ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

KEYTRUDA 50 mg powder for concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of powder contains 50 mg of pembrolizumab.

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

Pembrolizumab is a humanised monoclonal anti-programmed cell death-1 (PD-1) antibody (IgG4/kappa isotype with a stabilising sequence alteration in the Fc region) produced in Chinese hamster ovary cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

White to off-white lyophilised powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

KEYTRUDA as monotherapy is indicated for the first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations.

KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 with a ≥ 1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving KEYTRUDA.

KEYTRUDA as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV.

KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy (see section 5.1).

KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy.

4.2 Posology and method of administration

Therapy must be initiated and supervised by specialist physicians experienced in the treatment of cancer.

PD-L1 testing for patients with NSCLC
Patients with NSCLC should be selected for treatment based on the tumour expression of PD-L1 confirmed by a validated test (see section 5.1).

Posology
KEYTRUDA should be administered as an intravenous infusion over 30 minutes every 3 weeks.

The recommended dose of KEYTRUDA is:

- 200 mg for NSCLC that has not been previously treated with chemotherapy, cHL or for urothelial carcinoma.
- 2 mg/kg for NSCLC that has been previously treated with chemotherapy or for melanoma.

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. It is recommended to continue treatment for clinically stable patients with initial evidence of disease progression until disease progression is confirmed.

Dose delay or discontinuation (see also section 4.4)

Table 1: Recommended treatment modifications for KEYTRUDA

Immune-related adverse reactions	**Severity**	**Treatment modification**
Pneumonitis	Grade 2	Withhold until adverse reactions recover to Grade 0-1*
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue
Colitis	Grade 2 or 3	Withhold until adverse reactions recover to Grade 0-1*
	Grade 4 or recurrent Grade 3	Permanently discontinue
Nephritis	Grade 2 with creatinine > 1.5 to ≤ 3 times upper limit of normal (ULN)	Withhold until adverse reactions recover to Grade 0-1*
	Grade ≥ 3 with creatinine > 3 times ULN	Permanently discontinue

Endocrinopathies	Symptomatic hypophysitis Type 1 diabetes associated with Grade > 3 hyperglycaemia (glucose > 250 mg/dL or > 13.9 mmol/L) or associated with ketoacidosis Hyperthyroidism Grade ≥ 3	Withhold until adverse reactions recover to Grade 0-1* For patients with Grade 3 or Grade 4 endocrinopathy that improved to Grade 2 or lower and is controlled with hormone replacement, if indicated, continuation of pembrolizumab may be considered after corticosteroid taper, if needed. Otherwise treatment should be discontinued. Hypothyroidism may be managed with replacement therapy without treatment interruption.
Hepatitis	Grade 2 with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 to 5 times ULN or total bilirubin > 1.5 to 3 times ULN	Withhold 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
	In case of liver metastasis with baseline Grade 2 elevation of AST or ALT, hepatitis with AST or ALT increases ≥ 50% and lasts ≥ 1 week	Permanently discontinue
Skin reactions	Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold until adverse reactions recover to Grade 0-1*
	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) Grade 3 or 4 myocarditis Grade 3 or 4 encephalitis Grade 3 or 4 Guillain-Barré syndrome Grade 4 or recurrent Grade 3	Withhold until adverse reactions recover to Grade 0-1* Permanently discontinue Permanently discontinue
Infusion-related reactions	Grade 3 or 4	Permanently discontinue

Note: toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE v.4).

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

The safety of re-initiating pembrolizumab therapy in patients previously experiencing immune-related myocarditis is not known.

KEYTRUDA should be permanently discontinued for Grade 4 or recurrent Grade 3 adverse reactions, unless otherwise specified in Table 1.

For Grade 4 haematological toxicity, only in patients with cHL, KEYTRUDA should be withheld until adverse reactions recover to Grade 0-1.

Patients treated with KEYTRUDA must be given the Patient Alert Card and be informed about the risks of KEYTRUDA (see also package leaflet).

Special populations
Elderly
No overall differences in safety or efficacy were reported between elderly patients (≥ 65 years) and younger patients (< 65 years). No dose adjustment is necessary in this population.

Data from patients ≥ 65 years are too limited to draw conclusions on cHL population (see section 5.1).

Renal impairment
No dose adjustment is needed for patients with mild or moderate renal impairment. KEYTRUDA has not been studied in patients with severe renal impairment (see sections 4.4 and 5.2).

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 sections 4.4 and 5.2).

Ocular melanoma
There are limited data on the safety and efficacy of KEYTRUDA in patients with ocular melanoma (see section 5.1).

Eastern Cooperative Oncology Group (ECOG) performance status score ≥ 2
Patients with ECOG performance status score ≥ 2 were excluded from the clinical trials of melanoma, NSCLC and cHL (see sections 4.4 and 5.1).

Paediatric population
The safety and efficacy of KEYTRUDA in children below 18 years of age have not yet been established. No data are available.

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

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Assessment of PD-L1 status
When assessing the PD-L1 status of the tumour, it is important that a well-validated and robust methodology is chosen to minimise false negative or false positive determinations.

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

For suspected immune-related adverse reactions, adequate evaluation to confirm aetiology or exclude other causes should be ensured. Based on the severity of the adverse reaction, pembrolizumab should be withheld and corticosteroids administered. Upon improvement to Grade ≤ 1, corticosteroid taper should be initiated and continued over at least 1 month. Based on limited data from clinical studies in patients whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered.

Pembrolizumab 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.

Pembrolizumab must be permanently discontinued for any Grade 3 immune-related adverse reaction that recurs and for any Grade 4 immune-related adverse reaction toxicity, except for endocrinopathies that are controlled with replacement hormones (see sections 4.2 and 4.8).

Immune-related pneumonitis
Pneumonitis, including fatal cases, has been reported in patients receiving pembrolizumab (see section 4.8). Patients should be monitored for signs and symptoms of pneumonitis. Suspected pneumonitis should be confirmed with radiographic imaging and other causes excluded. Corticosteroids should be administered for Grade ≥ 2 events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper); pembrolizumab should be withheld for Grade 2 pneumonitis, and permanently discontinued for Grade 3, Grade 4 or recurrent Grade 2 pneumonitis (see section 4.2).

Immune-related colitis
Colitis has been reported in patients receiving pembrolizumab (see section 4.8). Patients should be monitored for signs and symptoms of colitis, and other causes excluded. Corticosteroids should be administered for Grade ≥ 2 events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper); pembrolizumab should be withheld for Grade 2 or Grade 3 colitis, and permanently discontinued for Grade 4 colitis (see section 4.2). The potential risk of gastrointestinal perforation should be taken into consideration.

Immune-related hepatitis
Hepatitis has been reported in patients receiving pembrolizumab (see section 4.8). Patients should be monitored for changes in liver function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and symptoms of hepatitis, and other causes excluded. Corticosteroids should be administered (initial dose of 0.5-1 mg/kg/day (for Grade 2 events) and 1-2 mg/kg/day (for Grade ≥ 3 events) prednisone or equivalent followed by a taper) and, based on severity of liver enzyme elevations, pembrolizumab should be withheld or discontinued (see section 4.2).

Immune-related nephritis
Nephritis has been reported in patients receiving pembrolizumab (see section 4.8). Patients should be monitored for changes in renal function, and other causes of renal dysfunction excluded. Corticosteroids should be administered for Grade ≥ 2 events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper) and, based on severity of creatinine elevations, pembrolizumab should be withheld for Grade 2, and permanently discontinued for Grade 3 or Grade 4 nephritis (see section 4.2).

Immune-related endocrinopathies
Severe endocrinopathies, including hypophysitis, type 1 diabetes mellitus, diabetic ketoacidosis, hypothyroidism, and hyperthyroidism have been observed with pembrolizumab treatment.

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

Hypophysitis has been reported in patients receiving pembrolizumab (see section 4.8). Patients should be monitored for signs and symptoms of hypophysitis (including hypopituitarism and secondary adrenal insufficiency) and other causes excluded. Corticosteroids to treat secondary adrenal insufficiency and other hormone replacement should be administered as clinically indicated, and pembrolizumab should be withheld for symptomatic hypophysitis until the event is controlled with hormone replacement. Continuation of pembrolizumab may be considered, after corticosteroid taper, if needed (see section 4.2). Pituitary function and hormone levels should be monitored to ensure appropriate hormone replacement.

Type 1 diabetes mellitus, including diabetic ketoacidosis, has been reported in patients receiving pembrolizumab (see section 4.8). Patients should be monitored for hyperglycaemia or other signs and symptoms of diabetes. Insulin should be administered for type 1 diabetes, and pembrolizumab should be withheld in cases of Grade 3 hyperglycaemia until metabolic control is achieved (see section 4.2).

Thyroid disorders, including hypothyroidism, hyperthyroidism and thyroiditis, have been reported in patients receiving pembrolizumab and can occur at any time during treatment; therefore, patients should be monitored 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. Pembrolizumab should be withheld for Grade ≥ 3 until recovery to Grade ≤ 1 hyperthyroidism. For patients with Grade 3 or Grade 4 hyperthyroidism that improved to Grade 2 or lower, continuation of pembrolizumab may be considered, after corticosteroid taper, if needed (see sections 4.2 and 4.8). Thyroid function and hormone levels should be monitored to ensure appropriate hormone replacement.

Immune-related skin adverse reactions
Immune-related severe skin reactions have been reported in patients receiving pembrolizumab (see section 4.8). Patients should be monitored for suspected severe skin reactions and other causes should be excluded. Based on the severity of the adverse reaction, pembrolizumab should be withheld or permanently discontinued, and corticosteroids should be administered (see section 4.2).

Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some with fatal outcome, have been reported in patients receiving pembrolizumab (see section 4.8). For signs or symptoms of SJS or TEN, pembrolizumab should be withheld and the patient should be referred to a specialised unit for assessment and treatment. If SJS or TEN is confirmed, pembrolizumab should be permanently discontinued (see section 4.2).

Caution should be used when considering the use of pembrolizumab in a patient who has previously experienced a severe or life-threatening skin adverse reaction on prior treatment with other immune-stimulatory anticancer agents.

Other immune-related adverse reactions
The following additional clinically significant, immune-related adverse reactions, including severe and fatal cases, have been reported in clinical trials or in post-marketing experience: uveitis, arthritis, myositis, myocarditis, pancreatitis, Guillain-Barré syndrome, myasthenic syndrome, haemolytic anaemia, sarcoidosis and encephalitis (see sections 4.2 and 4.8).

Based on the severity of the adverse reaction, pembrolizumab should be withheld and corticosteroids administered.

Pembrolizumab 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.

Pembrolizumab must be permanently discontinued for any Grade 3 immune related adverse reaction that recurs and for any Grade 4 immune related adverse reaction (see sections 4.2 and 4.8).

Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with PD-1 inhibitors. Treatment with pembrolizumab may increase the risk of rejection in solid organ transplant recipients. The benefit of treatment with pembrolizumab versus the risk of possible organ rejection should be considered in these patients.

Complications of allogeneic Haematopoietic Stem Cell Transplant (HSCT)
Allogeneic HSCT after treatment with pembrolizumab
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 pembrolizumab. 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 section 4.8).

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

Infusion-related reactions
Severe infusion-related reactions, including hypersensitivity and anaphylaxis, have been reported in patients receiving pembrolizumab (see section 4.8). For severe infusion reactions, infusion should be stopped and pembrolizumab permanently discontinued (see section 4.2). Patients with mild or moderate infusion reaction may continue to receive pembrolizumab with close monitoring; premedication with antipyretic and antihistamine may be considered.

Disease-specific precautions

Use of pembrolizumab in urothelial carcinoma patients who have received prior platinum-containing chemotherapy
Physicians should consider the delayed onset of pembrolizumab effect before initiating treatment in patients with poorer prognostic features and/or aggressive disease. In urothelial cancer, a higher number of deaths within 2 months was observed in pembrolizumab compared to chemotherapy (see section 5.1). Factors associated with early deaths were fast progressive disease on prior platinum therapy and liver metastases.

Use of pembrolizumab in urothelial cancer for patients who are considered cisplatin ineligible
The baseline and prognostic disease characteristics of the study population of KEYNOTE-052 included a proportion of patients eligible for a carboplatin-based combination or mono-chemotherapy for whom the benefit has not yet been assessed in a comparative study. No safety and efficacy data are available in frailer patients (e.g., ECOG performance status 3) considered not eligible for chemotherapy. In the absence of these data, pembrolizumab should be used with caution in this population after careful consideration of the potential risk-benefit on an individual basis.

Patients excluded from clinical trials
Patients with the following conditions were excluded from clinical trials: active CNS metastases; ECOG PS ≥ 2 (except for urothelial carcinoma); HIV, hepatitis B or hepatitis C infection; active systemic autoimmune disease; interstitial lung disease; prior pneumonitis requiring systemic corticosteroid therapy; a history of severe hypersensitivity to another monoclonal antibody; receiving immunosuppressive therapy and a history of severe immune-related adverse reactions from treatment with ipilimumab, defined as any Grade 4 toxicity or Grade 3 toxicity requiring corticosteroid treatment (> 10 mg/day prednisone or equivalent) for greater than 12 weeks. Patients with active infections were excluded from clinical trials and were required to have their infection treated prior to receiving pembrolizumab. Patients with active infections occurring during treatment with pembrolizumab were managed with appropriate medical therapy. Patients with clinically significant renal (creatinine > 1.5 x ULN) or hepatic (bilirubin > 1.5 x ULN, ALT, AST > 2.5 x ULN in the absence of liver metastases) abnormalities at baseline were excluded from clinical trials, therefore information is limited in patients with severe renal and moderate to severe hepatic impairment.

For subjects with relapsed or refractory classical Hodgkin lymphoma, clinical data for the use of pembrolizumab in patients ineligible to ASCT due to reasons other than failure to salvage chemotherapy are limited (see section 5.1).

After careful consideration of the potential increased risk, pembrolizumab may be used with appropriate medical management in these patients.

Patient Alert Card
All prescribers of KEYTRUDA must be familiar with the Physician Information and Management Guidelines. The prescriber must discuss the risks of KEYTRUDA therapy with the patient. The patient will be provided with the Patient Alert Card with each prescription.

4.5 Interaction with other medicinal products and other forms of interaction

No formal pharmacokinetic drug interaction studies have been conducted with pembrolizumab. 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 pembrolizumab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of pembrolizumab. However, systemic corticosteroids or other immunosuppressants can be used after starting pembrolizumab to treat immune-related adverse reactions (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Women of childbearing potential should use effective contraception during treatment with pembrolizumab and for at least 4 months after the last dose of pembrolizumab.

Pregnancy
There are no data on the use of pembrolizumab in pregnant women. Animal reproduction studies have not been conducted with pembrolizumab; however, in murine models of pregnancy blockade of PD-L1 signaling has been shown to disrupt tolerance to the foetus and to result in an increased foetal loss (see section 5.3). These results indicate a potential risk, based on its mechanism of action, that administration of pembrolizumab during pregnancy could cause foetal harm, including increased rates of abortion or stillbirth. Human immunoglobulins G4 (IgG4) are known to cross the placental barrier; therefore, being an IgG4, pembrolizumab has the potential to be transmitted from the mother to the developing foetus. Pembrolizumab should not be used during pregnancy unless the clinical condition of the woman requires treatment with pembrolizumab.

Breast-feeding
It is unknown whether pembrolizumab is secreted in human milk. Since it is known that antibodies can be secreted in human milk, a risk to the newborns/infants cannot be excluded. A decision should be made whether to discontinue breast-feeding or to discontinue pembrolizumab, taking into account the benefit of breast-feeding for the child and the benefit of pembrolizumab therapy for the woman.

Fertility
No clinical data are available on the possible effects of pembrolizumab on fertility. There were no notable effects in the male and female reproductive organs in monkeys based on 1-month and 6-month repeat dose toxicity studies (see section 5.3).

4.7 Effects on ability to drive and use machines

Pembrolizumab may have a minor influence on the ability to drive and use machines. Fatigue has been reported following administration of pembrolizumab (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile
Pembrolizumab is most commonly associated with immune-related adverse reactions. Most of these, including severe reactions, resolved following initiation of appropriate medical therapy or withdrawal of pembrolizumab (see "Description of selected adverse reactions" below).

The safety of pembrolizumab has been evaluated in 3,830 patients with advanced melanoma, NSCLC, cHL or urothelial carcinoma across four doses (2 mg/kg every 3 weeks, 200 mg every 3 weeks, or 10 mg/kg every 2 or 3 weeks) in clinical studies. In this patient population, the most common adverse reactions (> 10%) with pembrolizumab were fatigue (21%), pruritus (16%), rash (13%), diarrhoea (12%) and nausea (10%). The majority of adverse reactions reported were of Grade 1 or 2 severity. The most serious adverse reactions were immune-related adverse reactions and severe infusion-related reactions (see section 4.4).

Tabulated list of adverse reactions
Adverse reactions observed in clinical studies and reported from post-marketing use of pembrolizumab are listed in Table 2. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 2: Adverse reactions in patients treated with pembrolizumab

Infections and infestations	
Uncommon	pneumonia
Blood and lymphatic system disorders	
Common	anaemia
Uncommon	neutropenia, thrombocytopenia, leukopenia, lymphopenia, eosinophilia
Rare	immune thrombocytopenic purpura, haemolytic anaemia
Immune system disorders	
Common	infusion related reaction[a]
Rare	sarcoidosis
Not known	solid organ transplant rejection
Endocrine disorders	
Common	hyperthyroidism, hypothyroidism[b]

Uncommon	hypophysitis[c], adrenal insufficiency, thyroiditis
Metabolism and nutrition disorders	
Common	decreased appetite
Uncommon	type 1 diabetes mellitus[d], hyponatraemia, hypokalaemia, hypocalcaemia
Psychiatric disorders	
Uncommon	insomnia
Nervous system disorders	
Common	headache, dizziness, dysgeusia
Uncommon	epilepsy, lethargy, neuropathy peripheral
Rare	Guillain-Barré syndrome, myasthenic syndrome, encephalitis
Eye disorders	
Uncommon	uveitis[e], dry eye
Cardiac disorders	
Uncommon	myocarditis
Vascular disorders	
Uncommon	hypertension
Respiratory, thoracic and mediastinal disorders	
Common	pneumonitis[f], dyspnoea, cough
Gastrointestinal disorders	
Very common	diarrhoea, nausea
Common	colitis[g], vomiting, abdominal pain[h], constipation, dry mouth
Uncommon	pancreatitis[i]
Rare	small intestinal perforation
Hepatobiliary disorders	
Uncommon	hepatitis[j]
Skin and subcutaneous tissue disorders	
Very common	rash[k], pruritus[l]
Common	severe skin reactions[m], vitiligo[n], dry skin, erythema
Uncommon	lichenoid keratosis[o], psoriasis, alopecia, dermatitis, dermatitis acneiform, eczema, hair colour changes, papule
Rare	toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema nodosum
Musculoskeletal and connective tissue disorders	
Common	arthralgia, myositis[p], musculoskeletal pain[q], arthritis[r], pain in extremity,
Uncommon	tenosynovitis[s]
Renal and urinary disorders	
Uncommon	nephritis[t]
General disorders and administration site conditions	
Very common	fatigue
Common	asthenia, oedema[u], pyrexia, influenza like illness, chills
Investigations	
Common	alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood creatinine increased
Uncommon	blood bilirubin increased, amylase increased, hypercalcaemia

The following terms represent a group of related events that describe a medical condition rather than a single event.

a. infusion-related reactions (drug hypersensitivity, anaphylactic reaction, hypersensitivity and cytokine release syndrome)
b. hypothyroidism (myxoedema)
c. hypophysitis (hypopituitarism)
d. type 1 diabetes mellitus (diabetic ketoacidosis)
e. uveitis (iritis and iridocyclitis)
f. pneumonitis (interstitial lung disease)
g. colitis (colitis microscopic and enterocolitis)
h. abdominal pain (abdominal discomfort, abdominal pain upper and abdominal pain lower)
i. pancreatitis (autoimmune pancreatitis and pancreatitis acute)
j. hepatitis (autoimmune hepatitis and drug induced liver injury)
k. rash (rash erythematous, rash follicular, rash generalised, rash macular, rash maculo-papular, rash papular, rash pruritic, rash vesicular and genital rash)
l. pruritus (urticaria, urticaria papular, pruritus generalized and pruritus genital)
m. severe skin reactions (dermatitis exfoliative, erythema multiforme, exfoliative rash, pemphigoid and Grade ≥ 3 of the following: pruritus, rash, rash generalised and rash maculo-papular, dermatitis psoriasiform, pruritus generalised)
n. vitiligo (skin depigmentation, skin hypopigmentation and hypopigmentation of the eyelid)
o. lichenoid keratosis (lichen planus and lichen sclerosus)
p. myositis (myalgia, myopathy, polymyalgia rheumatica and rhabdomyolysis)
q. musculoskeletal pain (musculoskeletal discomfort, back pain, musculoskeletal stiffness, musculoskeletal chest pain and torticollis)
r. arthritis (joint swelling, polyarthritis and joint effusion)
s. tenosynovitis (tendonitis, synovitis and tendon pain)
t. nephritis (nephritis autoimmune, tubulointerstitial nephritis and renal failure or renal failure acute with evidence of nephritis, nephrotic syndrome)
u. oedema (oedema peripheral, generalised oedema, fluid overload, fluid retention, eyelid oedema and lip oedema, face oedema, localized oedema and periorbital oedema)

Description of selected adverse reactions

Data for the following immune-related adverse reactions are based on patients who received pembrolizumab across three doses (2 mg/kg every 3 weeks or 10 mg/kg every 2 or 3 weeks) in clinical studies (see section 5.1). The management guidelines for these adverse reactions are described in section 4.4.

Immune-related adverse reactions (see section 4.4)

Immune-related pneumonitis

Pneumonitis occurred in 139 (3.6%) patients, including Grade 2, 3, 4 or 5 cases in 56 (1.5%), 38 (1.0%), 9 (0.2%) and 5 (0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of pneumonitis was 3.7 months (range 2 days to 21.3 months). The median duration was 2.1 months (range 1 day to 17.2+ months). Pneumonitis led to discontinuation of pembrolizumab in 60 (1.6%) patients. Pneumonitis resolved in 81 patients, 1 with sequelae.

Immune-related colitis

Colitis occurred in 71 (1.9%) patients, including Grade 2, 3 or 4 cases in 15 (0.4%), 44 (1.1%) and 3 (< 0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of colitis was 3.6 months (range 7 days to 16.2 months). The median duration was 1.3 months (range 1 day to 8.7+ months). Colitis led to discontinuation of pembrolizumab in 18 (0.5%) patients. Colitis resolved in 61 patients.

Immune-related hepatitis

Hepatitis occurred in 23 (0.6%) patients, including Grade 2, 3 or 4 cases in 4 (0.1%), 16 (0.4%) and 2 (< 0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of hepatitis was 1.3 months (range 8 days to 21.4 months). The median duration was 1.5 months (range 8 days to 20.9+ months). Hepatitis led to discontinuation of pembrolizumab in 7 (0.2%) patients. Hepatitis resolved in 19 patients.

Immune-related nephritis
Nephritis occurred in 15 (0.4%) patients, including Grade 2, 3 or 4 cases in 3 (0.1%), 10 (0.3%) and 1 (< 0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of nephritis was 4.9 months (range 12 days to 12.8 months). The median duration was 1.8 months (range 10 days to 10.5+ months). Nephritis led to discontinuation of pembrolizumab in 7 (0.2%) patients. Nephritis resolved in 9 patients.

Immune-related endocrinopathies
Hypophysitis occurred in 21 (0.5%) patients, including Grade 2, 3 or 4 cases in 6 (0.2%), 12 (0.3%) and 1 (< 0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of hypophysitis was 3.7 months (range 1 day to 17.7 months). The median duration was 3.3 months (range 4 days to 12.7+ months). Hypophysitis led to discontinuation of pembrolizumab in 6 (0.2%) patients. Hypophysitis resolved in 10 patients, 2 with sequelae.

Hyperthyroidism occurred in 135 (3.5%) patients, including Grade 2 or 3 cases in 32 (0.8%) and 4 (0.1%) patients, respectively, receiving pembrolizumab. 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 10 days to 15.5+ months). Hyperthyroidism led to discontinuation of pembrolizumab in 2 (0.1%) patients. Hyperthyroidism resolved in 104 (77%) patients, 1 with sequelae.

Hypothyroidism occurred in 345 (9.0%) patients, including Grade 2 or 3 cases in 251 (6.6%) and 4 (0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of hypothyroidism was 3.5 months (range 1 day to 18.9 months). The median duration was not reached (range 2 days to 29.9+ months). One patient (< 0.1%) discontinued pembrolizumab due to hypothyroidism. Hypothyroidism resolved in 81 (23%) patients, 6 with sequelae. In patients with cHL (n=241) the incidence of hypothyroidism was 14.1% (all Grades) with 0.4% Grade 3.

Immune-related skin adverse reactions
Immune-related severe skin reactions occurred in 63 (1.6%) patients, including Grade 2 or 3 cases in 4 (0.1%) and 52 (1.4%) patients, respectively, receiving pembrolizumab. The median time to onset of severe skin reactions was 2.5 months (range 4 days to 21.5 months). The median duration was 2.0 months (range 3 days to 17.8+ months). Severe skin reactions led to discontinuation of pembrolizumab in 6 (0.2%) patients. Severe skin reactions resolved in 41 patients.

Rare cases of SJS and TEN, some of them with fatal outcome, have been observed (see sections 4.2 and 4.4).

Complications of allogeneic HSCT in classical Hodgkin lymphoma
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).

Immunogenicity
In clinical studies in patients treated with pembrolizumab 2 mg/kg every three weeks, 200 mg every three weeks, or 10 mg/kg every two or three weeks, 36 (1.8%) of 2,034 evaluable patients tested positive for treatment-emergent antibodies to pembrolizumab, of which 9 (0.4%) patients had neutralising antibodies against pembrolizumab. There was no evidence of an altered pharmacokinetic or safety profile with anti-pembrolizumab binding or neutralising antibody development.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no information on overdose with pembrolizumab.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies. ATC code: L01XC18

Mechanism of action
KEYTRUDA is a humanised monoclonal antibody which binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with ligands PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. KEYTRUDA potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment.

Clinical efficacy and safety
Dosing for patients with melanoma and previously treated NSCLC
In clinical studies comparing pembrolizumab doses of 2 mg/kg every 3 weeks, 10 mg/kg every 3 weeks, and 10 mg/kg every 2 weeks in patients with melanoma or previously treated patients with NSCLC, efficacy and safety were similar. The recommended dose is 2 mg/kg every 3 weeks.

Melanoma
KEYNOTE-006: Controlled trial in melanoma patients naïve to treatment with ipilimumab
The safety and efficacy of pembrolizumab were investigated in KEYNOTE-006, a multicentre, controlled, Phase III study for the treatment of advanced melanoma in patients who were naïve to ipilimumab. Patients were randomised (1:1:1) to receive pembrolizumab 10 mg/kg every 2 (n=279) or 3 weeks (n=277) or ipilimumab 3 mg/kg every 3 weeks (n=278). Patients with BRAF V600E mutant melanoma were not required to have received prior BRAF inhibitor therapy.

Patients were treated with pembrolizumab until disease progression or unacceptable toxicity. Clinically stable patients with initial evidence of disease progression were permitted to remain on treatment until disease progression was confirmed. Assessment of tumour status was performed at 12 weeks, then every 6 weeks through week 48, followed by every 12 weeks thereafter.

Of the 834 patients, 60% were male, 44% were ≥ 65 years (median age was 62 years [range 18-89]) and 98% were white. Sixty-five percent of patients had M1c stage, 9% had a history of brain metastases, 66% had no and 34% had one prior therapy. Thirty-one percent had an ECOG Performance Status of 1, 69% had ECOG Performance Status of 0 and 32% had elevated LDH. BRAF mutations were reported in 302 (36%) patients. Among patients with BRAF mutant tumours, 139 (46%) were previously treated with a BRAF inhibitor.

The primary efficacy outcome measures were progression free survival (PFS; as assessed by Integrated Radiology and Oncology Assessment [IRO] review using Response Evaluation Criteria in Solid Tumours [RECIST], version 1.1) and overall survival (OS). Secondary efficacy outcome measures were overall response rate (ORR) and response duration. Table 3 summarises key efficacy measures in patients naïve to treatment with ipilimumab at the final analysis performed after a

minimum of 21 months of follow-up. Kaplan-Meier curves for OS and PFS based on the final analysis are shown in Figures 1 and 2.

Table 3: Efficacy results in KEYNOTE-006

Endpoint	Pembrolizumab 10 mg/kg every 3 weeks n=277	Pembrolizumab 10 mg/kg every 2 weeks n=279	Ipilimumab 3 mg/kg every 3 weeks n=278
OS			
Number (%) of patients with event	119 (43%)	122 (44%)	142 (51%)
Hazard ratio* (95% CI)	0.68 (0.53, 0.86)	0.68 (0.53, 0.87)	---
p-Value†	< 0.001	< 0.001	---
Median in months (95% CI)	Not reached (24, NA)	Not reached (22, NA)	16 (14, 22)
PFS			
Number (%) of patients with event	183 (66%)	181 (65%)	202 (73%)
Hazard ratio* (95% CI)	0.61 (0.50, 0.75)	0.61 (0.50, 0.75)	---
p-Value†	< 0.001	< 0.001	---
Median in months (95% CI)	4.1 (2.9, 7.2)	5.6 (3.4, 8.2)	2.8 (2.8, 2.9)
Best overall response			
ORR % (95% CI)	36% (30, 42)	37% (31, 43)	13% (10, 18)
Complete response %	13%	12%	5%
Partial response %	23%	25%	8%
Response duration‡			
Median in months (range)	Not reached (2.0, 22.8+)	Not reached (1.8, 22.8+)	Not reached (1.1+, 23.8+)
% ongoing at 18 months	68%§	71%§	70%§

* Hazard ratio (pembrolizumab compared to ipilimumab) based on the stratified Cox proportional hazard model

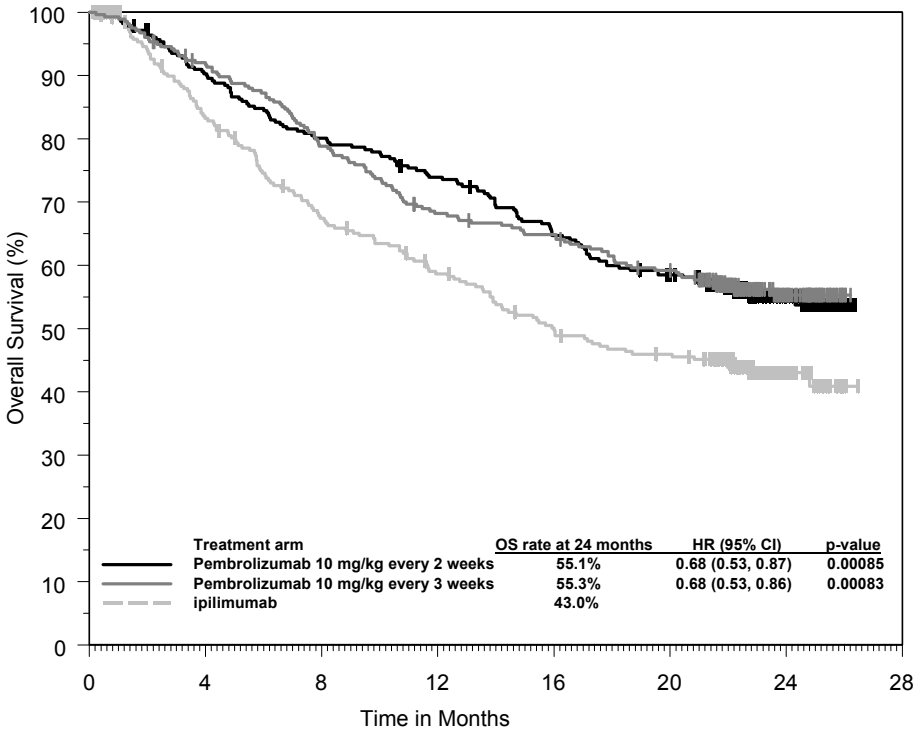
† Based on stratified Log rank test

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

§ Based on Kaplan-Meier estimation

NA = not available

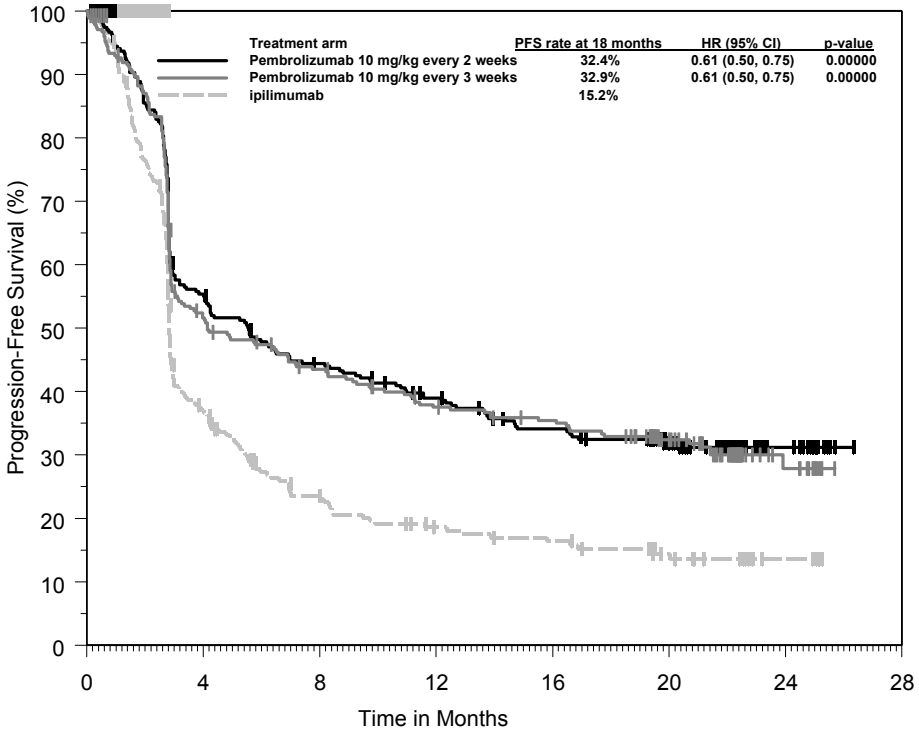
Figure 1: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-006 (intent to treat population)



Number at Risk

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

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



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

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

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

Patients were treated with pembrolizumab until disease progression or unacceptable toxicity. Clinically stable patients with initial evidence of disease progression were permitted to remain on treatment until disease progression was confirmed. Assessment of tumour status was performed at 12 weeks, then every 6 weeks through week 48, followed by every 12 weeks thereafter. Patients on chemotherapy who experienced independently verified progression of disease after the first scheduled disease assessment were able to crossover and receive 2 mg/kg or 10 mg/kg of pembrolizumab every 3 weeks in a double blind fashion.

Of the 540 patients, 61% were male, 43% were ≥ 65 years (median age was 62 years [range 15-89]) and 98% were white. Eighty-two percent had M1c stage, 73% had at least two and 32% of patients

had three or more prior systemic therapies for advanced melanoma. Forty-five percent had an ECOG Performance Status of 1, 40% had elevated LDH and 23% had a BRAF mutated tumour.

The primary efficacy outcome measures were PFS as assessed by IRO using RECIST version 1.1 and OS. Secondary efficacy outcome measures were ORR and response duration. Table 4 summarises key efficacy measures at the final analysis in patients previously treated with ipilimumab, and the Kaplan-Meier curve for PFS is shown in Figure 3. Both pembrolizumab arms were superior to chemotherapy for PFS, and there was no difference between pembrolizumab doses. 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 randomised to the chemotherapy arm, 55% crossed over and subsequently received treatment with pembrolizumab.

Table 4: Efficacy results in KEYNOTE-002

Endpoint	Pembrolizumab 2 mg/kg every 3 weeks n=180	Pembrolizumab 10 mg/kg every 3 weeks n=181	Chemotherapy n=179
PFS			
Number (%) of patients with event	150 (83%)	144 (80%)	172 (96%)
Hazard ratio* (95% CI)	0.58 (0.46, 0.73)	0.47 (0.37, 0.60)	---
p-Value†	< 0.001	< 0.001	---
Median in months (95% CI)	2.9 (2.8, 3.8)	3.0 (2.8, 5.2)	2.8 (2.6, 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†	0.1173	0.0106‡	---
Median in months (95% CI)	13.4 (11.0, 16.4)	14.7 (11.3, 19.5)	11.0 (8.9, 13.8)
Best overall response			
ORR % (95% CI)	22% (16, 29)	28% (21, 35)	5% (2, 9)
Complete response %	3%	7%	0%
Partial response %	19%	20%	5%
Response duration§			
Median in months (range)	22.8 (1.4+, 25.3+)	Not reached (1.1+, 28.3+)	6.8 (2.8, 11.3)
% ongoing at 12 months	73%¶	79%¶	0%¶

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

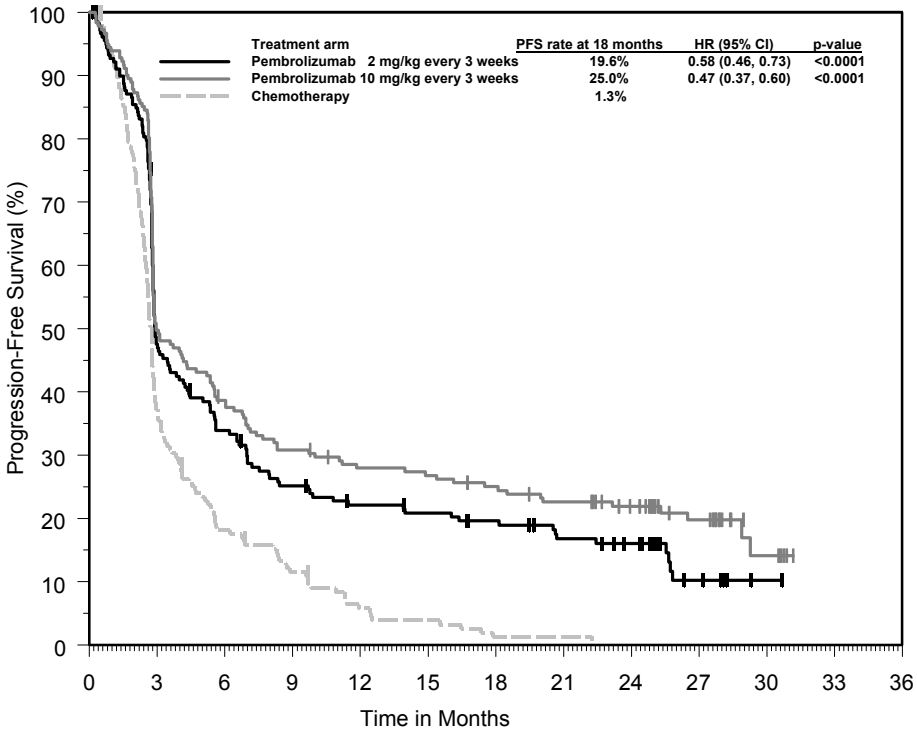
† Based on stratified Log rank test

‡ Not statistically significant after adjustment for multiplicity

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

¶ Based on Kaplan-Meier estimation

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



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

KEYNOTE-001: Open label study in melanoma patients naïve and previously treated with ipilimumab

The safety and efficacy of pembrolizumab for patients with advanced melanoma were investigated in an uncontrolled, open-label study, KEYNOTE-001. Efficacy was evaluated for 276 patients from two defined cohorts, one which included patients previously treated with ipilimumab (and if BRAF V600 mutation-positive, with a BRAF or MEK inhibitor) and the other which included patients naïve to treatment with ipilimumab. Patients were randomly assigned to receive pembrolizumab at a dose of 2 mg/kg every 3 weeks or 10 mg/kg every 3 weeks. Patients were treated with pembrolizumab until disease progression or unacceptable toxicity. Clinically stable patients with initial evidence of disease progression were permitted to remain on treatment until disease progression was confirmed. Exclusion criteria were similar to those of KEYNOTE-002.

Of the 89 patients receiving 2 mg/kg of pembrolizumab who were previously treated with ipilimumab, 53% were male, 33% were ≥ 65 years of age and the median age was 59 years (range 18-88). All but two patients were white. Eighty-four percent had M1c stage and 8% of patients had a history of brain metastases. Seventy percent had at least two and 35% of patients had three or more prior systemic therapies for advanced melanoma. BRAF mutations were reported in 13% of the study population. All patients with BRAF mutant tumours were previously treated with a BRAF inhibitor.

Of the 51 patients receiving 2 mg/kg of pembrolizumab who were naïve to treatment with ipilimumab, 63% were male, 35% were ≥ 65 years of age and the median age was 60 years (range 35-80). All but one patient was white. Sixty-three percent had M1c stage and 2% of patients had a history of brain metastases. Forty-five percent had no prior therapies for advanced melanoma. BRAF mutations were reported in 20 (39%) patients. Among patients with BRAF mutant tumours, 10 (50%) were previously treated with a BRAF inhibitor.

The primary efficacy outcome measure was ORR as assessed by independent review using RECIST 1.1. Secondary efficacy outcome measures were disease control rate (DCR; including

complete response, partial response and stable disease), response duration, PFS and OS. Tumour response was assessed at 12-week intervals. Table 5 summarises key efficacy measures in patients previously treated or naïve to treatment with ipilimumab, receiving pembrolizumab at the recommended dose based on a minimum follow-up time of 30 months for all patients.

Table 5: Efficacy results in KEYNOTE-001

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

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

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

Sub-population analyses

BRAF mutation status in melanoma
A subgroup analysis was performed as part of the final analysis of KEYNOTE-002 in patients who were BRAF wild type (n=414; 77%) or BRAF mutant with prior BRAF treatment (n=126; 23%) as summarised in Table 6.

Table 6: Efficacy results by BRAF mutation status in KEYNOTE-002

	BRAF wild type		BRAF mutant with prior BRAF treatment	
Endpoint	**Pembrolizumab 2mg/kg every 3 weeks (n=136)**	**Chemotherapy (n=137)**	**Pembrolizumab 2mg/kg every 3 weeks (n=44)**	**Chemotherapy (n=42)**
PFS Hazard ratio* (95% CI)	0.50 (0.39, 0.66)	---	0.79 (0.50, 1.25)	---
OS Hazard ratio* (95% CI)	0.78 (0.58, 1.04)	---	1.07 (0.64, 1.78)	---
ORR %	26%	6%	9%	0%

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

A subgroup analysis was performed as part of the final analysis of KEYNOTE-006 in patients who were BRAF wild type (n=525; 63%), BRAF mutant without prior BRAF treatment (n=163; 20%) and BRAF mutant with prior BRAF treatment (n=139; 17%) as summarised in Table 7.

Table 7: Efficacy results by BRAF mutation status in KEYNOTE-006

	BRAF wild type		BRAF mutant without prior BRAF treatment		BRAF mutant with prior BRAF treatment	
Endpoint	**Pembrolizumab 10mg/kg every 2 or 3 weeks (pooled)**	**Ipilimumab (n=170)**	**Pembrolizumab 10mg/kg every 2 or 3 weeks (pooled)**	**Ipilimumab (n=55)**	**Pembrolizumab 10mg/kg every 2 or 3 weeks (pooled)**	**Ipilimumab (n=52)**
PFS Hazard ratio* (95% CI)	0.61 (0.49, 0.76)	---	0.52 (0.35, 0.78)	---	0.76 (0.51, 1.14)	---
OS Hazard ratio* (95% CI)	0.68 (0.52, 0.88)	---	0.70 (0.40, 1.22)	---	0.66 (0.41, 1.04)	---
ORR %	38%	14%	41%	15%	24%	10%

* Hazard ratio (pembrolizumab compared to ipilimumab) based on the stratified Cox proportional hazard model

PD-L1 status in melanoma

A subgroup analysis was performed as part of the final analysis of KEYNOTE-002 in patients who were PD-L1 positive (PD-L1 expression in ≥ 1% of tumour and tumour-associated immune cells) vs. PD-L1 negative. PD-L1 expression was tested retrospectively by immunohistochemistry assay with the 22C3 anti-PD-L1 antibody. Among patients who were evaluable for PD-L1 expression (79%), 69% (n=294) were PD-L1 positive and 31% (n=134) were PD-L1 negative. Table 8 summarises efficacy results by PD-L1 expression.

Table 8: Efficacy results by PD-L1 expression in KEYNOTE-002

Endpoint	Pembrolizumab 2 mg/kg every 3 weeks	Chemotherapy	Pembrolizumab 2 mg/kg every 3 weeks	Chemotherapy
	PD-L1 positive		PD-L1 negative	
PFS Hazard ratio* (95% CI)	0.55 (0.40, 0.76)	---	0.81 (0.50, 1.31)	---
OS Hazard ratio* (95% CI)	0.90 (0.63, 1.28)	---	1.18 (0.70, 1.99)	---
ORR %	25%	4%	10%	8%

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

A subgroup analysis was performed as part of the final analysis of KEYNOTE-006 in patients who were PD-L1 positive (n=671; 80%) vs. PD-L1 negative (n=150; 18%). Among patients who were evaluable for PD-L1 expression (98%), 82% were PD-L1 positive and 18% were PD-L1 negative. Table 9 summarizes efficacy results by PD-L1 expression.

Table 9: Efficacy results by PD-L1 expression in KEYNOTE-006

Endpoint	Pembrolizumab 10 mg/kg every 2 or 3 weeks (pooled)	Ipilimumab	Pembrolizumab 10 mg/kg every 2 or 3 weeks (pooled)	Ipilimumab
	PD L1 positive		PD L1 negative	
PFS Hazard ratio* (95% CI)	0.53 (0.44, 0.65)	---	0.87 (0.58, 1.30)	---
OS Hazard ratio* (95% CI)	0.63 (0.50, 0.80)	---	0.76 (0.48, 1.19)	---
ORR %	40%	14%	24%	13%

* Hazard ratio (pembrolizumab compared to ipilimumab) based on the stratified Cox proportional hazard model

Ocular melanoma

In 20 subjects with ocular melanoma included in KEYNOTE-001, no objective responses were reported; stable disease was reported in 6 patients.

NSCLC

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

The safety and efficacy of pembrolizumab were investigated in KEYNOTE-024, a multicentre, controlled study for the treatment of previously untreated metastatic NSCLC. Patients had PD-L1 expression with a ≥ 50% tumour proportion score (TPS) based on the PD-L1 IHC 22C3 pharmDx™ Kit. Patients were randomised (1:1) to receive pembrolizumab at a dose of 200 mg every 3 weeks (n=154) or investigator's choice platinum-containing chemotherapy (n=151; including pemetrexed+carboplatin, pemetrexed+cisplatin, gemcitabine+cisplatin, gemcitabine+carboplatin, or paclitaxel+carboplatin. Non-squamous patients could receive pemetrexed maintenance). Patients were treated with pembrolizumab until unacceptable toxicity or disease progression. Treatment could continue beyond disease progression if the patient was clinically stable and was considered to be deriving clinical benefit by the investigator. Patients without disease progression could be treated for up to 24 months. The study excluded 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. Assessment of tumour status was performed every 9 weeks. Patients on chemotherapy who experienced independently-verified progression of disease were able to crossover and receive pembrolizumab.

Among the 305 patients in KEYNOTE-024, baseline characteristics were: median age 65 years (54% age 65 or older); 61% male; 82% White, 15% Asian; and ECOG performance status 0 and 1 in 35% and 65%, respectively. Disease characteristics were squamous (18%) and non-squamous (82%); M1 (99%); and brain metastases (9%).

The primary efficacy outcome measure was PFS as assessed by BICR using RECIST 1.1. Secondary efficacy outcome measures were OS and ORR (as assessed by BICR using RECIST 1.1). Table 10 summarizes key efficacy measures for the entire ITT population.

Table 10: Efficacy results in KEYNOTE-024

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

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

† Based on stratified Log rank test

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

§ Based on Kaplan-Meier estimates; includes 43 patients with responses of 6 months or longer

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

NA = not available

Figure 4: Kaplan-Meier curve for progression-free survival by treatment arm in KEYNOTE-024 (intent to treat population)

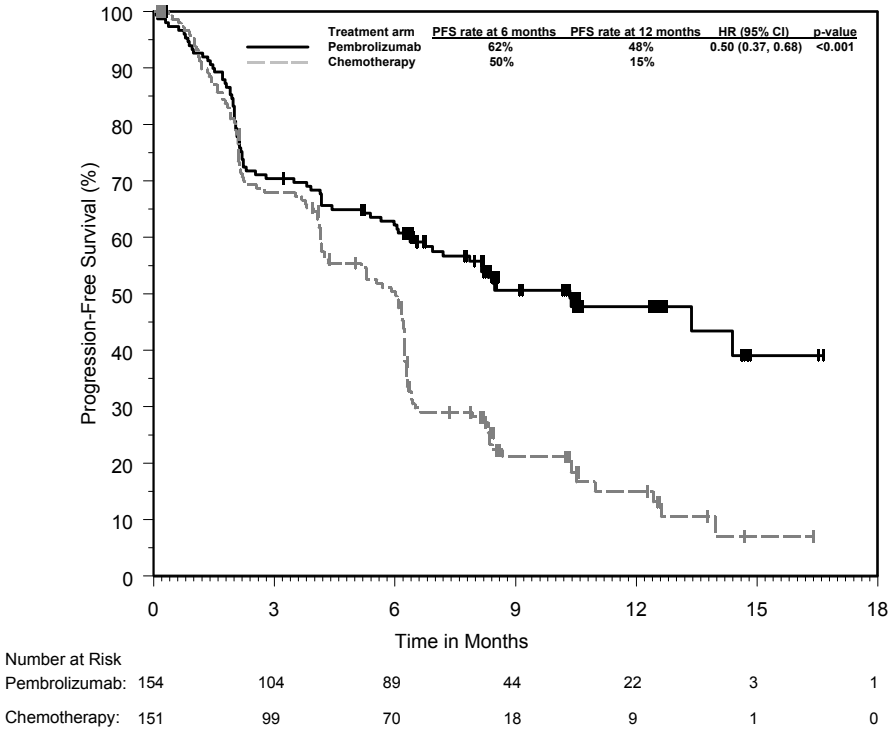
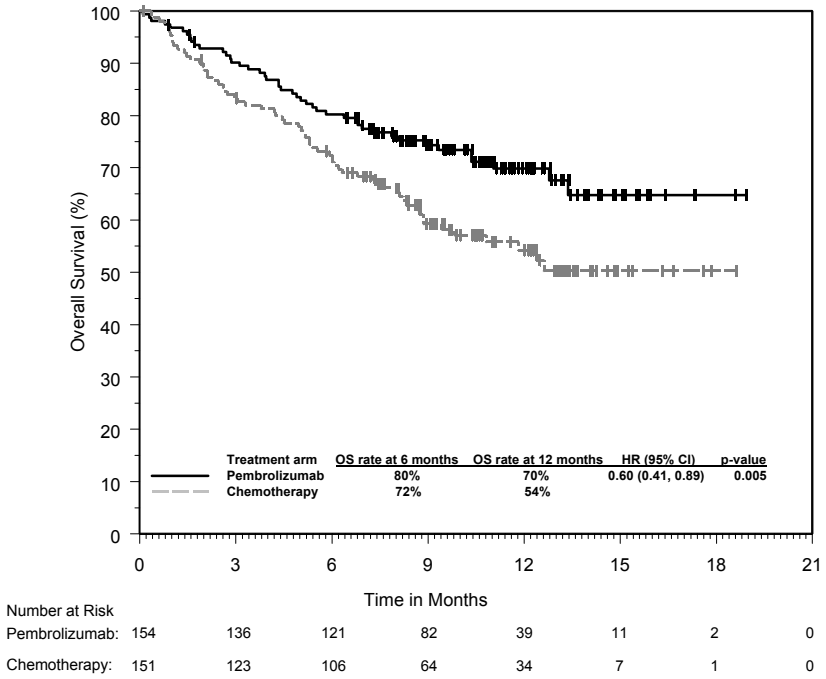


Figure 5: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-024 (intent to treat population)



In a subgroup analysis, a reduced survival benefit of pembrolizumab compared to chemotherapy was observed in the small number of patients who were never-smokers; however, due to the small number of patients, no definitive conclusions can be drawn from these data.

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

The safety and efficacy of pembrolizumab were investigated in KEYNOTE-010, a multicentre, open-label, controlled study for the treatment of advanced NSCLC in patients previously treated with platinum-containing chemotherapy. Patients had PD-L1 expression with a ≥ 1% TPS based on the PD-L1 IHC 22C3 pharmDx™ Kit. Patients with EGFR activation mutation or ALK translocation also had disease progression on approved therapy for these mutations prior to receiving pembrolizumab. Patients were randomised (1:1:1) to receive pembrolizumab at a dose of 2 (n=344) or 10 mg/kg (n=346) every 3 weeks or docetaxel at a dose of 75 mg/m^2 every 3 weeks (n=343) until disease progression or unacceptable toxicity. The trial excluded patients with autoimmune disease; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks. Assessment of tumour status was performed every 9 weeks. The baseline characteristics for this population included: median age 63 years (42% age 65 or older); 61% male; 72% White and 21% Asian and 34% and 66% with an ECOG performance status 0 and 1, respectively. Disease characteristics were squamous (21%) and non-squamous (70%); M1 (91%); stable brain metastases (15%) and the incidence of mutations was EGFR (8%) or ALK (1%). Prior therapy included platinum-doublet regimen (100%); patients received one (69%) or two or more (29%) treatment lines.

The primary efficacy outcome measures were OS and PFS as assessed by blinded independent central review (BICR) using RECIST 1.1. Secondary efficacy outcome measures were ORR and response duration. Table 11 summarises key efficacy measures for the entire population (TPS ≥ 1%) and for the patients with TPS ≥ 50% and the Kaplan-Meier curve for OS (TPS ≥ 1%) is shown in Figure 6.

Table 11: Response to pembrolizumab 2 or 10 mg/kg every 3 weeks in previously treated patients with NSCLC in KEYNOTE-010

Endpoint	Pembrolizumab 2 mg/kg every 3 weeks	Pembrolizumab 10 mg/kg every 3 weeks	Docetaxel 75 mg/m^2 every 3 weeks
TPS ≥ 1%			
Number of patients	344	346	343
OS			
Number (%) of patients with event	172 (50%)	156 (45%)	193 (56%)
Hazard ratio* (95% CI)	0.71 (0.58, 0.88)	0.61 (0.49, 0.75)	---
p-Value[†]	< 0.001[‡]	< 0.001[‡]	---
Median in months (95% CI)	10.4 (9.4, 11.9)	12.7 (10.0, 17.3)	8.5 (7.5, 9.8)
PFS[§]			
Number (%) of patients with event	266 (77%)	255 (74%)	257 (75%)
Hazard ratio* (95% CI)	0.88 (0.73, 1.04)	0.79 (0.66, 0.94)	---
p-Value[†]	0.068	0.005	---
Median in months (95% CI)	3.9 (3.1, 4.1)	4.0 (2.6, 4.3)	4.0 (3.1, 4.2)
Overall response rate[§]			
ORR %[¶] (95% CI)	18% (14, 23)	18% (15, 23)	9% (7, 13)
Response duration[§,#,Þ]			
Median in months (range)	Not reached (0.7+, 20.1+)	Not reached (2.1+, 17.8+)	6.2 (1.4+, 8.8+)
% ongoing	73%	72%	34%
TPS ≥ 50%			
Number of patients	139	151	152
OS			
Number (%) of patients with event	58 (42%)	60 (40%)	86 (57%)
Hazard ratio* (95% CI)	0.54 (0.38, 0.77)	0.50 (0.36, 0.70)	---
p-Value[†]	< 0.001[‡]	< 0.001[‡]	---
Median in months (95% CI)	14.9 (10.4, NA)	17.3 (11.8, NA)	8.2 (6.4, 10.7)
PFS[§]			
Number (%) of patients with event	89 (64%)	97 (64%)	118 (78%)
Hazard ratio* (95% CI)	0.58 (0.43, 0.77)	0.59 (0.45, 0.78)	---
p-Value[†]	< 0.001[‡]	< 0.001[‡]	---
Median in months (95% CI)	5.2 (4.0, 6.5)	5.2 (4.1, 8.1)	4.1 (3.6, 4.3)
Overall response rate[§]			
ORR %[¶] (95% CI)	30% (23, 39)	29% (22, 37)	8% (4, 13)
Response duration[§,#,ß]			
Median in months (range)	Not reached (0.7+, 16.8+)	Not reached (2.1+, 17.8+)	8.1 (2.1+, 8.8+)
% ongoing	76%	75%	33%

* Hazard ratio (pembrolizumab compared to docetaxel) based on the stratified Cox proportional hazard model

† Based on stratified Log rank test

‡ Statistically significant based on a pre-specified α level adjusted for multiplicity

§ Assessed by blinded independent central review (BICR) using RECIST 1.1

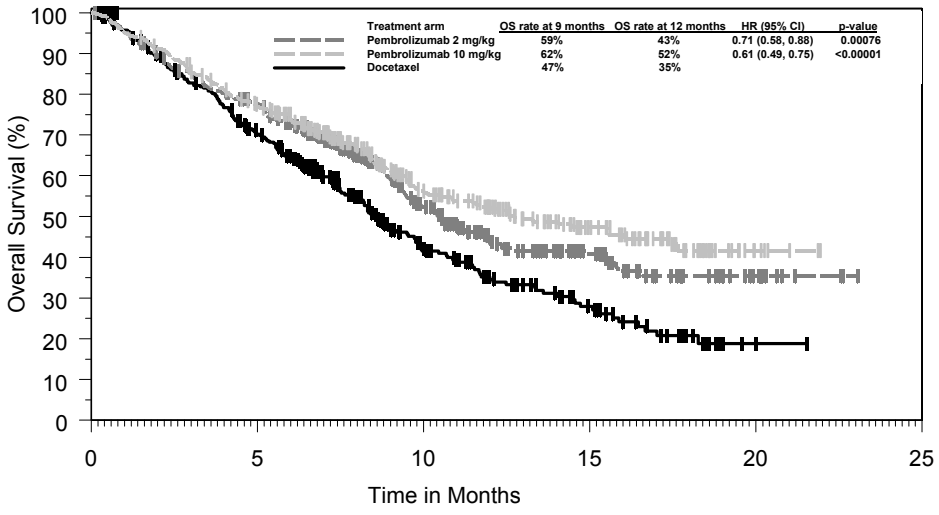
¶ All responses were partial responses

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

Þ Includes 30, 31 and 2 patients with ongoing responses of 6 months or longer in the pembrolizumab 2 mg/kg, pembrolizumab 10 mg/kg and docetaxel arms respectively

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

Figure 6: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-010 (patients with PD-L1 expression tumour proportion score ≥ 1%, intent to treat population)



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

Efficacy results were similar for the 2 mg/kg and 10 mg/kg pembrolizumab arms. Efficacy results for OS were consistent regardless of the age of tumour specimen (new vs. archival) based on an intergroup comparison.

In subgroup analyses, a reduced survival benefit of pembrolizumab compared to docetaxel was observed for patients who were never-smokers or patients with tumours harbouring EGFR activating mutations who received at least platinum-based chemotherapy and a tyrosine kinase inhibitor; however, due to the small numbers of patients, no definitive conclusions can be drawn from these data.

The efficacy and safety of pembrolizumab in patients with tumours that do not express PD-L1 have not been established.

Classical Hodgkin lymphoma
KEYNOTE-087 and KEYNOTE-013: Open-label studies in patients with relapsed or refractory classical Hodgkin lymphoma (cHL)
The efficacy of pembrolizumab was investigated in KEYNOTE-087 and KEYNOTE-013, two multicentre, open-label studies for the treatment of 241 patients with cHL. These studies enrolled patients who failed ASCT and BV, who were ineligible for ASCT because they were unable to achieve a complete or partial remission to salvage chemotherapy and failed BV, or who failed ASCT and did not receive BV. Five study subjects were ineligible to ASCT due to reasons other than failure to salvage chemotherapy. Both studies included patients regardless of PD-L1 expression. Patients with active, non-infectious pneumonitis, an allogeneic transplant within the past 5 years (or > 5 years but with GVHD), active autoimmune disease or a medical condition that required immunosuppression were ineligible for either trial. Patients received pembrolizumab 200 mg every 3 weeks (n=210; KEYNOTE-087) or 10 mg/kg every 2 weeks (n=31; KEYNOTE-013) until unacceptable toxicity or documented disease progression.

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. Disease subtypes were 80% nodular sclerosis, 11% mixed cellularity, 4% lymphocyte-rich and 2% lymphocyte-depleted.

Among KEYNOTE-013 patients, the baseline characteristics were median age 32 years (7% age 65 or older), 58% male, 94% White; and 45% and 55% had an ECOG performance status 0 and 1, respectively. The median number of prior lines of therapy administered for the treatment of cHL was 5 (range 2 to 15). Eighty-seven percent were refractory to at least one prior therapy, including 39% who were refractory to first line therapy. Seventy-four percent of patients had received Auto-SCT, 26% were transplant ineligible, and 42% of patients had prior radiation therapy. Disease subtypes were 97% nodular sclerosis and 3% mixed cellularity.

The major efficacy outcome measures (ORR and CRR) were assessed by blinded independent central review according to the 2007 revised International Working Group (IWG) criteria. Secondary efficacy outcome measures were duration of response, PFS and OS. Response was assessed in KN087 and KN013 every 12 and 8 weeks, respectively, with the first planned post-baseline assessment at week 12. Efficacy results are summarized in Table 12.

Table 12: Efficacy results in KEYNOTE-087 and KEYNOTE-013

	KEYNOTE-087[a]	KEYNOTE-013[b]
Endpoint	Pembrolizumab 200 mg every 3 weeks n=210	Pembrolizumab 10 mg/kg every 2 weeks n=31
Objective response rate[c]		
ORR % (95% CI)	69% (62.3, 75.2)	58% (39.1, 75.5)
Complete Remission	22%	19%
Partial Remission	47%	39%
Response duration[c]		
Median in months (range)	11.1 (0.0+, 11.1)[d]	Not reached (0.0+, 26.1+)[e]
% with duration ≥ 6-months	76%[f]	80%[g]
% with duration ≥ 12-months	---	70%[h]
Time to response		
Median in months (range)	2.8 (2.1, 8.8)[d]	2.8 (2.4, 8.6)[e]
PFS[c]		
Number (%) of patients with event	70 (33%)	18 (58%)
Median in months (95% CI)	11.3 (10.8, Not reached)	11.4 (4.9, 27.8)
6-month PFS rate	72%	66%
9-month PFS rate	62%	---
12-month PFS rate	---	48%
OS		
Number (%) of patients with event	4 (2%)	4 (13%)
6-month OS rate	99.5%	100%
12-month OS rate	97.6%	87.1%

[a] Median follow-up time of 10.1 months
[b] Median follow-up time of 28.7 months
[c] Assessed by blinded independent central review according to the 2007 revised International Working Group (IWG) criteria by PET CT scans
[d] Based on patients (n=145) with a response by independent review
[e] Based on patients (n=18) with a response by independent review
[f] Based on Kaplan-Meier estimation; includes 31 patients with responses of 6 months or longer
[g] Based on Kaplan-Meier estimation; includes 9 patients with responses of 6 months or longer
[h] Based on Kaplan-Meier estimation; includes 7 patients with responses of 12 months or longer

Safety and efficacy in elderly patients
Overall, 20 cHL patients ≥ 65 years were treated with pembrolizumab in studies KEYNOTE-087 and KEYNOTE-013. Data from these patients are too limited to draw any conclusion on safety or efficacy in this population.

Urothelial Carcinoma
KEYNOTE-045: Controlled trial in urothelial carcinoma patients who have received prior platinum-containing chemotherapy
The safety and efficacy of pembrolizumab were evaluated in KEYNOTE-045, a multicentre, randomised (1:1), controlled study for the treatment of locally advanced or metastatic urothelial carcinoma in patients with disease progression on or after platinum-containing chemotherapy. Patients must have received first line platinum-containing regimen for locally advanced/metastatic disease or as neoadjuvant/adjuvant treatment, with recurrence/progression ≤ 12 months following completion of therapy. Patients were randomised (1:1) to receive either KEYTRUDA 200 mg every 3 weeks (n=270) or investigator's choice of any of the following chemotherapy regimens all given intravenously every 3 weeks (n=272): paclitaxel 175 mg/m^2 (n=84), docetaxel 75 mg/m^2 (n=84), or vinflunine 320 mg/m^2 (n=87). Patients were treated with pembrolizumab until unacceptable toxicity or disease progression. Treatment could continue beyond progression if the patient was clinically stable and was considered to be deriving clinical benefit by the investigator. Patients without disease

progression could be treated for up to 24 months. The study excluded patients with autoimmune disease, a medical condition that required immunosuppression and patients with more than 2 prior lines of systemic chemotherapy for metastatic urothelial cancer. Patients with an ECOG performance status of 2 had to have a hemoglobin ≥ 10 g/dL, could not have liver metastases, and must have received the last dose of their last prior chemotherapy regimen ≥ 3 months prior to enrollment. Assessment of tumour status was performed at 9 weeks after the first dose, then every 6 weeks through the first year, followed by every 12 weeks thereafter.

Among the 542 randomised patients in KEYNOTE-045, baseline characteristics were: median age 66 years (range: 26 to 88), 58% age 65 or older; 74% male; 72% White and 23% Asian; 56% ECOG performance status of 1 and 1% ECOG performance status of 2; and 96% M1 disease and 4% M0 disease. Eighty-seven percent of patients had visceral metastases, including 34% with liver metastases. Eighty-six percent had a primary tumour in the lower tract and 14% had a primary tumour in the upper tract. Fifteen percent of patients had disease progression following prior platinum-containing neoadjuvant or adjuvant chemotherapy. Twenty-one percent had received 2 prior systemic regimens in the metastatic setting. Seventy-six percent of patients received prior cisplatin, 23% had prior carboplatin, and 1% was treated with other platinum-based regimens.

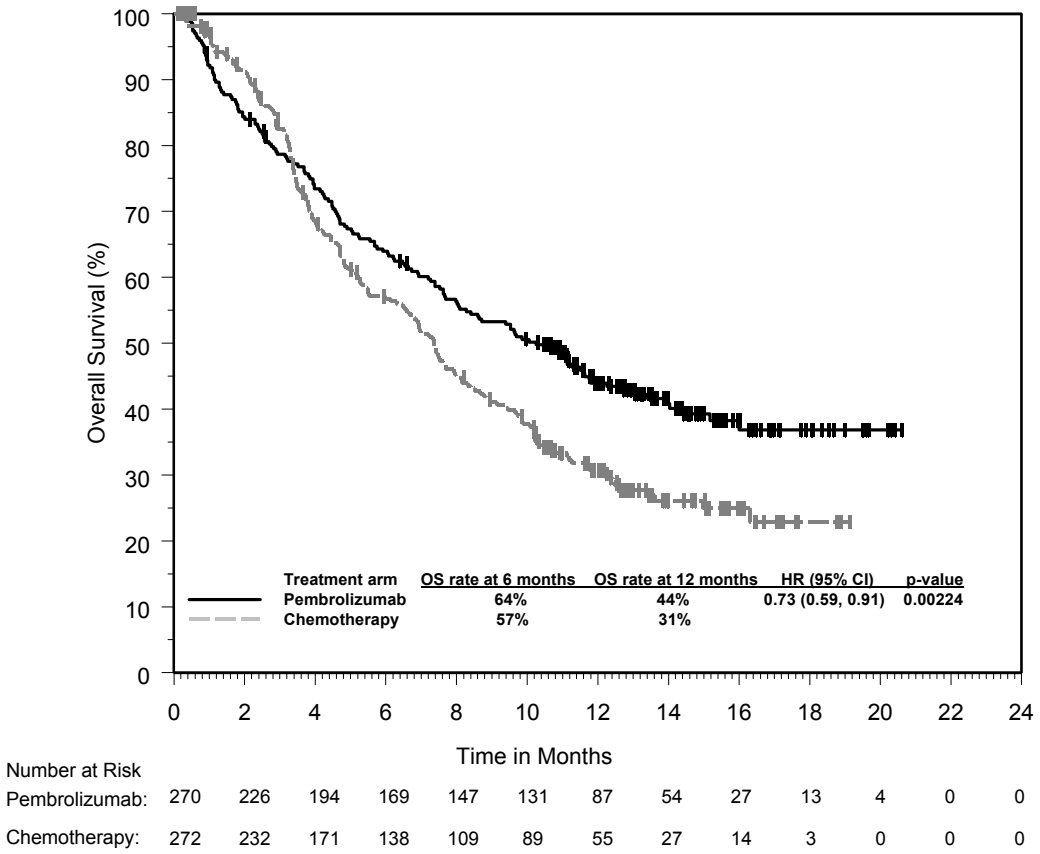
The primary efficacy outcomes were OS and PFS as assessed by BICR using RECIST v1.1. Secondary outcome measures were ORR (as assessed by BICR using RECIST v1.1) and duration of response. Table 13 summarises the key efficacy measures for the ITT population. The Kaplan-Meier curve for OS is shown in Figure 7. The study demonstrated statistically significant improvements in OS and ORR for patients randomised to pembrolizumab as compared to chemotherapy. There was no statistically significant difference between pembrolizumab and chemotherapy with respect to PFS.

Table 13: Response to pembrolizumab 200 mg every 3 weeks in patients with urothelial carcinoma previously treated with chemotherapy in KEYNOTE-045

Endpoint	Pembrolizumab 200 mg every 3 weeks n=270	Chemotherapy n=272
OS		
Number (%) of patients with event	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)
p-Value§	0.001	
Complete Response	7%	3%
Partial Response	14%	8%
Stable Disease	17%	34%
Response duration‡,¶		
Median in months (range)	Not reached (1.6+, 15.6+)	4.3 (1.4+, 15.4+)
Number (%#) of patients with duration ≥6 months	41 (78%)	7 (40%)
Number (%#) of patients with duration ≥12 months	14 (68%)	3 (35%)

* Hazard ratio (pembrolizumab compared to chemotherapy) based on the stratified Cox proportional hazard model
† Based on stratified Log rank test
‡ Assessed by BICR using RECIST 1.1
§ Based on method by Miettinen and Nurminen
¶ Based on patients with a best overall response as confirmed complete or partial response
# Based on Kaplan-Meier estimation

Figure 7: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-045 (intent to treat population)



An analysis was performed in KEYNOTE-045 in patients who had PD-L1 Combined Positive Score (CPS) < 10 [pembrolizumab: n=186 (69%) vs. chemotherapy: n= 176 (65%)] or ≥ 10 [pembrolizumab: n=74 (27%) vs. chemotherapy: n= 90 (33%)] in both pembrolizumab- and chemotherapy-treated arms (see Table 14).

Table 14: OS by PD-L1 Expression

PD-L1 Expression	Pembrolizumab	Chemotherapy	
	OS by PD-L1 Expression Number of Events (number of patients)		Hazard Ratio* (95% CI)
CPS < 10	106 (186)	116 (176)	0.80 (0.61, 1.05)
CPS ≥ 10	44 (74)	60 (90)	0.57 (0.37, 0.88)

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

Patient-reported outcomes (PROs) were assessed using EORTC QLQ-C30. A prolonged time to deterioration in EORTC QLQ-C30 global health status/QoL was observed for patients treated with pembrolizumab compared to investigator's choice chemotherapy (HR 0.70; 95% CI 0.55-0.90). Over 15 weeks of follow-up, patients treated with pembrolizumab had stable global health status/QoL, while those treated with investigator's choice chemotherapy had a decline in global health status/QoL. These results should be interpreted in the context of the open-label study design and therefore taken cautiously.

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

The safety and efficacy of pembrolizumab were investigated in KEYNOTE-052, a multicentre, open-label study for the treatment of locally advanced or metastatic urothelial carcinoma in patients who were not eligible for cisplatin-containing chemotherapy. Patients received pembrolizumab at a dose of 200 mg every 3 weeks until unacceptable toxicity or disease progression. Treatment could continue beyond progression if the patient was clinically stable and was considered to be deriving clinical benefit by the investigator. Patients without disease progression could be treated for up to 24 months. The study excluded patients with autoimmune disease or a medical condition that required immunosuppression. Assessment of tumour status was performed at 9 weeks after the first dose, then every 6 weeks through the first year, followed by every 12 weeks thereafter.

Among 370 patients with urothelial carcinoma who were not eligible for cisplatin-containing chemotherapy baseline characteristics were: median age 74 years (82% age 65 or older); 77% male; and 89% White and 7% Asian. Eighty-seven percent had M1 disease and 13% had M0 disease. Eighty-five percent of patients had visceral metastases, including 21% with liver metastases. Reasons for cisplatin ineligibility included: baseline creatinine clearance of <60 mL/min (50%), ECOG performance status of 2 (32%), ECOG performance status of 2 and baseline creatinine clearance of <60 mL/min (9%), and other (Class III heart failure, Grade 2 or greater peripheral neuropathy, and Grade 2 or greater hearing loss; 9%). Ninety percent of patients were treatment naïve, and 10% received prior adjuvant or neoadjuvant platinum-based chemotherapy. Eighty-one percent had a primary tumour in the lower tract, and 19% of patients had a primary tumour in the upper tract.

The primary efficacy outcome measure was ORR as assessed by BICR using RECIST 1.1. Secondary efficacy outcome measures were duration of response, PFS, and OS. Table 15 summarises the key efficacy measures for the study population based on a median follow-up time of 9.5 months for all patients.

Table 15: Response to pembrolizumab 200 mg every 3 weeks in patients with urothelial carcinoma ineligible for cisplatin-containing chemotherapy in KEYNOTE-052

Endpoint	n=370
Objective Response Rate*	
ORR %, (95% CI)	29% (25, 34)
Disease Control Rate†	47%
Complete Response	7%
Partial Response	22%
Stable Disease	18%
Response Duration	
Median in months (range)	Not reached (1.4+, 19.6+)
% with duration ≥ 6-months	82%‡
Time to Response	
Median in months (range)	2.1 (1.3, 9.0)
PFS*	
Median in months (95% CI)	2.3 (2.1, 3.4)
6-month PFS rate	34%
OS*	
Median in months (95% CI)	11.0 (10.0, 13.6)
6-month OS rate	67%

* Assessed by BICR using RECIST 1.1
† Based on best response of stable disease or better
‡ Based on Kaplan-Meier estimates; includes 77 patients with response of 6 months or longer

An analysis was performed in KEYNOTE-052 in patients who had PD-L1 CPS < 10 (n=251; 68%) or ≥ 10 (n=110; 30%) (see Table 16).

Table 16: ORR by PD-L1 Expression

	ORR % by PD-L1 Expression* (95% CI)
PD-L1 Expression	**Pembrolizumab**
CPS < 10	21 (16.2, 26.7)
CPS ≥ 10	47 (37.7, 57.0)

* BICR-RECIST 1.1

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with pembrolizumab in one or more subsets of the paediatric population in treatment of all conditions included in the category of malignant neoplasms (except nervous system, haematopoietic and lymphoid tissue) (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics of pembrolizumab was studied in 2,993 patients with metastatic or unresectable melanoma, NSCLC, or carcinoma who received doses in the range of 1 to 10 mg/kg every 2 or 3 weeks.

Absorption
Pembrolizumab is dosed via the intravenous 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 (~7.5 L; CV: 20%). As expected for an antibody, pembrolizumab does not bind to plasma proteins in a specific manner.

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

Elimination
The systemic clearance of pembrolizumab is ~0.2 L/day (CV: 37%) and the terminal half-life (t½) is ~25 days (CV: 38%).

Linearity/non-linearity
Exposure to pembrolizumab as expressed by peak concentration (C_{max}) or area under the plasma concentration time curve (AUC) increased dose proportionally within the dose range for efficacy. Upon repeated dosing, the clearance of pembrolizumab was found to be independent of time, and systemic accumulation was approximately 2.1-fold when administered every 3 weeks. Near steady-state concentrations of pembrolizumab were achieved by 18 weeks; the median steady-state through concentrations (C_{min}) at 18 weeks were approximately 21 mcg/mL at a dose of 2 mg/kg every 3 weeks and 28 mcg/mL at a dose of 200 mg every 3 weeks. The median area under the concentration time curve at steady state over 3 weeks ($AUC_{0\text{-}3weeks}$) was 658 mcg·day/mL at a dose of 2 mg/kg every 3 weeks and 876 mcg·day/mL at a dose of 200 mg every 3 weeks.

Following administration of pembrolizumab 200 mg every 3 weeks in patients with cHL, the observed median C_{min} at steady-state was up to 40% higher than that in other tumour types treated with the same dosage; however, the range of trough concentrations is similar. There are no notable differences in median C_{max} between cHL and other tumour types. Based on available safety data in cHL and other tumour types, these differences are not clinically meaningful.

Special populations
The effects of various covariates on the pharmacokinetics of pembrolizumab were assessed in population pharmacokinetic analyses. The following factors had no clinically important effect on the clearance of pembrolizumab: age (range 15-94 years), gender, race, mild or moderate renal impairment, mild hepatic impairment and tumour burden. The relationship between body weight and clearance supports the use of either fixed dose or body weight-based dosing to provide adequate and similar control of exposure.

Renal impairment
The effect of renal impairment on the clearance of pembrolizumab was evaluated by population pharmacokinetic analyses in patients with mild or moderate renal impairment compared to patients with normal 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. Pembrolizumab has not been studied in patients with severe renal impairment.

Hepatic impairment
The effect of hepatic impairment on the clearance of pembrolizumab was evaluated by population pharmacokinetic analyses in patients with mild hepatic impairment (as defined using the US National Cancer Institute criteria of hepatic dysfunction) compared to patients with normal hepatic function. No clinically important differences in the clearance of pembrolizumab were found between patients

with mild hepatic impairment and normal hepatic function. Pembrolizumab has not been studied in patients with moderate or severe hepatic impairment (see section 4.2).

5.3 Preclinical safety data

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

Animal reproduction studies have not been conducted with pembrolizumab. The PD-1/PD-L1 pathway is thought to be involved in maintaining tolerance to the foetus throughout pregnancy. Blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the foetus and to result in an increase in foetal loss.

Animal fertility studies have not been conducted with pembrolizumab. In 1 month and 6 month repeat-dose toxicology studies in monkeys, there were no notable effects in the male and female reproductive organs; however, many animals in these studies were not sexually mature.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-histidine
L-histidine hydrochloride monohydrate
Sucrose
Polysorbate 80

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial
3 years.

After reconstitution
From a microbiological point of view, the reconstituted or diluted solution should be used immediately. The reconstituted or diluted solution must not be frozen. If not used immediately, chemical and physical in-use stability of KEYTRUDA has been demonstrated for 24 hours at 2°C to 8°C. This 24 hour total hold from reconstitution may include up to 6 hours at room temperature (at or below 25°C). If refrigerated, the vials and/or intravenous bags must be allowed to come to room temperature prior to use.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

For storage conditions after reconstitution or dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

15 mL Type I glass vial, with a grey bromobutyl stopper and an aluminium seal with an avocado coloured flip-off cap, containing 50 mg pembrolizumab.

Each carton contains one vial.

6.6 Special precautions for disposal and other handling

Preparation and administration

- Prior to reconstitution, the vial of lyophilised powder can be out of refrigeration (temperatures at or below 25°C) for up to 24 hours.
- Aseptically add 2.3 mL of water for injections to yield a 25 mg/mL (pH 5.2-5.8) solution of KEYTRUDA. Each vial contains an excess fill of 10 mg (0.4 mL) to ensure the recovery of 50 mg of KEYTRUDA per vial. After reconstitution, 1 mL of concentrate contains 25 mg of pembrolizumab.
- To avoid foaming, deliver the water along the walls of the vial and not directly on the lyophilised powder.
- Slowly swirl the vial to allow reconstitution of the lyophilised powder. Allow up to 5 minutes for the bubbles to clear. Do not shake the vial.
- Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration. Reconstituted KEYTRUDA is a clear to slightly opalescent, colourless to slightly yellow solution. Discard the vial if visible particles are observed.
- Withdraw the required volume up to 2 mL (50 mg) of KEYTRUDA and transfer into an intravenous bag containing sodium chloride 9 mg/mL (0.9%) or glucose 50 mg/mL (5%) to prepare a diluted solution with a final concentration ranging from 1 to 10 mg/mL. Mix diluted solution by gentle inversion.
- From a microbiological point of view, the reconstituted or diluted solution should be used immediately. The reconstituted or diluted solution must not be frozen. If not used immediately, chemical and physical in-use stability of KEYTRUDA has been demonstrated for 24 hours at 2°C to 8°C. This 24 hour total hold from reconstitution may include up to 6 hours at room temperature (at or below 25°C). If refrigerated, the vials and/or intravenous bags must be allowed to come to room temperature prior to use. Administer the 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 medicinal products through the same infusion line.
- KEYTRUDA is for single use only. Discard any unused portion left in the vial.

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

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Limited
Hertford Road
Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1024/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 July 2015

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

KEYTRUDA 25 mg/mL concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of 4 mL of concentrate contains 100 mg of pembrolizumab.
Each mL of concentrate contains 25 mg of pembrolizumab.

Pembrolizumab is a humanised monoclonal anti-programmed cell death-1 (PD-1) antibody (IgG4/kappa isotype with a stabilising sequence alteration in the Fc region) produced in Chinese hamster ovary cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear to slightly opalescent, colourless to slightly yellow solution, pH 5.2 – 5.8.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

KEYTRUDA as monotherapy is indicated for the first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a ≥ 50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations.

KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic NSCLC in adults whose tumours express PD-L1 with a ≥ 1% TPS and who have received at least one prior chemotherapy regimen. Patients with EGFR or ALK positive tumour mutations should also have received targeted therapy before receiving KEYTRUDA.

KEYTRUDA as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV.

KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy (see section 5.1).

KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy.

4.2 Posology and method of administration

Therapy must be initiated and supervised by specialist physicians experienced in the treatment of cancer.

PD-L1 testing for patients with NSCLC
Patients with NSCLC should be selected for treatment based on the tumour expression of PD-L1 confirmed by a validated test (see section 5.1).

Posology
KEYTRUDA should be administered as an intravenous infusion over 30 minutes every 3 weeks.

The recommended dose of KEYTRUDA is:
- 200 mg for NSCLC that has not been previously treated with chemotherapy cHL or for urothelial carcinoma.
- 2 mg/kg for NSCLC that has been previously treated with chemotherapy or for melanoma.

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. It is recommended to continue treatment for clinically stable patients with initial evidence of disease progression until disease progression is confirmed.

Dose delay or discontinuation (see also section 4.4)

Table 1: Recommended treatment modifications for KEYTRUDA

Immune-related adverse reactions	**Severity**	**Treatment modification**
Pneumonitis	Grade 2	Withhold until adverse reactions recover to Grade 0-1*
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue
Colitis	Grade 2 or 3	Withhold until adverse reactions recover to Grade 0-1*
	Grade 4 or recurrent Grade 3	Permanently discontinue
Nephritis	Grade 2 with creatinine > 1.5 to ≤ 3 times upper limit of normal (ULN)	Withhold until adverse reactions recover to Grade 0-1*
	Grade ≥ 3 with creatinine > 3 times ULN	Permanently discontinue

Endocrinopathies	Symptomatic hypophysitis Type 1 diabetes associated with Grade > 3 hyperglycaemia (glucose > 250 mg/dL or > 13.9 mmol/L) or associated with ketoacidosis Hyperthyroidism Grade ≥ 3	Withhold until adverse reactions recover to Grade 0-1* For patients with Grade 3 or Grade 4 endocrinopathy that improved to Grade 2 or lower and is controlled with hormone replacement, if indicated, continuation of pembrolizumab may be considered after corticosteroid taper, if needed. Otherwise treatment should be discontinued. Hypothyroidism may be managed with replacement therapy without treatment interruption.
Hepatitis	Grade 2 with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 to 5 times ULN or total bilirubin > 1.5 to 3 times ULN	Withhold 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
	In case of liver metastasis with baseline Grade 2 elevation of AST or ALT, hepatitis with AST or ALT increases ≥ 50% and lasts ≥ 1 week	Permanently discontinue
Skin reactions	Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold until adverse reactions recover to Grade 0-1*
	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) Grade 3 or 4 myocarditis Grade 3 or 4 encephalitis Grade 3 or 4 Guillain-Barré syndrome Grade 4 or recurrent Grade 3	Withhold until adverse reactions recover to Grade 0-1* Permanently discontinue Permanently discontinue
Infusion-related reactions	Grade 3 or 4	Permanently discontinue

Note: toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE v.4).

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

The safety of re-initiating pembrolizumab therapy in patients previously experiencing immune-related myocarditis is not known.

KEYTRUDA should be permanently discontinued for Grade 4 or recurrent Grade 3 adverse reactions, unless otherwise specified in Table 1.

For Grade 4 haematological toxicity, only in patients with cHL, KEYTRUDA should be withheld until adverse reactions recover to Grade 0-1.

Patients treated with KEYTRUDA must be given the Patient Alert Card and be informed about the risks of KEYTRUDA (see also package leaflet).

Special populations
Elderly
No overall differences in safety or efficacy were reported between elderly patients (≥ 65 years) and younger patients (< 65 years). No dose adjustment is necessary in this population.

Data from patients ≥ 65 years are too limited to draw conclusions on cHL population (see section 5.1).

Renal impairment
No dose adjustment is needed for patients with mild or moderate renal impairment. KEYTRUDA has not been studied in patients with severe renal impairment (see sections 4.4 and 5.2).

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 sections 4.4 and 5.2).

Ocular melanoma
There are limited data on the safety and efficacy of KEYTRUDA in patients with ocular melanoma (see section 5.1).

Eastern Cooperative Oncology Group (ECOG) performance status score ≥ 2
Patients with ECOG performance status score ≥ 2 were excluded from the clinical trials of melanoma, NSCLC and cHL (see sections 4.4 and 5.1).

Paediatric population
The safety and efficacy of KEYTRUDA in children below 18 years of age have not yet been established. No data are available.

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

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Assessment of PD-L1 status
When assessing the PD-L1 status of the tumour, it is important that a well-validated and robust methodology is chosen to minimise false negative or false positive determinations.

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

For suspected immune-related adverse reactions, adequate evaluation to confirm aetiology or exclude other causes should be ensured. Based on the severity of the adverse reaction, pembrolizumab should be withheld and corticosteroids administered. Upon improvement to Grade ≤ 1, corticosteroid taper should be initiated and continued over at least 1 month. Based on limited data from clinical studies in patients whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered.

Pembrolizumab 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.

Pembrolizumab must be permanently discontinued for any Grade 3 immune-related adverse reaction that recurs and for any Grade 4 immune-related adverse reaction toxicity, except for endocrinopathies that are controlled with replacement hormones (see sections 4.2 and 4.8).

Immune-related pneumonitis
Pneumonitis, including fatal cases, has been reported in patients receiving pembrolizumab (see section 4.8). Patients should be monitored for signs and symptoms of pneumonitis. Suspected pneumonitis should be confirmed with radiographic imaging and other causes excluded. Corticosteroids should be administered for Grade ≥ 2 events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper); pembrolizumab should be withheld for Grade 2 pneumonitis, and permanently discontinued for Grade 3, Grade 4 or recurrent Grade 2 pneumonitis (see section 4.2).

Immune-related colitis
Colitis has been reported in patients receiving pembrolizumab (see section 4.8). Patients should be monitored for signs and symptoms of colitis, and other causes excluded. Corticosteroids should be administered for Grade ≥ 2 events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper); pembrolizumab should be withheld for Grade 2 or Grade 3 colitis, and permanently discontinued for Grade 4 colitis (see section 4.2). The potential risk of gastrointestinal perforation should be taken into consideration.

Immune-related hepatitis
Hepatitis has been reported in patients receiving pembrolizumab (see section 4.8). Patients should be monitored for changes in liver function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and symptoms of hepatitis, and other causes excluded. Corticosteroids should be administered (initial dose of 0.5-1 mg/kg/day (for Grade 2 events) and 1-2 mg/kg/day (for Grade ≥ 3 events) prednisone or equivalent followed by a taper) and, based on severity of liver enzyme elevations, pembrolizumab should be withheld or discontinued (see section 4.2).

Immune-related nephritis
Nephritis has been reported in patients receiving pembrolizumab (see section 4.8). Patients should be monitored for changes in renal function, and other causes of renal dysfunction excluded. Corticosteroids should be administered for Grade ≥ 2 events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper) and, based on severity of creatinine elevations, pembrolizumab should be withheld for Grade 2, and permanently discontinued for Grade 3 or Grade 4 nephritis (see section 4.2).

Immune-related endocrinopathies
Severe endocrinopathies, including hypophysitis, type 1 diabetes mellitus, diabetic ketoacidosis, hypothyroidism, and hyperthyroidism have been observed with pembrolizumab treatment.

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

Hypophysitis has been reported in patients receiving pembrolizumab (see section 4.8). Patients should be monitored for signs and symptoms of hypophysitis (including hypopituitarism and secondary adrenal insufficiency) and other causes excluded. Corticosteroids to treat secondary adrenal insufficiency and other hormone replacement should be administered as clinically indicated, and pembrolizumab should be withheld for symptomatic hypophysitis until the event is controlled with hormone replacement. Continuation of pembrolizumab may be considered, after corticosteroid taper, if needed (see section 4.2). Pituitary function and hormone levels should be monitored to ensure appropriate hormone replacement.

Type 1 diabetes mellitus, including diabetic ketoacidosis, has been reported in patients receiving pembrolizumab (see section 4.8). Patients should be monitored for hyperglycaemia or other signs and symptoms of diabetes. Insulin should be administered for type 1 diabetes, and pembrolizumab should be withheld in cases of Grade 3 hyperglycaemia until metabolic control is achieved (see section 4.2).

Thyroid disorders, including hypothyroidism, hyperthyroidism and thyroiditis, have been reported in patients receiving pembrolizumab and can occur at any time during treatment; therefore, patients should be monitored 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. Pembrolizumab should be withheld for Grade ≥ 3 until recovery to Grade ≤ 1 hyperthyroidism. For patients with Grade 3 or Grade 4 hyperthyroidism that improved to Grade 2 or lower, continuation of pembrolizumab may be considered, after corticosteroid taper, if needed (see sections 4.2 and 4.8). Thyroid function and hormone levels should be monitored to ensure appropriate hormone replacement.

Immune-related skin adverse reactions
Immune-related severe skin reactions have been reported in patients receiving pembrolizumab (see section 4.8). Patients should be monitored for suspected severe skin reactions and other causes should be excluded. Based on the severity of the adverse reaction, pembrolizumab should be withheld or permanently discontinued, and corticosteroids should be administered (see section 4.2).

Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some with fatal outcome, have been reported in patients receiving pembrolizumab (see section 4.8). For signs or symptoms of SJS or TEN, pembrolizumab should be withheld and the patient should be referred to a specialised unit for assessment and treatment. If SJS or TEN is confirmed, pembrolizumab should be permanently discontinued (see section 4.2).

Caution should be used when considering the use of pembrolizumab in a patient who has previously experienced a severe or life-threatening skin adverse reaction on prior treatment with other immune-stimulatory anticancer agents.

Other immune-related adverse reactions
The following additional clinically significant, immune-related adverse reactions, including severe and fatal cases, have been reported in clinical trials or in post-marketing experience: uveitis, arthritis, myositis, myocarditis, pancreatitis, Guillain-Barré syndrome, myasthenic syndrome, haemolytic anaemia, sarcoidosis and encephalitis (see sections 4.2 and 4.8).

Based on the severity of the adverse reaction, pembrolizumab should be withheld and corticosteroids administered.

Pembrolizumab 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.

Pembrolizumab must be permanently discontinued for any Grade 3 immune related adverse reaction that recurs and for any Grade 4 immune related adverse reaction (see sections 4.2 and 4.8).

Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with PD-1 inhibitors. Treatment with pembrolizumab may increase the risk of rejection in solid organ transplant recipients. The benefit of treatment with pembrolizumab versus the risk of possible organ rejection should be considered in these patients.

Complications of allogeneic Haematopoietic Stem Cell Transplant (HSCT)
Allogeneic HSCT after treatment with pembrolizumab
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 pembrolizumab. 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 section 4.8).

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

Infusion-related reactions
Severe infusion-related reactions, including hypersensitivity and anaphylaxis, have been reported in patients receiving pembrolizumab (see section 4.8). For severe infusion reactions, infusion should be stopped and pembrolizumab permanently discontinued (see section 4.2). Patients with mild or moderate infusion reaction may continue to receive pembrolizumab with close monitoring; premedication with antipyretic and antihistamine may be considered.

Disease-specific precautions

Use of pembrolizumab in urothelial carcinoma patients who have received prior platinum-containing chemotherapy
Physicians should consider the delayed onset of pembrolizumab effect before initiating treatment in patients with poorer prognostic features and/or aggressive disease. In urothelial cancer, a higher number of deaths within 2 months was observed in pembrolizumab compared to chemotherapy (see section 5.1). Factors associated with early deaths were fast progressive disease on prior platinum therapy and liver metastases.

Use of pembrolizumab in urothelial cancer for patients who are considered cisplatin ineligible
The baseline and prognostic disease characteristics of the study population of KEYNOTE-052 included a proportion of patients eligible for a carboplatin-based combination or mono-chemotherapy for whom the benefit has not yet been assessed in a comparative study. No safety and efficacy data are available in frailer patients (e.g., ECOG performance status 3) considered not eligible for chemotherapy. In the absence of these data, pembrolizumab should be used with caution in this population after careful consideration of the potential risk-benefit on an individual basis.

Patients excluded from clinical trials
Patients with the following conditions were excluded from clinical trials: active CNS metastases; ECOG PS ≥ 2 (except for urothelial carcinoma); HIV, hepatitis B or hepatitis C infection; active systemic autoimmune disease; interstitial lung disease; prior pneumonitis requiring systemic corticosteroid therapy; a history of severe hypersensitivity to another monoclonal antibody; receiving immunosuppressive therapy and a history of severe immune-related adverse reactions from treatment with ipilimumab, defined as any Grade 4 toxicity or Grade 3 toxicity requiring corticosteroid treatment (> 10 mg/day prednisone or equivalent) for greater than 12 weeks. Patients with active infections were excluded from clinical trials and were required to have their infection treated prior to receiving pembrolizumab. Patients with active infections occurring during treatment with pembrolizumab were managed with appropriate medical therapy. Patients with clinically significant renal (creatinine > 1.5 x ULN) or hepatic (bilirubin > 1.5 x ULN, ALT, AST > 2.5 x ULN in the absence of liver metastases) abnormalities at baseline were excluded from clinical trials, therefore information is limited in patients with severe renal and moderate to severe hepatic impairment.

For subjects with relapsed or refractory classical Hodgkin lymphoma, clinical data for the use of pembrolizumab in patients ineligible to ASCT due to reasons other than failure to salvage chemotherapy are limited (see section 5.1).

After careful consideration of the potential increased risk, pembrolizumab may be used with appropriate medical management in these patients.

Patient Alert Card
All prescribers of KEYTRUDA must be familiar with the Physician Information and Management Guidelines. The prescriber must discuss the risks of KEYTRUDA therapy with the patient. The patient will be provided with the Patient Alert Card with each prescription.

4.5 Interaction with other medicinal products and other forms of interaction

No formal pharmacokinetic drug interaction studies have been conducted with pembrolizumab. 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 pembrolizumab should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of pembrolizumab. However, systemic corticosteroids or other immunosuppressants can be used after starting pembrolizumab to treat immune-related adverse reactions (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Women of childbearing potential should use effective contraception during treatment with pembrolizumab and for at least 4 months after the last dose of pembrolizumab.

Pregnancy
There are no data on the use of pembrolizumab in pregnant women. Animal reproduction studies have not been conducted with pembrolizumab; however, in murine models of pregnancy blockade of PD-L1 signaling has been shown to disrupt tolerance to the foetus and to result in an increased foetal loss (see section 5.3). These results indicate a potential risk, based on its mechanism of action, that administration of pembrolizumab during pregnancy could cause foetal harm, including increased rates of abortion or stillbirth. Human immunoglobulins G4 (IgG4) are known to cross the placental barrier; therefore, being an IgG4, pembrolizumab has the potential to be transmitted from the mother to the developing foetus. Pembrolizumab should not be used during pregnancy unless the clinical condition of the woman requires treatment with pembrolizumab.

Breast-feeding
It is unknown whether pembrolizumab is secreted in human milk. Since it is known that antibodies can be secreted in human milk, a risk to the newborns/infants cannot be excluded. A decision should be made whether to discontinue breast-feeding or to discontinue pembrolizumab, taking into account the benefit of breast-feeding for the child and the benefit of pembrolizumab therapy for the woman.

Fertility
No clinical data are available on the possible effects of pembrolizumab on fertility. There were no notable effects in the male and female reproductive organs in monkeys based on 1-month and 6-month repeat dose toxicity studies (see section 5.3).

4.7 Effects on ability to drive and use machines

Pembrolizumab may have a minor influence on the ability to drive and use machines. Fatigue has been reported following administration of pembrolizumab (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile
Pembrolizumab is most commonly associated with immune-related adverse reactions. Most of these, including severe reactions, resolved following initiation of appropriate medical therapy or withdrawal of pembrolizumab (see "Description of selected adverse reactions" below).

The safety of pembrolizumab has been evaluated in 3,830 patients with advanced melanoma, NSCLC, cHL or urothelial carcinoma across four doses (2 mg/kg every 3 weeks, 200 mg every 3 weeks, or 10 mg/kg every 2 or 3 weeks) in clinical studies. In this patient population, the most common adverse reactions (> 10%) with pembrolizumab were fatigue (21%), pruritus (16%), rash (13%), diarrhoea (12%) and nausea (10%). The majority of adverse reactions reported were of Grade 1 or 2 severity. The most serious adverse reactions were immune-related adverse reactions and severe infusion-related reactions (see section 4.4).

Tabulated list of adverse reactions
Adverse reactions observed in clinical studies and reported from post-marketing use of pembrolizumab are listed in Table 2. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 2: Adverse reactions in patients treated with pembrolizumab

Infections and infestations	
Uncommon	pneumonia
Blood and lymphatic system disorders	
Common	anaemia
Uncommon	neutropenia, thrombocytopenia, leukopenia, lymphopenia, eosinophilia
Rare	immune thrombocytopenic purpura, haemolytic anaemia
Immune system disorders	
Common	infusion related reaction[a]
Rare	sarcoidosis
Not known	solid organ transplant rejection
Endocrine disorders	
Common	hyperthyroidism, hypothyroidism[b]
Uncommon	hypophysitis[c], adrenal insufficiency, thyroiditis

Metabolism and nutrition disorders	
Common	decreased appetite
Uncommon	type 1 diabetes mellitus[d], hyponatraemia, hypokalaemia, hypocalcaemia
Psychiatric disorders	
Uncommon	insomnia
Nervous system disorders	
Common	headache, dizziness, dysgeusia
Uncommon	epilepsy, lethargy, neuropathy peripheral
Rare	Guillain-Barré syndrome, myasthenic syndrome, encephalitis
Eye disorders	
Uncommon	uveitis[e], dry eye
Cardiac disorders	
Uncommon	myocarditis
Vascular disorders	
Uncommon	hypertension
Respiratory, thoracic and mediastinal disorders	
Common	pneumonitis[f], dyspnoea, cough
Gastrointestinal disorders	
Very common	diarrhoea, nausea
Common	colitis[g], vomiting, abdominal pain[h], constipation, dry mouth
Uncommon	pancreatitis[i]
Rare	small intestinal perforation
Hepatobiliary disorders	
Uncommon	hepatitis[j]
Skin and subcutaneous tissue disorders	
Very common	rash[k], pruritus[l]
Common	severe skin reactions[m], vitiligo[n], dry skin, erythema
Uncommon	lichenoid keratosis[o], psoriasis, alopecia, dermatitis, dermatitis acneiform, eczema, hair colour changes, papule
Rare	toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema nodosum
Musculoskeletal and connective tissue disorders	
Common	arthralgia, myositis[p], musculoskeletal pain[q], arthritis[r], pain in extremity,
Uncommon	tenosynovitis[s]
Renal and urinary disorders	
Uncommon	nephritis[t]
General disorders and administration site conditions	
Very common	fatigue
Common	asthenia, oedema[u], pyrexia, influenza like illness, chills
Investigations	
Common	alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood creatinine increased
Uncommon	blood bilirubin increased, amylase increased, hypercalcaemia

The following terms represent a group of related events that describe a medical condition rather than a single event.

a. infusion-related reactions (drug hypersensitivity, anaphylactic reaction, hypersensitivity and cytokine release syndrome)
b. hypothyroidism (myxoedema)
c. hypophysitis (hypopituitarism)
d. type 1 diabetes mellitus (diabetic ketoacidosis)
e. uveitis (iritis and iridocyclitis)
f. pneumonitis (interstitial lung disease)
g. colitis (colitis microscopic and enterocolitis)
h. abdominal pain (abdominal discomfort, abdominal pain upper and abdominal pain lower)
i. pancreatitis (autoimmune pancreatitis and pancreatitis acute)
j. hepatitis (autoimmune hepatitis and drug induced liver injury)
k. rash (rash erythematous, rash follicular, rash generalised, rash macular, rash maculo-papular, rash papular, rash pruritic, rash vesicular and genital rash)
l. pruritus (urticaria, urticaria papular, pruritus generalized and pruritus genital)
m. severe skin reactions (dermatitis exfoliative, erythema multiforme, exfoliative rash, pemphigoid and Grade ≥ 3 of the following: pruritus, rash, rash generalised and rash maculo-papular, dermatitis psoriasiform, pruritus generalised)
n. vitiligo (skin depigmentation, skin hypopigmentation and hypopigmentation of the eyelid)
o. lichenoid keratosis (lichen planus and lichen sclerosus)
p. myositis (myalgia, myopathy, polymyalgia rheumatica and rhabdomyolysis)
q. musculoskeletal pain (musculoskeletal discomfort, back pain, musculoskeletal stiffness, musculoskeletal chest pain and torticollis)
r. arthritis (joint swelling, polyarthritis and joint effusion)
s. tenosynovitis (tendonitis, synovitis and tendon pain)
t. nephritis (nephritis autoimmune, tubulointerstitial nephritis and renal failure or renal failure acute with evidence of nephritis, nephrotic syndrome)
u. oedema (oedema peripheral, generalised oedema, fluid overload, fluid retention, eyelid oedema and lip oedema, face oedema, localized oedema and periorbital oedema)

Description of selected adverse reactions

Data for the following immune-related adverse reactions are based on patients who received pembrolizumab across three doses (2 mg/kg every 3 weeks or 10 mg/kg every 2 or 3 weeks) in clinical studies (see section 5.1). The management guidelines for these adverse reactions are described in section 4.4.

Immune-related adverse reactions (see section 4.4)

Immune-related pneumonitis

Pneumonitis occurred in 139 (3.6%) patients, including Grade 2, 3, 4 or 5 cases in 56 (1.5%), 38 (1.0%), 9 (0.2%) and 5 (0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of pneumonitis was 3.7 months (range 2 days to 21.3 months). The median duration was 2.1 months (range 1 day to 17.2+ months). Pneumonitis led to discontinuation of pembrolizumab in 60 (1.6%) patients. Pneumonitis resolved in 81 patients, 1 with sequelae.

Immune-related colitis

Colitis occurred in 71 (1.9%) patients, including Grade 2, 3 or 4 cases in 15 (0.4%), 44 (1.1%) and 3 (< 0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of colitis was 3.6 months (range 7 days to 16.2 months). The median duration was 1.3 months (range 1 day to 8.7+ months). Colitis led to discontinuation of pembrolizumab in 18 (0.5%) patients. Colitis resolved in 61 patients.

Immune-related hepatitis

Hepatitis occurred in 23 (0.6%) patients, including Grade 2, 3 or 4 cases in 4 (0.1%), 16 (0.4%) and 2 (< 0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of hepatitis was 1.3 months (range 8 days to 21.4 months). The median duration was 1.5 months (range 8 days to 20.9+ months). Hepatitis led to discontinuation of pembrolizumab in 7 (0.2%) patients. Hepatitis resolved in 19 patients.

Immune-related nephritis
Nephritis occurred in 15 (0.4%) patients, including Grade 2, 3 or 4 cases in 3 (0.1%), 10 (0.3%) and 1 (< 0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of nephritis was 4.9 months (range 12 days to 12.8 months). The median duration was 1.8 months (range 10 days to 10.5+ months). Nephritis led to discontinuation of pembrolizumab in 7 (0.2%) patients. Nephritis resolved in 9 patients.

Immune-related endocrinopathies
Hypophysitis occurred in 21 (0.5%) patients, including Grade 2, 3 or 4 cases in 6 (0.2%), 12 (0.3%) and 1 (< 0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of hypophysitis was 3.7 months (range 1 day to 17.7 months). The median duration was 3.3 months (range 4 days to 12.7+ months). Hypophysitis led to discontinuation of pembrolizumab in 6 (0.2%) patients. Hypophysitis resolved in 10 patients, 2 with sequelae.

Hyperthyroidism occurred in 135 (3.5%) patients, including Grade 2 or 3 cases in 32 (0.8%) and 4 (0.1%) patients, respectively, receiving pembrolizumab. 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 10 days to 15.5+ months). Hyperthyroidism led to discontinuation of pembrolizumab in 2 (0.1%) patients. Hyperthyroidism resolved in 104 (77%) patients, 1 with sequelae.

Hypothyroidism occurred in 345 (9.0%) patients, including Grade 2 or 3 cases in 251 (6.6%) and 4 (0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of hypothyroidism was 3.5 months (range 1 day to 18.9 months). The median duration was not reached (range 2 days to 29.9+ months). One patient (< 0.1%) discontinued pembrolizumab due to hypothyroidism. Hypothyroidism resolved in 81 (23%) patients, 6 with sequelae. In patients with cHL (n=241) the incidence of hypothyroidism was 14.1% (all Grades) with 0.4% Grade 3.

Immune-related skin adverse reactions
Immune-related severe skin reactions occurred in 63 (1.6%) patients, including Grade 2 or 3 cases in 4 (0.1%) and 52 (1.4%) patients, respectively, receiving pembrolizumab. The median time to onset of severe skin reactions was 2.5 months (range 4 days to 21.5 months). The median duration was 2.0 months (range 3 days to 17.8+ months). Severe skin reactions led to discontinuation of pembrolizumab in 6 (0.2%) patients. Severe skin reactions resolved in 41 patients.

Rare cases of SJS and TEN, some of them with fatal outcome, have been observed (see sections 4.2 and 4.4).

Complications of allogeneic HSCT in classical Hodgkin lymphoma
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).

Immunogenicity
In clinical studies in patients treated with pembrolizumab 2 mg/kg every three weeks, 200 mg every three weeks, or 10 mg/kg every two or three weeks, 36 (1.8%) of 2,034 evaluable patients tested positive for treatment-emergent antibodies to pembrolizumab, of which 9 (0.4%) patients had neutralising antibodies against pembrolizumab. There was no evidence of an altered pharmacokinetic or safety profile with anti-pembrolizumab binding or neutralising antibody development.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no information on overdose with pembrolizumab.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies. ATC code: L01XC18

Mechanism of action
KEYTRUDA is a humanised monoclonal antibody which binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with ligands PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. KEYTRUDA potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment.

Clinical efficacy and safety
Dosing for patients with melanoma and previously treated NSCLC
In clinical studies comparing pembrolizumab doses of 2 mg/kg every 3 weeks, 10 mg/kg every 3 weeks, and 10 mg/kg every 2 weeks in patients with melanoma or previously treated patients with NSCLC, efficacy and safety were similar. The recommended dose is 2 mg/kg every 3 weeks.

Melanoma
KEYNOTE-006: Controlled trial in melanoma patients naïve to treatment with ipilimumab
The safety and efficacy of pembrolizumab were investigated in KEYNOTE-006, a multicentre, controlled, Phase III study for the treatment of advanced melanoma in patients who were naïve to ipilimumab. Patients were randomised (1:1:1) to receive pembrolizumab 10 mg/kg every 2 (n=279) or 3 weeks (n=277) or ipilimumab 3 mg/kg every 3 weeks (n=278). Patients with BRAF V600E mutant melanoma were not required to have received prior BRAF inhibitor therapy.

Patients were treated with pembrolizumab until disease progression or unacceptable toxicity. Clinically stable patients with initial evidence of disease progression were permitted to remain on treatment until disease progression was confirmed. Assessment of tumour status was performed at 12 weeks, then every 6 weeks through week 48, followed by every 12 weeks thereafter.

Of the 834 patients, 60% were male, 44% were ≥ 65 years (median age was 62 years [range 18-89]) and 98% were white. Sixty-five percent of patients had M1c stage, 9% had a history of brain metastases, 66% had no and 34% had one prior therapy. Thirty-one percent had an ECOG Performance Status of 1, 69% had ECOG Performance Status of 0 and 32% had elevated LDH. BRAF mutations were reported in 302 (36%) patients. Among patients with BRAF mutant tumours, 139 (46%) were previously treated with a BRAF inhibitor.

The primary efficacy outcome measures were progression free survival (PFS; as assessed by Integrated Radiology and Oncology Assessment [IRO] review using Response Evaluation Criteria in Solid Tumours [RECIST], version 1.1) and overall survival (OS). Secondary efficacy outcome measures were overall response rate (ORR) and response duration. Table 3 summarises key efficacy measures in patients naïve to treatment with ipilimumab at the final analysis performed after a

minimum of 21 months of follow-up. Kaplan-Meier curves for OS and PFS based on the final analysis are shown in Figures 1 and 2.

Table 3: Efficacy results in KEYNOTE-006

Endpoint	Pembrolizumab 10 mg/kg every 3 weeks n=277	Pembrolizumab 10 mg/kg every 2 weeks n=279	Ipilimumab 3 mg/kg every 3 weeks n=278
OS			
Number (%) of patients with event	119 (43%)	122 (44%)	142 (51%)
Hazard ratio* (95% CI)	0.68 (0.53, 0.86)	0.68 (0.53, 0.87)	---
p-Value†	< 0.001	< 0.001	---
Median in months (95% CI)	Not reached (24, NA)	Not reached (22, NA)	16 (14, 22)
PFS			
Number (%) of patients with event	183 (66%)	181 (65%)	202 (73%)
Hazard ratio* (95% CI)	0.61 (0.50, 0.75)	0.61 (0.50, 0.75)	---
p-Value†	< 0.001	< 0.001	---
Median in months (95% CI)	4.1 (2.9, 7.2)	5.6 (3.4, 8.2)	2.8 (2.8, 2.9)
Best overall response			
ORR % (95% CI)	36% (30, 42)	37% (31, 43)	13% (10, 18)
Complete response %	13%	12%	5%
Partial response %	23%	25%	8%
Response duration‡			
Median in months (range)	Not reached (2.0, 22.8+)	Not reached (1.8, 22.8+)	Not reached (1.1+, 23.8+)
% ongoing at 18 months	68%§	71%§	70%§

* Hazard ratio (pembrolizumab compared to ipilimumab) based on the stratified Cox proportional hazard model

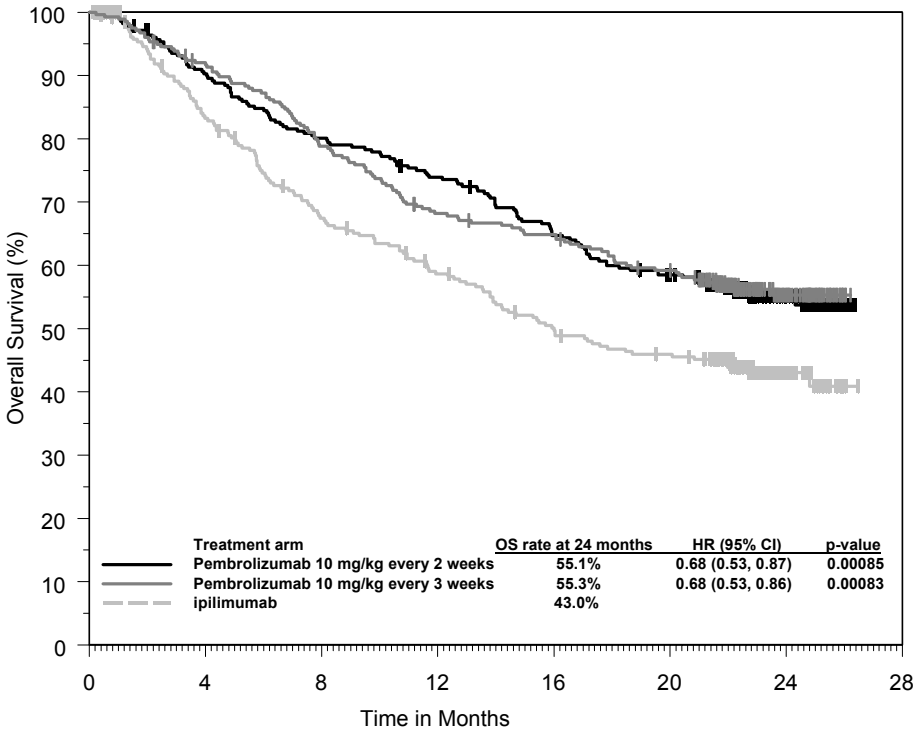
† Based on stratified Log rank test

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

§ Based on Kaplan-Meier estimation

NA = not available

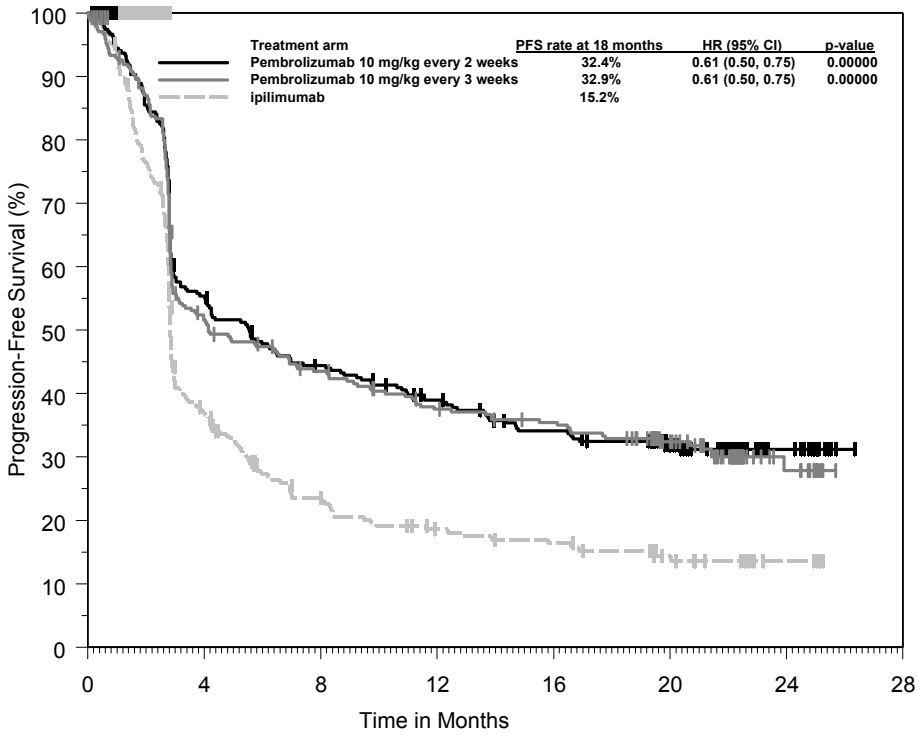
Figure 1: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-006 (intent to treat population)



Number at Risk

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

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



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

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

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

Patients were treated with pembrolizumab until disease progression or unacceptable toxicity. Clinically stable patients with initial evidence of disease progression were permitted to remain on treatment until disease progression was confirmed. Assessment of tumour status was performed at 12 weeks, then every 6 weeks through week 48, followed by every 12 weeks thereafter. Patients on chemotherapy who experienced independently verified progression of disease after the first scheduled disease assessment were able to crossover and receive 2 mg/kg or 10 mg/kg of pembrolizumab every 3 weeks in a double blind fashion.

Of the 540 patients, 61% were male, 43% were ≥ 65 years (median age was 62 years [range 15-89]) and 98% were white. Eighty-two percent had M1c stage, 73% had at least two and 32% of patients

had three or more prior systemic therapies for advanced melanoma. Forty-five percent had an ECOG Performance Status of 1, 40% had elevated LDH and 23% had a BRAF mutated tumour.

The primary efficacy outcome measures were PFS as assessed by IRO using RECIST version 1.1 and OS. Secondary efficacy outcome measures were ORR and response duration. Table 4 summarises key efficacy measures at the final analysis in patients previously treated with ipilimumab, and the Kaplan-Meier curve for PFS is shown in Figure 3. Both pembrolizumab arms were superior to chemotherapy for PFS, and there was no difference between pembrolizumab doses. 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 randomised to the chemotherapy arm, 55% crossed over and subsequently received treatment with pembrolizumab.

Table 4: Efficacy results in KEYNOTE-002

Endpoint	Pembrolizumab 2 mg/kg every 3 weeks n=180	Pembrolizumab 10 mg/kg every 3 weeks n=181	Chemotherapy n=179
PFS			
Number (%) of patients with event	150 (83%)	144 (80%)	172 (96%)
Hazard ratio* (95% CI)	0.58 (0.46, 0.73)	0.47 (0.37, 0.60)	---
p-Value†	< 0.001	< 0.001	---
Median in months (95% CI)	2.9 (2.8, 3.8)	3.0 (2.8, 5.2)	2.8 (2.6, 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†	0.1173	0.0106‡	---
Median in months (95% CI)	13.4 (11.0, 16.4)	14.7 (11.3, 19.5)	11.0 (8.9, 13.8)
Best overall response			
ORR % (95% CI)	22% (16, 29)	28% (21, 35)	5% (2, 9)
Complete response %	3%	7%	0%
Partial response %	19%	20%	5%
Response duration§			
Median in months (range)	22.8 (1.4+, 25.3+)	Not reached (1.1+, 28.3+)	6.8 (2.8, 11.3)
% ongoing at 12 months	73%¶	79%¶	0%¶

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

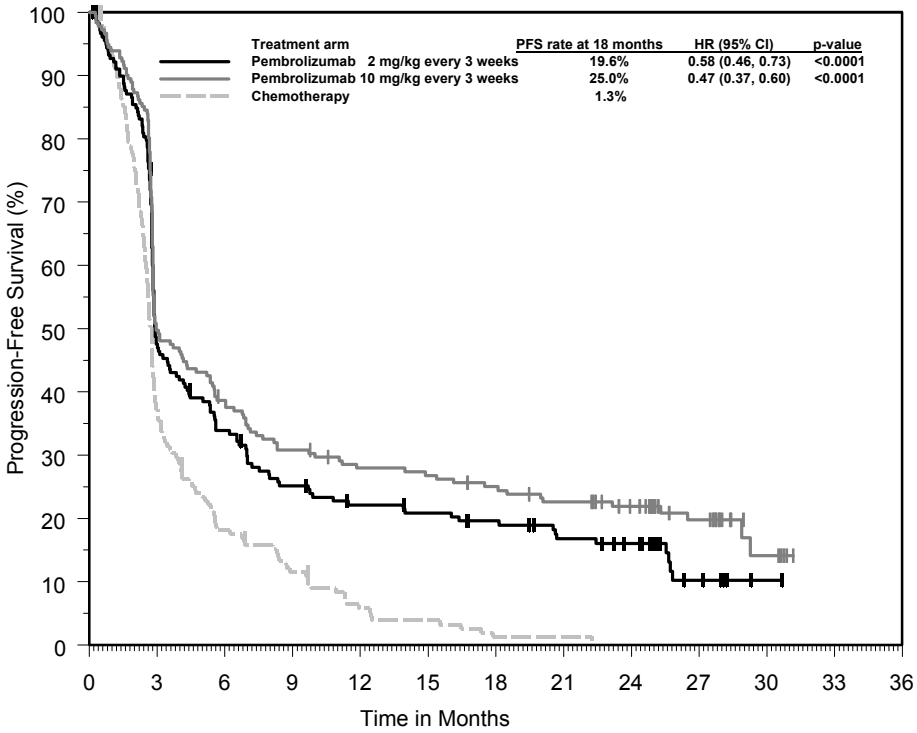
† Based on stratified Log rank test

‡ Not statistically significant after adjustment for multiplicity

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

¶ Based on Kaplan-Meier estimation

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



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

KEYNOTE-001: Open label study in melanoma patients naïve and previously treated with ipilimumab

The safety and efficacy of pembrolizumab for patients with advanced melanoma were investigated in an uncontrolled, open-label study, KEYNOTE-001. Efficacy was evaluated for 276 patients from two defined cohorts, one which included patients previously treated with ipilimumab (and if BRAF V600 mutation-positive, with a BRAF or MEK inhibitor) and the other which included patients naïve to treatment with ipilimumab. Patients were randomly assigned to receive pembrolizumab at a dose of 2 mg/kg every 3 weeks or 10 mg/kg every 3 weeks. Patients were treated with pembrolizumab until disease progression or unacceptable toxicity. Clinically stable patients with initial evidence of disease progression were permitted to remain on treatment until disease progression was confirmed. Exclusion criteria were similar to those of KEYNOTE-002.

Of the 89 patients receiving 2 mg/kg of pembrolizumab who were previously treated with ipilimumab, 53% were male, 33% were ≥ 65 years of age and the median age was 59 years (range 18-88). All but two patients were white. Eighty-four percent had M1c stage and 8% of patients had a history of brain metastases. Seventy percent had at least two and 35% of patients had three or more prior systemic therapies for advanced melanoma. BRAF mutations were reported in 13% of the study population. All patients with BRAF mutant tumours were previously treated with a BRAF inhibitor.

Of the 51 patients receiving 2 mg/kg of pembrolizumab who were naïve to treatment with ipilimumab, 63% were male, 35% were ≥ 65 years of age and the median age was 60 years (range 35-80). All but one patient was white. Sixty-three percent had M1c stage and 2% of patients had a history of brain metastases. Forty-five percent had no prior therapies for advanced melanoma. BRAF mutations were reported in 20 (39%) patients. Among patients with BRAF mutant tumours, 10 (50%) were previously treated with a BRAF inhibitor.

The primary efficacy outcome measure was ORR as assessed by independent review using RECIST 1.1. Secondary efficacy outcome measures were disease control rate (DCR; including

complete response, partial response and stable disease), response duration, PFS and OS. Tumour response was assessed at 12-week intervals. Table 5 summarises key efficacy measures in patients previously treated or naïve to treatment with ipilimumab, receiving pembrolizumab at the recommended dose based on a minimum follow-up time of 30 months for all patients.

Table 5: Efficacy results in KEYNOTE-001

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

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

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

Sub-population analyses

BRAF mutation status in melanoma
A subgroup analysis was performed as part of the final analysis of KEYNOTE-002 in patients who were BRAF wild type (n=414; 77%) or BRAF mutant with prior BRAF treatment (n=126; 23%) as summarised in Table 6.

Table 6: Efficacy results by BRAF mutation status in KEYNOTE-002

	BRAF wild type		BRAF mutant with prior BRAF treatment	
Endpoint	**Pembrolizumab 2mg/kg every 3 weeks (n=136)**	**Chemotherapy (n=137)**	**Pembrolizumab 2mg/kg every 3 weeks (n=44)**	**Chemotherapy (n=42)**
PFS Hazard ratio* (95% CI)	0.50 (0.39, 0.66)	---	0.79 (0.50, 1.25)	---
OS Hazard ratio* (95% CI)	0.78 (0.58, 1.04)	---	1.07 (0.64, 1.78)	---
ORR %	26%	6%	9%	0%

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

A subgroup analysis was performed as part of the final analysis of KEYNOTE-006 in patients who were BRAF wild type (n=525; 63%), BRAF mutant without prior BRAF treatment (n=163; 20%) and BRAF mutant with prior BRAF treatment (n=139; 17%) as summarised in Table 7.

Table 7: Efficacy results by BRAF mutation status in KEYNOTE-006

	BRAF wild type		BRAF mutant without prior BRAF treatment		BRAF mutant with prior BRAF treatment	
Endpoint	**Pembrolizumab 10mg/kg every 2 or 3 weeks (pooled)**	**Ipilimumab (n=170)**	**Pembrolizumab 10mg/kg every 2 or 3 weeks (pooled)**	**Ipilimumab (n=55)**	**Pembrolizumab 10mg/kg every 2 or 3 weeks (pooled)**	**Ipilimumab (n=52)**
PFS Hazard ratio* (95% CI)	0.61 (0.49, 0.76)	---	0.52 (0.35, 0.78)	---	0.76 (0.51, 1.14)	---
OS Hazard ratio* (95% CI)	0.68 (0.52, 0.88)	---	0.70 (0.40, 1.22)	---	0.66 (0.41, 1.04)	---
ORR %	38%	14%	41%	15%	24%	10%

* Hazard ratio (pembrolizumab compared to ipilimumab) based on the stratified Cox proportional hazard model

PD-L1 status in melanoma

A subgroup analysis was performed as part of the final analysis of KEYNOTE-002 in patients who were PD-L1 positive (PD-L1 expression in ≥ 1% of tumour and tumour-associated immune cells) vs. PD-L1 negative. PD-L1 expression was tested retrospectively by immunohistochemistry assay with the 22C3 anti-PD-L1 antibody. Among patients who were evaluable for PD-L1 expression (79%), 69% (n=294) were PD-L1 positive and 31% (n=134) were PD-L1 negative. Table 8 summarises efficacy results by PD-L1 expression.

Table 8: Efficacy results by PD-L1 expression in KEYNOTE-002

Endpoint	Pembrolizumab 2 mg/kg every 3 weeks	Chemotherapy	Pembrolizumab 2 mg/kg every 3 weeks	Chemotherapy
	PD-L1 positive		PD-L1 negative	
PFS Hazard ratio* (95% CI)	0.55 (0.40, 0.76)	---	0.81 (0.50, 1.31)	---
OS Hazard ratio* (95% CI)	0.90 (0.63, 1.28)	---	1.18 (0.70, 1.99)	---
ORR %	25%	4%	10%	8%

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

A subgroup analysis was performed as part of the final analysis of KEYNOTE-006 in patients who were PD-L1 positive (n=671; 80%) vs. PD-L1 negative (n=150; 18%). Among patients who were evaluable for PD-L1 expression (98%), 82% were PD-L1 positive and 18% were PD-L1 negative. Table 9 summarizes efficacy results by PD-L1 expression.

Table 9: Efficacy results by PD-L1 expression in KEYNOTE-006

Endpoint	Pembrolizumab 10 mg/kg every 2 or 3 weeks (pooled)	Ipilimumab	Pembrolizumab 10 mg/kg every 2 or 3 weeks (pooled)	Ipilimumab
	PD L1 positive		PD L1 negative	
PFS Hazard ratio* (95% CI)	0.53 (0.44, 0.65)	---	0.87 (0.58, 1.30)	---
OS Hazard ratio* (95% CI)	0.63 (0.50, 0.80)	---	0.76 (0.48, 1.19)	---
ORR %	40%	14%	24%	13%

* Hazard ratio (pembrolizumab compared to ipilimumab) based on the stratified Cox proportional hazard model

Ocular melanoma

In 20 subjects with ocular melanoma included in KEYNOTE-001, no objective responses were reported; stable disease was reported in 6 patients.

NSCLC

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

The safety and efficacy of pembrolizumab were investigated in KEYNOTE-024, a multicentre, controlled study for the treatment of previously untreated metastatic NSCLC. Patients had PD-L1 expression with a ≥ 50% tumour proportion score (TPS) based on the PD-L1 IHC 22C3 pharmDx™ Kit. Patients were randomised (1:1) to receive pembrolizumab at a dose of 200 mg every 3 weeks (n=154) or investigator's choice platinum-containing chemotherapy (n=151; including pemetrexed+carboplatin, pemetrexed+cisplatin, gemcitabine+cisplatin, gemcitabine+carboplatin, or paclitaxel+carboplatin. Non-squamous patients could receive pemetrexed maintenance). Patients were treated with pembrolizumab until unacceptable toxicity or disease progression. Treatment could continue beyond disease progression if the patient was clinically stable and was considered to be deriving clinical benefit by the investigator. Patients without disease progression could be treated for up to 24 months. The study excluded 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. Assessment of tumour status was performed every 9 weeks. Patients on chemotherapy who experienced independently-verified progression of disease were able to crossover and receive pembrolizumab.

Among the 305 patients in KEYNOTE-024, baseline characteristics were: median age 65 years (54% age 65 or older); 61% male; 82% White, 15% Asian; and ECOG performance status 0 and 1 in 35% and 65%, respectively. Disease characteristics were squamous (18%) and non-squamous (82%); M1 (99%); and brain metastases (9%).

The primary efficacy outcome measure was PFS as assessed by BICR using RECIST 1.1. Secondary efficacy outcome measures were OS and ORR (as assessed by BICR using RECIST 1.1). Table 10 summarizes key efficacy measures for the entire ITT population.

Table 10: Efficacy results in KEYNOTE-024

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

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

† Based on stratified Log rank test

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

§ Based on Kaplan-Meier estimates; includes 43 patients with responses of 6 months or longer

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

NA = not available

Figure 4: Kaplan-Meier curve for progression-free survival by treatment arm in KEYNOTE-024 (intent to treat population)

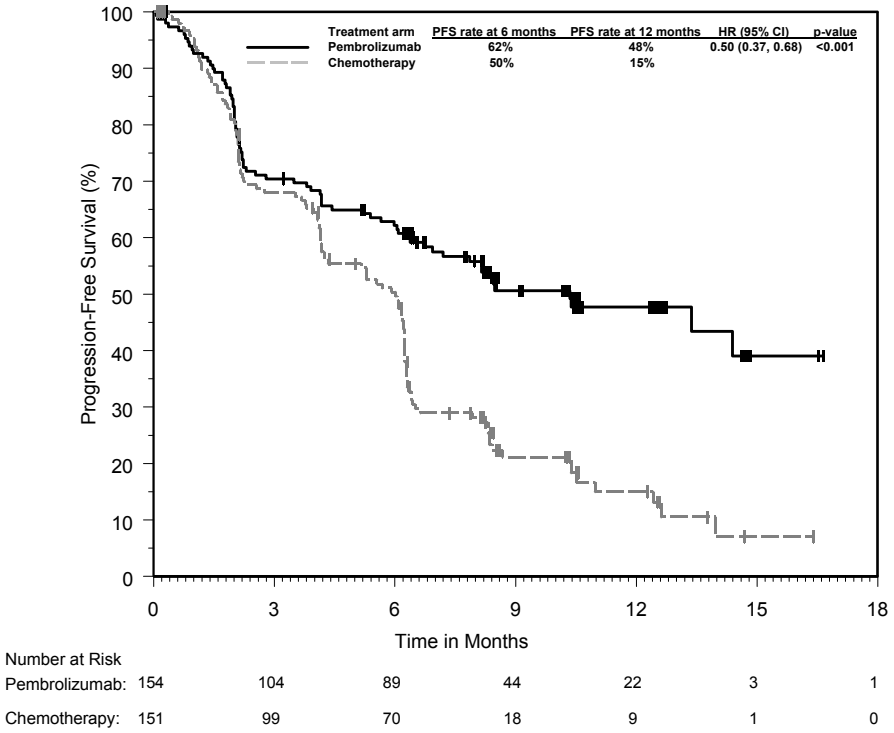
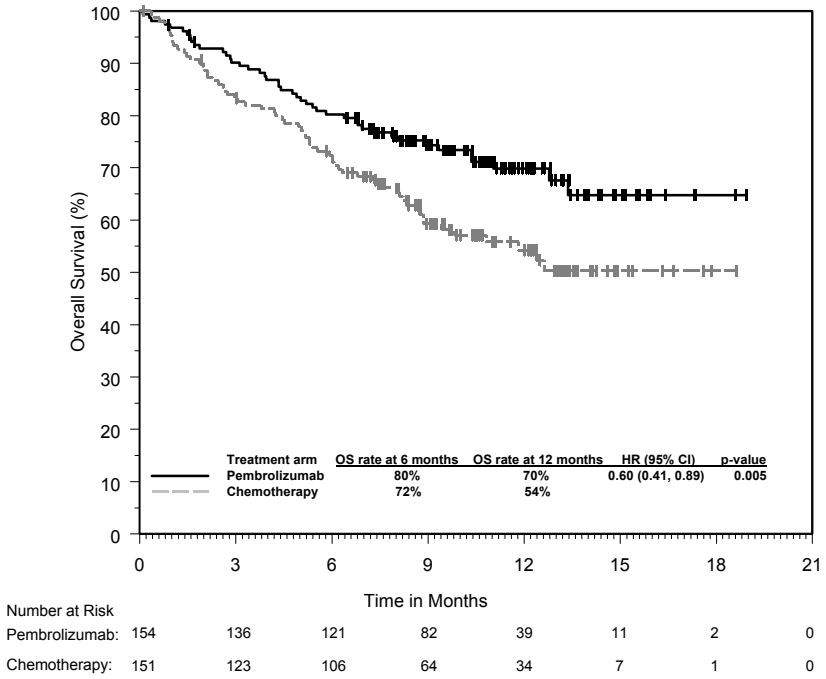


Figure 5: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-024 (intent to treat population)



In a subgroup analysis, a reduced survival benefit of pembrolizumab compared to chemotherapy was observed in the small number of patients who were never-smokers; however, due to the small number of patients, no definitive conclusions can be drawn from these data.

KEYNOTE-010: Controlled trial of NSCLC patients previously treated with chemotherapy
The safety and efficacy of pembrolizumab were investigated in KEYNOTE-010, a multicentre, open-label, controlled study for the treatment of advanced NSCLC in patients previously treated with platinum-containing chemotherapy. Patients had PD-L1 expression with a ≥ 1% TPS based on the PD-L1 IHC 22C3 pharmDx™ Kit. Patients with EGFR activation mutation or ALK translocation also had disease progression on approved therapy for these mutations prior to receiving pembrolizumab. Patients were randomised (1:1:1) to receive pembrolizumab at a dose of 2 (n=344) or 10 mg/kg (n=346) every 3 weeks or docetaxel at a dose of 75 mg/m^2 every 3 weeks (n=343) until disease progression or unacceptable toxicity. The trial excluded patients with autoimmune disease; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks. Assessment of tumour status was performed every 9 weeks.

The baseline characteristics for this population included: median age 63 years (42% age 65 or older); 61% male; 72% White and 21% Asian and 34% and 66% with an ECOG performance status 0 and 1, respectively. Disease characteristics were squamous (21%) and non-squamous (70%); M1 (91%); stable brain metastases (15%) and the incidence of mutations was EGFR (8%) or ALK (1%). Prior therapy included platinum-doublet regimen (100%); patients received one (69%) or two or more (29%) treatment lines.

The primary efficacy outcome measures were OS and PFS as assessed by blinded independent central review (BICR) using RECIST 1.1. Secondary efficacy outcome measures were ORR and response duration. Table 11 summarises key efficacy measures for the entire population (TPS ≥ 1%) and for the patients with TPS ≥ 50% and the Kaplan-Meier curve for OS (TPS ≥ 1%) is shown in Figure 6.

Table 11: Response to pembrolizumab 2 or 10 mg/kg every 3 weeks in previously treated patients with NSCLC in KEYNOTE-010

Endpoint	Pembrolizumab 2 mg/kg every 3 weeks	Pembrolizumab 10 mg/kg every 3 weeks	Docetaxel 75 mg/m^2 every 3 weeks
TPS ≥ 1%			
Number of patients	344	346	343
OS			
Number (%) of patients with event	172 (50%)	156 (45%)	193 (56%)
Hazard ratio* (95% CI)	0.71 (0.58, 0.88)	0.61 (0.49, 0.75)	---
p-Value[†]	< 0.001[‡]	< 0.001[‡]	---
Median in months (95% CI)	10.4 (9.4, 11.9)	12.7 (10.0, 17.3)	8.5 (7.5, 9.8)
PFS[§]			
Number (%) of patients with event	266 (77%)	255 (74%)	257 (75%)
Hazard ratio* (95% CI)	0.88 (0.73, 1.04)	0.79 (0.66, 0.94)	---
p-Value[†]	0.068	0.005	---
Median in months (95% CI)	3.9 (3.1, 4.1)	4.0 (2.6, 4.3)	4.0 (3.1, 4.2)
Overall response rate[§]			
ORR %[¶] (95% CI)	18% (14, 23)	18% (15, 23)	9% (7, 13)
Response duration[§,#,Þ]			
Median in months (range)	Not reached (0.7+, 20.1+)	Not reached (2.1+, 17.8+)	6.2 (1.4+, 8.8+)
% ongoing	73%	72%	34%
TPS ≥ 50%			
Number of patients	139	151	152
OS			
Number (%) of patients with event	58 (42%)	60 (40%)	86 (57%)
Hazard ratio* (95% CI)	0.54 (0.38, 0.77)	0.50 (0.36, 0.70)	---
p-Value[†]	< 0.001[‡]	< 0.001[‡]	---
Median in months (95% CI)	14.9 (10.4, NA)	17.3 (11.8, NA)	8.2 (6.4, 10.7)
PFS[§]			
Number (%) of patients with event	89 (64%)	97 (64%)	118 (78%)
Hazard ratio* (95% CI)	0.58 (0.43, 0.77)	0.59 (0.45, 0.78)	---
p-Value[†]	< 0.001[‡]	< 0.001[‡]	---
Median in months (95% CI)	5.2 (4.0, 6.5)	5.2 (4.1, 8.1)	4.1 (3.6, 4.3)
Overall response rate[§]			
ORR %[¶] (95% CI)	30% (23, 39)	29% (22, 37)	8% (4, 13)
Response duration[§,#,ß]			
Median in months (range)	Not reached (0.7+, 16.8+)	Not reached (2.1+, 17.8+)	8.1 (2.1+, 8.8+)
% ongoing	76%	75%	33%

* Hazard ratio (pembrolizumab compared to docetaxel) based on the stratified Cox proportional hazard model

† Based on stratified Log rank test

‡ Statistically significant based on a pre-specified α level adjusted for multiplicity

§ Assessed by blinded independent central review (BICR) using RECIST 1.1

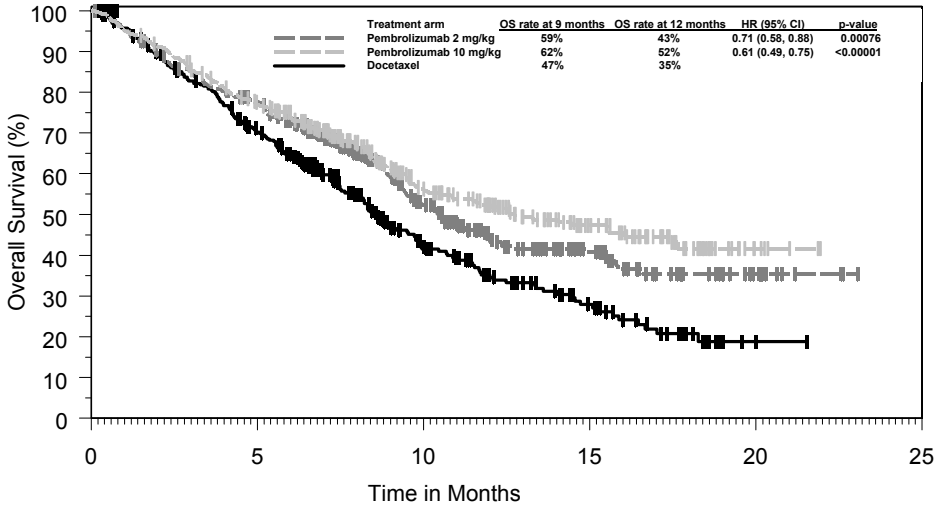
¶ All responses were partial responses

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

Þ Includes 30, 31 and 2 patients with ongoing responses of 6 months or longer in the pembrolizumab 2 mg/kg, pembrolizumab 10 mg/kg and docetaxel arms respectively

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

Figure 6: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-010 (patients with PD-L1 expression tumour proportion score ≥ 1%, intent to treat population)



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

Efficacy results were similar for the 2 mg/kg and 10 mg/kg pembrolizumab arms. Efficacy results for OS were consistent regardless of the age of tumour specimen (new vs. archival) based on an intergroup comparison.

In subgroup analyses, a reduced survival benefit of pembrolizumab compared to docetaxel was observed for patients who were never-smokers or patients with tumours harbouring EGFR activating mutations who received at least platinum-based chemotherapy and a tyrosine kinase inhibitor; however, due to the small numbers of patients, no definitive conclusions can be drawn from these data.

The efficacy and safety of pembrolizumab in patients with tumours that do not express PD-L1 have not been established.

Classical Hodgkin lymphoma
KEYNOTE-087 and KEYNOTE-013: Open-label studies in patients with relapsed or refractory classical Hodgkin lymphoma (cHL)
The efficacy of pembrolizumab was investigated in KEYNOTE-087 and KEYNOTE-013, two multicentre, open-label studies for the treatment of 241 patients with cHL. These studies enrolled patients who failed ASCT and BV, who were ineligible for ASCT because they were unable to achieve a complete or partial remission to salvage chemotherapy and failed BV, or who failed ASCT and did not receive BV. Five study subjects were ineligible to ASCT due to reasons other than failure to salvage chemotherapy. Both studies included patients regardless of PD-L1 expression. Patients with active, non-infectious pneumonitis, an allogeneic transplant within the past 5 years (or > 5 years but with GVHD), active autoimmune disease or a medical condition that required immunosuppression were ineligible for either trial. Patients received pembrolizumab 200 mg every 3 weeks (n=210; KEYNOTE-087) or 10 mg/kg every 2 weeks (n=31; KEYNOTE-013) until unacceptable toxicity or documented disease progression.

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. Disease subtypes were 80% nodular sclerosis, 11% mixed cellularity, 4% lymphocyte-rich and 2% lymphocyte-depleted.

Among KEYNOTE-013 patients, the baseline characteristics were median age 32 years (7% age 65 or older), 58% male, 94% White; and 45% and 55% had an ECOG performance status 0 and 1, respectively. The median number of prior lines of therapy administered for the treatment of cHL was 5 (range 2 to 15). Eighty-seven percent were refractory to at least one prior therapy, including 39% who were refractory to first line therapy. Seventy-four percent of patients had received Auto-SCT, 26% were transplant ineligible, and 42% of patients had prior radiation therapy. Disease subtypes were 97% nodular sclerosis and 3% mixed cellularity.

The major efficacy outcome measures (ORR and CRR) were assessed by blinded independent central review according to the 2007 revised International Working Group (IWG) criteria. Secondary efficacy outcome measures were duration of response, PFS and OS. Response was assessed in KN087 and KN013 every 12 and 8 weeks, respectively, with the first planned post-baseline assessment at week 12. Efficacy results are summarized in Table 12.

Table 12: Efficacy results in KEYNOTE-087 and KEYNOTE-013

	KEYNOTE-087[a]	KEYNOTE-013[b]
Endpoint	Pembrolizumab 200 mg every 3 weeks n=210	Pembrolizumab 10 mg/kg every 2 weeks n=31
Objective response rate[c]		
ORR % (95% CI)	69% (62.3, 75.2)	58% (39.1, 75.5)
Complete Remission	22%	19%
Partial Remission	47%	39%
Response duration[c]		
Median in months (range)	11.1 (0.0+, 11.1)[d]	Not reached (0.0+, 26.1+)[e]
% with duration ≥ 6-months	76%[f]	80%[g]
% with duration ≥ 12-months	---	70%[h]
Time to response		
Median in months (range)	2.8 (2.1, 8.8)[d]	2.8 (2.4, 8.6)[e]
PFS[c]		
Number (%) of patients with event	70 (33%)	18 (58%)
Median in months (95% CI)	11.3 (10.8, Not reached)	11.4 (4.9, 27.8)
6-month PFS rate	72%	66%
9-month PFS rate	62%	---
12-month PFS rate	---	48%
OS		
Number (%) of patients with event	4 (2%)	4 (13%)
6-month OS rate	99.5%	100%
12-month OS rate	97.6%	87.1%

[a] Median follow-up time of 10.1 months
[b] Median follow-up time of 28.7 months
[c] Assessed by blinded independent central review according to the 2007 revised International Working Group (IWG) criteria by PET CT scans
[d] Based on patients (n=145) with a response by independent review
[e] Based on patients (n=18) with a response by independent review
[f] Based on Kaplan-Meier estimation; includes 31 patients with responses of 6 months or longer
[g] Based on Kaplan-Meier estimation; includes 9 patients with responses of 6 months or longer
[h] Based on Kaplan-Meier estimation; includes 7 patients with responses of 12 months or longer

Safety and efficacy in elderly patients
Overall, 20 cHL patients ≥ 65 years were treated with pembrolizumab in studies KEYNOTE-087 and KEYNOTE-013. Data from these patients are too limited to draw any conclusion on safety or efficacy in this population.

Urothelial Carcinoma
KEYNOTE-045: Controlled trial in urothelial carcinoma patients who have received prior platinum-containing chemotherapy
The safety and efficacy of pembrolizumab were evaluated in KEYNOTE-045, a multicentre, randomised (1:1), controlled study for the treatment of locally advanced or metastatic urothelial carcinoma in patients with disease progression on or after platinum-containing chemotherapy. Patients must have received first line platinum-containing regimen for locally advanced/metastatic disease or as neoadjuvant/adjuvant treatment, with recurrence/progression ≤ 12 months following completion of therapy. Patients were randomised (1:1) to receive either KEYTRUDA 200 mg every 3 weeks (n=270) or investigator's choice of any of the following chemotherapy regimens all given intravenously every 3 weeks (n=272): paclitaxel 175 mg/m^2 (n=84), docetaxel 75 mg/m^2 (n=84), or vinflunine 320 mg/m^2 (n=87). Patients were treated with pembrolizumab until unacceptable toxicity or disease progression. Treatment could continue beyond progression if the patient was clinically stable and was considered to be deriving clinical benefit by the investigator. Patients without disease

progression could be treated for up to 24 months. The study excluded patients with autoimmune disease, a medical condition that required immunosuppression and patients with more than 2 prior lines of systemic chemotherapy for metastatic urothelial cancer. Patients with an ECOG performance status of 2 had to have a hemoglobin ≥ 10 g/dL, could not have liver metastases, and must have received the last dose of their last prior chemotherapy regimen ≥ 3 months prior to enrollment. Assessment of tumour status was performed at 9 weeks after the first dose, then every 6 weeks through the first year, followed by every 12 weeks thereafter.

Among the 542 randomised patients in KEYNOTE-045, baseline characteristics were: median age 66 years (range: 26 to 88), 58% age 65 or older; 74% male; 72% White and 23% Asian; 56% ECOG performance status of 1 and 1% ECOG performance status of 2; and 96% M1 disease and 4% M0 disease. Eighty-seven percent of patients had visceral metastases, including 34% with liver metastases. Eighty-six percent had a primary tumour in the lower tract and 14% had a primary tumour in the upper tract. Fifteen percent of patients had disease progression following prior platinum-containing neoadjuvant or adjuvant chemotherapy. Twenty-one percent had received 2 prior systemic regimens in the metastatic setting. Seventy-six percent of patients received prior cisplatin, 23% had prior carboplatin, and 1% was treated with other platinum-based regimens.

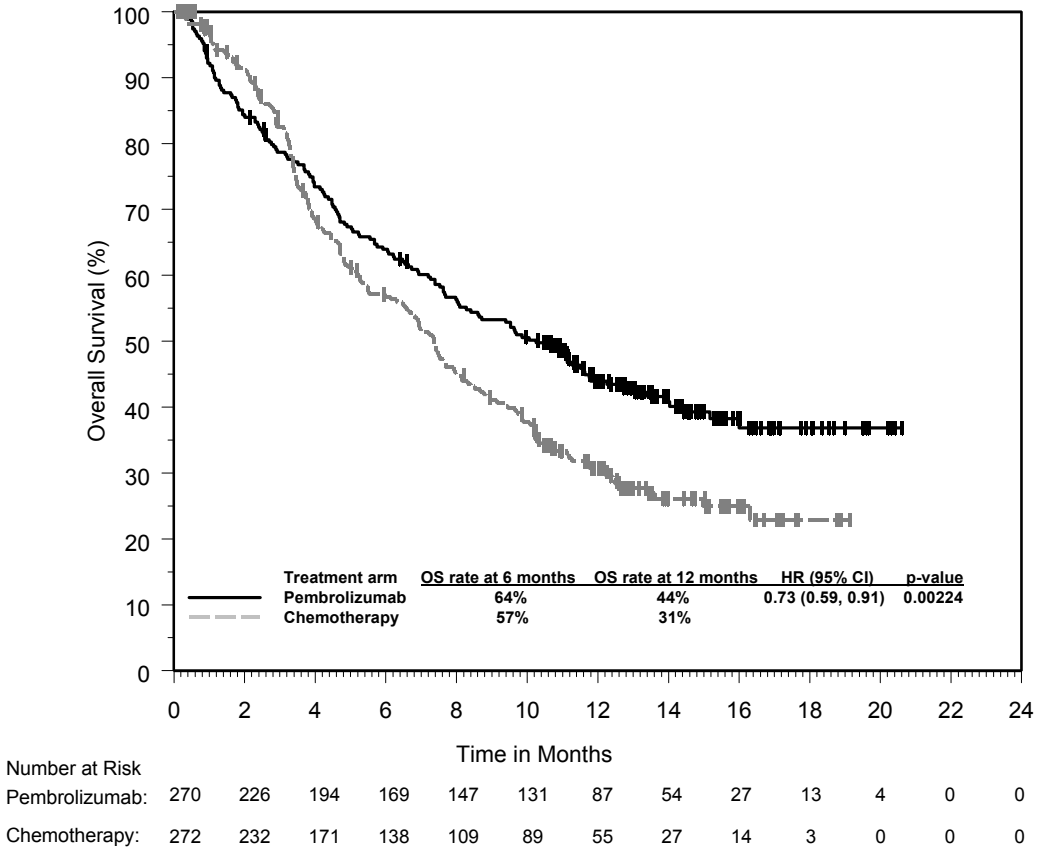
The primary efficacy outcomes were OS and PFS as assessed by BICR using RECIST v1.1. Secondary outcome measures were ORR (as assessed by BICR using RECIST v1.1) and duration of response. Table 13 summarises the key efficacy measures for the ITT population. The Kaplan-Meier curve for OS is shown in Figure 7. The study demonstrated statistically significant improvements in OS and ORR for patients randomised to pembrolizumab as compared to chemotherapy. There was no statistically significant difference between pembrolizumab and chemotherapy with respect to PFS.

Table 13: Response to pembrolizumab 200 mg every 3 weeks in patients with urothelial carcinoma previously treated with chemotherapy in KEYNOTE-045

Endpoint	Pembrolizumab 200 mg every 3 weeks n=270	Chemotherapy n=272
OS		
Number (%) of patients with event	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)
p-Value§	0.001	
Complete Response	7%	3%
Partial Response	14%	8%
Stable Disease	17%	34%
Response duration‡,¶		
Median in months (range)	Not reached (1.6+, 15.6+)	4.3 (1.4+, 15.4+)
Number (%#) of patients with duration ≥6 months	41 (78%)	7 (40%)
Number (%#) of patients with duration ≥12 months	14 (68%)	3 (35%)

* Hazard ratio (pembrolizumab compared to chemotherapy) based on the stratified Cox proportional hazard model
† Based on stratified Log rank test
‡ Assessed by BICR using RECIST 1.1
§ Based on method by Miettinen and Nurminen
¶ Based on patients with a best overall response as confirmed complete or partial response
# Based on Kaplan-Meier estimation

Figure 7: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-045 (intent to treat population)



An analysis was performed in KEYNOTE-045 in patients who had PD-L1 Combined Positive Score (CPS) < 10 [pembrolizumab: n=186 (69%) vs. chemotherapy: n= 176 (65%)] or ≥ 10 [pembrolizumab: n=74 (27%) vs. chemotherapy: n= 90 (33%)] in both pembrolizumab- and chemotherapy-treated arms (see Table 14).

Table 14: OS by PD-L1 Expression

PD-L1 Expression	Pembrolizumab	Chemotherapy	
	OS by PD-L1 Expression Number of Events (number of patients)		Hazard Ratio* (95% CI)
CPS < 10	106 (186)	116 (176)	0.80 (0.61, 1.05)
CPS ≥ 10	44 (74)	60 (90)	0.57 (0.37, 0.88)

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

Patient-reported outcomes (PROs) were assessed using EORTC QLQ-C30. A prolonged time to deterioration in EORTC QLQ-C30 global health status/QoL was observed for patients treated with pembrolizumab compared to investigator's choice chemotherapy (HR 0.70; 95% CI 0.55-0.90). Over 15 weeks of follow-up, patients treated with pembrolizumab had stable global health status/QoL, while those treated with investigator's choice chemotherapy had a decline in global health status/QoL. These results should be interpreted in the context of the open-label study design and therefore taken cautiously.

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

The safety and efficacy of pembrolizumab were investigated in KEYNOTE-052, a multicentre, open-label study for the treatment of locally advanced or metastatic urothelial carcinoma in patients who were not eligible for cisplatin-containing chemotherapy. Patients received pembrolizumab at a dose of 200 mg every 3 weeks until unacceptable toxicity or disease progression. Treatment could continue beyond progression if the patient was clinically stable and was considered to be deriving clinical benefit by the investigator. Patients without disease progression could be treated for up to 24 months. The study excluded patients with autoimmune disease or a medical condition that required immunosuppression. Assessment of tumour status was performed at 9 weeks after the first dose, then every 6 weeks through the first year, followed by every 12 weeks thereafter.

Among 370 patients with urothelial carcinoma who were not eligible for cisplatin-containing chemotherapy baseline characteristics were: median age 74 years (82% age 65 or older); 77% male; and 89% White and 7% Asian. Eighty-seven percent had M1 disease and 13% had M0 disease. Eighty-five percent of patients had visceral metastases, including 21% with liver metastases. Reasons for cisplatin ineligibility included: baseline creatinine clearance of <60 mL/min (50%), ECOG performance status of 2 (32%), ECOG performance status of 2 and baseline creatinine clearance of <60 mL/min (9%), and other (Class III heart failure, Grade 2 or greater peripheral neuropathy, and Grade 2 or greater hearing loss; 9%). Ninety percent of patients were treatment naïve, and 10% received prior adjuvant or neoadjuvant platinum-based chemotherapy. Eighty-one percent had a primary tumour in the lower tract, and 19% of patients had a primary tumour in the upper tract.

The primary efficacy outcome measure was ORR as assessed by BICR using RECIST 1.1. Secondary efficacy outcome measures were duration of response, PFS, and OS. Table 15 summarises the key efficacy measures for the study population based on a median follow-up time of 9.5 months for all patients.

Table 15: Response to pembrolizumab 200 mg every 3 weeks in patients with urothelial carcinoma ineligible for cisplatin-containing chemotherapy in KEYNOTE-052

Endpoint	n=370
Objective Response Rate*	
ORR %, (95% CI)	29% (25, 34)
Disease Control Rate†	47%
Complete Response	7%
Partial Response	22%
Stable Disease	18%
Response Duration	
Median in months (range)	Not reached (1.4+, 19.6+)
% with duration ≥ 6-months	82%‡
Time to Response	
Median in months (range)	2.1 (1.3, 9.0)
PFS*	
Median in months (95% CI)	2.3 (2.1, 3.4)
6-month PFS rate	34%
OS*	
Median in months (95% CI)	11.0 (10.0, 13.6)
6-month OS rate	67%

* Assessed by BICR using RECIST 1.1
† Based on best response of stable disease or better
‡ Based on Kaplan-Meier estimates; includes 77 patients with response of 6 months or longer

An analysis was performed in KEYNOTE-052 in patients who had PD-L1 CPS < 10 (n=251; 68%) or ≥ 10 (n=110; 30%) (see Table 16).

Table 16: ORR by PD-L1 Expression

	ORR % by PD-L1 Expression* (95% CI)
PD-L1 Expression	**Pembrolizumab**
CPS < 10	21 (16.2, 26.7)
CPS ≥ 10	47 (37.7, 57.0)

* BICR-RECIST 1.1

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with pembrolizumab in one or more subsets of the paediatric population in treatment of all conditions included in the category of malignant neoplasms (except nervous system, haematopoietic and lymphoid tissue) (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics of pembrolizumab was studied in 2,993 patients with metastatic or unresectable melanoma, NSCLC, or carcinoma who received doses in the range of 1 to 10 mg/kg every 2 or 3 weeks.

Absorption
Pembrolizumab is dosed via the intravenous 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 (~7.5 L; CV: 20%). As expected for an antibody, pembrolizumab does not bind to plasma proteins in a specific manner.

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

Elimination
The systemic clearance of pembrolizumab is ~0.2 L/day (CV: 37%) and the terminal half-life (t½) is ~25 days (CV: 38%).

Linearity/non-linearity
Exposure to pembrolizumab as expressed by peak concentration (C_{max}) or area under the plasma concentration time curve (AUC) increased dose proportionally within the dose range for efficacy. Upon repeated dosing, the clearance of pembrolizumab was found to be independent of time, and systemic accumulation was approximately 2.1-fold when administered every 3 weeks. Near steady-state concentrations of pembrolizumab were achieved by 18 weeks; the median steady-state through concentrations (C_{min}) at 18 weeks were approximately 21 mcg/mL at a dose of 2 mg/kg every 3 weeks and 28 mcg/mL at a dose of 200 mg every 3 weeks. The median area under the concentration-time curve at steady state over 3 weeks ($AUC_{0\text{-}3weeks}$) was 658 mcg·day/mL at a dose of 2 mg/kg every 3 weeks and 876 mcg·day/mL at a dose of 200 mg every 3 weeks.

Following administration of pembrolizumab 200 mg every 3 weeks in patients with cHL, the observed median C_{min} at steady-state was up to 40% higher than that in other tumour types treated with the same dosage; however, the range of trough concentrations is similar. There are no notable differences in median C_{max} between cHL and other tumour types. Based on available safety data in cHL and other tumour types, these differences are not clinically meaningful.

Special populations
The effects of various covariates on the pharmacokinetics of pembrolizumab were assessed in population pharmacokinetic analyses. The following factors had no clinically important effect on the clearance of pembrolizumab: age (range 15-94 years), gender, race, mild or moderate renal impairment, mild hepatic impairment and tumour burden. The relationship between body weight and clearance supports the use of either fixed dose or body weight-based dosing to provide adequate and similar control of exposure.

Renal impairment
The effect of renal impairment on the clearance of pembrolizumab was evaluated by population pharmacokinetic analyses in patients with mild or moderate renal impairment compared to patients with normal 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. Pembrolizumab has not been studied in patients with severe renal impairment.

Hepatic impairment
The effect of hepatic impairment on the clearance of pembrolizumab was evaluated by population pharmacokinetic analyses in patients with mild hepatic impairment (as defined using the US National Cancer Institute criteria of hepatic dysfunction) compared to patients with normal hepatic function. No clinically important differences in the clearance of pembrolizumab were found between patients

with mild hepatic impairment and normal hepatic function. Pembrolizumab has not been studied in patients with moderate or severe hepatic impairment (see section 4.2).

5.3 Preclinical safety data

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

Animal reproduction studies have not been conducted with pembrolizumab. The PD-1/PD-L1 pathway is thought to be involved in maintaining tolerance to the foetus throughout pregnancy. Blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the foetus and to result in an increase in foetal loss.

Animal fertility studies have not been conducted with pembrolizumab. In 1 month and 6 month repeat-dose toxicology studies in monkeys, there were no notable effects in the male and female reproductive organs; however, many animals in these studies were not sexually mature.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-histidine
L-histidine hydrochloride monohydrate
Sucrose
Polysorbate 80
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial
2 years.

After preparation of infusion
From a microbiological point of view, the product, once diluted, should be used immediately. The diluted solution must not be frozen. If not used immediately, chemical and physical in-use stability of KEYTRUDA has been demonstrated for 24 hours at 2ºC to 8ºC. This 24 hour hold may include up to 6 hours at room temperature (at or below 25°C). If refrigerated, the vials and/or intravenous bags must be allowed to come to room temperature prior to use.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Store in the original carton in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

4 mL of concentrate in a 10 mL Type I clear glass vial, with a coated grey chlorobutyl stopper and an aluminium seal with a dark blue coloured flip-off cap, containing 100 mg pembrolizumab.

Each carton contains one vial.

6.6 Special precautions for disposal and other handling

Preparation and administration of the infusion

- Do not shake the vial.
- Equilibrate the vial to room temperature (at or below 25°C).
- Prior to dilution, the vial of liquid can be out of refrigeration (temperatures at or below 25°C) for up to 24 hours.
- Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration. The concentrate is a clear to slightly opalescent, colourless to slightly yellow solution. Discard the vial if visible particles are observed.
- Withdraw the required volume up to 4 mL (100 mg) of concentrate and transfer into an intravenous bag containing sodium chloride 9 mg/mL (0.9%) or glucose 50 mg/mL (5%) to prepare a diluted solution with a final concentration ranging from 1 to 10 mg/mL. Each vial contains an excess fill of 0.25 ml (total content per vial 4.25 ml) to ensure the recovery of 4 ml of concentrate. Mix diluted solution by gentle inversion.
- From a microbiological point of view, the product, once diluted, should be used immediately. The diluted solution must not be frozen. If not used immediately, chemical and physical in-use stability of KEYTRUDA has been demonstrated for 24 hours at 2ºC to 8ºC. This 24 hour hold may include up to 6 hours at room temperature (at or below 25°C). If refrigerated, the vials and/or intravenous bags must be allowed to come to room temperature prior to use. Administer the 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 medicinal products through the same infusion line.
- KEYTRUDA is for single use only. Discard any unused portion left in the vial.

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

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme Limited
Hertford Road
Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1024/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 July 2015

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

AstraZeneca Pharmaceuticals LP,
Frederick Manufacturing Center (FMC)
633 Research Court
Frederick, Maryland (MD) 21703
United States (USA)

Boehringer Ingelheim (BIB)
Pharma GmbH & Co. KG
Birkendorfer Straße 65
88397 Biberach an der Riss
Germany

Name and address of the manufacturer responsible for batch release

Schering-Plough Labo NV
Industriepark 30, Heist-op-den-Berg
B-2220, Belgium

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to launch of KEYTRUDA in each Member State the MAH must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at increasing the awareness of physicians about the potential:
- immune-mediated adverse events
- infusion-related reactions

associated with KEYTRUDA use and on how to manage them and to enhance the awareness of patients and/or their caregivers on the signs and symptoms relevant to the early recognition/identification of those adverse events.

The MAH shall ensure that in each Member State where KEYTRUDA is marketed, all healthcare professionals and patients/caregivers who are expected to prescribe and use KEYTRUDA have access to/are provided with the following educational package:
- Physician educational material
- Patient educational material

The physician educational material should contain:
- The Summary of Product Characteristics
- Healthcare professional Frequently Asked Questions (FAQ) Brochure

The healthcare professional FAQ Brochure shall contain the following key elements:
List of important immune-related adverse reactions (irARs) and their symptoms including precautions and treatment, as outlined in section 4.4 of the Summary of Product Characteristics:
    - irARs
        - Pneumonitis
        - Colitis
        - Hepatitis
        - Nephritis
        - Severe endocrinopathies, including hypophysitis (including hypopituitarism and secondary adrenal insufficiency), type 1 diabetes mellitus, diabetic ketoacidosis, hypothyroidism, hyperthyroidism and thyroiditis
        - Severe skin reactions including Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)
    - Other irARs including:
        - uveitis, myositis, myocarditis, pancreatitis, Guillain Barré syndrome, solid organ transplant rejection following pembrolizumab treatment in donor organ recipients, encephalitis, sarcoidosis
        - potential risk of complications of allogeneic stem cell transplant (SCT) including graft versus host disease (GVHD) in patients who have previously received pembrolizumab for haematologic malignancies or after pembrolizumab administration in patients with a history of allogeneic SCT
    - Infusion-related reactions.

- Details on how to minimise the safety concerns through appropriate monitoring and management
- Reminder to distribute the Patient Information Brochure and Patient Alert Card.

The patient educational material should contain:

- Patient Information Brochure
- The Patient Alert Card

The Patient Information Brochure and Patient Alert Card shall contain the following key elements:

- Description of the main signs or symptoms of the irARs and the importance of notifying their treating physician immediately if symptoms occur
- The importance of not attempting to self-treat any symptoms without consulting their healthcare professional first
- The importance of carrying the Patient Alert Card at all times and to show it at all medical visits to healthcare professionals other than the prescriber (e.g. emergency healthcare professionals).

The Card reminds patients about key symptoms that need to be reported immediately to the physician/nurse. It also contains prompts to enter contact details of the physician and to alert other physicians that the patient is treated with KEYTRUDA

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
1. Post-authorisation efficacy study (PAES): The MAH should submit the final study report for study P087, A Phase II Clinical Trial of MK-3475 (Pembrolizumab) in Subjects with Relapsed or Refractory (R/R) Classical Hodgkin Lymphoma (cHL) – Final Study Report	3Q 2021
2. Post-authorisation efficacy study (PAES): The MAH should submit the final study report for study P013, A Phase Ib Multi-Cohort Trial of MK-3475 (pembrolizumab) in Subjects with Hematologic Malignancies – Final Study Report	1Q 2019
3. Post-authorisation efficacy study (PAES): The MAH should submit the final study report for study P204: A Phase III, Randomized, Open-label, Clinical Trial to Compare Pembrolizumab with Brentuximab Vedotin in Subjects with Relapsed or Refractory Classical Hodgkin Lymphoma – Final Study Report	2Q 2021
4. The value of biomarkers to predict the efficacy of pembrolizumab should be further explored, specifically: Additional biomarkers other than PD-L1 expression status by Immunohistochemistry (IHC) (e.g. PD-L2, RNA signature, etc.) predictive of pembrolizumab efficacy should be investigated together with more information regarding the pattern of expression of PD-L1 obtained in the ongoing NSCLC studies (P001, P010, P024 and P042) and urothelial carcinoma studies (KN045, KN052): • Data on the Nanostring RNA gene signature • IHC staining for PD-L2 • Data on RNA and proteomic serum profiling	 2Q 2020 2Q 2019

Description	Due date
5. Post-authorisation efficacy study (PAES): The MAH should submit the final study report for study P045: A Phase III Randomized Clinical Trial of Pembrolizumab (MK-3475) versus Paclitaxel, Docetaxel or Vinflunine in Subjects with Recurrent or Progressive Metastatic Urothelial Cancer – Final Study Report	3Q 2018
6. Post-authorisation efficacy study (PAES): The MAH should submit the final study report for study P052: A Phase II Clinical Trial of Pembrolizumab (MK-3475) in Subjects with Advanced/Unresectable or Metastatic Urothelial Cancer – Final Study Report	2Q 2019
7. Post-authorisation efficacy study (PAES): The MAH should provide the study report for study P361: A Phase III Randomized, Controlled Clinical Trial of Pembrolizumab with or without Platinum-Based Combination Chemotherapy versus Chemotherapy in Subjects with Advanced or Metastatic Urothelial Carcinoma – Study Report	2Q 2019

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

KEYTRUDA 50 mg powder for concentrate for solution for infusion
pembrolizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 50 mg of pembrolizumab. After reconstitution, 1 mL of concentrate contains 25 mg of pembrolizumab.

3. LIST OF EXCIPIENTS

Excipients: L-histidine, L-histidine hydrochloride monohydrate, sucrose, polysorbate 80.

4. PHARMACEUTICAL FORM AND CONTENTS

powder for concentrate for solution for infusion
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use.
For single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

The reconstituted vials and/or diluted intravenous bags may be stored for a cumulative time of up to 24 hours in a refrigerator (2°C – 8°C).

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C).

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp &Dohme Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1024/001 (1 vial)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

KEYTRUDA 50 mg powder for concentrate for solution for infusion
pembrolizumab
Intravenous use
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

KEYTRUDA 25 mg/mL concentrate for solution for infusion
pembrolizumab
100 mg/4 mL

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of 4 mL contains 100 mg of pembrolizumab. Each mL of concentrate contains 25 mg of pembrolizumab.

3. LIST OF EXCIPIENTS

Excipients: L-histidine, L-histidine hydrochloride monohydrate, sucrose, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use after dilution.
For single use only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not shake.

8. EXPIRY DATE

EXP

The diluted solution may be stored for up to 24 hours in a refrigerator (2°C – 8°C).

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C).
Do not Freeze.
Store in the original carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp &Dohme Limited
Hertford Road, Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1024/002 (1 vial)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:

SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

KEYTRUDA 25 mg/mL concentrate for solution for infusion
pembrolizumab
100 mg/4 mL
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

KEYTRUDA 50 mg powder for concentrate for solution for infusion
pembrolizumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- It is important that you keep the Alert Card with you during treatment.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What KEYTRUDA is and what it is used for

KEYTRUDA contains the active substance pembrolizumab, which is a monoclonal antibody. KEYTRUDA works by helping your immune system fight your cancer.

KEYTRUDA is used in adults to treat:
- a kind of skin cancer called melanoma
- a kind of lung cancer called non-small cell lung cancer
- a kind of cancer called classical Hodgkin lymphoma
- a kind of cancer called bladder cancer (urothelial carcinoma).

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

2. What you need to know before you are given KEYTRUDA

You should not be given KEYTRUDA:
- if you are allergic to pembrolizumab or any of the other ingredients of this medicine (listed in section 6 “Contents of the pack and other information”). Talk to your doctor if you are not sure.

Warnings and precautions
Talk to your doctor or nurse before receiving KEYTRUDA.

Before you get KEYTRUDA, tell your doctor if you:
- have an autoimmune disease (a condition where the body attacks its own cells)
- 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
- have kidney damage
- have had a solid organ transplant or a bone marrow (stem cell) transplant that used donor stem cells (allogeneic)

When you get KEYTRUDA, you can have some serious side effects. You may experience more than one side effect at the same time.
If you have any of the following conditions, call or see your doctor right away. Your doctor may give you other medicines in order to prevent more severe complications and reduce your symptoms. Your doctor may withhold the next dose of KEYTRUDA or stop your treatment with KEYTRUDA.

- inflammation of the lungs, which may include shortness of breath, chest pain or coughing (possibly fatal)
- inflammation of the intestines, which may include diarrhoea 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 liver, which may include nausea or vomiting, feeling less hungry, pain on the right side of stomach, yellowing of skin or whites of eyes, dark urine or bleeding or bruising more easily than normal
- inflammation of the kidneys, which may include changes in the amount or colour of your urine
- inflammation of hormone glands (especially the thyroid, pituitary and adrenal glands), which may include rapid heartbeat, weight loss, increased sweating, weight gain, hair loss, feeling cold, constipation, deeper voice, muscle aches, dizziness or fainting, headaches that will not go away or unusual headache
- type 1 diabetes, which may include feeling more hungry or thirsty than usual, need to urinate more often or weight loss
- inflammation of the eyes, which may include changes in eyesight
- inflammation in the muscles, which may include muscle pain or weakness
- inflammation of the heart muscle, which may include shortness of breath, irregular heartbeat, feeling tired, or chest pain
- inflammation of the pancreas, which may include abdominal pain, nausea and vomiting
- inflammation of the skin, which may include rash, itching, skin blistering, peeling or sores, and/or ulcers in mouth or in lining of nose, throat, or genital area (possibly fatal)
- an immune disorder that can affect the lungs, skin, eyes and/or lymph nodes (sarcoidosis)
- inflammation of the brain, which may include confusion, fever, memory problems or seizures (encephalitis)
- infusion reactions, which may include shortness of breath, itching or rash, dizziness or fever

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 signs and symptoms, which may include skin rash, liver inflammation, abdominal pain, or diarrhoea.
Children and adolescents
KEYTRUDA should not be used in children and adolescents below 18 years of age.

Other medicines and KEYTRUDA
Tell your doctor
- If you are taking other medicines that make your immune system weak. Examples of these may include corticosteroids, such as prednisone. These medicines may interfere with the effect of KEYTRUDA. However, once you are treated with KEYTRUDA, your doctor may give you corticosteroids to reduce the side-effects that you may have with KEYTRUDA.
- If you are taking, have recently taken or might take any other medicines.

Pregnancy
- You must not use KEYTRUDA if you are pregnant unless your doctor specifically recommends it.
- 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.
- If you are a woman who could become pregnant, you must use adequate birth control while you are being treated with KEYTRUDA and for at least 4 months after your last dose.

Breast-feeding
- If you are breast-feeding, tell your doctor.
- Do not breast-feed while taking KEYTRUDA.
- It is not known if KEYTRUDA passes into your breast milk.

Driving and using machines
Do not drive or use machines after you have been given KEYTRUDA unless you are sure you are feeling well. Feeling tired or weak is a very common side effect of KEYTRUDA. This can affect your ability to drive or to use machines.

3. How you are given KEYTRUDA

KEYTRUDA will be given to you in a hospital or clinic under the supervision of a doctor experienced in cancer treatment.
- Your doctor will give you KEYTRUDA through an infusion into your vein (IV) for about 30 minutes, every 3 weeks.
- Your doctor will decide how many treatments you need.

The recommended dose is:
- 200 mg of pembrolizumab if you have non-small cell lung cancer that has not been previously treated with chemotherapy, classical Hodgkin lymphoma or if you have bladder cancer.
- 2 mg of pembrolizumab per kilogram of your body weight if you have melanoma or if you have non-small cell lung cancer that has been previously treated with chemotherapy.

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.

If you stop receiving KEYTRUDA
Stopping your treatment may stop the effect of the medicine. Do not stop treatment with KEYTRUDA unless you have discussed this with your doctor.
If you have any further questions about your treatment, ask your doctor.

You will also find this information in the Patient Alert Card you have been given by your doctor. It is important that you keep this Alert Card and show it to your partner or caregivers.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

When you get KEYTRUDA, you can have some serious side effects. See section 2.

The following side effects have been reported:

Very common (may affect more than 1 in 10 people)
- diarrhoea; nausea
- itching; skin rash
- feeling tired

Common (may affect up to 1 in 10 people)
- joint pain
- decrease in the number of red blood cells
- thyroid gland problems; hot flush
- feeling less hungry
- headache; dizziness; change in your sense of taste
- inflammation of the lungs; shortness of breath; cough
- inflammation of the intestines; dry mouth
- stomach pain; constipation; vomiting
- red raised rash sometimes with blisters; patches of skin which have lost colour
- muscle pain, aches or tenderness; pain in the muscles and bones; pain in arms or legs; joint pain with swelling
- swelling; unusual tiredness or weakness; chills; flu-like illness; fever
- increased liver enzyme levels in the blood; abnormal kidney function test
- reaction related to the infusion of the medicine

Uncommon (may affect up to 1 in 100 people)
- lung infection
- a decreased number of white blood cells (neutrophils, leukocytes, lymphocytes and eosinophils); decrease in the number of platelets (bruising or bleeding more easily)
- inflammation of the pituitary gland situated at the base of the brain; decreased secretion of hormones produced by the adrenal glands; inflammation of the thyroid
- type 1 diabetes; decreased sodium, potassium and calcium in the blood
- trouble sleeping
- seizure; lack of energy; inflammation of the nerves causing numbness, weakness, tingling or burning pain of the arms and legs
- dry eye; inflammation of the eyes; eye pain, irritation, itchiness or redness; uncomfortable sensitivity to light; seeing spots
- inflammation of the heart muscle, which may present as shortness of breath, irregular heartbeat, feeling tired, or chest pain
- high blood pressure
- inflammation of the pancreas
- inflammation of the liver
- dry, itchy skin; thickened, sometimes scaly, skin growth; hair loss; inflammation of the skin; acne-like skin problem; hair colour changes; small skin bumps, lumps or sores
- inflammation of the sheath that surrounds tendons
- inflammation of the kidneys
- increased level of amylase, an enzyme that breaks down starch; increased calcium in the blood

Rare (may affect up to 1 in 1,000 people)
- inflammation response against platelets or red blood cells
- an immune disorder that can affect the lungs, skin, eyes and/or lymph nodes (sarcoidosis)

- a temporary inflammation of the nerves that causes pain, weakness, and paralysis in the extremities; a condition in which the muscles become weak and tire easily
- inflammation of the brain, which may present as confusion, fever, memory problems or seizures (encephalitis)
- a hole in the small intestines
- tender red bumps under the skin
- itching, skin blistering, peeling or sores, and/or ulcers in mouth or in lining of nose, throat, or genital area (toxic epidermal necrolysis or Stevens-Johnson syndrome)

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store KEYTRUDA

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

Do not use this medicine after the expiry date which is stated on the carton and vial label after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C).

From a microbiological point of view, the reconstituted or diluted solution should be used immediately. The reconstituted or diluted solution must not be frozen. If not used immediately, chemical and physical in-use stability of KEYTRUDA has been demonstrated for 24 hours at 2°C to 8°C. This 24 hour total hold from reconstitution may include up to 6 hours at room temperature (at or below 25°C). If refrigerated, the vials and/or intravenous bags must be allowed to come to room temperature prior to use.

Do not store any unused portion of the infusion solution for reuse. Any unused medicine or waste material should be disposed of in accordance with local requirements.

6. Contents of the pack and other information

What KEYTRUDA contains
The active substance is pembrolizumab. One vial contains 50 mg of pembrolizumab.

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

The other ingredients are L-histidine, L-histidine hydrochloride monohydrate, sucrose and polysorbate 80.

What KEYTRUDA looks like and contents of the pack
KEYTRUDA is a white to off-white lyophilised powder.
It is available in cartons containing one glass vial.

Marketing Authorisation Holder
Merck Sharp & Dohme Limited
Hertford Road
Hoddesdon
Hertfordshire EN11 9BU
United Kingdom

Manufacturer
Schering-Plough Labo NV
Industriepark 30
B-2220 Heist-op-den-Berg
Belgium

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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medicalinformationuk@merck.com

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

Preparation and administration

- Prior to reconstitution, the vial of lyophilised powder can be out of refrigeration (temperatures at or below 25°C) for up to 24 hours.
- Aseptically add 2.3 mL of water for injections to yield a 25 mg/mL (pH 5.2-5.8) solution of KEYTRUDA. Each vial contains an excess fill of 10 mg (0.4 mL) to ensure the recovery of 50 mg of KEYTRUDA per vial. After reconstitution, 1 mL of concentrate contains 25 mg of pembrolizumab.
- To avoid foaming, deliver the water along the walls of the vial and not directly on the lyophilised powder.

- Slowly swirl the vial to allow reconstitution of the lyophilised powder. Allow up to 5 minutes for the bubbles to clear. Do not shake the vial.
- Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration. Reconstituted KEYTRUDA is a clear to slightly opalescent, colourless to slightly yellow solution. Discard the vial if visible particles are observed.
- Withdraw the required volume up to 2 mL (50 mg) of KEYTRUDA and transfer into an intravenous bag containing sodium chloride 9 mg/mL (0.9%) or glucose 50 mg/mL (5%) to prepare a diluted solution with a final concentration ranging from 1 to 10 mg/mL. Mix diluted solution by gentle inversion.
- From a microbiological point of view, the reconstituted or diluted solution should be used immediately. The reconstituted or diluted solution must not be frozen. If not used immediately, chemical and physical in-use stability of KEYTRUDA has been demonstrated for 24 hours at 2°C to 8°C. This 24 hour total hold from reconstitution may include up to 6 hours at room temperature (at or below 25°C). If refrigerated, the vials and/or intravenous bags must be allowed to come to room temperature prior to use. Administer the 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 medicinal products through the same infusion line.
- KEYTRUDA is for single use only. Discard any unused portion left in the vial.

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

Package leaflet: Information for the patient

KEYTRUDA 25 mg/mL concentrate for solution for infusion
pembrolizumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- It is important that you keep the Alert Card with you during treatment.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What KEYTRUDA is and what it is used for

KEYTRUDA contains the active substance pembrolizumab, which is a monoclonal antibody. KEYTRUDA works by helping your immune system fight your cancer.

KEYTRUDA is used in adults to treat:
- a kind of skin cancer called melanoma
- a kind of lung cancer called non-small cell lung cancer
- a kind of cancer called classical Hodgkin lymphoma
- a kind of cancer called bladder cancer (urothelial carcinoma).

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

2. What you need to know before you are given KEYTRUDA

You should not be given KEYTRUDA:
- if you are allergic to pembrolizumab or any of the other ingredients of this medicine (listed in section 6 “Contents of the pack and other information”). Talk to your doctor if you are not sure.

Warnings and precautions
Talk to your doctor or nurse before receiving KEYTRUDA.

Before you get KEYTRUDA, tell your doctor if you:
- have an autoimmune disease (a condition where the body attacks its own cells)
- 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
- have kidney damage
- have had a solid organ transplant or a bone marrow (stem cell) transplant that used donor stem cells (allogeneic)

When you get KEYTRUDA, you can have some serious side effects. You may experience more than one side effect at the same time.
If you have any of the following conditions, call or see your doctor right away. Your doctor may give you other medicines in order to prevent more severe complications and reduce your symptoms. Your doctor may withhold the next dose of KEYTRUDA or stop your treatment with KEYTRUDA.

- inflammation of the lungs, which may include shortness of breath, chest pain or coughing (possibly fatal)
- inflammation of the intestines, which may include diarrhoea 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 liver, which may include nausea or vomiting, feeling less hungry, pain on the right side of stomach, yellowing of skin or whites of eyes, dark urine or bleeding or bruising more easily than normal
- inflammation of the kidneys, which may include changes in the amount or colour of your urine
- inflammation of hormone glands (especially the thyroid, pituitary and adrenal glands), which may include rapid heartbeat, weight loss, increased sweating, weight gain, hair loss, feeling cold, constipation, deeper voice, muscle aches, dizziness or fainting, headaches that will not go away or unusual headache
- type 1 diabetes, which may include feeling more hungry or thirsty than usual, need to urinate more often or weight loss
- inflammation of the eyes, which may include changes in eyesight
- inflammation in the muscles, which may include muscle pain or weakness
- inflammation of the heart muscle, which may include shortness of breath, irregular heartbeat, feeling tired, or chest pain
- inflammation of the pancreas, which may include abdominal pain, nausea and vomiting
- inflammation of the skin, which may include rash, itching, skin blistering, peeling or sores, and/or ulcers in mouth or in lining of nose, throat, or genital area (possibly fatal)
- an immune disorder that can affect the lungs, skin, eyes and/or lymph nodes (sarcoidosis)
- inflammation of the brain, which may include confusion, fever, memory problems or seizures (encephalitis)
- infusion reactions, which may include shortness of breath, itching or rash, dizziness or fever

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 signs and symptoms, which may include skin rash, liver inflammation, abdominal pain, or diarrhoea.

Children and adolescents

KEYTRUDA should not be used in children and adolescents below 18 years of age.

Other medicines and KEYTRUDA
Tell your doctor
- If you are taking other medicines that make your immune system weak. Examples of these may include corticosteroids, such as prednisone. These medicines may interfere with the effect of KEYTRUDA. However, once you are treated with KEYTRUDA, your doctor may give you corticosteroids to reduce the side-effects that you may have with KEYTRUDA.
- If you are taking, have recently taken or might take any other medicines.

Pregnancy
- You must not use KEYTRUDA if you are pregnant unless your doctor specifically recommends it.
- 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.
- If you are a woman who could become pregnant, you must use adequate birth control while you are being treated with KEYTRUDA and for at least 4 months after your last dose.

Breast-feeding
- If you are breast-feeding, tell your doctor.
- Do not breast-feed while taking KEYTRUDA.
- It is not known if KEYTRUDA passes into your breast milk.

Driving and using machines
Do not drive or use machines after you have been given KEYTRUDA unless you are sure you are feeling well. Feeling tired or weak is a very common side effect of KEYTRUDA. This can affect your ability to drive or to use machines.

3. How you are given KEYTRUDA

KEYTRUDA will be given to you in a hospital or clinic under the supervision of a doctor experienced in cancer treatment.
- Your doctor will give you KEYTRUDA through an infusion into your vein (IV) for about 30 minutes, every 3 weeks.
- Your doctor will decide how many treatments you need.

The recommended dose is:
- 200 mg of pembrolizumab if you have non-small cell lung cancer that has not been previously treated with chemotherapy, classical Hodgkin lymphoma or if you have bladder cancer.
- 2 mg of pembrolizumab per kilogram of your body weight if you have melanoma or if you have non-small cell lung cancer that has been previously treated with chemotherapy.

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.

If you stop receiving KEYTRUDA
Stopping your treatment may stop the effect of the medicine. Do not stop treatment with KEYTRUDA unless you have discussed this with your doctor.
If you have any further questions about your treatment, ask your doctor.

You will also find this information in the Patient Alert Card you have been given by your doctor. It is important that you keep this Alert Card and show it to your partner or caregivers.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

When you get KEYTRUDA, you can have some serious side effects. See section 2.

The following side effects have been reported:

Very common (may affect more than 1 in 10 people)
- diarrhoea; nausea
- itching; skin rash
- feeling tired

Common (may affect up to 1 in 10 people)
- joint pain
- decrease in the number of red blood cells
- thyroid gland problems; hot flush
- feeling less hungry
- headache; dizziness; change in your sense of taste
- inflammation of the lungs; shortness of breath; cough
- inflammation of the intestines; dry mouth
- stomach pain; constipation; vomiting
- red raised rash sometimes with blisters; patches of skin which have lost colour
- muscle pain, aches or tenderness; pain in the muscles and bones; pain in arms or legs; joint pain with swelling
- swelling; unusual tiredness or weakness; chills; flu-like illness; fever
- increased liver enzyme levels in the blood; abnormal kidney function test
- reaction related to the infusion of the medicine

Uncommon (may affect up to 1 in 100 people)
- lung infection
- a decreased number of white blood cells (neutrophils, leukocytes, lymphocytes and eosinophils); decrease in the number of platelets (bruising or bleeding more easily)
- inflammation of the pituitary gland situated at the base of the brain; decreased secretion of hormones produced by the adrenal glands; inflammation of the thyroid
- type 1 diabetes; decreased sodium, potassium and calcium in the blood
- trouble sleeping
- seizure; lack of energy; inflammation of the nerves causing numbness, weakness, tingling or burning pain of the arms and legs
- dry eye; inflammation of the eyes; eye pain, irritation, itchiness or redness; uncomfortable sensitivity to light; seeing spots
- inflammation of the heart muscle, which may present as shortness of breath, irregular heartbeat, feeling tired, or chest pain
- high blood pressure
- inflammation of the pancreas
- inflammation of the liver
- dry, itchy skin; thickened, sometimes scaly, skin growth; hair loss; inflammation of the skin; acne-like skin problem; hair colour changes; small skin bumps, lumps or sores
- inflammation of the sheath that surrounds tendons
- inflammation of the kidneys
- increased level of amylase, an enzyme that breaks down starch; increased calcium in the blood

Rare (may affect up to 1 in 1,000 people)
- inflammation response against platelets or red blood cells
- an immune disorder that can affect the lungs, skin, eyes and/or lymph nodes (sarcoidosis)

- a temporary inflammation of the nerves that causes pain, weakness, and paralysis in the extremities; a condition in which the muscles become weak and tire easily
- inflammation of the brain, which may present as confusion, fever, memory problems or seizures (encephalitis)
- a hole in the small intestines
- tender red bumps under the skin
- itching, skin blistering, peeling or sores, and/or ulcers in mouth or in lining of nose, throat, or genital area (toxic epidermal necrolysis or Stevens-Johnson syndrome)

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store KEYTRUDA

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

Do not use this medicine after the expiry date which is stated on the carton and vial label after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Store in the original carton in order to protect from light.

From a microbiological point of view, the product, once diluted, should be used immediately. The diluted solution must not be frozen. If not used immediately, chemical and physical in-use stability of KEYTRUDA has been demonstrated for 24 hours at 2ºC to 8ºC. This 24 hour hold may include up to 6 hours at room temperature (at or below 25°C). If refrigerated, the vials and/or intravenous bags must be allowed to come to room temperature prior to use.

Do not store any unused portion of the infusion solution for reuse. Any unused medicine or waste material should be disposed of in accordance with local requirements.

6. Contents of the pack and other information

What KEYTRUDA contains
The active substance is pembrolizumab.

One vial of 4 mL contains 100 mg of pembrolizumab.
Each mL of concentrate contains 25 mg of pembrolizumab.

The other ingredients are L-histidine, L-histidine hydrochloride monohydrate, sucrose, polysorbate 80 and water for injections.

What KEYTRUDA looks like and contents of the pack
KEYTRUDA is a clear to slightly opalescent, colourless to slightly yellow solution, pH 5.2 – 5.8.
It is available in cartons containing one glass vial.

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

Preparation and administration of the infusion
- Do not shake the vial.
- Equilibrate the vial to room temperature (at or below 25°C).
- Prior to dilution, the vial of liquid can be out of refrigeration (temperatures at or below 25°C) for up to 24 hours.
- Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration. The concentrate is a clear to slightly opalescent, colourless to slightly yellow solution. Discard the vial if visible particles are observed.

- Withdraw the required volume up to 4 mL (100 mg) of concentrate and transfer into an intravenous bag containing sodium chloride 9 mg/mL (0.9%) or glucose 50 mg/mL (5%) to prepare a diluted solution with a final concentration ranging from 1 to 10 mg/mL. Each vial contains an excess fill of 0.25 ml (total content per vial 4.25 ml) to ensure the recovery of 4 ml of concentrate. Mix diluted solution by gentle inversion.
- From a microbiological point of view, the product, once diluted, should be used immediately. The diluted solution must not be frozen. If not used immediately, chemical and physical in-use stability of KEYTRUDA has been demonstrated for 24 hours at 2ºC to 8ºC. This 24 hour hold may include up to 6 hours at room temperature (at or below 25°C). If refrigerated, the vials and/or intravenous bags must be allowed to come to room temperature prior to use. Administer the 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 medicinal products through the same infusion line.
- KEYTRUDA is for single use only. Discard any unused portion left in the vial.

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