PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

KEYTRUDA®

Pembrolizumab

powder for solution for infusion 50 mg
solution for infusion 100 mg/4mL vial

Antineoplastic agent, monoclonal antibody

KEYTRUDA® has been issued marketing authorization **with conditions**, pending the results of studies to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for KEYTRUDA®, please refer to Health Canada's Notice of Compliance with conditions – drug products website: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php

KEYTRUDA® is indicated for the treatment of patients with:

- Unresectable or metastatic melanoma and disease progression following ipilimumab therapy and, if BRAF V600 mutation positive, following a BRAF or MEK inhibitor as per proposed indication.

- Metastatic non-small cell lung carcinoma (NSCLC) as monotherapy, in adults whose tumours express PD-L1 (TPS ≥ 1%) as determined by a validated test and who have disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have received authorized therapy for these aberrations prior to receiving KEYTRUDA®.

KEYTRUDA® has been issued marketing authorization **without conditions** for the treatment of patients with:

- Unresectable or metastatic melanoma who have not received prior treatment with ipilimumab. Subjects with BRAF V600 mutant melanoma may have received prior BRAF inhibitor therapy.

- Metastatic non-small cell lung carcinoma (NSCLC) as monotherapy, in adults whose tumours have high PD-L1 expression [(Tumour Proportion Score (TPS) ≥50%)] as determined by a validated test, with no EGFR or ALK genomic tumour aberrations, and no prior systemic chemotherapy treatment for metastatic NSCLC.

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Date of Approval:
July 20, 2017

Submission Control No: 197355

This product has been approved under the Notice of Compliance with Conditions (NOC/c) policy for one or all of its indicated uses.

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of **promising** evidence of clinical effectiveness following review of the submission by Health Canada.

Products approved under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

What will be different about this Product Monograph?
The following Product Monograph will contain boxed text at the beginning of each major section clearly stating the nature of the market authorization. Sections for which NOC/c status holds particular significance will be identified in the left margin by the symbol NOC/c. These sections may include, but are not limited to, the following: /
- Indications and Clinical Uses;
- Action;
- Warnings and Precautions;
- Adverse Reactions;
- Dosage and Administration; and
- Clinical Trials.

Adverse Reaction Reporting and Re-Issuance of the Product Monograph
Health care providers are encouraged to report Adverse Drug Reactions associated with normal use of these and all drug products to Health Canada's Canada Vigilance Program at 1-866-234-2345. The Product Monograph will be re-issued in the event of serious safety concerns previously unidentified or at such time as the sponsor provides the additional data in support of the product's clinical benefit. Once the latter has occurred, and in accordance with the NOC/c policy, the conditions associated with market authorization will be removed.

Table of Contents

KEYTRUDA®

pembrolizumab

PART I: HEALTH PROFESSIONAL INFORMATION

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KEYTRUDA® is indicated for the treatment of patients with:

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- Metastatic non-small cell lung carcinoma (NSCLC) as monotherapy, in adults whose tumours express PD-L1 (TPS ≥ 1%) as determined by a validated test and who have disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have received authorized therapy for these aberrations prior to receiving KEYTRUDA®.

KEYTRUDA® has been issued marketing authorization **without conditions** for the treatment of patients with:

- Unresectable or metastatic melanoma who have not received prior treatment with ipilimumab. Subjects with BRAF V600 mutant melanoma may have received prior BRAF inhibitor therapy.

- Metastatic non-small cell lung carcinoma (NSCLC) as monotherapy, in adults whose tumours have high PD-L1 expression [(Tumour Proportion Score (TPS) ≥50%)] as determined by a validated test, with no EGFR or ALK genomic tumour aberrations, and no prior systemic chemotherapy treatment for metastatic NSCLC.

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients

Intravenous infusion	Powder for solution for infusion 50 mg Solution for infusion 100 mg/4mL vial	None *For a complete listing see Dosage Forms, Composition and Packaging section.*

DESCRIPTION

KEYTRUDA® (pembrolizumab) is a selective humanized monoclonal antibody designed to block the interaction between programmed cell death receptor-1 (PD-1) and its ligands, PD-L1 and PD-L2. Pembrolizumab is an IgG4 kappa immunoglobulin with an approximate molecular weight of 149 kDa.

INDICATIONS AND CLINICAL USE

Melanoma

KEYTRUDA® is indicated for the treatment of patients with unresectable or metastatic melanoma who have not received prior treatment with ipilimumab. Subjects with BRAF V600 mutant melanoma may have received prior BRAF inhibitor therapy.

NOC/c KEYTRUDA® is indicated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab therapy and, if BRAF V600 mutation positive, following a BRAF or MEK inhibitor. An improvement in survival or disease-related symptoms has not yet been established.

Non-Small Cell Lung Carcinoma
KEYTRUDA® as monotherapy is indicated for the treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours have high PD-L1 expression [Tumour Proportion Score (TPS) ≥50%] as determined by a validated test, with no EGFR or ALK genomic tumour aberrations, and no prior systemic chemotherapy treatment for metastatic NSCLC.

NOC/c KEYTRUDA® as monotherapy is indicated for the treatment of metastatic non-small cell lung carcinoma (NSCLC), in adults whose tumours express PD-L1 (TPS ≥ 1%) as determined by a validated test and who have disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have received an authorized therapy for these aberrations prior to receiving KEYTRUDA®.

Geriatrics (> 65 years of age):
No overall differences in safety or efficacy were reported between elderly patients (65 years and over) and younger patients (less than 65 years) (See WARNINGS AND PRECAUTIONS; Geriatrics).

Pediatrics (<18 years of age):
Safety and efficacy of KEYTRUDA® in pediatric patients have not been established.

NOC/c CONTRAINDICATIONS

KEYTRUDA® is contraindicated in patients who have experienced a severe hypersensitivity reaction (See WARNINGS AND PRECAUTIONS) to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the Product Monograph.

NOC/c WARNINGS AND PRECAUTIONS

General
KEYTRUDA® (pembrolizumab) should be administered under the supervision of physicians experienced in the treatment of cancer.

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

For suspected immune-mediated adverse reactions, ensure adequate evaluation to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, withhold KEYTRUDA® and consider administration of corticosteroids. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Based on limited data from clinical studies in patients whose immune-mediated adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered. KEYTRUDA® may be restarted within 12 weeks after last dose of KEYTRUDA® if the adverse reaction remains at Grade ≤ 1 and corticosteroid dose has been reduced to ≤ 10 mg prednisone or equivalent per day. KEYTRUDA® must be permanently discontinued for any Grade 3 immune-mediated adverse reaction that recurs and for any Grade 4 immune-mediated adverse reaction toxicity, except for endocrinopathies that are controlled with replacement hormones (See DOSAGE AND ADMINISTRATION, and ADVERSE REACTIONS).

The data described in the WARNINGS AND PRECAUTIONS section reflect exposure to KEYTRUDA® in 2799 patients in three randomized, open-label, active-controlled clinical trials (KEYNOTE-002, KEYNOTE-006, and KEYNOTE-010), which enrolled 912 patients with melanoma and 682 patients with NSCLC, and one single-arm trial (KEYNOTE-001) which enrolled 655 patients with melanoma and 550 patients with NSCLC (See CLINICAL TRIALS).

Immune-mediated pneumonitis:
KEYTRUDA® can cause immune-mediated pneumonitis, including fatal cases Monitor patients for signs and symptoms of pneumonitis. Evaluate patients with suspected pneumonitis with radiographic imaging and administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper) for Grade 2 or greater pneumonitis. Withhold KEYTRUDA® for moderate (Grade 2) pneumonitis, and permanently discontinue KEYTRUDA® for severe (Grade 3) life-threatening (Grade 4) or recurrent moderate (Grade 2) pneumonitis (See DOSAGE AND ADMINISTRATION and ADVERSE REACTIONS).

Pneumonitis occurred in 94 (3.4%) of 2799 patients, including Grade 2 (1.3%), 3 (0.9%), 4 (0.3%), or 5 (0.1%) pneumonitis in patients receiving KEYTRUDA® in KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, and KEYNOTE-010.

Immune-mediated colitis:
KEYTRUDA® can cause immune-mediated colitis. Monitor patients for signs and symptoms of colitis. Administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper) for Grade 2 or greater colitis. Withhold KEYTRUDA® for moderate (Grade 2) or severe (Grade 3) colitis, and permanently discontinue KEYTRUDA® for life-threatening (Grade 4) colitis (See DOSAGE AND ADMINISTRATION and ADVERSE REACTIONS).

Colitis occurred in 48 (1.7%) of 2799 patients, including Grade 2 (0.4%), Grade 3 (1.1%), and Grade 4 (<0.1%) colitis in patients receiving KEYTRUDA® in KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, and KEYNOTE-010.

Immune-mediated hepatitis:
KEYTRUDA® can cause immune-mediated hepatitis. Monitor patients for changes in liver function. Administer corticosteroids (initial dose of 0.5 to 1 mg/kg/day [for Grade 2 hepatitis] and 1 to 2 mg/kg/day [for Grade 3 or greater hepatitis] prednisone or equivalent followed by a taper) and, based on severity of liver enzyme elevations, withhold or discontinue KEYTRUDA® (See DOSAGE AND ADMINISTRATION and ADVERSE REACTIONS).

Hepatitis occurred in 19 (0.7%) of 2799 patients, including Grade 2 (0.1%), Grade 3 (0.4%), and Grade 4 (<0.1%) hepatitis in patients receiving KEYTRUDA® in KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, and KEYNOTE-010.

Immune-mediated nephritis and renal dysfunction:
KEYTRUDA® can cause immune-mediated nephritis. Monitor patients for changes in renal function. Administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper) for Grade 2 or greater nephritis. Withhold KEYTRUDA® for moderate (Grade 2), and permanently discontinue KEYTRUDA® for severe (Grade 3) or life-threatening (Grade 4) nephritis (See DOSAGE AND ADMINISTRATION and ADVERSE REACTIONS).

Nephritis occurred in 9 (0.3%) of 2799 patients, including Grade 2 (0.1%), Grade 3 (0.1%), and Grade 4 (<0.1%) nephritis in patients receiving KEYTRUDA® in KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, and KEYNOTE-010.

Immune mediated endocrinopathies:
Severe endocrinopathies, including hypophysitis, type 1 diabetes mellitus, diabetic ketoacidosis, hypothyroidism, and hyperthyroidism have been observed with KEYTRUDA® treatment.

Long-term hormone replacement therapy may be necessary in cases of immune-related endocrinopathies.

Hypophysitis
KEYTRUDA® can cause hypophysitis. Monitor patients for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency). Administer corticosteroids and hormone replacement as clinically indicated. Withhold KEYTRUDA® for moderate (Grade 2) hypophysitis and withhold or discontinue KEYTRUDA® for severe (Grade 3) or life-threatening (Grade 4) hypophysitis (See DOSAGE AND ADMINISTRATION and ADVERSE REACTIONS).

Hypophysitis occurred in 17 (0.6%) of 2799 patients, including Grade 2 (0.2%), Grade 3 (0.3%), and Grade 4 (<0.1%) hypophysitis in patients receiving KEYTRUDA® in KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, and KEYNOTE-010.

Type 1 diabetes mellitus
KEYTRUDA® can cause type 1 diabetes mellitus, including diabetic ketoacidosis, which have been reported in 6 (0.2%) of 2799 patients receiving KEYTRUDA®. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Administer insulin for type 1 diabetes,

and withhold KEYTRUDA® in cases of severe hyperglycemia until metabolic control is achieved.

Thyroid disorders

KEYTRUDA® can cause thyroid disorders, including hypothyroidism, hyperthyroidism and thyroiditis, which 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. Withold or discontinue KEYTRUDA® for severe (Grade 3) or life-threatening (Grade 4) hyperthyroidism (See DOSAGE AND ADMINISTRATION and Immune-mediated adverse reactions above).

Hyperthyroidism occurred in 96 (3.4%) of 2799 patients, including Grade 2 (0.8%) and Grade 3 (0.1%) hyperthyroidism in patients receiving KEYTRUDA® in KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, and KEYNOTE-010.

Hypothyroidism occurred in 237 (8.5%) of 2799 patients, including Grade 3 (0.1%) hypothyroidism in patients receiving KEYTRUDA® in KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, and KEYNOTE-010.

Severe skin reactions

KEYTRUDA® can cause immune-mediated severe skin reactions. Monitor patients for suspected severe skin reactions and exclude other causes. Based on the severity of the adverse reaction, withhold or permanently discontinue KEYTRUDA® and administer corticosteroids (see Dosage and Administration).

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

Other immune-mediated adverse reactions:

KEYTRUDA® can cause other clinically important immune-mediated adverse reactions including severe and fatal cases.
Based on the severity of the adverse reaction, KEYTRUDA® should be withheld and corticosteroids administered.

The following additional clinically significant, immune-mediated adverse reactions were reported in less than 1% (unless otherwise indicated) of patients treated with KEYTRUDA® in KEYNOTE-001, KEYNOTE-002, KEYNOTE-006 and KEYNOTE-010: uveitis, arthritis (1.5%), myositis, bullous pemphigoid, myasthenic syndrome, vasculitis, Guillain-Barré syndrome, hemolytic anemia, pancreatitis, partial seizures arising in a patient with inflammatory foci in brain parenchyma, and severe skin reactions (1.4%).

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.

The following was reported in other clinical studies with KEYTRUDA® or in post-marketing use: myocarditis.

Infusion-related reactions:
KEYTRUDA® can cause severe infusion-related reactions, including hypersensitivity and anaphylaxis, which have been reported in 6 (0.2%) of 2799 patients receiving KEYTRUDA® in KEYNOTE-001, KEYNOTE-002, KEYNOTE-006 and KEYNOTE-010. For severe or life-threatening infusion reactions, stop infusion and permanently discontinue KEYTRUDA® (See DOSAGE AND ADMINISTRATION). Patients with mild or moderate infusion reaction may continue to receive KEYTRUDA® with close monitoring; premedication with antipyretic and antihistamine may be considered.

Embryofetal toxicity:
KEYTRUDA® can cause fetal harm. Pregnant women or women with childbearing potential should be advised of the potential risk to the fetus (See Special Populations, Pregnant Women).

Special Populations
Pregnant Women: There are no data on the use of pembrolizumab in pregnant women. Animal reproduction studies have not been conducted with pembrolizumab; however, blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to result in an increase in fetal loss (See TOXICOLOGY). These results indicate a potential risk, based on its mechanism of action, that administration of KEYTRUDA® during pregnancy could cause fetal harm, including increased rates of abortion or stillbirth. Human IgG4 (immunoglobulin) is known to cross the placental barrier and pembrolizumab is an IgG4; therefore, pembrolizumab has the potential to be transmitted from the mother to the developing fetus. KEYTRUDA® is not recommended during pregnancy unless the clinical benefit outweighs the potential risk to the fetus. Women of childbearing potential should use effective contraception during treatment with KEYTRUDA® and for 4 months after the last dose of KEYTRUDA®.

Nursing Women: 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.

Pediatrics (< 18 years of age): Safety and efficacy of KEYTRUDA® in pediatric patients of age have not been established.

Geriatrics (> 65 years of age): 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.

Hepatic Impairment: No dose adjustment is needed for patients with mild hepatic impairment. KEYTRUDA® has not been studied in patients with moderate or severe hepatic impairment (See DOSAGE AND ADMINISTRATION).

Renal Impairment: No dose adjustment is needed for patients with mild (estimated Glomerular Filtration Rate (eGFR) <90 and ≥60 mL/min/1.73 m^2) or moderate (eGFR <60 and ≥30 mL/min/1.73 m^2) renal impairment. KEYTRUDA® has not been studied in patients with severe (eGFR <30 and ≥15 mL/min/1.73 m^2) renal impairment (See DOSAGE AND ADMINISTRATION).

Monitoring and Laboratory Tests:
Liver function tests (hepatic transaminase and bilirubin levels), thyroid function tests and electrolytes should be monitored at the start of treatment, periodically during treatment and as indicated based on clinical evaluation. Patients should be closely monitored during treatment for signs and symptoms of immune-mediated adverse reactions, including but not limited to, dyspnea, hypoxia; increased frequency of bowel movements, diarrhea; elevated transaminase and bilirubin levels; elevated creatinine levels; rash pruritus; headache, fatigue, hypotension, mental status changes; visual disturbances; muscle pain or weakness; paresthesias (See DOSAGE AND ADMINISTRATION and WARNINGS AND PRECAUTIONS).

NOC/c ADVERSE REACTIONS

Adverse Drug Reaction Overview

The safety and efficacy of KEYTRUDA® was investigated in three controlled, randomized studies (KEYNOTE-002, KEYNOTE-006, and KEYNOTE-010) for the treatment of unresectable or metastatic melanoma or metastatic NSCLC and in an uncontrolled, open-label study (KEYNOTE-001) for the treatment of unresectable or metastatic melanoma or metastatic NSCLC. Overall, 1567 patients with melanoma (699 previously treated with ipilimumab and 868 naïve to ipilimumab) and 1232 patients with NSCLC were treated. Safety is described for the pooled population of 2799 patients (studied across three doses; 2 mg/kg every 3 weeks and 10 mg/kg every 2 or 3 weeks). The median treatment duration was 4.2 months (range 1 day to 30.4 months) including 1153 patients treated for greater than or equal to six months and 600 patients treated for greater than or equal to one year.

KEYTRUDA® was discontinued for treatment-related adverse reactions in 5% of melanoma and NSCLC patients.

Treatment-related serious adverse events (SAEs) reported up to 90 days after the last dose occurred in 10% of patients receiving KEYTRUDA® (See WARNINGS AND PRECAUTIONS). Of these treatment-related SAEs, those occurring in more than ten patients (out of 2799) were: pneumonitis (n=44), colitis (n=25), diarrhea (n=17), and pyrexia (n=10).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Immune-mediated adverse reactions
Immune-mediated adverse reactions are presented based on 2799 patients with melanoma or NSCLC in KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, and KEYNOTE-010. The safety profile was generally similar for patients with melanoma and NSCLC.

Table 1 presents the incidence of immune-mediated adverse reactions by Grade that occurred in patients receiving KEYTRUDA®.

Table 1: 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
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

Pneumonitis:
The median time to onset of pneumonitis was 3.3 months (range 2 days to 19.3 months), and the median duration was 1.5 months (range 1 day to 17.2+ months). Pneumonitis occurred more frequently in patients with a history of prior thoracic radiation (6.9%) than in patients who did not receive prior thoracic radiation (2.9%). Pneumonitis led to discontinuation of KEYTRUDA® in 36 (1.3%) patients. Pneumonitis resolved in 55/94 patients (59%).

Colitis:
The median time to onset of colitis was 3.5 months (range 10 days to 16.2 months), and 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 41/48 patients (85%).

Hepatitis:
The median time to onset of hepatitis was 1.3 months (range 8 days to 21.4 months), and 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 15/19 patients (79%).

Nephritis and renal dysfunction:
The median time to onset of nephritis was 5.1 months (range 12 days to 12.8 months), and 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 5/9 patients (56%).

Endocrinopathies:
Hypophysitis:
The median time to onset of hypophysitis was 3.7 months (range 1 day to 11.9 months), and 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 7/17 patients (41%).

Hyperthyroidism:
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 71/96 patients (74%).

Hypothyroidism:
The median time to onset of hypothyroidism was 3.5 months (range 1 day to 18.9 months), and the median duration was not reached (range 2 days to 27.7+ months). One (<0.1%) patient discontinued KEYTRUDA® due to hypothyroidism.

Other adverse events

Melanoma

Treatment was discontinued for treatment-related adverse events in 5.4% of the 555 patients receiving KEYTRUDA® and in 9.4% of the 256 patients receiving ipilimumab.

Table 2 summarizes the treatment-related adverse events that occurred in at least 1% of patients with melanoma treated with KEYTRUDA® in KEYNOTE-006. The most common treatment-related adverse events (reported in at least 15% of patients) were diarrhea and fatigue.

Table 2: Treatment-Related Adverse Events (incidence ≥ 1%) KEYTRUDA® Treatment Groups Combined, APaT Population in KEYNOTE 006.

Adverse Reaction	KEYTRUDA® 10 mg/kg every 2 or 3 weeks n=555			Ipilimumab 3 mg/kg every 3 weeks n=256		
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Blood and lymphatic system disorders						
Anemia	9 (1.6)	2 (0.4)	0	1 (0.4)	1 (0.4)	0
Endocrine disorders						
Hyperthyroidism	24 (4.3)	0	0	6 (2.3)	1 (0.4)	0
Hypothyroidism	46 (8.3)	1 (0.2)	0	2 (0.8)	0	0
Gastrointestinal disorders						
Abdominal pain	15 (2.7)	0	0	15 (5.9)	0	0
Abdominal pain upper	7 (1.3)	0	0	1 (0.4)	0	0
Colitis	12 (2.2)	7 (1.3)	2 (0.4)	19 (7.4)	14 (5.5)	2 (0.8)
Constipation	12 (2.2)	0	0	5 (2.0)	0	0
Diarrhea	87 (15.7)	10 (1.8)	0	58 (22.7)	8 (3.1)	0
Dry mouth	31 (5.6)	0	0	1 (0.4)	0	0
Nausea	59 (10.6)	1 (0.2)	0	22 (8.6)	1 (0.4)	0
Vomiting	15 (2.7)	1 (0.2)	0	14 (5.5)	0	0
General disorders and administration site conditions						
Asthenia	63 (11.4)	1 (0.2)	0	16 (6.3)	2 (0.8)	0
Fatigue	111(20.0)	1 (0.2)	0	39 (15.2)	3 (1.2)	0
Influenza like illness	8 (1.4)	0	0	4 (1.6)	1 (0.4)	0
Pyrexia	14 (2.5)	0	0	6 (2.3)	0	0
Injury, poisoning and procedural complications						
Infusion related reaction	6 (1.1)	0	0	0	0	0

Adverse Reaction	KEYTRUDA® 10 mg/kg every 2 or 3 weeks n=555			Ipilimumab 3 mg/kg every 3 weeks n=256		
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Investigations						
Alanine aminotransferase increased	16 (2.9)	1 (0.2)	0	9 (3.5)	1 (0.4)	1 (0.4)
Aspartate aminotransferase increased	20 (3.6)	0	1 (0.2)	6 (2.3)	2 (0.8)	0
Blood bilirubin increased	7 (1.3)	0	0	0	0	0
Blood creatinine increased	7 (1.3)	0	0	1 (0.4)	0	0
Blood thyroid stimulating hormone decreased	6 (1.1)	0	0	2 (0.8)	1 (0.4)	0
Weight decreased	6 (1.1)			5 (2.0)	1 (0.4)	0
Metabolism and nutrition disorders						
Decreased appetite	35 (6.3)	0	0	20 (7.8)	0	0
Hypocalcemia	8 (1.4)	0	0	0	0	0
Musculoskeletal and connective tissue Disorders						
Arthralgia	58 (10.5)	1 (0.2)	0	13 (5.1)	2 (0.8)	0
Arthritis	6 (1.1)	0	0	0	0	0
Back pain	12 (2.2)	0	0	0 (0.0)	0	0
Muscle spasms	7 (1.3)	0	0	1 (0.4)	0	0
Myalgia	25 (4.5)	1 (0.2)	0	5 (2.0)	1 (0.4)	0
Pain in extremity	7 (1.3)	2 (0.4)	0	1 (0.4)	0	0
Nervous system disorders						
Dizziness	9 (1.6)	0	0	2 (0.8)	0	0
Dysgeusia	15 (2.7)	0	0	3 (1.2)	0	0
Headache	15 (2.7)	0	0	9 (3.5)	0	0
Psychiatric disorders						
Insomnia	7 (1.3)	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders						
Cough	22 (4.0)	0	0	0	0	0
Dyspnea	12 (2.2)	1 (0.2)	0	3 (1.2)	1 (0.4)	0
Skin and subcutaneous tissue disorders						
Dry skin	14 (2.5)	0	0	3 (1.2)	0	0
Eczema	7 (1.3)	0	0	1 (0.4)	0	0
Erythema	11 (2.0)	0	0	5 (2.0)	0	0
Hair colour changes	6 (1.1)	0	0	0	0	0
Papule	6 (1.1)	0	0	0	0	0
Pruritus	79 (14.2)	0	0	65 (25.4)	1 (0.4)	0

Adverse Reaction	KEYTRUDA® 10 mg/kg every 2 or 3 weeks n=555			Ipilimumab 3 mg/kg every 3 weeks n=256		
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Rash	78 (14.1)	0	0	37 (14.5)	1 (0.4)	1 (0.4)
Rash maculo-papular	16 (2.9)	1 (0.2)	0	7 (2.7)	1 (0.4)	0
Rash pruritic	7 (1.3)	0	0	4 (1.6)	0	0
Skin hypopigmentation	9 (1.6)	0	0	0	0	0
Vitiligo	56 (10.1)	0	0	4 (1.6)	0	0
Vascular disorders						
Flushing	6 (1.1)	0	0	2 (0.8)	0	0

Treatment-related adverse events reported in <1% patients with melanoma treated with KEYTRUDA® 10 mg/kg every 2 or 3 weeks (n=555) by system organ class (SOC) are shown below.

Endocrine disorders: adrenal insufficiency, hypophysitis, hypopituitarism
Eye disorders: uveitis
Gastrointestinal disorders: pancreatitis
Hepatobiliary disorders: hepatitis
Metabolism and nutrition disorders: Type 1 diabetes mellitus
Musculoskeletal and connective tissue disorders: myositis
Nervous system disorders: Guillain-Barré syndrome
Respiratory, thoracic and mediastinal disorders: pneumonitis

Table 3: Treatment-Related Adverse Events (incidence ≥ 1%) KEYTRUDA® Treatment Groups Combined, APaT Population in KEYNOTE 002.

Adverse Reaction	KEYTRUDA® 2 or 10 mg/kg every 3 weeks n=357			Chemotherapy n=171		
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Blood and lymphatic system disorders						
Anemia	12 (3.4)	1 (0.3)	0	35 (20.5)	9 (5.3)	0
Ear and labyrinth disorders						
Vertigo	5 (1.4)	0	0	2 (1.2)	0	0
Endocrine disorders						
Hyperthyroidism	8 (2.2)	0	0	0	0	0
Hypothyroidism	22 (6.2)	0	0	0	0	0
Gastrointestinal disorders						
Abdominal pain	10 (2.8)	1 (0.3)	0	4 (2.3)	0	0
Colitis	4 (1.1)	2 (0.6)	0	0		0
Constipation	14 (3.9)	0	0	14 (8.2)	0	0
Diarrhea	34 (9.5)	2 (0.6)	0	14(8.2)	3 (1.8)	0
Dry mouth	6 (1.7)	0	0	0	0	0
Nausea	24 (6.7)	1 (0.3)	0	56 (32.7)	3 (1.8)	1 (0.6)
Vomiting	12 (3.4)	2 (0.6)	0	26 (15.2)	3 (1.8)	1 (0.6)
General disorders and administration site conditions						
Asthenia	14 (3.9)	2 (0.6)	0	10 (5.8)	1 (0.6)	0
Chills	11 (3.1)	0	0	6 (3.5)	0	0
Fatigue	92 (25.8)	3 (0.8)	0	62 (36.3)	8 (4.7)	0
Influenza like illness	9 (2.5)	0	0	1 (0.6)	0	0
Malaise	4 (1.1)	0	0	1 (0.6)	0	0
Edema peripheral	8 (2.2)	0	0	4 (2.3)	0	0
Pyrexia	17 (4.8)	0	0	8 (4.7)	1 (0.6)	0
Investigations						
Alanine aminotransferase increased	11 (3.1)	1 (0.3)	0	3 (1.8)	0	0
Aspartate aminotransferase increased	10 (2.8)	2 (0.6)	0	0	0	0
Blood alkaline phosphatase increased	6 (1.7)	0	0	0	0	0
Blood bilirubin increased	4 (1.1)	0	0	3 (1.8)	0	0
Lymphocyte count decreased	4 (1.1)	1 (0.3)	0	7 (4.1)	2 (1.2)	0
Metabolism and nutrition disorders						
Decreased appetite	25 (7.0)	2 (0.6)	0	26 (15.2)	0	0
Musculoskeletal and connective tissue Disorders						

Adverse Reaction	KEYTRUDA® 2 or 10 mg/kg every 3 weeks n=357			Chemotherapy n=171		
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Arthralgia	25 (7.0)	2 (0.6)	0	9 (5.3)	1 (0.6)	0
Back pain	5 (1.4)	0	0	2 (1.2)	1 (0.6)	0
Joint stiffness	4 (1.1)	0	0	1 (0.6)	0	0
Myalgia	16 (4.5)	2 (0.6)	0	10 (5.8)	1 (0.6)	0
Pain in extremity	4 (1.1)	0	0	3 (1.8)	0	0
Nervous system disorders						
Dysgeusia	4 (1.1)	0	0	7 (4.1)	0	0
Headache	12 (3.4)	0	0	6 (3.5)	0	0
Respiratory, thoracic and mediastinal disorders						
Cough	12 (3.4)	0	0	1 (0.6)	0	0
Dyspnea	12 (3.4)	0	1 (0.3)	4 (2.3)	0	0
Pneumonitis	4 (1.1)	2 (0.6)	0	0	0	0
Skin and subcutaneous tissue disorders						
Alopecia	6 (1.7)	0	0	35 (20.5)	1 (0.6)	0
Dermatitis acneiform	4 (1.1)	0	0	0	0	0
Dry skin	18 (5.0)	0	0	2 (1.2)	0	0
Eczema	7 (2.0)	0	0	0	0	0
Erythema	4 (1.1)	0	0	4 (2.3)	0	0
Hyperhidrosis	4 (1.1)	0	0	2 (1.2)	0	0
Pruritus	79 (22.1)	0	0	6 (3.5)	0	0
Rash	39 (10.9)	0	0	8 (4.7)	0	0
Rash generalized	4 (1.1)	0	0	1 (0.6)	0	0
Rash maculo-papular	15 (4.2)	2 (0.6)	0	0	0	0
Skin hypopigmentation	6 (1.7)	0	0	0	0	0
Vitiligo	19 (5.3)	0	0	2 (1.2)	0	0

Treatment-related adverse events reported in <1% patients with melanoma treated with KEYTRUDA® 2 mg/kg or 10 mg/kg every 3 weeks (n=357) by SOC are shown below.

Blood and lymphatic system disorders: hemolytic anemia
Endocrine disorders: hypophysitis, hypopituitarism
Eye disorders: uveitis
Gastrointestinal disorders: pancreatitis
Hepatobiliary disorders: hepatitis
Musculoskeletal and connective tissue disorders: arthritis

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

Treatment-related adverse events at an incidence ≥ 1% reported in KEYNOTE-001, Part B2 with advanced melanoma previously treated with ipilimumab are presented in Table 4. Patients were treated with pembrolizumab at 2 mg/kg (n=89) or 10 mg/kg (n=84) every 3 weeks.

Table 4: Treatment-Related Adverse Events Occurring in ≥ 1% of Patients with Melanoma Treated with KEYTRUDA® (KEYNOTE-001)*

	KEYTRUDA® 2 mg/kg Q3W (n= 89)			KEYTRUDA® 10 mg/kg Q3W (n= 84)		
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Blood and lymphatic system disorders						
Anaemia	4 (4.5)	2 (2.2)	0	1 (1.2)	0	0
Leukopenia	0	0	0	1 (1.2)	0	0
Lymphopenia	1 (1.1)	0	0	0	0	0
Thrombocytopenia	0	0	0	2 (2.4)	0	0
Ear and labyrinth disorders						
External ear pain	1 (1.1)	0	0	0	0	0
Vertigo	0	0	0	2 (2.4)	0	0
Endocrine disorders						
Hyperthyroidism	1 (1.1)	0	0	2 (2.4)	0	0
Hypophysitis	2 (2.2)	0	1 (1.1)	0	0	0
Hypothyroidism	6 (6.7)	0	0	3 (3.6)	0	0
Eye disorders						
Dry eye	2 (2.2)	0	0	0	0	0
Eye pain	0	0	0	1 (1.2)	1 (1.2)	0
Eye pruritus	1 (1.1)	0	0	0	0	0
Uveitis	1 (1.1)	0	0	0	0	0
Vision blurred	0	0	0	1 (1.2)	0	0
Visual impairment	2 (2.2)	0	0	0	0	0
Gastrointestinal disorders						
Abdominal discomfort	2 (2.2)	0	0	0	0	0
Abdominal distension	0	0	0	1 (1.2)	0	0
Abdominal pain	3 (3.4)	0	0	0	0	0
Abdominal pain lower	1 (1.1)	0	0	0	0	0
Abdominal pain upper	0	0	0	2 (2.4)	0	0
Cheilitis	1 (1.1)	0	0	0	0	0
Constipation	5 (5.6)	0	0	4 (4.8)	0	0
Diarrhea	10 (11.2)	0	0	13 (15.5)	1 (1.2)	0
Dry mouth	0	0	0	2 (2.4)	0	0
Dyspepsia	1 (1.1)	0	0	0	0	0
Dysphagia	0	0	0	1 (1.2)	0	0

	KEYTRUDA® 2 mg/kg Q3W (n= 89)			KEYTRUDA® 10 mg/kg Q3W (n= 84)		
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Epigastric discomfort	1 (1.1)	0	0	0	0	0
Gastritis	0	0	0	1 (1.2)	0	0
Gastrooesophageal reflux disease	3 (3.4)	0	0	0	0	0
Gingival pain	1 (1.1)	0	0	0	0	0
Nausea	7 (7.9)	0	0	13 (15.5)	0	0
Oral pain	0	0	0	1 (1.2)	0	0
Pancreatitis	0	0	0	1 (1.2)	1 (1.2)	0
Vomiting	3 (3.4)	0	0	3 (3.6)	0	0
General disorders and administration site conditions						
Asthenia	5 (5.6)	0	0	6 (7.1)	0	0
Chest pain	0	0	0	2 (2.4)	0	0
Chills	7 (7.9)	0	0	3 (3.6)	0	0
Face edema	2 (2.2)	0	0	1 (1.2)	0	0
Facial pain	0	0	0	1 (1.2)	0	0
Fatigue	29 (32.6)	5 (5.6)	0	32 (38.1)	0	0
Inflammatory pain	1 (1.1)	0	0	0	0	0
Influenza like illness	1 (1.1)	0	0	1 (1.2)	0	0
Malaise	1 (1.1)	0	0	0	0	0
Mucosal inflammation	1 (1.1)	0	0	1 (1.2)	0	0
Edema	0	0	0	1 (1.2)	0	0
Edema peripheral	4 (4.5)	0	0	3 (3.6)	0	0
Pain	2 (2.2)	0	0	0	0	0
Pyrexia	3 (3.4)	0	0	5 (6.0)	0	0
Swelling	1 (1.1)	0	0	0	0	0
Xerosis	1 (1.1)	0	0	0	0	0
Hepatobiliary disorders						
Autoimmune hepatitis	1 (1.1)	0	1 (1.1)	0	0	0
Hepatitis	1 (1.1)	0	0	0	0	0
Immune system disorders						
Atopy	0	0	0	1 (1.2)	0	0
Cytokine release syndrome	0	0	0	1 (1.2)	0	0
Drug hypersensitivity	1` (1.1)	0	0	0	0	0
Infections and infestations						

	KEYTRUDA® 2 mg/kg Q3W (n= 89)			KEYTRUDA® 10 mg/kg Q3W (n= 84)		
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Candida infection	0	0	0	1 (1.2)	0	0
Folliculitis	1 (1.1)	0	0	0	0	0
Influenza	1 (1.1)	0	0	1 (1.2)	0	0
Nasopharyngitis	1 (1.1)	0	0	1 (1.2)	0	0
Oral herpes	1 (1.1)	0	0	0	0	0
Pneumonia	0	0	0	1 (1.2)	0	0
Injury, poisoning and procedural complications						
Excoriation	0	0	0	1 (1.2)	0	0
Infusion related reaction	0	0	0	1 (1.2)	0	0
Investigations						
Alanine aminotransferase increased	4 (4.5)	0	0	2 (2.4)	0	0
Amylase increased	1 (1.1)	1 (1.1)	0	0	0	0
Aspartate aminotransferase increased	3 (3.4)	0	0	2 (2.4)	0	0
Blood bilirubin increased	0	0	0	1 (1.2)	0	0
Blood calcium increased	1 (1.1)	0	0	0	0	0
Blood creatinine increased	0	0	0	1 (1.2)	0	0
Blood thyroid stimulating hormone decreased	0	0	0	2 (2.4)	0	0
Blood thyroid stimulating hormone increased	1 (1.1)	0	0	3 (3.6)	0	0
Thyroxine decreased	1 (1.1)	0	0	3 (3.6)	0	0
Thyroxine free increased	1 (1.1)	0	0	0	0	0
Tri-iodothyronine decreased	0	0	0	1 (1.2)	0	0
Tri-iodothyronine increased	1 (1.1)	0	0	0	0	0
Weight decreased	3 (3.4)	0	0	2 (2.4)	0	0
White blood cell count increased	1 (1.1)	0	0	0	0	0

	KEYTRUDA® 2 mg/kg Q3W (n= 89)			KEYTRUDA® 10 mg/kg Q3W (n= 84)		
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Metabolism and nutrition disorders						
Decreased appetite	9 (10.1)	0	0	5 (6.0)	0	0
Dehydration	1 (1.1)	0	0	1 (1.2)	0	0
Hypokalaemia	0	0	0	1 (1.2)	0	0
Hypomagnesaemia	0	0	0	1 (1.2)	0	0
Musculoskeletal and connective tissue disorders						
Arthralgia	12 (13.5)	0	0	12 (14.3)	0	0
Arthritis	1 (1.1)	0	0	0	0	0
Arthropathy	0	0	0	1 (1.2)	0	0
Back pain	3 (3.4)	0	0	2 (2.4)	0	0
Flank pain	0	0	0	1 (1.2)	0	0
Joint swelling	0	0	0	2 (2.4)	0	0
Muscle spasms	2 (2.2)	0	0	2 (2.4)	0	0
Muscular weakness	3 (3.4)	1 (1.1)	0	4 (4.8)	0	0
Musculoskeletal pain	0	0	0	1 (1.2)	1 (1.2)	0
Musculoskeletal stiffness	1 (1.1)	0	0	0	0	0
Myalgia	6 (6.7)	0	0	4 (4.8)	0	0
Neck pain	1 (1.1)	0	0	0	0	0
Pain in extremity	1 (1.1)	0	0	0	0	0
Pain in jaw	1 (1.1)	0	0	1 (1.2)	0	0
Polyarthritis	1 (1.1)	0	0	0	0	0
Tenosynovitis	0	0	0	1 (1.2)	0	0
Neoplasms benign, malignant and unspecified						
Neoplasm swelling	0	0	0	1 (1.2)	0	0
Skin papilloma	0	0	0	1 (1.2)	0	0
Tumour pain	1 (1.1)	0	0	2 (2.4)	0	0
Nervous system disorders						
Cognitive disorder	1 (1.1)	0	0	0	0	0
Dizziness	2 (2.2)	0	0	0	0	0
Dysgeusia	0	0	0	1 (1.2)	0	0
Encephalopathy	1 (1.1)	1 (1.1)	0	0	0	0
Headache	6 (6.7)	0	0	3 (3.6)	0	0
Hyperesthesia	1 (1.1)	0	0	0	0	0
Hypoesthesia	3 (3.4)	0	0	0	0	0
Lethargy	4 (4.5)	0	0	0	0	0
Neuropathy peripheral	1 (1.1)	0	0	2 (2.4)	0	0
Paresthesia	1 (1.1)	0	0	3 (3.6)	0	0
Partial seizures	1 (1.1)	0	0	0	0	0

	KEYTRUDA® 2 mg/kg Q3W (n= 89)			KEYTRUDA® 10 mg/kg Q3W (n= 84)		
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Peripheral motor neuropathy	1 (1.1)	1 (1.1)	0	0	0	0
Peripheral sensory neuropathy	1 (1.1)	0	0	0	0	0
Psychiatric disorders						
Confusional state	1 (1.1)	1 (1.1)	0	0	0	0
Disorientation	0	0	0	1 (1.2)	0	0
Insomnia	0	0	0	1 (1.2)	0	0
Sleep disorder	0	0	0	1 (1.2)	0	0
Renal and urinary disorders						
Pollakiuria	0	0	0	1 (1.2)	0	0
Reproductive system and breast disorders						
Breast pain	1 (1.1)	0	0	0	0	0
Genital rash	0	0	0	1 (1.2)	0	0
Hematospermia	1 (1.1)	0	0	0	0	0
Menorrhagia	1 (1.1)	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders						
Cough	9 (10.1)	0	0	6 (7.1)	0	0
Dyspnea	7 (7.9)	0	0	7 (8.3)	1 (1.2)	0
Dyspnea exertional	1 (1.1)	0	0	1 (1.2)	0	0
Epistaxis	1 (1.1)	0	0	0	0	0
Hypoxia	0	0	0	1 (1.2)	1 (1.2)	0
Nasal dryness	1 (1.1)	0	0	0	0	0
Oropharyngeal pain	0	0	0	1 (1.2)	0	0
Pleuritic pain	0	0	0	1 (1.2)	0	0
Pneumonitis	2 (2.2)	1 (1.1)	0	1 (1.2)	0	0
Productive cough	1 (1.1)	0	0	0	0	0
Sinus congestion	0	0	0	1 (1.2)	0	0
Wheezing	0	0	0	2 (2.4)	0	0
Skin and subcutaneous tissue disorders						
Alopecia	1 (1.1)	0	0	0	0	0
Blister	1 (1.1)	0	0	0	0	0
Dermatitis acneiform	0	0	0	1 (1.2)	0	0
Dry skin	2 (2.2)	0	0	0	0	0
Eczema	0	0	0	1 (1.2)	0	0
Erythema	5 (5.6)	0	0	2 (2.4)	0	0
Hair color changes	1 (1.1)	0	0	0	0	0
Hyperhidrosis	0	0	0	1 (1.2)	0	0
Nail discoloration	1 (1.1)	0	0	0	0	0
Neutrophilic	1 (1.1)	0	0	0	0	0

	KEYTRUDA® 2 mg/kg Q3W (n= 89)			KEYTRUDA® 10 mg/kg Q3W (n= 84)		
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
dermatosis						
Night sweats	4 (4.5)	0	0	1 (1.2)	0	0
Onychoclasis	1 (1.1)	0	0	0	0	0
Palmar-plantar erythrodysaesthesia syndrome	1 (1.1)	0	0	0	0	0
Pigmentation disorder	2 (2.2)	0	0	0	0	0
Pruritus	23 (25.8)	0	0	17 (20.2)	0	0
Pruritus generalised	0	0	0	1 (1.2)	0	0
Rash	17 (19.1)	0	0	16 (19.0)	1 (1.2)	0
Rash erythematous	0	0	0	1 (1.2)	0	0
Rash generalised	1 (1.1)	0	0	2 (2.4)	0	0
Rash maculo-papular	2 (2.2)	0	0	2 (2.4)	1 (1.2)	0
Rash papular	1 (1.1)	0	0	0	0	0
Scab	1 (1.1)	0	0	0	0	0
Skin depigmentation	0	0	0	1 (1.2)	0	0
Skin disorder	0	0	0	1 (1.2)	0	0
Skin hyperpigmentation	1 (1.1)	0	0	0	0	0
Skin hypopigmentation	0	0	0	2 (2.4)	0	0
Vitiligo	8 (9.0)	0	0	5 (6.0)	0	0
Vascular disorders						
Flushing	0	0	0	1 (1.2)	0	0
Raynaud's phenomenon	1 (1.1)	0	0	0	0	0

In the 411 patients studied across three doses (2 mg/kg every 3 weeks and 10 mg/kg every 2 or 3 weeks), the pooled safety profile was generally similar to that seen for the subset of patients receiving the recommended dose of 2 mg/kg or 10 mg/kg every 3 weeks. In this pooled dose population, KEYTRUDA® was discontinued for treatment-related adverse events in 4% of patients and treatment-related serious adverse events (SAEs) reported up to 90 days after the last dose occurred in 9% of patients. Of these treatment-related SAEs, those occurring in more than 1 patient were: hyperthyroidism (n=2), hypophysitis (n=2), colitis (including colitis microscopic) (n=5), nausea (n=2), vomiting (n=2), pyrexia (n=4), dehydration (n=2), confusional state (n=2), renal failure (including acute renal failure) (n=4), dyspnea (n=2) and pneumonitis (n=3).

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

NSCLC

Table 5 summarizes the treatment-related adverse events that occurred in at least 1% of patients with NSCLC treated with KEYTRUDA® in KEYNOTE-024. The most common treatment-related adverse events (reported in at least 10% of patients) were diarrhea, fatigue, and pyrexia. The most common Grade 3-5 treatment-related adverse events for patients treated with KEYTRUDA® in KEYNOTE-024 were diarrhea (3.9%), pneumonitis (2.6%), and anemia (1.9%).

Treatment was discontinued for treatment related adverse events in 7.1% of the 154 patients receiving KEYTRUDA® and in 10.7% of the 150 patients receiving chemotherapy. The most common treatment-related adverse event leading to study drug discontinuation (occurring in more than 2 patients) was: pneumonitis (n=6). The median time to discontinuation for treatment-related adverse events was 0.7 months. There were 9 (5.8%) deaths reported in the KEYTRUDA® arm: pneumonia (n=2), respiratory failure (n=2), cardiac arrest (n=1), hemorrhagic stroke (n=1), sepsis (n=1), general physical health deterioration (n=1), and sudden death (n=1). One of the deaths (sudden death) was considered by the investigator to be related to treatment. There were 7 (4.7%) death in the chemotherapy arm; cardiac arrest/failure (n=3), sepsis (n=1), pulmonary embolism (n=1), pulmonary alveolar hemorrhage (n=1) and not specified (n=1). Three of the deaths (sepsis, pulmonary alveolar hemorrhage, and not specified) were considered to be treatment related.

Table 5: Treatment-Related Adverse Events (incidence ≥ 1%) in Patients Treated with KEYTRUDA®, APaT Population in KEYNOTE 024

	KEYTRUDA® 200 mg every 3 weeks n=154			**Chemotherapy n=150**		
Adverse Reaction	**Any Grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Any Grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**
Blood and lymphatic system disorders						
Anemia	8 (5.2)	3 (1.9)	0	66 (44.0)	29 (19.3)	0
Eosinophilia	3 (1.9)	0	0	0	0	0
Lymphopenia	2 (1.3)	0	0	0	0	0
Endocrine disorders						
Hyperthyroidism	11 (7.1)	0	0	0	0	0
Hypothyroidism	12 (7.8)	0	0	1 (0.7)	0	0
Thyroiditis	3 (1.9)	0	0	0	0	0
Gastrointestinal disorders						
Abdominal pain	4 (2.6)	0	0	3 (2.0)	0	0
Abdominal distention	2 (1.3)	0	0	0	0	0
Colitis	2 (1.3)	2 (1.3)	0	0	0	0
Constipation	6 (3.9)	0	0	17 (11.3)	0	0

	KEYTRUDA® 200 mg every 3 weeks n=154			Chemotherapy n=150		
Adverse Reaction	**Any Grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Any Grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**
Diarrhea	22(14.3)	6 (3.9)	0	20 (13.3)	2 (1.3)	0
Dyspepsia	2 (1.3)	0	0	4 (2.7)	0	0
Nausea	15 (9.7)	0	0	65 (43.3)	3 (2.0)	0
Stomatitis	4 (2.6)	0	0	18 (12.0)	2 (1.3)	0
Vomiting	4 (2.6)	1 (0.6)	0	30 (20.0)	1(0.7)	0
General disorders and administration site conditions						
Asthenia	5 (3.2)	1 (0.6)	0	11 (7.3)	2 (1.3)	0
Chills	3 (1.9)	0	0	0	0	0
Fatigue	16 (10.4)	2 (1.3)	0	43 (28.7)	5 (3.3)	0
Edema	2 (1.3)	0	0	2 (1.3)	0	0
Edema peripheral	4 (2.6)	1 (0.6)	0	6 (4.0)	0	0
Pyrexia	16 (10.4)	0	0	8 (5.3)	0	0
Lower respiratory tract infection	2 (1.3)	2 (1.3)				
Infusion related reaction	3 (1.9)	0	0	0	0	0
Investigations						
Alanine aminotransferase increased	10 (6.5)	0	0	7 (4.7)	0	0
Aspartate aminotransferase increased	8 (5.2)	2 (1.3)	0	5 (3.3)	0	0
Blood creatinine increased	3 (1.9)	0	0	15 (10.0)	1 (0.7)	0
Blood thyroid stimulating hormone increased	5 (3.2)	0	0	0	0	0
Blood thyroid stimulating hormone decreased	4 (2.6)	0	0	0	0	0
Gamma-glutamyltransferase increased	3 (1.9)	1 (0.6)	0	4 (2.7)	0	0
Hepatic enzyme increased	2 (1.3)	1 (0.6)	0	0	0	0
Transaminase increased	3 (1.9)	2 (1.3)	0	0	0	0
Metabolism and nutrition disorders						
Weight decreased	5 (3.2)	0	0	4 (2.7)	0	0
Decreased appetite	14 (9.1)	0	0	39 (26.0)	4 (2.7)	0
Disabetes Mellitus	2 (1.3)	2 (1.3)	0	0	0	0
Hyperglycemia	2 (1.3)	0	1 (0.6)	2 (1.3)	0	0
Hyperkalemia	3 (1.9)	0	0	1 (0.7)	0	0
Hypoalbumineamea	3 (1.9)	2 (1.3)	0	4 (2.7)	2 (1.3)	0
Hyponatremia	5 (3.2)	0	0	2 (1.3)	1 (0.7)	0

	KEYTRUDA® 200 mg every 3 weeks n=154			Chemotherapy n=150		
Adverse Reaction	**Any Grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Any Grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**
Musculoskeletal and connective tissue Disorders						
Arthralgia	13 (8.4)	0	0	4 (2.7)	0	0
Arthritis	2 (1.3)	0	0	0	0	0
Back pain	2 (1.3)	0	0	1 (0.7)	0	0
Myalgia	3 (1.9)	0	0	1 (0.7)	0	0
Dizziness	2 (1.3)	0	0	3 (2.0)	0	0
Neuropathy peripheral	2 (1.3)	0	0	9 (6.0)	1 (0.7)	0
Paresthesia	2 (1.3)	0	0	2 (1.3)	0	0
Respiratory, thoracic and mediastinal disorders						
Dysuria	2 (1.3)	0	0	1 (0.7)	0	0
Cough	5 (3.2)	0	0	0	0	0
Dyspnea	4 (2.6)	1 (0.6)	0	5 (3.3)	1 (0.7)	0
Hiccups	2 (1.3)	0	0	7 (4.7)	0	0
Pneumonitis	8 (5.2)	2 (1.3)	2 (1.3)	1 (0.7)	1 (0.7)	0
Skin and subcutaneous tissue disorders						
Dry skin	8 (5.2)	0	0	1 (0.7)	0	0
Erythema	3 (1.9)	0	0	0	0	0
Night sweats	3 (1.9)	0	0	0	0	0
Pruritus	12 (7.8)	0	0	3 (2.0)	0	0
Pruritus generalized	3 (1.9)	0	0	1 (0.7)	0	0
Psoriasis	2 (1.3)	1 (0.6)	0	0	0	0
Rash	11 (7.1)	1 (0.6)	0	3 (2.0)	0	0
Rash maculo-papular	5 (3.2)	1 (0.6)	0	1 (0.7)	0	0
Rash pruritic	2 (1.3)	0	0	1 (0.7)	0	0
Skin exfoliation	2 (1.3)	0	0	0	0	0
Urticaria	2 (1.3)	0	0	1 (0.7)	0	0

Treatment-related adverse events reported in <1% patients with NSCLC treated with KEYTRUDA® 200 mg every 3 weeks (n=154) by SOC are shown below.

Endocrine disorders: hypophysitis
Gastrointestinal disorders: pancreatitis
Metabolism and nutrition disorders: diabetic ketoacidosis
Musculoskeletal and connective tissue disorders: myositis

Table 6 summarizes the treatment-related adverse events that occurred in at least 1% of patients with NSCLC treated with KEYTRUDA® in KEYNOTE-010. Clinically important adverse reactions occurring in patients receiving KEYTRUDA® were fatigue (25%), diarrhea (14%),

asthenia (11%) and pyrexia (11%). The most common treatment-related adverse events (reported in at least 10% of patients) were fatigue, decreased appetite, rash, and nausea. The most common Grade 3-5 treatment-related adverse events for patients treated with KEYTRUDA® in KEYNOTE-010 were pneumonitis (1.8%) and fatigue (1.5%).

In KEYNOTE-010, the adverse reaction profile was similar for the 2 mg/kg and 10 mg/kg dose, therefore summary safety results are provided in a pooled analysis (n=682). Treatment was discontinued for treatment-related adverse events in 5% of patients receiving KEYTRUDA®. The most common treatment-related adverse event resulting in permanent discontinuation of KEYTRUDA® was pneumonitis (1.8%, n =12). The median time to discontinuation for treatment-related adverse events was 2.5 months. Treatment-related adverse events leading to interruption of KEYTRUDA® occurred in 13% of patients; the most common (≥1%) were fatigue (1.2%) and decreased appetite (1%).

Table 6: Treatment-Related Adverse Events (incidence ≥ 1%) KEYTRUDA® Treatment Groups Combined, APaT Population in KEYNOTE 010.

Adverse Reaction	KEYTRUDA® 2 or 10 mg/kg every 3 weeks n=682				Docetaxel 75 mg/m^2 every 3 weeks n=309			
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Blood and lymphatic system disorders								
Anemia	24 (3.5)	4 (0.6)	0	0	40 (12.9)	5 (1.6)	0	0
Endocrine disorders								
Hyperthyroidism	25 (3.7)	1 (0.1)	0	0	0	0	0	0
Hypothyroidism	48 (7.0)	0	0	0	1 (0.3)	0	0	0
Eye disorders								
Dry eye	10 (1.5)	0	0	0	1 (0.3)	0	0	0
Gastrointestinal disorders								
Abdominal pain	7 (1.0)	0	0	0	4 (1.3)	0	0	0
Constipation	23 (3.4)	0	0	0	14 (4.5)	0	0	0
Diarrhea	46 (6.7)	2 (0.3)	0	0	56 (18.1)	6 (1.9)	1 (0.3)	0
Dry mouth	8 (1.2)	0	0	0	3 (1.0)	0	0	0
Nausea	68 (10.0)	3 (0.4)	0	0	45 (14.6)	1 (0.3)	0	0
Stomatitis	20 (2.9)	1 (0.1)	0	0	43 (13.9)	3 (1.0)	0	0
Vomiting	25 (3.7)	1 (0.1)	0	0	24 (7.8)	2 (0.6)	0	0
General disorders and administration site conditions								
Asthenia	39 (5.7)	3 (0.4)	0	0	35 (11.3)	6 (1.9)	0	0

Adverse Reaction	KEYTRUDA® 2 or 10 mg/kg every 3 weeks n=682				Docetaxel 75 mg/m^2 every 3 weeks n=309			
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Fatigue	95(13.9)	10 (1.5)	0	0	76 (24.9)	11 (3.6)	0	0
Influenza like illness	7 (1.0)	0	0	0	0	0	0	0
Malaise	14 (2.1)	0	0	0	11 (3.6)	0	0	0
Edema peripheral	9 (1.3)	0	0	0	21 (6.8)	0	0	0
Pyrexia	24 (3.5)	1 (0.1)	0	0	17 (5.5)	1 (0.3)	0	0
Infections and infestations								
Pneumonia	10 (1.5)	4 (0.6)	0	2 (0.3)	5 (1.6)	2 (0.6)	2 (0.6)	0
Investigations								
Alanine aminotransferase increased	24 (3.5)	3 (0.4)	0	0	4 (1.3)	0	0	0
Aspartate aminotransferase increased	17 (2.5)	2 (0.3)	0	0	3 (1.0)	0	0	0
Blood alkaline phosphatase increased	11 (1.6)	2 (0.3)	0	0	2 (0.6)	0	0	0
Blood creatinine increased	13 (1.9)	0	0	0	0	0	0	0
Blood thyroid stimulating hormone increased	7 (1.0)	0	0	0	0	0	0	0
Weight decreased	15 (2.2)	1 (0.1)	0	0	2 (0.6)	0	0	0
Metabolism and nutrition disorders								
Decreased appetite	79 (11.6)	4 (0.6)	0	0	49 (15.9)	3 (1.0)	0	0
Hypertriglyceridemia	10 (1.5)	2 (0.3)	2 (0.3)	0	0	0	0	0
Musculoskeletal and connective tissue Disorders								
Arthralgia	32 (4.7)	2 (0.3)	0	0	18 (5.8)	0 (0.0)	0	0
Back pain	9 (1.3)	1 (0.1)	0	0	0	0	0	0
Musculoskeletal pain	8 (1.2)	0	0	0	4 (1.3)	0	0	0
Myalgia	19 (2.8)	0	0	0	29 (9.4)	0	0	0

Adverse Reaction	KEYTRUDA® 2 or 10 mg/kg every 3 weeks n=682				Docetaxel 75 mg/m^2 every 3 weeks n=309			
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Nervous system disorders								
Dizziness	11 (1.6)	0	0	0	5 (1.6)	1 (0.3)	0	0
Dysgeusia	11 (1.6)	0	0	0	16 (5.2)	0	0	0
Headache	14 (2.1)	0	0	0	2 (0.6)	0	0	0
Respiratory, thoracic and mediastinal disorders								
Cough	11 (1.6)	0	0	0	3 (1.0)	0	0	0
Dyspnea	21 (3.1)	4 (0.6)	0	0	13 (4.2)	4 (1.3)	0	0
Pneumonitis	26 (3.8)	5 (0.7)	4 (0.6)	3 (0.4)	3 (1.0)	1 (0.3)	0	0
Skin and subcutaneous tissue disorders								
Dry skin	18 (2.6)	0	0	0	4 (1.3)	0	0	0
Pruritus	57 (8.4)	0	0	0	5 (1.6)	1 (0.3)	0	0
Rash	73 (10.7)	2 (0.3)	0	0	14 (4.5)	0	0	0
Rash maculo-papular	9 (1.3)	1 (0.1)	0	0	0	0	0	0

Treatment-related adverse events reported in <1% patients with NSCLC treated with pembrolizumab 2 mg/kg or 10 mg/kg every 3 weeks (n=682) by SOC are shown below.

Endocrine disorders: hypopituitarism, adrenal insufficiency
Gastrointestinal disorders: colitis, pancreatitis
Injury, poisoning and procedural complications: infusion related reaction
Metabolism and nutrition disorders: diabetic ketoacidosis, Type 1 diabetes mellitus
Musculoskeletal and connective tissue disorders: arthritis
Skin and subcutaneous tissue disorders: pemphigoid

Abnormal Hematologic and Clinical Chemistry Findings
Laboratory abnormalities (worsened from baseline in ≥ 10% of patients), reported in KEYNOTE-006 in patients with advanced melanoma are presented in Table 7.

Table 7: Laboratory Abnormalities Worsened from Baseline in ≥10% of Patients with Unresectable or Metastatic Melanoma Treated with KEYTRUDA® 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	33	6	25	6
Leukopenia	12	0	5	0
Thrombocytopenia	11	1	6	1
Chemistry				
Hypertriglyceridemia	42	3	33	1
Hypercholesterolemia	22	1	17	0

Laboratory abnormalities (worsened from baseline in ≥ 10% of patients), reported in KEYNOTE-002 in patients with advanced melanoma are presented in Table 8.

Table 8: Laboratory Abnormalities Worsened from Baseline in ≥10% of Patients with Unresectable or Metastatic Melanoma 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 or 10 mg/kg every 3 weeks n=357		Chemotherapy n=171	
Laboratory Test	**All Grades %**	**Grades 3-4 %**	**All Grades %**	**Grades 3-4 %**
Chemistry				
Hyperglycemia	48	6	42	6
Hypoalbuminemia	35	2	30	1
Hyponatremia	36	7	24	4
Increased Alkaline Phosphatase	26	3	17	2
Increased Aspartate Aminotransferase	23	2	16	1
Hypercholesterolemia	20	1	11	0
Increased Alanine Aminotransferase	20	2	15	1
Bicarbonate decreased	18	0	10	0
Hyperkalemia	15	1	8	1
Creatinine increased	14	1	9	1

NSCLC
Laboratory abnormalities (worsened from baseline in ≥ 10% of patients), reported in KEYNOTE-024 in patients with NSCLC, are presented in Table 9.

Table 9: Laboratory Abnormalities Worsened from Baseline in ≥ 10% of Patients with NSCLC 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]), APaT population in KEYNOTE 024

	KEYTRUDA® 200 mg every 3 weeks n=154		Chemotherapy n=150	
Laboratory Test	**All Grades %**	**Grades 3-4 %**	**All Grades %**	**Grades 3-4 %**
Chemistry				
Glucose Increased	80 (51.9)	12 (7.8)	69 (46.0)	9 (6.0)
Alanine Aminotransferase Increased	47 (30.5)	7 (4.5)	46 (30.7)	0
Calcium Decreased	39 (25.3)	0	30 (20.0)	0
Aspartate Aminotransferase Increased	38 (24.7)	6 (3.9)	49 (32.7)	0
Alkaline Phosphatase Increased	34 (22.1)	4 (2.6)	36 (24.0)	0

Laboratory abnormalities (worsened from baseline in ≥ 10% of patients), reported in KEYNOTE-010, in patients with NSCLC, are presented in Table 10. Patients were treated with pembrolizumab at 2 mg/kg or 10 mg/kg every 3 weeks.

Table 10: Laboratory Abnormalities Worsened from Baseline in ≥ 10% of Patients with NSCLC Treated with KEYTRUDA and at a Higher Incidence than in the Docetaxel Arm (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-4]) (KEYNOTE-010)

	KEYTRUDA® 2 or 10 mg/kg every 3 weeks n=682		Docetaxel 75 mg/m^2 every 3 weeks n=309	
Laboratory Test	**All Grades (%)**	**Grades 3-4 (%)**	**All Grades (%)**	**Grades 3-4 (%)**
Chemistry				
Hyponatremia	31	8	25	3
Increased alkaline phosphatase	28	3	16	0.6
Increased aspartate aminotransferase	25	2	12	0.6
Alanine aminotransferase increased	21	2	9	0.3
Hypomagnesia	19	0.3	13	0.3
Creatinine increased	18	0.9	9	0.6

Immunogenicity
As with all therapeutic proteins, there is the potential for immunogenicity. Trough levels of pembrolizumab interfere with the electrochemiluminescent (ECL) assay results; therefore, a subset analysis was performed in the patients with a concentration of pembrolizumab below the drug tolerance level of the anti-product antibody assay. In clinical studies in patients treated with pembrolizumab at a dose of 2 mg/kg every 3 weeks, 200 mg every 3 weeks, or 10 mg/kg every two or three weeks, 26 (2.0%) of 1289 evaluable patients tested positive for treatment-emergent anti-pembrolizumab antibodies. Among the 26 patients who tested positive for treatment emergent anti-pembrolizumab antibodies, only 4 patients were tested for neutralizing antibodies and one was positive. There was no evidence of an altered pharmacokinetic profile or increased infusion reactions with anti-pembrolizumab binding antibody development.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to KEYTRUDA® with the incidences of antibodies to other products may be misleading.

NOC/c DRUG INTERACTIONS

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

The use of systemic corticosteroids or immunosuppressants before starting KEYTRUDA® should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of KEYTRUDA®. However, systemic corticosteroids or other immunosuppressants can be used after starting KEYTRUDA® to treat immune-mediated adverse reactions (See WARNINGS AND PRECAUTIONS).

NOC/c DOSAGE AND ADMINISTRATION

Patient Selection
Non-Small Cell Lung Carcinoma
Patients should be selected for treatment of metastatic NSCLC with KEYTRUDA® based on the presence of positive PD-L1 expression defined as a Tumour Proportion Score (TPS) ≥ 1%, PD-Ll expression with TPS ≥ 1% should be determined by an experienced laboratory using a validated test. It is preferred that, a test authorized by Health Canada, or one that is equivalent to that used in clinical trials (e.g. PD-Ll IHC 22C3 pharmDx™ kit from Dako; see CLINICAL TRIALS) be considered.

Recommended Dose and Dosage Adjustment (See WARNINGS AND PRECAUTIONS)

Recommended Dosage for Melanoma
The recommended dose of KEYTRUDA® is 2 mg/kg body weight administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity.

Recommended Dosage for NSCLC – Previously Untreated
The recommended dose of KEYTRUDA® is 200 mg fixed dose administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity or up to 24 months in patients without disease progression.

NOC/c - Recommended Dosage for NSCLC – Previously Treated
The recommended dose of KEYTRUDA® is 2 mg/kg body weight administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity.

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

Table 11: Recommended treatment modifications for KEYTRUDA®

Immune-related adverse reactions	**Severity**	**Treatment modification**
Pneumonitis	Grade 2	Withhold*
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue
Colitis	Grade 2 or 3	Withhold*
	Grade 4	Permanently discontinue
Nephritis	Grade 2 with creatinine > 1.5 to ≤ 3 times upper limit of normal (ULN)	Withhold*
	Grade ≥ 3 with creatinine > 3 times ULN	Permanently discontinue

Endocrinopathies	Symptomatic hypophysitis Type 1 diabetes associated with Grade > 3 hyperglycaemia (glucose > 250 mg/dL or > 13.9 mmol/L) or associated with ketoacidosis Hyperthyroidism Grade ≥ 3	Withhold* For patients with Grade 3 or Grade 4 endocrinopathy that improved to Grade 2 or lower and is controlled with hormone replacement, if indicated, continuation of pembrolizumab may be considered after corticosteroid taper, if needed. Otherwise treatment should be discontinued. Hypothyroidism may be managed with replacement therapy without treatment interruption.
Hepatitis	Grade 2 with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 to 5 times ULN or total bilirubin > 1.5 to 3 times ULN	Withhold*
	Grade ≥ 3 with AST or ALT > 5 times ULN or total bilirubin > 3 times ULN	Permanently discontinue
	In case of liver metastasis with baseline Grade 2 elevation of AST or ALT, hepatitis with AST or ALT increases ≥ 50% and lasts ≥ 1 week	Permanently discontinue
Skin reactions	Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold*
	Grade 4 or confirmed SJS or TEN	Permanently discontinue
Infusion-related reactions	Grade 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).

* until adverse reactions recover to Grade 0-1.

KEYTRUDA® should be permanently discontinued:

- For Grade 4 toxicity except for endocrinopathies that are controlled with replacement hormones
- If corticosteroid dosing cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks
- If a treatment-related toxicity does not resolve to Grade 0-1 within 12 weeks after last dose of KEYTRUDA®
- If any event occurs a second time at Grade ≥ 3 severity.

Renal Impairment: No dose adjustment is needed for patients with mild (eGFR) < 90 and ≥ 60 mL/min/1.73 m^2) or moderate (eGFR < 60 and ≥ 30 mL/min/1.73 m^2) renal impairment. KEYTRUDA® has not been studied in patients with severe (eGFR < 30 and ≥ 15 mL/min/1.73 m^2) renal impairment.

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

Eastern Cooperative Oncology Group (ECOG) performance status score ≥ 2: Patients with ECOG performance status score ≥ 2 were excluded from the clinical trials (see CLINICAL TRIALS).

Preparation and Administration

Reconstitution of KEYTRUDA® (Lyophilized Powder)

- Prior to reconstitution, the vial of lyophilized 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 lyophilized powder.
- Slowly swirl the vial to allow reconstitution of the lyophilized powder. Allow up to 5 minutes for the bubbles to clear. Do not shake the vial.

Preparation for Intravenous Infusion

- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. KEYTRUDA® is a clear to slightly opalescent, colorless to slightly yellow solution. Discard the vial if visible particles are observed. Dilute KEYTRUDA® solution or reconstituted lyophilized powder prior to intravenous administration.
- Withdraw the required volume from the vial(s) 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.

Storage of Reconstituted and Diluted Solutions

- Do not freeze the infusion solution.
- 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® solutions 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 24 hours. If refrigerated, allow the vials and/or IV bags to come to room temperature prior to use.

Administration

- Administer infusion solution intravenously over 30 minutes using a sterile, non-pyrogenic, low-protein binding 0.2 to 5 µm in-line or add-on filter.
- Do not co-administer other drugs through the same infusion line.
- Discard any unused portion left in the vial.

OVERDOSAGE

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 management of a suspected drug overdose, contact your regional Poison Control Centre.

NOC/c ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

PD-1 is an immune-checkpoint receptor that limits the activity of T lymphocytes in peripheral tissues. The PD-1 pathway is an immune control checkpoint that may be engaged by 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 thereby also reactivates anti-tumour immunity.

Pharmacodynamics

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.

Pharmacokinetics

The pharmacokinetics of pembrolizumab was studied in 2188 patients with unresectable or metastatic melanoma; with NSCLC; with other solid tumour types who received doses in the range of 1 to 10 mg/kg every 2 or 3 weeks. Population pharmacokinetic analyses were performed in patients with solid tumours (predominantly melanoma) and in patients with NSCLC.

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 (approximately 7.5L; Coefficient of Variation (CV): 21%). As expected for an antibody, pembrolizumab does not bind to plasma proteins in a specific manner.

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

Excretion: The systemic clearance of pembrolizumab is - approximately 0.2 L/day (CV: 37%) and the terminal half-life (t½) is approximately 26 days (CV: 39%).

Exposure to pembrolizumab as expressed by peak concentration (Cmax) or area under the plasma concentration time curve (AUC) increased dose proportionally within the dose range for efficacy. Upon repeated dosing, the clearance of pembrolizumab was found to be independent of time, and systemic accumulation was approximately 2.2-fold when administered every 3 weeks. Steady-state concentrations of pembrolizumab were reached by 18 weeks; the median C_{min} at steady state was 22.8 mcg/mL during a regimen of 2 mg/kg every 3 weeks.

Table 12: Summary of Pharmacokinetic Parameters

Parameters	**Mean***	**%CV†**
Half-life (days)	26	39%
Vdss (L) ‡	7.5	21%
CL (L/day)	0.2	37%
Time to steady state (weeks)	18	N/A

* Mean values are based on a population pharmacokinetics model
† %CV: coefficient of variation
‡ Volume of distribution at steady state

Special Populations and Conditions
The effects of various covariates on the pharmacokinetics of pembrolizumab were assessed in population pharmacokinetic analyses using a two compartment model with linear clearance from the central compartment. The clearance of pembrolizumab increased with increasing body weight; resulting exposure differences are adequately addressed by administration on a mg/kg basis. 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.

Hepatic Insufficiency: The effect of hepatic impairment on the clearance of pembrolizumab was evaluated by population pharmacokinetic analysis in patients with melanoma and NSCLC 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 WARNINGS AND PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

Renal Insufficiency: The effect of renal impairment on the clearance of pembrolizumab was evaluated by population pharmacokinetic analysis in patients with melanoma and NSCLC with mild (estimated Glomerular Filtration Rate (eGFR) < 90 and ≥ 60 mL/min/1.73 m^2) or moderate (eGFR < 60 and ≥ 30 mL/min/1.73 m^2) renal impairment compared to patients with normal (eGFR ≥ 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 (eGFR < 30 and ≥ 15 mL/min/1.73 m^2) renal impairment (See WARNINGS AND PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

STORAGE AND STABILITY

KEYTRUDA® Powder for Solution for Infusion: Store under refrigeration at 2°C to 8°C.

KEYTRUDA® Solution for Infusion: Store under refrigeration at 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 DOSAGE AND ADMINISTRATION.

SPECIAL HANDLING INSTRUCTIONS

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

DOSAGE FORMS, COMPOSITION AND PACKAGING

KEYTRUDA® is supplied as

- Powder for Solution for Infusion: 50 mg lyophilized powder of pembrolizumab in a single-use vial, white to off-white lyophilized powder for reconstitution.
  One vial contains 50 mg of pembrolizumab with a controlled excess fill of 20% (total content per vial 60 mg). After reconstitution with 2.3 mL of sterile water for injection, each 1 mL of solution contains 25 mg of pembrolizumab
- Solution for Infusion: 100 mg/4 mL (25 mg/mL) solution in a single-use vial, clear to slightly opalescent, colorless to slightly yellow solution.
  Each vial of 4 mL contains 100 mg of pembrolizumab with a controlled excess fill of 0.25 mL (total content per vial 4.25 mL).

The following inactive ingredients: L-histidine, polysorbate 80, L-histidine Monohydrochloride Monohydrate, sucrose, and water for injection.

PART II: SCIENTIFIC INFORMATION

KEYTRUDA® has been issued marketing authorization **with conditions** for the following patients, pending the results of studies to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for KEYTRUDA®, please refer to Health Canada's Notice of Compliance with conditions – drug products website: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php

KEYTRUDA® is indicated for the treatment of patients with:

- Unresectable or metastatic melanoma and disease progression following ipilimumab therapy and, if BRAF V600 mutation positive, following a BRAF or MEK inhibitor as per proposed indication.

- Metastatic non-small cell lung carcinoma (NSCLC) as monotherapy, in adults whose tumours express PD-L1 (TPS ≥ 1%) as determined by a validated test and who have disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have received authorized therapy for these aberrations prior to receiving KEYTRUDA®.

KEYTRUDA® has been issued marketing authorization **without conditions** for the treatment of patients with:

- Unresectable or metastatic melanoma who have not received prior treatment with ipilimumab. Subjects with BRAF V600 mutant melanoma may have received prior BRAF inhibitor therapy.

- Metastatic non-small cell lung carcinoma (NSCLC) as monotherapy, in adults whose tumours have high PD-L1 expression [(Tumour Proportion Score (TPS) ≥50%)] as determined by a validated test, with no EGFR or ALK genomic tumour aberrations, and no prior systemic chemotherapy treatment for metastatic NSCLC.

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: pembrolizumab

Structure: pembrolizumab is an IgG4 monoclonal antibody subtype and contains 32 cysteine residues. A correctly folded antibody molecule includes 4 disulfide linkages as interchain bonds and 12 intrachain bonds.

Molecular Weight: The observed molecular weight of the most abundant form of the intact antibody is 149 kDa.

Physical and Chemical Characteristics: is an aqueous solution stored frozen at –40 °C at a concentration of 22.5–27.5 mg/mL in 10 mM histidine buffer, pH 5.2–5.8, containing 7% sucrose and 0.02% polysorbate 80.

The pembrolizumab drug substance solution is colorless to slightly yellow. The solution clarity is clear to opalescent. It is essentially free of extraneous particulates and may contain some proteinaceous particulates.

The pH of pembrolizumab drug substance is 5.2–5.8.

The theoretical extinction coefficient of pembrolizumab at 280 nm is 1.42 $L \cdot g^{-1} \cdot cm^{-1}$

The pI of pembrolizumab is 6.8–6.9 as determined by capillary isoelectric focusing (cIEF).

NOC/c CLINICAL TRIALS

Study demographics and trial design

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 multicentre, controlled, Phase III study for the treatment of unresectable or metastatic melanoma in patients who were naïve to ipilimumab and who received no or one prior systemic therapy. Patients were 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 at a dose of 3 mg/kg every 3 weeks (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, unacceptable toxicity, 24 months of therapy, or in the case of complete response, 6 months of therapy plus at least two doses beyond complete response. 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.

Table 13: Baseline Characteristics in KEYNOTE-006

	KEYTRUDA® 10 mg/kg every 3 weeks n=277	KEYTRUDA® 10 mg/kg every 2 weeks n=279	Ipilimumab n=278
Men	63%	58%	58%
Women	37%	42%	42%
Age (median)	63	61	62
Age (range)	22-89 years	18-89 years	18-88 years
Prior systemic therapies			
0	67%	66%	65%
1	33%	34%	35%
ECOG PS			
0	68%	70%	68%
1	32%	30%	32%
PD-L1 status*			
Positive	80%	81%	81%
Negative	19%	18%	17%
M-stage at study entry			
M0	3%	3%	5%
M1	1%	2%	2%
M1a	12%	8%	11%
M1b	15%	23%	19%
M1c	68%	64%	64%
Baseline LDH			
normal	63%	69%	64%
elevated	35%	29%	33%
BRAF status			
wild type	64%	63%	61%
V600 mutant	35%	35%	38%
History of Brain Metastases			
no	89%	91%	90%
yes	10%	8%	10%

* Based on an immunohistochemistry research assay with the 22C3 anti-PD-L1 antibody. PD-L1 positive = membrane expression in ≥1% of cells within tumour nests as assessed prospectively

The median duration of exposure was 5.6 months (range: 1 day to 11.0 months) for KEYTRUDA® and similar in both treatment arms. Fifty-one and 46% of patients received KEYTRUDA® 10 mg/kg every 2 or 3 weeks, respectively, for ≥ 6 months. No patients in either arm received treatment for more than one year.

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 14 summarizes key efficacy measures, and the Kaplan-Meier curves for OS and PFS are shown in Figures 1 and 2.

Based on a formal interim analysis for OS that occurred at a minimum of 12 months follow up in which 289 deaths were observed, pembrolizumab demonstrated clinically meaningful and statistically significant improvement in OS compared in patients with unresectable or metastatic melanoma previously untreated with ipilimumab. The OS HRs vs. ipilimumab were 0.69 (95% CI: 0.52, 0.90; p 0.00358) for patients treated with KEYTRUDA® 10 mg/kg every 3 weeks and 0.63 (95% CI: 0.47, 0.83; p=0.00052) for patients treated with KEYTRUDA® 10 mg/kg every 2 weeks. The OS rate at 12 months was 68.4% (95% CI: 62.5, 73.6) for patients treated with KEYTRUDA® 10 mg/kg every 3 weeks, 74.1% (95% CI: 68.5, 78.9) for patients treated with KEYTRUDA® 10 mg/kg every 2 weeks, and 58.2% (95% CI: 51.8, 64.0) for patients treated with ipilimumab. Median OS was not reached for any of the three treatment arms. The PFS HRs vs. ipilimumab were 0.58 (95% CI: 0.47, 0.72; p<0.00001) for patients treated with KEYTRUDA® 10 mg/kg every 3 weeks and 0.58 (95% CI: 0.46, 0.72; p<0.00001) for patients treated with KEYTRUDA® 10 mg/kg every 2 weeks. The median PFS in months was 4.1 (95% CI: 2.9, 6.9) for patients treated with KEYTRUDA® 10 mg/kg every 3 weeks, 5.5 (95% CI: 3.4, 6.9) for patients treated with KEYTRUDA® 10 mg/kg every 2 weeks, and 2.8 (95% CI: 2.8, 2.9) for patients treated with ipilimumab.

Table 14: Response to KEYTRUDA® 10 mg/kg every 2 or 3 weeks in patients with ipilimumab naïve advanced melanoma in KEYNOTE-006 (Intent-to-Treat Analysis)

Endpoint	**KEYTRUDA® 10 mg/kg every 3 weeks n=277**	**KEYTRUDA® 10 mg/kg every 2 weeks n=279**	**Ipilimumab n=278**
Primary Efficacy Outcome Measure 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)
Primary Efficacy Outcome Measure 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)
Secondary Efficacy Outcome Measure Best overall response by IRO*			

ORR % (95% CI)	33% (27, 39)	34% (28, 40)	12% (8, 16)
Complete response n (%)	17 (6%)	14 (5%)	4 (1%)
Partial response n (%)	74 (27%)	80 (29%)	29 (10%)
Secondary Efficacy Outcome Measure **Response duration[§] by IRO***			
Median in months (range)	Not reached (1.4+, 8.1+)	8.3 (1.4+, 8.3)	Not reached (1.1+, 7.9+)
% ongoing	97%	89%	88%

* IRO = Independent radiology plus oncologist review using RECIST 1.1

† Hazard ratio (KEYTRUDA® compared to ipilimumab) based on the Cox proportional hazard model stratified by line of therapy, ECOG performance status, and PD-L1 expression status

‡ Based on stratified Log rank test

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

NA = not available

Figure 1: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-006 (intent to treat population)

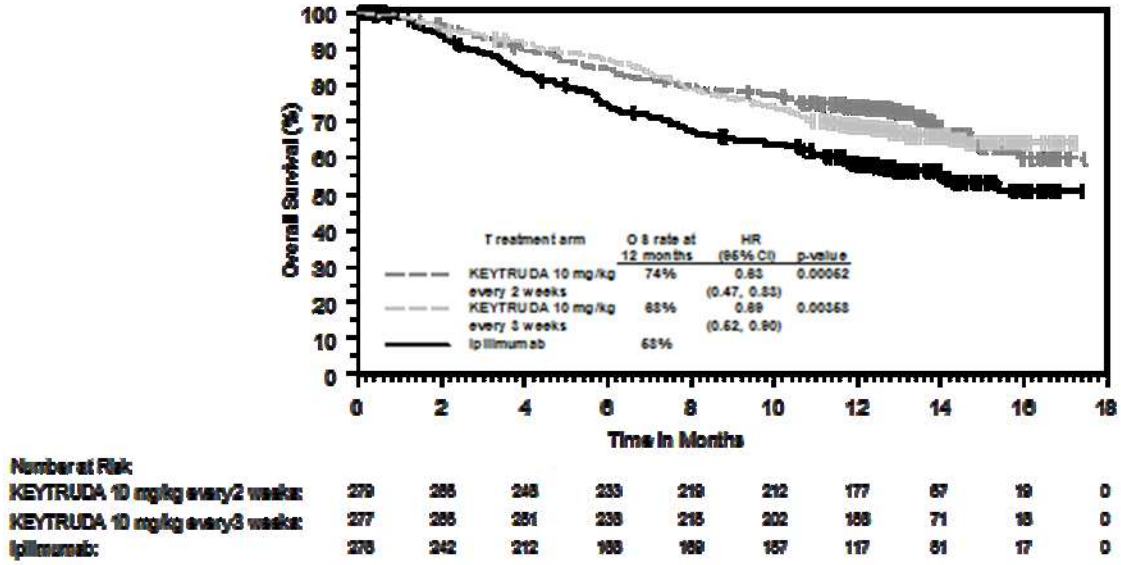
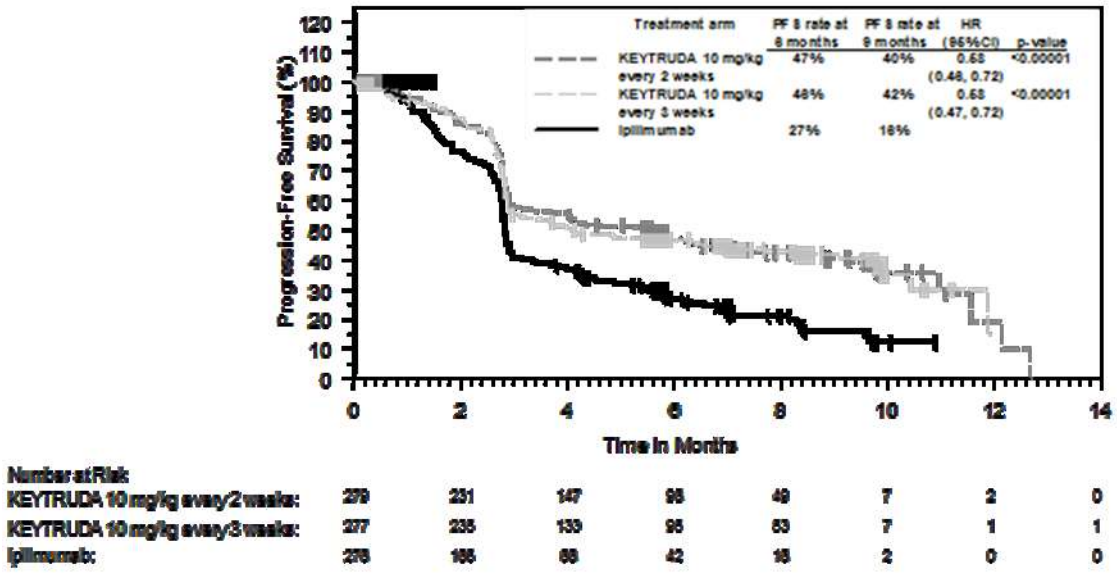


Figure 2: Kaplan-Meier curve for progression-free survival (based on IRO) by treatment arm in KEYNOTE-006 (intent to treat population)



Sub-population analysis by PD-L1 status

In a subgroup analysis of KEYNOTE-006, the association between PD-L1 expression status using pre-defined 1% expression levels and efficacy measures suggested a clinically important signal predictive of the treatment effect in PFS and OS. In PD-L1 positive patients, pembrolizumab demonstrated improved efficacy vs ipilimumab in ipilimumab-naïve subjects with advanced melanoma across all efficacy endpoints. In contrast, no meaningful difference was detected in efficacy between the treatment groups in the PD-L1 negative patients. Among patients who were evaluable for PD-L1 expression (98%), 82% were PD-L1 positive and 18% were PD-L1 negative. The PFS HRs (pooled pembrolizumab [10 mg/kg every 2 or 3 weeks] vs. ipilimumab) were 0.53 (95% CI: 0.43, 0.65) for PD-L1 positive patients and 0.73 (95% CI: 0.47, 1.11) for PD-L1 negative patients. The OS HRs for pooled pembrolizumab vs. ipilimumab were 0.56 (95% CI: 0.43, 0.73) for PD-L1 positive patients and 0.95 (95% CI: 0.56, 1.62) for PD-L1 negative patients.

Sub-population analysis by BRAF mutation status

A subgroup analysis of KEYNOTE-006 in patients who were BRAF wild type, BRAF mutant without prior BRAF treatment and BRAF mutant with prior BRAF treatment was performed. The PFS hazard ratios (HRs) (pooled KEYTRUDA® [10 mg/kg every 2 or 3 weeks] vs. ipilimumab) were 0.57 (95% CI: 0.45, 0.73) for BRAF wild type, 0.50 (95% CI: 0.32, 0.77) for BRAF mutant without prior BRAF treatment, and 0.73 (95% CI: 0.48, 1.11) for BRAF mutant with prior BRAF treatment. The OS HRs for pooled KEYTRUDA® vs. ipilimumab were 0.61 (95% CI: 0.46, 0.82) for BRAF wild type, 0.69 (95% CI: 0.33, 1.45) for BRAF mutant without prior BRAF treatment, and 0.75 (95% CI: 0.45, 1.26) for BRAF mutant with prior BRAF treatment. ORR for pooled KEYTRUDA® vs. ipilimumab was 34% vs. 13% for BRAF wild type, 41% vs. 13% for BRAF mutant without prior BRAF treatment, and 21% vs. 6% for BRAF mutant with prior BRAF treatment.

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

The safety and efficacy of KEYTRUDA® were investigated in KEYNOTE-002, a multicentre, controlled study for the treatment of unresectable or metastatic melanoma in patients previously treated with ipilimumab and if BRAF V600 mutation-positive, a BRAF or MEK inhibitor. Patients were randomized (1:1:1) to receive KEYTRUDA® at a dose of 2 mg/kg (n=180) or 10 mg/kg (n=181) every 3 weeks or chemotherapy (n=179; including dacarbazine (26%), temozolamide (25%), paclitaxel and carboplatin (25%), paclitaxel (16%), or carboplatin (8%)). 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.

Table 15 Baseline Characteristics in KEYNOTE-002

	KEYTRUDA® 2 mg/kg every 3 weeks n=180	KEYTRUDA® 10 mg/kg every 3 weeks n=181	Chemotherapy* n=179
Men	58%	60%	64%
Women	42%	40%	36%
Age (median)	60	62	63
Age (range)	15-87 years	27-89 years	27-87 years
Prior systemic therapies			
At least 2	77%	69%	74%
3 or more	33%	33%	30%
ECOG PS			
0	54%	54%	55%
1	44%	46%	45%
M-stage at study entry			
M0	1%	1%	1%
M1a	5%	7%	8%
M1b	12%	9%	8%
M1c	82%	83%	82%
Baseline LDH			
normal	55%	58%	60%
elevated	43%	40%	38%
BRAF status			
wild type	76%	78%	77%
V600 mutant	24%	22%	23%

* Chemotherapy : dacarbazine, temozolomide, carboplatin plus paclitaxel, paclitaxel, or carboplatin

The median duration of exposure to KEYTRUDA® 2 mg/kg every 3 weeks was 3.7 months (range: 1 day to 16.6 months) and to KEYTRUDA® 10 mg/kg every 3 weeks was 4.8 months (range: 1 day to 16.8 months). The data described below reflect exposure to KEYTRUDA® 2 mg/kg in 36% of patients exposed to KEYTRUDA® for ≥6 months and in 4% of patients exposed for ≥12 months. In the KEYTRUDA® 10 mg/kg arm, 41% of patients were exposed to KEYTRUDA® for ≥6 months and 6% of patients were exposed to KEYTRUDA® for ≥12 months.

The co-primary efficacy outcome measures were PFS (as assessed by IRO review using RECIST 1.1), and OS. Secondary efficacy outcome measures were PFS (as assessed by Investigator using RECIST 1.1), ORR and response duration. Table 16 summarizes key efficacy measures in patients previously treated with ipilimumab, and the Kaplan-Meier curve for PFS is shown in Figure 3. Of the patients randomized to the chemotherapy arm, 48% crossed over and subsequently received treatment with KEYTRUDA®.

Table 16: 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
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)

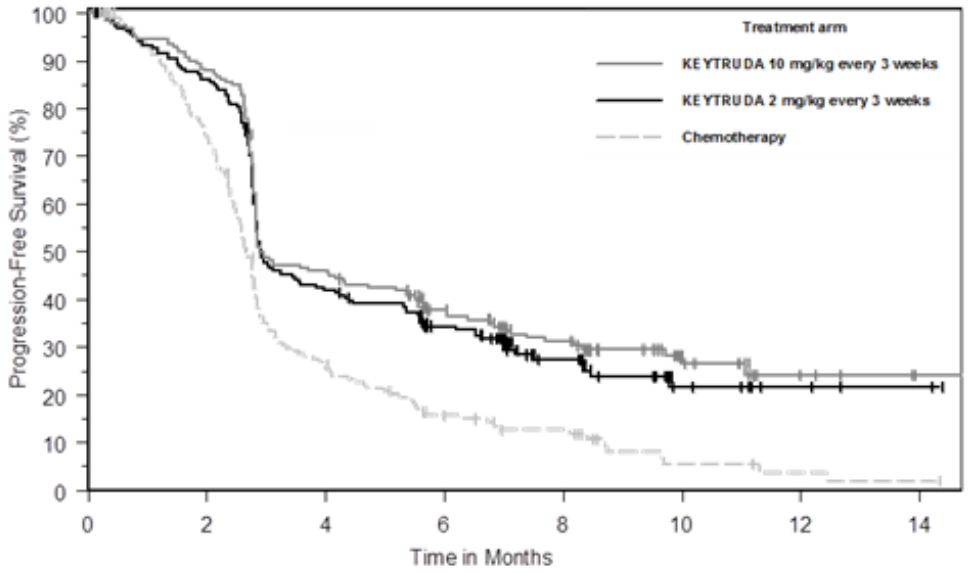
* IRO = Independent radiology plus oncologist review using RECIST 1.1

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

‡ Based on stratified Log rank test

The ORR was 21% (95% CI: 15, 28), 25% (95% CI: 19, 32) and 4% (95%: CI 2, 9) for the KEYTRUDA® 2mg/kg every 3 weeks, KEYTRUDA® 10mg/kg every 3 weeks, and chemotherapy arms, respectively. ORR consisted of 4 (2%) complete responses and 34 (19%) partial responses for the KEYTRUDA® 2mg/kg treatment arm, 5 (3%) complete responses and 41 (23%) partial responses for the KEYTRUDA® 10mg/kg treatment arm, and 0 (0%) complete responses and 8 (4%) partial responses for the chemotherapy arm. Median duration of response was not reached in either of the KEYTRUDA® arms (range 1.4+ to 11.5+ months and 1.2+ to 11.1+ months in the 2 mg/kg and 10 mg/kg KEYTRUDA® arms, respectively) and was 8.5 months (range: 1.6+ to 9.5 months) in the chemotherapy arm. At the time of the analysis, responses were ongoing in 87%, 80%, and 63% of patients in the KEYTRUDA® 2 mg/kg, KEYTRUDA® 10 mg/kg, and chemotherapy arms, respectively.

Figure 3: Kaplan-Meier curve for progression free survival (based on IRO) by treatment arm in KEYNOTE-002 (intent to treat population)



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

KEYNOTE-001: Open label study in melanoma patients

The efficacy of KEYTRUDA® for this indication was also investigated in a Phase 1, multicentre, uncontrolled, open-label, dose-comparative trial (KEYNOTE-001, Part B2). Patients were randomized to receive 2 mg/kg (n=89) or 10 mg/kg (n=84) of KEYTRUDA® every 3 weeks until unacceptable toxicity or disease progression that was symptomatic, was rapidly progressive, required urgent intervention, occurred with a decline in performance status, or was confirmed at 4 to 6 weeks with repeat imaging. Assessment of tumour status was performed every 12 weeks. Eligibility and exclusion criteria were similar to those of KEYNOTE-002.

Among the 173 patients enrolled, the median age was 61 years (36% age 65 or older); 60% male; 97% White; and 66% and 34% with and ECOG performance status 0 and 1, respectively. Disease characteristics were BRAF V600 mutation (17%), elevated lactate dehydrogenase (39%), M1c (82%), brain metastases (9%), and two or more prior therapies for advanced or metastatic disease (73%).

The primary efficacy outcome measure was overall response rate (ORR) as assessed by independent review, including independent radiology and oncology reviews, using confirmed responses and Response Evaluation Criteria in Solid Tumours (RECIST 1.1). The secondary efficacy outcome measure was response duration. The ORR was 25% (95% confidence interval: 16, 35) in the 2 mg/kg arm, consisting of 3 complete responses and 19 partial responses. Among the 22 patients with an objective response, 3 (14%) had progression of disease 2.8, 2.9, and 8.9 months after initial response. Seventy-three percent of the 89 patients discontinued treatment, including 14 (16%) for adverse events and 38 (43%) for progressive disease. Objective responses were reported in patients with and without BRAF mutations. In addition, atypical responses (i.e.,

tumour shrinkage following initial RECIST progression) have been observed with KEYTRUDA®. See Table 17 for a summary of key efficacy measures in patients previously treated with ipilimumab, receiving KEYTRUDA® at the recommended dose.

Table 17: Response to KEYTRUDA® 2 mg/kg every 3 Weeks in Patients with Unresectable or Metastatic Melanoma

Endpoint	KEYTRUDA® 2 mg/kg every 3 weeks in patients previously treated with ipilimumab
Best Overall Response*	**n=89**
ORR %, (95% CI)	25% (16, 35)
Complete response	3
Partial response	19
Response Duration*	**n=22**
Median in weeks (range)	Not reached (12+, 62+)
% ongoing	86%

* Based on patients with a confirmed response by independent review

Non-Small Cell Lung Carcinoma

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

The efficacy of KEYTRUDA® was investigated in KEYNOTE-024, a multicenter, open-label randomized, controlled trial. Key eligibility criteria were metastatic NSCLC, PD-L1 expression tumour proportion score (TPS) of 50% or greater by an immunohistochemistry assay using the PD-L1 IHC 22C3 pharmDx® Kit, and no prior systemic treatment for metastatic NSCLC. Patients with EGFR or ALK genomic 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. Randomization was stratified by ECOG performance status (0 vs 1), histology (squamous vs non-squamous), and geographic region (East Asia vs. non East-Asia). Patients were randomized (1:1) to receive KEYTRUDA® 200 mg intravenously every 3 weeks (n = 154) or investigator's choice of any of the following platinum-containing chemotherapy regimens (n = 151):

- Pemetrexed 500 mg/m2 every 3 weeks and carboplatin AUC 5 to 6 mg/mL/min every three weeks on Day 1 for 4 to 6 cycles followed by optional pemetrexed 500 mg/m2 every 3 weeks for patients with non-squamous histologies;
- Pemetrexed 500 mg/m2 every 3 weeks and cisplatin 75 mg/m2 every 3 weeks on Day 1 for 4 to 6 cycles followed by optional pemetrexed 500 mg/m2 every 3 weeks for patients with non-squamous histologies;
- Gemcitabine 1250 mg/m2 on days 1 and 8 and cisplatin 75 mg/m2 every 3 weeks on Day 1 for 4 to 6 cycles;
- Gemcitabine 1250 mg/m2 on Days 1 and 8 and carboplatin AUC 5 to 6 mg/mL/min every 3 weeks on day 1 for 4 to 6 cycles;
- Paclitaxel 200 mg/m2 every 3 weeks and carboplatin AUC 5 to 6 mg/mL/min every 3 weeks on Day 1 for 4 to 6 cycles followed by optional pemetrexed maintenance (for non-squamous histologies).

Treatment with KEYTRUDA® continued until RECIST 1.1-defined progression of disease as determined by an independent radiology committee or unacceptable toxicity. 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 were treated for up to 24 months or 35 administrations, whichever was longer. Subsequent disease progression could be retreated for up to 1 additional year. Patients on chemotherapy who experienced independently-verified progression of disease were able to crossover and receive KEYTRUDA®.

Table 18: Baseline Characteristics in KEYNOTE-024

	KEYTRUDA® 200 mg every 3 weeks n=154	**Chemotherapy n=151**
Men	60%	63%
Women	40%	37%
Age (median)	65	66
Age (range)	33-90 years	38-85 years
ECOG PS		
0	35%	35%
1	64%	65%
2	1%	0%
Geographic region		
East Asia	14%	13%
Non-East Asia	86%	87%
Histology		
Squamous	19%	18%
Non-squamous	81%	82%
Cancer stage at study entry		
IIIB	1%	1%
IV	99%	99%

The median duration of exposure was 7.0 months (range 1 day to 18.7 months) in the KEYTRUDA® arm and 3.5 months (range 1 day to 16.8 months) in the chemotherapy arm.

The primary efficacy outcome measure was PFS as assessed by blinded independent central review (BICR) using RECIST 1.1. Assessment of tumour status was performed every 9 weeks. Secondary efficacy outcome measures were OS and ORR (as assessed by BICR using RECIST 1.1). Table 19 summarizes key efficacy measures for the entire ITT population.

Table 19: Efficacy Results in KEYNOTE-024

Endpoint	KEYTRUDA 200 mg every 3 weeks n=154	Chemotherapy n=151
Primary Efficacy Outcome Measure 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)
Key Secondary Efficacy Outcome Measure 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)
Secondary Efficacy Outcome Measure Objective response rate*		
ORR % (95% CI)	45% (37, 53)	28% (21, 36)
Complete response %	4%	1%
Partial response %	41%	27%

* 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; includes 43 patients with responses of 6 months or longer

Based on Kaplan-Meier estimates; includes 16 patients with responses of 6 months or longer

NA = not available

In exploratory subgroup analyses, a reduced survival benefit of KEYTRUDA® compared to chemotherapy was observed in females as well as in never-smokers. In females, the HR for PFS was 0.75 (95% CI: 0.46, 1.21) and the HR for OS was 0.95 (95% CI: 0.50, 1.83). In never-smokers, the HR for PFS was 0.90 (95% CI: 0.11, 7.59) and the HR for OS was 1.69 (95% CI: 0.19, 15.25).

Figure 4: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-024 (Intent to Treat Population)

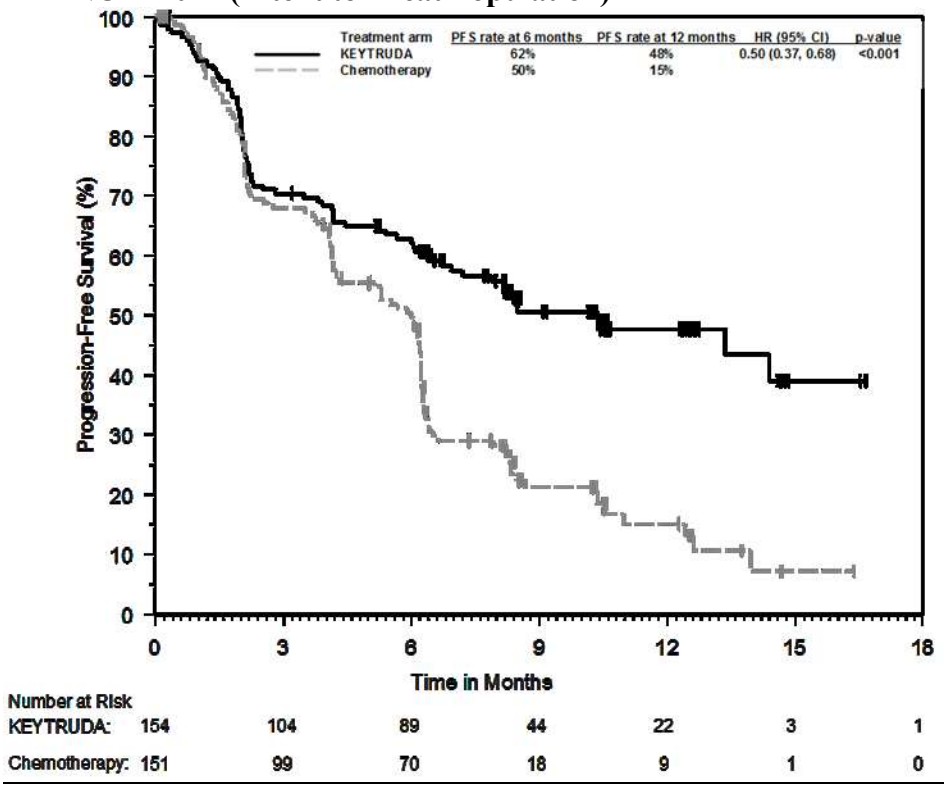
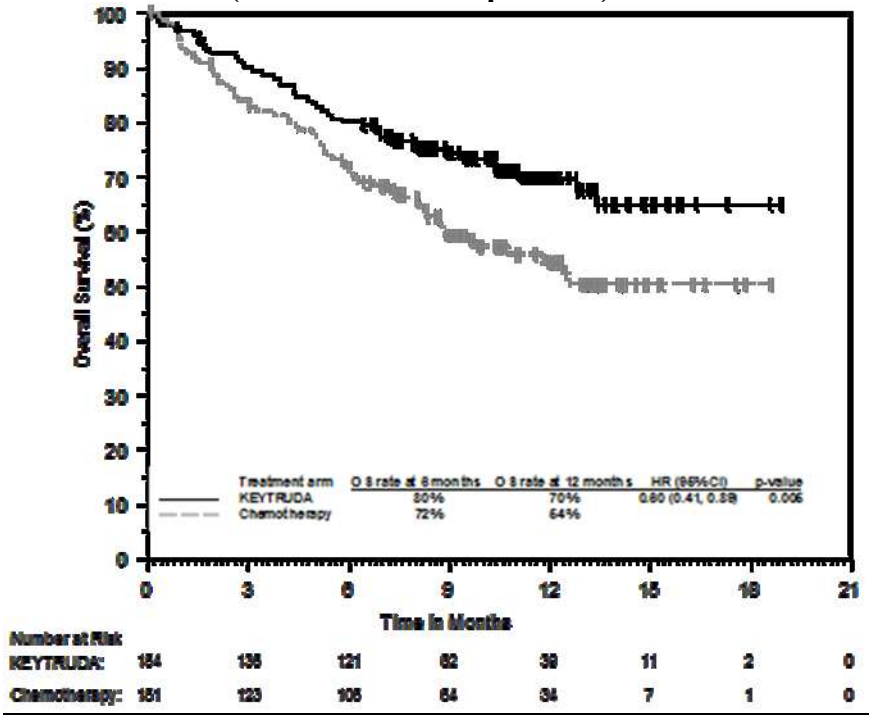


Figure 5: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-024 (Intent to Treat Population)



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

The efficacy of KEYTRUDA® was investigated in KEYNOTE-010, a multicenter, randomized, open-label controlled trial. Key eligibility criteria were metastatic NSCLC that had progressed following platinum-containing chemotherapy, and if appropriate, targeted therapy for ALK or EGFR mutations, and PD-L1 expression tumour proportion score (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. Randomization was stratified by tumour PD-L1 expression (PD-L1 expression TPS ≥50% vs. PD-L1 expression TPS=1-49%), ECOG performance scale (0 vs. 1), and geographic region (East Asia vs. non-East Asia). Patients were randomized (1:1:1) to receive KEYTRUDA® 2 mg/kg intravenously every 3 weeks (n=344), KEYTRUDA® 10 mg/kg intravenously every 3 weeks (n=346) or docetaxel 75 mg/m^2 intravenously every 3 weeks (n=343). Patients randomized to KEYTRUDA® were permitted to continue until disease progression that was symptomatic, rapidly progressive, required urgent intervention, occurred with a decline in performance status, or confirmation of progression at 4 to 6 weeks with repeat imaging or for up to 24 months without disease progression.

Table 20: Baseline Characteristics in KEYNOTE-010

	KEYTRUDA® 2 mg/kg every 3 weeks n=344	KEYTRUDA® 10 mg/kg every 3 weeks n=346	Docetaxel 75 mg/m^2 every 3 weeks n=343
Men	62%	62%	61%
Women	38%	38%	39%
Age (median)	63 years	63 years	62 years
Age (range)	29-82 years	20-88 years	33-82 years
ECOG PS			
0	33%	35%	34%
1	67%	65%	65%
2	1%	0%	0%
Geographic region			
East Asia	19%	19%	18%
Non-East Asia	81%	82%	82%
Histology			
Squamous	22%	23%	19%
Non-squamous	70%	71%	70%
Cancer stage at study entry			
IIIB	6%	8%	6%
IV	92%	91%	91%
Brain Metastasis	16%	14%	14%
EGFR Mutant	8%	9%	8%
ALK Translocation Mutant	1%	1%	1%
Prior Lines of Systemic Therapy			
One	71%	68%	69%
Two or more	27%	30%	30%

The median duration of exposure to treatment to KEYTRUDA® 2 mg/kg every 3 weeks was 3.5 months (range: 1 day to 22.4 months) and to KEYTRUDA® 10 mg/kg every 3 weeks was 3.5 months (range 1 day to 20.8 months). The median duration of exposure to docetaxel 75 mg/m^2 every 3 weeks was 2.0 months (range: 1 day to 13.7 months).

The primary efficacy outcome measures were OS and PFS as assessed by a Blinded Independent Central Review (BICR) according to RECIST 1.1 in the subgroup of patients with TPS ≥ 50% and the overall population with TPS ≥ 1%. Assessment of tumour status was performed every 9 weeks. A secondary efficacy outcome measure was ORR in the subgroup of patients with TPS ≥ 50% and the overall population with TPS ≥ 1%. Table 20 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 6 and 7.

Table 21: Response to KEYTRUDA® 2 or 10 mg/kg every 3 Weeks in Previously Treated Patients with NSCLC in KEYNOTE-010, with TPS ≥ 1%

Endpoint	KEYTRUDA® 2 mg/kg every 3 weeks	KEYTRUDA® 10 mg/kg every 3 weeks	Docetaxel 75 mg/m^2 every 3 weeks
TPS ≥1%			
Number of patients	344	346	343
Primary Efficacy Outcome Measure OS			
Number (%) of patients with event	172 (50%)	156 (45%)	193 (56%)
Hazard ratio (98.35% CI)*	0.71 (0.55, 0.92)	0.61 (0.47, 0.79)	---
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)
Primary Efficacy Outcome Measure PFS‡,§			
Number (%) of patients with event	266 (77%)	255 (74%)	257 (75%)
Hazard ratio (99.80% CI)*	0.88 (0.66, 1.15)	0.79 (0.60, 1.05)	---
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)
Secondary Efficacy Outcome Measure Overall response rate§			
ORR %¶ (95% CI)	18% (14, 23)	18% (15, 23)	9% (7, 13)

* Hazard ratio (KEYTRUDA® compared to docetaxel) based on the stratified Cox proportional hazard model. The confidence levels correspond to the allocated Type I error of 0.00825 and 0.001 for the OS and PFS endpoints, respectively.

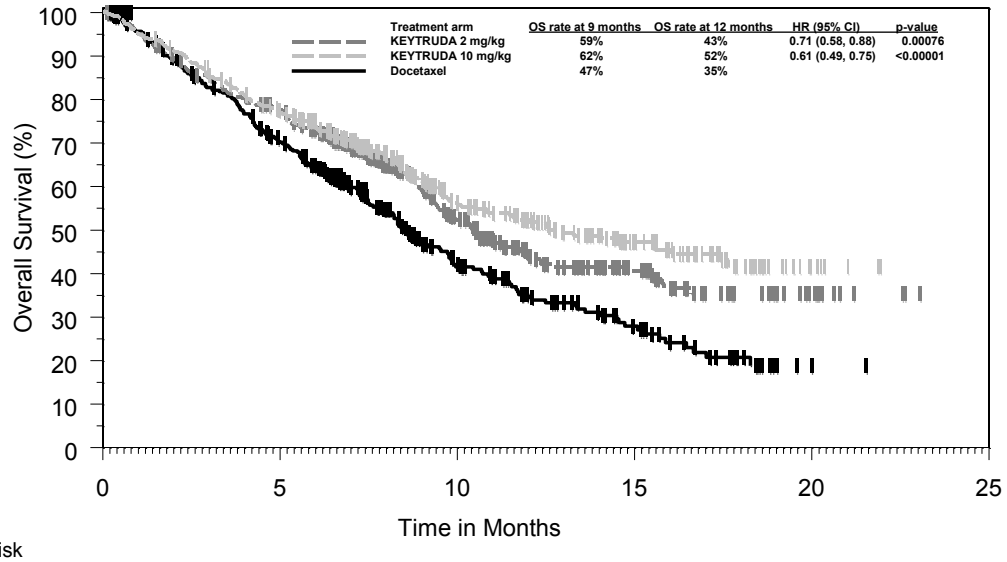
† Based on one-sided stratified Log rank test

‡ Statistically significant based on a pre-specified α level of 0.00825 for the two pairwise comparisons versus docetaxel using a Hochberg procedure

§ Assessed by BICR using RECIST 1.1

¶ All responses were partial responses.

Figure 6: 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 7: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-010 (TPS ≥ 1%, Intent to Treat Population)

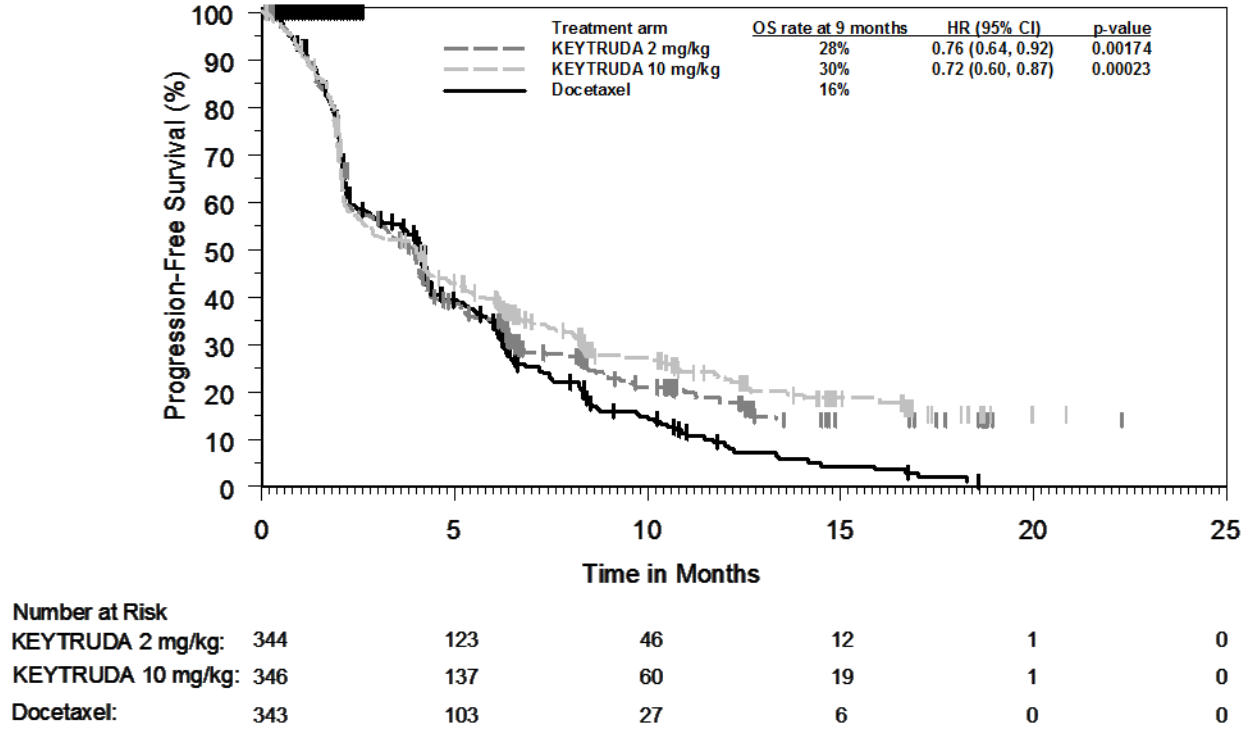


Table 22: Response to KEYTRUDA® 2 or 10 mg/kg every 3 Weeks in Previously Treated Patients with NSCLC in KEYNOTE-010, with TPS ≥ 50%

Endpoint	KEYTRUDA® 2 mg/kg every 3 weeks	KEYTRUDA® 10 mg/kg every 3 weeks	Docetaxel 75 mg/m^2 every 3 weeks
TPS ≥50%			
Number of patients	139	151	152
Primary Efficacy Outcome Measure OS			
Number (%) of patients with event	58 (42%)	60 (40%)	86 (57%)
Hazard ratio (98.35% CI)*	0.54 (0.35, 0.83)	0.50 (0.33, 0.75)	---
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)
Primary Efficacy Outcome Measure PFS‡, §			
Number (%) of patients with event	89 (64%)	97 (64%)	118 (78%)
Hazard ratio (99.80% CI)*	0.58 (0.37, 0.92)	0.59 (0.38, 0.91)	---
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)
Secondary Efficacy Outcome Measure **Overall response rate**[§]			
ORR %[#] (95% CI)	30% (23, 39)	29% (22, 37)	8% (4, 13)

* Hazard ratio (KEYTRUDA® compared to docetaxel) based on the stratified Cox proportional hazard model. The confidence levels correspond to the allocated Type I error of 0.00825 and 0.001 for the OS and PFS endpoints, respectively.

† Based on one-sided stratified Log rank test

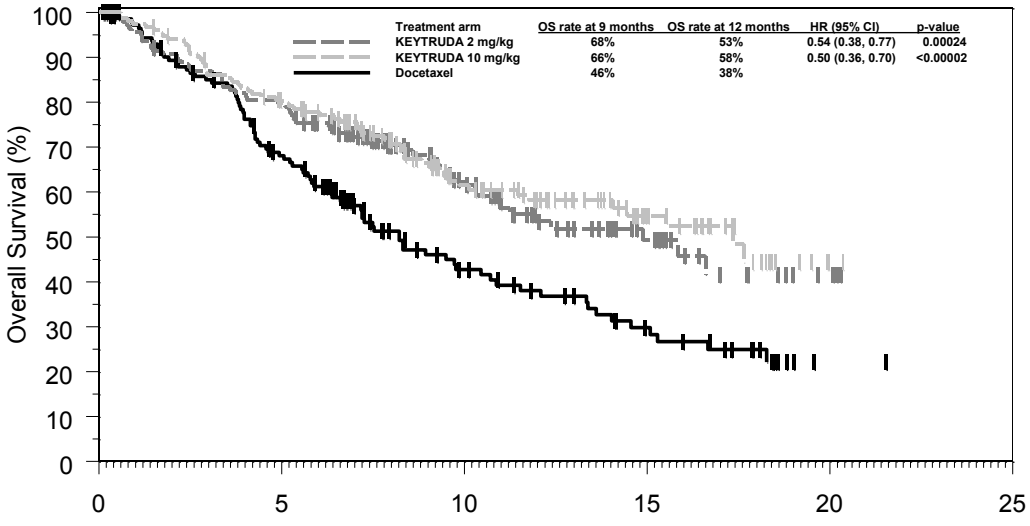
‡ Statistically significant based on a pre-specified α level of 0.00825 for the two pairwise comparisons versus docetaxel using a Hochberg procedure

§ Assessed by BICR using RECIST 1.1

¶ Statistically significant based on a pre-specified α level of 0.001 for the two pairwise comparisons versus docetaxel using a Hochberg procedure

All responses were partial responses.

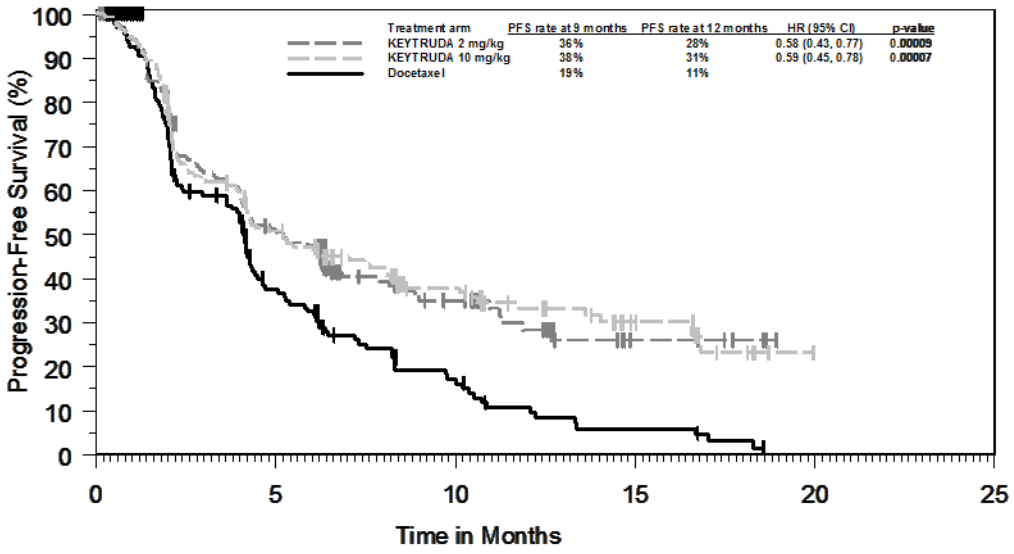
Figure 8: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-010 (TPS ≥ 50%, Intent to Treat Population)



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

Figure 9: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-010 (TPS ≥ 50%, Intent to Treat Population)



Number at Risk						
KEYTRUDA 2 mg/kg:	139	67	29	6	0	0
KEYTRUDA 10 mg/kg:	151	72	36	12	0	0
Docetaxel:	152	45	17	5	0	0

In exploratory subgroup analyses, a reduced survival benefit of KEYTRUDA® compared to chemotherapy was observed in patients with tumours harbouring EGFR activating mutations (n=54), never-smokers (n=130) and patients of East Asian Ethnicity (n=126). In patients with tumours expressing PD-L1 with a TPS ≥ 1% that received KEYTRUDA® at 2 mg/kg every three weeks, with EGFR activating mutations, the HR for PFS was 1.78 (95% CI: 0.82, 3.85) and the HR for OS was 1.07 (95% CI: 0.49, 2.37). In never smokers, the HR for PFS was 1.33 (95% CI: 0.86, 2.04) and the HR for OS was 0.84 (95% CI: 0.48, 1.49). In patients of East Asian Ethnicity the HR for PFS was 1.38 (95% CI: 0.87, 2.21) and the HR for OS was 1.39 (95% CI: 0.72, 2.68). The efficacy and safety of pembrolizumab in patients with tumours that do not express PD-L1 (TPS < 1%) have not been established.

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).

TOXICOLOGY

Repeat-dose toxicity

Repeat-dose toxicology studies were carried out in monkeys. In a 1-month study, monkeys received 0, 6, 40 or 200 mg/kg IV pembrolizumab administered weekly for a total of 5 doses followed by a 4 month recovery period. In the 6 month study, monkeys received 0, 6, 40 or 200 mg/kg IV pembrolizumab administered biweekly for a total of 12 doses, followed by a 4-month recovery period. In both studies, all dose levels administered exceeded the recommended human dose and resulted in exposures and peak serum concentrations that were greater than those observed in humans receiving the recommended dose. Pembrolizumab was not associated with any adverse test article-related findings at doses up to 200 mg/kg administered weekly for 1-month (NOAEL (No Observed Adverse Effect Level) > 200 mg/kg) or at doses up to 200 mg/kg adminstered biweekly for 6 months (NOAEL > 200 mg/kg).

In an exploratory study, 4 chimpanzees with naturally occuring chronic hepatitis B virus (HBV) infection received rising doses of IV pembrolizumab over 5 weeks. Chimpanzees were administered pembrolizumab (IV) doses of 1, 2, 5, 10 and 10 mg/kg on Day 0, 7, 14, 21, and 28, respectively. Two (2) of the four HBV infected chimpanzees had significantly increased levels of serum ALT, AST, and GGT beginning on day 21 and persisting for at least 1 month after the discontinuation of pembrolizumab.

Reproduction

Animal reproduction studies have not been conducted with KEYTRUDA®. The central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining immune tolerance to the fetus. Blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to result in an increase in fetal loss. These results indicate a potential risk that administration of KEYTRUDA® during pregnancy could cause fetal harm, including increased rates of abortion or stillbirth.

Development

Fertility studies have not been conducted with pembrolizumab. There were no notable effects in the male and female reproductive organs in a limited number of sexually mature monkeys based on1-month and 6-month repeat dose toxicity studies.

Special Toxicology Studies

PD-1 deficiency was associated with enhanced inflammatory responses, increased severity of infections and reduced survival in some animal models. Compared to wild-type mice, PD-1 knockout mice infected with *M. tuberculosis* had enhanced inflammatory responses, increased bacterial proliferation and decreased survival. Decreased survival has also been observed in PD-1 knockout mice infected with LCMV.

Carcinogenesis

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

Mutagenesis
The genotoxic potential of pembrolizumab has not been evaluated.

Table 23: Summary of Toxicology Studies

Study Type	Treatment Duration and Dosing Schedule	Species/Test system	Gender and No. per Group	Doses (mg/kg)[a]	Findings/Conclusions
Pharmacokinetic Studies					
Non-GLP Pharmacokinetic study IV	Single dose	Monkey/ Cynomolgus	3F per group	0.3, 3 and 30mg/kg	The decline of serum concentration followed multiphasic kinetics. Slightly greater than dose proportional exposure between 0.3 and 3.0 mg/kg and approximately linear exposure between 3.0 and 30 mg/kg was observed. Anti-drug antibodies (ADA) were detected in most of the treated animals. Clearance (CL) and terminal half-life (t1/2) appeared to be dose dependent in the dose range tested with CL ranging from 3.7 to 5.7 mL/day/kg and t1/2 ranging from 4 to 10 days
General Toxicity					
Repeat-Dose Toxicity IV	1-month Dosing Period with 4-month treatment-free Postdose Period, dosing once weekly (total	Monkey/ Cynomolgus	4F, 4M per group (dosing period); 2 F, 2M per group (treatment-free postdose	0, 6, 40, 200	There was no test article-related mortality. Test article-related changes were limited to an increased incidence of inguinal swelling, and increased splenic

Study Type	Treatment Duration and Dosing Schedule	Species/Test system	Gender and No. per Group	Doses (mg/kg)[a]	Findings/Conclusions
	of 5 doses)		period)		weights in males receiving 200 mg/kg at end of the Dosing Period. Both of these findings were not considered adverse and there was no histopathologic correlate. Splenic weights were normal at the necropsy performed after the treatment-free period. Based on the lack of adverse test article-related findings, the NOAEL was > 200 mg/kg
Repeat-Dose Toxicity IV	6-month Dosing Period with 4-month treatment-free Postdose Period, dosing once every other week (total of 12 doses)	Monkey/ Cynomolgus	3F, 3M per group (dosing period); 2F, 2M per group (treatment-free postdose period)	0, 6, 40, 200	There were no test article-related antemortem, electrocardiographic or ophthalmic findings. There were no test article-related changes at injection sites. Following the interim and final necropsies, there were no identified test article-related postmortem findings. The NOAEL was > 200 mg/kg
Other Studies					
Tissue Cross-reactivity *in vitro*	N/A	Cryosections of normal human tissues	n = 3 donors per tissue (~ 32 tissues/donor)	1, 10 µg/mL MK-3475 precomplexed with biotinylated secondary	Positive staining of mononuclear leukocyte membranes was considered on-target binding consistent with the

Study Type	Treatment Duration and Dosing Schedule	Species/Test system	Gender and No. per Group	Doses (mg/kg)[a]	Findings/Conclusions
				antibody	known biology and expression of PD-1. Off-target cross-reactivity staining was noted in the cytoplasm of various cell types/tissues and the stroma (extracellular connective tissue matrix) of many tissues. These off-target findings were interpreted as spurious binding inherent to the experimental conditions of the *in vitro* tissue cross-reactivity studies with no *in vivo* toxicological significance.
Tissue Cross-reactivity *in vitro*	N/A	Cryosections of normal Cynomolgus monkey tissues	n = 3 donors per tissue (~ 32 tissues/donor)	1, 10 µg/mL MK-3475 precomplexed with biotinylated secondary antibody	Positive staining of mononuclear leukocyte membranes was considered on-target binding consistent with the known biology and expression of PD-1. Off-target cross-reactivity staining was noted in the cytoplasm of various cell types/tissues, the extracellular material in the neurohypophysis and the stroma (extracellular connective tissue matrix) of many

Study Type	Treatment Duration and Dosing Schedule	Species/Test system	Gender and No. per Group	Doses (mg/kg)[a]	Findings/Conclusions
					tissues. These off-target findings were interpreted as spurious binding inherent to the experimental conditions of the *in vitro* tissue cross-reactivity studies with no *in vivo* toxicological significance.
Cytokine Release Studies *In vitro*	[b, c, d, e] 4 days culture for cytokine release after Staphylococcus enterotoxin B (SEB) stimulation [f] 48 hr for cytokine release, dry coat assay	[b, f] Human, normal donors [c] Human, advanced metastatic melanoma patients [d] Human, prostate cancer patients [e] Cynomolgus monkey	[b] n = 3 [c] n = 8 [d] n = 8 [e] n = 6 [f] n = 7	[b, c, d, e] 25, 2.5, 0.25, 0.025, 0.0025, 0.00025 µg/mL [b] 25 µg/mL [f] 25, 2.5, 0.25, 0.025, 0.0025, 0.00025 µg/mL for dry coat assay	[b, c, d] MK-3475 enhances SEB-induced IL-2 production from approximately 2- to 4-fold; MK-3475 modestly enhances production TNF-α, IFNγ, IL-6, and IL-17 (less than 2-fold). In the absence of SEB stimulation, MK-3475 did not induce cytokine production. [e] MK-3475 enhances SEB-induced IL-2 production. [f] MK-3475 did not induce cytokine release. Superagonist anti-CD28 induced robust cytokine release.

Study Type	Treatment Duration and Dosing Schedule	Species/Test system	Gender and No. per Group	Doses (mg/kg)[a]	Findings/Conclusions
Other Studies					
T-cell recall for Tetanus toxoid	[g] 7 days	Human donors, recently revaccinated with tetanus toxoid	n = 2	25, 2.5, 0.25, 0.025, 0.0025, 0.00025 µg/mL	MK-3475 enhanced tetanus toxoid-induced production of IFNγ in a dose-dependent manner.
HBV infection	Once per week, 5 dose, rising dose escalation. Post-dose (last dose) period of 1 month	HBV-infected chimpanzees	n = 4	All doses IV. First dose = 1 mg/kg, second dose = 2 mg/kg, third dose = 5 mg/kg, fourth and fifth dose = 10 mg/kg	No changes in viral load were observed. ALT/AST/GGT flares were observed in 2 animals following the fifth dose (10 mg/kg); ALT/AST/GGT levels remained elevated for at least one month.

[a]For Repeat-Dose Toxicity, the highest NOAEL (No Observed Adverse Effect Level) is underlined.
[b, c, d, e] MK-3475 or control human IgG4 antibody was pre-incubated with heparinized whole blood for 30-60 minutes, and then cultured for 4 days after stimulation with 0.1 µg/mL Staphylococcus enterotoxin B (SEB). Cytokine levels were assessed by immunoassay.
[f] MK-3475 or superagonistic anti-human CD28 antibody were immobilized by air drying directly onto microtiter plates. Human peripheral blood mononuclear cells (PBMC) were cultured in the wells for 48 hr; cytokine levels were assessed by immunoassay.
[g] Peripheral blood mononuclear cells from donors recently revaccinated with tetanus toxoid (TT) were stimulated *in vitro* for 7 days with 1 µg/mL TT in the presence or absence of MK-3475 or a human IgG4 isotype control antibody. Cytokine levels were assessed by immunoassay.
IL-2 = interleukin 2; TNF-α = tumour necrosis factor-alpha; IFNγ = interferon gamma; IL-6 = interleukin 6; IL-17 = interleukin 17

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

KEYTRUDA® has been issued marketing authorization **with conditions** for the following patients, pending the results of studies to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for KEYTRUDA®, please refer to Health Canada's Notice of Compliance with conditions – drug products website: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php

KEYTRUDA® is indicated for the treatment of patients with:

- Unresectable or metastatic melanoma and disease progression following ipilimumab therapy and, if BRAF V600 mutation positive, following a BRAF or MEK inhibitor as per proposed indication.

- Metastatic non-small cell lung carcinoma (NSCLC) as monotherapy, in adults whose tumours express PD-L1 (TPS ≥ 1%) as determined by a validated test and who have disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have received authorized therapy for these aberrations prior to receiving KEYTRUDA®.

KEYTRUDA® has been issued marketing authorization **without conditions** for the treatment of patients with:

- Unresectable or metastatic melanoma who have not received prior treatment with ipilimumab. Subjects with BRAF V600 mutant melanoma may have received prior BRAF inhibitor therapy.

- Metastatic non-small cell lung carcinoma (NSCLC) as monotherapy, in adults whose tumours have high PD-L1 expression [(Tumour Proportion Score (TPS) ≥50%)] as determined by a validated test, with no EGFR or ALK genomic tumour aberrations, and no prior systemic chemotherapy treatment for metastatic NSCLC.

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of **promising** evidence of clinical effectiveness following review of the submission by Health Canada.

Products approved under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical

need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

℞ **KEYTRUDA®**
pembrolizumab

Read this carefully before you start taking KEYTRUDA® and each time you get an infusion. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about KEYTRUDA®.

What is KEYTRUDA® (key-true-duh) **used for?**
KEYTRUDA® is a prescription medicine used to treat:

- a kind of skin cancer called melanoma
- a kind of lung cancer called non-small cell lung cancer

KEYTRUDA® may be used when your melanoma:

- has spread or cannot be removed by surgery (advanced melanoma),

KEYTRUDA® may be used when your lung cancer:

- tests positive for "PD-L1"

and,

- has spread or cannot be removed by surgery (advanced lung cancer)

and,

- If your tumour has an abnormal "EGFR" or "ALK" gene, and you have tried chemotherapy that contains platinum and an EGFR or ALK inhibitor medicine.

It is not known if KEYTRUDA® is safe and effective in children less than 18 years of age.

People get KEYTRUDA® when their cancer has spread or cannot be taken out by surgery.

How does KEYTRUDA® work?
KEYTRUDA® works by helping your immune system fight your cancer.

What are the ingredients in KEYTRUDA®?
The active substance is pembrolizumab.
The other ingredients are L-histidine, polysorbate-80, L-histidine Monohydrochloride Monohydrate, sucrose, and water for infusion.

KEYTRUDA® comes in the following dosage forms:
Powder for solution for infusion, 50 mg per vial
Solution for infusion 100 mg/4mL vial

Do not use KEYTRUDA® if:

- you have had a severe allergic reaction to pembrolizumab or any other ingredients in KEYTRUDA®

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take KEYTRUDA®. Talk about any health conditions or problems you may have, including if you:

- have an autoimmune disease (a condition where the body attacks its own cells), such as Crohn's disease, Ulcerative Colitis or Lupus
- have pneumonia or inflammation of your lungs (called pneumonitis)
- were previously given ipilimumab, another medicine for treating melanoma, and experienced serious side effects because of that medicine
- had an allergic reaction to other monoclonal antibody therapies
- have or have had chronic viral infection of the liver, including hepatitis B (HBV) or hepatitis C (HCV)
- have human immunodeficiency virus (HIV) infection or acquired immune deficiency syndrome (AIDS)
- have liver damage or have had a liver transplant
- have kidney damage or have had (kidney transplant)
- take other medicines that make your immune system weak. Examples of these may include steroids, such as prednisone.

Pregnancy

- If you are pregnant, think you may be pregnant or are planning to have a baby, tell your doctor.
- KEYTRUDA® can cause harm or death to your unborn baby.
- You must use effective contraception while you are being treated with KEYTRUDA® and for at least 4 months after the last dose of KEYTRUDA® if you are a woman who could become pregnant.

Breast-feeding

- If you are breast-feeding, tell your doctor.
- Do not breast-feed while taking KEYTRUDA®.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How you are given KEYTRUDA®:

- Your doctor will give you KEYTRUDA® through an infusion into your vein (IV) for about 30 minutes.
- Most people get KEYTRUDA® every 3 weeks.
- Your doctor will decide how many treatments you need.

Usual dose:

Melanoma and previously treated Metastatic Non Small Cell Lung Cancer: The recommended dose is 2 mg of pembrolizumab per kilogram of your body weight.
Previously untreated Non Small Cell Lung Cancer: The recommended dose is 200 mg.

If you miss an appointment to get KEYTRUDA®
- Call your doctor right away to reschedule your appointment.
- It is very important that you do not miss a dose of this medicine.

What are possible side effects from using KEYTRUDA®?
When you get KEYTRUDA®, you can have some serious side effects. You may experience more than one side effect at the same time. The following lists do not include all the possible side effects you may feel when taking KEYTRUDA®. If you experience any side effects not listed here, contact your healthcare professional.

The following side effects have been reported in clinical trials:

Very common (may affect more than 1 in 10 people)
- diarrhea, nausea
- itching, rash
- joint pain
- feeling unusually tired or weak
- feever
- feeling less hungry
- shortness of breath
- patches of skin which have lost colour (Vitiligo)

Common (may affect more than 2 in 100 people and up to 1 in 10 people)
- flu-like illness
- dry mouth
- headache
- change in your sense of taste
- cough
- stomach pain, constipation, vomiting, inflammation of the mucous membrane in the mouth dry skin, redness of the skin, red raised skin rash
- back pain, muscle aches
- chills
- swelling of the face, legs or arms
- changes in test results:
    - decrease in the number of red blood cells
    - abnormal liver enzyme levels in the blood
    - decreased sodium levels in the blood
    - abnormal levels of thyroid stimulating hormone in the blood
    - weight loss

If you have any of the following conditions, call or see your doctor right away. Your doctor may give you other medicines in order to prevent more severe complications and reduce your symptoms. Your doctor may withhold the next dose of KEYTRUDA® or stop your treatment with KEYTRUDA®.

Serious side effects and what to do about them		
Symptom / effect	Talk to your healthcare professional	
	Only if severe	In all cases
COMMON Inflammation of the lungs (pneumonitis) which can cause shortness of breath, chest pain, or coughing		√
Inflammation of the intestines (colitis) which can cause diarrhea or more bowel movements than usual, black, tarry, sticky stools or stools with blood or mucus, severe stomach pain or tenderness, nausea, vomiting		√
Inflammation of the pituitary or thyroid gland (hypophysitis, hypopituitarism, including secondary adrenal insufficiency; hyperthyroidism, hypothyroidism) which can cause rapid heart beat, weight loss, increased sweating, weight gain, hair loss, feeling cold, constipation, your voice gets deeper, muscle aches, dizziness or fainting, headaches that will not go away or unusual headache, feeling more hungry or thirsty, urinating more often than usual.		√
Skin problems which can cause rash, itching; skin blistering, peeling, or sores; ulcers in mouth or in lining of nose, throat, or genital area		√
UNCOMMON Inflammation of the liver (hepatitis) which can cause nausea or vomiting, feeling less hungry, pain on the right side of stomach, yellowing of skin or whites of eyes, dark urine, bleeding or bruising more easily than normal		√
Inflammation of the kidneys (nephritis) which can cause changes in the amount or colour of your urine		√
Muscle problems, which can cause muscle pain or weakness, severe or persistent muscle or joint pains; low red blood cell count (anemia).		√
Eye problems, which can cause changes in eyesight		√
Shortness of breath, irregular heartbeat, feeling tired, or chest pain (myocarditis).		√
Blood sugar problems (type 1 diabetes mellitus) which can cause hunger or thirst, a need to urinate		√

more often, or weight loss		
Inflammation of the pancreas(pancreatitis), which can cause abdominal pain, nausea, and vomiting		√
Reactions related to the infusion such as shortness of breath, itching or rash, dizziness, or fever, wheezing, flushing, feeling like passing out.		√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:
- Online at MedEffect (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 1908C
    Ottawa, ON
    K1A 0K9

  Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Also, to report an adverse event related to KEYTRUDA®, please contact Merck Canada at 1-800-567-2594.

Storage:
It is unlikely that you will be asked to store KEYTRUDA® yourself**.** It will be stored in the hospital or clinic where it is given to you.

Keep this medicine out of the sight and reach of children.

Powder for Solution for Infusion: Store in a refrigerator (2°C to 8°C).
Solution for Infusion: Store in a refrigerator (2°C to 8°C). Protect from light.

If you want more information about KEYTRUDA®:
- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes

this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); or Merck Canada website http://www.merck.ca, or by calling Merck Canada at 1-800-567-2594.

To report an adverse event related to KEYTRUDA®, please contact 1-800-567-2594.

This leaflet was prepared by Merck Canada Inc.

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