NEW ZEALAND DATA SHEET

1 PRODUCT NAME

KEYTRUDA® 50 mg powder for solution for infusion.

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

CAS No.: 1374853-91-4

KEYTRUDA 50 mg powder for solution for infusion

One vial contains 50 mg of pembrolizumab.

After reconstitution, 1 mL of solution contains 25 mg of pembrolizumab.

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

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 powder for solution for infusion is a sterile, preservative-free, white to off-white lyophilized powder. It is reconstituted and diluted for intravenous infusion.

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 patients with melanoma with lymph node involvement 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.

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.

Head and Neck Squamous Cell Cancer (HNSCC)

KEYTRUDA® is indicated for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy. This indication is approved based on overall response rate and duration of response. Improvements in overall survival, progression-free survival or health-related quality of life have not been established.

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. Continued approval for this indication depends on verification and description of clinical benefit in the confirmatory trials.

Non-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) tumours that have progressed following prior treatment and when there are no satisfactory alternative treatment options. This indication was approved based on the pooling of data on objective response rate and response duration across multiple different tissue types in a single-arm trial. 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. Continued approval for this indication depends on verification and description of clinical benefit in the confirmatory trials.

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

Renal Cell Carcinoma

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

4.2 Dose and method of administration

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

Patient Selection

For single-agent treatment of Non-Small Cell Lung Carcinoma or Urothelial Carcinoma

Select patients for treatment with KEYTRUDA based on the presence of positive PD-L1 expression [see section 5.1] in:

- stage III NSCLC who are not candidates for surgical resection or definitive chemoradiation.
- metastatic NSCLC.
- locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy.

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

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 for adjuvant treatment of melanoma, head and neck cancer, classical Hodgkin Lymphoma, urothelial carcinoma, MSI-H/dMMR cancer, previously untreated NSCLC, or RCC.
- Either 2 mg/kg every 3 weeks or a fixed dose of 200 mg every 3 weeks or 400 mg every 6 weeks for unresectable or metastatic melanoma or previously treated NSCLC.

The recommended dose of KEYTRUDA in paediatric patients is 2 mg/kg (up to a maximum of 200 mg) every 3 weeks for cHL, or MSI-H/dMMR cancer.

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).

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, KEYTRUDA should be administered for up to one year 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, 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 hematological toxicity, KEYTRUDA should be withheld until adverse reactions recover to Grades 0-1.

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

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

Paediatric Patients

For MSI-H/dMMR cancer, 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 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

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

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

4.3 Contraindications

None.

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) and toxic epidermal necrolysis (TEN), some with fatal outcome, have been reported in patients treated with KEYTRUDA. For signs or symptoms of SJS or TEN, withhold KEYTRUDA and refer the patient for specialized care for assessment and treatment. If SJS or TEN is confirmed, permanently discontinue KEYTRUDA. [see 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-Barre syndrome, pancreatitis, encephalitis, sarcoidosis, myasthenic syndrome/myasthenia gravis (including exacerbation) and myelitis. The following was reported in other clinical studies with KEYTRUDA or in post-marketing use: myocarditis.

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

Infusion-related reactions

Severe 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-1 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://nzphvc.otago.ac.nz/reporting/

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 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, diarrhea, 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 patients with HNSCC (n=192) the incidence of hypothyroidism was 14.1% (all Grades) with 0.5% Grade 3.
† In individual studies of patients with NSCLC treated with KEYTRUDA as monotherapy (total n=2022), 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 summarizes 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 %**
Hematology				
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 (%)**	**Grade 3-4* (%)**	**All Grades (%)**	**Grade 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
Hematology				
Anemia	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 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 summarizes 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* (%)**	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
General Disorders and Administration Site Conditions				
Fatigue	41	6	38	2.5
Asthenia	20	6	24	3.5
Gastrointestinal Disorders				
Diarrhea	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

Monotherapy

Table 8 summarizes 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 dyspnea 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				
Dyspnea	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

Other Cancers

Monotherapy

Adverse events occurring in patients with HNSCC, urothelial carcinoma, cHL, or MSI-H/dMMR cancer were generally similar to those occurring in patients with melanoma or NSCLC.

Combination Therapy

Renal Cell Carcinoma

The most common adverse reactions 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).

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 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

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 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.

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

Patients were treated with KEYTRUDA until disease progression or unacceptable toxicity. Clinically stable patients with initial evidence of disease progression were permitted to remain on treatment until disease progression was confirmed. Assessment of 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 9 summarizes key efficacy measures.

Table 9: 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)

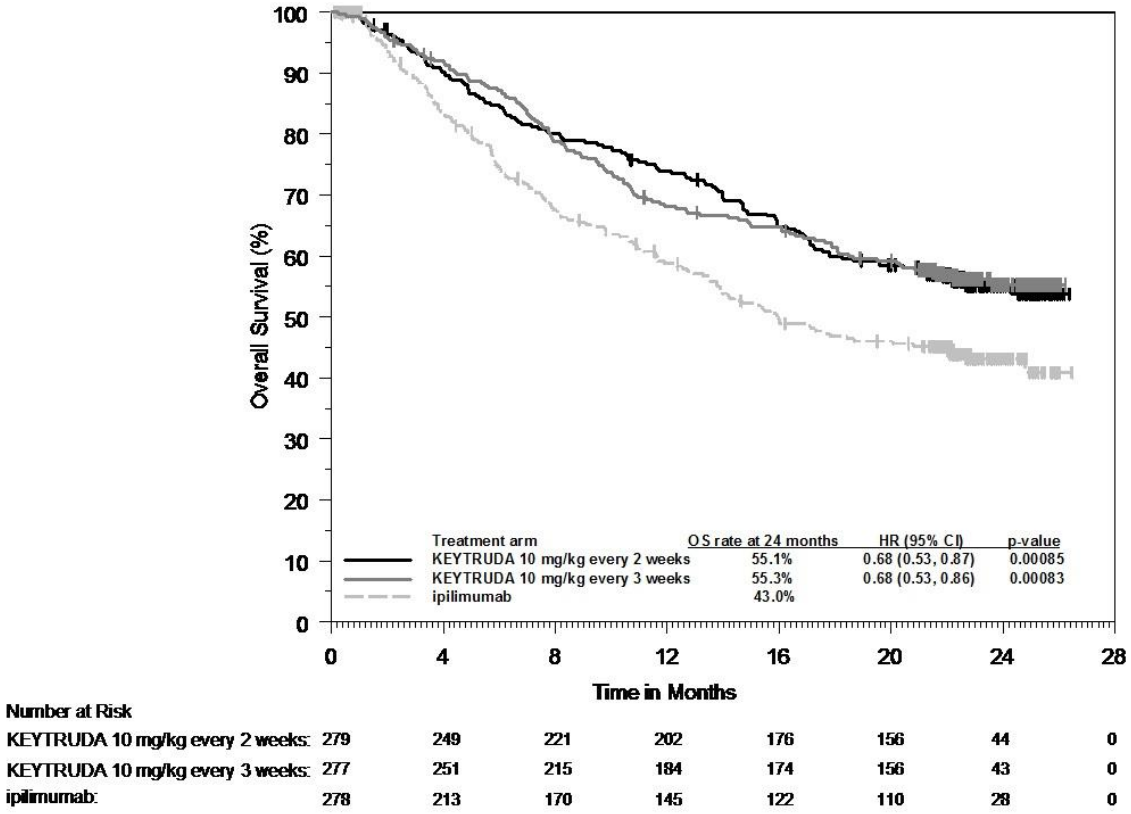
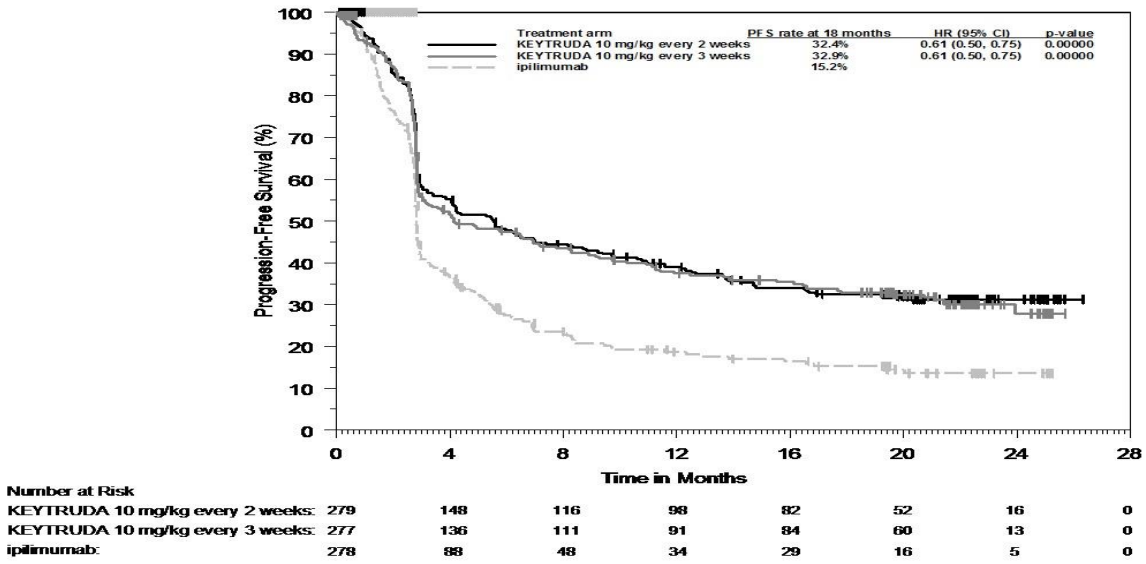


Figure 2: Kaplan-Meier Curve for Progression-Free Survival (Based on IRO) by Treatment Arm in KEYNOTE-006 (Intent to Treat Population)



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

Patients were treated with KEYTRUDA until disease progression or unacceptable toxicity. Clinically stable patients with initial evidence of disease progression were permitted to remain on treatment until disease progression was confirmed. Assessment of 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 10 summarizes key

efficacy measures in patients previously treated with ipilimumab. There was no statistically significant difference between KEYTRUDA and chemotherapy in the final OS analysis that was not adjusted for the potentially confounding effects of crossover. Of the patients randomized to the chemotherapy arm, 55% crossed over and subsequently received treatment with KEYTRUDA.

Table 10: 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

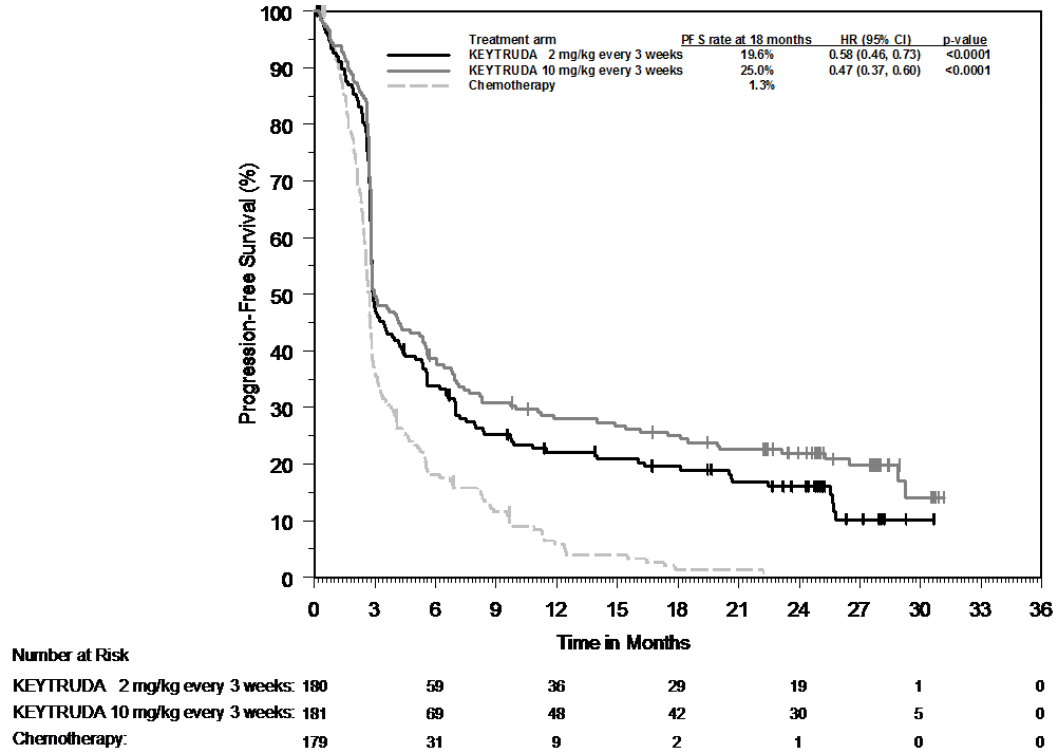
è Not statistically significant after adjustment for multiplicity

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 safety and efficacy of KEYTRUDA were also investigated in an uncontrolled, open-label study for the treatment of unresectable or metastatic melanoma. Efficacy was evaluated for 276 patients from two defined cohorts of KEYNOTE-001, one which included patients previously treated with ipilimumab (and if BRAF V600 mutation-positive, a BRAF or MEK inhibitor) and another which included patients naïve to treatment with ipilimumab. Patients were randomized to receive KEYTRUDA at a dose of 2 mg/kg every 3 weeks or 10 mg/kg every 3 weeks. 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 11 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 11: Response to KEYTRUDA 2 mg/kg Every 3 Weeks in Patients with Unresectable or Metastatic Melanoma in KEYNOTE-001

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

* Includes patients without measurable disease at baseline by independent radiology
† IRO = Independent radiology plus oncologist review using RECIST 1.1
‡ Based on best response of stable disease or better
§ Based on patients with a confirmed response by independent review, starting from the date the response was first recorded; n=23 for patients previously treated with ipilimumab; n=18 for patients naïve to treatment with ipilimumab
¶ Based on Kaplan-Meier estimation

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

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

The efficacy of KEYTRUDA was evaluated in KEYNOTE-054, a multicenter, 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 unacceptable toxicity. Randomisation was stratified by American Joint Committee on Cancer 7th edition (AJCC) stage (IIIA vs. IIIB vs. IIIC 1-3 positive lymph nodes vs. IIIC ≥4 positive lymph nodes) and geographic region (North America, European countries Australia and other countries as designated). Patients must have undergone lymph node dissection and if indicated, radiotherapy within 13 weeks prior to starting treatment. 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 recurrence free survival (RFS) in the whole population and in the population with PD-L1 positive tumours 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 occurs first. The trial demonstrated a statistically significant improvement in RFS for patients randomised to the KEYTRUDA arm compared with placebo. Efficacy results are summarised in Table 12 and Figure 4.

Table 12: Efficacy Results in KEYNOTE-054

Endpoint	**KEYTRUDA 200 mg every 3 weeks n=514**	**Placebo n=505**
RFS at 6 months		
Number (%) of patients with event	135 (26%)	216 (43%)
RFS rate	82%	73%
Median in months (95% CI)	NR	20.4 (16.2, NR)
Hazard ratio* (98% CI)	0.57 (0.43, 0.74)	
p-Value (stratified log-rank)	<0.0001†	
RFS at 12 months		
RFS rate	75%	61%

* Based on the stratified Cox proportional hazard model

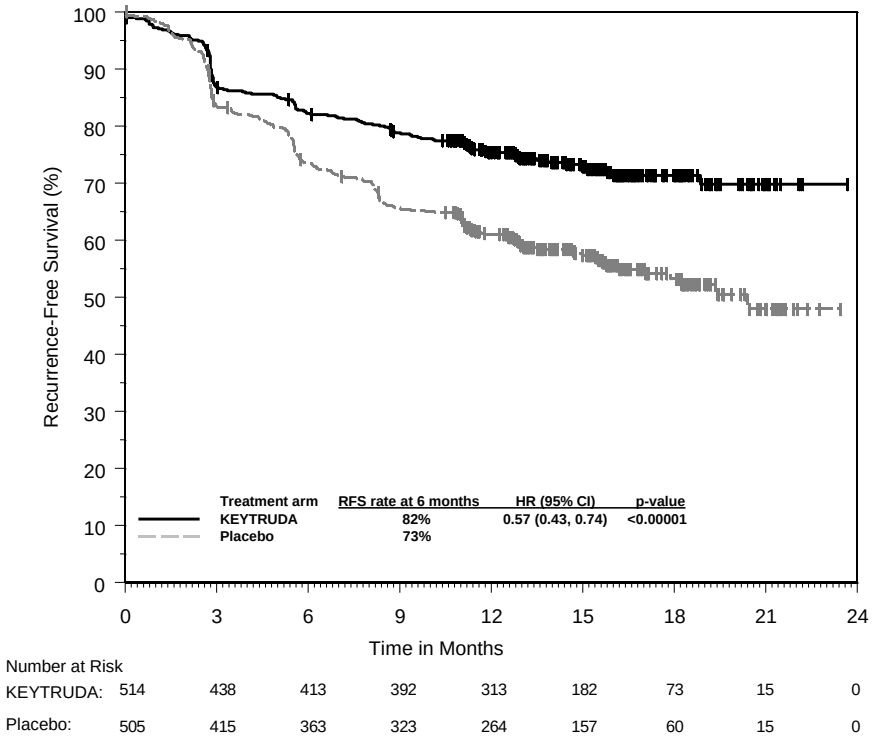
† p-Value is compared with 0.008 of the allocated alpha for this interim analysis.

NR = not reached

For patients with PD-L1 positive tumours, the RFS rate at 6 months was 84% in the KEYTRUDA arm and 75% in the placebo arm (HR was 0.54 (95% CI: 0.42, 0.69); p<0.0001). Additionally, pre-defined subgroup analyses were performed in patients whose tumours were PD-L1 negative, BRAF mutation positive or 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 0.47 (95% CI: 0.26, 0.85) for patients with PD-L1 negative tumours. The RFS HR was 0.49 (95% CI: 0.33, 0.67) for patients with BRAF mutation

positive tumours, and 0.64 (95% CI: 0.47, 0.87) for patients with BRAF mutation negative tumours.

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



Non-Small Cell Lung Carcinoma

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

The efficacy of KEYTRUDA in combination with pemetrexed and platinum chemotherapy was investigated in a multicenter, randomized, active-controlled, double-blind trial, KEYNOTE-189. Key eligibility criteria were metastatic non-squamous NSCLC, no prior systemic treatment for metastatic NSCLC, and no EGFR or ALK genomic 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 randomized (2:1) to receive one of the following regimens:

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

Treatment with KEYTRUDA continued until RECIST 1.1-defined progression of disease as determined by the investigator, unacceptable toxicity, or a maximum of 24 months. Administration of KEYTRUDA was permitted beyond RECIST-defined disease progression by BICR or beyond discontinuation of pemetrexed if the patient was clinically stable and deriving

clinical benefit as determined by the investigator. For patients who completed 24 months of therapy or had a complete response, treatment with KEYTRUDA could be reinitiated for disease progression and administered for up to 1 additional year. Assessment of 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 13 summarizes key efficacy measures.

Table 13: 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	254 (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 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 5 and 6.

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 5: Kaplan-Meier curve for Overall Survival by Treatment Arm in KEYNOTE-189 (Intent to Treat Population)

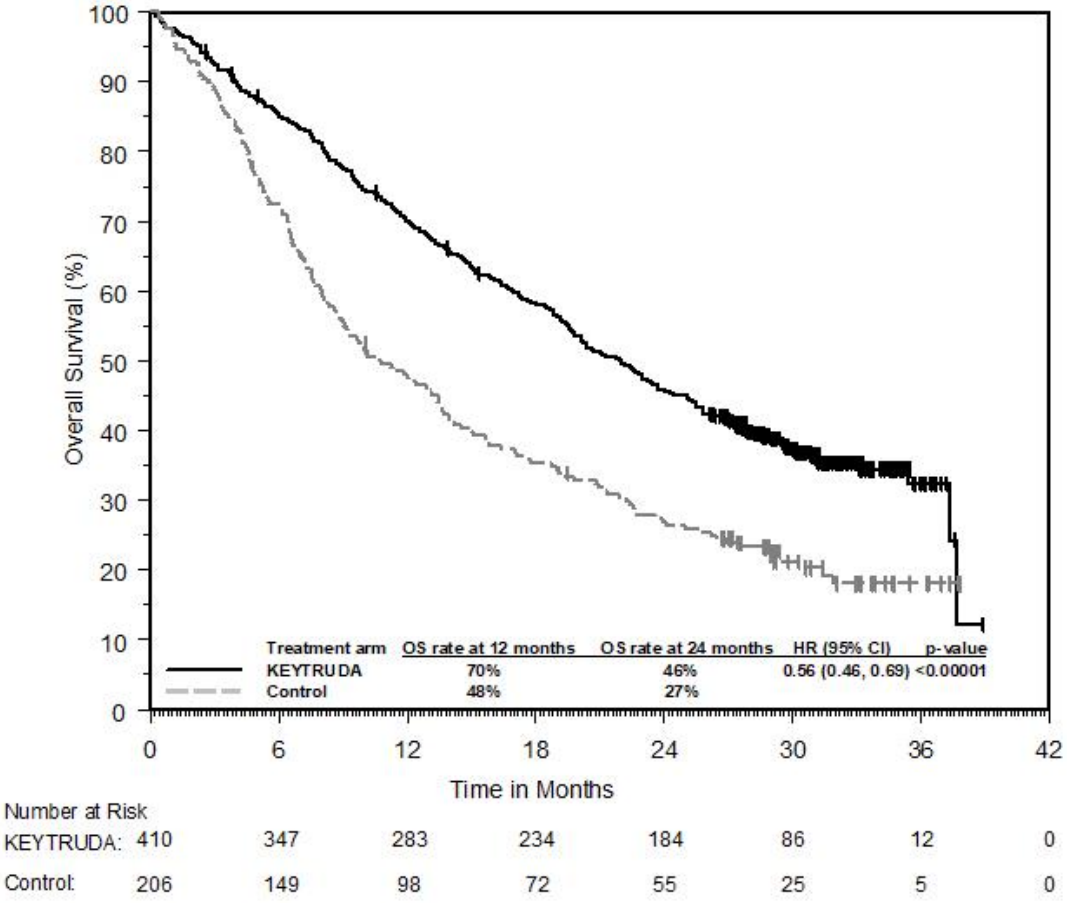
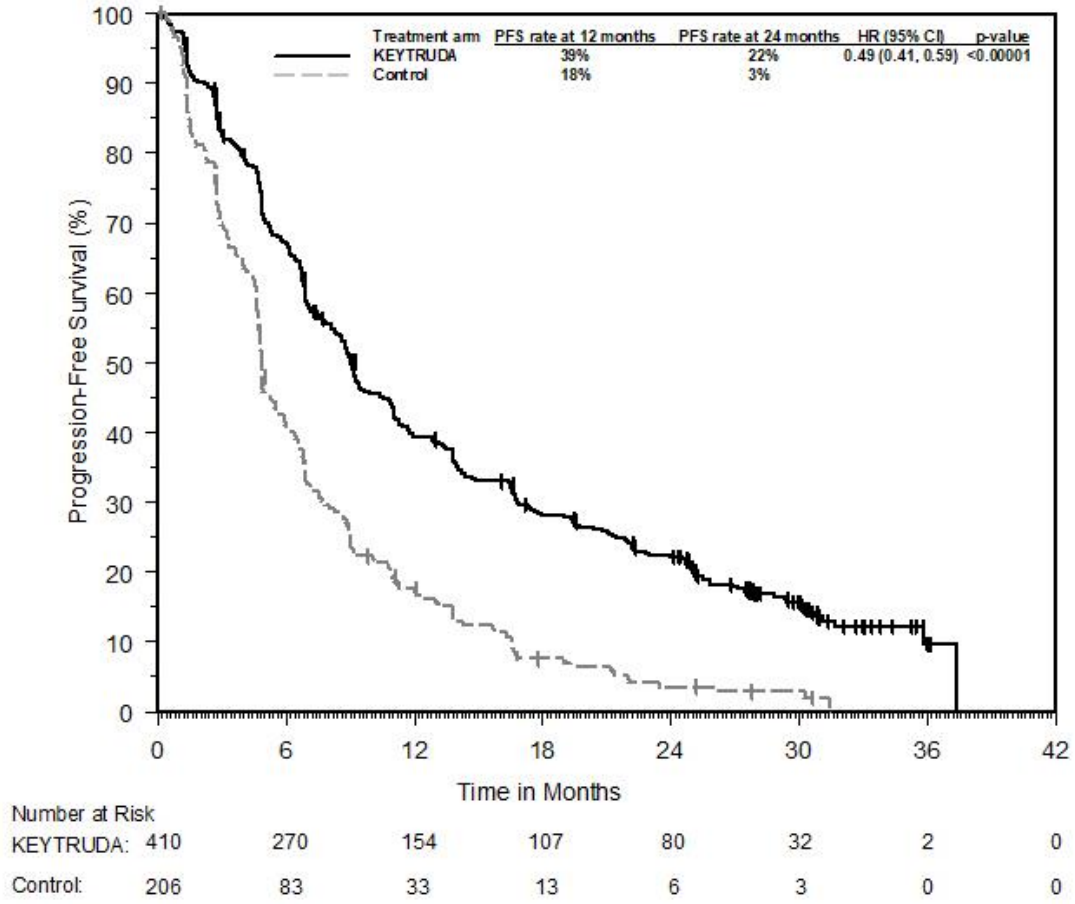


Figure 6: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-189 (Intent to Treat Population)



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

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

The efficacy of KEYTRUDA in combination with carboplatin and either paclitaxel or nab-paclitaxel was investigated in Study KEYNOTE-407, a randomised, double-blind, multicenter, 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 randomized: 278 patients to the KEYTRUDA arm and 281 to the placebo arm. The study population characteristics were: median age of 65 years (range: 29 to 88); 55% age 65 or older; 81% male; 77% White; ECOG performance status of 0 (29%) and 1 (71%); and 8% with treated brain metastases at baseline. Thirty-five percent had 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 randomized 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 14)

Table 14: Efficacy Results in KEYNOTE-407

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

* Based on the stratified Cox proportional hazard model
† At the initial interim analysis (n=101 for KEYTRUDA combination therapy, n=102 for placebo), a statistically significant difference was observed; ORR was 58% [95% CI (48, 68)] and 35% [95% CI (26, 45)] for placebo, p=0.0004
‡ Based on Kaplan-Meier estimation
NA = not available

The final OS analysis was performed at a median duration of follow-up of 14.3 months after 365 patient events (168 for KEYTRUDA combination arm and 197 for 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 7 and 8.

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

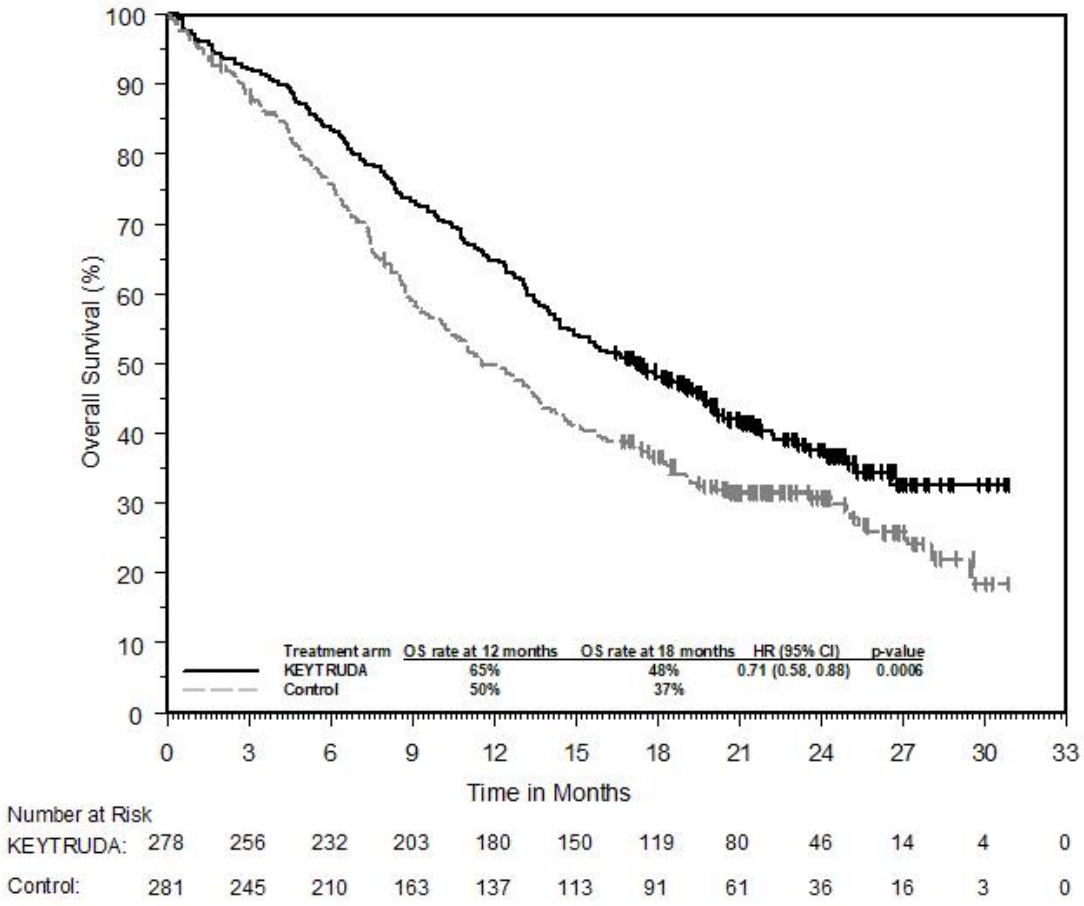
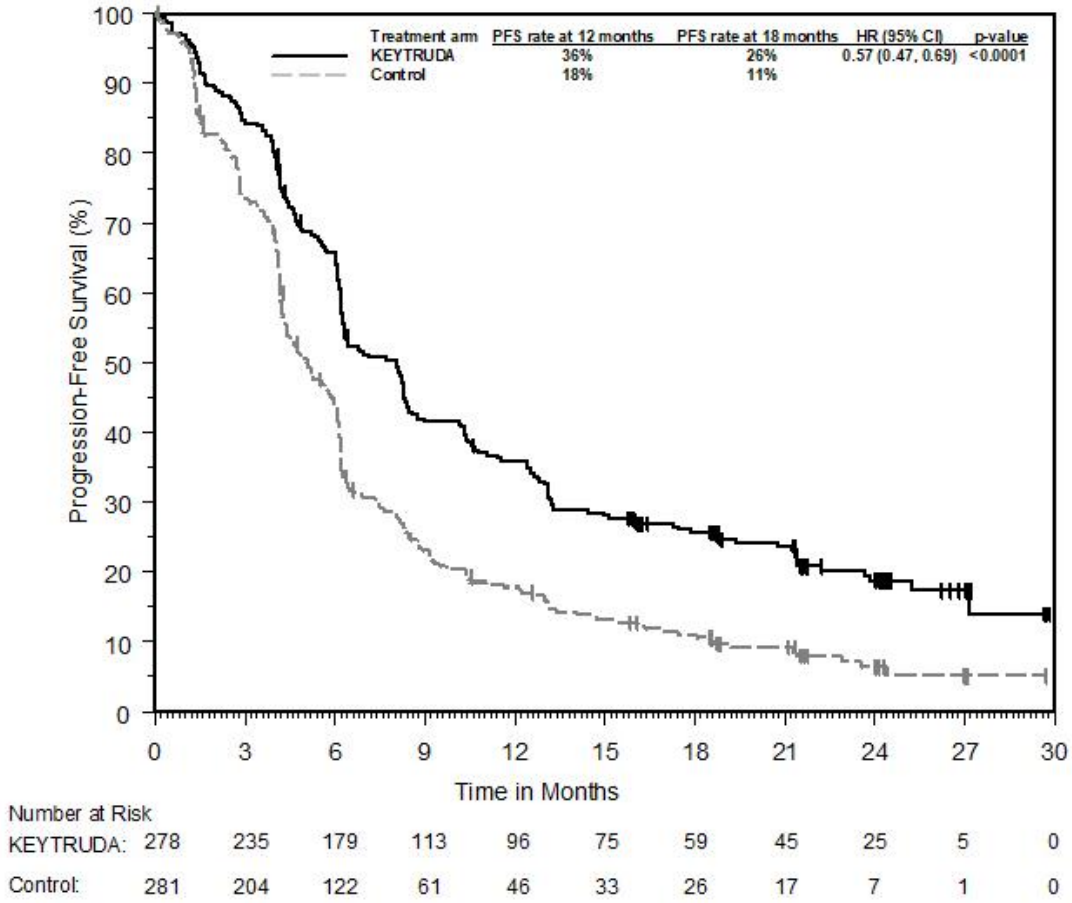


Figure 8: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-407



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

The efficacy of KEYTRUDA was investigated in KEYNOTE-042, a multicenter, randomized, 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 randomized (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%.

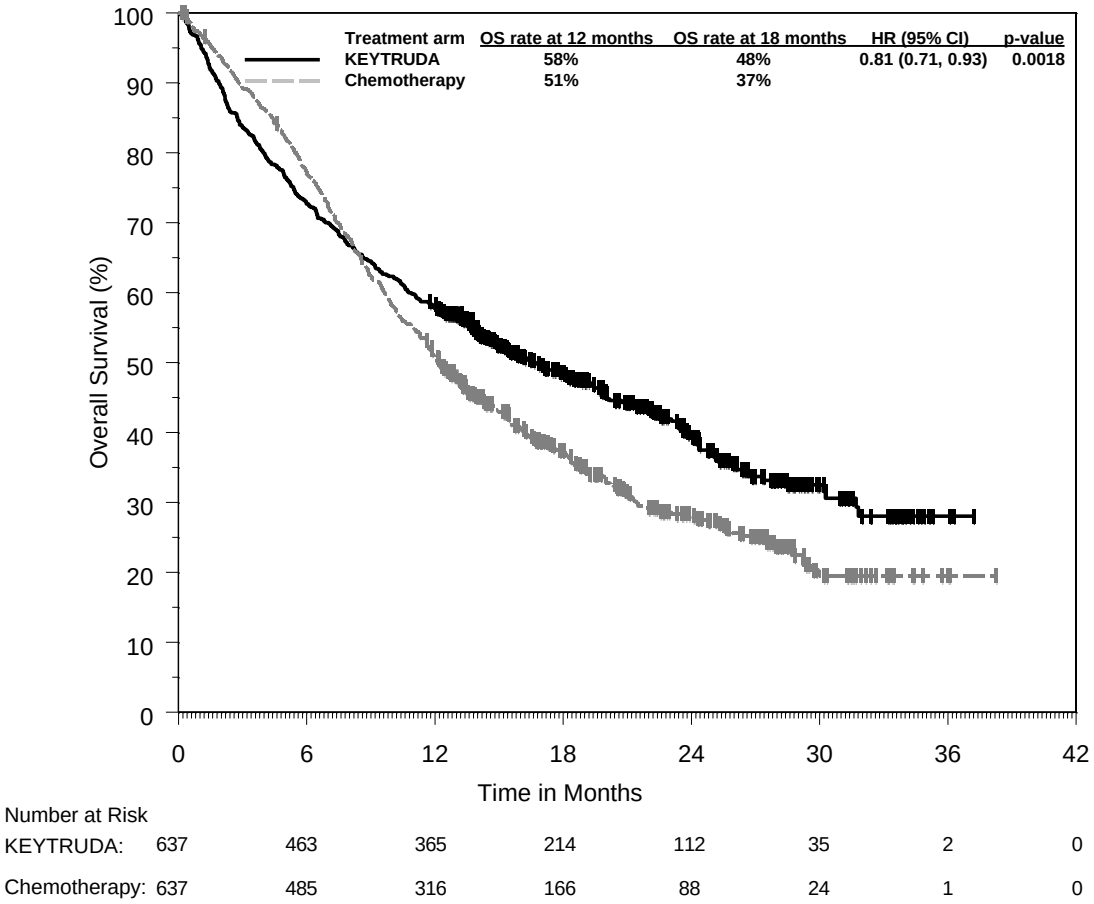
The primary efficacy outcome measure was OS. Secondary efficacy outcome measures were PFS and ORR as assessed by blinded independent central review (BICR) using RECIST 1.1. Table 15 summarizes key efficacy measures for the entire ITT population (TPS ≥ 1%).

Table 15: 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 9: 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 multicenter, randomized, 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 randomized (1:1) to receive KEYTRUDA 200 mg every 3 weeks (n=154) or investigator's choice platinum-containing chemotherapy (n=151; including pemetrexed+carboplatin, pemetrexed+cisplatin, gemcitabine+cisplatin, gemcitabine+carboplatin, or paclitaxel+carboplatin. 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 16 summarizes key efficacy measures for the entire ITT population.

Table 16: Efficacy Results in KEYNOTE-024

Endpoint	KEYTRUDA 200 mg every 3 weeks n=154	Chemotherapy n=151
PFS*		
Number (%) of patients with event	73 (47%)	116 (77%)
Hazard ratio† (95% CI)	0.50 (0.37, 0.68)	
p-Value‡	<0.001	
Median in months (95% CI)	10.3 (6.7, NA)	6.0 (4.2, 6.2)
OS		
Number (%) of patients with event	44 (29%)	64 (42%)
Hazard ratio† (95% CI)	0.60 (0.41, 0.89)	
p-Value‡	0.005	
Median in months (95% CI)	Not reached (NA, NA)	Not reached (9.4, NA)
Objective Response Rate*		
ORR % (95% CI)	45% (37, 53)	28% (21, 36)
Complete response %	4%	1%
Partial response %	41%	27%
Response Duration§,¶		
Median in months (range)	Not reached (1.9+, 14.5+)	6.3 (2.1+, 12.6+)
% with duration ≥ 6 months	88%	59%

* Assessed by BICR using RECIST 1.1
† Hazard ratio (KEYTRUDA compared to chemotherapy) based on the stratified Cox proportional hazard model
‡ Based on stratified Log rank test
§ Based on patients with a best overall response as confirmed complete or partial response
¶ Based on Kaplan-Meier estimates
NA = not available

The final OS analysis was performed at a median follow-up of 25 months after 169 patient events (73 for KEYTRUDA and 96 for chemotherapy). Median OS was 30.0 months (95% CI: 18.3, NA) for KEYTRUDA and 14.2 months (95% CI: 9.8, 19.0) for chemotherapy. The OS HR was 0.63 (95% CI: 0.47, 0.86; p=0.002). See Figure 11.

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

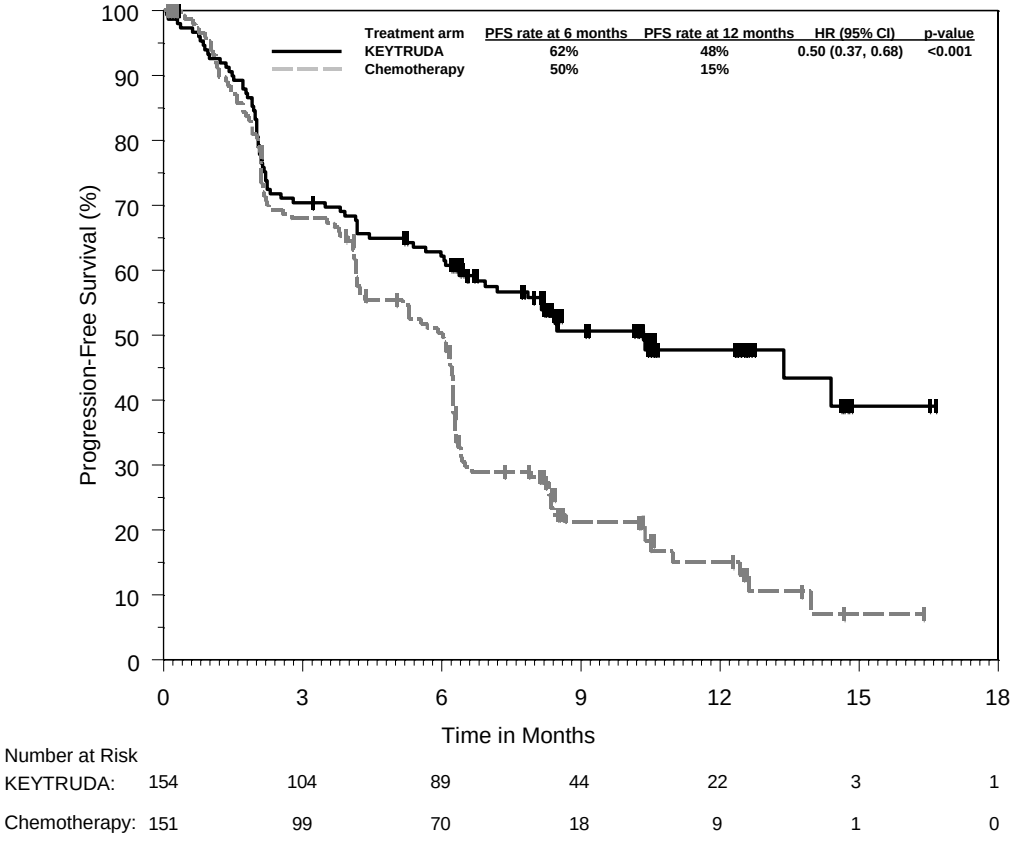
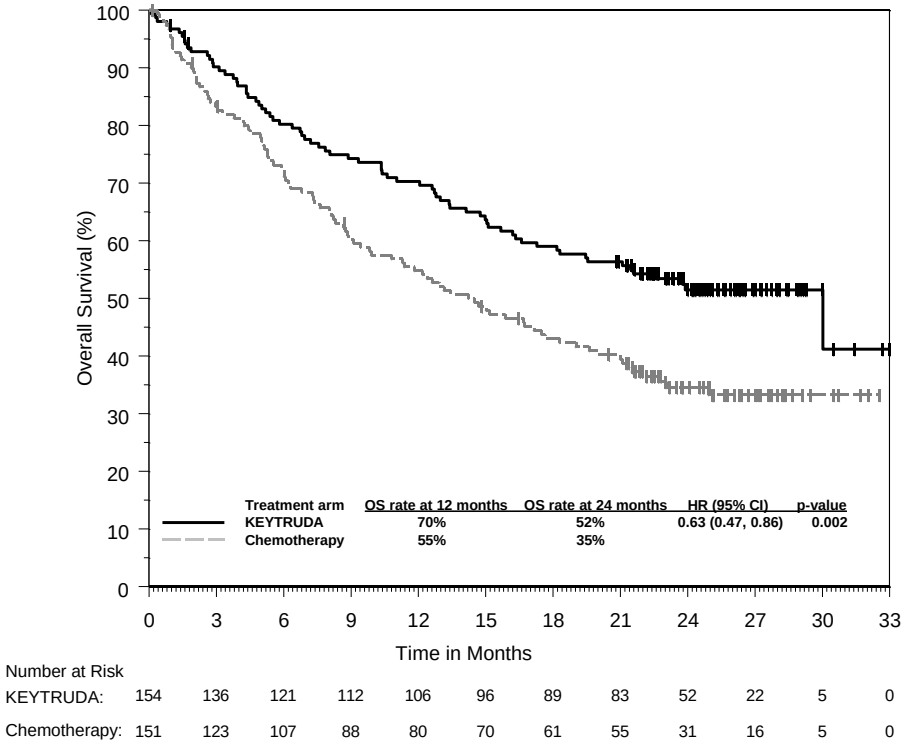


Figure 11: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-024 (Intent to Treat Population)



The improved benefit as assessed by PFS, OS, ORR, and response duration for KEYTRUDA as compared to chemotherapy in the population studied was associated with improvements

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

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

The efficacy of KEYTRUDA was investigated in KEYNOTE-010, a multicenter, randomized, controlled trial. Key eligibility criteria were advanced NSCLC that had progressed following platinum-containing chemotherapy, and if appropriate, targeted therapy for ALK or EGFR mutations, and PD-L1 expression TPS of 1% or greater by a clinical trial assay version of the PD-L1 IHC 22C3 pharmDx™ kit. Patients with autoimmune disease; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Patients were randomized (1:1:1) to receive 2 mg/kg (n=344) or 10 mg/kg (n=346) of KEYTRUDA every 3 weeks or 75 mg/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 17 summarizes key efficacy measures for the entire ITT population (TPS ≥1%) and for the subgroup of patients with TPS ≥50%. Kaplan-Meier curves for OS (TPS ≥1% and TPS ≥50%) are shown in Figures 12 and 13.

Table 17: Response to KEYTRUDA 2 or 10 mg/kg every 3 Weeks in Previously Treated Patients with NSCLC in KEYNOTE-010

Endpoint	KEYTRUDA 2 mg/kg every 3 weeks	KEYTRUDA 10 mg/kg every 3 weeks	Docetaxel 75 mg/m2 every 3 weeks
TPS ≥1%			
Number of patients	344	346	343
OS			
Number (%) of patients with event	172 (50%)	156 (45%)	193 (56%)
Hazard ratio* (95% CI)	0.71 (0.58, 0.88)	0.61 (0.49, 0.75)	---
p-Value†	<0.001	<0.001	---
Median in months (95% CI)	10.4 (9.4, 11.9)	12.7 (10.0, 17.3)	8.5 (7.5, 9.8)
PFS‡			
Number (%) of patients with event	266 (77%)	255 (74%)	257 (75%)
Hazard ratio* (95% CI)	0.88 (0.73, 1.04)	0.79 (0.66, 0.94)	---
p-Value†	0.068	0.005	---
Median in months (95% CI)	3.9 (3.1, 4.1)	4.0 (2.6, 4.3)	4.0 (3.1, 4.2)
Overall Response Rate‡			
ORR %§ (95% CI)	18% (14, 23)	18% (15, 23)	9% (7, 13)
Response Duration‡,¶,#			
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

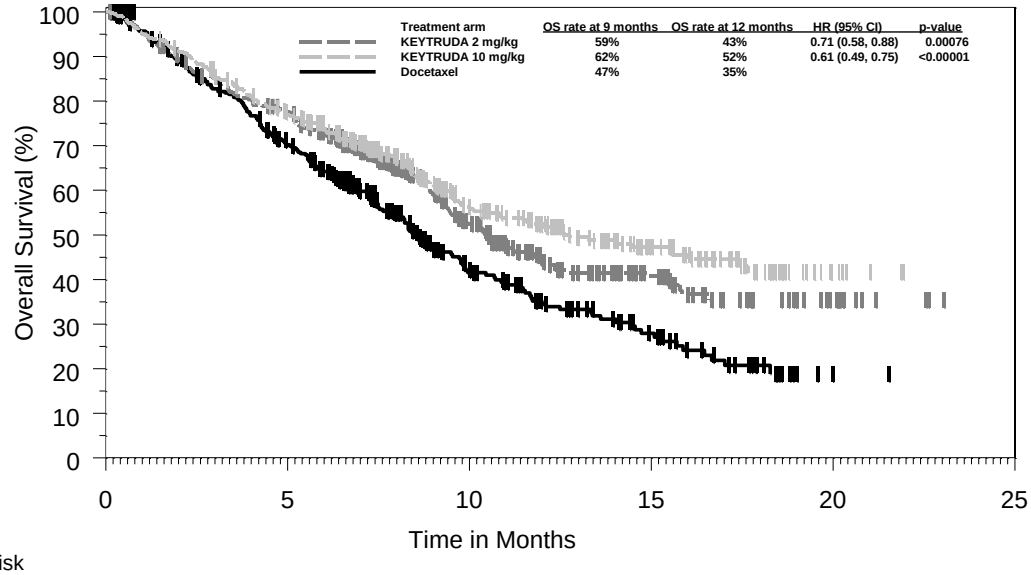
§ All responses were partial responses

¶ 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

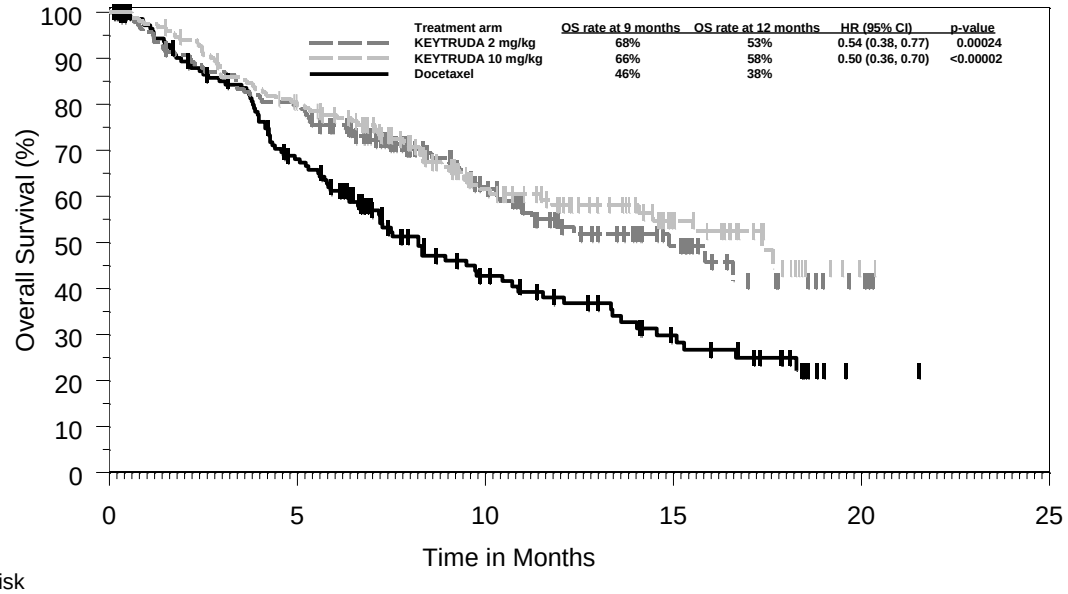
Þ Includes 22, 24, and 1 patients with ongoing responses of 6 months or longer in the KEYTRUDA 2 mg/kg, KEYTRUDA 10 mg/kg, and docetaxel groups respectively

Figure 12: 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 13: 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 multicenter, open-label, randomized, dose-comparative cohort of KEYNOTE-001. Patients had advanced NSCLC that was PD-L1 positive, with progression of disease following treatment with platinum-containing chemotherapy. Patients with EGFR or ALK genomic 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 randomized to receive 10 mg/kg of KEYTRUDA every 2 (n=69) or 3 (n=87) weeks until disease progression or unacceptable toxicity. Assessment of 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 randomized 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 summarized in Table 18.

Table 18: Response to KEYTRUDA 10 mg/kg every 2 or 3 Weeks in Previously Treated NSCLC Patients with PD-L1 expression TPS ≥50% (n=61)

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

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

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

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

§ Based on all treated patients (n=61)

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

Head and Neck Cancer

KEYNOTE-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 multicenter, nonrandomized, 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 summarized in Table 19.

Table 19 Efficacy Results in Patients with HNSCC

	Previously treated with platinum without cetuximab	Previously treated with platinum and cetuximab
Endpoint	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 Lymhoma (cHL)

KEYNOTE-204 was a randomized, open-label, active-controlled trial conducted in 304 patients with relapsed or refractory cHL. Patients with active, non-infectious pneumonitis, an allogeneic HSCT within the past 5 years (or >5 years but with symptoms of GVHD), active autoimmune disease, a medical condition that required immunosuppression, or an active infection requiring systemic therapy were ineligible for the trial. Randomization was stratified by prior auto-SCT (yes vs. no) and disease status after frontline therapy (primary refractory vs. relapse less than 12 months after completion vs. relapse 12 months or more after completion). Patients were randomized (1:1) to one of the following treatment arms:

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

Patients received KEYTRUDA 200 mg intravenously every 3 weeks until unacceptable toxicity or documented disease progression. Disease assessment was performed every 12 weeks.

The major efficacy outcome measures were PFS and ORR as assessed by BICR according to the 2007 revised International Working Group (IWG) criteria.

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

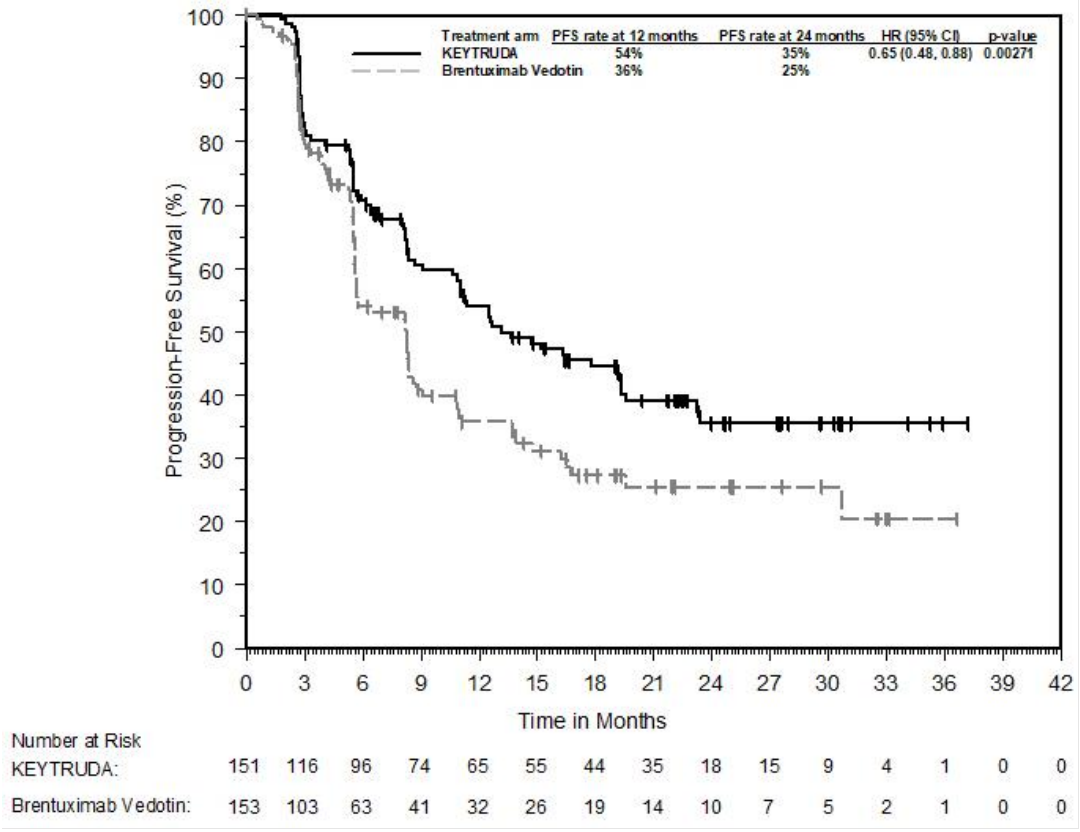
The median follow-up time for 151 patients treated with KEYTRUDA was 24.9 months (range: 1.8 to 42.0 months). Efficacy results are summarized in Table 20.

Table 20: Efficacy Results in Patients with Refractory or Relapsed Classical Hodgkin Lymphoma

Endpoint	**KEYTRUDA** **200 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 14: 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 multicenter, nonrandomized, 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 summarized in Table 21.

Table 21: Efficacy Results in Patients with Refractory or Relapsed Classical Hodgkin Lymphoma

	KEYNOTE-013	KEYNOTE-087
Endpoint	n=31	n=210
Objective Response Rate*		
ORR %, (95% CI)	58% (39.1, 75.5)	71% (64, 77)
Complete remission	19%	28%
Partial remission	39%	43%
Response Duration*		
Median in months (range)	Not reached (0.0+, 26.1+)†	16.6 (0.0+, 39.1+) ‡
% with duration ≥ 6-months	80%§	74%¶
% with duration ≥ 12-months	70%#	59%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.

Metastatic 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 multicenter, 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 summarized in Table 22. The data presented for subjects with PD L1 CPS ≥10 are based on a subgroup analysis in a single-arm trial. A randomized, controlled confirmatory trial is ongoing.

Table 22: 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 multicenter, randomized (1:1), active-controlled trial in patients with locally advanced or metastatic urothelial carcinoma with disease progression on or after platinum-containing chemotherapy. The trial excluded patients with autoimmune disease or a medical condition that required immunosuppression.

Patients were randomized to receive either KEYTRUDA 200 mg every 3 weeks (n=270) or investigator's choice of any of the following chemotherapy regimens all given intravenously every 3 weeks (n=272): paclitaxel 175 mg/m^2 (n=84), docetaxel 75 mg/m^2 (n=84), or vinflunine 320 mg/m^2 (n=87). 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 randomization, then every 6 weeks through the first year, followed by every 12 weeks thereafter. The major efficacy

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

Among the 542 randomized patients, the study population characteristics were: median age 66 years (range: 26 to 88), 58% age 65 or older; 74% male; 72% White and 23% Asian; 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 randomized to KEYTRUDA as compared to chemotherapy (Table 23). There was no statistically significant difference between KEYTRUDA and chemotherapy with respect to PFS. Efficacy results are summarised in Table 23.

Table 23: 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

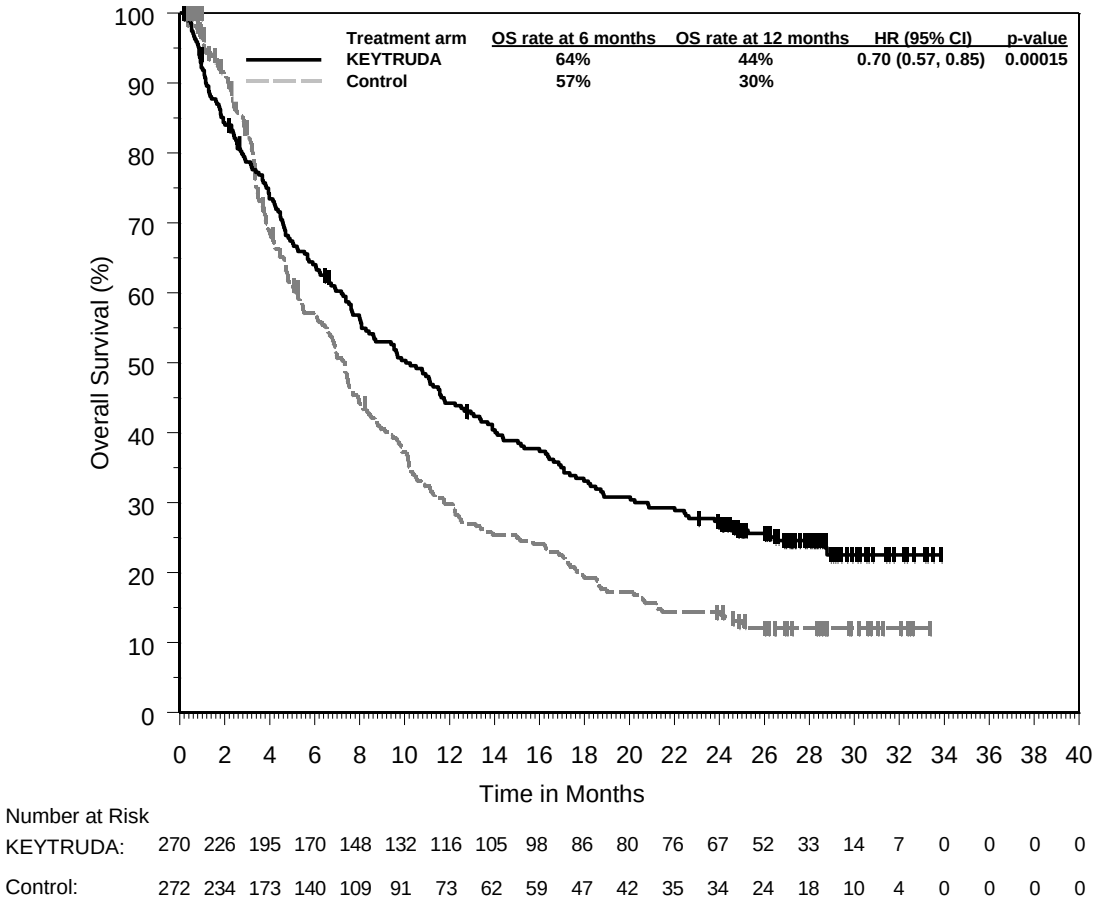
¶ Based on patients with a best overall response as confirmed complete or partial response

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 15. 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 15: 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.

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 multicenter, nonrandomized, 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 summarized in Table 24 and Table 25

Table 24: 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 25: 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

Paediatric Patients

Efficacy for paediatric patients with MSI-H cancer is extrapolated from the results in the adult population.

Renal Cell Carcinoma

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

The efficacy of KEYTRUDA in combination with axitinib was investigated in a randomized, multicenter, open-label, active-controlled trial KEYNOTE-426, conducted in patients with advanced RCC, 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. Randomization was stratified by risk categories (favorable versus intermediate versus poor) and geographic

region (North America versus Western Europe versus “Rest of the World”). Patients were randomized (1:1) to one of the following treatment arms:

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

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

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

The primary efficacy outcome measures were OS and PFS (as assessed by BICR according to RECIST 1.1). Secondary efficacy outcome measures were ORR and response duration, as assessed by BICR using RECIST 1.1. The median follow-up time for 432 patients treated with KEYTRUDA and axitinib was 13.2 months (range: 0.1 – 21.5 months). Table 26 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 26: Response to KEYTRUDA and Axitinib in Patients with Advanced RCC in KEYNOTE-426

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

* Based on the stratified Cox proportional hazard model

† Based on stratified log-rank test

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

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

¶ Based on Kaplan-Meier estimation

NA = not available

Figure 16: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-426 (Intent to Treat Population)

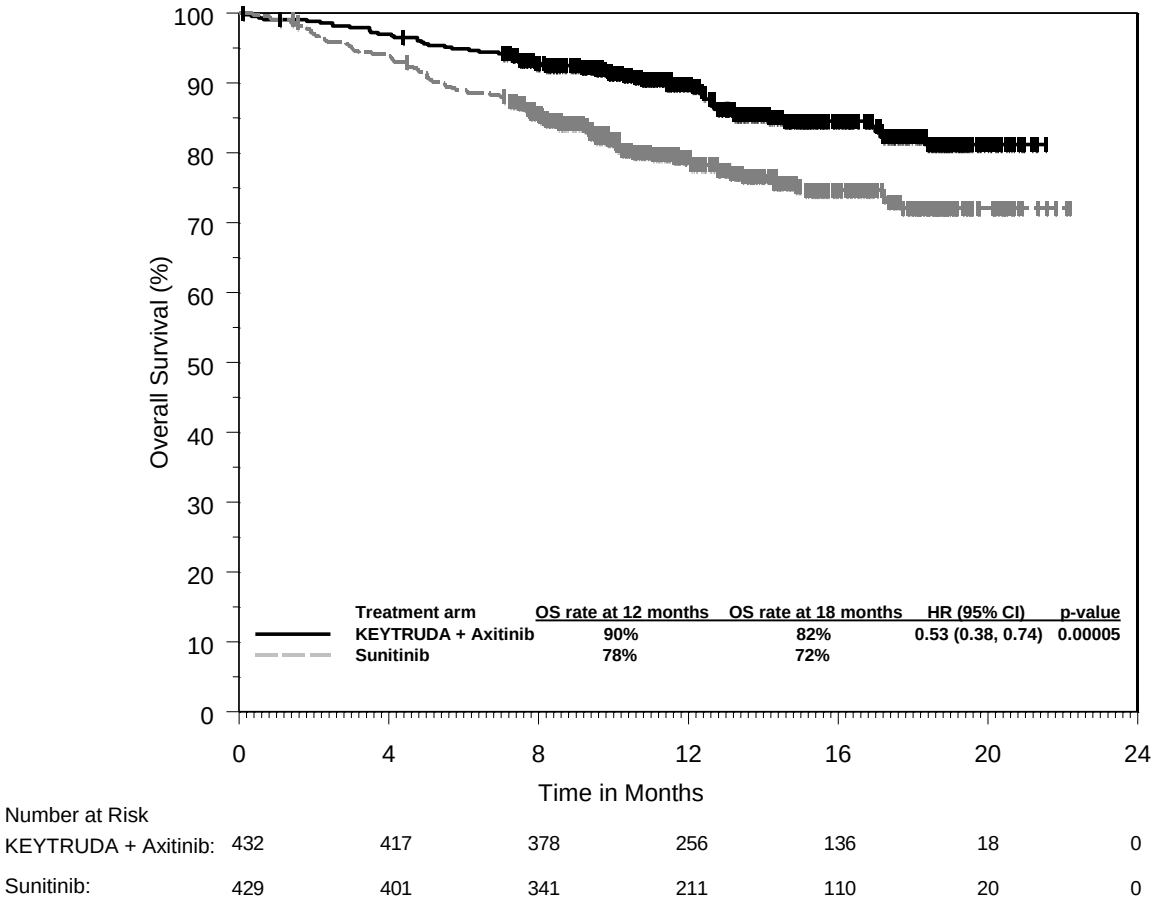
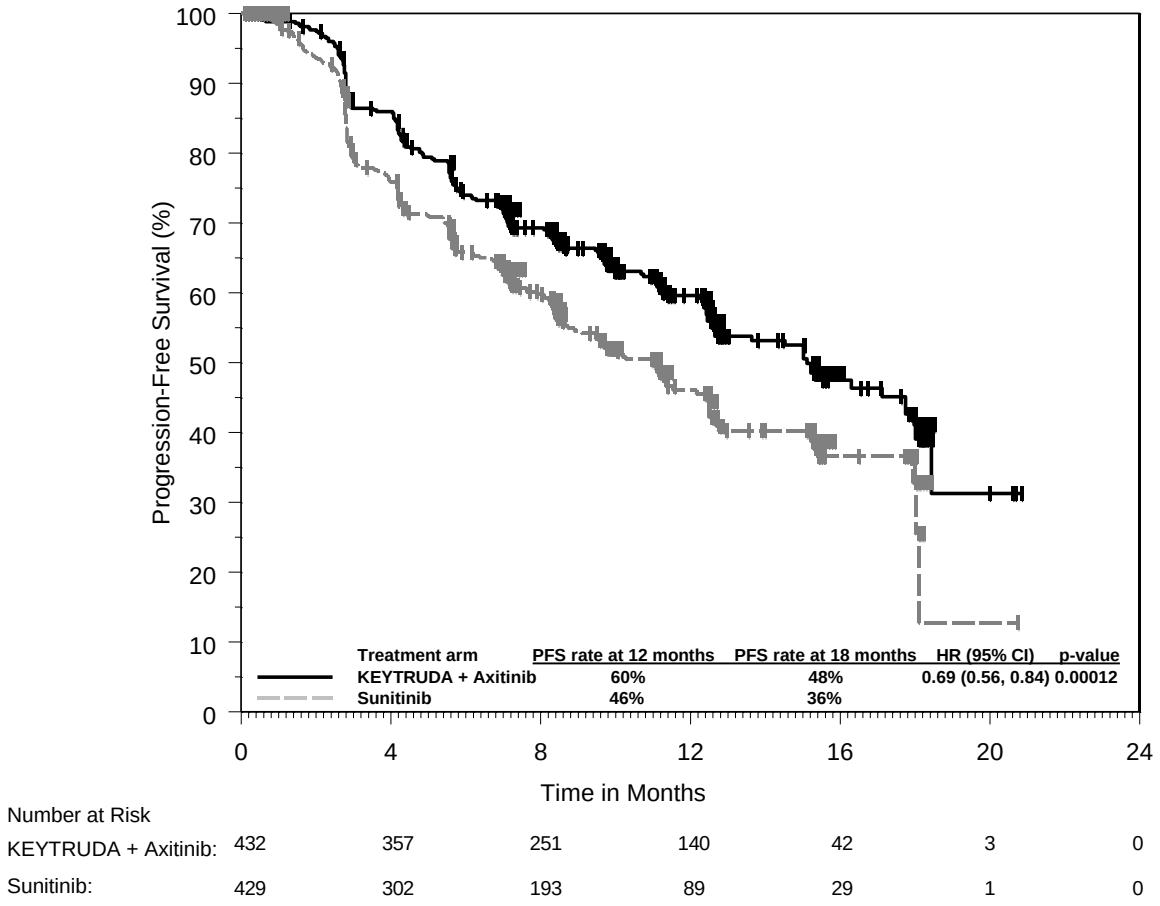


Figure 17: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-426 (Intent to Treat Population)



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 ($t_{½}$) 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

KEYTRUDA 50 mg powder for solution for infusion

Histidine

Histidine monohydrochloride monohydrate

Sucrose

Polysorbate 80

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

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

KEYTRUDA 50 mg powder for solution for infusion

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

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

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 reconstitution or dilution of the medicinal product, *see section 6.6*.

6.5 Nature and Contents of Container

Carton of one 50 mg powder for solution for infusion or one 100 mg/4 mL concentrate for solution for infusion single-use vial.

6.6 Special precautions for disposal and other handling

Preparation of KEYTRUDA 50 mg powder for solution for infusion

- Prior to reconstitution, the vial of lyophilised powder can be out of refrigeration (temperatures at or below 25°C) for up to 24 hours.
- Aseptically add 2.3 mL of sterile water for injection to yield a 25 mg/mL (pH 5.2-5.8) solution of KEYTRUDA.
- To avoid foaming, deliver the water along the walls of the vial and not directly on the lyophilised powder.
- Slowly swirl the vial to allow reconstitution of the lyophilised powder. Allow up to 5 minutes for the bubbles to clear. Do not shake the vials.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Reconstituted 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 2 mL (50 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 (see ***Administration***).

Preparation of KEYTRUDA 100 mg/4 mL (25 mg/mL) concentrate for solution for infusion

- 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 (see ***Administration***).

Administration

- Do not freeze the infusion solution.
- Do not shake.
- The product does not contain preservative. The reconstituted and/or diluted product should be used immediately. If not used immediately, reconstituted and diluted solutions of KEYTRUDA may be stored at room temperature for a cumulative time of up to 6 hours. Reconstituted and diluted solutions of KEYTRUDA may also be stored under refrigeration at 2°C to 8°C; however, the total time from reconstitution or 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

12 November 2020

Summary table of changes

Section changed	Summary of new information
4.1	Revised cHL indication to broaden indication patient population
4.2	Added cHL for dose recommendations in paediatric patients
4.8	Updated AE data for cHL patients (Table 2 - footnote); Added safety information for paediatric patients based on KEYNOTE-051
5.1	Updated efficacy information based on KEYNOTE-204;

	Updated data of prior therapies and efficacy results based on latest outcome from KEYNOTE-087
All	Editorial revision to update Table or Figure numbers

RCN000015213