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:

- adult patients with metastatic non-small cell lung carcinoma (NSCLC) as monotherapy, whose tumours express PD-L1 [(Tumour Proportion Score (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®.

- adult patients with refractory or relapsed classical Hodgkin Lymphoma (cHL), as monotherapy, who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV) or who are not ASCT candidates and have failed BV.

- adult and pediatric patients with refractory Primary Mediastinal B-cell Lymphoma (PMBCL) or who have relapsed after 2 or more lines of therapy, as monotherapy.

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

- adult patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)
  - colorectal cancer whose tumours have progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, as monotherapy, or

- endometrial cancer whose tumours have progressed following prior therapy and who have no satisfactory alternative treatment options, as monotherapy.

KEYTRUDA® has been issued marketing authorization **without conditions** for:

- 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.

- 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.

- Adjuvant treatment of patients with Stage III melanoma with lymph node involvement who have undergone complete resection.

- Treatment of patients with metastatic non-small cell lung carcinoma (NSCLC) as monotherapy, in adults whose tumours have high PD-L1 expression (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.

- Treatment of patients with metastatic non-squamous NSCLC in combination with pemetrexed and platinum chemotherapy, in adults with no EGFR or ALK genomic tumour aberrations, and no prior systemic chemotherapy treatment for metastatic NSCLC.

- Treatment of patients with metastatic squamous NSCLC in combination with carboplatin and either paclitaxel or nab-paclitaxel, in adults with no prior systemic chemotherapy treatment for metastatic NSCLC.

- Treatment of patients with locally advanced or metastatic urothelial carcinoma, as monotherapy, in adults who have disease progression during or following platinum-containing chemotherapy or within 12 months of completing neoadjuvant or adjuvant platinum-containing chemotherapy.

Merck Canada Inc.
16750 route Transcanadienne
Kirkland QC Canada H9H 4M7
http://www.merck.ca

Date of Initial Approval:
May 19, 2015

Date of Revision:
July 4, 2019

Submission Control No: 219700

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.

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KEYTRUDA®

pembrolizumab

PART I: HEALTH PROFESSIONAL INFORMATION

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- adult patients with refractory or relapsed classical Hodgkin Lymphoma (cHL), as monotherapy, who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV) or who are not ASCT candidates and have failed BV.

- adult and pediatric patients with refractory Primary Mediastinal B-cell Lymphoma (PMBCL) or who have relapsed after 2 or more lines of therapy, as monotherapy.

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

- adult patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)
    - colorectal cancer whose tumours have progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, as monotherapy, or
    - endometrial cancer whose tumours have progressed following prior therapy and who have no satisfactory alternative treatment options, as monotherapy.

KEYTRUDA® has been issued marketing authorization **without conditions** for:

- 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.

- 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.

- Adjuvant treatment of patients with Stage III melanoma with lymph node involvement who have undergone complete resection.

- Treatment of patients with metastatic non-small cell lung carcinoma (NSCLC) as monotherapy, in adults whose tumours have high PD-L1 expression (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.

- Treatment of patients with metastatic non-squamous NSCLC in combination with pemetrexed and platinum chemotherapy, in adults with no EGFR or ALK genomic tumour aberrations, and no prior systemic chemotherapy treatment for metastatic NSCLC.

- Treatment of patients with metastatic squamous NSCLC in combination with carboplatin and either paclitaxel or nab-paclitaxel, in adults with no prior systemic chemotherapy treatment for metastatic NSCLC.

- Treatment of patients with locally advanced or metastatic urothelial carcinoma, as monotherapy, in adults who have disease progression during or following platinum-containing chemotherapy or within 12 months of completing neoadjuvant or adjuvant platinum-containing chemotherapy.

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/4 mL 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.

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.

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

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.

KEYTRUDA®, in combination with pemetrexed and platinum chemotherapy, is indicated for the treatment of metastatic non-squamous NSCLC, in adults with no EGFR or ALK genomic tumour aberrations, and no prior systemic chemotherapy treatment for metastatic NSCLC.

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

NOC/c Hodgkin Lymphoma

KEYTRUDA® as monotherapy is indicated for the treatment of adult patients with refractory or relapsed classical Hodgkin Lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV) or who are not ASCT candidates and have failed BV. An improvement in survival or disease-related symptoms has not yet been established.

NOC/c **Primary Mediastinal B-cell Lymphoma**

KEYTRUDA® as monotherapy is indicated for the treatment of adult and pediatric patients with refractory primary mediastinal B-cell lymphoma (PMBCL), or who have relapsed after 2 or more lines of therapy. An improvement in survival or disease-related symptoms has not been established.

Urothelial Carcinoma

KEYTRUDA® is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma as monotherapy, in adults who have disease progression during or following platinum-containing chemotherapy or within 12 months of completing neoadjuvant or adjuvant platinum-containing chemotherapy.

NOC/c KEYTRUDA® is indicated for the treatment of patients with locally advanced unresectable or metastatic urothelial carcinoma, as monotherapy, in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by a validated test, or in adults who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status. An improvement in survival or disease-related symptoms has not yet been established.

NOC/c **Microsatellite Instability-High Cancer (MSI-H)**

KEYTRUDA® is indicated as monotherapy for the treatment of adult patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)

- colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, or
- endometrial cancer that has progressed following prior therapy and who have no satisfactory alternative treatment options.

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). Limited safety and efficacy information is

available for KEYTRUDA® in cHL ≥ 65 years of age (n=20) (See WARNINGS AND PRECAUTIONS; Geriatrics).

NOC/c Pediatrics (<18 years of age):

KEYTRUDA® is indicated for the treatment of pediatric patients with refractory PMBCL, or pediatric PMBCL patients whose disease has relapsed after 2 or more prior lines of therapy (See **WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS & DOSAGE AND ADMINISTRATION)**. The safety and efficacy of KEYTRUDA® has not been established for pediatric patients with conditions other than relapsed or refractory PMBCL.

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.

The data described in the WARNINGS AND PRECAUTIONS section reflect exposure to KEYTRUDA® as monotherapy 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). This is termed the Reference Safety Data set and will be referred to as the data set against which safety data from the first-line NSCLC, second-line urothelial cancer, and cHL indications were compared.

Immune-mediated adverse reactions:

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

For suspected immune-mediated adverse reactions, ensure adequate evaluation to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, withhold KEYTRUDA® and consider administration of corticosteroids. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Based on limited

data from clinical studies in patients whose immune-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).

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 in the Reference Safety Data set, including Grade 2 (1.3%), 3 (0.9%), 4 (0.3%), or 5 (0.1%) pneumonitis.

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 in the Reference Safety Data set, including Grade 2 (0.4%), Grade 3 (1.1%), and Grade 4 (<0.1%) colitis.

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 in the Reference safety Data set, including Grade 2 (0.1%), Grade 3 (0.4%), and Grade 4 (<0.1%) hepatitis.

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 in the Reference Safety Data set, including Grade 2 (0.1%), Grade 3 (0.1%), and Grade 4 (<0.1%) nephritis.

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 in the Reference Safety Data set, including Grade 2 (0.2%), Grade 3 (0.3%), and Grade 4 (<0.1%) hypophysitis.

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 hyperthyroidism, hypothyroidism, 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 in the Reference Safety Data set, including Grade 2 (0.8%) and Grade 3 (0.1%) hyperthyroidism.

Hypothyroidism occurred in 237 (8.5%) of 2799 patients in the Reference Safety Data set, including Grade 3 (0.1%) hypothyroidism.

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 the 2799 patients treated with KEYTRUDA® in the Reference Safety Data set: uveitis, arthritis (1.5%), myositis, encephalitis, sarcoidosis, myasthenic syndrome/myasthenia gravis (including exacerbation), vasculitis, Guillain-Barré syndrome, hemolytic anemia, and pancreatitis.

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

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.

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

Complications of allogeneic Hematopoietic Stem Cell Transplant (HSCT)
Allogeneic HSCT after treatment with KEYTRUDA®:
Cases of graft-versus-host-disease (GVHD) and hepatic veno-occlusive disease (VOD) have been observed in patients with classical Hodgkin lymphoma undergoing allogeneic HSCT after

previous exposure to KEYTRUDA®. Until further data become available, careful consideration to the potential benefits of HSCT and the possible increased risk of transplant-related complications should be made case by case (See ADVERSE REACTIONS).

Allogeneic HSCT prior to treatment with KEYTRUDA®:
In patients with a history of allogeneic HSCT, acute GVHD, including fatal GVHD, has been reported after treatment with KEYTRUDA®. Patients who experienced GVHD after their transplant procedure may be at an increased risk for GVHD after treatment with KEYTRUDA®. Consider the benefit of treatment with KEYTRUDA® versus the risk of possible GVHD in patients with a history of allogeneic HSCT.

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 the Reference Safety Data set. 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): There is limited experience with KEYTRUDA® in pediatric patients. In a single trial that enrolled pediatric patients, immune mediated adverse reactions were observed. The observed immune mediated adverse reactions included pneumonitis, colitis,

thyroid disorders (hyperthyroidism, hypothyroidism and thryroiditis) and skin reactions. Infusion reactions were also observed (see ADVERSE REACTIONS). Monitor pediatric patients for signs and symptoms of immune mediated adverse reactions and/or infusion reactions and manage as is described throughout the WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION sections.

Efficacy for pediatric patients with PMBCL is extrapolated from the results in the respective adult populations [see **CLINICAL TRIALS**].

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. Limited safety and efficacy information is available for KEYTRUDA® in cHL patients ≥ 65 years of age (n=20).

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 serum 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 2799 patients treated with KEYTRUDA® in the Reference Safety Data set 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 the 2799 patients that composed the Reference Safety Data set (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 the 2799 patients treated with KEYTRUDA® in the Reference Safety Data set. 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

Adverse Reaction	KEYTRUDA® 2 mg/kg every 3 weeks or 10 mg/kg every 2 or 3 weeks n=2799				
	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

In patients with cHL (n=241) the incidence of hypothyroidism was 14.1% (all Grades) with 0.4% Grade 3. In patients with completely resected stage III melanoma, the incidence of hypothyroidism was 14.7% (all Grades) with 0% Grade 3 and hyperthyroidism was 10.4% (all Grades) with 0.2% Grade 3.

In patients with non-squamous NSCLC treated with KEYTRUDA® 200 mg in combination with pemetrexed and platinum chemotherapy (n=405) the incidence of nephritis was 1.7% (all

Grades) with 1.0% Grade 3 and 0.5% Grade 4.

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.

In KEYNOTE-002, the adverse reaction profile was similar for the 2 mg/kg dose and 10 mg/kg dose, therefore summary safety results are provided in a pooled analysis (n=357) of both KEYTRUDA® arms. Adverse reactions resulting in permanent discontinuation occurred in 12% of patients receiving KEYTRUDA®; the most common (≥1%) were general physical health deterioration (1%), asthenia (1%), dyspnea (1%), pneumonitis (1%), and generalized edema (1%). Adverse reactions leading to interruption of KEYTRUDA® occurred in 14% of patients; the most common (≥1%) were dyspnea (1%), diarrhea (1%), and maculo-papular rash (1%). The most common adverse reactions (reported in at least 20% of patients) of KEYTRUDA® were fatigue, pruritus, rash, constipation, nausea, diarrhea, and decreased appetite.

There were no new safety signals observed at the final analysis and therefore with additional follow-up, no meaningful changes occurred in the safety profile of pembrolizumab.

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.

In KEYNOTE-006, the adverse reaction profile was similar for the every 2 week and every 3 week schedule, therefore summary safety results are provided in a pooled analysis (n=555) of both KEYTRUDA® arms. Adverse reactions leading to permanent discontinuation of KEYTRUDA® occurred in 9% of patients. Adverse reactions leading to discontinuation of KEYTRUDA® in more than one patient were colitis (1.4%), autoimmune hepatitis (0.7%), allergic reaction (0.4%), polyneuropathy (0.4%), and cardiac failure (0.4%). Adverse reactions leading to interruption of KEYTRUDA® occurred in 21% of patients; the most common (≥1%) was diarrhea (2.5%). The most common adverse reactions (reported in at least 20% of patients) were fatigue and diarrhea.

There were no new safety signals observed at the final analysis. After 9 additional months of follow-up from the second interim analysis to final analysis, no meaningful changes occurred in the safety profile of pembrolizumab.

Table 2: Treatment-Related Adverse Events (incidence ≥ 1%) KEYTRUDA® Treatment Groups Combined, All patients as treated (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						

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 (%)
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
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

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 (%)
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
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

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 (%)
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						
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.

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

Table 4 summarizes the treatment-related adverse events that occurred in at least 1% of patients with resected melanoma treated with KEYTRUDA® in KEYNOTE-054. The most common treatment-related adverse events (reported in at least 15% of patients) were diarrhea, fatigue, and pruritis.

KEYTRUDA® was discontinued for treatment-related adverse events in 12% of patients in KEYNOTE 054. The most common treatment-related adverse event leading to study drug discontinuation was: pneumonitis (n=7, 1.4%). The median time to discontinuation for treatment-related adverse events was 5.8 months. There were 2 (0.4%) deaths reported in the KEYTRUDA® arm: drug reaction with eosinophilia and systemic symptoms (n=1) and autoimmune myositis with respiratory failure (n=1).

Table 4: Treatment-Related Adverse Events (incidence ≥ 1%) in patients treated with KEYTRUDA® APaT Population in KEYNOTE 054

Adverse Reaction	KEYTRUDA® 200 mg every 3 weeks n=509			Placebo n=502		
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Blood and lymphatic system disorders						
Eosinophilia	5 (1.0)	0	0	1 (0.2)	0	0
Lymphopenia	5 (1.0)	1 (0.2)	0	1 (0.2)	0	0
Endocrine disorders						
Hyperthyroidism	49 (9.6)	1 (0.2)	0	4 (0.8)	0	0
Hypophysitis	8 (1.6)	2 (0.4)	0	0	0	0
Hypothyroidism	73 (14.3)	0	0	13 (2.6)	0	0
Thyroiditis	12 (2.4)	0	0	0	0	0
Eye disorders						

Adverse Reaction	KEYTRUDA® 200 mg every 3 weeks n=509			Placebo n=502		
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Dry eye	7 (1.4)	0	0	4 (0.8)	0	0
Gastrointestinal disorders						
Abdominal pain	20 (3.9)	0	0	15 (3.0)	0	0
Abdominal pain upper	9 (1.8)	1 (0.2)	0	10 (2.0)	0	0
Autoimmune colitis	5 (1.0)	3 (0.6)	0	1 (0.2)	1 (0.2)	0
Colitis	13 (2.6)	6 (1.2)	0	1 (0.2)	0	0
Constipation	12 (2.4)	0	0	8 (1.6)	0	0
Diarrhoea	94 (18.5)	3 (0.6)	1 (0.2)	82 (16.3)	3 (0.6)	0
Dry mouth	23 (4.5)	0	0	10 (2.0)	0	0
Dyspepsia	8 (1.6)	0	0	2 (0.4)	0	0
Gastritis	5 (1.0)	1 (0.2)	0	0	0	0
Nausea	58 (11.4)	0	0	43 (8.6)	0	0
Vomiting	17 (3.3)	0	0	9 (1.8)	0	0
General disorders and administration site conditions						
Asthenia	48 (9.4)	0	0	34 (6.8)	0	0
Chills	6 (1.2)	0	0	4 (0.8)	0	0
Fatigue	143 (28.1)	4 (0.8)	0	135 (26.9)	2 (0.4)	0
Influenza like illness	14 (2.8)	0	0	9 (1.8)	0	0
Pyrexia	6 (1.2)	1 (0.2)	0	6 (1.2)	0	0
Immune system disorders						
Sarcoidosis	6 (1.2)	0	0	0	0	0
Investigations						
Alanine aminotransferase increased	26 (5.1)	3 (0.6)	0	16 (3.2)	1 (0.2)	0
Investigations						
Aspartate aminotransferase increased	19 (3.7)	1 (0.2)	0	14 (2.8)	1 (0.2)	0
Blood alkaline phosphatase increased	6 (1.2)	0	0	2 (0.4)	0	0
Blood bilirubin increased	7 (1.4)	0	0	4 (0.8)	0	0
Blood creatine phosphokinase increased	6 (1.2)	1 (0.2)	1 (0.2)	2 (0.4)	0	0
Blood creatinine increased	6 (1.2)	0	0	1 (0.2)	0	0
Blood thyroid stimulating hormone decreased	7 (1.4)	0	0	1 (0.2)	0	0
Eosinophil count increased	5 (1.0)	0	0	0	0	0
Gamma-glutamyltransferase increased	9 (1.8)	2 (0.4)	0	4 (0.8)	1 (0.2)	0
Lipase increased	7 (1.4)	3 (0.6)	1 (0.2)	3 (0.6)	3 (0.6)	0
Lymphocyte count decreased	5 (1.0)	0	0	2 (0.4)	0	0
Weight decreased	12 (2.4)	0	0	11 (2.2)	0	0
Weight increased	15 (2.9)	0	0	4 (0.8)	0	0
Metabolism and nutrition disorders						
Decreased appetite	25 (4.9)	1 (0.2)	0	8 (1.6)	0	0

Adverse Reaction	KEYTRUDA® 200 mg every 3 weeks n=509			Placebo n=502		
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Hypophosphataemia	5 (1.0)	1 (0.2)	0	1 (0.2)	0	0
Type 1 diabetes mellitus	5 (1.0)	5 (1.0)	0	0	0	0
Musculoskeletal and connective tissue disorders						
Arthralgia	51 (10.0)	3 (0.6)	0	47 (9.4)	0	0
Arthritis	5 (1.0)	0	0	0	0	0
Musculoskeletal and connective tissue disorders						
Muscle spasms	5 (1.0)	0	0	1 (0.2)	0	0
Musculoskeletal pain	5 (1.0)	0	0	3 (0.6)	0	0
Myalgia	26 (5.1)	0	0	15 (3.0)	0	0
Pain in extremity	7 (1.4)	0	0	3 (0.6)	0	0
Nervous system disorders						
Dizziness	10 (2.0)	0	0	13 (2.6)	0	0
Dysgeusia	9 (1.8)	0	0	10 (2.0)	0	0
Headache	37 (7.3)	0	0	33 (6.6)	1 (0.2)	0
Respiratory, thoracic and mediastinal disorders						
Cough	17 (3.3)	0	0	16 (3.2)	0	0
Dyspnoea	27 (5.3)	1 (0.2)	0	14 (2.8)	0	0
Pneumonitis	15 (2.9)	3 (0.6)	0	3 (0.6)	0	0
Skin and subcutaneous tissue disorders						
Alopecia	10 (2.0)	0	0	8 (1.6)	0	0
Dermatitis acneiform	8 (1.6)	0	0	5 (1.0)	0	0
Dry skin	20 (3.9)	0	0	8 (1.6)	0	0
Eczema	11 (2.2)	0	0	3 (0.6)	0	0
Erythema	6 (1.2)	0	0	4 (0.8)	0	0
Lichenoid keratosis	5 (1.0)	1 (0.2)	0	0	0	0
Pruritus	85 (16.7)	0	0	49 (9.8)	0	0
Pruritus generalized	6 (1.2)	0	0	3 (0.6)	0	0
Rash	49 (9.6)	0	0	32 (6.4)	0	0
Rash maculo-papular	24 (4.7)	1 (0.2)	0	21 (4.2)	0	0
Skin hypopigmentation	8 (1.6)	0	0	3 (0.6)	0	0
Vitiligo	23 (4.5)	0	0	7 (1.4)	0	0
Vascular disorders						
Hypertension	5 (1.0)	1 (0.2)	0	5 (1.0)	2 (0.4)	0

Treatment-related adverse events reported in <1% of patients with complete resection of Stage IIIA (>1 mm metastasis), IIIB and IIIC melanoma treated with KEYTRUDA® (n=509) by SOC are shown below.

Cardiac disorders: myocarditis
Endocrine disorders: adrenal insufficiency

Eye disorders: uveitis
Gastrointestinal disorders: pancreatitis
Hepatobiliary disorders: hepatitis
Injury, poisoning and procedural complications: infusion related reaction
Metabolism and nutrition disorders: diabetic ketoacidosis
Musculoskeletal and connective tissue disorders: myositis

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.

There were no new safety signals observed at the final analysis and therefore with additional follow-up, no meaningful changes occurred in the safety profile of pembrolizumab.

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

Adverse Reaction	KEYTRUDA® 200 mg every 3 weeks n=154			Chemotherapy n=150		
	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

Adverse Reaction	KEYTRUDA® 200 mg every 3 weeks n=154			Chemotherapy n=150		
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
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
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
Weight decreased	5 (3.2)	0	0	4 (2.7)	0	0
Metabolism and nutrition disorders						
Decreased appetite	14 (9.1)	0	0	39 (26.0)	4 (2.7)	0
Diabetes 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
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
Nervous system disorders						
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
Renal and urinary disorders						
Dysuria	2 (1.3)	0	0	1 (0.7)	0	0
Respiratory, thoracic and mediastinal disorders						

Adverse Reaction	KEYTRUDA® 200 mg every 3 weeks n=154			Chemotherapy n=150		
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
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-189. The most common treatment-related adverse events (reported in at least 20% of patients) were nausea, anemia, fatigue, neutropenia, and decreased appetite. The most common Grade 3-5 treatment-related adverse events for patients treated with KEYTRUDA® in KEYNOTE-189 were neutropenia (14.6%), anemia (13.6%), thrombocytopenia (7.7%) and febrile neutropenia (5.9%).

Treatment was discontinued for treatment-related adverse events in 9.6% of the 405 patients receiving KEYTRUDA®, pemetrexed, and chemotherapy and in 4.0% of the 202 patients receiving placebo, pemetrexed, and chemotherapy. The most common treatment-related adverse events leading to study drug discontinuation (occurring in more than 3 patients) were acute kidney injury (n=7) and pneumonitis (n=7). The median time to discontinuation for treatment-related adverse events was 4.0 months.

Table 6: Treatment-Related Adverse Events (Incidence ≥ 1%) in Patients Treated with KEYTRUDA® in Combination with Pemetrexed and Platinum Chemotherapy, APaT Population in KEYNOTE-189

Adverse Reaction	KEYTRUDA® + Pemetrexed + Platinum chemotherapy n=405				Placebo + Pemetrexed + Platinum chemotherapy n=202			
	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	154 (38.0)	53 (13.1)	2 (0.5)	0	77 (38.1)	27 (13.4)	0	0
Febrile neutropenia	25 (6.2)	16 (4.0)	8 (2.0)	0	4 (2.0)	2 (1.0)	2 (1.0)	0
Leukopenia	22 (5.4)	6 (1.5)	2 (0.5)	0	12 (5.9)	1 (0.5)	0	0
Neutropenia	101 (24.9)	34 (8.4)	25 (6.2)	0	45 (22.3)	16 (7.9)	6 (3.0)	0
Pancytopenia	6 (1.5)	4 (1.0)	2 (0.5)	0	2 (1.0)	0	2 (1.0)	0
Thrombocytopenia	69 (17.0)	16 (4.0)	15 (3.7)	0	27 (13.4)	6 (3.0)	7 (3.5)	0
Ear and labyrinth disorders								
Tinnitus	9 (2.2)	0	0	0	9 (4.5)	0	0	0
Endocrine disorders								
Hyperthyroidism	13 (3.2)	0	0	0	6 (3.0)	0	0	0
Hypothyroidism	22 (5.4)	2 (0.5)	0	0	3 (1.5)	0	0	0
Eye disorders								
Dry eye	10 (2.5)	0	0	0	2 (1.0)	0	0	0
Eye pruritus	5 (1.2)	0	0	0	1 (0.5)	0	0	0
Lacrimation increased	51 (12.6)	0	0	0	14 (6.9)	0	0	0
Vision blurred	5 (1.2)	0	0	0	1 (0.5)	0	0	0
Gastrointestinal disorders								
Abdominal pain	10 (2.5)	1 (0.2)	0	0	4 (2.0)	1 (0.5)	0	0
Abdominal pain upper	9 (2.2)	0	0	0	0	0	0	0
Colitis	5 (1.2)	2 (0.5)	0	0	0	0	0	0
Constipation	67 (16.5)	0	0	0	24 (11.9)	0	0	0
Diarrhea	78 (19.3)	15 (3.7)	0	0	22 (10.9)	4 (2.0)	0	0
Dry mouth	7 (1.7)	0	0	0	2 (1.0)	0	0	0
Dyspepsia	15 (3.7)	0	0	0	3 (1.5)	0	0	0
Nausea	187 (46.2)	12 (3.0)	0	0	90 (44.6)	4 (2.0)	0	0
Stomatitis	26 (6.4)	2 (0.5)	0	0	15 (7.4)	1 (0.5)	0	0
Vomiting	74 (18.3)	7 (1.7)	0	0	39 (19.3)	4 (2.0)	0	0
General disorders and administration site conditions								
Asthenia	53 (13.1)	16 (4.0)	0	0	31 (15.3)	3 (1.5)	0	0
Fatigue	134 (33.1)	20 (4.9)	0	0	62 (30.7)	3 (1.5)	0	0
General physical health deterioration	7 (1.7)	4 (1.0)	0	0	2 (1.0)	2 (1.0)	0	0
Mucosal inflammation	30 (7.4)	3 (0.7)	0	0	14 (6.9)	1 (0.5)	0	0
Edema	7 (1.7)	0	0	0	2 (1.0)	0	0	0

Adverse Reaction	KEYTRUDA® + Pemetrexed + Platinum chemotherapy n=405				Placebo + Pemetrexed + Platinum chemotherapy n=202			
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Edema peripheral	27 (6.7)	0	0	0	12 (5.9)	0	0	0
Pyrexia	24 (5.9)	1 (0.2)	0	0	4 (2.0)	0	0	0
Infections and infestations								
Cellulitis	7 (1.7)	5 (1.2)	0	0	0	0	0	0
Conjunctivitis	20 (4.9)	1 (0.2)	0	0	10 (5.0)	0	0	0
Oral candidiasis	11 (2.7)	1 (0.2)	0	0	2 (1.0)	0	0	0
Pneumonia	7 (1.7)	3 (0.7)	0	1 (0.2)	1 (0.5)	0	0	1 (0.5)
Upper respiratory tract infection	6 (1.5)	2 (0.5)	0	0	0	0	0	0
Urinary tract infection	5 (1.2)	0	0	0	0	0	0	0
Investigations								
Alanine aminotransferase increased	38 (9.4)	2 (0.5)	0	0	16 (7.9)	3 (1.5)	0	0
Aspartate aminotransferase increased	28 (6.9)	0	0	0	10 (5.0)	1 (0.5)	0	0
Blood alkaline phosphatase increased	6 (1.5)	0	0	0	3 (1.5)	1 (0.5)	0	0
Blood creatinine increased	32 (7.9)	1 (0.2)	0	0	12 (5.9)	0	0	0
Blood thyroid stimulating hormone decreased	9 (2.2)	0	0	0	2 (1.0)	0	0	0
Blood thyroid stimulating hormone increased	5 (1.2)	0	0	0	1 (0.5)	0	0	0
Gamma-glutamyltransferase increased	8 (2.0)	2 (0.5)	1 (0.2)	0	4 (2.0)	1 (0.5)	0	0
Lymphocyte count decreased	8 (2.0)	1 (0.2)	0	0	4 (2.0)	0	1 (0.5)	0
Neutrophil count decreased	11 (2.7)	4 (1.0)	3 (0.7)	0	3 (1.5)	2 (1.0)	0	0
Platelet count decreased	10 (2.5)	3 (0.7)	2 (0.5)	0	0	0	0	0
Weight decreased	15 (3.7)	2 (0.5)	0	0	5 (2.5)	0	0	0
White blood cell count decreased	22 (5.4)	7 (1.7)	0	0	12 (5.9)	6 (3.0)	0	0
Metabolism and nutrition disorders								
Decreased appetite	84 (20.7)	4 (1.0)	0	0	42 (20.8)	1 (0.5)	0	0
Dehydration	8 (2.0)	3 (0.7)	0	0	4 (2.0)	1 (0.5)	0	0
Hypocalcemia	6 (1.5)	0	0	0	1 (0.5)	0	0	0

Adverse Reaction	KEYTRUDA® + Pemetrexed + Platinum chemotherapy n=405				Placebo + Pemetrexed + Platinum chemotherapy n=202			
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Hypokalemia	9 (2.2)	2 (0.5)	0	0	4 (2.0)	1 (0.5)	0	0
Hypomagnesemia	22 (5.4)	4 (1.0)	1 (0.2)	0	3 (1.5)	0	0	0
Hyponatremia	5 (1.2)	2 (0.5)	0	0	3 (1.5)	1 (0.5)	0	0
Hypophosphatemia	8 (2.0)	3 (0.7)	0	0	2 (1.0)	1 (0.5)	0	0
Musculoskeletal and connective tissue disorders								
Arthralgia	15 (3.7)	1 (0.2)	0	0	8 (4.0)	1 (0.5)	0	0
Muscular weakness	7 (1.7)	1 (0.2)	0	0	2 (1.0)	1 (0.5)	0	0
Myalgia	10 (2.5)	1 (0.2)	0	0	2 (1.0)	0	0	0
Nervous system disorders								
Dizziness	10 (2.5)	0	0	0	5 (2.5)	0	0	0
Dysgeusia	37 (9.1)	1 (0.2)	0	0	14 (6.9)	0	0	0
Headache	9 (2.2)	0	0	0	3 (1.5)	0	0	0
Hypoasthesia	5 (1.2)	0	0	0	0	0	0	0
Lethargy	7 (1.7)	0	0	0	1 (0.5)	0	0	0
Neuropathy peripheral	10 (2.5)	0	0	0	3 (1.5)	0	0	0
Paresthesia	12 (3.0)	0	0	0	6 (3.0)	0	0	0
Peripheral sensory neuropathy	7 (1.7)	0	0	0	2 (1.0)	0	0	0
Renal and urinary disorders								
Acute kidney injury	14 (3.5)	5 (1.2)	0	2 (0.5)	0	0	0	0
Renal failure	9 (2.2)	2 (0.5)	0	0	4 (2.0)	0	0	0
Respiratory, thoracic and mediastinal disorders								
Cough	8 (2.0)	0	0	0	5 (2.5)	0	0	0
Dyspnea	16 (4.0)	3 (0.7)	1 (0.2)	0	7 (3.5)	1 (0.5)	0	0
Epistaxis	10 (2.5)	0	0	0	3 (1.5)	0	0	0
Hiccups	12 (3.0)	0	0	0	2 (1.0)	0	0	0
Oropharyngeal pain	5 (1.2)	0	0	0	1 (0.5)	0	0	0
Pneumonitis	16 (4.0)	6 (1.5)	1 (0.2)	3 (0.7)	3 (1.5)	3 (1.5)	0	0
Rhinorrhoea	12 (3.0)	0	0	0	4 (2.0)	0	0	0
Skin and subcutaneous tissue disorders								
Alopecia	20 (4.9)	0	0	0	9 (4.5)	0	0	0
Dermatitis acneiform	7 (1.7)	0	0	0	2 (1.0)	0	0	0
Dry skin	11 (2.7)	0	0	0	12 (5.9)	0	0	0
Erythema	10 (2.5)	0	0	0	2 (1.0)	0	0	0
Pruritus	37 (9.1)	0	0	0	12 (5.9)	0	0	0
Rash	51 (12.6)	5 (1.2)	0	0	17 (8.4)	3 (1.5)	0	0
Rash maculo-papular	8 (2.0)	0	0	0	7 (3.5)	1 (0.5)	0	0
Rash pruritic	5 (1.2)	0	0	0	1 (0.5)	0	0	0

Treatment-related adverse events attributable to KEYTRUDA® and reported in <1% patients with non-squamous NSCLC treated with KEYTRUDA® in combination with pemetrexed and platinum chemotherapy (n=405) by SOC are shown below.

Endocrine disorders: adrenal insufficiency, hypophysitis, hypopituitarism, thyroiditis
Gastrointestinal disorders: pancreatitis
Hepatobiliary disorders: hepatitis
Injury, poisoning and procedural complications: infusion related reaction
Metabolism and nutrition disorders: Type 1 diabetes mellitus
Musculoskeletal and connective tissue disorders: arthritis
Renal and urinary disorders: nephritis

Table 7 summarizes the treatment-related adverse events that occurred in at least 1% of patients with NSCLC treated with KEYTRUDA® in KEYNOTE-407. The most common treatment-related adverse events (reported in at least 20% of patients) were alopecia, anemia, neutropenia, nausea, thrombocytopenia, and diarrhea. The most common Grade 3-5 treatment-related adverse events for patients treated with KEYTRUDA® in KEYNOTE-407 were neutropenia (21.2%), anemia (13.7%), thrombocytopenia (6.5%), neutrophil count decreased (6.1%), and febrile neutropenia (5.0%).

Treatment was discontinued for treatment-related adverse events in 9.0% of the 278 patients receiving KEYTRUDA®, carboplatin and either paclitaxel or nab-paclitaxel and in 3.2% of the 280 patients receiving placebo, carboplatin and either paclitaxel or nab-paclitaxel. The most common treatment-related adverse events leading to study discontinuation (occurring in more than 3 patients) were pneumonitis (n=4) and sepsis (n=3). The median time to discontinuation for treatment-related adverse events was 1.9 months.

Table 7: Treatment-Related Adverse Events (Incidence ≥ 1%) in Patients Treated with KEYTRUDA® in Combination with Carboplatin and Either Paclitaxel or Nab-paclitaxel, APaT Population in KEYNOTE-407

	KEYTRUDA® + Carboplatin + Paclitaxel or Nab-Paclitaxel n=278				**Placebo + Carboplatin + Paclitaxel or Nab-Paclitaxel n=280**			
Adverse Reaction	**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	123 (44.2)	38 (13.7)	0	0	117 (41.8)	43 (15.4)	0	0
Febrile neutropenia	14 (5.0)	12 (4.3)	2 (0.7)	0	10 (3.6)	8 (2.9)	2 (0.7)	0
Leukopenia	23 (8.3)	8 (2.9)	4 (1.4)	0	19 (6.8)	12 (4.3)	0	0
Lymphopenia	5 (1.8)	1 (0.4)	1 (0.4)	0	4 (1.4)	2 (0.7)	0	0
Neutropenia	97 (34.9)	35 (12.6)	24 (8.6)	0	86 (30.7)	40 (14.3)	23 (8.2)	0
Thrombocytopenia	81 (29.1)	12 (4.3)	6 (2.2)	0	58 (20.7)	12 (4.3)	4 (1.4)	0
Endocrine disorders								
Hyperthyroidism	17 (6.1)	1 (0.4)	0	0	2 (0.7)	0	0	0
Hypothyroidism	16 (5.8)	0	0	0	3 (1.1)	0	0	0
Gastrointestinal disorders								
Abdominal pain	4 (1.4)	0	0	0	3 (1.1)	0	0	0

	KEYTRUDA® + Carboplatin + Paclitaxel or Nab-Paclitaxel n=278				Placebo + Carboplatin + Paclitaxel or Nab-Paclitaxel n=280			
Adverse Reaction	**Any Grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**	**Any Grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**
Abdominal pain upper	4 (1.4)	0	0	0	2 (0.7)	0	0	0
Colitis	6 (2.2)	4 (1.4)	2 (0.7)	0	3 (1.1)	2 (0.7)	0	0
Constipation	31 (11.2)	1 (0.4)	0	0	25 (8.9)	0	0	0
Diarrhea	61 (21.9)	8 (2.9)	0	0	47 (16.8)	4 (1.4)	0	0
Dry mouth	4 (1.4)	0	0	0	1 (0.4)	0	0	0
Gastroesophageal reflux disease	3 (1.1)	0	0	0	1 (0.4)	0	0	0
Nausea	85 (30.6)	2 (0.7)	0	0	71 (25.4)	3 (1.1)	0	0
Retching	3 (1.1)	0	0	0	0	0	0	0
Stomatitis	9 (3.2)	0	0	0	11 (3.9)	1 (0.4)	0	0
Vomiting	36 (12.9)	1 (0.4)	0	0	25 (8.9)	3 (1.1)	0	0
General disorders and administration site conditions								
Asthenia	46 (16.5)	3 (1.1)	0	0	41 (14.6)	6 (2.1)	0	0
Fatigue	54 (19.4)	7 (2.5)	0	0	52 (18.6)	6 (2.1)	1 (0.4)	0
Malaise	10 (3.6)	0	0	0	12 (4.3)	1 (0.4)	0	0
Mucosal inflammation	8 (2.9)	1 (0.4)	0	0	6 (2.1)	0	0	0
Edema peripheral	7 (2.5)	0	0	0	6 (2.1)	1 (0.4)	0	0
Pain	3 (1.1)	1 (0.4)	0	0	3 (1.1)	0	0	0
Pyrexia	8 (2.9)	2 (0.7)	0	0	11 (3.9)	0	0	0
Hepatobiliary disorders								
Autoimmune hepatitis	5 (1.8)	4 (1.4)	1 (0.4)	0	0	0	0	0
Infections and infestations								
Pneumonia	9 (3.2)	6 (2.2)	2 (0.7)	0	4 (1.4)	2 (0.7)	0	1 (0.4)
Rhinitis	3 (1.1)	0	0	0	0	0	0	0
Sepsis	4 (1.4)	0	0	3 (1.1)	0	0	0	0
Upper respiratory tract infection	3 (1.1)	0	0	0	2 (0.7)	0	0	0
Urinary tract infection	4 (1.4)	0	0	0	0	0	0	0
Injury, poisoning and procedural complications								
Infusion related reaction	4 (1.4)	2 (0.7)	1 (0.4)	0	3 (1.1)	0	1 (0.4)	0
Investigations								
Alanine aminotransferase increased	11 (4.0)	1 (0.4)	0	0	8 (2.9)	1 (0.4)	0	0
Aspartate aminotransferase increased	14 (5.0)	0	0	0	5 (1.8)	1 (0.4)	0	0
Blood alkaline phosphatase increased	6 (2.2)	0	0	4 (1.4)	0	0	0	0
Blood bilirubin increased	3 (1.1)	0	0	0	3 (1.1)	1 (0.4)	0	0

	KEYTRUDA® + Carboplatin + Paclitaxel or Nab-Paclitaxel n=278				Placebo + Carboplatin + Paclitaxel or Nab-Paclitaxel n=280			
Adverse Reaction	**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 creatinine increased	9 (3.2)	0	0	0	6 (2.1)	1 (0.4)	0	0
Lymphocyte count decreased	3 (1.1)	2 (0.7)	0	0	7 (2.5)	2 (0.7)	0	0
Neutrophil count decreased	24 (8.6)	5 (1.8)	12 (4.3)	0	28 (10.0)	12 (4.3)	12 (4.3)	0
Platelet count decreased	23 (8.3)	5 (1.8)	0	0	16 (5.7)	6 (2.1)	0	0
Weight decreased	10 (3.6)	1 (0.4)	0	0	8 (2.9)	1 (0.4)	0	0
White blood cell count decreased	30 (10.8)	7 (2.5)	4 (1.4)	0	28 (10.0)	10 (3.6)	0	0
Metabolism and nutrition disorders								
Decreased appetite	47 (16.9)	5 (1.8)	0	0	57 (20.4)	4 (1.4)	0	0
Dehydration	4 (1.4)	2 (0.7)	0	0	5 (1.8)	1 (0.4)	1 (0.4)	0
Hyperglycemia	3 (1.1)	0	0	0	1 (0.4)	0	0	0
Hypomagnesemia	15 (5.4)	1 (0.4)	0	0	9 (3.2)	2 (0.7)	0	0
Hyponatremia	6 (2.2)	5 (1.8)	0	0	4 (1.4)	0	1 (0.4)	0
Hypophosphatemia	4 (1.4)	1 (0.4)	0	0	4 (1.4)	1 (0.4)	0	0
Musculoskeletal and connective tissue disorders								
Arthralgia	36 (12.9)	1 (0.4)	0	0	24 (8.6)	2 (0.7)	0	0
Bone pain	4 (1.4)	0	0	0	5 (1.8)	0	0	0
Musculoskeletal pain	5 (1.8)	1 (0.4)	0	0	5 (1.8)	0	0	0
Myalgia	32 (11.5)	2 (0.7)	0	0	26 (9.3)	1 (0.4)	0	0
Pain in extremity	8 (2.9)	0	0	0	12 (4.3)	0	0	0
Nervous system disorders								
Dizziness	6 (2.2)	0	0	0	7 (2.5)	0	0	0
Dysgeusia	23 (8.3)	0	0	0	7 (2.5)	0	0	0
Headache	7 (2.5)	0	0	0	7 (2.5)	0	0	0
Hypoasthesia	6 (2.2)	0	0	0	4 (1.4)	0	0	0
Lethargy	4 (1.4)	0	0	0	0	0	0	0
Neuropathy peripheral	55 (19.8)	3 (1.1)	0	0	37 (13.2)	2 (0.7)	0	0
Neurotoxicity	7 (2.5)	0	0	0	2 (0.7)	0	0	0
Paresthesia	15 (5.4)	1 (0.4)	0	0	13 (4.6)	1 (0.4)	0	0
Peripheral motor neuropathy	3 (1.1)	0	0	0	4 (1.4)	0	0	0
Peripheral sensory neuropathy	31 (11.2)	0	0	0	36 (12.9)	2 (0.7)	0	0
Polyneuropathy	6 (2.2)	1 (0.4)	0	0	5 (1.8)	1 (0.4)	0	0
Psychiatric disorders								
Insomnia	4 (1.4)	0	0	0	0	0	0	0
Renal and urinary disorders								
Acute kidney injury	5 (1.8)	1 (0.4)	0	0	4 (1.4)	2 (0.7)	0	1 (0.4)
Respiratory, thoracic and mediastinal disorders								
Dyspnea	4 (1.4)	0	0	0	5 (1.8)	0	0	0
Epistaxis	11 (4.0)	0	0	0	9 (3.2)	1 (0.4)	0	0
Hiccups	11 (4.0)	0	0	0	4 (1.4)	0	0	0

	KEYTRUDA® + Carboplatin + Paclitaxel or Nab-Paclitaxel n=278				Placebo + Carboplatin + Paclitaxel or Nab-Paclitaxel n=280			
Adverse Reaction	**Any Grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**	**Any Grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**
Interstitial lung disease	3 (1.1)	0	0	0	2 (0.7)	1 (0.4)	1 (0.4)	0
Pneumonitis	11 (4.0)	4 (1.4)	0	1 (0.4)	3 (1.1)	0	0	0
Skin and subcutaneous tissue disorders								
Alopecia	126 (45.3)	1 (0.4)	0	0	100 (35.7)	3 (1.1)	0	0
Dry skin	9 (3.2)	0	0	0	5 (1.8)	1 (0.4)	0	0
Pruritus	29 (10.4)	0	0	0	15 (5.4)	0	0	0
Rash	28 (10.1)	0	0	0	20 (7.1)	0	0	0
Rash maculo-papular	6 (2.2)	0	0	0	3 (1.1)	0	0	0
Rash papular	3 (1.1%)	0	0	0	0	0	0	0
Vascular disorders								
Hot flush	3 (1.1)	0	0	0	0	0	0	0
Hypotension	5 (1.8)	2 (0.7)	0	0	7 (2.5)	3 (1.1)	0	0

Treatment –related adverse events attributable to KEYTRUDA® and reported in <1% patients with squamous NSCLC treated with KEYTRUDA® in combination with carboplatin and either paclitaxel or nab-paclitaxel (n=278) by SOC are shown below.

Endocrine disorders: hypophysitis, hypopituitarism
Renal and urinary disorders: nephritis

Table 8 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 8: 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
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

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 (%)
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
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

Hodgkin Lymphoma
Table 9 summarizes the treatment-related adverse events that occurred in at least 1% of patients with Hodgkin Lymphoma treated with KEYTRUDA® in KEYNOTE-013 and 087. The most common adverse event (reported in at least 10% of patients) was hypothyroidism. Eleven percent of patients had ≥ Grade 3 adverse events. The most common ≥ Grade 3 adverse events (occurring in more than 2 patients) were: neutropenia (n=5, 2.1%) and dyspnea (n=3, 1.2%).

KEYTRUDA® was discontinued for treatment-related adverse events in 5% of patients with Hodgkin Lymphoma. The most common treatment-related adverse event leading to study drug discontinuation (occurring in more than 2 patients) was: pneumonitis (n=5, 2.1%). The median time to discontinuation for treatment-related adverse events was 1.5 months.

Table 9: Treatment-Related Adverse Events Occurring in ≥ 1% of Patients with Hodgkin Lymphoma treated with KEYTRUDA® in KEYNOTE-013 and KEYNOTE-087

Adverse Event	KEYTRUDA® 10 mg/kg every 2 weeks or 200 mg every 3 weeks N=241	
	Any Grade n (%)	Grade 3 n (%)
Blood and lymphatic system disorders		
Neutropenia	11 (4.6)	5 (2.1)
Thrombocytopenia	3 (1.2)	1 (0.4)
Cardiac disorders		
Palpitations	3 (1.2)	0
Endocrine disorders		
Hyperthyroidism	6 (2.5)	0
Hypothyroidism	30 (12.4)	1 (0.4)
Gastrointestinal disorders		
Abdominal distension	3 (1.2)	0
Abdominal pain	5 (2.1)	0
Colitis	3 (1.2)	2 (0.8)
Constipation	7 (2.9)	0
Diarrhea	21 (8.7)	2 (0.8)
Dry mouth	3 (1.2)	0
Nausea	16 (6.6)	0
Stomatitis	3 (1.2)	0
Vomiting	10 (4.1)	0
General disorders and administration site conditions		
Asthenia	5 (2.1)	0
Chest pain	4 (1.7)	0
Chills	7 (2.9)	0
Fatigue	22 (9.1)	1 (0.4)
Pain	3 (1.2)	0
Pyrexia	22 (9.1)	1 (0.4)
Immune System Disorders		
Cytokine release syndrome	6 (2.5)	1 (0.4)
Infections and infestations		
Oral herpes	3 (1.2)	0
Upper respiratory tract infection	7 (2.9)	0
Injury, poisoning and procedural complications		
Infusion related reaction	10 (4.1)	0
Investigations		
Alanine aminotransferase increased	4 (1.7)	0
Aspartate aminotransferase increased	4 (1.7)	1 (0.4)
Platelet count decreased	5 (2.1)	0
Weight decreased	5 (2.1)	1 (0.4)
Weight increased	3 (1.2)	0
White blood cell count decreased	3 (1.2)	0
Metabolism and nutrition disorders		
Decreased appetite	6 (2.5)	1 (0.4)
Musculoskeletal and connective tissue disorders		
Arthralgia	11 (4.6)	1 (0.4)
Back pain	5 (2.1)	1 (0.4)
Bone pain	4 (1.7)	1 (0.4)

Adverse Event	KEYTRUDA® 10 mg/kg every 2 weeks or 200 mg every 3 weeks N=241	
	Any Grade n (%)	Grade 3 n (%)
Muscle spasms	9 (3.7)	0
Myalgia	6 (2.5)	0
Nervous system disorders		
Headache	14 (5.8)	0
Respiratory, thoracic and mediastinal disorders		
Cough	13 (5.4)	1 (0.4)
Dyspnea	10 (4.1)	3 (1.2)
Nasal congestion	3 (1.2)	0
Pneumonitis	10 (4.1)	0
Skin and subcutaneous tissue disorders		
Alopecia	4 (1.7)	0
Dry skin	7 (2.9)	0
Pruritus	9 (3.7)	0
Rash	16 (6.6)	0

Two deaths due to adverse events regardless of relationship to therapy were reported among the 241 patients with HL in KEYNOTE-013 and 087. Cause of death for these patients was graft versus host disease and septic shock.

Of 23 patients with cHL who proceeded to allogeneic HSCT after treatment with pembrolizumab, 6 patients (26%) developed GVHD, one of which was fatal, and 2 patients (9%) developed severe hepatic VOD after reduced-intensity conditioning, one of which was fatal. The 23 patients had a median follow-up from subsequent allogeneic HSCT of 5.1 months (range: 0-26.2 months).

Treatment related adverse events reported in <1% patients with HL treated with KEYTRUDA® 10 mg/kg every 2 weeks or 200 mg every 3 weeks (n=241) by SOC are shown below:

Musculoskeletal and connective tissue disorders: arthritis, myositis

Primary Mediastinal B-cell Lymphoma (PMBCL)
Table 10 summarizes the treatment-related adverse events that occurred in at least 1% of patients with PMBCL treated with KEYTRUDA® in KEYNOTE-170. The most common adverse event (reported in at least 10% of patients) was neutropenia.

KEYTRUDA® was discontinued for treatment-related adverse events in 2.0% (1/49) of patients with PMBCL: increased AST after one dose of KEYTRUDA®.

Table 10: Treatment-Related Adverse Events Occurring in ≥ 1% of Patients with PMBCL treated with KEYTRUDA® in KEYNOTE-170

Adverse Event	KEYTRUDA® 200 mg every 3 weeks N=49	
	Any Grade n (%)	Grade 3/Grade 4 n (%)
Blood and lymphatic system disorders		
Neutropenia	9 (18.4)	5 (10.2) Grade 4: 1 (2.0)
Anemia	1 (2.0)	0
Leukopenia	1 (2.0)	0
Cardiac disorders		
Pericarditis	1 (2.0)	0
Endocrine disorders		
Hypothyroidism	3 (6.1)	0
Hyperthyroidism	1 (2.0)	0
Thyroiditis	1 (2.0)	0
Gastrointestinal disorders		
Abdominal pain	1 (2.0)	0
Diarrhea	1 (2.0)	0
Nausea	1 (2.0)	0
General disorders and administration site conditions		
Fatigue	2 (4.1)	0
Pyrexia	3 (6.1)	0
Asthenia	3 (6.1)	1 (2.0) 0
Hepatobiliary disorders		
Hepatic necrosis	1 (2.0)	0
Infections and infestations		
Clostridium difficile infection	1 (2.0)	1 (2.0) 0
Herpes zoster	1 (2.0)	0
Pneumonia	1 (2.0)	1 (2.0) 0
Upper respiratory tract infection	1 (2.0)	0
Vulvovaginal mycotic infection	1 (2.0)	0
Investigations		
Alanine aminotransferase increased	1 (2.0)	0
Aspartate aminotransferase increased	2 (4.1)	1 (2.0) 0
Hepatic enzyme increased	1 (2.0)	1 (2.0) 0
White blood cell count decreased	1 (2.0)	0
Metabolism and nutrition disorders		
Hyperglycemia	1 (2.0)	0
Musculoskeletal and connective tissue disorders		
Myalgia	2 (4.1)	0
Arthralgia	1 (2.0)	0
Back pain	1 (2.0)	0
Muscle spasms	1 (2.0)	0
Neoplasma benign, malignant and unspecified (includes cysts and polyps)		
Tumour flare	1 (2.0)	1 (2.0) 0
Nervous system disorders		
Paraesthesia	1 (2.0)	0
Psychiatric disorders		
Fear	1 (2.0)	0
Respiratory, thoracic and mediastinal disorders		
Pleural effusion	1 (2.0)	0

Adverse Event	KEYTRUDA® 200 mg every 3 weeks N=49	
	Any Grade n (%)	Grade 3/Grade 4 n (%)
Respiratory disorder	1 (2.0)	0
Skin and subcutaneous tissue disorders		
Erythema	1 (2.0)	0
Dermatitis allergic	1 (2.0)	0
Swelling Face	1 (2.0)	0

Two deaths due to adverse events regardless of relationship to therapy were reported among the 49 patients with PMBCL in KEYNOTE -170. Causes of death for these patients were *Aspergillu*s infection and myocardial infarction.

Urothelial Carcinoma

Table 11 summarizes the treatment-related adverse events that occurred in at least 1% of patients with urothelial carcinoma treated with KEYTRUDA® in KEYNOTE-045. The most common treatment-related adverse events (reported in at least 10% of patients) were pruritus, fatigue and nausea. Fifteen percent of patients had ≥ Grade 3 treatment-related adverse events. The most common ≥ Grade 3 adverse reactions (occurring in more than 2 patients) were: pneumonitis (n=4), diarrhea (n=3), fatigue (n=3) and aspartate aminotransferase increase (n=3).

KEYTRUDA® was discontinued for treatment-related adverse events in 5.6% of patients in KEYNOTE 045. The most common treatment-related adverse event leading to study drug discontinuation (occurring in more than 2 patients) was: pneumonitis (n=5). The median time to discontinuation for treatment-related adverse events was 0.7 months.

Table 11: Treatment-Related Adverse Events Occurring in ≥ 1% of Patients with Urothelial Carcinoma treated with KEYTRUDA® in KEYNOTE-045

Adverse Reaction	KEYTRUDA® 200 mg every 3 weeks n=266				Chemotherapy n=255			
	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	9 (3.4)	2 (0.8)	0 (0)	0 (0)	63 (24.7)	20 (7.8)	0 (0)	0 (0)
Endocrine disorders								
Hyperthyroidism	10 (3.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Hypothyroidism	15 (5.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Gastrointestinal disorders								
Abdominal pain	4 (1.5)	0 (0)	0 (0)	0 (0)	10 (3.9)	0 (0)	0 (0)	0 (0)
Colitis	5 (1.9)	2 (0.8)	0 (0)	0 (0)	1 (0.4)	0 (0)	0 (0)	0 (0)
Constipation	6 (2.3)	0 (0)	0 (0)	0 (0)	52 (20.4)	7 (2.7)	0 (0)	0 (0)
Diarrhea	24 (9.0)	3 (1.1)	0 (0)	0 (0)	33 (12.9)	1 (0.4)	1 (0.4)	0 (0)
Dry mouth	4 (1.5)	0 (0)	0 (0)	0 (0)	2 (0.8)	0 (0)	0 (0)	0 (0)
Flatulence	3 (1.1)	0 (0)	0 (0)	0 (0)	1 (0.4)	0 (0)	0 (0)	0 (0)

Adverse Reaction	KEYTRUDA® 200 mg every 3 weeks n=266				Chemotherapy n=255			
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Nausea	29 (10.9)	1 (0.4)	0 (0)	0 (0)	62 (24.3)	4 (1.6)	0 (0)	0 (0)
Stomatitis	4 (1.5)	1 (0.4)	0 (0)	0 (0)	21 (8.2)	1 (0.4)	0 (0)	0 (0)
Vomiting	12 (4.5)	0 (0)	0 (0)	0 (0)	25 (9.8)	1 (0.4)	0 (0)	0 (0)
General disorders and administration site conditions								
Asthenia	15 (5.6)	1 (0.4)	0 (0)	0 (0)	36 (14.1)	7 (2.7)	0 (0)	0 (0)
Chills	3 (1.1)	0 (0)	0 (0)	0 (0)	4 (1.6)	0 (0)	0 (0)	0 (0)
Fatigue	37 (13.9)	3 (1.1)	0 (0)	0 (0)	71 (27.8)	11 (4.3)	0 (0)	0 (0)
Influenza like illness	3 (1.1)	0 (0)	0 (0)	0 (0)	3 (1.2)	0 (0)	0 (0)	0 (0)
Malaise	4 (1.5)	0 (0)	0 (0)	0 (0)	8 (3.1)	0 (0)	0 (0)	0 (0)
Mucosal inflammation	3 (1.1)	1 (0.4)	0 (0)	0 (0)	17 (6.7)	2 (0.8)	0 (0)	0 (0)
Pyrexia	17 (6.4)	0 (0)	0 (0)	0 (0)	8 (3.1)	1 (0.4)	0 (0)	0 (0)
Infections and infestations								
Urinary Tract Infection	3 (1.1)	0 (0)	0 (0)	0 (0)	8 (3.1)	3 (1.2)	1 (0.4)	0 (0)
Investigations								
Alanine aminotransferase increased	9 (3.4)	2 (0.8)	0 (0)	0 (0)	3 (1.2)	0 (0)	0 (0)	0 (0)
Aspartate aminotransferase increased	7 (2.6)	3 (1.1)	0 (0)	0 (0)	2 (0.8)	0 (0)	0 (0)	0 (0)
Blood alkaline phosphatase increased	3 (1.1)	1 (0.4)	0 (0)	0 (0)	1 (0.4)	0 (0)	0 (0)	0 (0)
Blood thyroid stimulating hormone increased	3 (1.1)	0 (0)	0 (0)	0 (0)	0 (0.0)	0 (0.0)	0 (0)	0 (0)
Gamma-glutamyl transferase increased	3 (1.1)	2 (0.8)	0 (0)	0 (0)	1 (0.4)	0 (0)	0 (0)	0 (0)
Platelet count decreased	3 (1.1)	1 (0.4)	0 (0)	0 (0)	7 (2.7)	2 (0.8)	1 (0.4)	0 (0)
Weight decreased	4 (1.5)	0 (0)	0 (0)	0 (0)	8 (3.1)	0 (0)	0 (0)	0 (0)
Metabolism and nutrition disorders								
Decreased appetite	23 (8.6)	0 (0)	0 (0)	0 (0)	41 (16.1)	3 (1.2)	0 (0)	0 (0)
Hyperglycemia	3 (1.1)	1 (0.4)	0 (0)	0 (0)	0 (0.0)	0 (0.0)	0 (0)	0 (0)
Musculoskeletal and connective tissue disorders								
Arthralgia	8 (3.0)	0 (0)	0 (0)	0 (0)	17 (6.7)	0 (0)	0 (0)	0 (0)
Back pain	3 (1.1)	0 (0)	0 (0)	0 (0)	2 (0.8)	0 (0)	0 (0)	0 (0)
Muscle spasms	3 (1.1)	0 (0)	0 (0)	0 (0)	1 (0.4)	0 (0)	0 (0)	0 (0)

Adverse Reaction	KEYTRUDA® 200 mg every 3 weeks n=266				Chemotherapy n=255			
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Musculoskeletal chest pain	3 (1.1)	0 (0)	0 (0)	0 (0)	0 (0.0)	0 (0.0)	0 (0)	0 (0)
Myalgia	8 (3.0)	1 (0.4)	0 (0)	0 (0)	12 (4.7)	0 (0)	0 (0)	0 (0)
Pain in extremity	3 (1.1)	0 (0)	0 (0)	0 (0)	13 (5.1)	1 (0.4)	0 (0)	0 (0)
Nervous system disorders								
Dizziness	6 (2.3)	0 (0)	0 (0)	0 (0)	7 (2.7)	1 (0.4)	0 (0)	0 (0)
Dysgeusia	3 (1.1)	0 (0)	0 (0)	0 (0)	14 (5.5)	0 (0)	0 (0)	0 (0)
Headache	4 (1.5)	1 (0.4)	0 (0)	0 (0)	8 (3.1)	0 (0)	0 (0)	0 (0)
Psychiatric disorders								
Insomnia	3 (1.1)	0 (0)	0 (0)	0 (0)	5 (2.0)	0 (0)	0 (0)	0 (0)
Respiratory, thoracic and mediastinal disorders								
Cough	7 (2.6)	0 (0)	0 (0)	0 (0)	2 (0.8)	0 (0)	0 (0)	0 (0)
Dyspnea	7 (2.6)	0 (0)	0 (0)	0 (0)	6 (2.4)	1 (0.4)	0 (0)	0 (0)
Dyspnoea exertional	5 (1.9)	0 (0)	0 (0)	0 (0)	4 (1.6)	0 (0)	0 (0)	0 (0)
Pneumonitis	9 (3.4)	3 (1.1)	0 (0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0)	0 (0)
Skin and subcutaneous tissue disorders								
Dermatitis acneiform	3 (1.1)	0 (0)	0 (0)	0 (0)	2 (0.8)	0 (0)	0 (0)	0 (0)
Dry skin	6 (2.3)	0 (0)	0 (0)	0 (0)	7 (2.7)	0 (0)	0 (0)	0 (0)
Erythema	4 (1.5)	0 (0)	0 (0)	0 (0)	5 (2.0)	0 (0)	0 (0)	0 (0)
Pruritus	52 (19.5)	0 (0)	0 (0)	0 (0)	7 (2.7)	1 (0.4)	0 (0)	0 (0)
Rash	22 (8.3)	1 (0.4)	0 (0)	0 (0)	9 (3.5)	0 (0)	0 (0)	0 (0)
Rash maculo-papular	6 (2.3)	0 (0)	0 (0)	0 (0)	2 (0.8)	0 (0)	0 (0)	0 (0)
Urticaria	5 (1.9)	0 (0)	0 (0)	0 (0)	1 (0.4)	0 (0)	0 (0)	0 (0)
Vascular Disorders								
Hypertension	3 (1.1)	1 (0.4)	0 (0)	0 (0)	1 (0.4)	0 (0)	0 (0)	0 (0)

Treatment related adverse events reported in <1% patients with urothelial carcinoma treated with KEYTRUDA® 200 mg every 3 weeks (n=266) in KEYNOTE-045 by SOC are shown below:

Injury, poisoning and procedural complications: infusion related reaction
Musculoskeletal and connective tissue disorders: arthritis
Renal and urinary disorders: nephritis, acute renal injury
Blood and lymphatic system disorders: thrombocytopenia, eosinophilia
Endocrine disorders: adrenal insufficiency, thyroiditis

Table 12 summarizes the treatment-related adverse events that occurred in at least 1% of patients with urothelial carcinoma treated with KEYTRUDA® in KEYNOTE-052. The most common adverse events (reported in at least 10% of patients) were fatigue, pruritus, rash, decreased appetite and hypothyroidism. Twenty percent of patients had ≥ Grade 3 treatment-related adverse events. The most common ≥ Grade 3 treatment related adverse events (occurring in more than 1% of patients) were: fatigue (n=8; 2.2%), colitis (n=6; 1.6%), blood alkaline phosphatase

increased (n=5; 1.4%), muscular weakness (n=5; 1.4%), pneumonitis (n=4; 1.1%), diarrhea (n=4; 1.1%) and aspartate aminotransferase increased (n=4; 1.1%).

KEYTRUDA® was discontinued for treatment-related adverse events in 9.7 % of patients in KEYNOTE 052. The most common treatment-related adverse events leading to study drug discontinuation (occurring in more than 2 patients) were: pneumonitis (n=5, 1.4%), colitis (n=3, 0.8%) and diarrhea (n=3, 0.8%). The median time to discontinuation for treatment-related adverse events was 4.2 months.

Table 12: Treatment-Related Adverse Events Occurring in ≥ 1% of Patients with Urothelial Carcinoma Treated with KEYTRUDA® (KEYNOTE-052)

Adverse Reaction	KEYTRUDA® 200 mg once every three weeks N=370		
	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Blood and lymphatic system disorders			
Anemia	9 (2.4)	1 (0.3)	0
Thrombocytopenia	4 (1.1)	0	0
Endocrine disorders			
Hyperthyroidism	9 (2.4)	0	0
Hypothyroidism	37 (10.0)	0	0
Gastrointestinal disorders			
Abdominal pain	5 (1.4)	0	0
Colitis	9 (2.4)	5 (1.4)	1 (0.3)
Constipation	11 (3.0)	1 (0.3)	0
Diarrhea	34 (9.2)	4 (1.1)	0
Dry mouth	11 (3.0)	0	0
Nausea	32 (8.6)	1 (0.3)	0
Vomiting	13 (3.5)	0	0
General disorders and administration site conditions			
Asthenia	15 (4.1)	2 (0.5)	1 (0.3)
Chills	10 (2.7)	0	0
Fatigue	67 (18.1)	8 (2.2)	0
Influenza like illness	11 (3.0)	0	0
Oedema peripheral	11 (3.0)	0	0
Pyrexia	14 (3.8)	1 (0.3)	0
Investigations			
Alanine aminotransferase increased	14 (3.8)	3 (0.8)	0
Aspartate aminotransferase increased	15 (4.1)	4 (1.1)	0
Blood alkaline phosphatase increased	8 (2.2)	5 (1.4)	0
Blood bilirubin increased	6 (1.6)	1 (0.3)	0
Blood creatinine increased	9 (2.4)	1 (0.3)	0
Blood thyroid stimulating hormone increased	4 (1.1)	0	0
Weight decreased	10 (2.7)	1 (0.3)	0
Metabolism and nutrition disorders			
Decreased appetite	39 (10.5)	1 (0.3)	1 (0.3)
Dehydration	4 (1.1)	2 (0.5)	0
Hyperglycemia	5 (1.4)	3 (0.8)	0
Hyponatremia	8 (2.2)	2 (0.5)	0
Musculoskeletal and connective tissue disorders			
Arthralgia	10 (2.7)	1 (0.3)	0

Adverse Reaction	KEYTRUDA® 200 mg once every three weeks N=370		
	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Arthritis	8 (2.2)	2 (0.5)	0
Muscular weakness	6 (1.6)	5 (1.4)	0
Myalgia	7 (1.9)	0	0
Nervous system disorders			
Dizziness	6 (1.6)	1 (0.3)	0
Dysgeusia	13 (3.5)	0	0
Lethargy	6 (1.6)	0	0
Respiratory, thoracic and mediastinal disorders			
Cough	12 (3.2)	0	0
Dyspnea	8 (2.2)	0	0
Pneumonitis	13 (3.5)	4 (1.1)	0
Skin and subcutaneous tissue disorders			
Dermatitis acneiform	4 (1.1)	0	0
Dry skin	6 (1.6)	0	0
Erythema	4 (1.1)	0	0
Pruritus	66 (17.8)	2 (0.5)	0
Pruritus generalised	5 (1.4)	1 (0.3)	0
Psoriasis	5 (1.4)	0	0
Rash	44 (11.9)	2 (0.5)	0
Rash macular	4 (1.1)	0	0
Rash maculo-papular	15 (4.1)	1 (0.3)	0
Rash pruritic	6 (1.6)	0	0

Grade 5 adverse events (adverse events leading to death) occurred in 24 (6.5%) patients. The fatal events were urosepsis (n=4, 1.1%), pneumonia (n=3, 0.8%), sepsis (n=2, 0.5%), death (unknown cause, n=2, 0.5%) and others which were reported in 1 subject each: septic shock, clostridium difficile infection, ischemic cardiomyopathy, cerebrovascular accident, embolism, duodenal obstruction, large intestine perforation, colonic fistula, multiple organ dysfunction syndrome, type 2 diabetes mellitus, myositis, acute kidney injury, chronic kidney disease, renal failure, aspiration, and respiratory failure. One of the deaths (myositis) was considered to be related to the treatment by the investigator.

Treatment related adverse events reported in <1% patients with urothelial carcinoma treated with KEYTRUDA® 200 mg every 3 weeks (n=370) in KEYNOTE 052 by SOC are shown below:

Endocrine disorder: adrenal insufficiency, hypophysitis, thyroiditis
Hepatobiliary disorder: hepatitis
Metabolism and nutrition disorders: type 1 diabetes mellitus, diabetic ketoacidosis
Musculoskeletal and connective tissue disorder: myositis

Microsatellite Instability-High Cancer (MSI-H)
Table 13 summarizes the treatment-related adverse events that occurred in at least 1% of patients with MSI-H cancers treated with KEYTRUDA® in KEYNOTE-158 (adult patients with various types of solid tumours previously treated and who had progressed with no satisfactory alternative treatment options) and KEYNOTE-164 (adult patients with previously treated unresectable or

metastatic colorectal cancer). The most common adverse events (reported in at least 10% of patients) were pruritus, diarrhea, fatigue and nausea. Fourteen percent of patients had ≥ Grade 3 adverse events. The most common ≥ Grade 3 adverse events (occurring in more than 2 patients) were: pancreatitis (n=3, 1.9%), blood alkaline phosphatase increased (n=3, 1.9%) and gamma-glutamyltranferase increased (n=3, 1.9%).

KEYTRUDA® was discontinued for treatment-related adverse events in 4.5% of patients with MSI-H cancers. The most common treatment-related adverse events leading to study drug discontinuation (occurring in 2 or more patients) were: pneumonitis (n=2, 1.3%) and blood alkaline phosphatase increased (n=2, 1.3%). The median time to discontinuation for treatment-related adverse events was 0.7 months.

Table 13: Treatment-Related Adverse Events Occurring in ≥ 1% of Patients with MSI-H Cancer treated with KEYTRUDA® in KEYNOTE-158 and KEYNOTE-164

Adverse Event	KEYTRUDA® 200 mg every 3 weeks N=155	
	Any Grade n (%)	Grade 3* n (%)
Blood and lymphatic system disorders		
Anaemia	3 (1.9)	0
Endocrine disorders		
Hyperthyroidism	6 (3.9)	1 (0.6)
Hypothyroidism	6 (3.9)	0
Gastrointestinal disorders		
Diarrhea	17 (11.0)	1 (0.6)
Nausea	17 (11.0)	0
Vomiting	10 (6.5)	0
Dry mouth	4 (2.6)	0
Abdominal pain	3 (1.9)	0
Colitis	3 (1.9)	0
Constipation	3 (1.9)	0
Pancreatitits	3 (1.9)	3 (1.9)
Stomatitis	2 (1.3)	0
General disorders and administration site conditions		
Fatigue	17 (11.0)	2 (1.3)
Asthenia	15 (9.7)	2 (1.3)
Peripheral Edema	4 (2.6)	1 (0.6)
Pyrexia	3 (1.9)	0
Pain	2 (1.3)	0
Infections and infestations		
Conjunctivitis	2 (1.3)	0
Sinusitis	2 (1.3)	0
Investigations		
Aspartate aminotransferase increased	5 (3.2)	1 (0.6)
Alanine aminotransferase increased	4 (2.6)	1 (0.6)
Blood alkaline phosphatase increased	4 (2.6)	3 (1.9)
Gamma-glutamyltranferase increased	3 (1.9)	3 (1.9)
Blood Creatinine increased	2 (1.3)	0
Blood thyroid stimulating hormone decreased	2 (1.3)	0
Blood thyroid stimulating hormone increased	2 (1.3)	0

Adverse Event	KEYTRUDA® 200 mg every 3 weeks N=155	
	Any Grade n (%)	Grade 3* n (%)
Hemoglobin decreased	2 (1.3)	1 (0.6)
Lipase increased	2 (1.3)	2 (1.3)
Metabolism and nutrition disorders		
Decreased appetite	7 (4.5)	0
Hypercalcemia	2 (1.3)	0
Musculoskeletal and connective tissue disorders		
Arthralgia	13 (8.4)	0
Muscle spasms	3 (1.9)	0
Myalgia	3 (1.9)	0
Nervous system disorders		
Headache	4 (2.6)	0
Dysgeusia	2 (1.3)	0
Psychiatric disorders		
Insomnia	2 (1.3)	0
Respiratory, thoracic and mediastinal disorders		
Pneumonitis	5 (3.2)	1 (0.6)
Skin and subcutaneous tissue disorders		
Pruritus	18 (11.6)	0
Rash	7 (4.5)	0
Rash maculo-papular	6 (3.9)	0
Dry skin	3 (1.9)	0
Eczema	2 (1.3)	0
Rash-generalised	2 (1.3)	1 (0.6)

* No Grade 4 or Grade 5 treatment-related adverse events were reported to occur in ≥1% of patients with MSI-H cancer

Treatment related adverse events reported in <1% patients with MSI-H cancer treated with KEYTRUDA® 200 mg every 3 weeks (n=155) by SOC are shown below:

Injury, poisoning and procedural complications: infusion related reaction
Nervous system disorders: Guillain-Barré syndrome

Abnormal Hematologic and Clinical Chemistry Findings

Melanoma
Laboratory abnormalities (worsened from baseline in ≥ 10% of patients), reported in KEYNOTE-006 in patients with advanced melanoma are presented in Table 14.

Table 14: 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)

Laboratory Test	KEYTRUDA® 10 mg/kg every 2 or 3 weeks n=555		Ipilimumab n=256	
	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 15.

Table 15: 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)

Laboratory Test	KEYTRUDA® 2 or 10 mg/kg every 3 weeks n=357		Chemotherapy n=171	
	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

Adjuvant Melanoma

Laboratory abnormalities (worsened from baseline in ≥ 10% of patients), reported in KEYNOTE-054 in patients with lymph node involvement who have undergone complete resection are presented in Table 16.

Table 16: Laboratory Abnormalities Worsened from Baseline in ≥10% Treated with KEYTRUDA® and at a Higher Incidence than in Control Arm (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-4]) APaT Population

Laboratory Test	KEYTRUDA® 200 mg every 3 weeks n=509		Placebo n=502	
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
Alanine aminotransferase increased	27	2	16	0.2
Aspartate aminotransferase increased	24	2	15	0.4
Lymphocyte count decreased	23	1	16	1
Creatinine increased	15	0.6	10	0
Hypocalcemia	13	0	8	0.2
Hypoalbuminemia	13	0	4	0.2
Alkaline phosphatase increased	13	0.2	5	0.2

NSCLC

Laboratory abnormalities (worsened from baseline in ≥ 10% of patients), reported in KEYNOTE-024 in patients with NSCLC, are presented in Table 17.

Table 17: 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

Laboratory Test	KEYTRUDA® 200 mg every 3 weeks n=154		Chemotherapy n=150	
	All Grades n (%)	Grades 3-4 n (%)	All Grades n (%)	Grades 3-4 n (%)
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-189 in patients with non-squamous NSCLC treated with KEYTRUDA® in combination with pemetrexed and platinum chemotherapy, are presented in Table 18.

Table 18: Laboratory Abnormalities Worsened from Baseline in ≥10% of Patients with Non-squamous NSCLC Treated with KEYTRUDA® in Combination with Pemetrexed and Platinum Chemotherapy and at a Higher Incidence than in the Placebo, Pemetrexed and Platinum Chemotherapy Arm (Between Arm Difference of ≥5% [All Grades] or ≥ 2% [Grades 3-4]) (KEYNOTE-189)

Laboratory Test	KEYTRUDA® + Pemetrexed + Platinum chemotherapy n=405		Placebo + Pemetrexed + Platinum chemotherapy n=202	
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
Hematology				
Neutropenia	48	20	39	18
Platelet count decreased	29	11	28	7
Chemistry				
Hyperglycemia	62	9	57	7
Alanine aminotransferase increased	46	4	40	2
Aspartate aminotransferase increased	46	3	38	1
Creatinine increased	36	4	24	1
Hyponatremia	32	7	22	5
Hyperkalemia	24	3	18	3
Hypocalcemia	23	3	16	<1

Laboratory abnormalities (worsened from baseline in ≥ 10% of patients), reported in KEYNOTE-407 in patients with squamous NSCLC treated with KEYTRUDA® in combination with carboplatin and either paclitaxel or nab-paclitaxel are presented in Table 19.

Table 19: Laboratory Abnormalities Worsened from Baseline in ≥10% of Patients with Squamous NSCLC Treated with KEYTRUDA® in Combination with Carboplatin and either Paclitaxel or Nab-Paclitaxel and at a Higher Incidence than in the Placebo, Carboplatin and Either Paclitaxel or Nab-Paclitaxel Arm (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-4] (KEYNOTE-407)

	KEYTRUDA® + Carboplatin + Paclitaxel or Nab-Paclitaxel n=278		Placebo + Carboplatin + Paclitaxel or Nab-Paclitaxel n=280	
Laboratory Test	**All Grades (%)**	**Grades 3-4 (%)**	**All Grades (%)**	**Grades 3-4 (%)**
Hematology				
White blood cell decreased	65	20	58	20
Platelet count decreased	64	10	53	10
Lymphocyte count decreased	49	17	46	12
Hypoalbuminemia	36	3	32	1
Chemistry				
Aspartate aminotransferase increased	29	4	18	2
Alanine aminotransferase increased	27	3	20	2

Laboratory abnormalities (worsened from baseline in ≥ 10% of patients), reported in KEYNOTE-010, in patients with NSCLC, are presented in Table 20. Patients were treated with pembrolizumab at 2 mg/kg or 10 mg/kg every 3 weeks.

Table 20: 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)

Laboratory Test	KEYTRUDA® 2 or 10 mg/kg every 3 weeks n=682		Docetaxel 75 mg/m^2 every 3 weeks n=309	
	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

Hodgkin Lymphoma

Laboratory abnormalities (worsened from baseline in ≥ 20% of patients), reported in KEYNOTE-013 and KEYNOTE-087 in patients with Hodgkin Lymphoma are presented in Table 21.

Table 21: Laboratory Abnormalities Increased from Baseline in ≥ 20% of Patients with Hodgkin Lymphoma

Laboratory Test	KEYTRUDA® 10 mg/kg every 2 weeks or 200 mg every 3 weeks n=241	
	All Grades n (%)	Grades 3-4 n (%)
Alanine Aminotransferase Increased	58 (24.1)	9 (3.7)
Aspartate Aminotransferase Increased	61 (25.3)	3 (1.2)
Glucose Decreased	59 (24.5)	3 (1.2)
Glucose Increased	101 (41.9)	5 (2.1)
Hemoglobin Decreased	68 (28.2)	15 (6.2)
Leukocytes Decreased	63 (26.1)	6 (2.5)
Lymphocytes Decreased	72 (29.9)	25 (10.4)
Neurophils Decreased	61 (25.3)	19 (7.9)
Phosphate Decreased	54 (22.4)	13 (5.4)
Platelet Decreased	66 (27.4)	9 (3.7)
Sodium Decreased	62 (25.7)	6 (2.5)

Primary Mediastinal B-cell Lymphoma (PMBCL)

Laboratory abnormalities (worsened from baseline in ≥ 20% of patients), reported in KEYNOTE-170 in patients with PMBCL are presented in Table 22.

Table 22: Laboratory Abnormalities Increased from Baseline in ≥ 20% of Patients with PMBCL

Laboratory Test	KEYTRUDA® 200 mg every 3 weeks n=49

	All Grades n (%)	Grades 3-4 n (%)
Glucose Increased	16 (32.7)	2 (4.1)
Hemoglobin Decreased	16 (32.7)	0
Leukocytes Decreased	16 (32.7)	4 (8.2)
Lymphocytes Decreased	13 (26.5)	7 (14.3)
Neutrophils Decreased	12 (24.5)	4 (8.2)
Phosphate Decreased	11 (22.4)	4 (8.2)

Urothelial Carcinoma

Laboratory abnormalities (worsened from baseline in ≥ 10% of patients), reported in KEYNOTE-045 in patients with urothelial carcinoma are presented in Table 23.

Table 23: Laboratory Abnormalities Worsened from Baseline in ≥10% of Patients with Urothelial Carcinoma 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-045)

Laboratory Test	KEYTRUDA® 200 mg every 3 weeks n=266		Chemotherapy n=255	
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
Chemistry				
Alkaline Phosphatase Increased	35.4	7.2	32.2	4.7
Aspartate Aminotransferase Increased	26	3.8	19.6	2.4
Creatinine Increased	34.9	4.1	27.4	3.1

The most frequently (≥20%) reported laboratory values that showed clinically meaningful worsening in CTCAE grade from baseline on the pembrolizumab arm were lymphocytes decreased and phosphate decreased. The incidence in the pembrolizumab arm was lower than in the control arm (lymphocytes decreased: 25.6% with pembrolizumab vs 34.9% with chemotherapy; phosphate decreased: 23.7% with pembrolizumab vs 27.5% with chemotherapy). The most frequent liver function test elevation by predetermined normal limit cutoffs was alkaline phosphatase (31.6%), a rate only slightly higher than the chemotherapy control group (28.5%).

Laboratory abnormalities (worsened from baseline in ≥ 10% of patients), reported in KEYNOTE-052 in patients with urothelial carcinoma not eligible for cisplatin –containing chemotherapy are presented in Table 24.

Table 24: Laboratory Abnormalities Increased from Baseline in ≥ 10% of Patients with Urothelial Carcinoma Not Eligible to Cisplatin-Containing Chemotherapy (KEYNOTE-052)

Laboratory Test	KEYTRUDA® 200 mg every 3 weeks N=370	
	All Grades n (%)	Grades 3-4 n (%)
Chemistry		
Alanine Aminotransferase Increased	104 (28)	12 (3.2)
Albumin Decreased	159 (43)	11 (3.0)
Alkaline Phosphatase Increased	125 (32)	26 (7)
Aspartate Aminotransferase Increased	113 (31)	18 (5)
Calcium Decreased	105 (28)	8 (2.2)
Calcium Increased	49 (13)	9 (2.4)
Creatinine Increased	161 (44)	17 (4.6)
Glucose Decreased	38 (10)	5 (1.4)
Glucose Increased	201 (54)	31 (8)
Phosphate Decreased	79 (21)	20 (5)
Potassium Decreased	39 (11)	4 (1.1)
Potassium Increased	104 (28)	18 (4.9)
Sodium Decreased	152 (41)	50 (14)
Hematology		
Hemoglobin Decreased	198 (54)	36 (10)
Leukocytes Decreased	41 (11)	4 (1.1)
Lymphocytes Decreased	161 (44)	56 (15)
Neutrophil Decreased	38 (10)	18 (4.9)
Platelet Decreased	55 (15)	6 (1.6)

Microsatellite Instability-High Cancer (MSI-H)

Laboratory abnormalities (worsened from baseline in ≥ 20% of patients), reported in KEYNOTE-158 and KEYNOTE-164 in patients with MSI-H cancer are presented in Table 25.

Table 25: Laboratory Abnormalities Increased from Baseline in ≥ 20% of Patients with MSI-H

Laboratory Test	KEYTRUDA® 200 mg every 3 weeks n=155	
	All Grades n (%)	Grades 3-4 n (%)
Alanine Aminotransferase Increased	40 (25.8)	10 (6.5)
Albumin Deacreased	54 (34.8)	5 (3.2)
Alkaline Phosphatase Increased	54 (34.8)	11 (7.1)
Aspartate Aminotransferase Increased	44 (28.3)	7 (4.5)
Calcium Decreased	43 (27.7)	0
Glucose Increased	80 (51.6)	12 (7.7)
Hemoglobin Decreased	73 (47.1)	12 (7.7)
Lymphocytes Decreased	53 (34.2)	12 (7.7)
Potassium Increased	32 (20.6)	3 (1.9)
Sodium Decreased	43 (27.7)	10 (6.5)

Clinical Trial Adverse Reactions (Pediatrics)

In a study, 87 pediatric patients (36 children ages 9 months to less than 12 years and 51 adolescents ages 12 years to 18 years) with advanced melanoma, lymphoma, or PD-L1 positive advanced, relapsed, or refractory solid tumours were administered KEYTRUDA® 2 mg/kg every 3 weeks. Patients received KEYTRUDA® for a median of 3 doses (range 1-26 doses), with 71 patients (82%) receiving KEYTRUDA® for 2 doses or more. The concentrations of pembrolizumab in pediatric patients were comparable to those observed in adult patients at the same dose regimen of 2 mg/kg every 3 weeks.

The most common adverse reactions (reported in at least 20% of pediatric patients) were pyrexia, vomiting, fatigue, constipation, abdominal pain and nausea. Adverse reactions that occurred more frequently among pediatric patients (>15% increased) in comparison to a reference dataset of 2799 adult patients were: pyrexia (31%), vomiting 29.9 (%), abdominal pain (21.8%), and hypertransaminasemia (20.7%).

Post-Marketing Adverse Drug Reactions

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

Eye disorders: Vogt-Koyanagi-Harada syndrome

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

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

For treatment of Non-Small Cell Lung Carcinoma as Monotherapy and Urothelial Carcinoma

Select patients for treatment with KEYTRUDA® based on the presence of positive PD-L1 expression as determined by an experienced laboratory using a validated test in:

- metastatic NSCLC, using the Tumour Proportion Score (TPS) (See CLINICAL TRIALS, NSCLC)
- locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy, using the Combined Positive Score (CPS). CPS is the number of PD-L1 staining cells (tumour cells, lymphocytes, macrophages) divided by the total number of viable tumour cells, multiplied by 100 (See CLINICAL TRIALS, Urothelial Carcinoma).

A test authorized by Health Canada which is equivalent to that used in clinical trials should be required (See CLINICAL TRIALS).

MSI-H or dMMR colorectal cancer or endometrial cancer

Patients should be selected for treatment for MSI-H or dMMR solid tumours based on MSI-H or dMMR tumour status as determined by an experienced laboratory using a test authorized in Canada.

Recommended Dose and Dosage Adjustment (See WARNINGS AND PRECAUTIONS)

Recommended Dosage for Unresectable or Metastatic Melanoma

The current recommended dose of KEYTRUDA® is 200 mg fixed dose administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity. It is expected that the patient will continue to experience a similar safety and efficacy profile on this new regimen as they have had on the previous one of 2 mg/kg Q3W.

Recommended Dosage for Adjuvant Treatment of Melanoma
The recommended dose of KEYTRUDA® is 200 mg fixed dose administered as an intravenous infusion over 30 minutes every 3 weeks for up to one year or until disease recurrence or unacceptable toxicity.

Recommended Dosage for – Previously Untreated NSCLC as Monotherapy or in Combination with Chemotherapy
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.

When administering KEYTRUDA® as part of a combination with pemetrexed and platinum chemotherapy, KEYTRUDA® should be administered first. See also the Product Monographs for pemetrexed and the selected platinum chemotherapy.

NOC/c - Recommended Dosage for NSCLC – Previously Treated
The current recommended dose of KEYTRUDA® is 200 mg fixed dose administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity. It is expected that the patient will continue to experience a similar safety and efficacy profile on this new regimen as they have had on the previous one of 2 mg/kg Q3W.

NOC/c - Recommended Dosage for Hodgkin Lymphoma
The recommended dose of KEYTRUDA® is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks.

NOC/c - Recommended Dosage for PMBCL
The recommended dose of KEYTRUDA® administered as an intravenous infusion over 30 minutes every 3 weeks:

- in adult patients is 200 mg
- in pediatric patients is 2 mg/kg (up to a maximum of 200 mg)

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

NOC/c - Recommended Dosage for Urothelial Carcinoma – Not Eligible for Cisplatin-Containing Chemotherapy
The recommended dose of KEYTRUDA® is 200 mg 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 MSI-H
The recommended dose of KEYTRUDA® for adult patients is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

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.

Recommended Treatment Modifications

Table 26: Recommended treatment modifications for KEYTRUDA®

Immune-related adverse reactions	Severity	Treatment modification
Pneumonitis	Moderate (Grade 2)	Withhold until adverse reactions recover to Grade 0-1*
	Severe or life-threatening (Grade 3 or 4), or recurrent moderate (Grade 2)	Permanently discontinue
Colitis	Moderate or severe (Grade 2 or 3)	Withhold until adverse reactions recover to Grade 0-1*
	Life-threatening (Grade 4) or recurrent severe (Grade 3)	Permanently discontinue
Nephritis	Moderate (Grade 2) with creatinine > 1.5 to ≤ 3 times upper limit of normal (ULN)	Withhold until adverse reactions recover to Grade 0-1*
	Severe or life-threatening (Grade 3 or 4) (Grade ≥ 3 with creatinine > 3 times ULN)	Permanently discontinue
Endocrinopathies	Severe or life-threatening (Grade 3 or 4) 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 until adverse reactions recover to Grade 0-1* For patients with severe (Grade 3) or life-threatening (Grade 4) endocrinopathy that improved to Grade 2 or lower and is controlled with hormone replacement, if indicated, continuation of KEYTRUDA® may be considered after corticosteroid taper, if needed. Otherwise treatment should be discontinued. Hypothyroidism may be managed with replacement therapy without treatment interruption.
Hepatitis	Moderate (Grade 2) with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 to 5 times upper limit of normal (ULN) or total bilirubin > 1.5 to 3 times ULN	Withhold until adverse reactions recover to Grade 0-1*
	Grade ≥ 3 with AST or ALT > 5 times ULN or total bilirubin > 3 times ULN	Permanently discontinue
	For patients with liver metastasis who begin treatment with moderate (Grade 2) elevation of AST or ALT, if AST or ALT increases ≥ 50% relative to baseline and lasts ≥ 1 week	Permanently discontinue
Skin reactions or Stevens-Johnson	Severe skin reactions (Grade 3) or suspected SJS or TEN	Withhold until adverse reactions recover to Grade 0-1*

Immune-related adverse reactions	Severity	Treatment modification
syndrome (SJS) or toxic epidermal necrolysis (TEN)	Severe skin reactions (Grade 4) or confirmed SJS or TEN	Permanently discontinue
Other immune-related adverse reactions	Based on severity and type of reaction (Grade 2 or Grade 3)	Withhold until adverse reactions recover to Grade 0-1*
	Severe or life-threatening (Grade 3 or 4) myocarditis, encephalitis, or Guillain-Barré syndrome	Permanently discontinue
	Life-threatening (Grade 4) or recurrent severe (Grade 3)	Permanently discontinue
Infusion-related reactions	Severe or life-threatening (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).

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

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

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

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

Distribution: Consistent with a limited extravascular distribution, the volume of distribution of pembrolizumab at steady state is small (approximately 6.0L; Coefficient of Variation (CV): 20%). 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: Pembrolizumab clearance (CV%) is approximately 23% lower [geometric mean, 195 mL/day (40%)] after achieving maximal change at steady state compared with the first dose (252 mL/day [CV%: 37%]); this decrease in clearance with time is not considered clinically important. The geometric mean value (CV%) for the terminal half-life ($t_{½}$) is 22 days (32%).

Steady-state concentrations of pembrolizumab were reached by 16 weeks of repeated dosing with an every 3-week regimen and the systemic accumulation was 2.1-fold. The peak concentration (C_{max}), trough concentration (C_{min}), and area under the plasma concentration versus time curve at steady state (AUC_{ss}) of pembrolizumab increased dose proportionally in the dose range of 2 to 10 mg/kg every 3 weeks.

Table 27: Summary of Pharmacokinetic Parameters

Parameters		Mean*	%CV†
Half-life (days)		22	32%
Vdss (L) ‡		6.0	20%
CL (mL/day)	First dose	252	37%
	Steady state	195	40%
Time to steady state (weeks)		16	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 parameter in the current population pharmacokinetic model for pembrolizumab increases in a less than proportional manner with increasing body weight. Therefore, both body weight based dose and fixed-dose options provide similar control of variability in systemic pharmacokinetic exposures. 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. Based on population pharmacokinetic (PK) analysis, pembrolizumab exposures with weight-based dosing at 2 mg/kg every 3 weeks in patients aged 6-17 years are comparable to those of adults that receive the same dose. For patients aged 2-6 years, exposure is approximately 1.3 fold higher than in adults. For patients aged <2 years, exposure is predicted to be approximately 2.2 fold higher than in adults; this should be interpreted with caution as it is based on PK extrapolation.

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 sterile 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:

- adult patients with metastatic non-small cell lung carcinoma (NSCLC) as monotherapy, whose tumours express PD-L1 [(Tumour Proportion Score (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®.

- adult patients with refractory or relapsed classical Hodgkin Lymphoma (cHL), as monotherapy, who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV) or who are not ASCT candidates and have failed BV.

- adult and pediatric patients with refractory Primary Mediastinal B-cell Lymphoma (PMBCL) or who have relapsed after 2 or more lines of therapy, as monotherapy.

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

- adult patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)
    - colorectal cancer whose tumours have progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, as monotherapy, or
    - endometrial cancer whose tumours have progressed following prior therapy and who have no satisfactory alternative treatment options, as monotherapy.

KEYTRUDA® has been issued marketing authorization **without conditions** for :

- 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.

- 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.

- Adjuvant treatment of patients with Stage III melanoma with lymph node involvement who have undergone complete resection.

- Treatment of patients with metastatic non-small cell lung carcinoma (NSCLC) as monotherapy, in adults whose tumours have high PD-L1 expression (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.

- Treatment of patients with metastatic non-squamous NSCLC in combination with pemetrexed and platinum chemotherapy, in adults with no EGFR or ALK genomic tumour aberrations, and no prior systemic chemotherapy treatment for metastatic NSCLC.

- Treatment of patients with metastatic squamous NSCLC in combination with carboplatin and either paclitaxel or nab-paclitaxel, in adults with no prior systemic chemotherapy treatment for metastatic NSCLC.

- Treatment of patients with locally advanced or metastatic urothelial carcinoma as monotherapy, in adults who have disease progression during or following platinum-containing chemotherapy or within 12 months of completing neoadjuvant or adjuvant platinum-containing chemotherapy.

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).

CLINICAL TRIALS

Melanoma

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

Study demographics and trial design
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 28: 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.

Study Results

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 29 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 30: 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+)

* IRO = Independent radiology plus oncologist review using RECIST 1.1

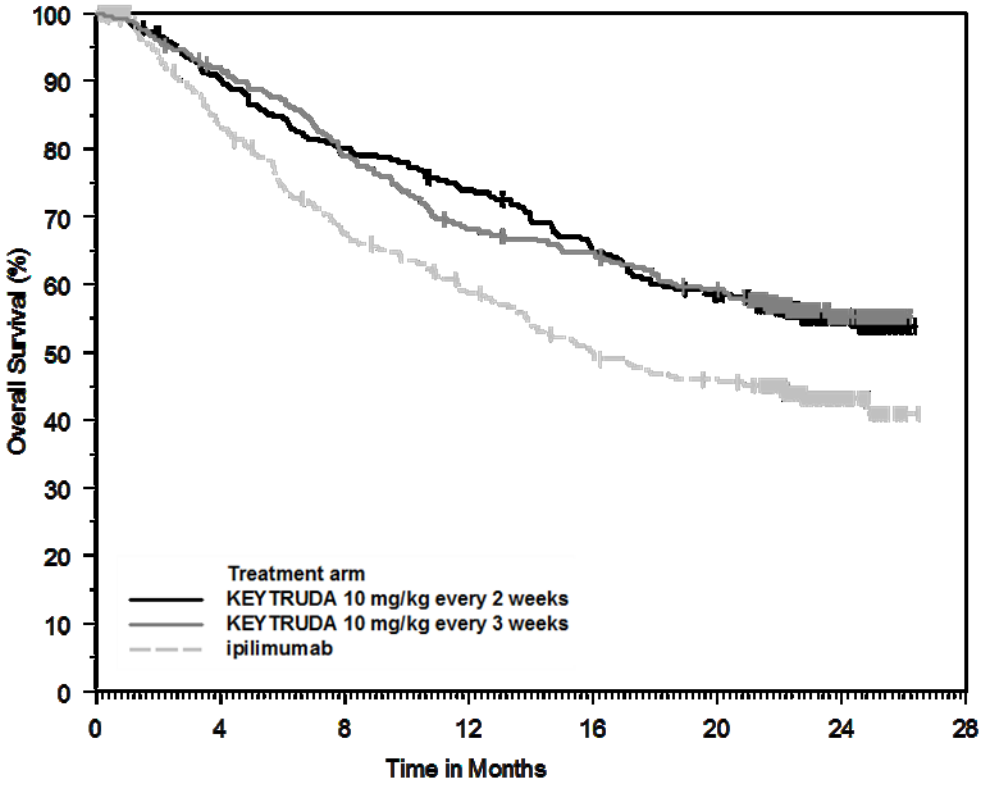
† Hazard ratio (KEYTRUDA® compared to ipilimumab) based on the Cox proportional hazard model stratified by line of therapy, ECOG performance status, and PD-L1 expression status

‡ Based on stratified Log rank test

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

NA = not available

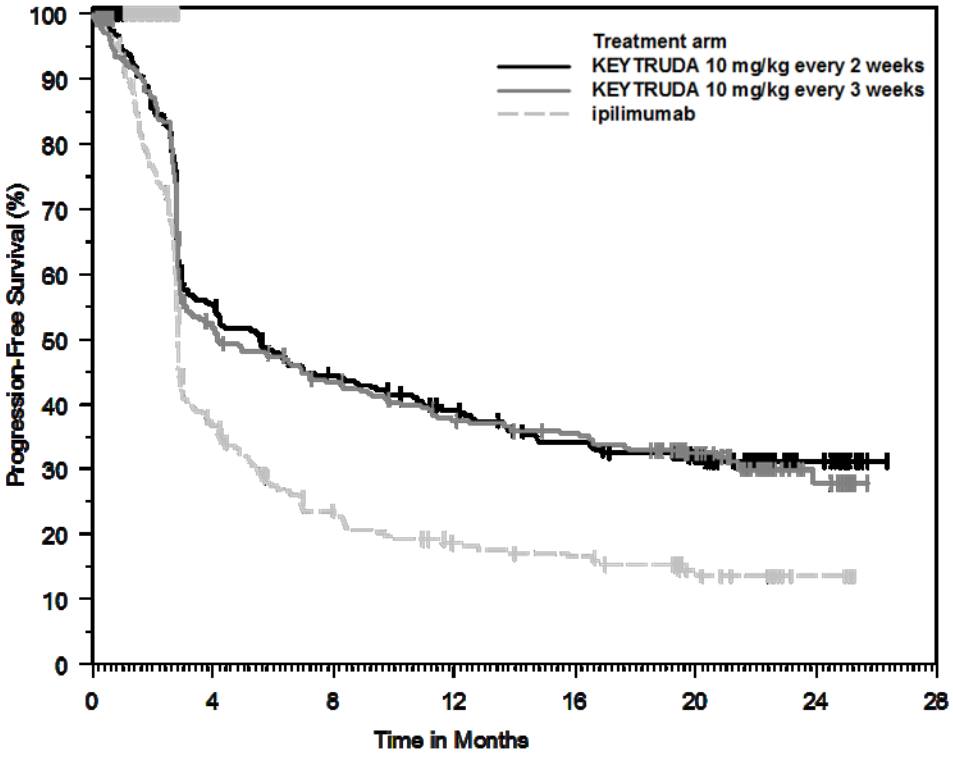
Figure 1: **Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-006 (intent to treat population) ***



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

**based on the final analysis with an additional follow-up of 9 months (total of 383 deaths as pre-specified in the protocol)*

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



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

**based on the final analysis with an additional follow-up of 9 months (total of 566 events)*

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

Study demographics and trial design

The safety and efficacy of KEYTRUDA® were investigated in KEYNOTE-002, a Phase II multicentre, randomized (1:1:1) 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. The treatment arms consisted of KEYTRUDA® 2 mg/kg or 10 mg/kg intravenously every 3 weeks or investigator's choice of any of the following chemotherapy regimens: dacarbazine 1000 mg/m2 intravenously every 3 weeks (26%), temozolomide 200 mg/m2 orally once daily for 5 days every 28 days (25%), carboplatin AUC 6 intravenously plus paclitaxel 225 mg/m2 intravenously every 3 weeks for four cycles then carboplatin AUC of 5 plus paclitaxel 175 mg/m2 every 3 weeks (25%), paclitaxel 175 mg/m2 intravenously every 3 weeks (16%), or carboplatin AUC 5 or 6 intravenously every 3 weeks (8%). Randomization was stratified by ECOG performance status (0 vs. 1), LDH levels (normal vs. elevated [≥110% ULN]) and BRAF V600 mutation status (wild-type [WT] or V600E). The trial included patients with unresectable or metastatic melanoma with progression of disease; refractory to two or more doses of ipilimumab (3 mg/kg or higher) and, if BRAF V600 mutation-positive, a BRAF or MEK inhibitor; and disease progression within 24 weeks following the last dose of ipilimumab. The study excluded patients with uveal melanoma and active brain metastasis, 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 received KEYTRUDA® until unacceptable toxicity; 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; withdrawal of consent; or physician's decision to stop therapy for the patient. Assessment of tumour status was performed at 12 weeks after randomization, 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.

Table31: 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)	62	60	63
Age (range)	15-87 years	27-89 years	27-87 years
Prior systemic therapies			
At least 2	77%	70%	74%
3 or more	33%	34%	30%
ECOG PS			
0	54%	55%	55%
1	44%	45%	45%
M-stage at study entry			
M0	1%	1%	1%
M1a	5%	7%	8%
M1b	12%	9%	8%
M1c	82%	82%	82%
Baseline LDH			
normal	56%	59%	61%
elevated	43%	40%	39%
BRAF status			
wild type	76%	78%	77%
V600 mutant	24%	22%	24%

* 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 32.5 months) and to KEYTRUDA® 10 mg/kg every 3 weeks was 4.8 months (range: 1 day to 31.8 months). The data described below reflect exposure to KEYTRUDA® 2 mg/kg in 37% of patients exposed to KEYTRUDA® for ≥6 months and in 22% of patients exposed for ≥12 months. In the KEYTRUDA® 10 mg/kg arm, 41% of patients were exposed to KEYTRUDA® for ≥6 months and 28% of patients were exposed to KEYTRUDA® for ≥12 months.

Study Results

The co-primary efficacy outcome measures were PFS (as assessed by IRO review using RECIST 1.1), and OS. Secondary efficacy outcome measures were, ORR and response duration. Table 32 summarizes key efficacy measures in patients previously treated with ipilimumab, and the Kaplan-Meier curves for PFS and OS are shown in Figures 3 and 4. Both pembrolizumab arms were superior to chemotherapy for PFS. There was no statistically significant difference between pembrolizumab and chemotherapy in the final OS analysis that was not adjusted for the potentially confounding effects of crossover. Of the patients randomized to the chemotherapy arm, 55% crossed over and subsequently received treatment with KEYTRUDA®.

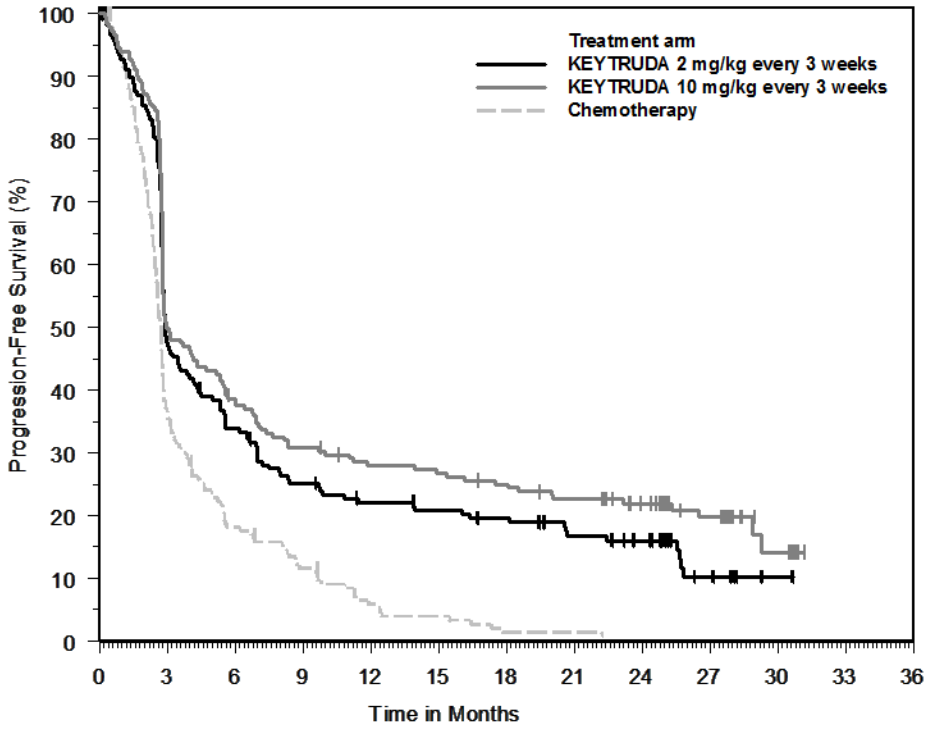
Table 32: Response to KEYTRUDA® 2 mg/kg or 10 mg/kg every 3 weeks in patients with unresectable or metastatic melanoma in KEYNOTE-002

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)
OS*			
Number (%) of patients with event	123 (68%)	117 (65%)	128 (72%)
Hazard ratio[†] (95% CI)	0.86 (0.67, 1.10)	0.74 (0.57, 0.96)	--
p-Value[‡]	0.117	0.011[-#]	--
Median in months (95% CI)	13.4 (11.0, 16.4)	14.7 (11.3, 19.5)	11.0 (8.9, 13.8)

* Based on final analysis
† Hazard ratio (KEYTRUDA® compared to chemotherapy) based on the stratified Cox proportional hazard model
‡ Based on stratified Log rank test
§ Based on second interim analysis
¶ IRO = Independent radiology plus oncologist review using RECIST 1.1
# Not statistically significant compared to multiplicity adjusted significance level of 0.01

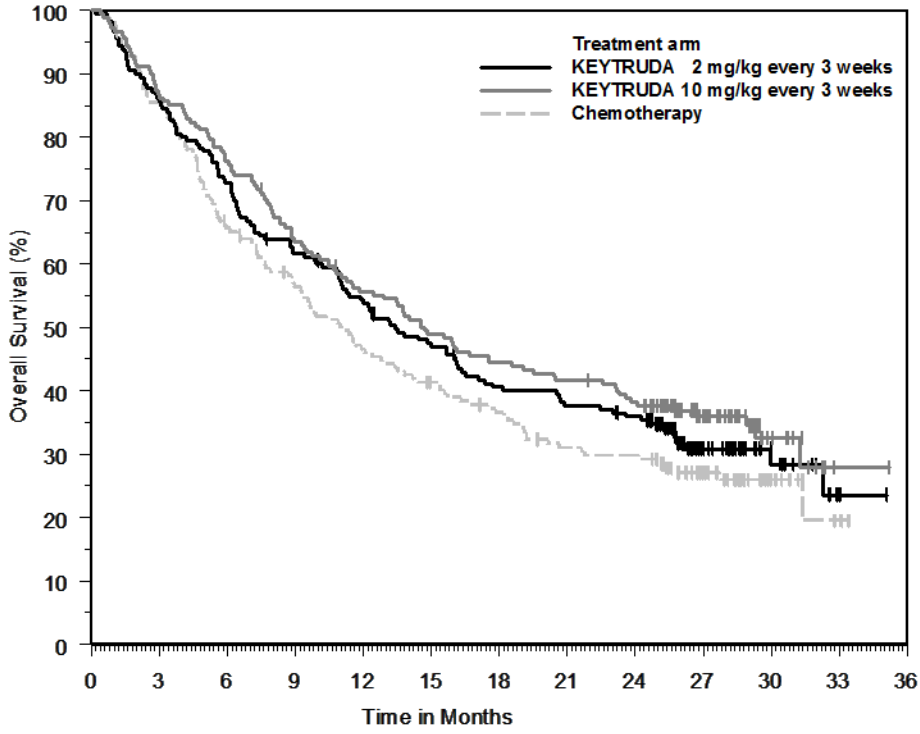
Based on the second interim analysis the ORR was 21% (95% CI: 15, 28), 25% (95% CI: 19, 32) and 4% (95%: CI 2, 9) for the KEYTRUDA® 2mg/kg every 3 weeks, KEYTRUDA® 10mg/kg every 3 weeks, and chemotherapy arms, respectively. ORR consisted of 4 (2%) complete responses and 34 (19%) partial responses for 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.

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



Number at Risk							
KEYTRUDA 2 mg/kg every 3 weeks:	180	59	36	29	19	1	0
KEYTRUDA 10 mg/kg every 3 weeks:	181	69	48	42	30	5	0
Chemotherapy:	179	31	9	2	1	0	0

Figure 4: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-002 (intent to treat population)



Number at Risk							
KEYTRUDA 2 mg/kg every 3 weeks:	180	131	95	70	61	11	0
KEYTRUDA 10 mg/kg every 3 weeks:	181	138	99	79	67	12	0
Chemotherapy:	179	115	80	60	48	9	0

Adjuvant Melanoma

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

Study demographics and trial design

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

Patients underwent imaging every 12 weeks after the first dose of KEYTRUDA® for the first two years, then every 6 months from year 3 to 5, and then annually.

Table 33: Baseline Characteristics in KEYNOTE-054

	KEYTRUDA® 200 mg every 3 weeks n=514	**Placebo n=505**
Men	63%	60%
Women	37%	40%
Age (median)	54 years	54 years
Age (range)	19 to 88 years	19 to 83 years
Age (≥ 65)	24%	25%
ECOG PS		
0	94%	94%
1	6%	6%
Stage		
IIIA (> 1 mm)	16%	16%
IIIB	46%	46%
IIIC (1-3 positive lymph nodes)	18%	18%
IIIC (≥ 4 positive lymph nodes)	20%	20%
BRAF Status		
Mutation Detected	48%	52%
Mutation Not Detected	45%	42%
Unknown	7%	6%
PD-L1 Status*		
Positive	83%	84%
Negative	11%	11%
Unknown	5%	5%

* Tumour PD-L1 expression was assessed by an immunohistochemistry research assay. Results were recorded as positive (≥ 1% PD-L1), negative (< 1% PD-L1) or unknown level of expression (indeterminate PD-L1).

The median duration of exposure to KEYTRUDA® was 11.7 months (range: 1 day to 21 months).

Study Results

The primary efficacy outcome measures were investigator-assessed recurrence free survival (RFS) in the ITT population and in the subgroup of patients with PD-L1 positive tumours. RFS was defined as the time between the date of randomization and the date of first recurrence (local, regional, or distant metastasis) or death, whichever occurs first. The trial demonstrated statistically significant improvement in RFS for patients randomized to the KEYTRUDA® arm compared with placebo. Efficacy results are summarized in Table 34 and Figure 5.

Table 34: Efficacy Results in KEYNOTE-054

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

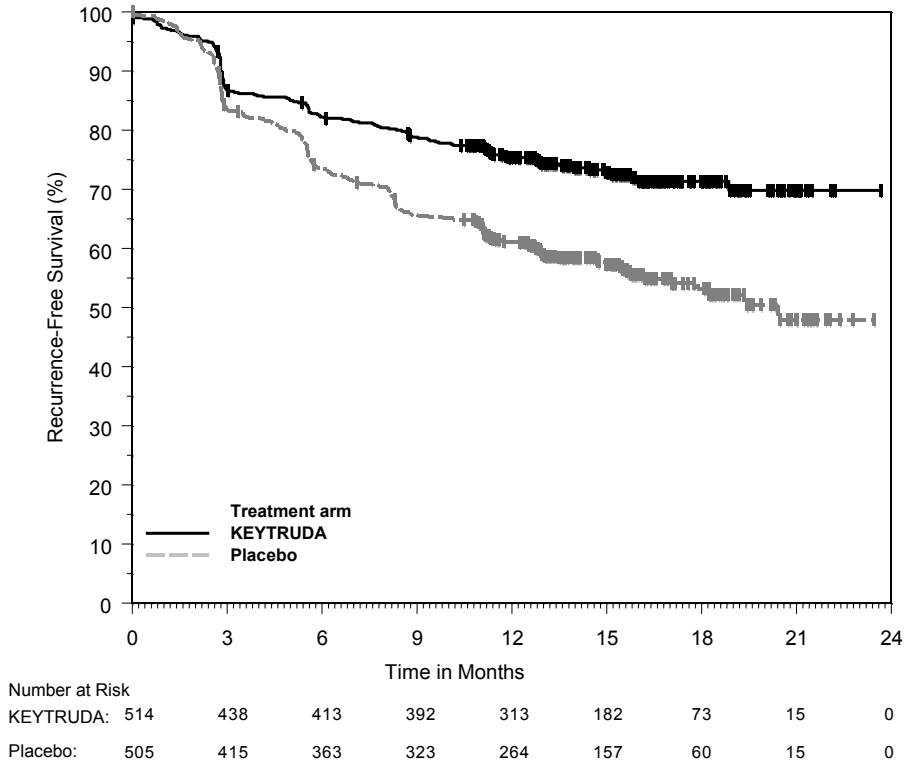
* Based on the stratified Cox proportional hazard model

† p-Value (based on stratified log rank test) is compared with 0.008 of the allocated alpha for this interim analysis.

NR = not reached

For patients with PD-L1 positive tumours, the RFS HR (KEYTRUDA® versus placebo) was 0.54 (95% CI: 0.42, 0.69). The RFS benefit for KEYTRUDA® compared to placebo was observed regardless of tumour PD-L1 expression or BRAF mutation status.

Figure 5: Kaplan-Meier Curve for Recurrence-Free Survival in KEYNOTE-054 (intent to treat population)



Non-Small Cell Lung Carcinoma

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

Study demographics and trial design
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 35: 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.

Study Results

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 36summarizes key efficacy measures for the entire ITT population.

Table 36: 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

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).

The final OS analysis was performed at a median follow-up of 25 months after 169 patient events (73 for KEYTRUDA® and 96 for chemotherapy). Median OS was 30.0 months (95% CI: 18.3, NA) for KEYTRUDA® and 14.2 months (95% CI: 9.8, 19.0) for chemotherapy. The OS HR was 0.63 (95% CI: 0.47, 0.86). See Figure 6.

Figure 6: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-024 (Intent to Treat Population)

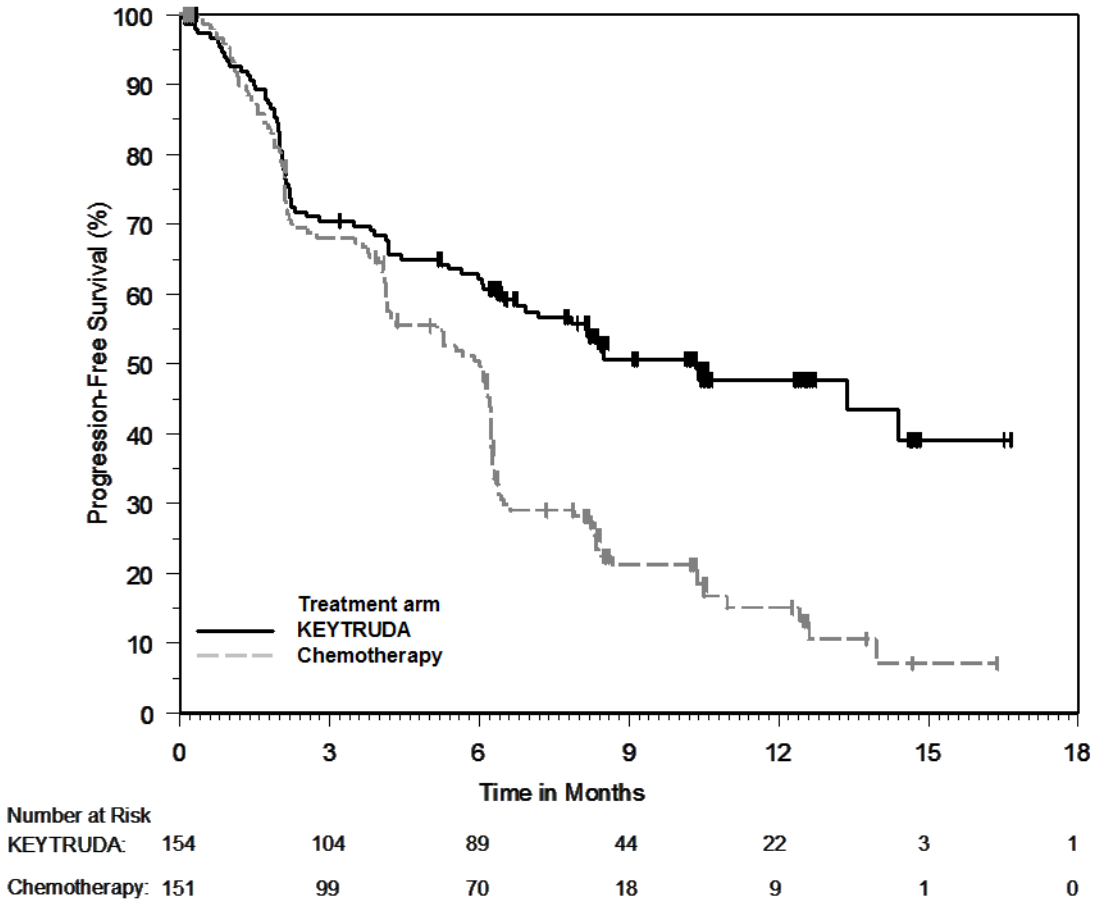
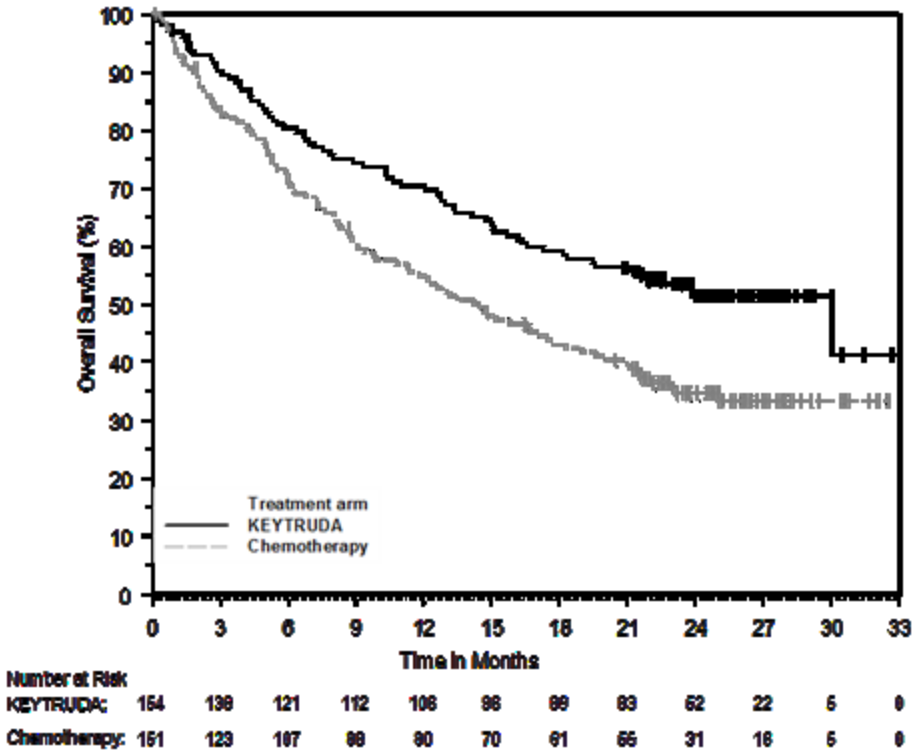


Figure 7: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-024 (Intent to Treat Population)



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

Study demographics and trial design

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

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

Treatment with KEYTRUDA® continued until RECIST 1.1-defined progression of disease as determined by the investigator, unacceptable toxicity, or a maximum of 24 months.

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

A total of 67 patients in the placebo plus chemotherapy arm crossed over to receive monotherapy KEYTRUDA® at the time of disease progression and 18 additional patients received a checkpoint inhibitor as subsequent therapy.

Table 37: Baseline Characteristics in KEYNOTE-189

	KEYTRUDA® + Pemetrexed + Platinum Chemotherapy n=410	**Placebo + Pemetrexed + Platinum Chemotherapy n=206**
Men	62%	53%
Women	38%	47%
Age (median)	65	63.5
Age (range)	34-84 years	34-84 years
ECOG PS		
0	45%	39%
1	54%	61%
2	<1%	0%
Geographic region		
East Asia	1%	3%
Non-East Asia	99%	97%
PD-L1 status		
< 1%	31%	31%
≥ 1%	63%	62%
Not evaluable	6%	7%
Brain metastases (treated or untreated) at baseline		
Yes	18%	17%
No	82%	83%
Platinum chemotherapy		
Cisplatin	28%	28%
Carboplatin	72%	72%

Study Results

The primary efficacy outcome measures were OS and PFS (as assessed by BICR using RECIST 1.1). Secondary efficacy outcome measures were ORR and response duration, as assessed by BICR using RECIST 1.1. The median follow-up time was 10.5 months (range: 0.2 – 20.4 months). Table 38 summarizes key efficacy measures.

Table 38: Response to KEYTRUDA®, pemetrexed, and platinum chemotherapy in patients with non-squamous NSCLC in KEYNOTE-189

Endpoint	KEYTRUDA® + Pemetrexed + Platinum Chemotherapy n=410	Placebo + Pemetrexed + Platinum Chemotherapy n=206
Primary Efficacy Outcome Measure OS		
Number (%) of patients with event	127 (31%)	108 (52%)
Hazard ratio* (95% CI)	0.49 (0.38, 0.64)	
p-Value†	<0.00001	
Median in months (95% CI)	Not reached (NA, NA)	11.3 (8.7, 15.1)
OS rate at 6 months (%)	85%	72%
OS rate at 9 months (%)	78%	56%
Primary Efficacy Outcome Measure PFS		
Number (%) of patients with event	244 (60%)	166 (81%)
Hazard ratio* (95% CI)	0.52 (0.43, 0.64)	
p-Value†	<0.00001	
Median in months (95% CI)	8.8 (7.6, 9.2)	4.9 (4.7, 5.5)
PFS rate at 6 months (%)	66%	40%
PFS rate at 9 months (%)	48%	25%
Secondary Efficacy Outcome Measure Objective Response Rate		
ORR‡ % (95% CI)	48% (43, 53)	19% (14, 25)
Complete response %	0.5%	0.5%
Partial response %	47%	18%
p-Value§	<0.0001	
Secondary Efficacy Outcome Measure Response duration		
Median in months (range)	11.2 (1.1+, 18.0+)	7.8 (2.1+, 16.4+)
% with duration ≥6 months¶	81%	63%
% with duration ≥9 months¶	60%	44%

* Based on the stratified Cox proportional hazard model
† Based on stratified log-rank test
‡ Based on patients with a best overall response as confirmed complete or partial response
§ Based on Miettinen and Nurminen method stratified by PD-L1 status, platinum chemotherapy and smoking status
¶ Based on Kaplan-Meier estimation
NA = not available

Figure 8: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-189 (intent to treat population)

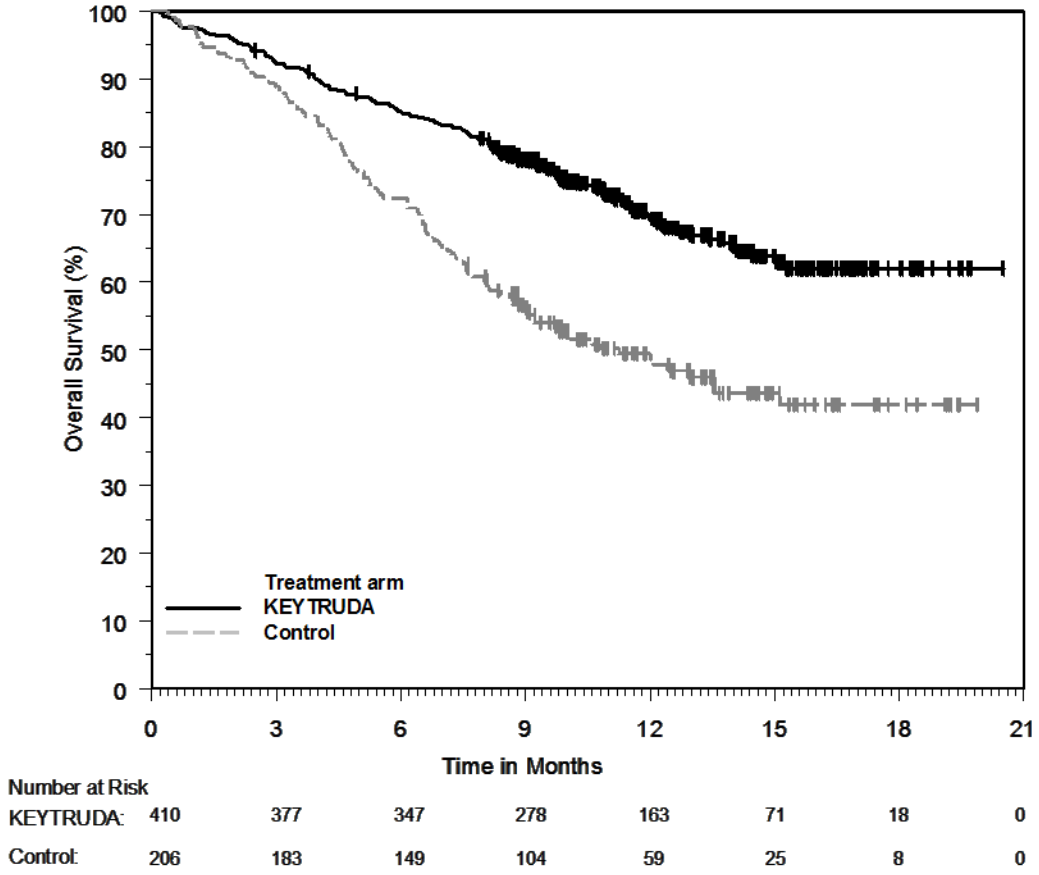
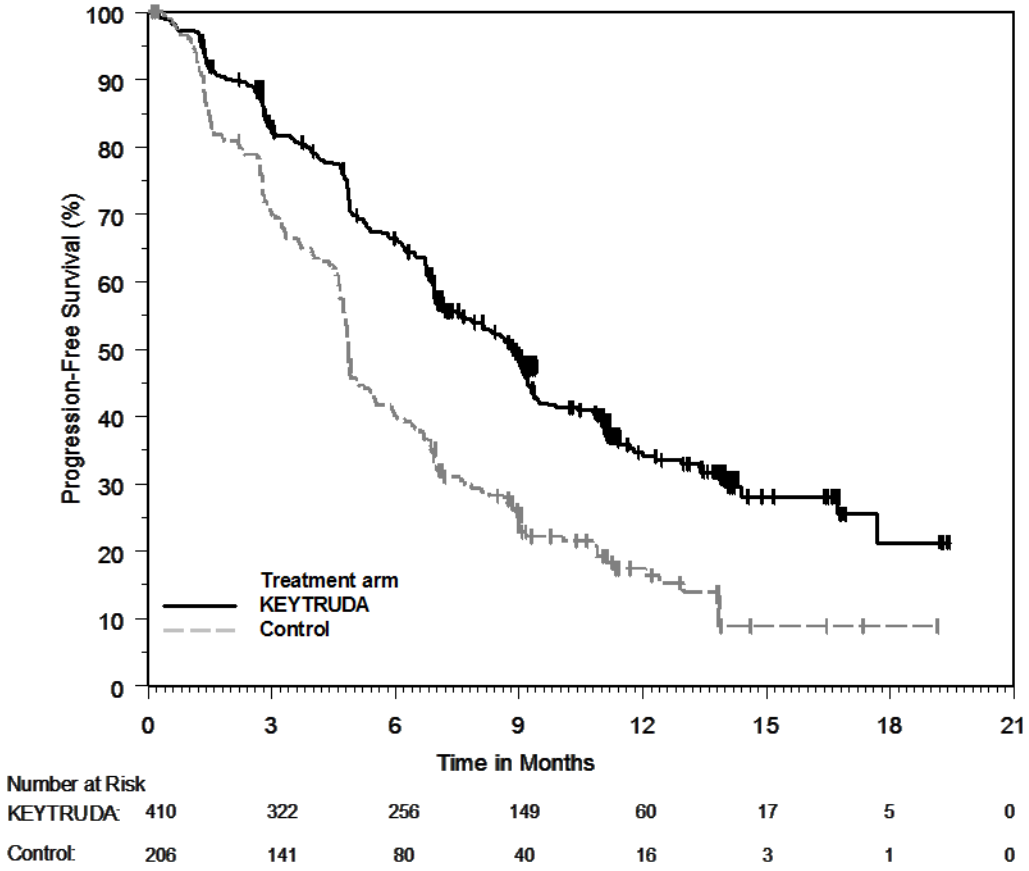


Figure 9: Kaplan-Meier curve for progression-free survival by treatment arm in KEYNOTE-189 (intent to treat population)



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

Study demographics and trial design

The efficacy of KEYTRUDA® in combination with carboplatin and either paclitaxel or nab-paclitaxel was investigated in Study KEYNOTE-407, a randomized, double-blind, multicenter, placebo-controlled study. The key eligibility criteria for this study were metastatic squamous NSCLC, regardless of tumour PD-L1 expression status, and no prior systemic treatment for metastatic disease. Patients with autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Randomization was stratified by tumour PD-L1 expression (TPS <1% [negative] vs. TPS ≥1%), investigator's choice of paclitaxel or nab-paclitaxel, and geographic region (East Asia vs. non-East Asia). Patients were randomized (1:1) to one of the following treatment arms; all study medications were administered via intravenous infusion.

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

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

Treatment with KEYTRUDA® or placebo continued until RECIST 1.1-defined progression of disease as determined by blinded independent central review (BICR), unacceptable toxicity, or a maximum of 24 months. Administration of KEYTRUDA® was permitted beyond RECIST-defined disease progression if the patient was clinically stable and deriving clinical benefit as determined by the investigator. Treatment with KEYTRUDA® could be reinitiated for subsequent disease progression and administered for up to 1 additional year.
Patients in the placebo arm were offered KEYTRUDA® as a single agent at the time of disease progression.

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

Table 39: Baseline Characteristics in KEYNOTE-407

	KEYTRUDA® + Carboplatin + Paclitaxel or Nab-Paclitaxel n=278	**Placebo + Carboplatin + Paclitaxel or Nab-Paclitaxel n=281**
Men	79%	84%
Women	21%	16%
Age (median)	65	65
Age (range)	29-87 years	36-88 years
ECOG PS		
0	26%	32%
1	74%	68%
Geographic region		
East Asia	19%	19%
Non-East Asia	81%	81%
PD-L1 status		
< 1%	34%	35%
≥ 1%	63%	63%
Not evaluable	3%	2%
Brain metastases (treated or untreated) at baseline		
Yes	7%	9%
No	93%	91%
Taxane chemotherapy		
Paclitaxel	61%	59%
Nab-Paclitaxel	39%	41%

Study Results

In KEYNOTE-407, there was a statistically significant improvement in OS, PFS and ORR in patients randomized to KEYTRUDA® in combination with carboplatin and either paclitaxel or nab-paclitaxel compared with patients randomized to placebo with carboplatin and either paclitaxel or nab-paclitaxel (see Table 40 and Figures 10 and 11).

Table 40: Efficacy Results in KEYNOTE-407

Endpoint	KEYTRUDA® Carboplatin Paclitaxel/Nab-Paclitaxel n=278	Placebo Carboplatin Paclitaxel/Nab-Paclitaxel n=281
Primary Efficacy Outcome Measure OS		
Number of events (%)	85 (31%)	120 (43%)
Median in months (95% CI)	15.9 (13.2, NA)	11.3 (9.5, 14.8)
Hazard ratio* (95% CI)	0.64 (0.49, 0.85)	
p-Value (stratified log rank)	0.0008	
Primary Efficacy Outcome Measure PFS†		
Number of events (%)	152 (55%)	197 (70%)
Median in months (95% CI)	6.4 (6.2, 8.3)	4.8 (4.3, 5.7)
Hazard ratio* (95% CI)	0.56 (0.45, 0.70)	
p-Value(stratified log rank)	<0.0001	
Secondary Efficacy Outcome Measure Objective Response Rate†		
Objective response rate ‡	58%	38%
(95% CI)	(52, 64)	(33, 44)
Secondary Efficacy Outcome Measure Duration of Response†		
Median duration of response in months (range)§	7.7 (1.1+, 14.7+)	4.8 (1.3+, 15.8+)
% with duration ≥ 6 months¶	62%	40%

* Based on the stratified Cox proportional hazard model

† Assessed by BICR using RECIST 1.1

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

§ '+' indicates there is no progressive disease by the time of last disease assessment

¶ Based on Kaplan-Meier estimation

NA = not available

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

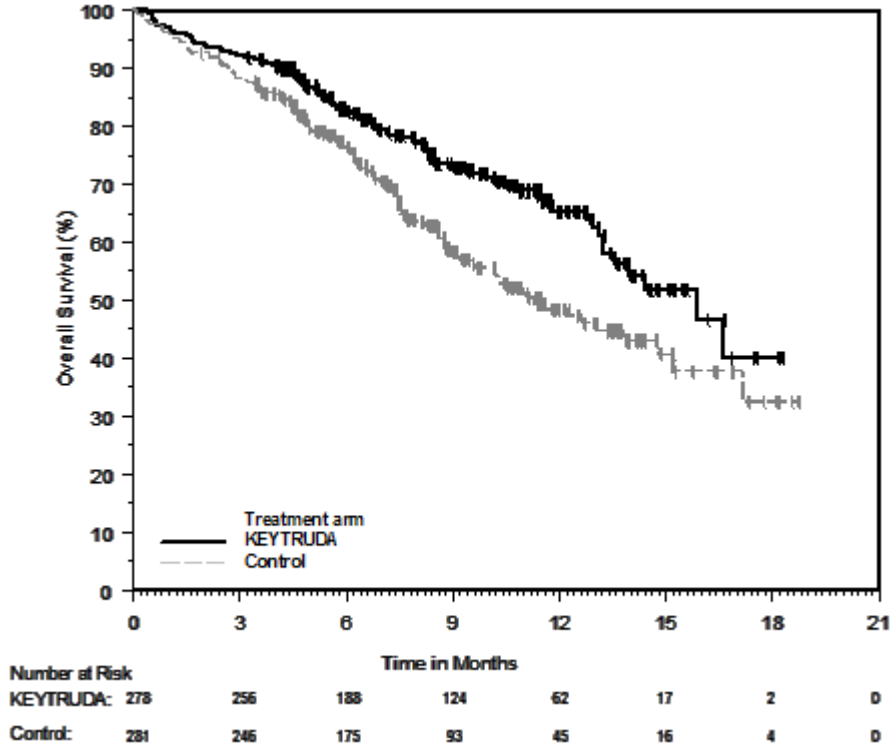
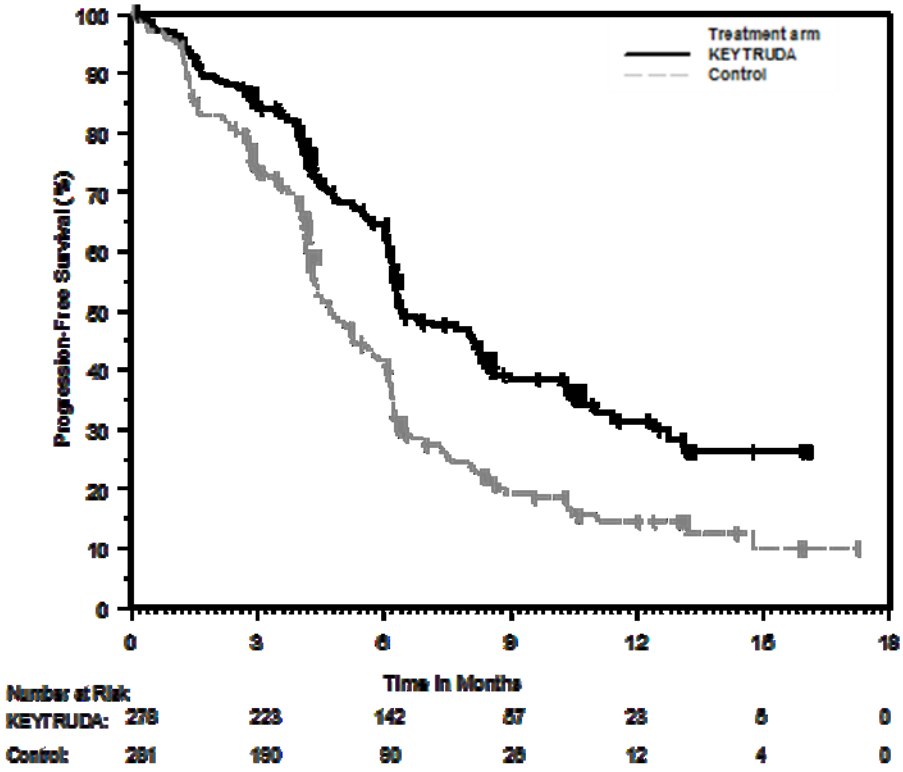


Figure 11: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-407



NOC/c *KEYNOTE-010: Controlled trial in NSCLC patients previously treated with chemotherapy*

Study demographics and trial design

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 41: 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).

Study Results

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%. Tables 42 and 43 summarize key efficacy measures for the entire ITT population (TPS ≥1%) and for the subgroup of patients with TPS ≥50%. Kaplan-Meier curves for OS (TPS ≥1% and TPS ≥50%) are shown in Figures 12 and 14 Kaplan-Meier curves for PFS (TPS ≥1% and TPS ≥50%) are shown in Figures 13 and 15.

Table 42: 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.

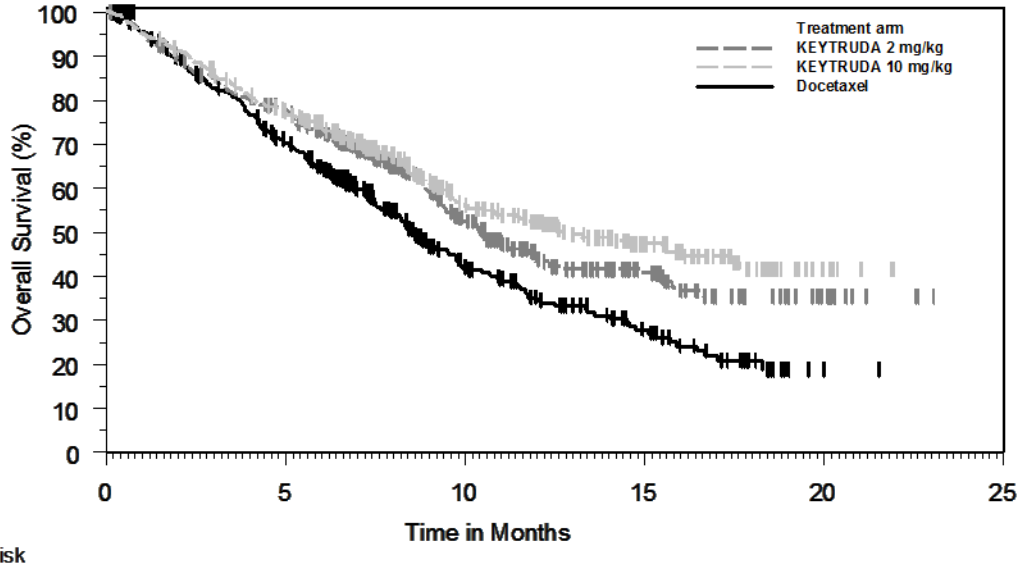
† Based on one-sided stratified Log rank test

‡ 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

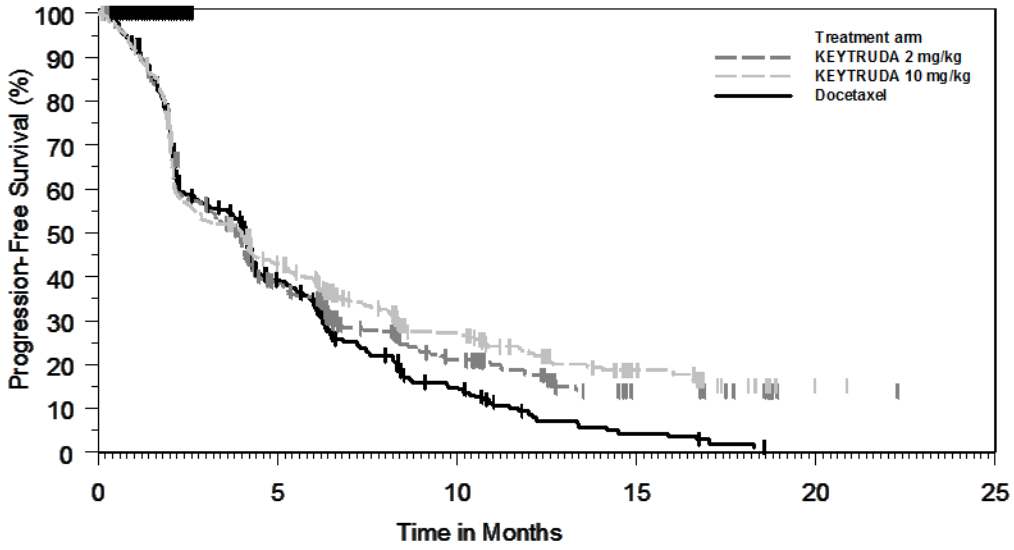
¶ All responses were partial responses.

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



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

Figure 13: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-010 (TPS ≥ 1%, Intent to Treat Population)



Number at Risk						
KEYTRUDA 2 mg/kg:	344	123	46	12	1	0
KEYTRUDA 10 mg/kg:	346	137	60	19	1	0
Docetaxel:	343	103	27	6	0	0

Table 43: 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

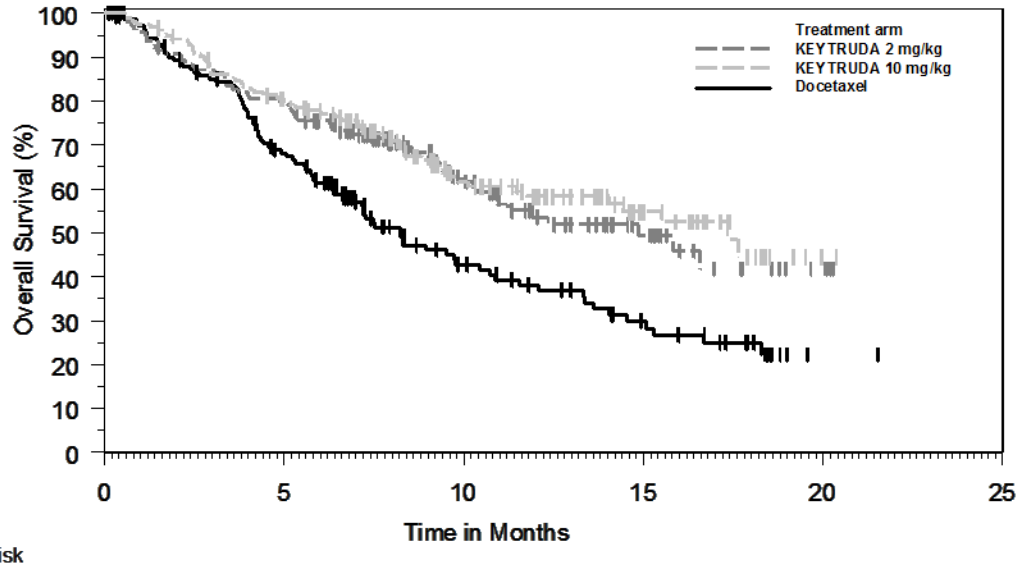
‡ Statistically significant based on a pre-specified α level of 0.00825 for the two pairwise comparisons versus docetaxel using a Hochberg procedure

§ 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

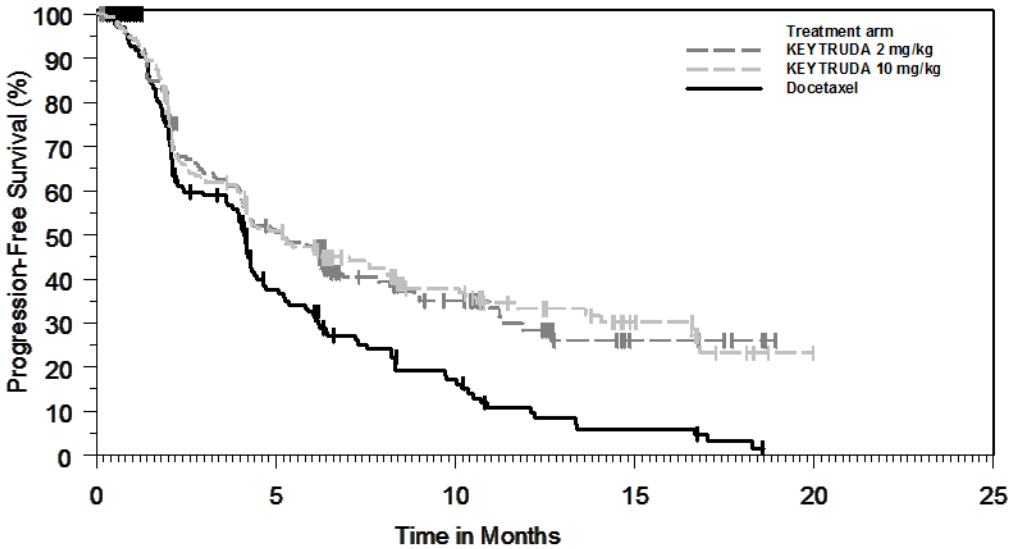
All responses were partial responses.

Figure 14: 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 15: 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).

NOC/c Classical Hodgkin Lymphoma

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

Study demographics and trial design

The efficacy of KEYTRUDA® was investigated in 241 patients with refractory classical Hodgkin Lymphoma, or who have relapsed after 3 or more prior lines of therapy including autologous stem cell transplantation (ASCT), enrolled in two multicenter, nonrandomized, open-label studies (KEYNOTE-013 and KEYNOTE-087). Both studies included patients regardless of PD-L1 expression. Patients with active, non-infectious pneumonitis, an allogeneic hematopoietic stem cell transplant within the past 5 years (or greater than 5 years but with GVHD), active autoimmune disease or a medical condition that required immunosuppression were ineligible for either trial. Patients received KEYTRUDA® 10 mg/kg every 2 weeks (n=31; KEYNOTE-013) or 200 mg every 3 weeks (n=210; KEYNOTE-087) until unacceptable toxicity or documented disease progression. Patients without disease progression could be treated for up to 24 months. Treatment with KEYTRUDA® could be reinitiated for subsequent disease progression and administered for up to 1 additional year. Response was assessed using the revised lymphoma criteria by PET CT scans, with the first planned post-baseline assessment at week 12. The major efficacy outcome measures (ORR, CRR, and duration of response) were assessed by blinded independent central review according to the 2007 revised International Working Group (IWG) criteria. Secondary efficacy outcome measures were PFS and OS.

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

Among KEYNOTE-087 patients, the baseline characteristics were median age 35 years (9% age 65 or older); 54% male; 88% White; and 49% and 51% had an ECOG performance status 0 and

1, respectively. The median number of prior lines of therapy administered for the treatment of cHL was 4 (range 1 to 12). Eighty-one percent were refractory to at least one prior therapy, including 35% who were refractory to first line therapy. Sixty-one percent of patients had received auto-SCT, 38% were transplant ineligible; 17% had no prior brentuximab vedotin use; and 36% of patients had prior radiation therapy.

Study Results
Efficacy results are summarized in Table 44.

Table 44: Efficacy Results in Patients with refractory or relapsed classical Hodgkin Lymphoma

Endpoint	KEYNOTE-013 n=31	KEYNOTE-087 n=210
Objective Response Rate*		
ORR %, (95% CI)	58% (39.1, 75.5)	68% (61.3, 74.3)
Complete Remission	19%	22%
Partial Remission	39%	46%
Response Duration*		
Median in months (range)	Not reached (0.0+, 21.4+)†	Not reached (0.0+, 8.3) ‡

* Assessed by blinded independent central review according to the 2007 revised International Working Group (IWG) criteria
† Based on patients (n=18) with a response by independent review.
‡ Based on patients (n=143) with a response by independent review

NOC/c Primary Mediastinal B-cell Lymphoma

KEYNOTE-170: Open-label study in patients with relapsed or refractory PMBCL

Study demographics and trial design
The efficacy of KEYTRUDA® was investigated in KEYNOTE-170, a multicenter, open-label, single-arm trial in 29 patients with relapsed or refractory PMBCL, Patients with active, non-infectious pneumonitis, an allogeneic HSCT within the past 5 years (or greater than 5 years but with symptoms of GVHD), active autoimmune disease, a medical condition that required immunosuppression, or an active infection requiring systemic therapy were ineligible for the trial. Patients received KEYTRUDA® 200 mg every 3 weeks until unacceptable toxicity or documented disease progression, or for up to 24 months in patients that did not progress. Disease assessment was performed every 12 weeks. The major efficacy outcome measures (ORR, CRR, PFS and duration of response) were assessed by blinded independent central review according to the 2007 revised IWG criteria.

Among the 29 patients, the baseline characteristics were: median age of 33 years (range: 20 to 58), 0% age 65 or older; 45% male; 93% White; 38% had an ECOG performance status (PS) of 0 and 62% had an ECOG PS of 1. The median number of prior lines of therapy administered for the treatment of PMBCL was 3 (range 2 to 8). Sixty-nine percent were refractory to the last prior therapy, including 38% with primary refractory disease and 79% whose disease was chemo-refractory to any prior regimen. Thirty-four percent of patients had undergone prior auto-HSCT, 66% did not receive prior transplant; and 38% of patients had prior radiation therapy.

Study Results
Efficacy from interim analysis was based on overall response rate (ORR) with the median follow-up duration of 6.6 months. The median duration of response was not reached. The efficacy results for KEYNOTE-170 are summarized in Table 45. For the 12 responders, the median time to first objective response was 2.9 months (range 2.4 to 8.5 months).

Table 45: Efficacy Results in Patients with refractory or relapsed PMBCL

Endpoint	KEYNOTE-170* n=29
Objective Response Rate*	
ORR %, (95% CI)	41% (24, 61)
Complete Remission	14%
Partial Remission	28%
Response Duration*	
Median in months (range)	Not reached (1.1+,8.2+)†

* Assessed by blinded independent central review according to the 2007 revised IWG criteria
† Based on patients (n=12) with a response by independent review

Urothelial Carcinoma

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

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

Patients were randomized to receive either KEYTRUDA® 200 mg every 3 weeks (n=270) or investigator's choice of any of the following chemotherapy regimens all given intravenously every 3 weeks (n=272): paclitaxel 175 mg/m^2 (n=84), docetaxel 75 mg/m^2 (n=84), or vinflunine 320 mg/m^2 (n=87). Patients received KEYTRUDA® until unacceptable toxicity or disease progression. Clinically stable patients with initial evidence of disease progression were permitted to remain on treatment until disease progression was confirmed. Patients without disease progression were treated for up to 24 months. Treatment with pembrolizumab could be reinitiated for subsequent disease progression and administered for up to 1 additional year. Assessment of tumour status was performed at 9 weeks after randomization, then every 6 weeks through the first year, followed by every 12 weeks thereafter.

The major efficacy outcomes were OS and PFS as assessed by BICR per RECIST v1.1 at the time of the second interim analysis using the intent-to-treat (ITT) population. These outcomes were also assessed for the subgroup defined by PD-L1 CPS cutoff of ≥ 10 (PD-L1 positive). Additional efficacy outcome measures were ORR as assessed by BICR per RECIST v1.1 and duration of response.

Among the 542 randomized patients, the study population characteristics were: median age 66 years (range: 26 to 88), 58% age 65 or older; 74% male; 72% White and 23% Asian; 57% ECOG performance status of 1 or greater; and 96% M1 disease and 4% M0 disease. Eight-seven percent of patients had visceral metastases, including 34% with liver metastases. Eighty-six percent had a primary tumour in the lower tract and 14% had a primary tumour in the upper tract. Fifteen percent of patients had disease progression following prior platinum-containing neoadjuvant or adjuvant chemotherapy as the most recent line of therapy. Twenty-one percent had received 2 or more prior systemic regimens in the metastatic setting. Seventy-six percent of patients received prior cisplatin, 23% had prior carboplatin, and 1% were treated with other platinum-based regimens.

At a pre-specified interim analysis, the median follow-up time for 270 patients treated with KEYTRUDA® was 10.3 months. The study demonstrated statistically significant improvements in OS and ORR for patients in the ITT population randomized to KEYTRUDA® as compared to chemotherapy. No statistically significant difference was demonstrated between KEYTRUDA® and chemotherapy with respect to PFS. Table 46 summarizes the key efficacy measures and Figure 16 shows the Kaplan-Meier survival curve for OS.

Table 46: Efficacy Results in Patients with Urothelial Carcinoma Previously Treated with Chemotherapy

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

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

† Based on stratified Log rank test

‡ Assessed by BICR using RECIST 1.1

§ Based on method by Miettinen and Nurminen

£ p-value is compared with 0.0123 of the allocated alpha for the interim analysis

€ p-value is compared with 0.0151 of the allocated alpha for the interim analysis

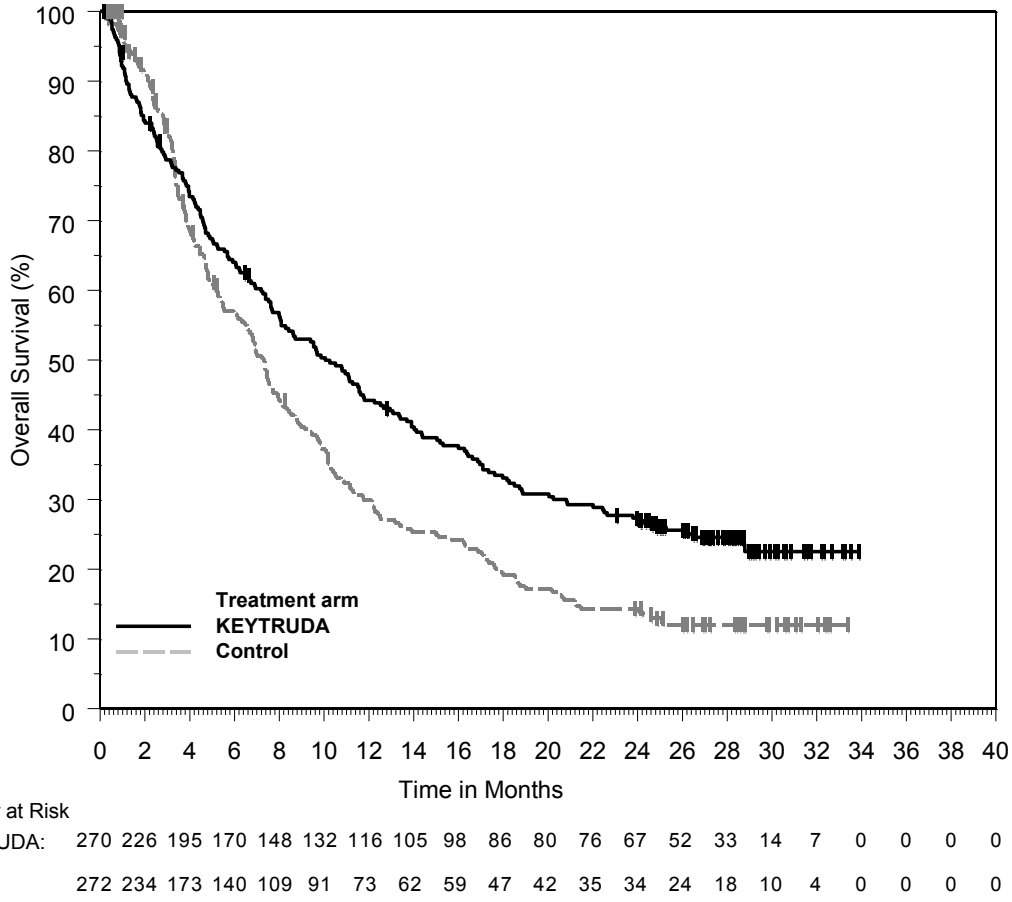
¥ p-value is compared with 0.0170 of the allocated alpha for the interim analysis

The interim analysis also demonstrated a statistically significant improvement in OS favouring KEYTRUDA® for patients whose tumours tested positive for PD-L1 CPS ≥ 10% [Hazard Ratio (HR) 0.57 (95% CI 0.37, 0.88)]. As with the ITT population, there was no statistically significant difference between KEYTRUDA® and chemotherapy with respect to PFS among patients whose tumours tested positive for PD-L1.

In exploratory subgroup analyses, a reduced survival benefit of KEYTRUDA® monotherapy compared to chemotherapy was observed in patients who were never smokers (n=187), who were classified as Non-White (n=133) (92% of whom identified with Asian ethnicity), or who lived in the East-Asia geographic region (n=106). In never smokers, the HR for OS was 1.06 (95% CI: 0.72, 1.55) and the HR for PFS was 1.13 (95% CI: 0.80, 1.60). In Non-White subjects, the HR for OS was 1.12 (95% CI 0.70, 1.79) and the HR for PFS was 1.48 (95% CI 0.99, 2.23). In subjects from the East-Asia geographic region, the HR for OS was 1.25 (95% CI: 0.72, 2.18) while the HR for PFS was 1.68 (95% CI: 1.05, 2.67).

The final descriptive analysis for OS was performed 13.6 months after the interim analysis with 419 patient events (200 for KEYTRUDA® and 219 for chemotherapy). Median OS was 10.1 months (95% CI: 8.0, 12.3) for KEYTRUDA® and 7.3 months (95% CI: 6.1, 8.1) for chemotherapy. The OS HR was 0.70 (95% CI: 0.57, 0.85). See Figure 16 for OS curve. In the final analysis of PFS there was no statistically significant difference between KEYTRUDA® and chemotherapy.

Figure 16: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-045 (Intent to Treat Population) *



Number at Risk

KEYTRUDA:	270	226	195	170	148	132	116	105	98	86	80	76	67	52	33	14	7	0	0	0	0
Control:	272	234	173	140	109	91	73	62	59	47	42	35	34	24	18	10	4	0	0	0	0

based on the final analysis (a total of 419 deaths)

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

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

Patients received KEYTRUDA® 200 mg every 3 weeks until unacceptable toxicity or disease progression. If benefits were deemed to outweigh the risks based on clinical judgement, clinically stable patients with initial radiographic disease progression could continue treatment until disease progression was confirmed. Patients without disease progression could be treated for up to 24 months. Assessment of tumour status was performed at 9 weeks after the first dose, then every 6 weeks through the first year, followed by every 12 weeks thereafter.

Among the 370 treated patients, baseline characteristics were: median age 74 years (82% age 65 or older); 77% male; and 89% White and 7% Asian. Eighty-one percent had a primary tumour in the lower tract, and 19% of patients had a primary tumour in the upper tract. Eighty-eight percent

had M1 disease, 12% had M0 disease. Eighty-five percent of patients had visceral metastases, including 21% with liver metastases. Ninety percent of patients were treatment naïve, and 10% received prior adjuvant or neoadjuvant platinum-based chemotherapy. Reasons for cisplatin ineligibility included: 50% with baseline creatinine clearance of <60 mL/min, 32% with ECOG performance status of 2, 9% with ECOG performance status of 2 and baseline creatinine clearance of <60 mL/min, and 9% with other reasons (Class III heart failure, Grade 2 or greater peripheral neuropathy, and Grade 2 or greater hearing loss). In the study, PD-L1 status by the combined positive score (CPS) was determined using the PD-L1 IHC 22C3 pharmDx Kit (see DOSAGE AND ADMINSTRATION: Patient Selection). Among the 370 patients, 30% (n = 110) had tumours that expressed PD-L1 CPS ≥ 10 and 68% (n = 251) had tumours that expressed PD-L1 CPS < 10.

The primary efficacy outcome measure was Objective Response Rate (ORR) according to RECIST 1.1 as assessed by the blinded independent central radiology review. The key secondary efficacy outcome measure was duration of response. A confirmation of response by repeat radiographic assessment was required 4 to 6 weeks after the initial assessment. The median follow-up time for the 370 patients treated with KEYTRUDA® was 11.5 months (range 0.1 – 31.3 months). Efficacy results are summarized in Table 47.

Table 47: Efficacy Results in Patients with Urothelial Carcinoma Ineligible for Cisplatin-Containing Chemotherapy in KEYNOTE-052

Endpoint	**All Subjects n=370**
Objective Response Rate*	
ORR %, (95% CI)	29% (25, 34)
Complete Response	8%
Partial Response	21%
Response Duration	
Median in months (range)	Not reached (1.4+, 27.9+)
% with duration ≥ 6-months	82% †

* Assessed by BICR using RECIST 1.1

† Based on Kaplan-Meier estimates; includes 85 patients with responses of 6 months or longer

In an exploratory subgroup analysis, the ORRs were 47% and 21% among subjects with PD-L1 CPS ≧ 10 and subjects with PD-L1 CPS < 10 respectively.

KEYNOTE-361 is an ongoing phase III, randomized trial of pembrolizumab with or without platinum-based combination chemotherapy versus chemotherapy in subjects with previously untreated metastatic urothelial carcinoma. The independent Data Monitoring Committee (iDMC) for the study conducted a review of early data and a decreased survival with pembrolizumab monotherapy was revealed as compared to chemotherapy among subjects with PD-L1 CPS <10 expressing tumours. Following the iDMC's recommendation, further accrual was stopped for subjects with PD-L1 CPS < 10 expression to the pembrolizumab monotherapy arm. However, no other changes were recommended, including any change of therapy for patients who had already been randomized to and were receiving treatment in the pembrolizumab monotherapy arm.

NOC/c Microsatellite Instability-High Cancer (MSI-H)

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

Study demographics and trial design

The efficacy of KEYTRUDA® was investigated in 85 patients with MSI-H or dMMR cancer enrolled in two single-arm multicenter, nonrandomized, open-label, multi-cohort Phase II studies. Regardless of histology, MSI or MMR tumour status was determined using polymerase chain reaction (PCR) or immunohistochemistry (IHC), respectively. Efficacy was evaluated in 61 patients enrolled in KEYNOTE-164 with advanced MSI-H or dMMR colorectal cancer (CRC) that progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. Efficacy was also evaluated in 24 patients enrolled in KEYNOTE-158, cohorts D and K, with advanced MSI-H or dMMR endometrial cancer who had disease progression following prior therapy and had no satisfactory alternative treatment options. Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible for either trial.

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

Among the 61 patients with MSI H colorectal cancer (CRC) and the 24 patients with endometrial cancer, the baseline characteristics were (for CRC and endometrial cancer, respectively): median age 53 years vs 66 years (31% vs 58% age 65 or older); 59% of patients with CRC were male; 69% vs 92% White, 31% vs 4% Asian; and ECOG PS 0 (48% vs 50%) and 1 (52% vs 50%); 100% of patients with CRC and 83% of patients with endometrial cancer had M1 disease, and 17% of patients with endometrial cancer had M0 disease. Ninety percent of patients with CRC and 54% of patients with endometrial cancer received two or more prior lines of therapy.

Study Results

The median follow-up times for 61 CRC patients and 24 endometrial cancer patients treated with KEYTRUDA® were 13.2 months and 8.4 months, respectively. Efficacy results are summarized in Table 48.

Table 48: Efficacy Results for Patients with MSI-H or dMMR CRC or Endometrial Cancer

Endpoint	CRC n=61	Endometrial Cancer n=24
Objective Response Rate*		
ORR %, (95% CI)	28% (17.1, 40.8)	54% (32.8, 74.4)
Complete Response	0	4%
Partial Response	28%	50%
Stable Disease	23%	25%
Disease Control Rate†	51%	79%
Response Duration*		
Median in months (range)	Not reached (2.9+, 12.5+)	Not reached (2.1+, 8.4+)
% with duration ≥ 6-months	82%‡	100%§
Time to Response		
Median in months (range)	4.0 (1.8, 10.4)	2.2 (1.3, 10.2)

* Assessed by BICR using RECIST 1.1
† Based on best response of stable disease or better
‡ Based on Kaplan-Meier estimates; includes 14 patients with response of 6 months or longer
§ Based on Kaplan-Meier estimates; includes 5 patients with response of 6 months or longer

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 49: 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	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 weights in males receiving 200 mg/kg at end of the Dosing Period. Both of these findings were not considered adverse

Study Type	Treatment Duration and Dosing Schedule	Species/Test system	Gender and No. per Group	Doses (mg/kg)[a]	Findings/Conclusions
	weekly (total of 5 doses)		period)		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 pre-complexed 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 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 pre-complexed 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

Study Type	Treatment Duration and Dosing Schedule	Species/Test system	Gender and No. per Group	Doses (mg/kg)[a]	Findings/Conclusions
					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.
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.
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:

- adult patients with metastatic non-small cell lung carcinoma (NSCLC) as monotherapy, whose tumours express PD-L1 [(Tumour Proportion Score (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®.

- adult patients with refractory or relapsed classical Hodgkin Lymphoma (cHL), as monotherapy, who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV) or who are not ASCT candidates and have failed BV.

- adult and pediatric patients with refractory Primary Mediastinal B-cell Lymphoma (PMBCL) or who have relapsed after 2 or more lines of therapy, as monotherapy.

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

- adult patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)
    - colorectal cancer whose tumours have progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, as monotherapy, or
    - endometrial cancer whose tumours have progressed following prior therapy and who have no satisfactory alternative treatment options, as monotherapy.

KEYTRUDA® has been issued marketing authorization **without conditions** for:

- 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.

- 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.

- Adjuvant treatment of patients with Stage III melanoma with lymph node involvement who have undergone complete resection.

- Treatment of patients with metastatic non-small cell lung carcinoma (NSCLC) as monotherapy, in adults whose tumours have high PD-L1 expression (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.

- Treatment of patients with metastatic non-squamous NSCLC in combination with pemetrexed and platinum chemotherapy, in adults with no EGFR or ALK genomic tumour aberrations, and no prior systemic chemotherapy treatment for metastatic NSCLC.

- Treatment of patients with metastatic squamous NSCLC in combination with carboplatin and either paclitaxel or nab-paclitaxel, in adults with no prior systemic chemotherapy treatment for metastatic NSCLC.

- Treatment of patients with locally advanced or metastatic urothelial carcinoma, as monotherapy, in adults who have disease progression during or following platinum-containing chemotherapy or within 12 months of completing neoadjuvant or adjuvant platinum-containing chemotherapy.

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 in adults when it has spread or cannot be removed by surgery (advanced melanoma) or when it has been removed by surgery to help prevent the cancer from coming back.
- a kind of lung cancer called non-small cell lung cancer in adults
    - KEYTRUDA® may be used with the medicine pemetrexed and chemotherapy that contains platinum as your first treatment when your lung cancer:
        - has spread or cannot be removed by surgery (advanced lung cancer)

        and
        - is a type called “non-squamous”.

        and,
        - If your tumour does not have an abnormal "EGFR" or "ALK" gene
    - KEYTRUDA® may be used with the chemotherapy medicines carboplatin and either paclitaxel or nab-paclitaxel as your first treatment when your lung cancer:
        - has spread or cannot be removed by surgery (advanced lung cancer)

        and
        - is a type called “squamous”.
    - KEYTRUDA® may be used alone as your first treatment when your lung cancer:
        - has spread or cannot be removed by surgery (advanced lung cancer)
          and,
        - tests positive for high levels of “PD-L1”
          and,
        - If your tumour does not have an abnormal "EGFR" or "ALK" gene
    - KEYTRUDA® may be used alone when your lung cancer:
        - has worsened on or after chemotherapy that contains platinum
          and
        - has spread or cannot be removed by surgery (advanced lung cancer)
          and
        - tests positive for “PD-L1”
          and,
        - if your tumour has an abnormal “EGFR” or “ALK” gene, you have tried chemotherapy that contains platinum and an EGFR or ALK gene inhibitor medicine.
- a kind of cancer called classical Hodgkin lymphoma (cHL) in adults:
    - that has come back after an authologous stem cell transplant (ASCT) and therapy with brentuximab vedotin (BV), or

    - that was not suitable for ASCT and has come back after treatment with BV
- a kind of cancer called primary mediastinal B-cell lymphoma in adults and children
    - that was not responsive to other treatments, or
    - that has come back after you have tried at least 2 other treatments
- a kind of bladder and urinary tract cancer called urothelial carcinoma, in adults when
    - it has spread or cannot be removed by surgery (advanced urothelial cancer) and
    - you have received chemotherapy that contains platinum, and it did not work or is no longer working, or.
        - you are not able to receive chemotherapy that contains a medicine called cisplatin, and your tumour tests positive for PD-L1, or
        - you are not able to receive a medicine called cisplatin or carboplatin
- a kind of colon or endometrial cancer in adults that is shown by a laboratory test to be microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR).

KEYTRUDA® can be used only in children with primary mediastinal B-cell lymphoma. It is not known if KEYTRUDA® is safe and effective in children less than 18 years of age for other pediatric diseases.

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 a kidney transplant
- have had a solid organ transplant or a bone marrow (stem cell) transplant that used donor stem cells (allogeneic)
- take other medicines that make your immune system weak. Examples of these may include steroids, such as prednisone.

There are possible side effects of KEYTRUDA® treatment in people who have received a transplant.

- **Rejection of a transplanted organ.** People who have had an organ transplant may have an increased risk of organ transplant rejection. Your doctor should tell you what signs and symptoms you should report and monitor you, depending on the type of organ transplant that you have had.
- **Complications, including graft-versus-host-disease (GVHD) in people with bone marrow (stem cell) transplant that uses donor stem cells (allogeneic).** These complications can be severe and can lead to death. They may occur if you had this kind of transplant in the past or if you get it in the future. Your doctor will monitor you for the following signs and symptoms: skin rash, liver inflammation, abdominal pain and diarrhea.

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:

The recommended dose is 200 mg.

Overdose:

If you think you have taken too much KEYTRUDA®, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

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. These side effects can sometimes become life-threatening and can lead to death. These side effects may happen anytime during treatment or even after your treatment has ended. 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 when KEYTRUDA® is given alone:

Very common (may affect more than 1 in 10 people)

- diarrhea, nausea
- itching, rash
- joint pain
- feeling unusually tired or weak
- fever
- 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
- lack of white blood cells
- rapid heart beat
- cold sores
- upper respiratory tract infection
- stuffy nose
- 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
    - decrease in the number of white blood cells
    - abnormal liver enzyme levels in the blood
    - decreased sodium levels in the blood
    - abnormal levels of thyroid stimulating hormone in the blood
    - increased creatinine levels in the blood
    - weight loss
    - weight gain

The following side effects have been reported in clinical trials when KEYTRUDA® is given in combination with chemotherapy. Ask your doctor for more information regarding side effects of your chemotherapy.

Very common (may affect more than 1 in 10 people)
- nausea
- decrease in red blood cell count
- fatigue
- decrease in white blood cell count
- decreased appetite
- diarrhea
- vomiting
- decrease in platelet count
- constipation
- weakness
- rash
- eye tearing

The most common side effects when KEYTRUDA® is given to children are:
- fever
- vomiting
- fatigue
- constipation
- abdominal pain
- nausea

If you are being treated with KEYTRUDA® either alone or in combination with chemotherapy and 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, voice getting 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		√
Confusion, fever, memory problems, or seizures (encephalitis)		√
Swollen lymph nodes, rash or tender lumps on skin, cough, or eye pain (sarcoidosis)		√
Inflammation of the pancreas(pancreatitis), which can cause abdominal pain, nausea, and vomiting		√

Serious side effects and what to do about them		
Symptom / effect	Talk to your healthcare professional	
	Only if severe	In all cases
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
    Marketed Health Products Safety and Effectiveness Information Bureau
    Marketed Health Products Directorate
    Health Products and Food Branch
    Health Canada,
    Address 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 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.

Last Revised: July 4, 2019

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