years 2 to 4, and then once in year 5 from randomisation 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; 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 randomisation 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 randomised 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 summarised in Table 14. Results reported from the pre-specified interim analysis for DMFS with a median follow-up of 26.9 months are summarised in Table 14 and Figure 5.

Table 14: 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 randomised to pembrolizumab versus patients randomised 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 randomised to the pembrolizumab arm compared with placebo (HR 0.64; 95% CI: 0.50, 0.84). These efficacy results are summarised in Figure 4.

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

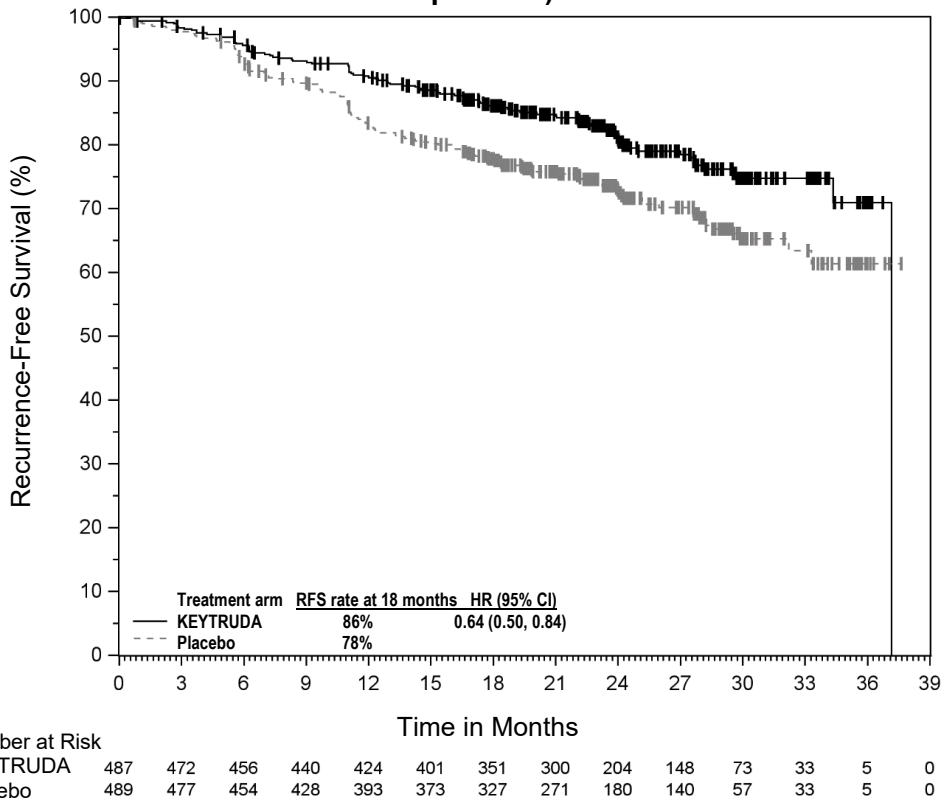
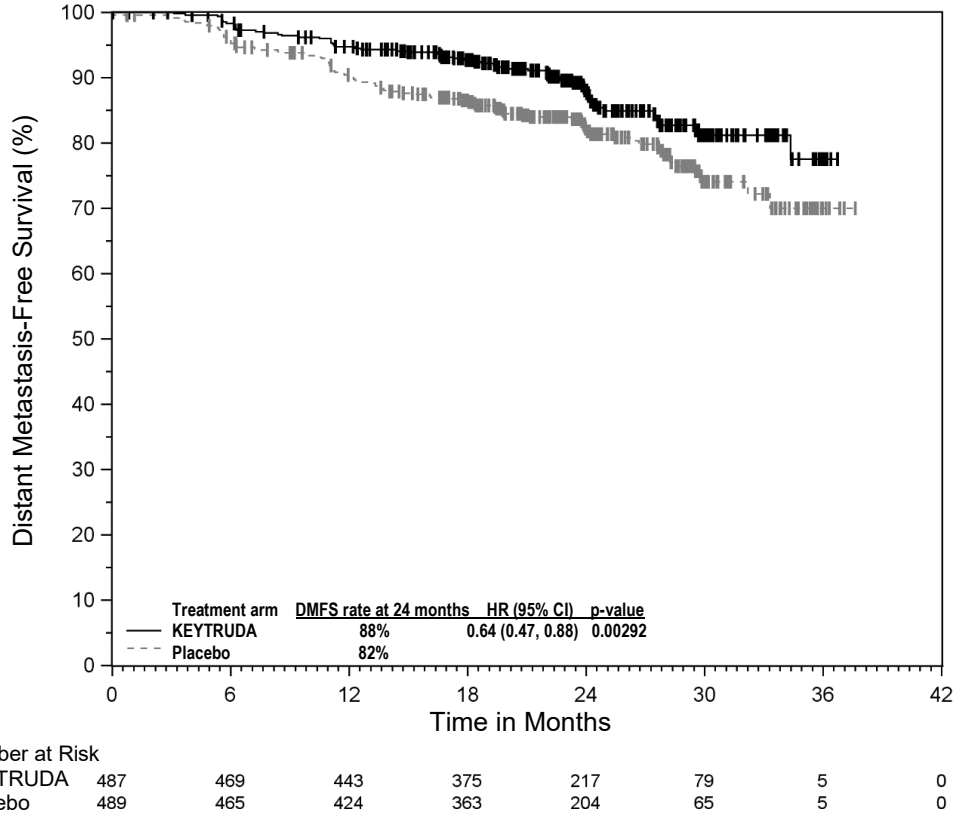


Figure 5: Kaplan-Meier Curve for Distant Metastasis-Free Survival in KEYNOTE-716 (Intent to Treat Population)



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 multicentre, randomised 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 randomised (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. Randomisation was stratified AJCC stage (IIIA vs. IIIB vs. IIIC 1-3 positive lymph nodes vs. IIIC ≥4 positive lymph nodes) and geographic region (North America, European countries Australia and other countries as designated). Patients must have undergone lymph node dissection and if indicated, radiotherapy within 13 weeks prior to starting treatment. 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 tumour 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 tumours. 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 randomised 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 summarised in Table 15 and Figure 6. DMFS efficacy results with a median follow-up time of 45.5 months are summarised in Table 15 and Figure 7.

Table 15: 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* (98.4% 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 tumours, 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 tumours were PD-L1 negative, BRAF mutation positive, or BRAF mutation negative. The RFS benefit for KEYTRUDA compared to placebo was observed regardless of tumour 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 tumours. The RFS HR was 0.52 (95% CI: 0.40, 0.66) for patients with BRAF mutation positive tumours, and 0.67 (95% CI: 0.51, 0.88) for patients with BRAF mutation negative tumours.

For patients with PD-L1 positive tumours, 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 tumours were PD-L1 negative, BRAF mutation positive, or BRAF mutation negative. The DMFS benefit for KEYTRUDA compared to placebo was observed regardless of tumours 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 tumours. The DMFS HR was 0.51 (95% CI: 0.39, 0.68) for patients with BRAF mutation positive tumours, and 0.73 (95% CI: 0.55, 0.98) for patients with BRAF mutation negative tumours.

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

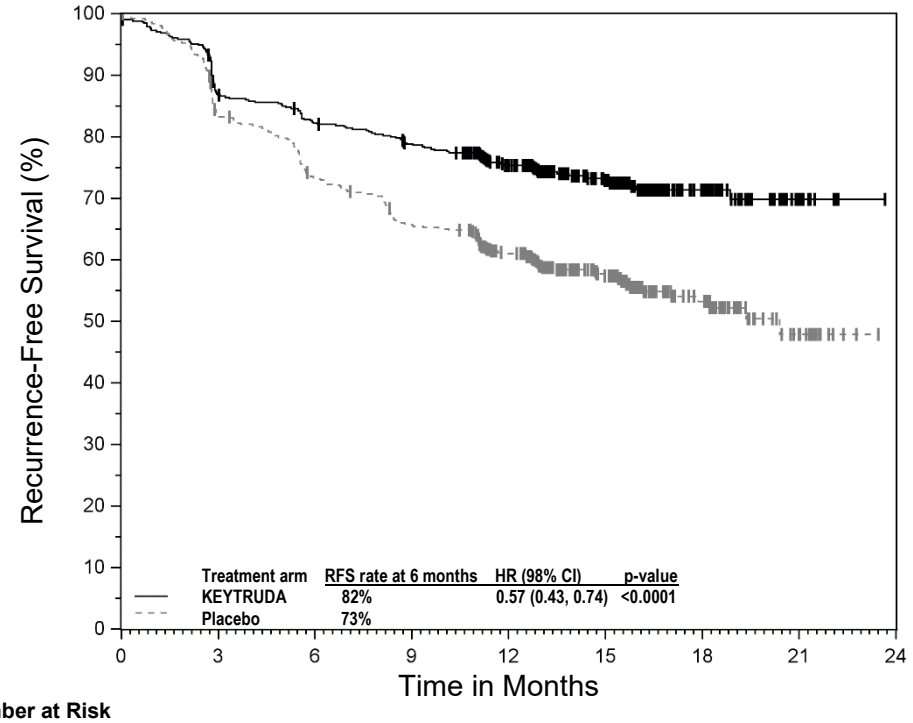
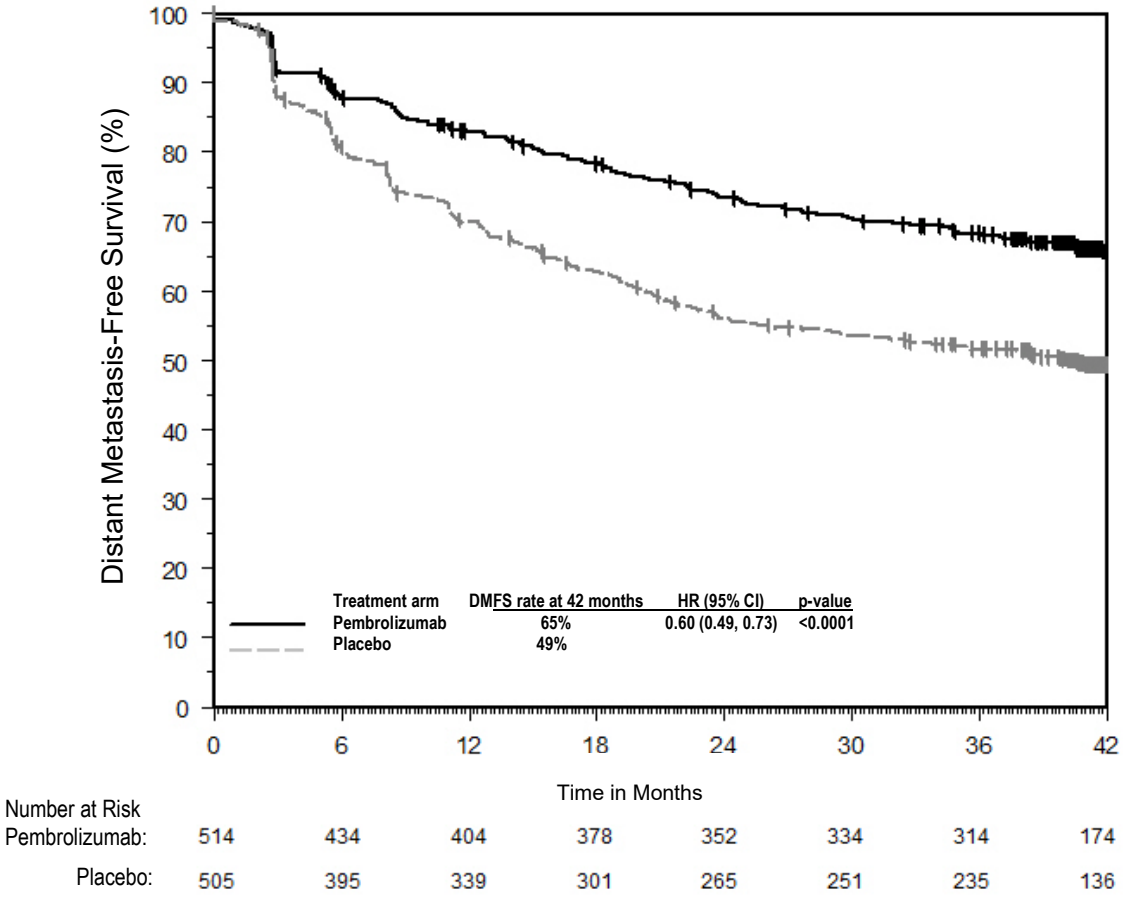


Figure 7: Kaplan-Meier Curve for Distant Metastasis-Free Survival in KEYNOTE-054 (Intent to Treat Population)



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 multicentre, randomised, 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 tumour 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 randomised (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 tumour 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 16 summarises key efficacy measures.

Table 16: Response to KEYTRUDA, Pemetrexed, and Platinum Chemotherapy in Patients with Non-Squamous NSCLC in KEYNOTE-189

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

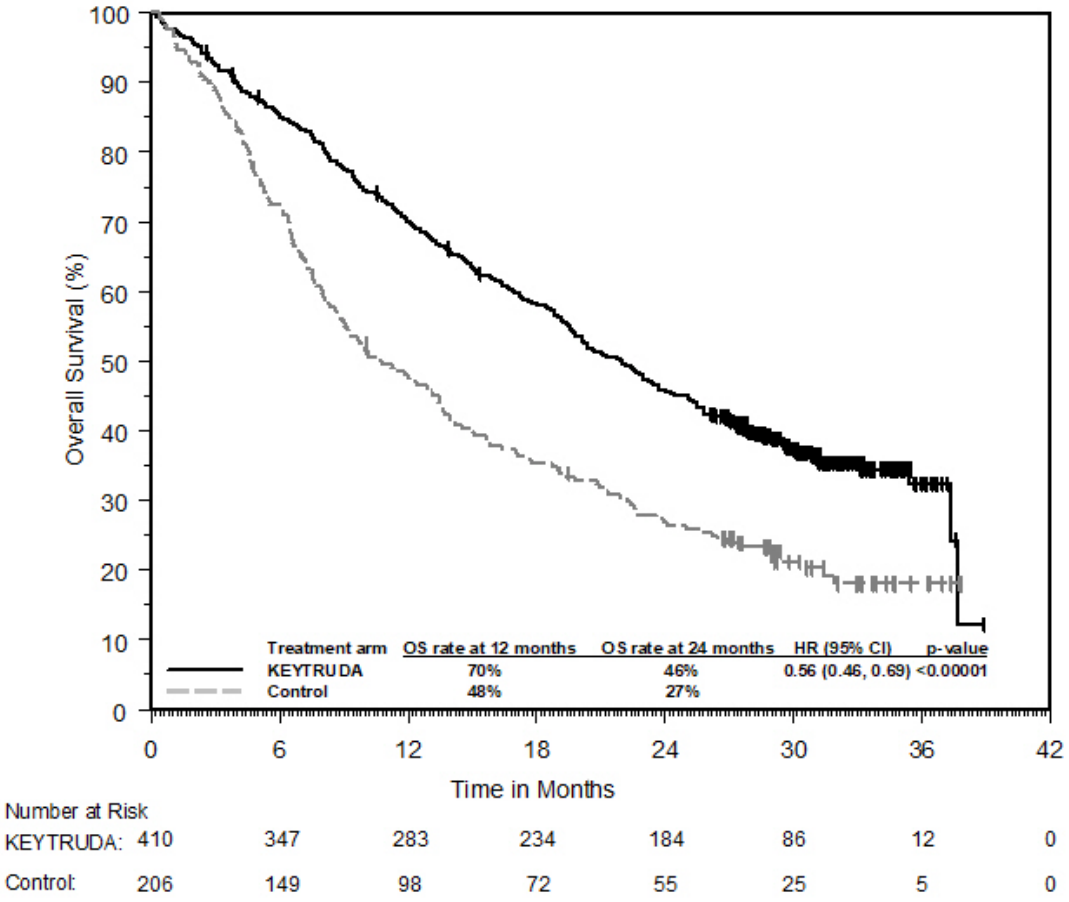
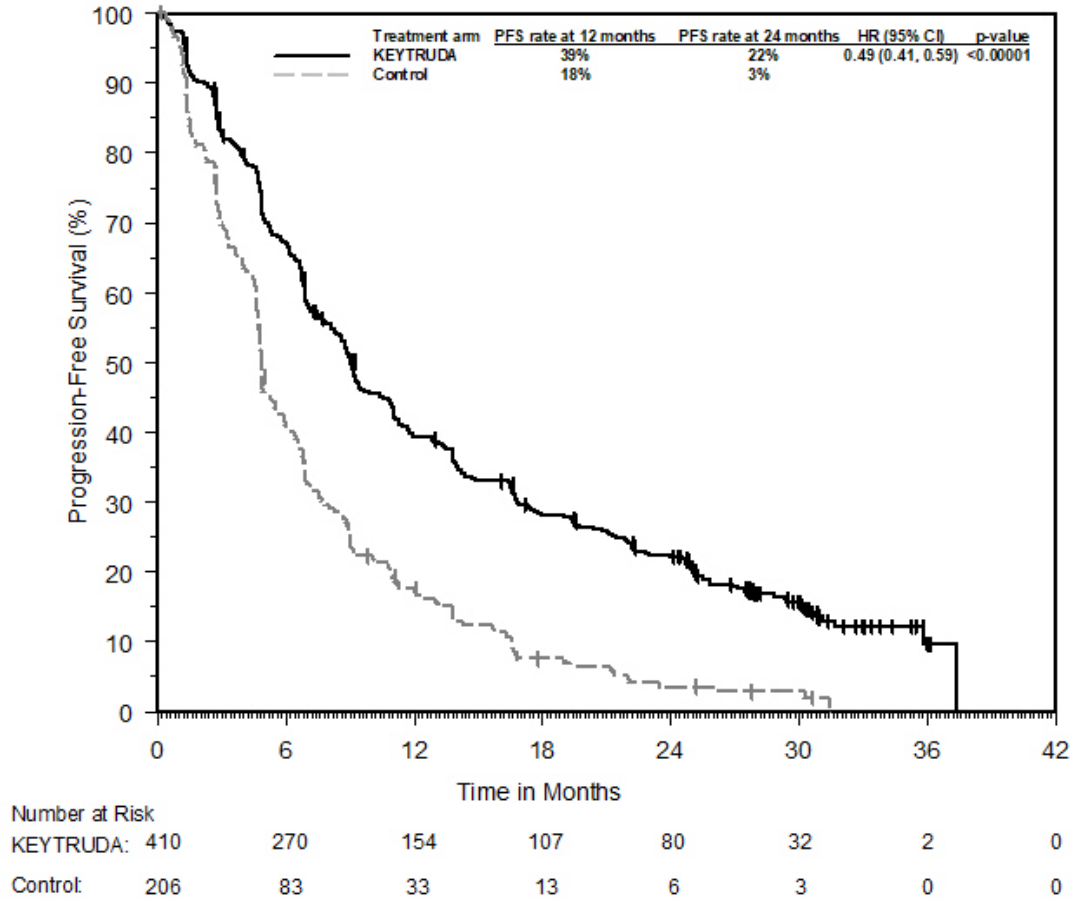


Figure 9: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-189 (Intent to Treat Population)



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, dyspnoea 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 randomised, double-blind, multicentre, placebo-controlled study. The key eligibility criteria for this study were metastatic squamous NSCLC, regardless of tumour 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. Randomisation was stratified by tumour 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 randomised (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 tumour 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 randomised: 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 tumour 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 randomised to KEYTRUDA in combination with carboplatin and either paclitaxel or nab-paclitaxel compared with patients randomised to placebo with carboplatin and either paclitaxel or nab-paclitaxel (see Table 17)

Table 17: 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

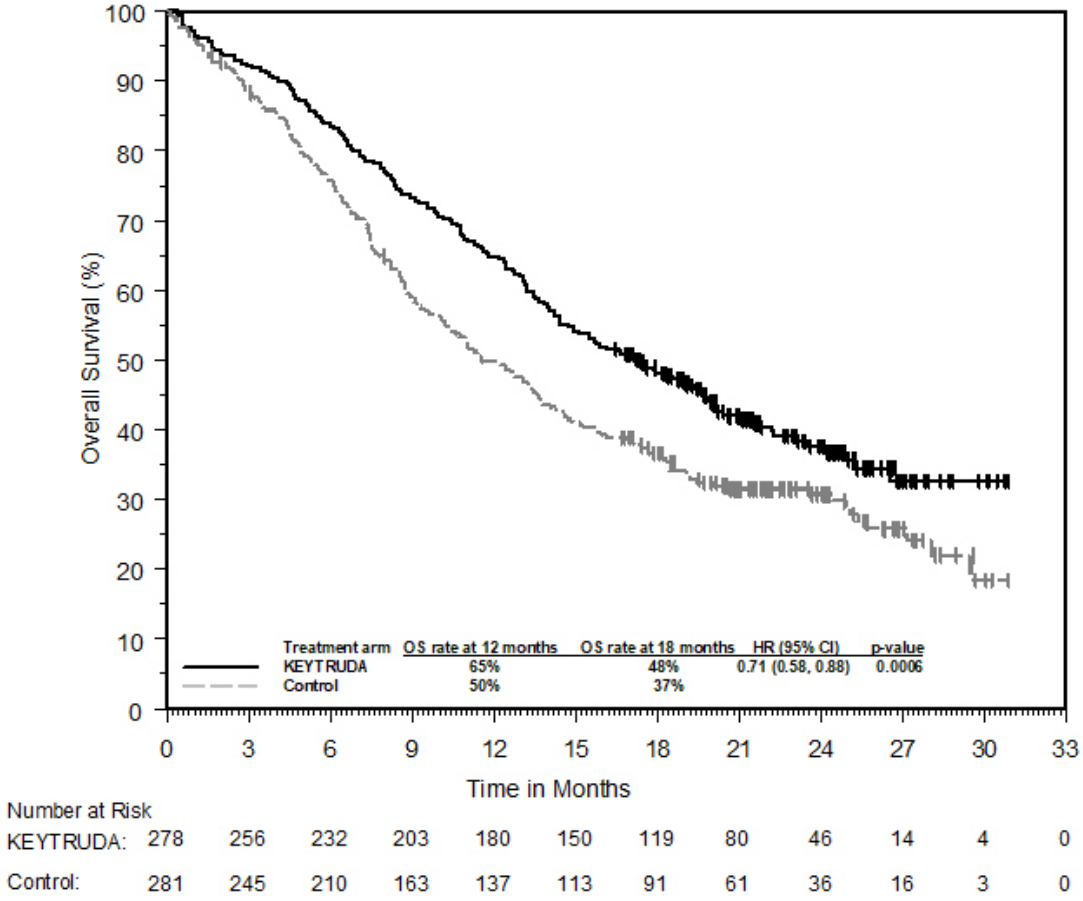
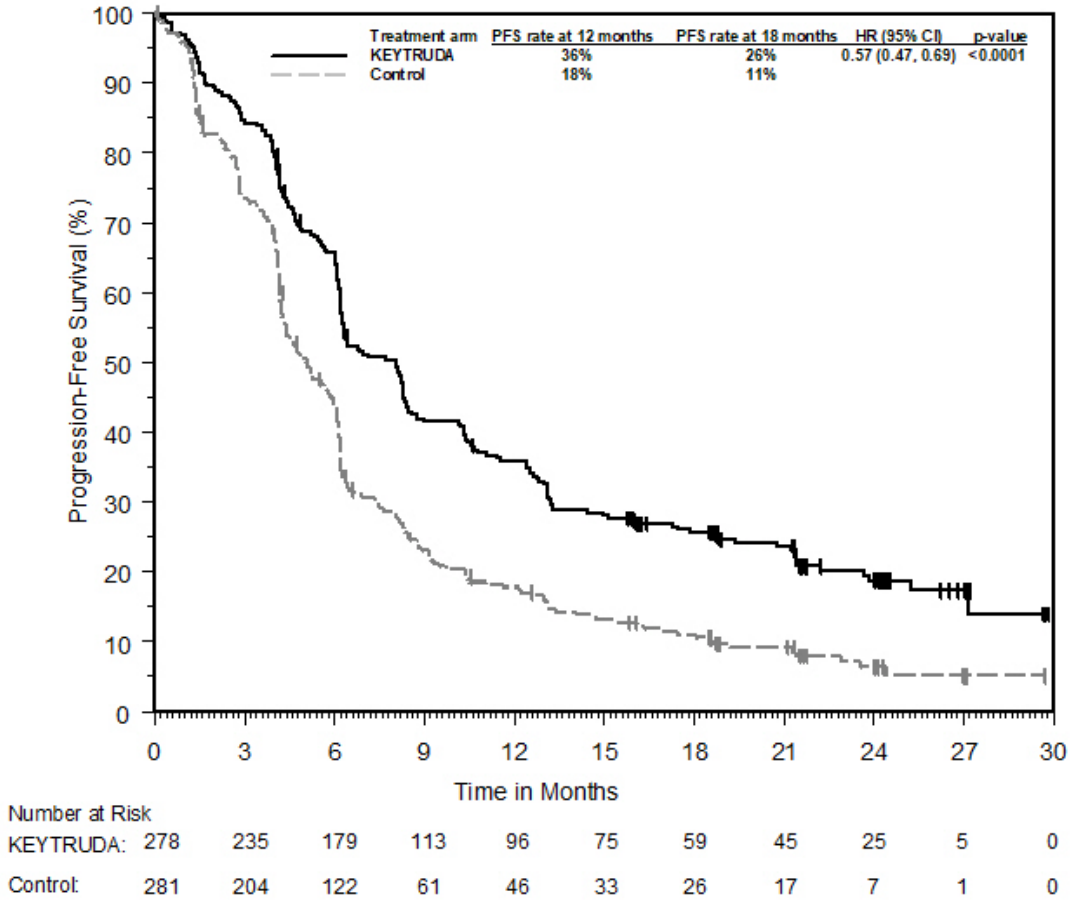


Figure 11: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-407



KEYNOTE-042: Controlled trial of NSCLC patients naïve to treatment

The efficacy of KEYTRUDA was investigated in KEYNOTE-042, a multicentre, randomised, controlled trial conducted in 1274 patients with stage III NSCLC who were not candidates for surgical resection or definitive chemoradiation, or patients with metastatic NSCLC. Only patients whose tumours expressed PD-L1 (TPS ≥1%) by an immunohistochemistry assay using the PD-L1 IHC 22C3 pharmDx™ kit and who had not received prior systemic treatment for metastatic NSCLC were eligible. Patients with EGFR or ALK genomic tumour 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 randomised (1:1) to receive KEYTRUDA 200 mg every 3 weeks (n=637) or investigator's choice platinum-containing chemotherapy (n=637; including pemetrexed+carboplatin or paclitaxel+carboplatin. Patients with non-squamous NSCLC 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 tumour status was performed every 9 weeks for the first 45 weeks, and every 12 weeks thereafter.

Among the 1274 patients in KEYNOTE-042, baseline characteristics were: median age 63 years (45% age 65 or older); 71% male; 64% White and 30% Asian: 19% Hispanic or Latino; and 31% and 69% with an ECOG performance status 0 and 1, respectively. Disease characteristics were squamous (39%) and non-squamous (61%); M0 (13%), M1 (87%); and treated brain metastases (6%). Forty-seven percent of patients had TPS ≥50%, and 53% had TPS 1 to 49%.

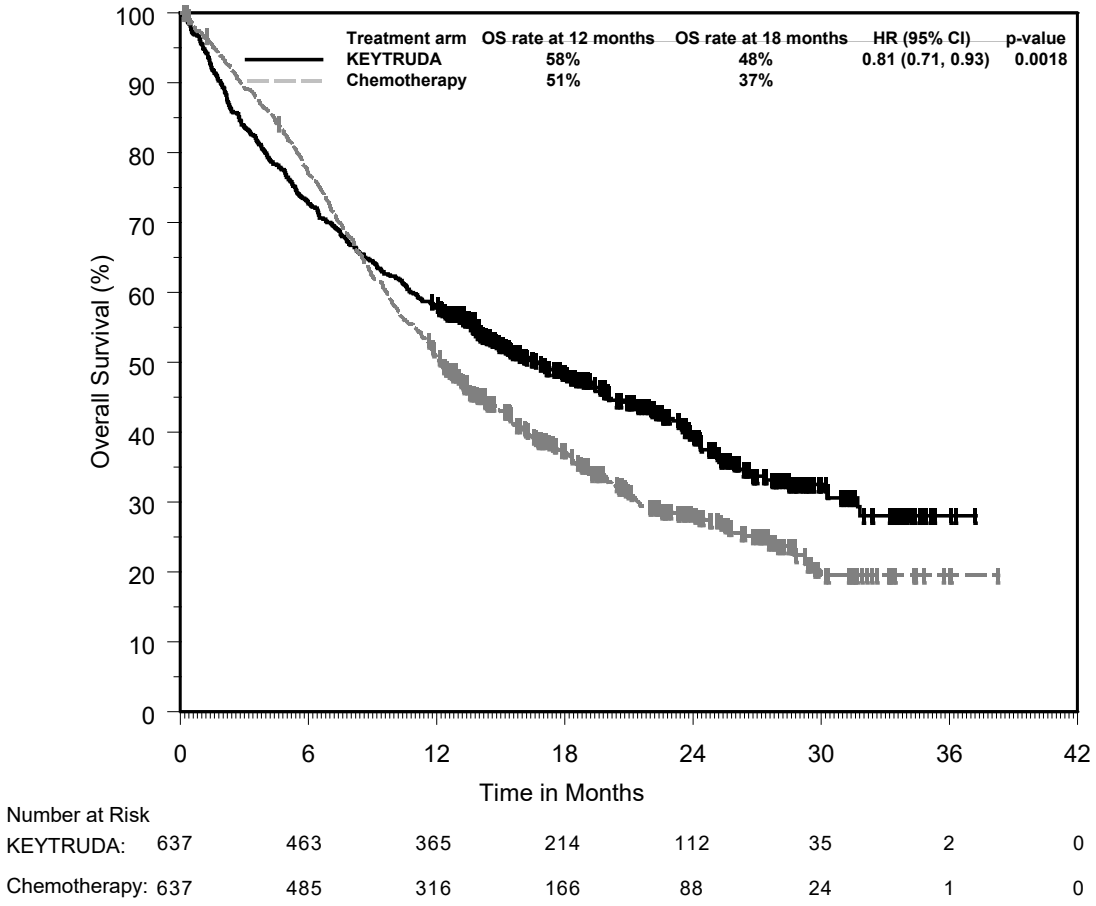
The primary efficacy outcome measure was OS. Secondary efficacy outcome measures were PFS and ORR as assessed by blinded independent central review (BICR) using RECIST 1.1. Table 18 summarises key efficacy measures for the entire ITT population (TPS ≥ 1%).

Table 18: Efficacy Results (PD-L1 TPS ≥ 1%) in KEYNOTE-042

Endpoint	**KEYTRUDA 200 mg every 3 weeks (n=637)**	**Chemotherapy (n=637)**
OS		
Number (%) of patients with event	371 (58%)	438 (69%)
Hazard ratio* (95% CI)	0.81 (0.71, 0.93)	
p-Value†	0.002	
Median in months (95% CI)	16.7 (13.9, 19.7)	12.1 (11.3, 13.3)
PFS‡		
Number (%) of patients with event	507 (80%)	506 (79%)
Hazard ratio*,§ (95% CI)	1.07 (0.94, 1.21)	
Median in months (95% CI)	5.4 (4.3, 6.2)	6.5 (6.3, 7.0)
Overall Response Rate‡		
ORR %§ (95% CI)	27% (24, 31)	27% (23, 30)
Complete response %	1%	1%
Partial response %	27%	26%
Response Duration‡,¶		
Median in months (range)	20.2 (2.1+, 31.2+)	8.3 (1.8+, 28.1)
% with duration ≥ 18 months	53%	30%

* 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
§ Not evaluated for statistical significance as a result of the sequential testing procedure for the secondary endpoints
¶ Based on patients with a best overall response as confirmed complete or partial response; based on Kaplan-Meier estimates

Figure 12: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-042 (TPS ≥ 1%, Intent to Treat Population



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

The efficacy of KEYTRUDA in previously untreated patients with NSCLC was also investigated in KEYNOTE-024, a multicentre, randomised, controlled trial. The study design was similar to that of KEYNOTE-042, except that only patients with metastatic NSCLC whose tumours expressed PD-L1 with tumour proportion score (TPS) of 50% or greater by an immunohistochemistry assay using the PD-L1 IHC 22C3 pharmDx™ Kit were eligible. Patients were randomised (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. Patients with non-squamous NSCLC could receive pemetrexed maintenance). Patients on chemotherapy who experienced independently-verified progression of disease were able to crossover and receive KEYTRUDA. Assessment of tumour status was performed every 9 weeks.

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 19 summarises key efficacy measures for the entire ITT population.

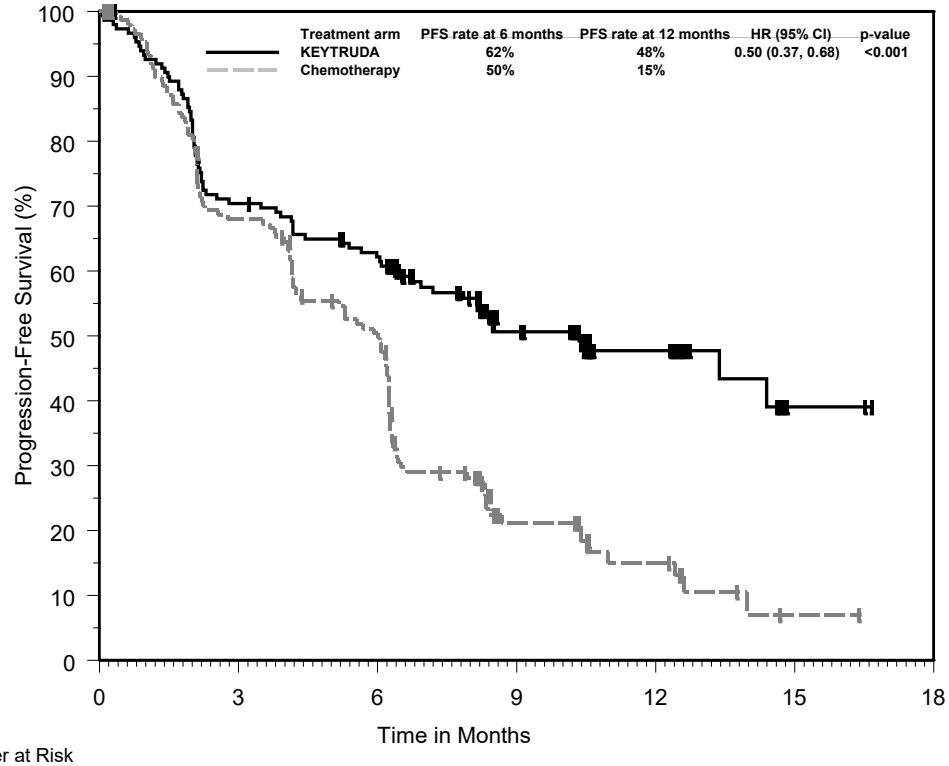
Table 19: Efficacy Results in KEYNOTE-024

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 14.

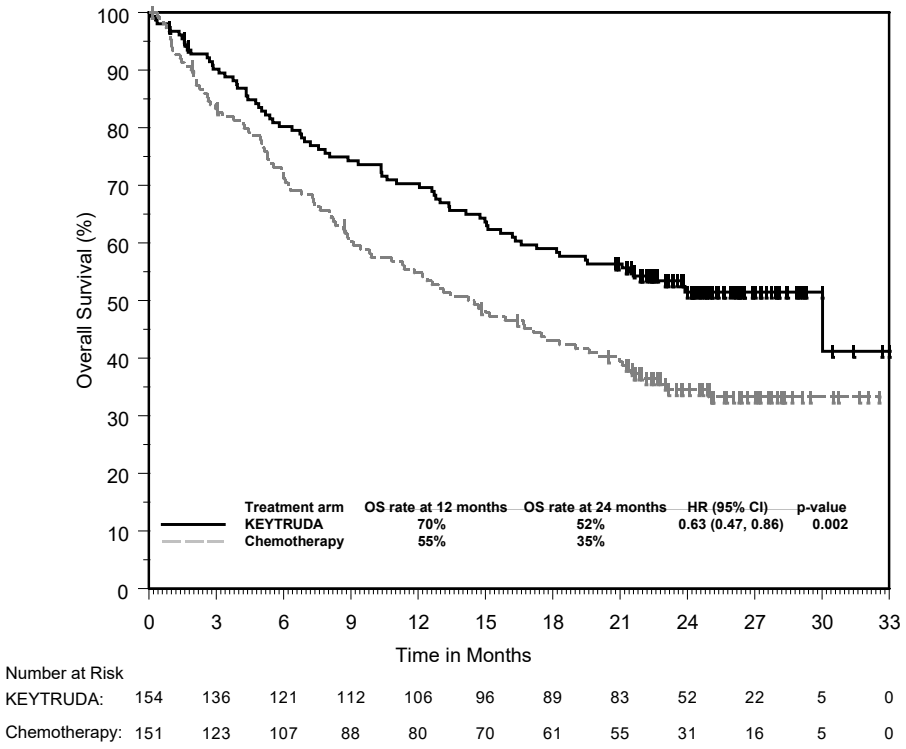
Figure 13: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-024 (Intent to Treat Population)



Number at Risk

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

Figure 14: 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, dyspnoea, 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 multicentre, randomised, 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 randomised (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 unacceptable toxicity or disease progression, up to a maximum of 35 treatments (24 months). Assessment of tumour 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 20 summarises 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 15 and 16.

Table 20: Response to KEYTRUDA 2 or 10 mg/kg Every 3 Weeks in Previously Treated Patients with NSCLC in KEYNOTE-010

Endpoint	KEYTRUDA 2 mg/kg every 3 weeks	KEYTRUDA 10 mg/kg every 3 weeks	Docetaxel 75 mg/m^2 every 3 weeks
TPS ≥ 1%			
Number of patients	344	346	343
OS			
Number (%) of patients with event	172 (50%)	156 (45%)	193 (56%)
Hazard ratio* (95% CI)	0.71 (0.58, 0.88)	0.61 (0.49, 0.75)	---
p-Value†	<0.001	<0.001	---
Median in months (95% CI)	10.4 (9.4, 11.9)	12.7 (10.0, 17.3)	8.5 (7.5, 9.8)
PFS‡			
Number (%) of patients with event	266 (77%)	255 (74%)	257 (75%)
Hazard ratio* (95% CI)	0.88 (0.73, 1.04)	0.79 (0.66, 0.94)	---
p-Value†	0.068	0.005	---
Median in months (95% CI)	3.9 (3.1, 4.1)	4.0 (2.6, 4.3)	4.0 (3.1, 4.2)
Overall Response Rate‡			
ORR %§ (95% CI)	18% (14, 23)	18% (15, 23)	9% (7, 13)
Response Duration‡,¶,#			
Median in months (range)	Not reached (0.7+, 20.1+)	Not reached (2.1+, 17.8+)	6.2 (1.4+, 8.8+)
% ongoing	73%	72%	34%
TPS ≥ 50%			
Number of patients	139	151	152
OS			
Number (%) of patients with event	58 (42%)	60 (40%)	86 (57%)
Hazard ratio* (95% CI)	0.54 (0.38, 0.77)	0.50 (0.36, 0.70)	---
p-Value†	<0.001	<0.001	---
Median in months (95% CI)	14.9 (10.4, NA)	17.3 (11.8, NA)	8.2 (6.4, 10.7)
PFS‡			
Number (%) of patients with event	89 (64%)	97 (64%)	118 (78%)
Hazard ratio* (95% CI)	0.58 (0.43, 0.77)	0.59 (0.45, 0.78)	---
p-Value†	<0.001	<0.001	---
Median in months (95% CI)	5.2 (4.0, 6.5)	5.2 (4.1, 8.1)	4.1 (3.6, 4.3)
Overall Response Rate‡			
ORR %§ (95% CI)	30% (23, 39)	29% (22, 37)	8% (4, 13)
Response Duration‡,¶,Þ			
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

‡ Assessed by BICR using RECIST 1.1

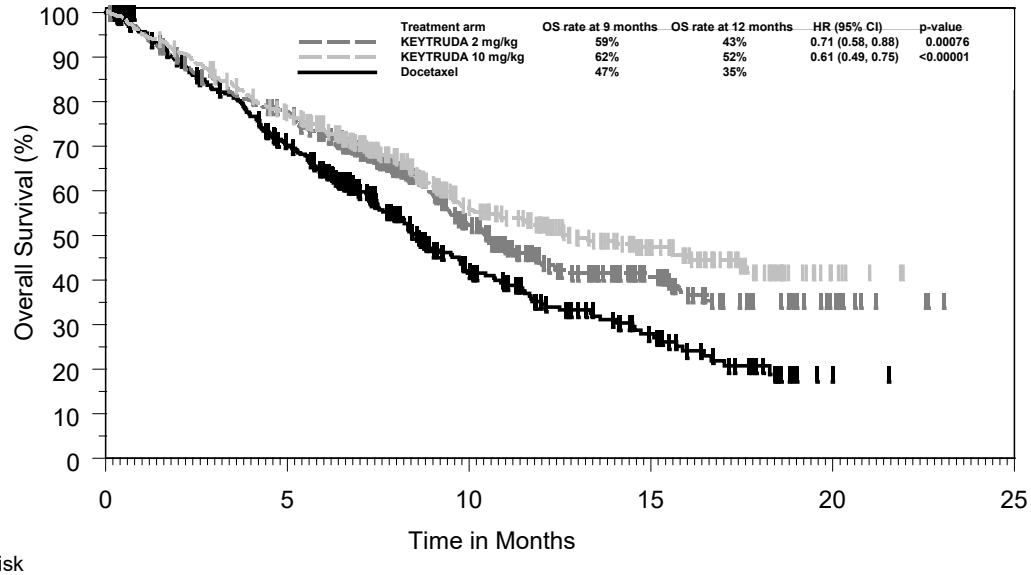
§ All responses were partial responses

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

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

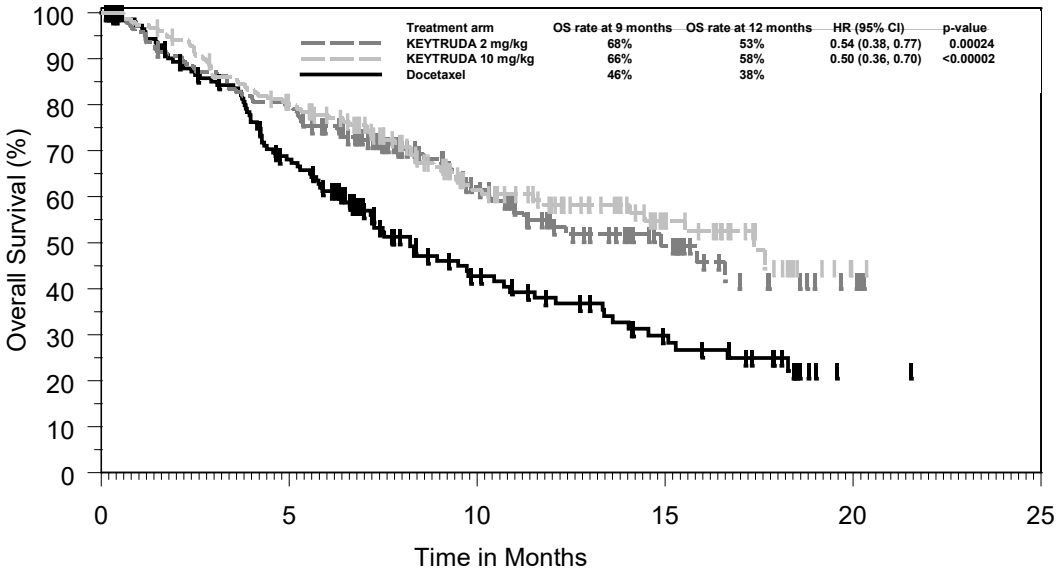
Þ Includes 22, 24, and 1 patients with ongoing responses of 6 months or longer in the KEYTRUDA 2 mg/kg, KEYTRUDA 10 mg/kg, and docetaxel groups respectively

Figure 15: 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 16: 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 tumour 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 multicentre, open-label, randomised, 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 tumour 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 randomised to receive 10 mg/kg of KEYTRUDA every 2 (n=69) or 3 (n=87) weeks until disease progression or unacceptable toxicity. Assessment of tumour 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 randomised patients with tumour 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 summarised in Table 21.

Table 21: 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 22 and Figure 17. 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 22.

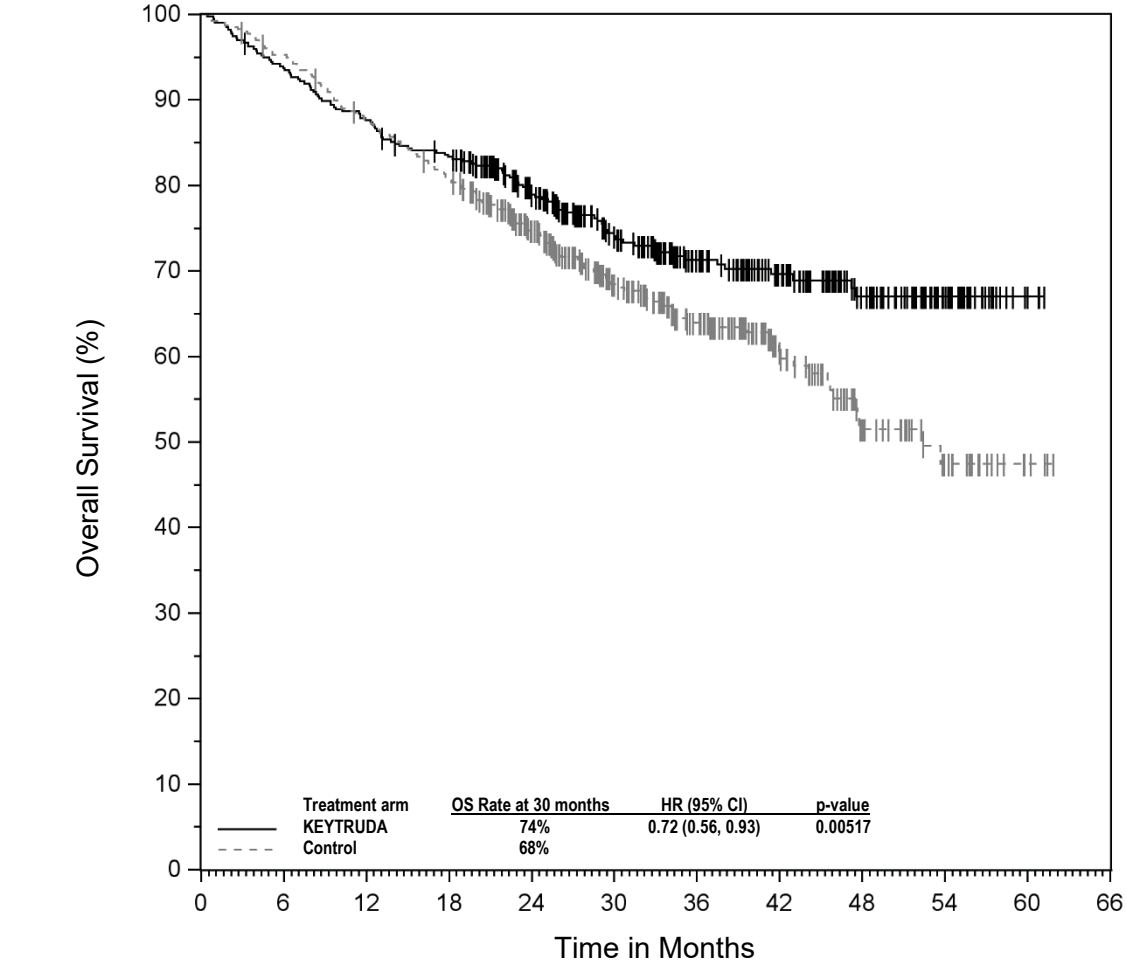
Table 22: Efficacy Results in KEYNOTE-671

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 18**.**

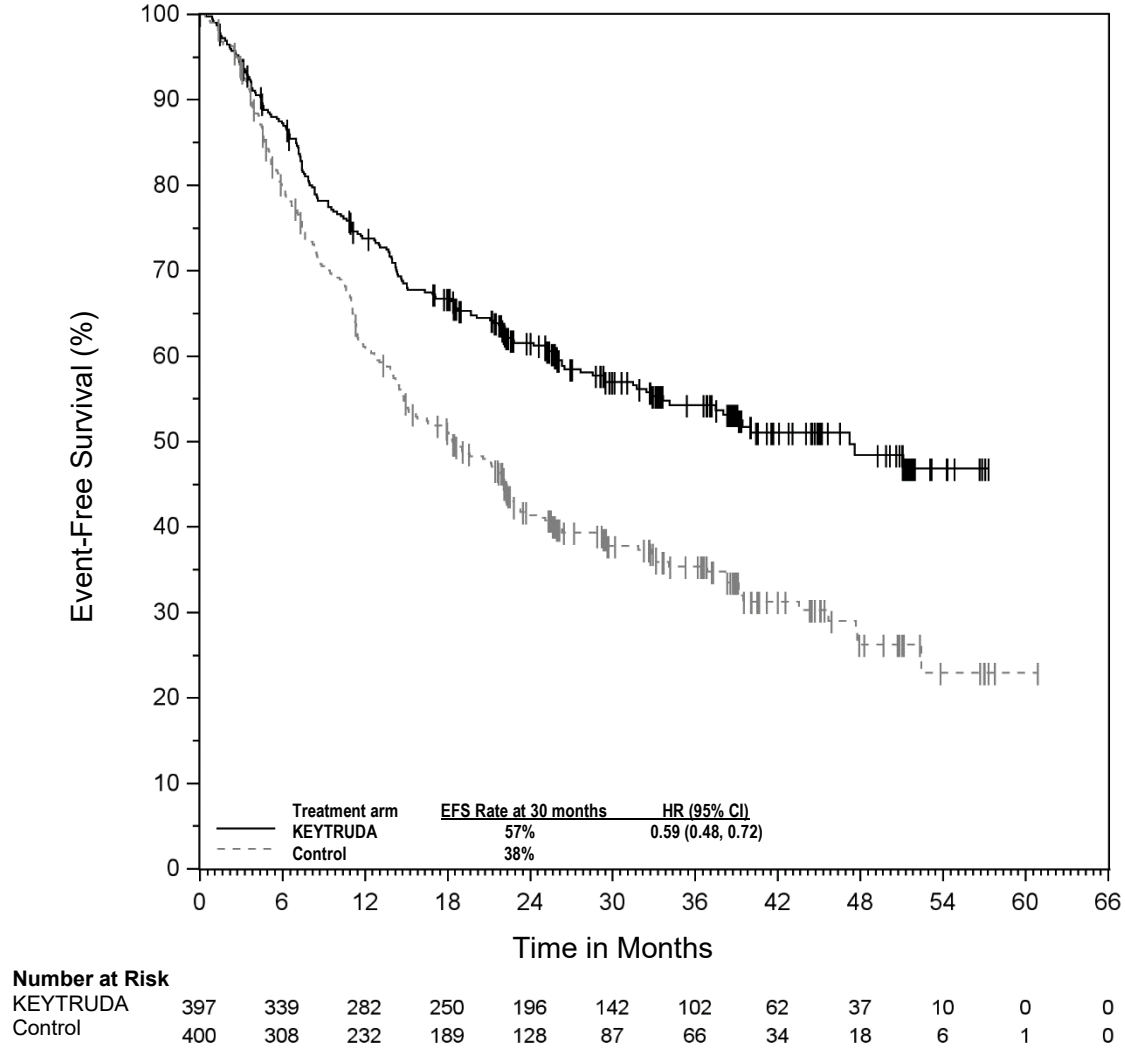
Figure 17: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-671 (Intent to Treat Population)



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 18: 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 multicentre, randomised, 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 tumour 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. Randomisation 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 randomised (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.

Among the 1177 patients in KEYNOTE-091 (590 patients in the KEYTRUDA arm and 587 in the placebo arm), baseline characteristics were: median age of 65 years (range: 31 to 87), 53% age 65 or older; 68% male; and 77% White, 18% Asian. Sixty-one percent and 39% had ECOG performance of 0 or 1, respectively. Fourteen percent had stage IB (T2a ≥4 cm), 57% had stage II, and 29% had stage IIIA disease. Forty percent had tumour PD-L1 expression TPS <1% [negative], 32% had TPS 1-49%, 28% had TPS ≥50%, and 86% received adjuvant chemotherapy. Fifty-one percent were from Western Europe.

The primary efficacy outcome measures were investigator-assessed disease-free survival (DFS) in the overall population and in the population with tumour PD-L1 expression TPS ≥50%, where DFS was defined as the time between the date of randomisation and the date of first recurrence (local/regional recurrence, distant metastasis), a second malignancy, or death, whichever occurred first. Secondary efficacy outcome measures were investigator-assessed DFS in the population with tumour PD-L1 expression TPS ≥1%, and OS in the overall population and in the populations with tumour PD-L1 expression TPS ≥50% and TPS ≥1%.

The trial demonstrated a statistically significant improvement in DFS in the overall population at a pre-specified interim analysis for patients randomised to the KEYTRUDA arm compared to patients randomised to the placebo arm. At the time of analysis, OS results were not mature (18% with events in the overall population). The median follow-up time was 32.4 months (range: 0.6 to 68 months). Efficacy results are summarised in Table 23 and Figure 19.

Table 23: Efficacy Results in KEYNOTE-091

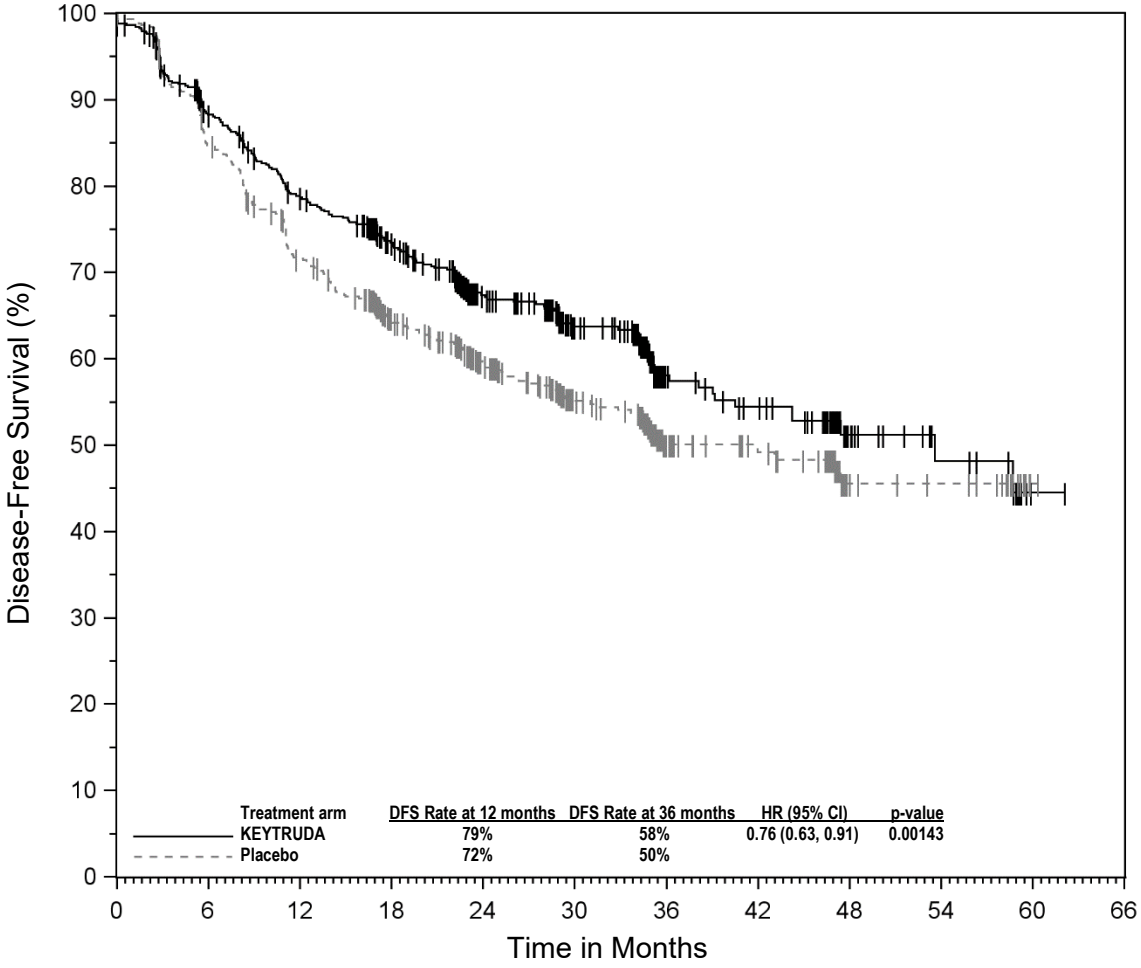
Endpoint	**KEYTRUDA 200 mg every 3 weeks n=590**	**Placebo n=587**
DFS (Overall)		
Number (%) of patients with event	212 (36%)	260 (44%)
Hazard ratio* (95% CI)	0.76 (0.63, 0.91)	
p-Value†	0.0014	
Median in months (95% CI)	53.6 (39.2, NR)	42.0 (31.3, NR)

* Based on the multivariate Cox regression model

† Based on the permutation test with multivariate Cox regression model

NR = not reached

Figure 19: Kaplan-Meier Curve for Disease-Free Survival by Treatment Arm in KEYNOTE-091 (Overall Intent to Treat Population)



Number at Risk

KEYTRUDA	590	493	434	358	264	185	82	70	28	16	1	0
Placebo	587	493	409	326	241	160	72	57	22	18	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, randomised, 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. Randomisation was stratified by histological subtype (epithelioid vs. non-epithelioid). Patients were randomised (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 tumour 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.

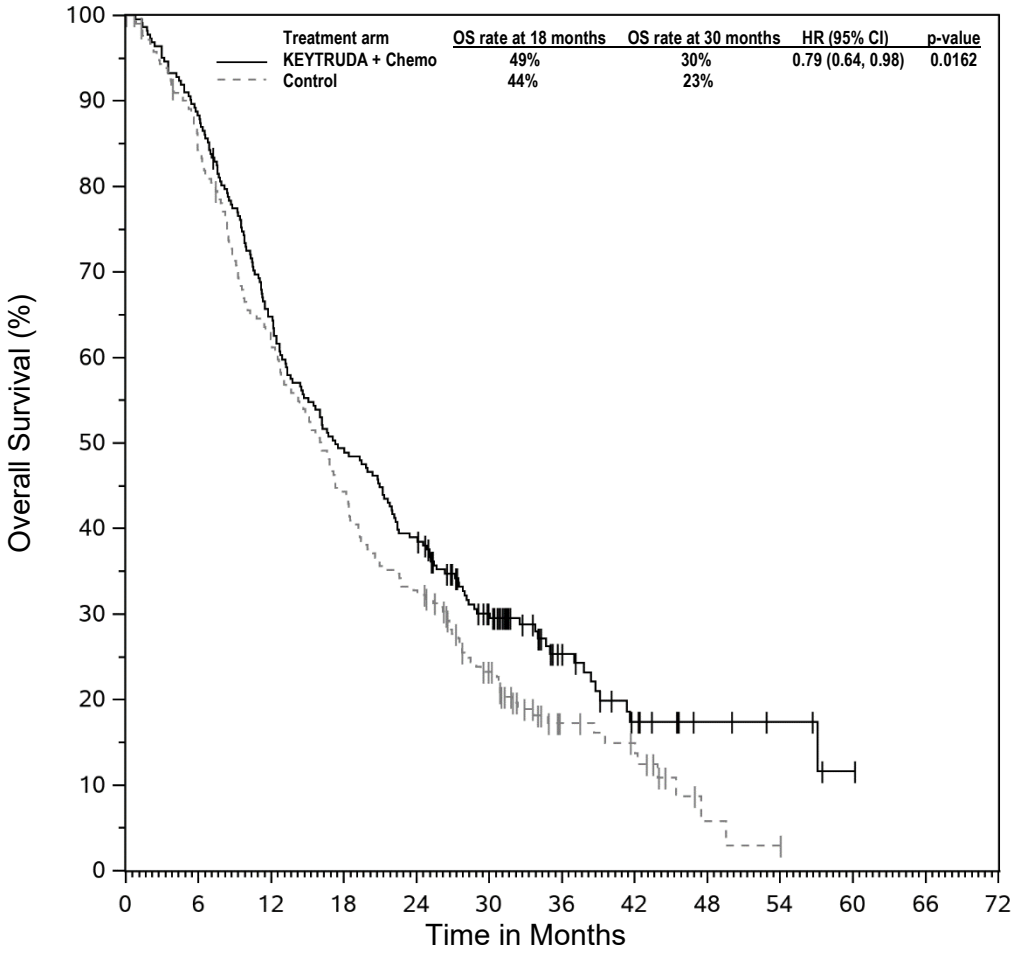
The primary efficacy outcome measure was OS. Additional efficacy outcome measures were PFS, ORR, and DoR, as assessed by BICR using mRECIST, and health related quality of life as assessed using EORTC QLQ-C30 and EORTC QLQ-LC13. The trial demonstrated a statistically significant improvement in OS, PFS, and ORR in patients randomised to KEYTRUDA in combination with chemotherapy compared with patients randomised to chemotherapy alone. The median follow-up time was 17 months (range: 0.8 – 60.3 months). Table 24 and Referenced in Figure 20 to Figure 21 summarise key efficacy measures for KEYNOTE-483.

Table 24: 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)
Overall 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 monthsβ	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 & 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

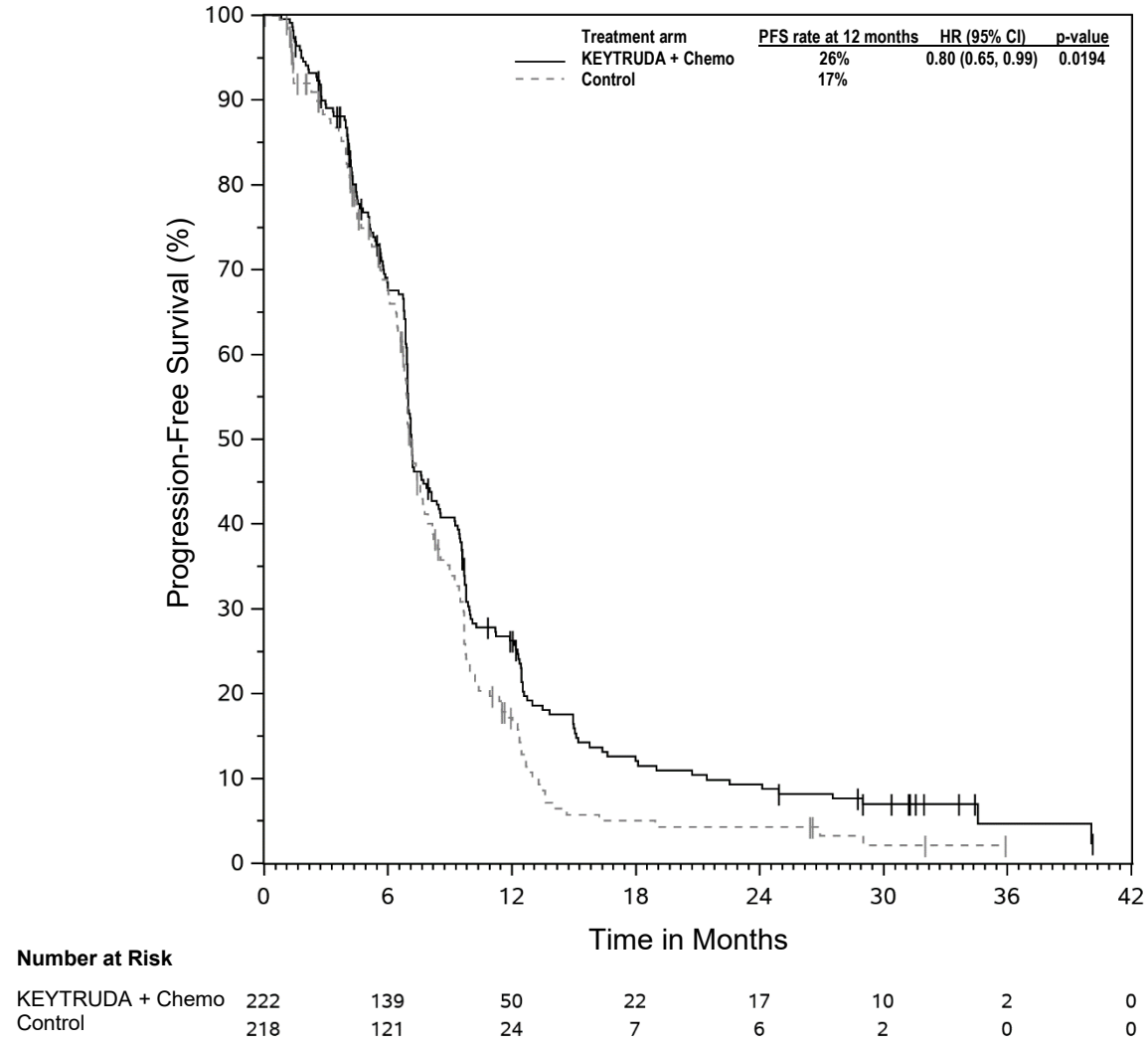
Figure 20: Kaplan-Meier Curve for Overall Survival in KEYNOTE-483



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



Health-related QoL as evaluated by the EORTC QLQ-C30 (GHS/QoL, physical functioning, and dyspnoea) 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 randomised, multicentre, 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. Randomisation was stratified by primary tumour site (oropharynx/oral cavity vs. larynx vs. hypopharynx), tumour stage (III vs. IVA) and PD-L1 status (TPS ≥ 50% vs. TPS<50%) based on the PD-L1 IHC 22C3 pharmDx™ kit.

Patients were randomised (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/m2 every 3 weeks for patients with high-risk pathological features after surgery or radiation alone for patients without high-risk pathological features after 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 tumour status was performed prior to surgery at Week 6 in the neoadjuvant phase. Following the start of the adjuvant phase, assessment of tumour 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. Eighty-eight percent of patients had surgery in both Arm A and Arm B. In Arm A, 35% of patients received KEYTRUDA and cisplatin plus radiation, 57% received KEYTRUDA with radiation alone, 3% of patients received cisplatin alone plus radiation, 5% of patients received radiation alone and one patient (0.4%) received KEYTRUDA. In Arm B, 52% of patients received cisplatin plus radiation, and 48% received radiation alone.

The main efficacy outcome measure was event-free survival (EFS) by BICR defined as the time from randomisation 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; 43% had ECOG PS of 1, and 79% were former/current smokers. Four percent of patients' tumours were HPV-positive, and 26% had Stage III disease, 74% had Stage IVA disease. Ninety-six percent of patients' tumours had PD-L1 expression of CPS ≥1 and 65% had CPS ≥10.

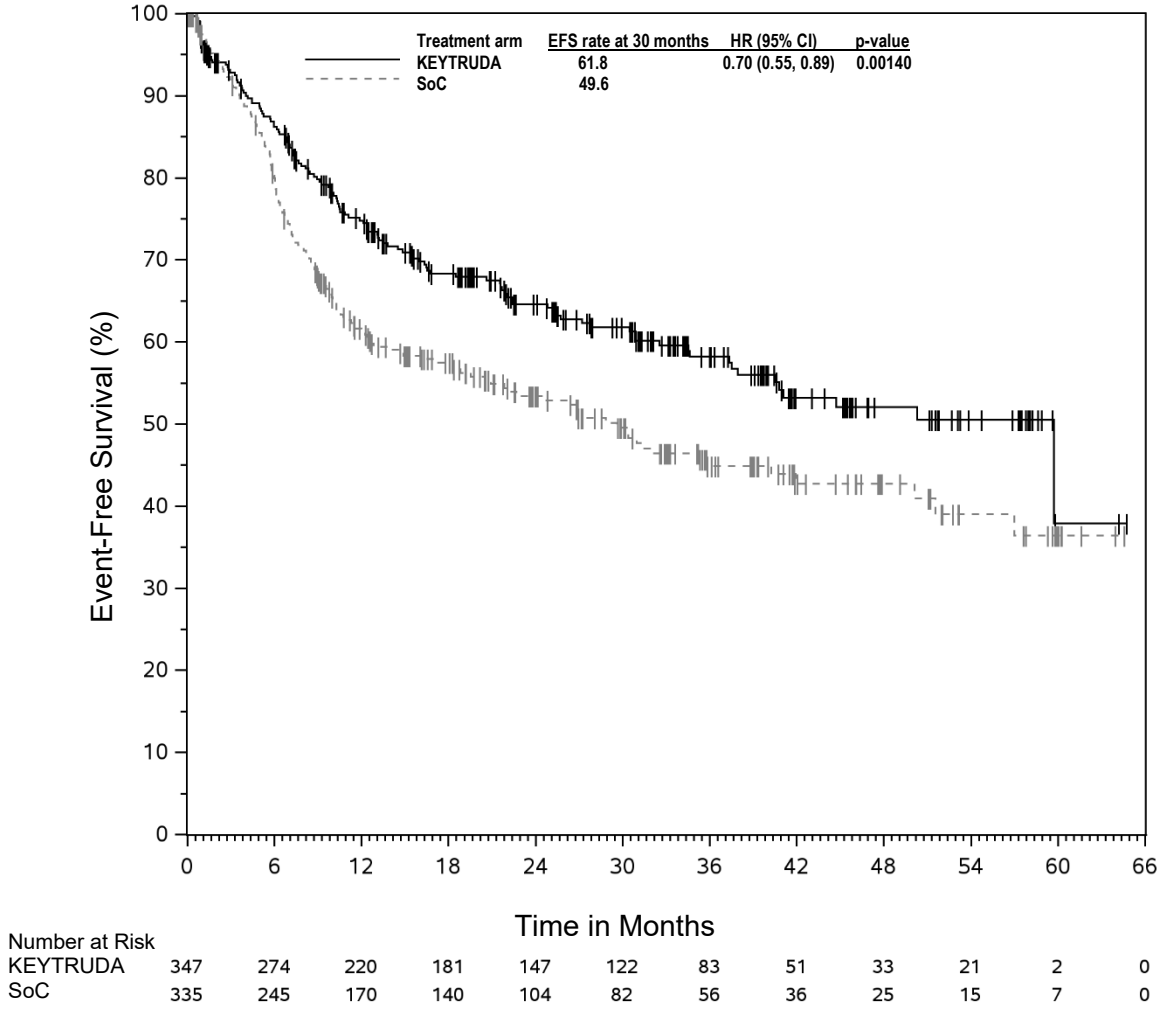
The trial demonstrated a statistically significant improvement in EFS for patients randomised to KEYTRUDA in combination with radiation with or without cisplatin compared to those randomised to radiation with or without cisplatin at the first pre-specified interim analysis in patients with HNSCC CPS ≥1. The median follow-up time for this trial was 27.1 months (range: 0.5 to 66.5 months). Table 25 and Figure 22 and Figure 23 describe efficacy results in KEYNOTE-689.

Table 25: 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	

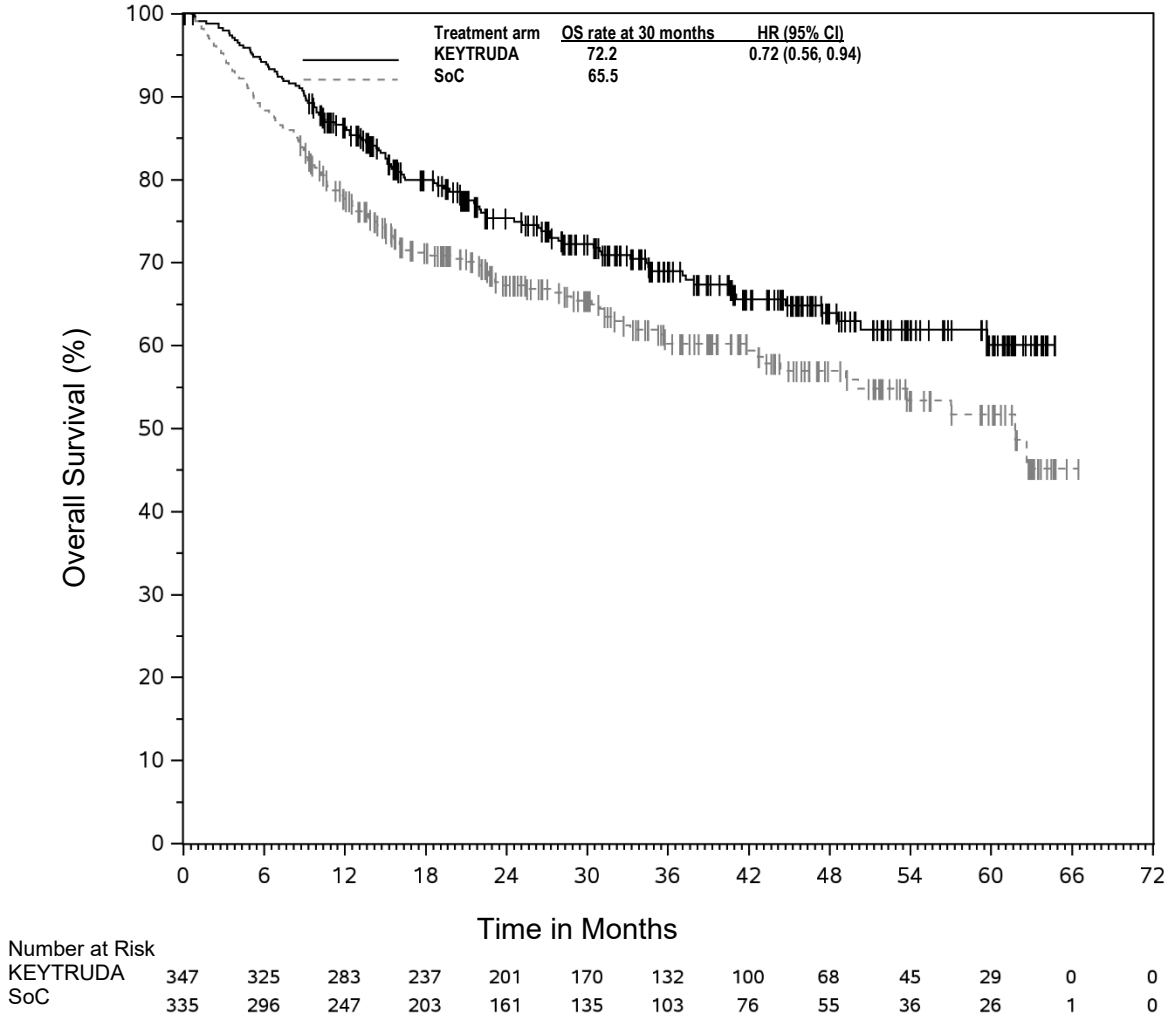
* From product-limit (Kaplan-Meier) method for censored data.
† Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by primary tumour site and tumour stage.
‡ One-sided p-value based on log-rank test stratified by primary tumour site and tumour stage. Compared to a one-sided p-value boundary of 0.0124
§ Based on Miettinen & Nurminen method stratified by primary tumour site and tumour stage.
‖ Compared to a one-sided p-value boundary of 0.0005
NR = not reached

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



Number at Risk												
KEYTRUDA	347	274	220	181	147	122	83	51	33	21	2	0
SoC	335	245	170	140	104	82	56	36	25	15	7	0

Figure 23: Kaplan-Meier Curve for Overall Survival for KEYTRUDA in Patients with HNSCC CPS ≥1 in KEYNOTE-689



At the time of the pre-specified interim analysis of OS with 76% of OS events, HR estimate (HR:0.72; 95%CI: 0.56, 0.94) favoured KEYTRUDA in combination with radiation with or without cisplatin compared to radiation with or without cisplatin in the overall population. The pCR rates were 3.2% in patients randomised to KEYTRUDA in combination with radiation with or without cisplatin and 0% in radiation with or without cisplatin in the overall population.

KEYNOTE-048: Controlled trial of first-line monotherapy or combination therapy in HNSCC

The efficacy of KEYTRUDA was investigated in Study KEYNOTE-048, a multicentre, randomised, open-label, active-controlled study in patients with metastatic or recurrent HNSCC who had not previously received systemic therapy for recurrent or metastatic disease and who were considered incurable by local therapies. Patients with active autoimmune disease that required systemic therapy within two years of treatment or a medical condition that required immunosuppression were ineligible for the study. Randomisation was stratified by tumour 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 randomised 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 tumour 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 randomised; 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 randomised to KEYTRUDA in combination with chemotherapy compared to standard treatment. OS for patients randomised to KEYTRUDA monotherapy was non-inferior compared to standard treatment. Table 26 and 27 and Figures 24 and 25 describe key efficacy results for KEYTRUDA in KEYNOTE-048.

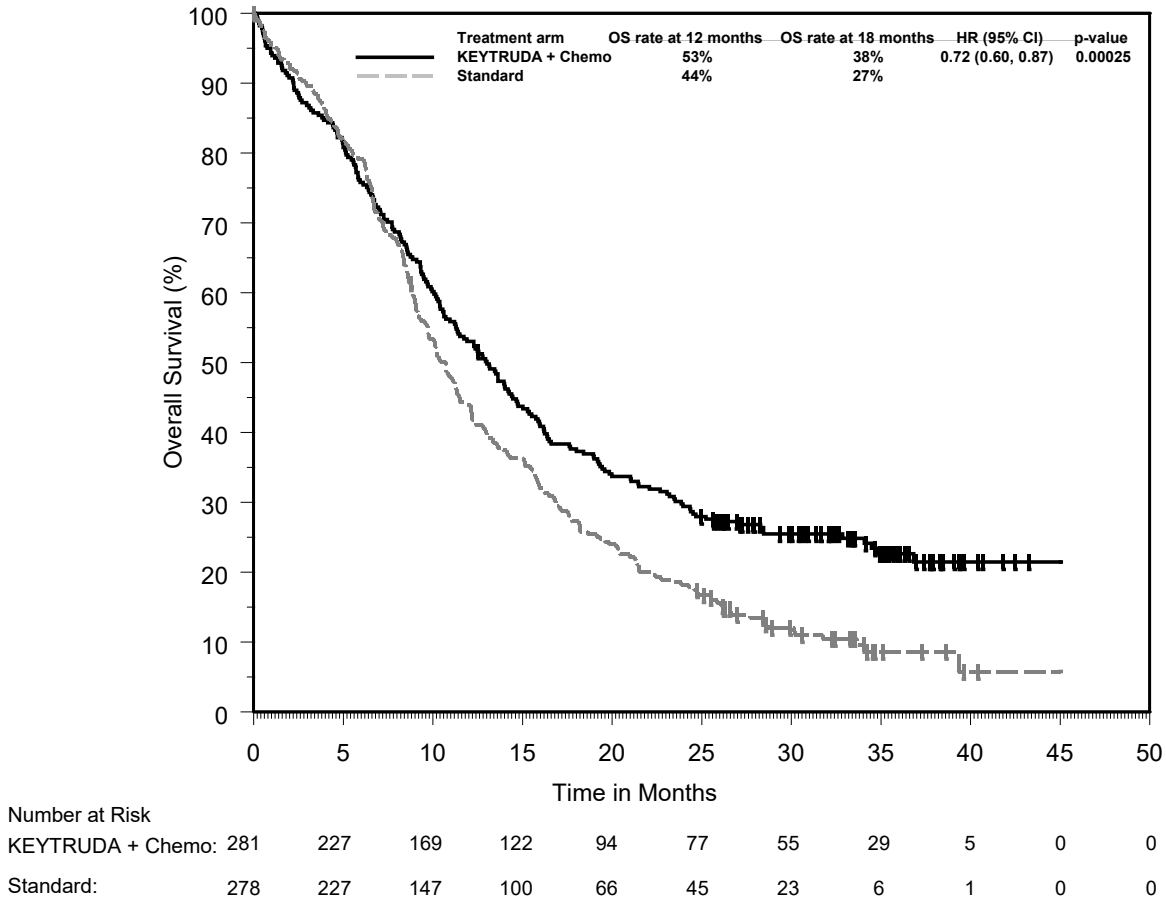
Table 26: Efficacy Results for KEYTRUDA plus Chemotherapy in KEYNOTE-048

Endpoint	KEYTRUDA Platinum Chemotherapy 5-FU n=281	Standard Treatment* n=278
OS		
Number (%) of patients with event	197 (70%)	223 (80%)
Median in months (95% CI)	13.0 (10.9, 14.7)	10.7 (9.3, 11.7)
Hazard ratio† (95% CI)	0.77 (0.63, 0.93)	
p-Value‡	0.0033	
PFS		
Number of patients with event (%)	244 (87%)	253 (91%)
Median in months (95% CI)	4.9 (4.7, 6.0)	5.1 (4.9, 6.0)
Hazard ratio† (95% CI)	0.92 (0.77, 1.10)	
p-Value‡	0.1697	
Objective Response Rate		
ORR§ (95% CI)	36% (30.0, 41.5)	36% (30.7, 42.3)
Complete response	6%	3%
Partial response	30%	33%
p-Value¶	0.5740	
Response Duration		
Median in months (range)	6.7 (1.6+, 30.4+)	4.3 (1.2+, 27.9+)
% with duration ≥6 months	54%	37%

* 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)

In KEYNOTE-048, OS HRs for patients randomised to KEYTRUDA in combination with chemotherapy, compared with cetuximab in combination with chemotherapy, were similar for all populations regardless of PD-L1 expression in a pre-specified interim analysis: ITT (HR 0.77, 95% CI: 0.63, 0.93), CPS ≥1 (HR 0.71, 95% CI: 0.57, 0.88), CPS ≥20 (HR 0.69, 95% CI: 0.51, 0.94). 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 24: Kaplan-Meier Curve for Overall Survival for KEYTRUDA plus Chemotherapy in KEYNOTE-048*



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

Table 27: 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	177 (69%)	206 (81%)
Median in months (95% CI)	12.3 (10.8, 14.9)	10.3 (9.0, 11.5)
Hazard ratio† (95% CI)	0.78 (0.64, 0.96)	
p-Value‡	0.0085	
PFS		
Number of patients with event (%)	225 (88%)	231 (91%)
Median in months (95% CI)	3.2 (2.2, 3.4)	5.0 (4.8, 5.8)
Hazard ratio† (95% CI)	1.16 (0.96, 1.39)	
p-Value§	0.9330	
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)	20.9 (1.5+, 34.8+)	4.5 (1.2+, 28.6+)
% with duration ≥6 months	79%	36%

* Cetuximab, platinum, and 5-FU

† Based on the stratified Cox proportional hazard model

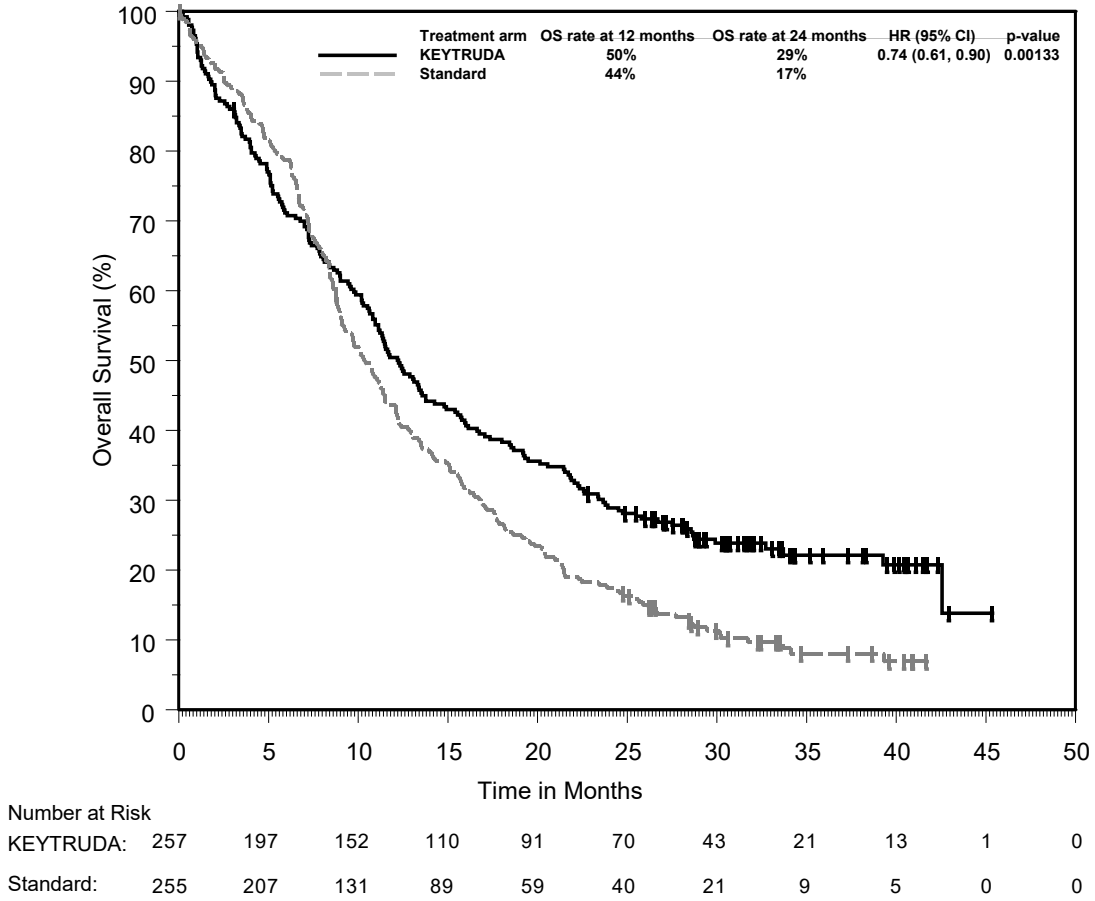
‡ Non-inferiority p-Value

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



*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 randomised 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 summarised in Table 28.

Table 28: 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).

KEYNOTE-040: Controlled trial in HNSCC patients previously treated with platinum-containing chemotherapy

The efficacy of KEYTRUDA was investigated in KEYNOTE-040, a multicentre, open-label, randomised, active-controlled study for the treatment of recurrent or metastatic HNSCC in patients with disease progression who received prior platinum-containing chemotherapy. The study excluded patients with active autoimmune disease that required systemic therapy within 2 years of treatment, a medical condition that required immunosuppression, or who were previously treated with 3 or more systemic regimens for recurrent and/or metastatic HNSCC.

Patients were stratified by PD-L1 expression, HPV status and ECOG performance status and then randomised (1:1) to receive either KEYTRUDA 200 mg every 3 weeks (n=247) or one of three standard treatments (n=248): methotrexate 40 mg/m^2 once weekly (n=64), docetaxel 75 mg/m^2 once every 3 weeks (n=99), or cetuximab 400 mg/m^2 loading dose and then 250 mg/m^2 once weekly (n=71). Patients were treated with KEYTRUDA for up to 24 months or 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. Assessment of tumour status was performed at 9 weeks, then every 6 weeks through week 52, followed by every 9 weeks through 24 months.

Among the 495 randomised patients in KEYNOTE-040, the baseline characteristics included: median age 60 years (33% age 65 or older); 83% male; 84% White, 6% Asian, and 2% Black; and 28% and 72% with an ECOG performance status 0 or 1, respectively. Disease characteristics were: HPV positive (24%) and PD-L1 expression defined as CPS ≥1 (78%) and TPS ≥50% (26%). Seventy-one percent (71%) of patients had M1 disease and the majority had Stage IV disease (Stage IV 33%, Stage IVa 11%, Stage IVb 5%, and Stage IVc 45%). Fifteen percent (15%) had disease progression following platinum-containing neoadjuvant or adjuvant chemotherapy, and 84% had received 1-2 prior systemic regimens for metastatic disease.

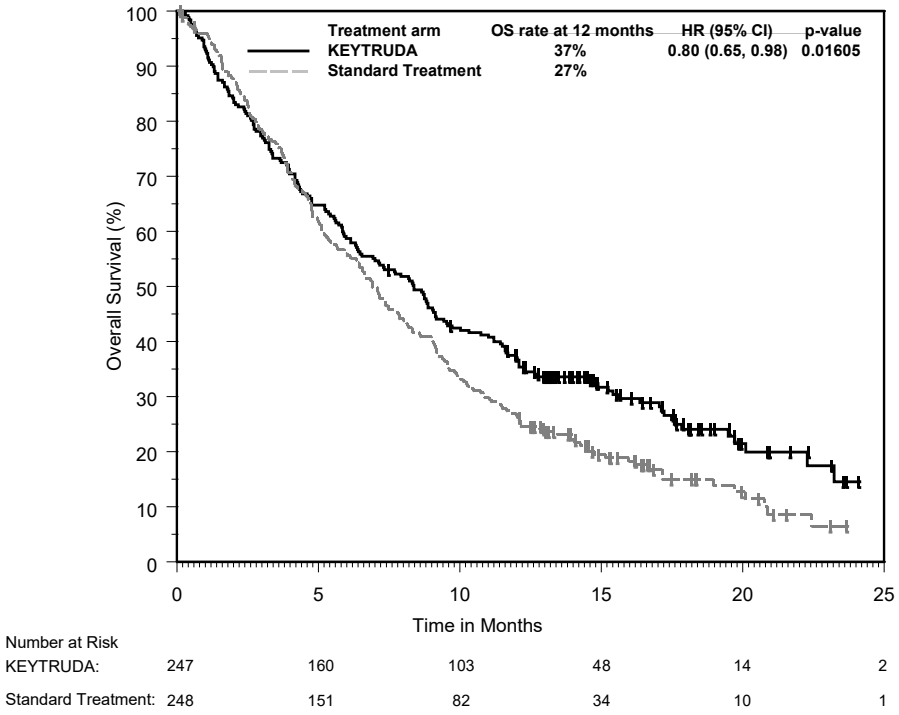
The primary efficacy outcome was OS. Secondary efficacy outcome measures were PFS, ORR, and response duration (as assessed by BICR using RECIST 1.1) and OS (PD-L1 CPS ≥1). Efficacy measures for KEYNOTE-040 are summarised in Table 29, and the Kaplan- Meier curve for OS is shown in Figure 26.

Table 29: Efficacy Results in KEYNOTE-040

Endpoint	KEYTRUDA 200 mg every 3 weeks n=247	Standard Treatment* n=248
OS		
Number (%) of patients with event	181 (73%)	207 (84%)
Hazard ratio† (95% CI)	0.80 (0.65, 0.98)	
p-Value‡	0.016	
Median in months (95% CI)	8.4 (6.4, 9.4)	6.9 (5.9, 8.0)
PFS§		
Number (%) of patients with event	218 (88%)	224 (90%)
Hazard ratio† (95% CI)	0.96 (0.79, 1.16)	
p-Value‡	0.325	
Median in months (95% CI)	2.1 (2.1, 2.3)	2.3 (2.1, 2.8)
Rate (%) at 6 months	25.6 (20.3, 31.2)	20 (15.1, 25.3)
Overall response rate§		
ORR (95% CI)	15% (10.4, 19.6)	10% (6.6, 14.5)
p-Value¶	0.061	
Complete response	2%	0.4%
Partial response	13%	10%
Stable disease	23%	26%
Response duration§,#		
Median in months (range)	18.4 (2.7, 18.4)	5 (1.4+, 18.8)
Number (%Þ) of patients with duration ≥6 months	16 (72%)	6 (47%)

* Methotrexate, docetaxel, and cetuximab
† Hazard ratio (KEYTRUDA compared to standard treatment) based on the stratified Cox proportional hazard model
‡ One-sided p-Value based on 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
Þ Based on Kaplan-Meier estimation

Figure 26: Kaplan-Meier Curve for Overall Survival in KEYNOTE-040



KEYNOTE-012: Open-label study in HNSCC patients previously treated with chemotherapy

The efficacy of KEYTRUDA was investigated in 192 patients with recurrent and/or metastatic HNSCC, regardless of tumour human papilloma virus (HPV) status (33% positive), enrolled in a multicentre, non-randomised, open-label multi-cohort study (KEYNOTE-012). One cohort (n=132) was included regardless of PD-L1 tumour status. Efficacy is reported for a subgroup of 110 patients with recurrent and/or metastatic HNSCC that progressed on or after treatment with platinum-containing chemotherapy and cetuximab, and for a subgroup of 64 patients with recurrent and/or metastatic HNSCC that progressed on or after treatment with platinum-containing chemotherapy without prior cetuximab. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible.

Patients received KEYTRUDA 10 mg/kg every 2 weeks (n=53), or 200 mg every 3 weeks (n=121) until disease progression or unacceptable toxicity. Assessment of tumour status was performed every 8 weeks. The major efficacy outcome measures were ORR according to RECIST 1.1, as assessed by blinded independent central review, and duration of response.

Among the 64 patients with disease progression after platinum-containing chemotherapy without prior cetuximab, the baseline characteristics were median age 60 years (28% age 65 or older); 77% male; 75% White, 20% Asian, and 3% Black; 88% had M1 stage disease; and 33% and 67% had an ECOG performance status 0 and 1, respectively. Thirty-six percent of patients had two or more lines of therapy in the recurrent and/or metastatic setting.

Among the 110 patients with disease progression after platinum-containing chemotherapy and cetuximab, the baseline characteristics were median age 60 years (34% age 65 or older); 85% male; 75% White, 14% Asian, and 7% Black; 87% had M1 stage disease; and 27% and 73% had an ECOG performance status 0 and 1, respectively. Eighty percent of patients had two or more lines of therapy in the recurrent and/or metastatic setting.

Efficacy results are summarised in Table 30.

Table 30: Efficacy Results in Patients with HNSCC

Endpoint	Previously treated with platinum without cetuximab	Previously treated with platinum and cetuximab
	n=64	n=110
Objective Response Rate*		
ORR %, (95% CI)	20% (11, 32)	15% (9,23)
Complete response	5%	4%
Partial response	16%	11%
Response Duration		
Median in months (range)	Not reached (1.8+, 21.8+)‡	Not reached (2.4+, 18.7+)†
% with duration ≥ 6-months	83%§	79%¶
Time to Response		
Median in months (range)	2.0 (1.6, 11.1)‡	3.7 (1.6, 16.7)†
PFS*		
Median in months (95% CI)	2.1 (1.9, 3.7)	2 (1.9, 2.1)
6-month PFS rate	31%	20%
OS*		
6-month OS rate	70%	53%
12-month OS rate	46%	34%

* Assessed by blinded independent central review using RECIST 1.1
† Based on patients (n=16) with a confirmed response by independent review
‡ Based on patients (n=13) with a confirmed response by independent review
§ Based on Kaplan-Meier estimates; includes 10 patients with responses of 6 months or longer including 3 patients with responses of 12 months or longer
¶ Based on Kaplan-Meier estimates; includes 11 patients with responses of 6 months or longer including 1 patient with response of 12 months or longer

There were objective responses in patients regardless of HPV tumour status.

Classical Hodgkin Lymphoma

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

KEYNOTE-204 was a randomised, 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. Randomisation 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 randomised (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.

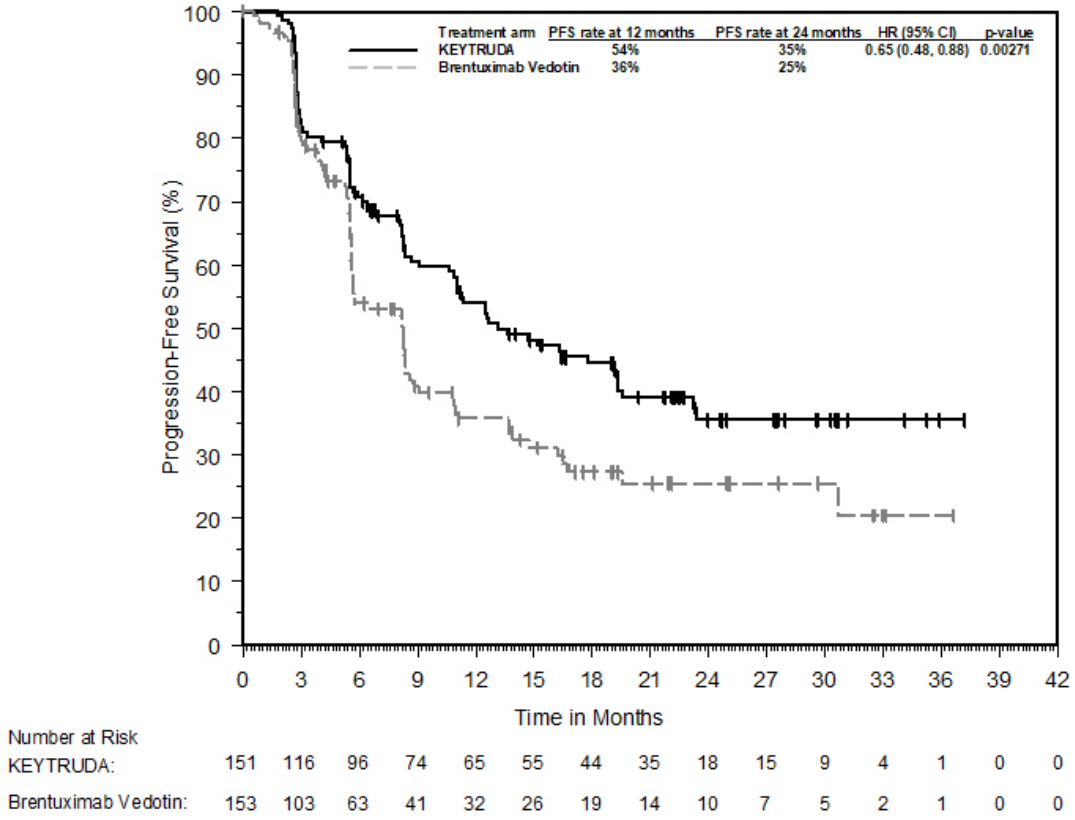
The median follow-up time for 151 patients treated with KEYTRUDA was 24.9 months (range: 1.8 to 42.0 months). Efficacy results are summarised in Table 31.

Table 31: Efficacy Results in Patients with Refractory or Relapsed Classical Hodgkin Lymphoma

Endpoint	**KEYTRUDA** **2 mg/kg 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 27: 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 3 or more 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 multicentre, non-randomised, 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.

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.

Efficacy results are summarised in Table 32.

Table 32: 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

The improved benefit as assessed by ORR, CRR, and response duration in the KEYNOTE-087 population was accompanied by overall improvements in health-related quality of life (HRQoL) as assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and the European Quality

of Life Five Dimensions Questionnaire (EQ-5D). Relative to subjects with stable disease or progressive disease, subjects with a complete or partial response had the largest improvement and the highest proportion with a 10 point or greater increase in their EORTC QLQ-C30 global health status/QoL score, as well as, had the largest improvement in their EQ-5D utility and VAS scores from baseline to Week 12.

Urothelial Carcinoma

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

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

Patients received KEYTRUDA 200 mg every 3 weeks until unacceptable toxicity or disease progression. Clinically stable patients with initial evidence of disease progression were permitted to remain on treatment until disease progression was confirmed. Patients without disease progression were treated for up to 24 months. Treatment with pembrolizumab could be reinitiated for subsequent disease progression and administered for up to 1 additional year. Assessment of 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. The major efficacy outcome measures were ORR according to RECIST 1.1 and duration of response. Efficacy is reported for patients who had the opportunity for at least 2 post-baseline scans representing at least 4 months of follow-up.

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, 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 tumours 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 tumour in the lower tract, and 18% of patients had a primary tumour 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.

At a pre-specified interim analysis, the median follow-up time for 370 patients treated with KEYTRUDA was 11.5 months. Efficacy results are summarised in Table 33. The data presented for subjects with PD-L1 CPS ≥10 are based on a subgroup analysis in a single-arm trial. A randomised, controlled confirmatory trial is ongoing.

Table 33: Efficacy Results in Patients with Urothelial Carcinoma Ineligible for Cisplatin-Containing Chemotherapy

Endpoint	All Subjects n=370	PD-L1 CPS ≥10 N=110
Objective Response Rate*		
ORR %, (95% CI)	29% (24, 34)	47% (38, 57)
Disease control rate†	47%	67%
Complete response	8%	19%
Partial response	21%	28%
Stable disease	18%	20%
Response Duration		
Median in months (range)	Not reached (1.4+, 27.9+)	Not reached (1.4+, 26.5+)
% with duration ≥ 6-months	82%‡	82%
Time to Response		
Median in months (range)	2.1 (1.3, 9.0)	2.1 (1.3, 4.7)
PFS*		
Median in months (95% CI)	2.3 (2.1, 3.4)	4.9 (3.8, 10.8)
6-month PFS rate	34%	49%
OS		
Median in months (95% CI)	11.5 (10.0, 13.3)	18.5 (12.2, NA§)
6-month OS rate	67%	76

* Assessed by BICR using RECIST 1.1
† Based on best response of stable disease or better
‡ Based on Kaplan-Meier estimates; includes 85 patients with responses of 6 months or longer
§ Not available

The final ORR analysis was performed 9.9 months after the interim analysis with 106 ORR events for all patients [median follow-up of 11.4 months (range: 0.1, 41.2 months)]. ORR was 29% (95% CI: 24, 34) and 47% (95% CI: 38, 57), respectively for all subjects and subjects with CPS ≥10. The complete and partial response rates were 9% and 20%, respectively in all subjects and 20% and 27%, respectively in subjects with CPS ≥10. At the final analysis among the responding patients, the median response duration was 30.1 months (range 1.4+ to 35.9+ months) in all subjects (n=106) and not reached (range 1.4+ to 35.4+ months) in subjects with CPS ≥10 (n=52). Responses of 6 months or longer (based on Kaplan-Meier estimation) were 81% and 82%, respectively for all subjects and subjects with CPS ≥10.

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

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

Patients were randomised 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 received KEYTRUDA until unacceptable toxicity or disease progression. Clinically stable patients with initial evidence of disease progression were permitted to remain on treatment until disease progression was confirmed. Patients without disease progression were treated for up to 24 months. Treatment with pembrolizumab could be reinitiated for subsequent disease progression and administered for up to 1 additional year. Assessment of tumour status was performed at 9 weeks after randomisation, then every 6 weeks through the first year, followed by every 12 weeks thereafter. The major efficacy

outcomes were OS and PFS as assessed by BICR per RECIST v1.1. Additional efficacy outcome measures were ORR as assessed by BICR per RECIST v1.1 and duration of response.

Among the 542 randomised patients, the study population characteristics were: median age 66 years (range: 26 to 88), 58% age 65 or older; 74% male; 72% White and 23% Asian; 57% ECOG performance status of 1 or greater; 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 as the most recent line of therapy. Twenty-one percent had received 2 or more prior systemic regimens in the metastatic setting. Seventy-six percent of patients received prior cisplatin, 23% had prior carboplatin, and 1% were treated with other platinum-based regimens.

At a pre-specified interim analysis, the median follow-up time for 270 patients treated with KEYTRUDA was 10.3 months. The study demonstrated statistically significant improvements in OS and ORR for patients randomised to KEYTRUDA as compared to chemotherapy (Table 34). There was no statistically significant difference between KEYTRUDA and chemotherapy with respect to PFS. Efficacy results are summarised in Table 34.

Table 34: Efficacy Results in Patients with Urothelial Carcinoma Previously Treated with Chemotherapy

Endpoint	**KEYTRUDA 200 mg every 3 weeks n=270**	**Chemotherapy n=272**
OS		
Number (%) of patients with event	155 (57%)	179 (66%)
Hazard ratio* (95% CI)	0.73 (0.59, 0.91)	
p-Value†	0.002	
Median in months (95% CI)	10.3 (8.0, 11.8)	7.4 (6.1, 8.3)
PFS‡		
Number (%) of patients with event	218 (81%)	219 (81%)
Hazard ratio* (95% CI)	0.98 (0.81, 1.19)	
p-Value†	0.416	
Median in months (95% CI)	2.1 (2.0, 2.2)	3.3 (2.3, 3.5)
Objective Response Rate‡		
ORR % (95% CI)	21% (16, 27)	11% (8, 16)
Complete response	7%	3%
Partial response	14%	8%
p-Value§,	0.001	
Response Duration‡,¶		
Median in months (range)	Not reached (1.6+, 15.6+)	4.3 (1.4+, 15.4+)
Number (%#) of patients with duration ≥6 months	41 (78%)	7 (40%)
Number (%#) of patients with duration ≥12 months	14 (68%)	3 (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

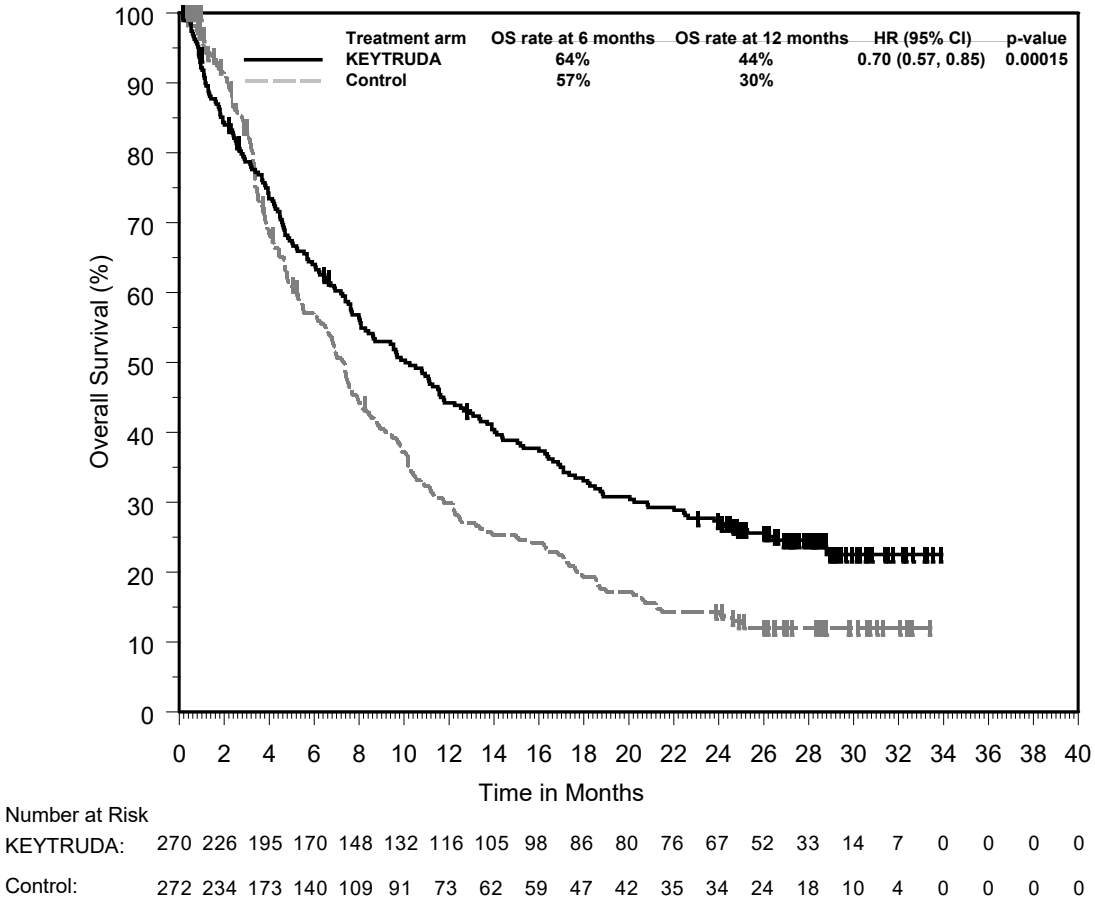
¶ Based on patients with a best overall response as confirmed complete or partial response

Based on Kaplan-Meier estimation

The final OS analysis was performed 13.6 months after the interim analysis with 419 patient events (200 for KEYTRUDA and 219 for chemotherapy). Median OS was 10.1 months (95% CI: 8.0, 12.3) for KEYTRUDA and 7.3 months (95% CI: 6.1, 8.1) for chemotherapy. The OS HR was 0.70 (95% CI: 0.57, 0.85; p<0.001). See Figure 28. In the final analysis there was no statistically significant difference between KEYTRUDA and chemotherapy with respect to PFS.

At the final analysis, among the 57 responding patients who received KEYTRUDA vs. 30 responding patients who received chemotherapy, the median response duration was not reached (range 1.6+ to 30.0+ months) in patients who received KEYTRUDA, vs. 4.4 months (range 1.4+ to 29.9+ months) in patients who received chemotherapy. In patients who received KEYTRUDA, 84% had responses of 6 months or longer and 68% had responses of 12 months or longer (based on Kaplan-Meier estimation) vs. 47% who had responses of 6 months or longer and 35% who had responses of 12 months or longer (based on Kaplan-Meier estimation) in patients who received chemotherapy. The complete and partial response rates were 9% and 12%, respectively in patients who received KEYTRUDA vs. 3% and 8%, respectively in patients who received chemotherapy.

Figure 28: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-045 (Intent to Treat Population)



Patient-reported outcomes (PROs) were assessed using the EORTC QLQ-C30. A prolonged time to deterioration in the EORTC QLQ-C30 global health status/QoL score 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 scores, while those treated with investigator's choice

chemotherapy had a decline in global health status/QoL scores. These results should be interpreted in the context of the open-label study design and therefore taken cautiously.

KEYNOTE-057: BCG-unresponsive High-Risk Non-Muscle Invasive Bladder Cancer

The efficacy of KEYTRUDA was investigated in KEYNOTE-057, a multicentre, open-label, single-arm trial in 96 patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in-situ (CIS) with or without papillary tumours who are ineligible for or have elected not to undergo cystectomy. BCG-unresponsive high-risk NMIBC is defined as persistent disease despite adequate BCG therapy, disease recurrence after an initial tumour-free state following adequate BCG therapy, or T1 disease following a single induction course of BCG. Prior to treatment, all patients had received adequate BCG therapy, had undergone recent cystoscopic procedure(s) and transurethral resection of bladder tumour (TURBT) to remove all resectable disease (Ta and T1 components) and assure the absence of muscle invasive disease. Residual CIS (Tis components) not amenable to complete resection was acceptable. The trial excluded patients with muscle invasive (i.e., T2, T3, T4) locally advanced non-resectable or metastatic urothelial carcinoma, concurrent extra-vesical (i.e., urethra, ureter or renal pelvis) non-muscle invasive transitional cell carcinoma of the urothelium, autoimmune disease or a medical condition that required immunosuppression.

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

The study population characteristics were: median age 73 years (69% age 65 or older); 84% male; 67% White; and 73% and 27% with an ECOG performance status of 0 or 1, respectively. Tumour pattern at study entry was CIS with T1 (13%), CIS with high grade TA (25%), and CIS (63%). Baseline high-risk NMIBC disease status was 27% persistent and 73% recurrent. The median number of prior instillations of BCG was 12.

The median follow-up time was 28.0 months (range: 4.6 to 40.5 months). Efficacy results are summarised in Table 35.

Table 35: Efficacy Results for Patients with BCG-unresponsive, High-Risk NMIBC

Endpoint	**n=96**
Complete Response Rate*	41%
Response Duration†	
Median in months (range)	16.2 (0.0+, 30.4+)
% with duration ≥ 6 months	78%‡
% with duration ≥ 12 months	57%§

* Based on negative cystoscopy (with TURBT/biopsies as applicable), urine cytology, and computed tomography urography (CTU imaging)
† Duration reflects period from the time complete response was achieved
‡ Based on Kaplan-Meier estimates; includes 27 patients with responses of 6 months or longer
§ Based on Kaplan-Meier estimates; includes 18 patients with responses of 12 months or longer

At the time of analysis, among the 96 patients there were no occurrences of progression to muscle-invasive disease (T2) or metastatic bladder cancer while on KEYTRUDA.

Patients who had a complete response to pembrolizumab in KEYNOTE-057 maintained their health-related quality of life (HRQoL), as assessed by the Functional Assessment of Cancer Therapy-Bladder Cancer (FACT-BI), the Core Lower Urinary Tract Symptom Score (CLSS), and the European Quality of Life Five Dimensions Questionnaire (EQ-5D).

Microsatellite Instability-High Cancer

KEYNOTE-164 and KEYNOTE-158 Open-label studies in patients with MSI-H, including mismatch repair deficient (dMMR), cancer who have received prior therapy

The efficacy of KEYTRUDA was investigated in 155 patients with MSI-H or dMMR cancer enrolled in two multicentre, non-randomised, open-label, multi-cohort Phase II studies (KEYNOTE-164 and KEYNOTE-158). Regardless of histology, MSI or MMR tumour status was determined using polymerase chain reaction (PCR) or immunohistochemistry (IHC), respectively. Efficacy was evaluated in 61 patients enrolled in KEYNOTE-164 with advanced MSI-H or dMMR colorectal cancer (CRC) that progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. Efficacy was also evaluated in 94 patients enrolled in KEYNOTE-158 with advanced MSI-H or dMMR non-colorectal cancer (non-CRC) who had disease progression following prior therapy. Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible for either trial.

Patients received KEYTRUDA 200 mg every 3 weeks until unacceptable toxicity or disease progression. Clinically stable patients with initial evidence of disease progression were permitted to remain on treatment until disease progression was confirmed. Patients without disease progression were treated for up to 24 months. Treatment with pembrolizumab could be reinitiated for subsequent disease progression and administered for up to 1 additional year. Assessment of tumour status in KEYNOTE-164 was performed every 9 weeks and in KEYNOTE-158 every 9 weeks through the first year, then every 12 weeks thereafter. The major efficacy outcome measures were ORR and duration of response according to RECIST 1.1.

Among the 155 patients with MSI-H cancer, the baseline characteristics were: median age 60 years (40% age 65 or older); 55% male; 78% White, 20% Asian; and ECOG PS 0 (49%) and 1 (51%). Ninety-three percent of patients had M1 disease and 6% had M0 disease. Ninety percent of patients with CRC and 51% of patients with non-CRC received two or more prior lines of therapy.

The median follow-up time for 155 patients treated with KEYTRUDA was 9.7 months. Efficacy results are summarised in Table 36 and Table 37.

Table 36: Efficacy Results for Patients with MSI-H Cancer

Endpoint	n=155
Objective Response Rate*	
ORR %, (95% CI)	34% (26, 42)
Complete response	3%
Partial response	31%
Stable disease	22%
Disease control rate†	55%
Response Duration*	
Median in months (range)	Not reached (2.1+, 12.5+)
% with duration ≥ 6-months	98%‡
Time to Response	
Median in months (range)	2.1 (1.3, 10.4)
PFS*	
Median in months (95% CI)	4.2 (2.5, 6.3)
6-month PFS rate	46%
9-month PFS rate	40%
OS	
Median in months (95% CI)	Not reached
6-month OS rate	80%
9-month OS rate	73%

* Assessed by BICR using RECIST 1.1
† Based on best response of stable disease or better
‡ Based on Kaplan-Meier estimates; includes 32 patients with response of 6 months or longer

Table 37: Efficacy Results for CRC and Non-CRC

Endpoint	CRC n=61	Non-CRC* N=94
Objective Response Rate†		
ORR %, (95% CI)	28% (17, 41)	37% (27, 48)
Response Duration†		
Median in months (range)	Not reached (2.9+, 12.5+)	Not reached (2.1+, 10.7+)

* Includes tumour type (n): endometrial (24), gastric (13), small intestinal (13), pancreatic (10), cholangiocarcinoma (9), mesothelioma (3), small cell lung (3), adrenocortical (3), cervical (2), neuroendocrine (2), thyroid (2), urothelial (2), brain (1), ovarian (1), prostate (1), retroperitoneal (1), salivary gland (1), sarcoma (1), testicular (1), tonsillar (1).
† Assessed by BICR using RECIST 1.1

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 multicentre, randomised, open-label, active-controlled trial that enrolled 307 patients with previously untreated unresectable or metastatic MSI-H or dMMR CRC. MSI or MMR tumour 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 randomised (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 5-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 5-FU 400 mg/m^2 bolus on Day 1, then 5-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 5-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 5-FU 400 mg/m^2 bolus on Day 1, then 5-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 tumour status was performed every 9 weeks. Patients randomised 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 randomised 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 randomised to KEYTRUDA compared with chemotherapy at an interim analysis. 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 randomised 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 38 and Figures 29 and 30 summarise the key efficacy measures for KEYNOTE 177.

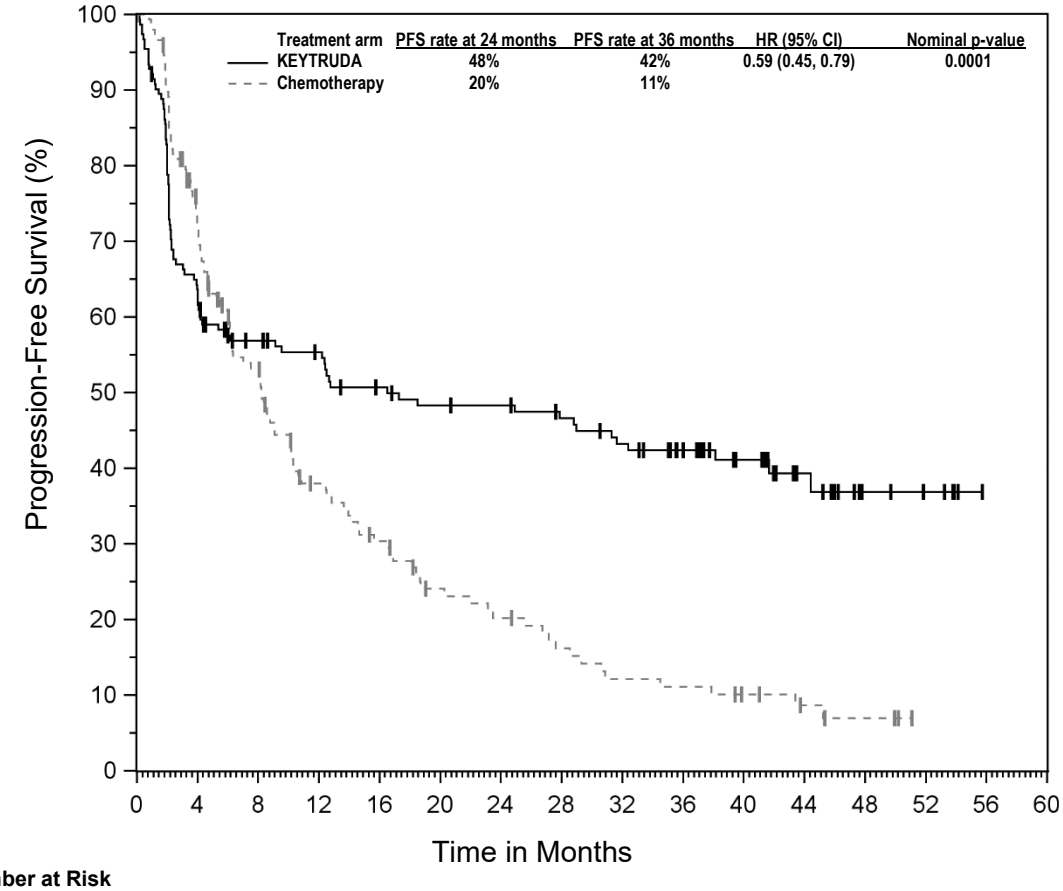
Table 38: Efficacy Results for First-line Treatment in Patients with MSI-H CRC in KEYNOTE-177

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 (compared to a significance level of 0.0117)
‡ 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 29). 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 29: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-177 (Intent to Treat Population)*

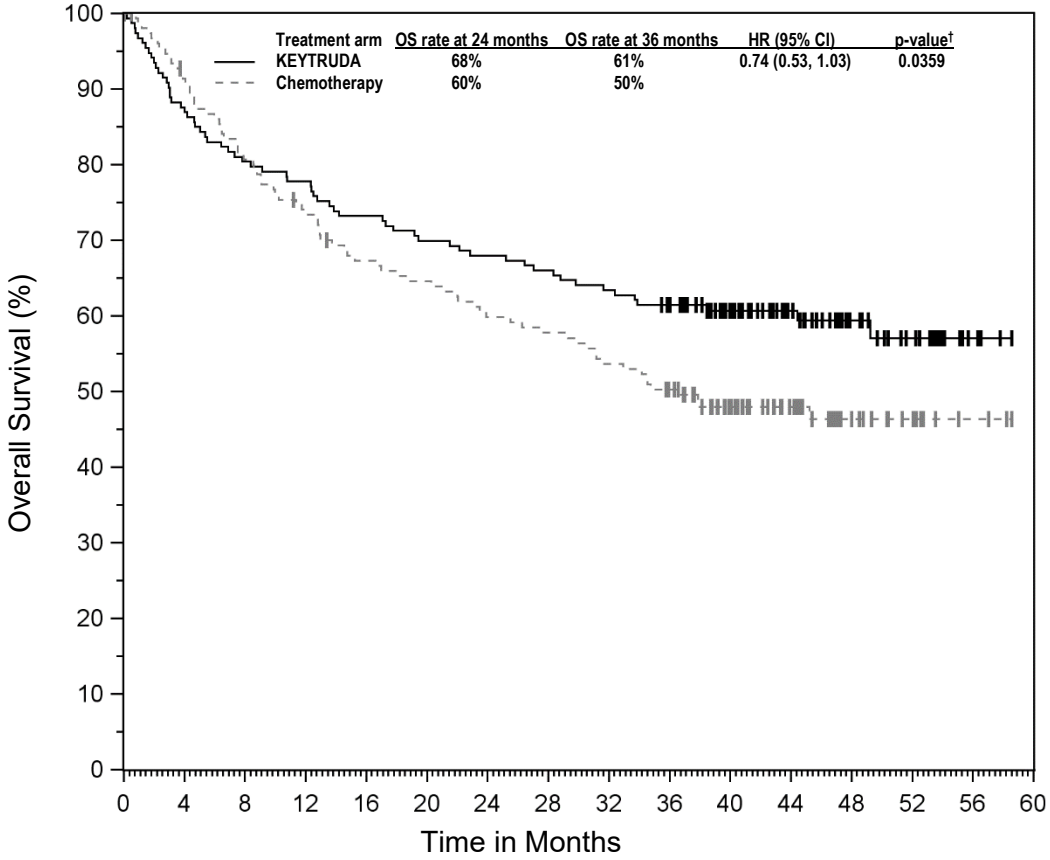


Number at Risk

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

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

Figure 30: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-177 (Intent to Treat Population)*



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

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, randomised, 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. Randomisation was stratified by region (Asia vs. non-Asia), locally advanced vs. metastatic, and site of origin (gallbladder, intrahepatic or extrahepatic cholangiocarcinoma).

Patients were randomised (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

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

Administration of KEYTRUDA with chemotherapy was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered by the investigator to be deriving clinical benefit. Assessment of tumour 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.

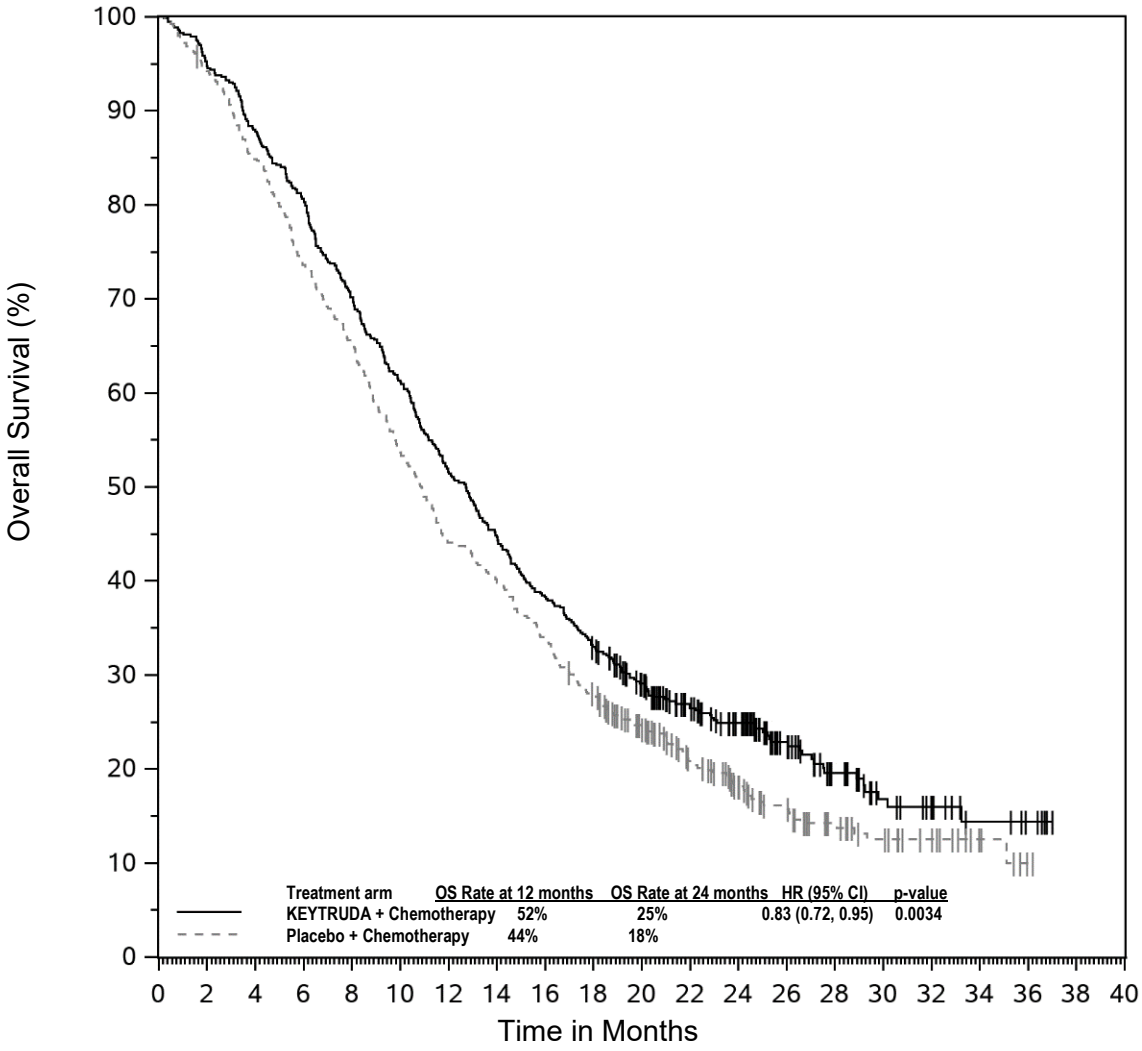
Table 39 and Figure 31 and Figure 32 summarise the efficacy results for KEYNOTE-966.

Table 39: 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‡	0.0225	
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#	0.4735	
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

Figure 31: Kaplan-Meier Curve for Overall Survival in KEYNOTE 966*

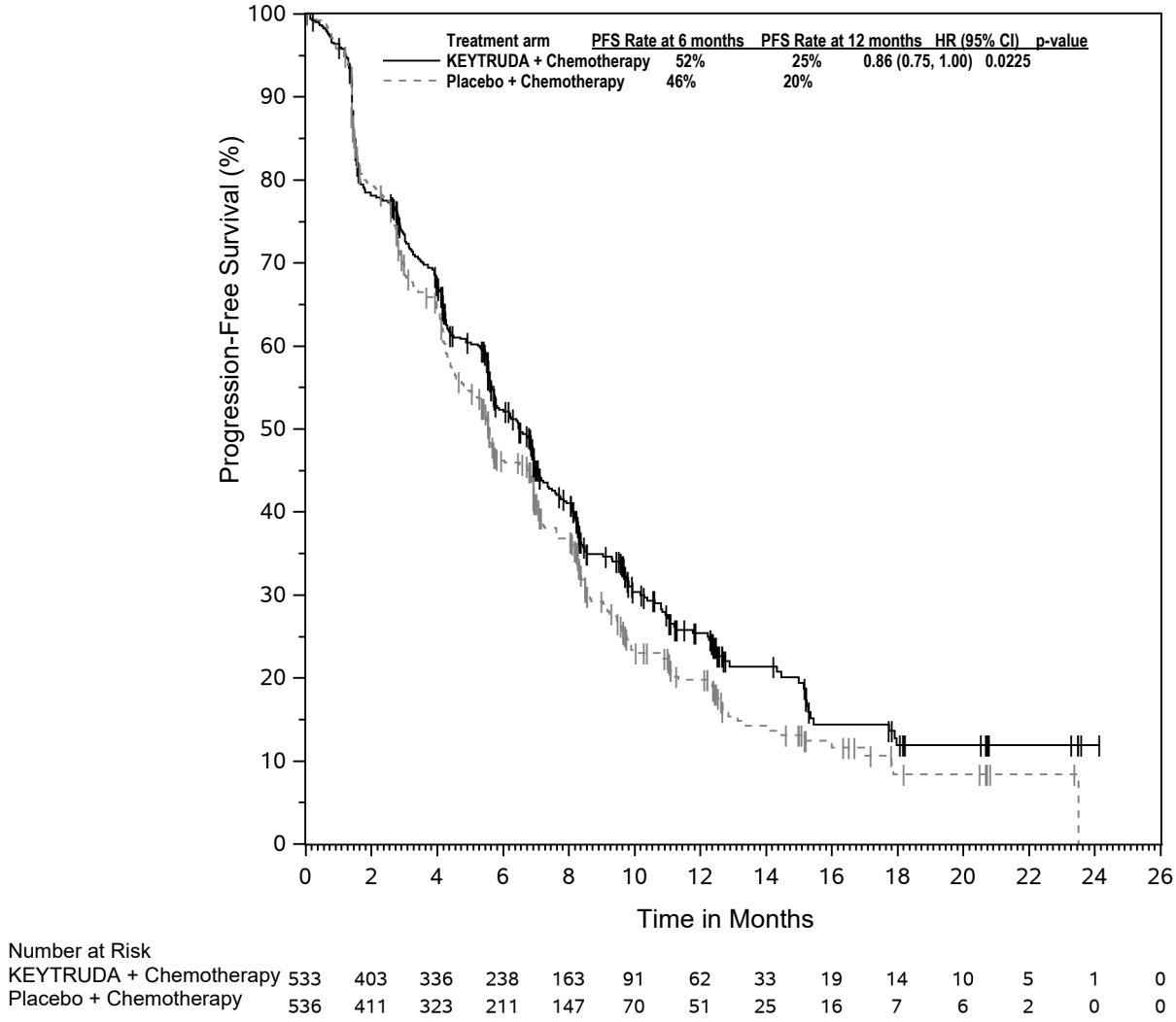


Number at Risk

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



*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 high-risk, 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 multicentre, randomised, double-blind, placebo-controlled trial that enrolled 1060 patients with high-risk, locally advanced cervical cancer who had not previously received any definitive surgery, radiation, or systemic therapy for cervical cancer. Eligible patients included high-risk FIGO

2014 Stage IB2-IIB (tumour 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, or Stage III-IVA (tumour involvement of the lower vagina with or without extension onto pelvic sidewall or hydronephrosis/nonfunctioning kidney or has spread to adjacent pelvic organs) with either node-positive or node-negative disease. Patients with autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Randomisation 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 randomised (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. Treatment 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 tumour 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 1060 patients enrolled in KEYNOTE-A18, the baseline characteristics were: median age of 50 years (range: 22 to 87); 13% age 65 or older, 49% White, 2% Black, 29% Asian; 32% Hispanic or Latino; 73% ECOG PS 0 and 27% ECOG PS 1; 94% with CPS ≥1; 44% were FIGO 2014 Stage IB2 to IIB, 56% were FIGO 2014 Stage III to IVA, 83% had positive pelvic and/or positive para-aortic lymph node(s), 17% had neither positive pelvic nor para-aortic lymph node, 89% IMRT or VMAT EBRT, 91% ≥70 Gy (EQD2). Eighty-three percent had squamous cell carcinoma and 17% had non-squamous histology.

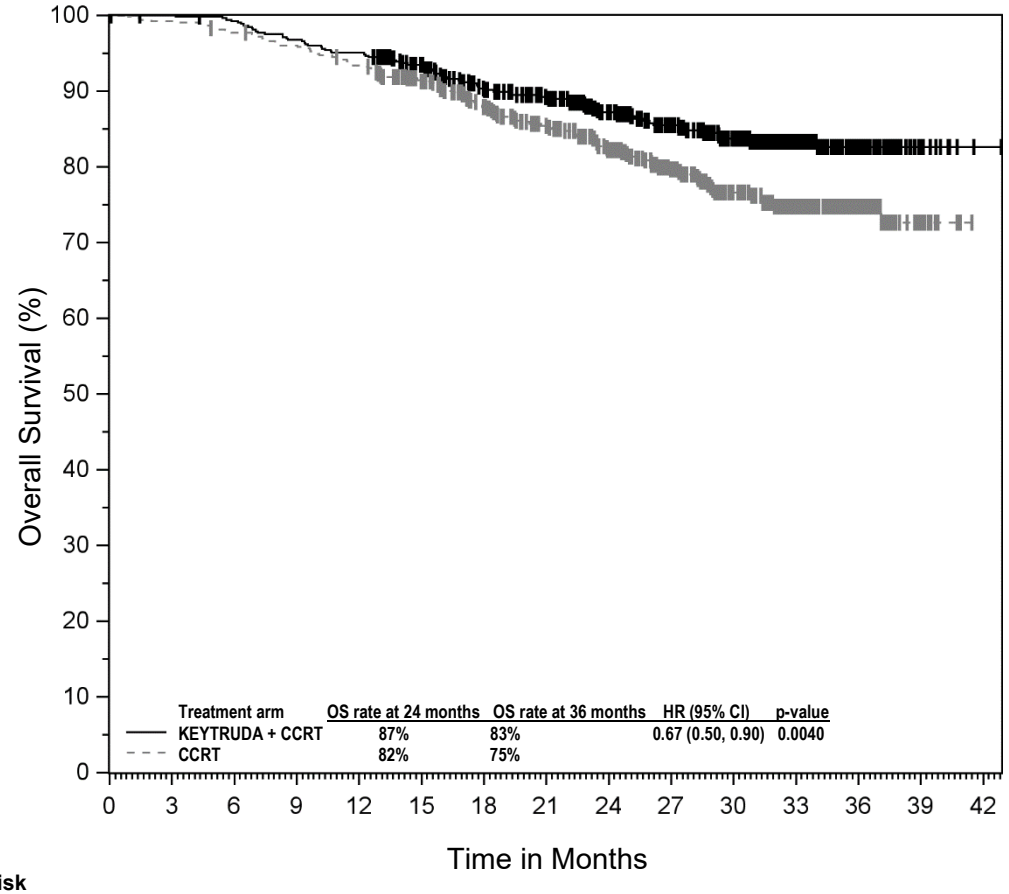
The trial demonstrated statistically significant improvements in PFS at the first prespecified interim analysis (IA1) and OS at the second pre-specified interim analysis (IA2) for patients randomised to KEYTRUDA with CRT compared to placebo with CRT. At the first pre-specified interim analysis (IA1), the HR for PFS was 0.70 (95% CI: 0.55, 0.89; p-Value 0.0020) and median follow-up time was 17 months (range: 0.9 to 31 months). Results reported from the pre-specified interim analysis for OS (IA2) with a median follow up of 28 months (range: 0.9 to 43 months) are summarised in Table 40, Figure 33 and Figure 34.

Table 40: Efficacy Results* for Patients in KEYNOTE-A18

Endpoint	KEYTRUDA 200 mg every 3 weeks and 400 mg every 6 weeks with CRT n=529	Placebo with CRT n=531
OS		
Number of patients with event (%)	75 (14%)	109 (21%)
Median in months (95% CI)	NR (NR, NR)	NR (NR, NR)
24-month OS rate (95% CI)	87% (84, 90)	82% (78, 85)
36-month OS rate (95% CI)	83% (78, 86)	75% (70, 79)
Hazard ratio† (95% CI)	0.67 (0.50, 0.90)	
p-Value‡	0.0040	
PFS by Investigator		
Number of patients with event (%)	155 (29%)	210 (40%)
Median in months (95% CI)	NR (NR, NR)	NR (32, NR)
12-month PFS rate (95% CI)	80% (76, 83)	73% (69, 77)
24-month PFS rate (95% CI)	71% (66, 75)	59% (54, 63)
Hazard ratio† (95% CI)	0.68 (0.56, 0.84)	

* Based on a pre-specified interim OS analysis (IA2; data cut-off 08-JAN-2024)
† Based on the stratified Cox proportional hazard model
‡ One-sided p-Value based on a stratified log-rank test
CRT = Chemoradiotherapy
NR = Not reached

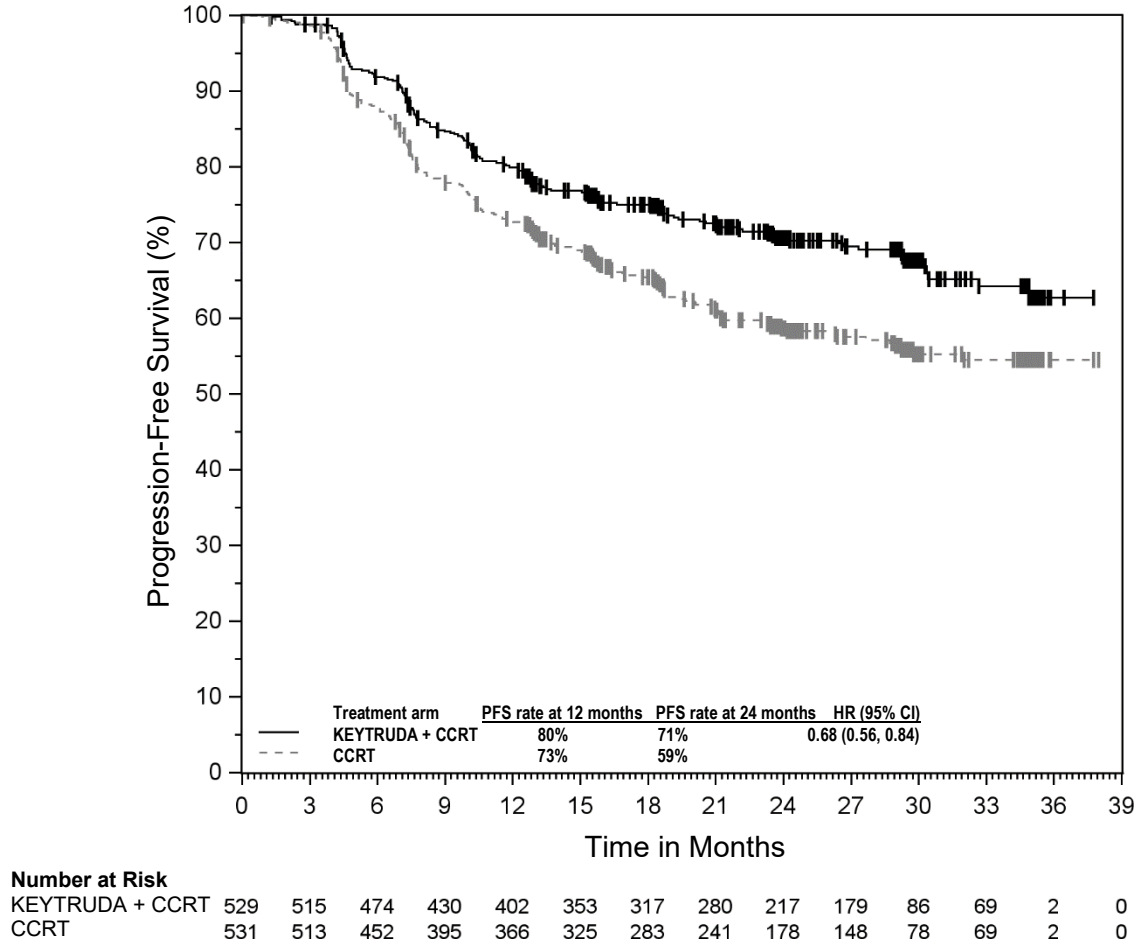
Figure 33: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-A18



Number at Risk

KEYTRUDA + CCRT	529	527	522	509	500	463	412	374	326	273	210	136	63	11	1
CCRT	531	527	518	508	493	455	405	366	316	259	194	125	58	12	0

Figure 34: Kaplan-Meier Curve for Progression Free Survival by Treatment Arm in KEYNOTE-A18*



*Based on pre-specified interim OS analysis

Patient-reported outcomes (PROs) were assessed using EORTC QLQ-C30. Analyses of EORTC QLQ-C30 global health status/QoL and physical functioning showed no clinically meaningful differences between participants treated with KEYTRUDA plus CRT compared with placebo plus CRT. Similar percentages of patients treated with KEYTRUDA plus CRT or placebo plus CRT experienced improved or stable scores on the EORTC QLQ-30 global health status/QoL (81% vs 82%) and physical functioning scales (81% vs. 83%).

At IA2, PFS and OS hazard ratios (HR; with 95% CI) by stage stratum were as follows:

- FIGO 2014 Stage III-IVA:
  - PFS HR: 0.57 (0.43, 0.76)
  - OS HR: 0.57 (0.39, 0.83)
- Node-positive FIGO 2014 Stage IB2-IIB:
  - PFS HR: 0.85 (0.62, 1.16)
  - OS HR: 0.89 (0.55, 1.44)

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 multicentre, randomised, 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 tumour 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. Randomisation 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). Patients were randomised (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 randomisation:

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 randomisation. 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 tumour 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 tumours expressing PD-L1 with a CPS ≥1. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx™ Kit. Among these 548 enrolled patients with tumours expressing PD-L1, 273 patients were randomised to KEYTRUDA in combination with chemotherapy with or without bevacizumab, and 275 patients were randomised 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 median follow-up time was 17.2 months (range: 0.3 to 29.4 months).

A statistically significant improvement in OS and PFS was demonstrated in patients randomised to receive KEYTRUDA compared with patients randomised to receive placebo. An updated OS analysis was conducted at the time of final analysis when 354 deaths in the

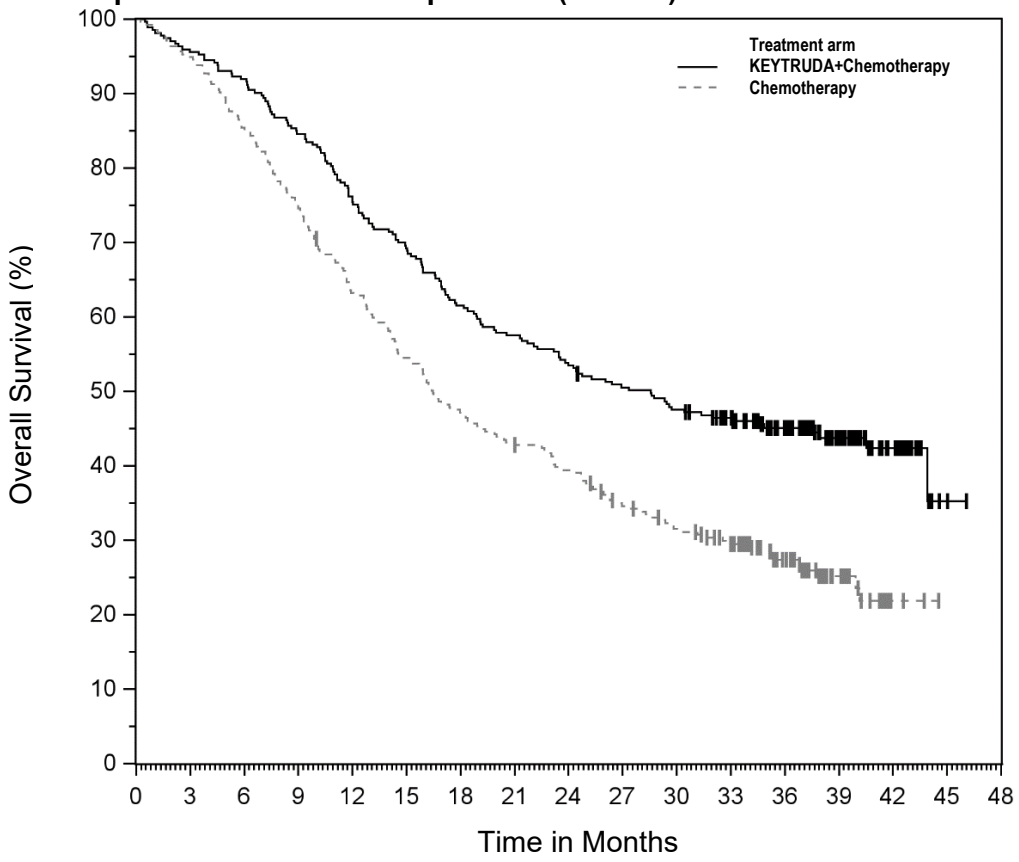
CPS ≥1 population were observed. Efficacy results for patients with tumours expressing PD-L1 (CPS ≥1) in KEYNOTE-826 are summarised in Table 41 and Figure 35.

Table 41: 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	
Updated OS		
Number of patients with event (%)	153 (56.0%)	201 (73.1%)
Median in months (95% CI)	28.6 (22.1, 38.0)	16.5 (14.5, 20.0)
Hazard ratio† (95% CI)	0.60 (0.49, 0.74)	
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 rate	23%	13%
Partial response rate	45%	37%
Duration of Response		
Median in months (range)	18.0 (1.3+, 24.2+)	10.4 (1.5+, 22.0+)
% of patients with duration ≥12 months#	56	46
% of patients with duration ≥18 months#	50	35

* Chemotherapy (paclitaxel and cisplatin or paclitaxel and carboplatin)
† Based on the stratified Cox proportional hazard model
‡ Based on stratified log-rank test (compared to an alpha boundary of 0.00549)
§ Based on stratified log-rank test (compared to an alpha boundary of 0.00144)
¶ Response: Best objective response as confirmed complete response or partial response
# Based on Kaplan-Meier estimation
NR = not reached

Figure 35: 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
† Based on the protocol-specified final OS analysis

Merkel Cell Carcinoma

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

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

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

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

Efficacy results are summarised in Table 42.

Table 42: Efficacy Results in KEYNOTE-017 and KEYNOTE-913

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

\+ Denotes ongoing response

NR = not reached

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 randomised, multicentre, open-label, active-controlled trial KEYNOTE-426, conducted in patients with advanced RCC, regardless of PD-L1 tumour 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. Randomisation was stratified by risk categories (favourable versus intermediate versus poor) and geographic region (North America versus Western Europe versus “Rest of the World”). Patients were randomised (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 tumour status was performed at baseline, after randomisation at Week 12, then every 6 weeks thereafter until Week 54, and then every 12 weeks thereafter. Chemistry and haematology 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% favourable, 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 43 summarises key efficacy measures. Improvements in OS, PFS and ORR were shown consistently across all tested subgroups, including subgroups by IMDC risk category and PD-L1 tumour expression status.

Table 43: 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%)

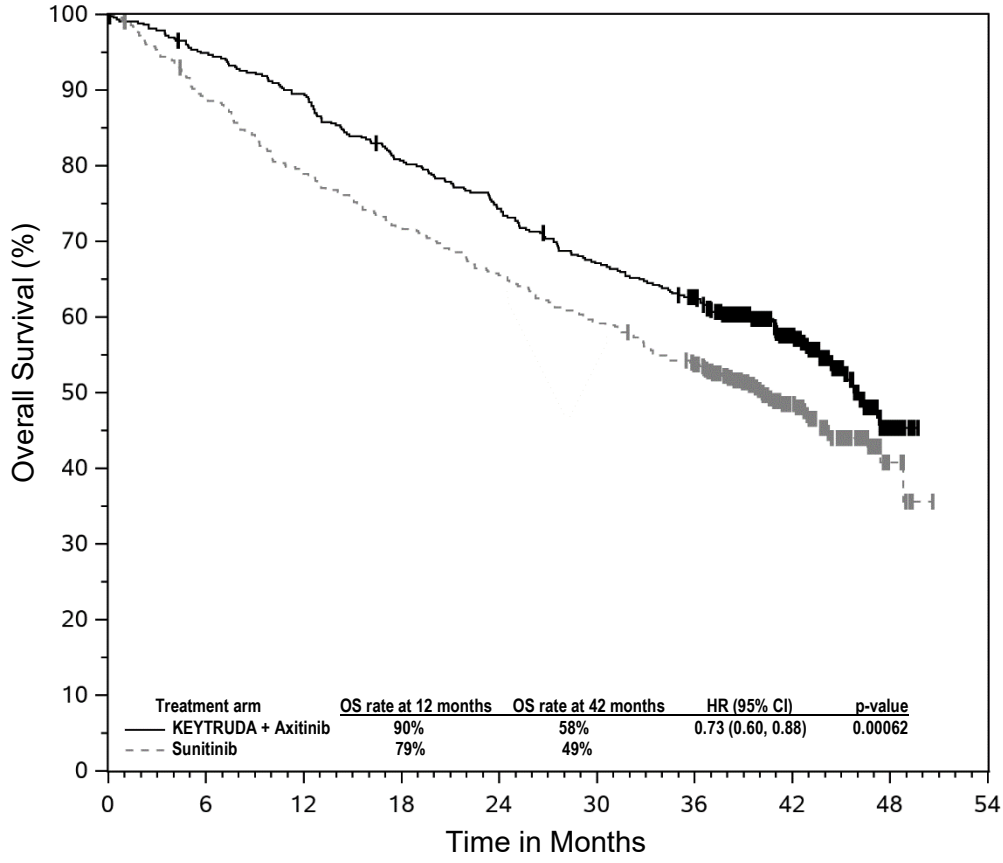
* Based on the stratified Cox proportional hazard model
† Based on stratified log-rank test
‡ Based on patients with a best overall response as confirmed complete or partial response
§ Based on Miettinen and Nurminen method stratified by IMDC risk group and geographic region
¶ Based on Kaplan-Meier estimation
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% (95% CI: 86, 92) in the KEYTRUDA and axitinib arm and 79% (95% CI: 75, 83) in the sunitinib arm. The 24-month OS rates were 74% (95% CI: 70, 78) in the KEYTRUDA and axitinib arm and 66% (95% CI: 61, 70) in the sunitinib arm. The 36-month OS rates were 63% (95% CI: 58, 67) in the KEYTRUDA and axitinib arm and 54% (95% CI: 49, 58) in the sunitinib arm. The 42-month OS rates were 58% (95% CI: 53, 62) in the KEYTRUDA and axitinib arm and 49% (95% CI: 44, 53) 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 71%, 59%, 49%, and 45% at 12, 18, 24, and 30 months, respectively, in patients with confirmed

response in the KEYTRUDA and axitinib arm, vs. 62%, 46%, 37%, and 32% in patients with confirmed response in the sunitinib arm.

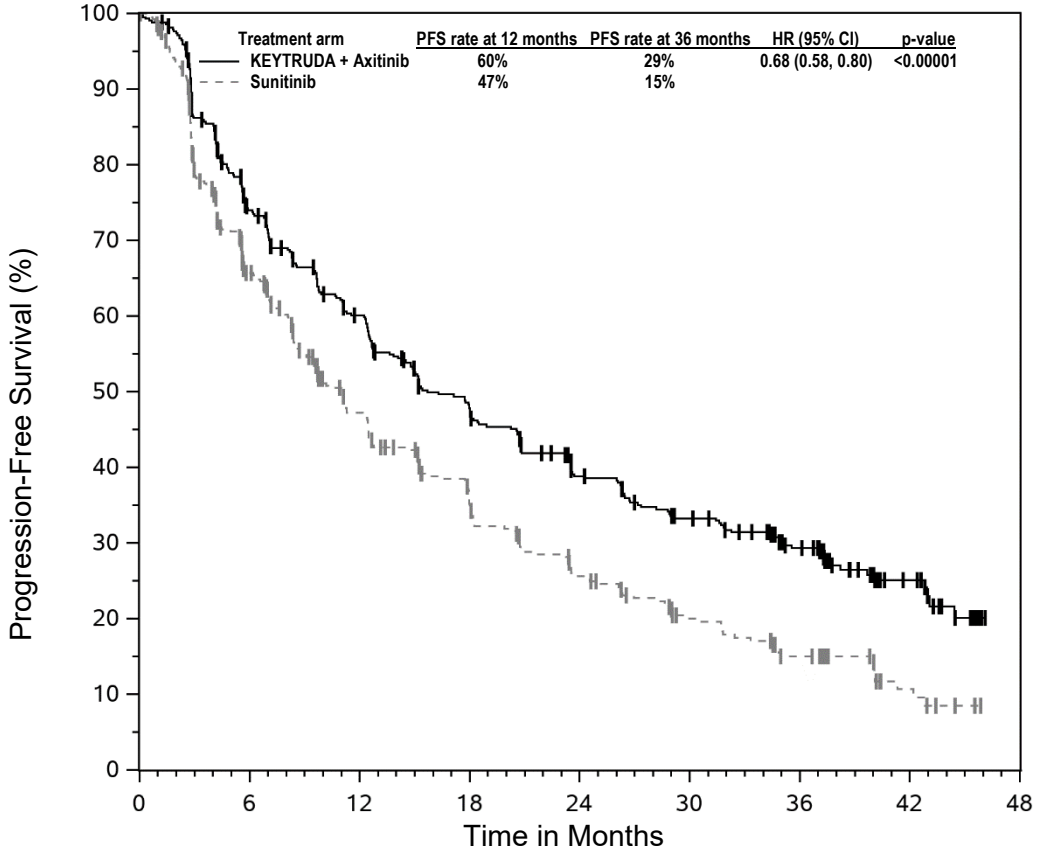
Figure 36: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-426 (Intent to Treat Population)



Number at Risk

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

Figure 37: 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 multicentre, open-label, randomised trial conducted in 1069 patients with advanced RCC in the first-line setting. Patients were enrolled regardless of PD-L1 tumour expression status. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible. Randomisation was stratified by geographic region (North America versus Western Europe versus "Rest of the World") and Memorial Sloan Kettering Cancer Center (MSKCC) prognostic groups (favourable versus intermediate versus poor risk).

Patients were randomised (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 tumour 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% favourable, 56% intermediate and 10% poor, and by MSKCC risk categories was 27% favourable, 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 randomised 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 summarised in Table 44. Consistent results were observed across pre-specified subgroups, MSKCC prognostic groups and PD-L1 tumour expression status.

Table 44: 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

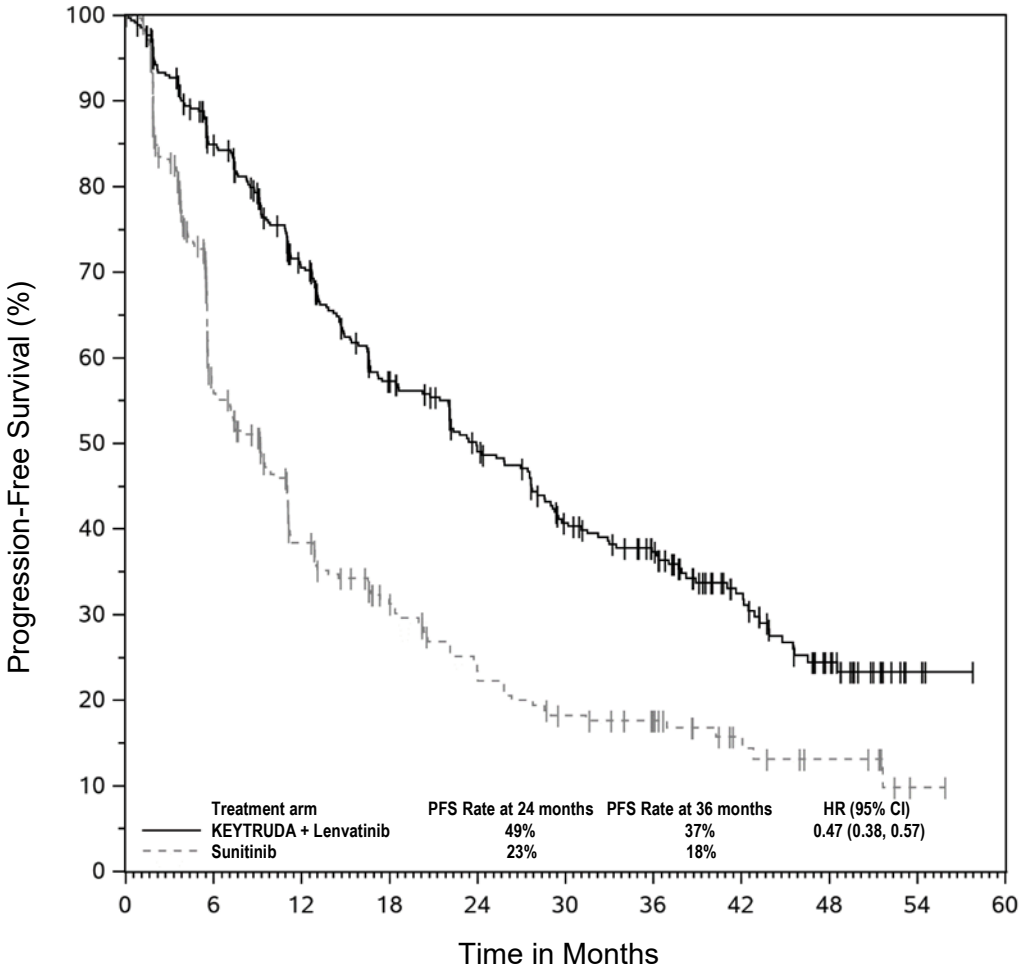
§ Nominal p-Value. At the earlier pre-specified final analysis of ORR (median follow-up time of 17.3 months), statistically significant superiority was achieved for ORR comparing KEYTRUDA plus lenvatinib with sunitinib, (odds ratio: 3.84 (95% CI: 2.81, 5.26), p-Value <0.0001)

¶ Based on Kaplan-Meier estimates

NR = not reached

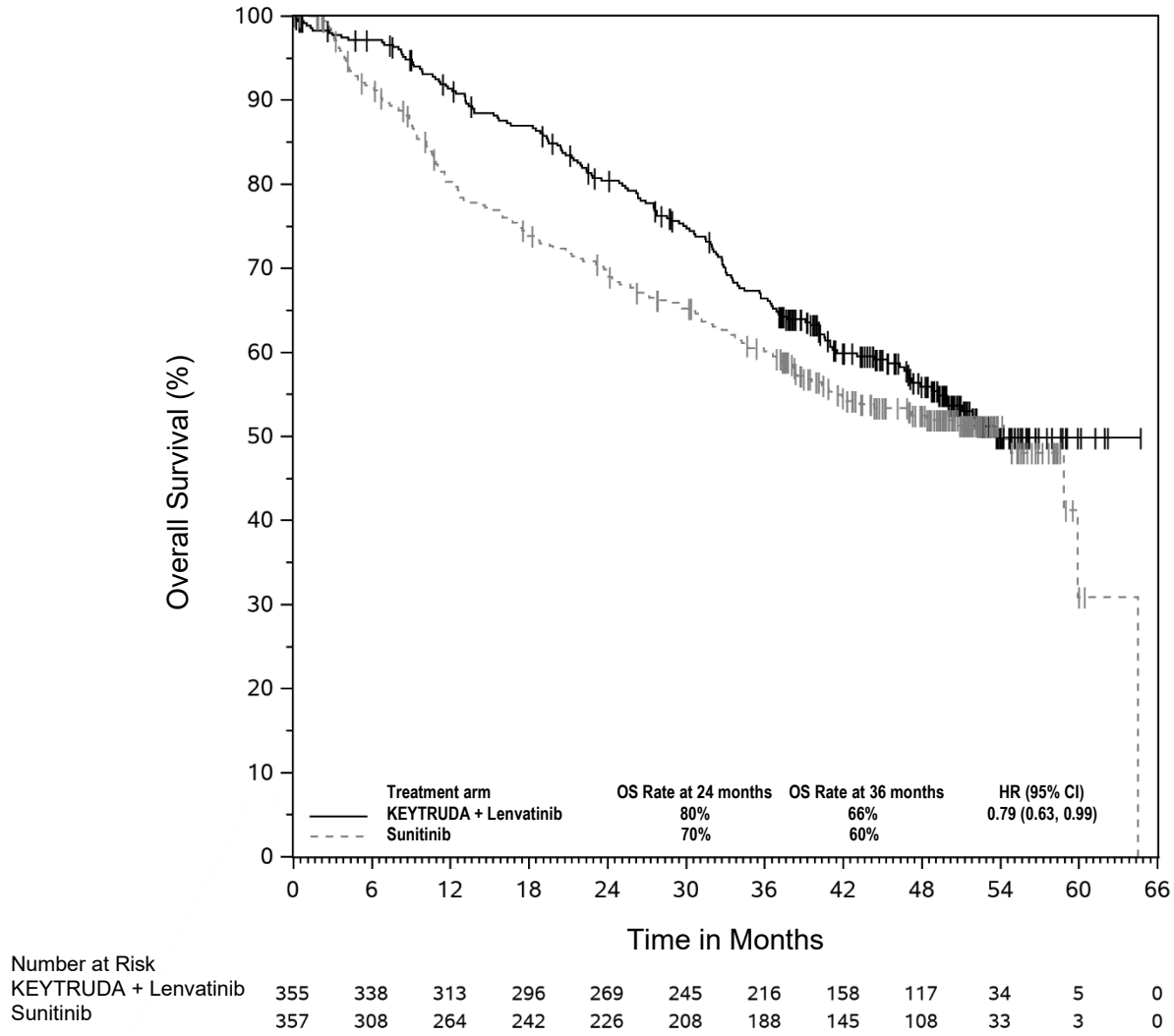
At the protocol-specified final analysis, median follow-up was 49.4 months. The median PFS was 23.9 months (95% CI: 20.8, 27.7) for KEYTRUDA in combination with lenvatinib and 9.2 months (95% CI: 6.0, 11.0) for sunitinib. The PFS HR was 0.47 (95% CI: 0.38, 0.57, nominal p<0.0001). Median OS was 53.7 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 Figure 38 and Figure 39.

Figure 38: 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 39: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-581



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, dyspnoea, 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]), dyspnoea (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 tumour 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 summarised in Table 45. Clinical activity was observed regardless of the histological subtype.

Table 45: 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%
Response Duration*,‡	
Median in months (range)	19.5 (1.5+, 23.5+)

* 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

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 multicentre, randomised, double-blind, placebo-controlled study in 994 patients with intermediate-high or high risk of recurrence of RCC, or M1 no evidence of disease (NED). The intermediate-high risk category included: pT2 with Grade 4 or sarcomatoid features; pT3, any Grade without nodal involvement (N0) or distant metastases (M0). The high risk category included: pT4, any Grade N0 and M0; any pT, any Grade with nodal involvement and M0. The M1 NED category included patients with metastatic disease who had undergone complete resection of primary and metastatic lesions. 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 randomised (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. Randomisation 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 randomisation, then every 16 weeks from year 3 to 5, and then every 24 weeks annually.

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

The primary efficacy outcome measure was investigator-assessed disease-free survival (DFS). The key secondary outcome measure was OS. The study demonstrated statistically significant improvements in DFS and OS for patients randomised to the KEYTRUDA arm compared with placebo. Generally consistent results were observed across pre-specified subgroups. Efficacy results are summarised in Table 46 and Figure 40 and Figure 41 .

Table 46: Efficacy Results in KEYNOTE-564

Endpoint	**KEYTRUDA 200 mg every 3 weeks n=496**	**Placebo n=498**
DFS*		
Number (%) of patients with event	109 (22%)	151 (30%)
Median in months (95% CI)	NR	NR
Hazard ratio‡ (95% CI)	0.68 (0.53, 0.87)	
p-Value	0.0010§	
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
Hazard ratio (95% CI)‡	0.62 (0.44, 0.87)	
p-Value	0.0024§	
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 40: Kaplan-Meier Curve for Disease-Free Survival by Treatment Arm in KEYNOTE-564

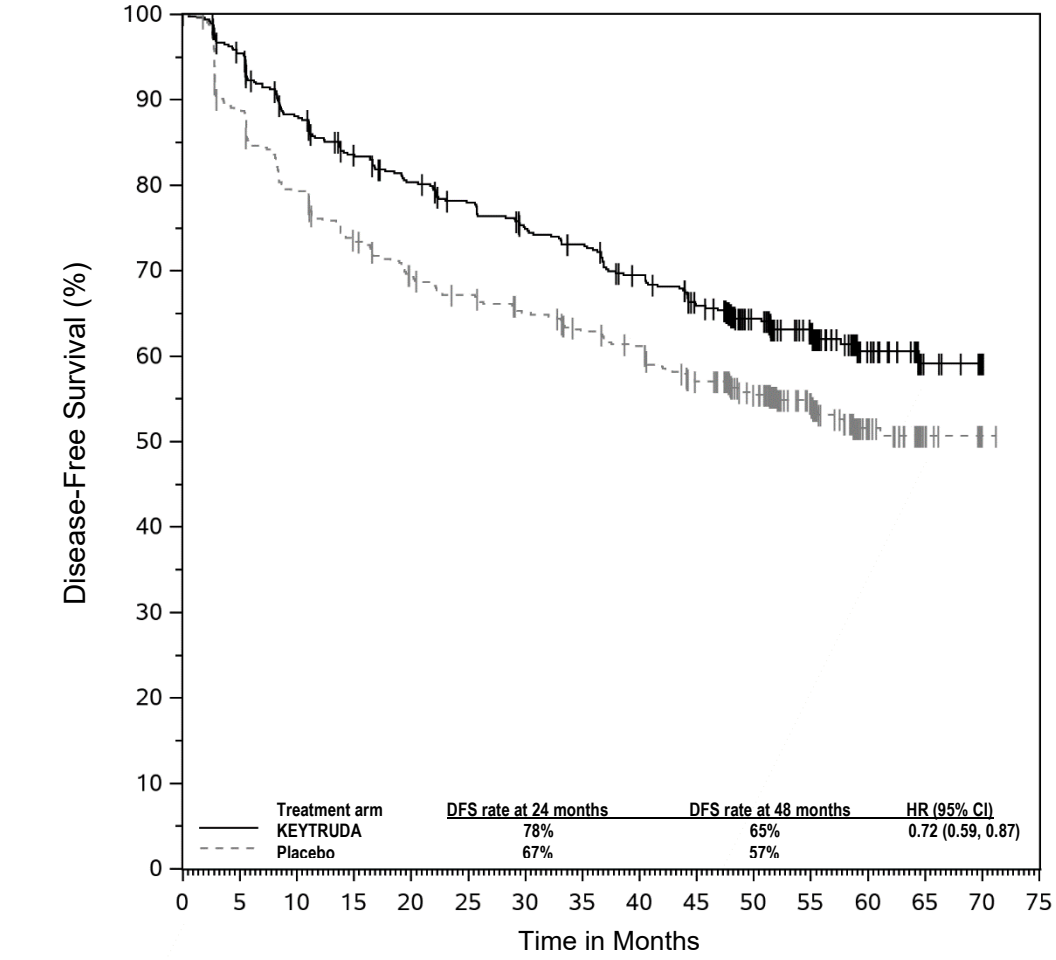
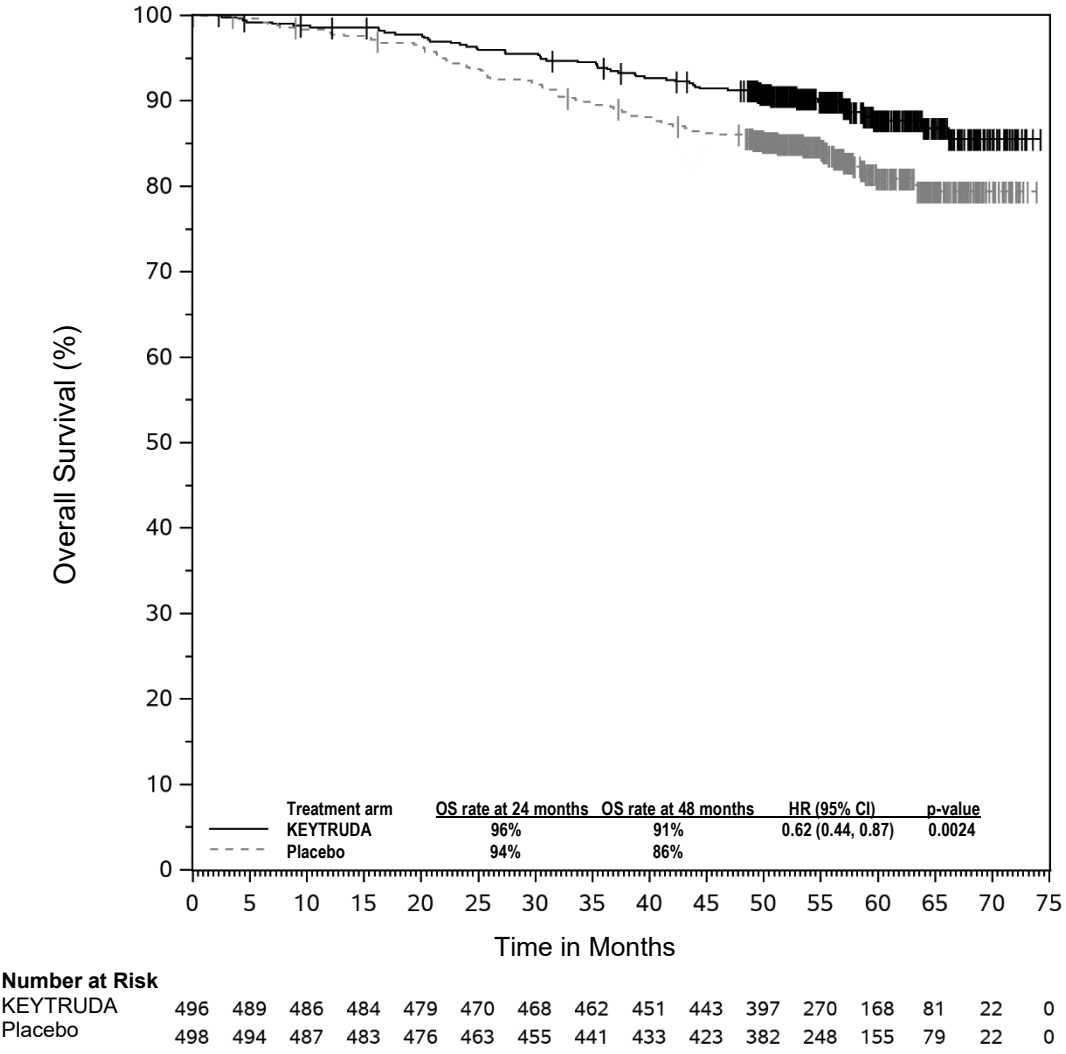


Figure 41: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-564



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 multicentre, randomised, double-blind, placebo-controlled trial in 810 patients with advanced or recurrent endometrial carcinoma including those with dMMR and pMMR tumours. 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. Randomisation was stratified according to MMR status, ECOG PS (0 or 1 vs. 2), and prior adjuvant chemotherapy. Patients were randomised (1:1) to one of the following treatment arms:

- KEYTRUDA 200 mg every 3 weeks, paclitaxel 175 mg/m2 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/m2 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 tumour status was performed every 9 weeks for the first 9 months and then every 12 weeks thereafter.

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

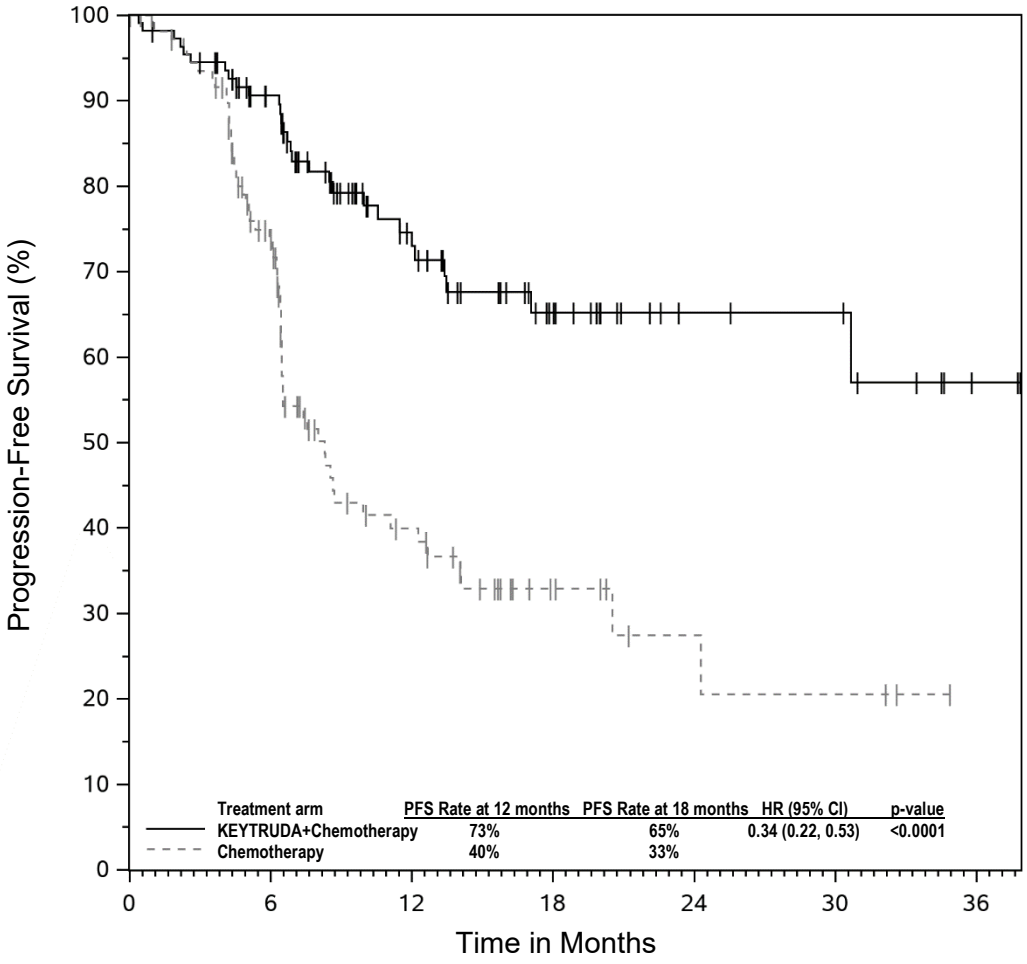
The primary efficacy outcome measure was PFS as assessed by the investigator according to RECIST 1.1. Secondary efficacy outcome measures included OS, ORR, and DoR. The trial demonstrated statistically significant improvements in PFS for patients randomised to KEYTRUDA in combination with chemotherapy 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 randomised 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 47 and Figure 42 and Figure 43 summarise the efficacy results for KEYNOTE-868 by MMR status.

Table 47: 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

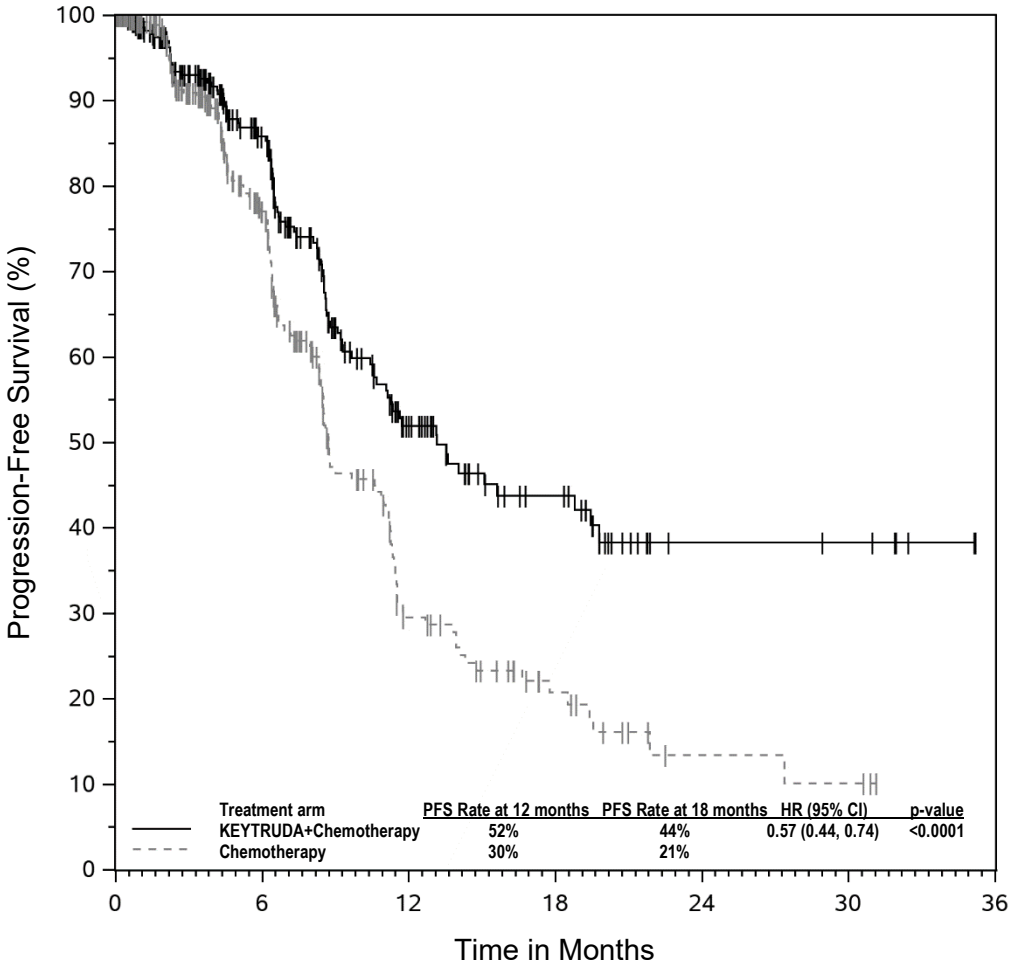
Figure 42: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-868 (dMMR Population)



Number at Risk

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

Figure 43: 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 multicentre, randomised, 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. Randomisation 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 randomised (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 tumour status was performed every 8 weeks.

A total of 827 patients were enrolled and randomised 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 tumour 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 summarised in Table 48. Improvements in OS, PFS, and ORR were consistently demonstrated across pre-specified subgroups, including histology, prior therapies, MMR status, and ECOG performance status.

Table 48: Efficacy Results in Patients with Advanced Endometrial Carcinoma in KEYNOTE-775

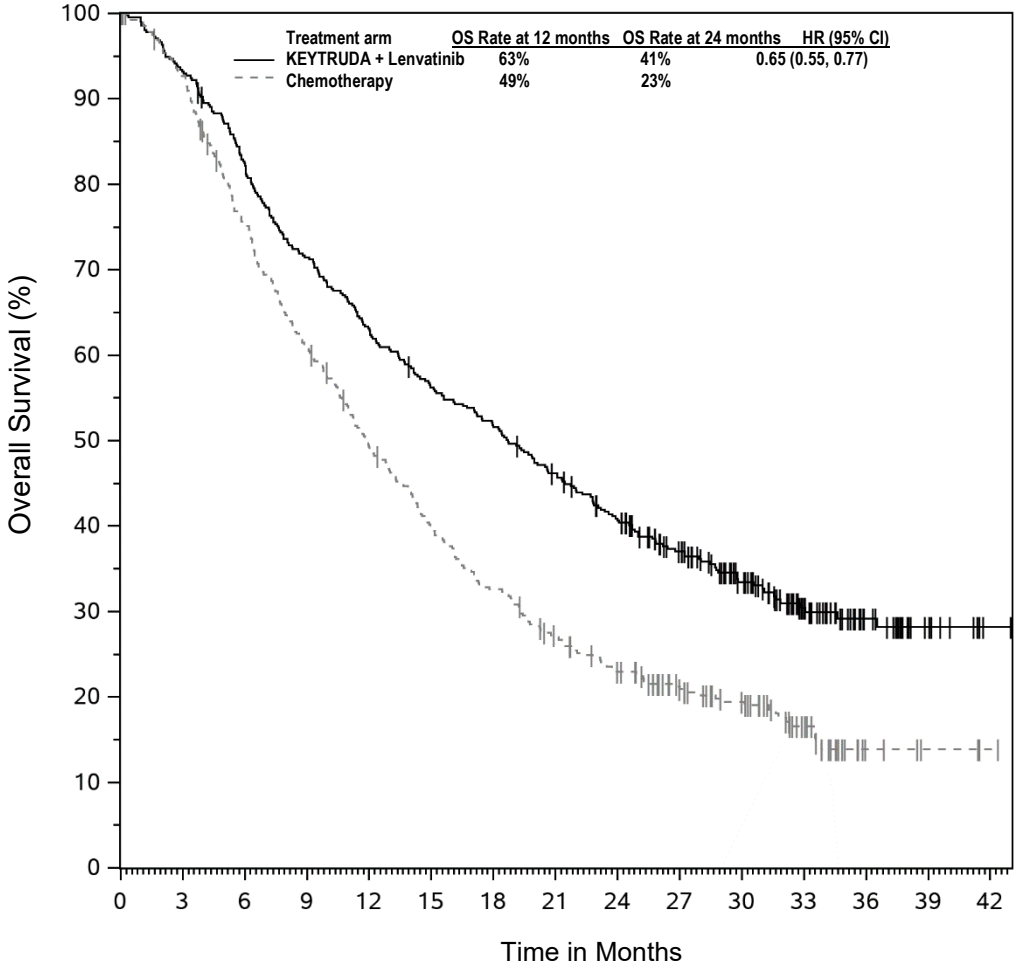
Endpoint	KEYTRUDA 200 mg every 3 weeks + lenvatinib n=411	Doxorubicin or paclitaxel n=416
OS		
Number (%) of patients with event	188 (46%)	245 (59%)
Median in months (95% CI)	18.3 (15.2, 20.5)	11.4 (10.5, 12.9)
Hazard ratio* (95% CI)	0.62 (0.51, 0.75)	
p-Value†	<0.0001	
PFS		
Number (%) of patients with 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 44 and 45.

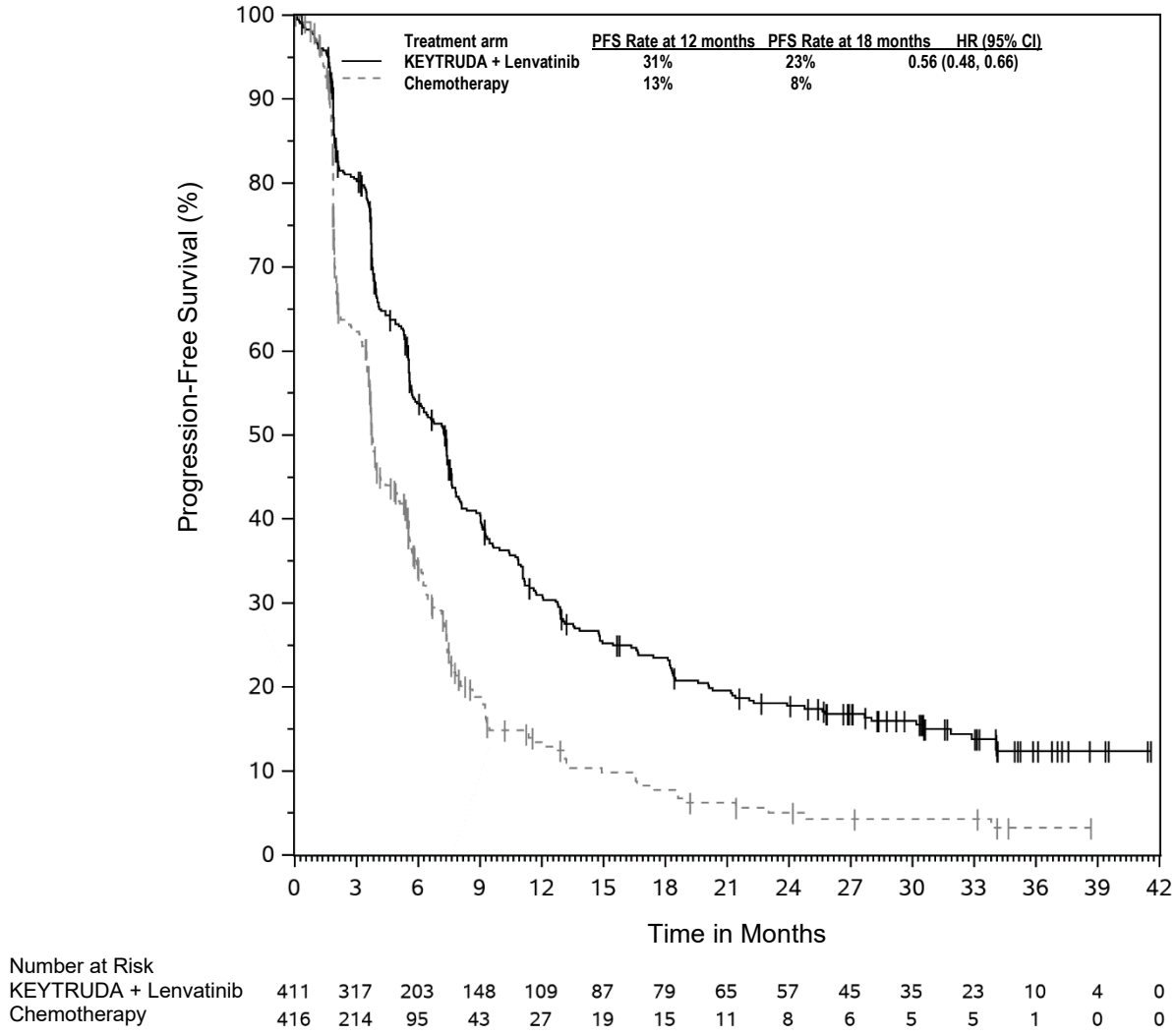
At the time of the protocol-specified final OS analysis, an updated ORR analysis demonstrated ORR of 34% for KEYTRUDA in combination with lenvatinib and 15% for doxorubicin or paclitaxel. The median duration of response was 12.9 months (range: 1.6+, 39.5+) for KEYTRUDA in combination with lenvatinib 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 44: 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 45: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-775 (Intent to Treat Population)



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-randomised, multicentre, open-label, multi-cohort trial KEYNOTE-146, conducted in 108 patients with 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 tumour 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 tumours that were not MSI-H or dMMR, 10% (n=11) had tumours that were MSI-H or dMMR, and in 3% (n=3) the status was not known. The baseline characteristics of the 94 patients with tumours 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 summarised in Table 49.

Table 49: Efficacy Results in Patients with Endometrial Carcinoma that is Not MSI-H or dMMR

Endpoint	**KEYTRUDA with lenvatinib n=94***
Best Overall Response†	
ORR %, (95% CI)	38.3% (29, 49)
Complete response	10.6%
Partial response	27.7%
Stable disease	40.4%
Disease control rate	78.7%
Response Duration†	
Median in months (range)	NR (1.2+, 33.1+)‡
% with duration ≥6 months	76%§
% with duration ≥12 months	51%¶
Time to Response	
Median in months (range)	1.4 (1.1, 8.0)
PFS†	
Median in months (95% CI)	5.4 (4.4, 7.6)
6-month PFS rate	49%
12-month PFS rate	33%
OS	
Median in months (95% CI)	16.4 (13.5, 25.9)
12-month OS rate	70%

* Median follow-up time of 18.7 months
† Assessed by BICR using RECIST 1.1
‡ Based on patients (n=36) with a response by independent review
§ Based on Kaplan-Meier estimates; includes 25 patients with responses of 6 months or longer
¶ Based on Kaplan-Meier estimates; includes 8 patients with responses of 12 months or longer
\+ Denotes ongoing
NR=not reached

Cutaneous Squamous Cell Carcinoma

KEYNOTE-629: Open-label trial of monotherapy in cSCC patients naïve to treatment

The efficacy of KEYTRUDA was investigated in KEYNOTE-629, a multicentre, multi-cohort, non-randomised, open-label trial that enrolled 159 patients with recurrent or metastatic cSCC or locally advanced cSCC. The trial excluded patients with autoimmune disease or a medical condition that required immunosuppression.

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

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

Among the 105 patients treated with recurrent or metastatic cSCC, the study population characteristics were: median age of 72 years (range: 29 to 95); 71% age 65 or older; 76% male; 71% White; 25% race unknown; 34% ECOG PS of 0 and 66% ECOG PS of 1. Forty-five percent of patients had locally recurrent only cSCC, 24% had metastatic only cSCC, and 31% had both locally recurrent and metastatic cSCC. Eighty-seven percent received one or more prior lines of therapy; 74% received prior radiation therapy.

Among the 54 patients with locally advanced cSCC treated, the study population characteristics were: median age of 76 years (range: 35 to 95), 80% age 65 or older; 72% male; 83% White, 13% race unknown; 41% ECOG PS of 0 and 59% ECOG PS of 1. Twenty-two percent received one or more prior lines of therapy; 63% received prior radiation therapy.

Efficacy results are summarised in Table 50.

Table 50: Efficacy Results for Patients with Cutaneous Squamous Cell Carcinoma

Endpoint	KEYTRUDA Recurrent or Metastatic cSCC n=105	KEYTRUDA Locally Advanced cSCC n=54	Combined cSCC n=159
Objective Response Rate			
ORR (95% CI)	35% (26, 45)	52% (38, 66)	41% (33, 49)
Complete response rate	12%	22%	16%
Partial response rate	23%	30%	25%
Time to Response			
Median in months (range)	1.6 (1.2, 24.7)	2.7 (1.1, 12.3)	2.0 (1.1, 24.7)
Duration of Response*	n=37	n=28	n=65
Median in months (range)	NR (2.7, 64.2+)†	47.2 (1.0+, 49.9+)‡	52.5 (1.0+, 64.2+)§
% with duration ≥6 months	81%	93%	86%
% with duration ≥12 months	78%	85%	81%

* Median follow-up time of: recurrent or metastatic cSCC: 23.8 months; locally advanced cSCC: 48.0 months
† Based on patients (n=37) with a confirmed response by independent review
‡ Based on patients (n=28) with a confirmed response by independent review
§ Based on patients (n=65) with a confirmed response by independent review
\+ Denotes ongoing response

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 multicentre, randomised, 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. Randomisation 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 randomised (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 tumour 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 tumours that expressed PD-L1 with a CPS ≥1 and 5% (n=74) of patients had tumours that were MSI-H. Eighty-six percent of patients received CAPOX.

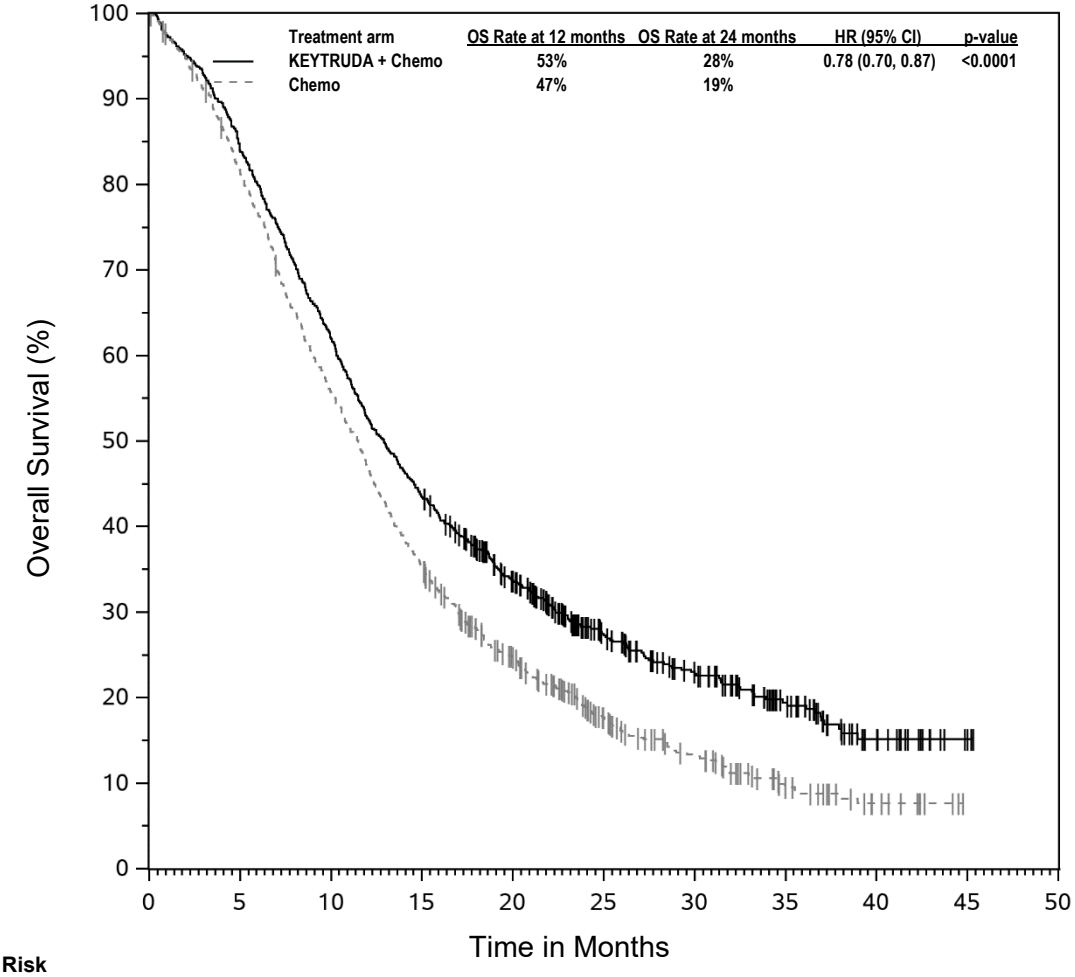
A statistically significant improvement in OS, PFS and ORR was demonstrated in patients randomised to KEYTRUDA in combination with chemotherapy compared with placebo in combination with chemotherapy. Efficacy results are summarised in Table 51.

Table 51: 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 & Nurminen method

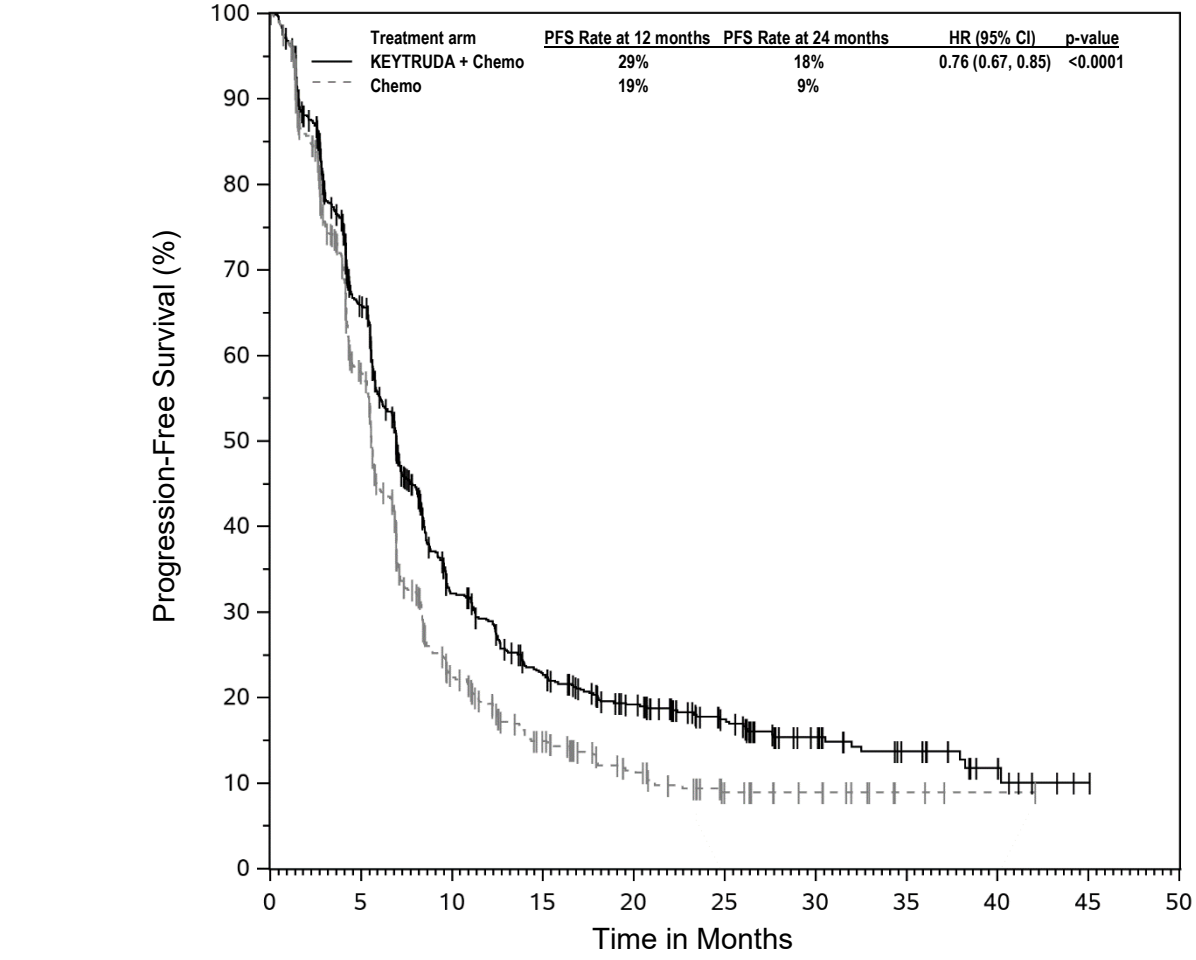
Figure 46: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-859



Number at Risk

KEYTRUDA + Chemo	790	663	490	343	240	143	95	55	19	3	0
Chemo	789	636	434	274	169	95	58	26	10	0	0

Figure 47: 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 multicentre, randomised, 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. Randomisation 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 randomised (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 tumour status was performed every 6 weeks.

Among the 698 patients randomised in KEYNOTE-811, 594 (85%) had tumours 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 tumours that were not MSI-H, 1% (n=8) had tumours 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 randomised 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 randomised 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 randomised 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 tumours express PD-L1 with a CPS of ≥1.

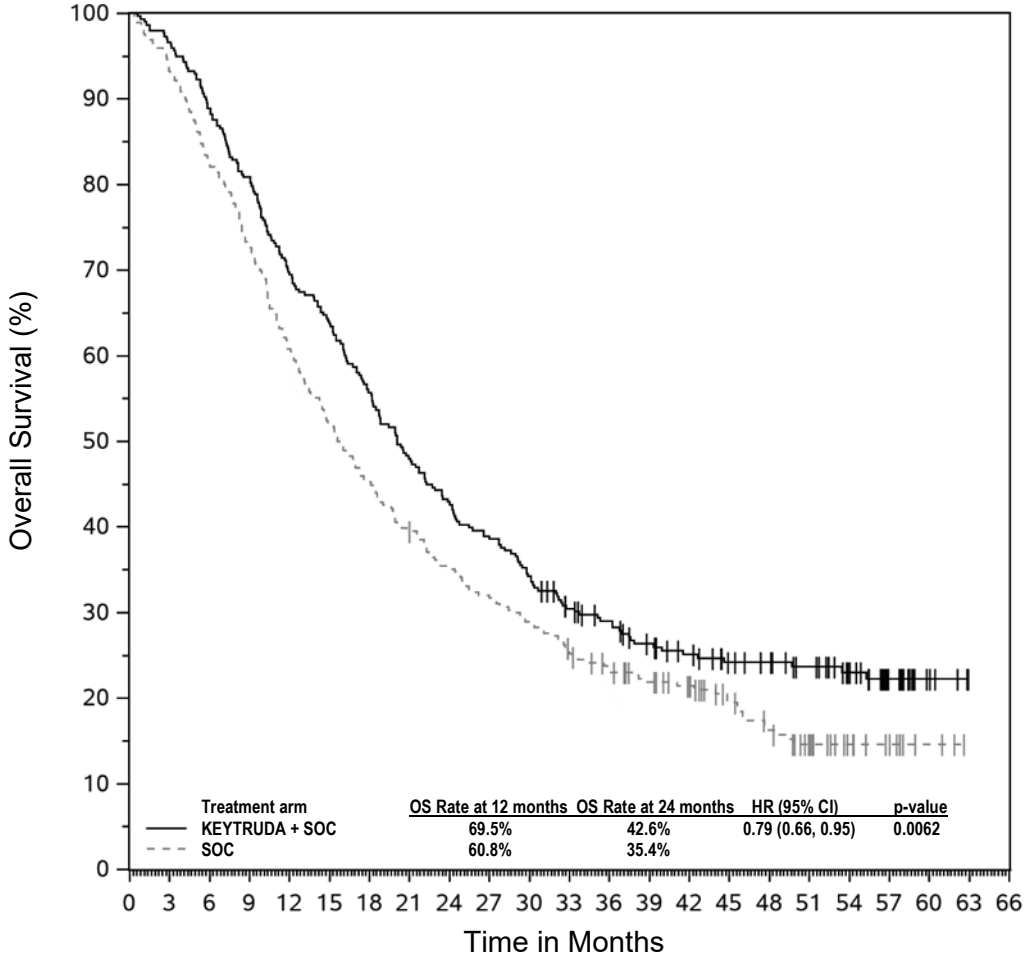
Efficacy results at the final analysis for the pre-specified subgroup of patients whose tumours expressed PD-L1 with a CPS ≥1 are summarised in Table 52 and Figures 48 and 49.

Table 52: 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 48: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-811 (CPS ≥1)

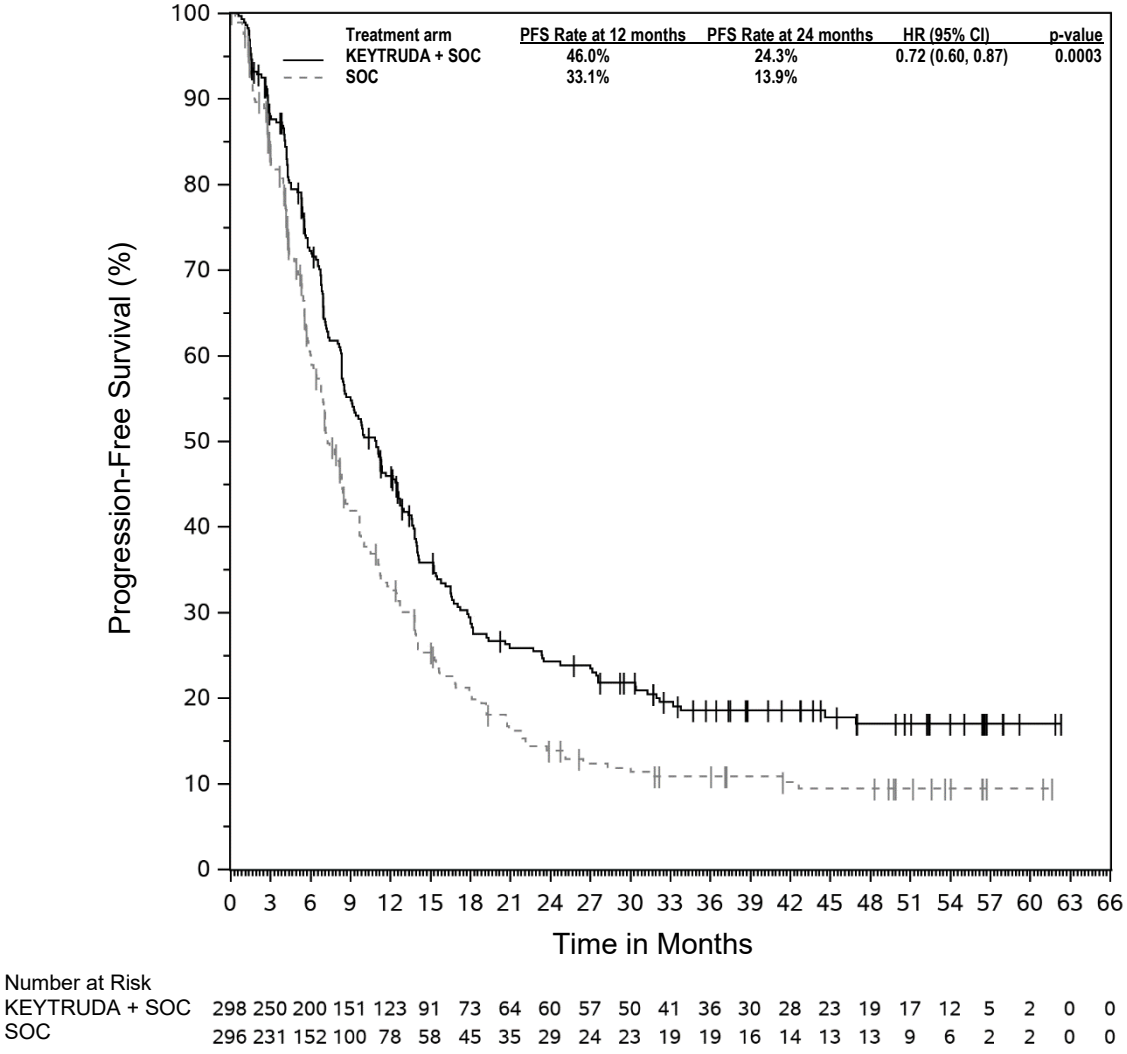


Number at Risk

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



*Based on the pre-specified final analysis

Oesophageal Cancer

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

The efficacy of KEYTRUDA was investigated in KEYNOTE590, a multicentre, randomised, placebo-controlled trial that enrolled 749 patients as a first-line treatment in patients with locally advanced unresectable or metastatic carcinoma of the oesophagus and gastroesophageal junction. All patients were required to have tumour 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. Randomisation was stratified by tumour histology (squamous cell carcinoma vs. adenocarcinoma), geographic region (Asia vs. ex-Asia), and ECOG performance status (0 vs. 1).

Patients were randomised (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 randomised 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 tumour 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 tumour histology of squamous cell carcinoma, and 27% had adenocarcinoma.

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 oesophagus or gastroesophageal junction. The investigator-assessed results were consistent with BICR.

Table 53 summarises the key efficacy measures for KEYNOTE-590. The Kaplan-Meier curves for OS and PFS are shown in Figure 50 and Figure 51.

Table 53: Efficacy Results in Patients with Locally Advanced Unresectable or Metastatic Oesophageal 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 50: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-590

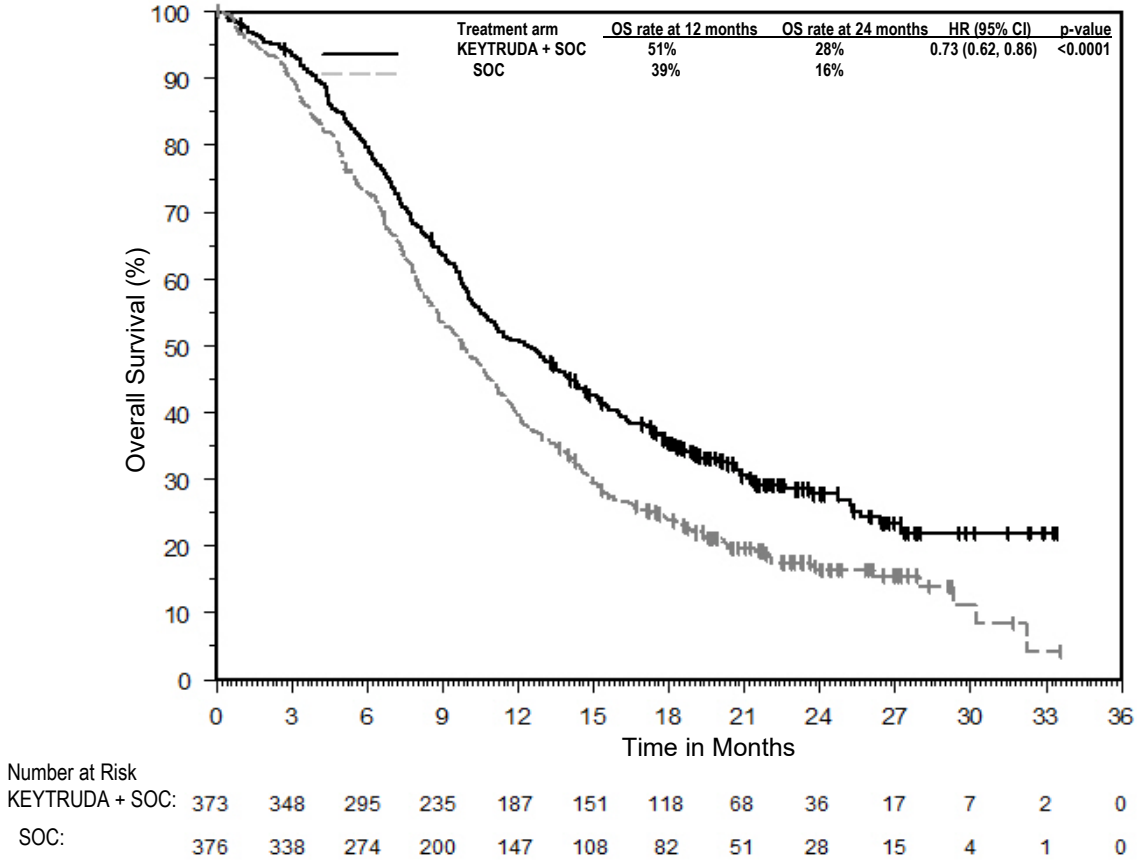
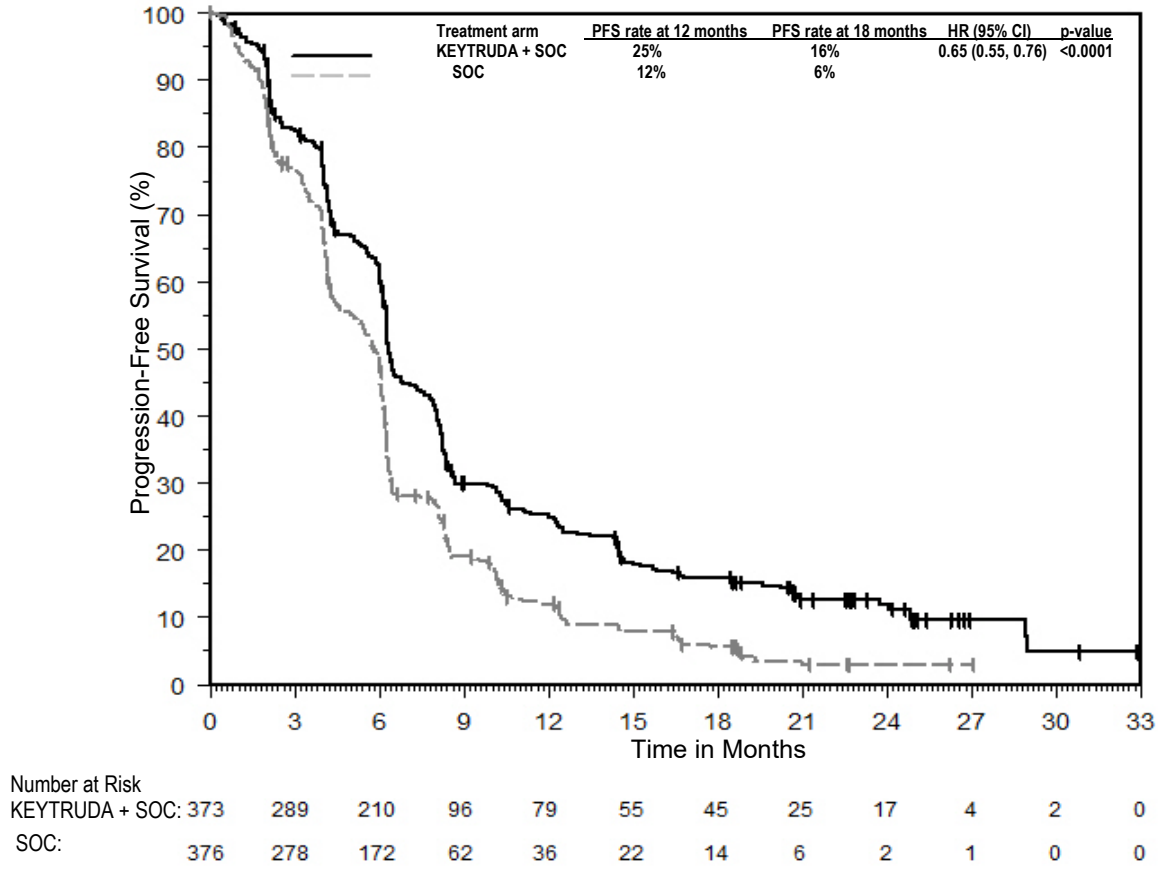


Figure 51: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-590



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 randomised, double-blind, multicentre, placebo-controlled study. The key eligibility criteria for this study were newly diagnosed previously untreated high-risk early-stage TNBC (tumour size >1 cm but ≤2 cm in diameter with nodal involvement or tumour size >2 cm in diameter regardless of nodal involvement), regardless of tumour 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. Randomisation was stratified by nodal status (positive vs. negative), tumour size (T1/T2 vs. T3/T4), and choice of carboplatin (dosed every 3 weeks vs. weekly).

Patients were randomised (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 pathological complete response (pCR) rate and event-free survival (EFS). pCR was defined as absence of invasive cancer in the breast and lymph nodes (ypT0/Tis ypN0) and was assessed by the blinded local pathologist at the time of definitive surgery. EFS was defined as the time from randomisation 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 randomised: 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 Tumour 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 randomised to KEYTRUDA in combination with chemotherapy followed by KEYTRUDA monotherapy compared with patients randomised to placebo in combination with chemotherapy followed by placebo alone. Efficacy results are summarised in Table 54 and Figure 52 and Figure 53.

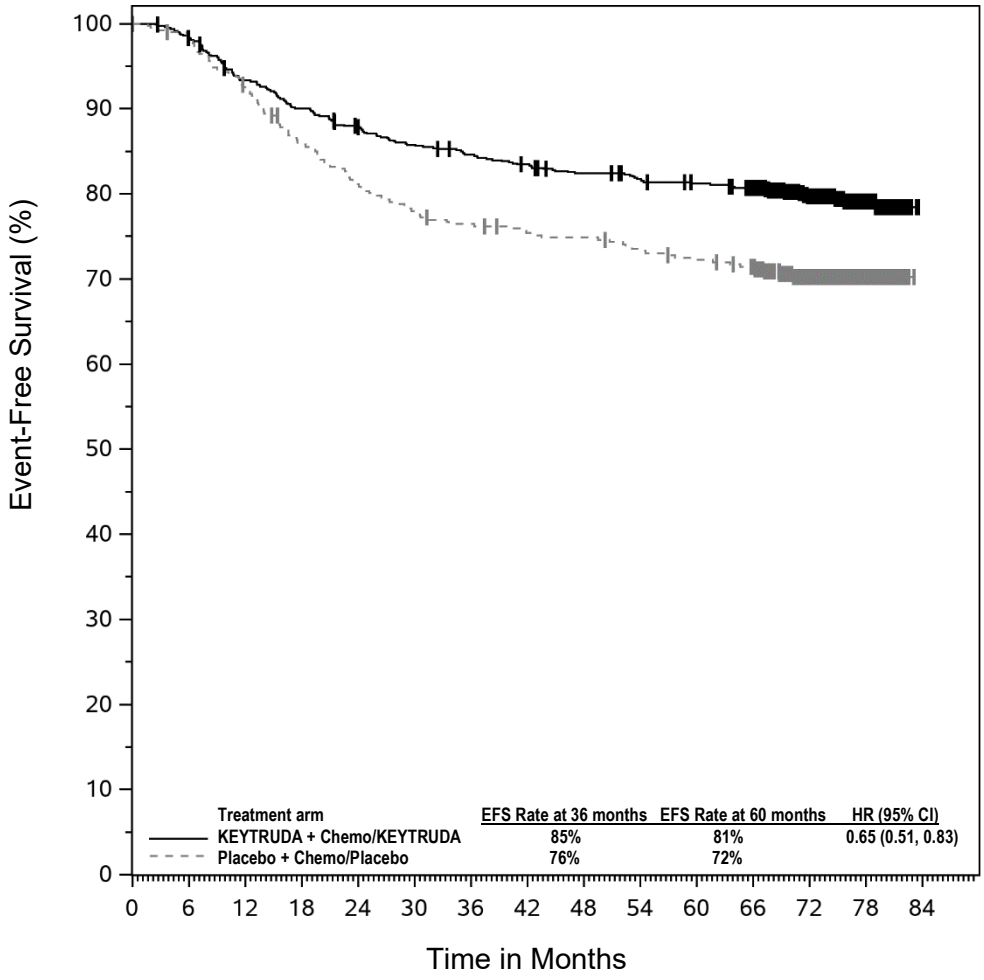
Table 54: Efficacy Results in Patients with High-Risk Early-Stage TNBC in KEYNOTE-522

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

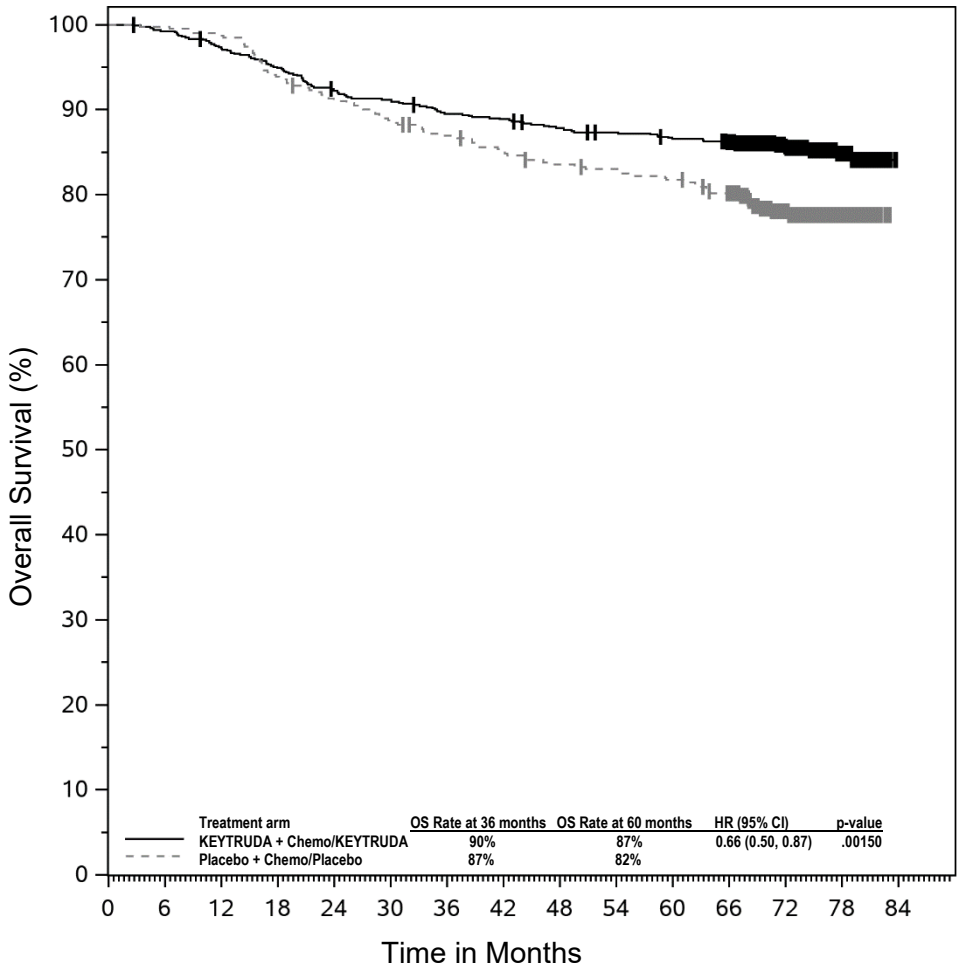
In a pre-specified interim analysis (median follow-up time was 73.1 months (range: 2.7 to 83.9 months), the EFS HR was 0.65 (95% CI: 0.51, 0.83). The 36-month EFS rates were 85% (95% CI: 82, 87) in the KEYTRUDA arm and 76% (95% CI: 72, 80) in the placebo arm. The 60-month EFS rates were 81% (95% CI: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

Figure 52: 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 53: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-522 (Intent to Treat Population)



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 randomised, double-blind, multicentre, placebo-controlled study. The key eligibility criteria for this study were locally

recurrent unresectable or metastatic TNBC, regardless of tumour 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. Randomisation was stratified by chemotherapy treatment (paclitaxel or nab-paclitaxel vs. gemcitabine and carboplatin), tumour 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 randomised (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 tumour 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 tumour 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 tumour PD-L1 expression CPS ≥10 as assessed by BICR using RECIST 1.1.

A total of 847 patients were randomised: 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 tumour PD-L1 expression defined as CPS ≥1 and 38% had tumour PD-L1 expression CPS ≥10.

In KEYNOTE-355, there was a statistically significant improvement in OS and PFS in patients with tumour PD-L1 expression CPS ≥10 randomised to KEYTRUDA in combination with paclitaxel, nab-paclitaxel, or gemcitabine and carboplatin compared with patients randomised 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 summarised in Table 55 and Figures 54 and 55.

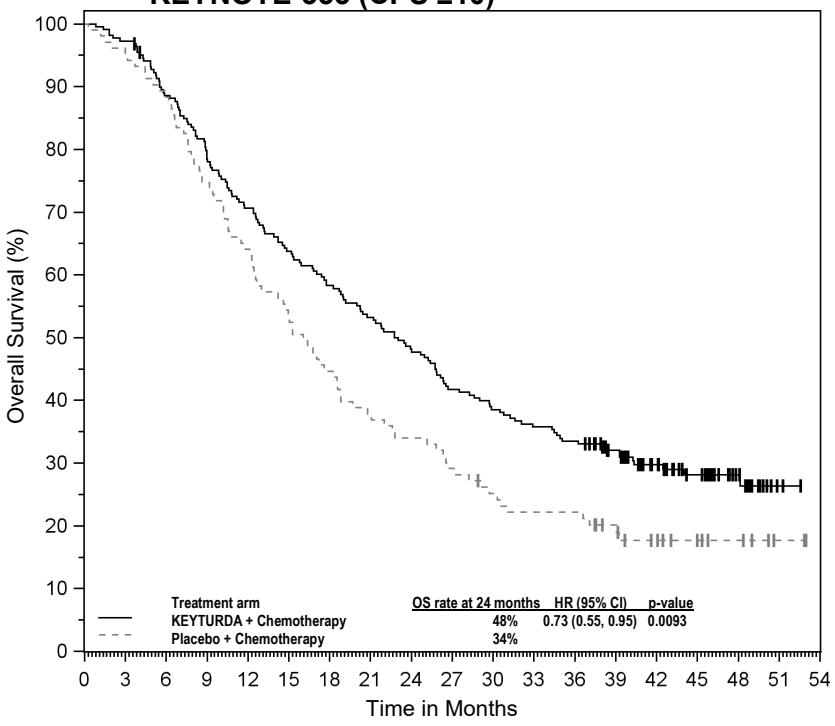
Table 55: Efficacy Results in Patients with Locally Recurrent Unresectable or Metastatic TNBC with PD-L1 Expression CPS ≥10 in KEYNOTE-355

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
β 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 54: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-355 (CPS ≥10)*

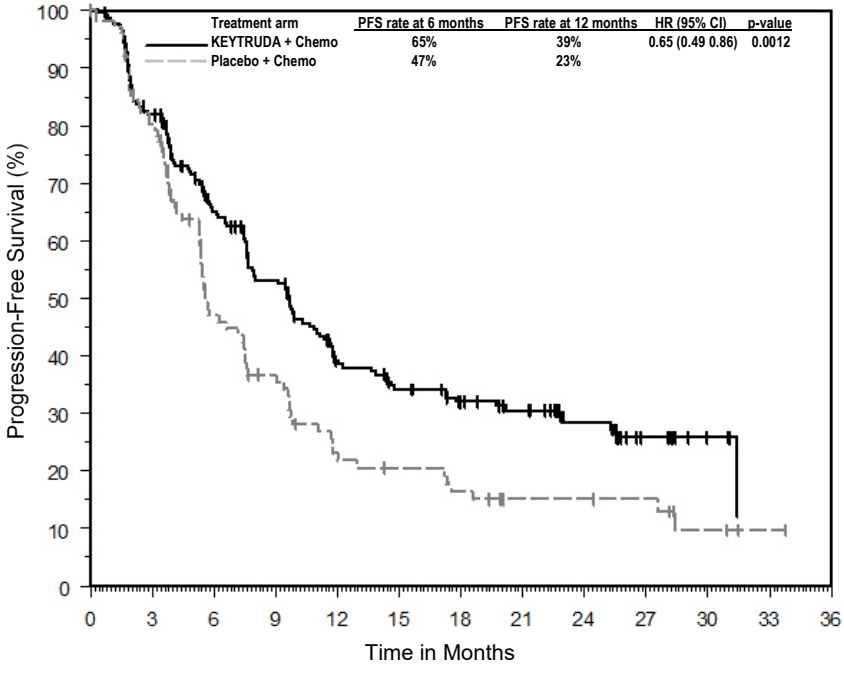


Number at Risk

KEYTURDA + 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 55: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-355 (CPS ≥10)*



Number at Risk

KEYTRUDA + Chemo:	220	173	122	96	63	52	44	37	25	12	5	0	0
Placebo + Chemo:	103	80	41	30	18	15	12	8	8	7	3	1	0

*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.

Paediatric Patients

Efficacy for paediatric patients with melanoma, MPM, cHL, MCC, or MSI-H cancer is extrapolated from the results in the respective adult populations.

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 neutralising antibodies against pembrolizumab. There was no evidence of an altered pharmacokinetic or safety profile with anti-pembrolizumab binding or neutralising antibody development.

5.2 Pharmacokinetic properties

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; CV: 20%). As an antibody, pembrolizumab is not expected to bind to plasma proteins in a specific manner.

Metabolism

Pembrolizumab is catabolised 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 hepatic impairment, and tumour 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.

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 section 4.2]

Hepatic Impairment

The effect of hepatic impairment on the clearance of pembrolizumab was evaluated by population pharmacokinetic analysis in patients with mild hepatic impairment (total bilirubin (TB) 1.0 to 1.5 x ULN or AST >ULN as defined using the National Cancer Institute criteria of hepatic dysfunction) compared to patients with normal hepatic function (TB and AST ≤ULN). No clinically important differences in the clearance of pembrolizumab were found between patients with mild hepatic impairment and normal hepatic function. KEYTRUDA has not been studied in patients with moderate (TB >1.5 to 3 x ULN and any AST) or severe (TB >3 x ULN and any AST) hepatic impairment [see section 4.2].

5.3 Preclinical safety data

Chronic Toxicity

The safety of pembrolizumab was evaluated in a 1-month and a 6-month repeat-dose toxicity study in Cynomolgus monkeys administered IV doses of 6, 40 or 200 mg/kg once a week in the 1-month study and once every two weeks in the 6-month study, followed by a 4-month treatment-free period. No findings of toxicological significance were observed and the no observed adverse effect level (NOAEL) in both studies was ≥200 mg/kg, which produced exposure multiples of 19 and 94 times the exposure in humans at doses of 10 and 2 mg/kg, respectively. The exposure multiple between the NOAEL and a human dose of 200 mg was 74.

Genotoxicity

The genotoxic potential of pembrolizumab has not been evaluated. As a large protein molecule, pembrolizumab is not expected to interact directly with DNA or other chromosomal material.

Carcinogenicity

The carcinogenic potential of pembrolizumab has not been evaluated in long-term animal studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine

Histidine monohydrochloride monohydrate

Sucrose

Polysorbate 80

Water for Injection

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

24 months from date of manufacture stored at 2° to 8°C (Refrigerate, do not freeze) protect from light.

6.4 Special precautions for storage

Store in a refrigerator (2°C to 8°C). Protect from light. Do not freeze. Do not shake.

For storage conditions after dilution of the medicinal product, *see section 6.6*.

6.5 Nature and Contents of Container

Carton of one 100 mg/4 mL concentrate for solution for infusion single-use vial.

6.6 Special precautions for disposal and other handling

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, colourless to slightly yellow solution. Discard the vial if visible particles are observed.
- Withdraw the required volume up to 4 mL (100 mg) of KEYTRUDA and transfer into an intravenous bag containing 0.9% sodium chloride or 5% glucose (dextrose) to prepare a diluted solution with a final concentration ranging from 1 to 10 mg/mL. Mix diluted solution by gentle inversion.
- Do not freeze the infusion solution.

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

7. MEDICINE SCHEDULE

Prescription

8. SPONSOR

Merck Sharp & Dohme (New Zealand) Limited
PO Box 99-851 Newmarket Auckland 1149
New Zealand
Telephone: 0800 500 673

9. DATE OF FIRST APPROVAL

03 September 2015

10. DATE OF REVISION OF THE TEXT

26 May 2026

Summary table of changes

Section changed	Summary of new information
4.2	Inclusion of statement relevant to the interchangeability of the IV and SC formulations Identifying the availability of the alternative SC formulation and includes corresponding safety information and administration guidance Minor editorial update to better clarify dosing text for locally advanced head and neck with no change to dosing information

RCN: 000027689-NZ, 000028947-NZ

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