SUMMARY OF PRODUCT CHARACTERISTICS

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

Melanoma

KEYTRUDA as monotherapy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.
KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection (see section 5.1).

Non-small cell lung carcinoma (NSCLC)

KEYTRUDA as monotherapy is indicated for the first-line treatment of metastatic non-small cell lung carcinoma in adults whose tumours express PD-L1 with a ≥ 50 % tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations.
KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of metastatic non-squamous non-small cell lung carcinoma in adults whose tumours have no EGFR or ALK positive mutations.
KEYTRUDA, in combination with carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of metastatic squamous non-small cell lung carcinoma in adults.
KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic non-small cell lung carcinoma 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.

Classical Hodgkin lymphoma (cHL)

KEYTRUDA as monotherapy is indicated for the treatment of adult and paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option.

Urothelial carcinoma

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 and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10 (see section 5.1).

Head and neck squamous cell carcinoma (HNSCC)
KEYTRUDA, as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, is indicated for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1 (see section 5.1).
KEYTRUDA as monotherapy is indicated for the treatment of recurrent or metastatic head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a ≥ 50 % TPS and progressing on or after platinum-containing chemotherapy (see section 5.1).

Renal cell carcinoma (RCC)
KEYTRUDA, in combination with axitinib, is indicated for the first-line treatment of advanced renal cell carcinoma in adults (see section 5.1).

Colorectal cancer (CRC)
KEYTRUDA as monotherapy is indicated for the first-line treatment of metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer in adults.

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, urothelial carcinoma or HNSCC
For treatment with KEYTRUDA as monotherapy, testing for PD-L1 tumour expression using a validated test is recommended to select patients with NSCLC or previously untreated urothelial carcinoma (see sections 4.1, 4.4, 4.8 and 5.1).
Patients with HNSCC should be selected for treatment with KEYTRUDA as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy based on the tumour expression of PD-L1 confirmed by a validated test (see sections 4.1, 4.4, 4.8 and 5.1).

MSI-H/dMMR testing for patients with CRC
For treatment with KEYTRUDA as monotherapy, testing for MSI-H/dMMR tumour status using a validated test is recommended to select patients with CRC (see sections 4.1 and 5.1).

Posology
The recommended dose of KEYTRUDA as monotherapy in adults is either 200 mg every 3 weeks or 400 mg every 6 weeks administered as an intravenous infusion over 30 minutes.
The recommended dose of KEYTRUDA as monotherapy in paediatric patients aged 3 years and older with cHL is 2 mg/kg bodyweight (up to a maximum of 200 mg), every 3 weeks administered as an intravenous infusion over 30 minutes.
The recommended dose of KEYTRUDA as part of combination therapy in adults is 200 mg every 3 weeks administered as an intravenous infusion over 30 minutes.
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.
For the adjuvant treatment of melanoma, KEYTRUDA should be administered until disease recurrence, unacceptable toxicity, or for a duration of up to one year.

Dose delay or discontinuation (see also section 4.4)
No dose reductions of KEYTRUDA are recommended. KEYTRUDA should be withheld or discontinued to manage adverse reactions as described in Table 1.

Table 1: Recommended treatment modifications for KEYTRUDA

Immune-related adverse reactions	**Severity**	**Treatment modification**
Pneumonitis	Grade 2	Withhold until adverse reactions recover to Grades 0-1*
	Grades 3 or 4 or recurrent Grade 2	Permanently discontinue
Colitis	Grades 2 or 3	Withhold until adverse reactions recover to Grades 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 Grades 0-1*
	Grade ≥ 3 with creatinine > 3 times ULN	Permanently discontinue
Endocrinopathies	Grade 2 adrenal insufficiency and hypophysitis	Withhold treatment until controlled by hormone replacement
	Grades 3 or 4 adrenal insufficiency or 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 Grades 0-1* For patients with Grade 3 or Grade 4 endocrinopathies that improved to Grade 2 or lower and are controlled with hormone replacement, if indicated, continuation of pembrolizumab may be considered after corticosteroid taper, if needed. Otherwise treatment should be discontinued.
	Hypothyroidism	Hypothyroidism may be managed with replacement therapy without treatment interruption.

Hepatitis **NOTE:** for RCC patients treated with **pembrolizumab in combination with axitinib** with liver enzyme elevations, see dosing guidelines following this table.	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 Grades 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 Grades 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) Grades 3 or 4 myocarditis Grades 3 or 4 encephalitis Grades 3 or 4 Guillain-Barré syndrome Grade 4 or recurrent Grade 3	Withhold until adverse reactions recover to Grades 0-1* Permanently discontinue Permanently discontinue
Infusion-related reactions	Grades 3 or 4	Permanently discontinue

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

*If treatment-related toxicity does not resolve to Grades 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, as monotherapy or as combination therapy, should be permanently discontinued for Grade 4 or recurrent Grade 3 immune-related 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 Grades 0-1.

KEYTRUDA in combination with axitinib in RCC

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

For liver enzyme elevations, in patients with RCC being treated with KEYTRUDA in combination with axitinib:

- If ALT or AST ≥ 3 times ULN but < 10 times ULN without concurrent total bilirubin ≥ 2 times ULN, both KEYTRUDA and axitinib should be withheld until these adverse reactions recover to Grades 0-1. Corticosteroid therapy may be considered. Rechallenge with a single medicine or sequential rechallenge with both medicines after recovery may be considered. If rechallenging with axitinib, dose reduction as per the axitinib SmPC may be considered.
- If ALT or AST ≥ 10 times ULN or > 3 times ULN with concurrent total bilirubin ≥ 2 times ULN, both KEYTRUDA and axitinib should be permanently discontinued and corticosteroid therapy may be considered.

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 dose adjustment is necessary in patients ≥ 65 years (see section 5.1). Data from patients ≥ 65 years are too limited to draw conclusions on cHL population (see section 5.1). Data are limited in patients ≥ 75 years for pembrolizumab monotherapy in patients with resected Stage III melanoma and MSI-H or dMMR CRC; for pembrolizumab in combination with axitinib in patients with advanced RCC; for chemotherapy combination in patients with metastatic NSCLC; and for pembrolizumab (with or without chemotherapy) in patients receiving first-line treatment for metastatic or unresectable recurrent HNSCC (see sections 4.4 and 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).

Paediatric population

The safety and efficacy of KEYTRUDA in children below 18 years of age have not been established except in paediatric patients with cHL. Currently available data are described in sections 4.8, 5.1 and 5.2.

Method of administration

KEYTRUDA is for intravenous use. It must be administered by infusion over 30 minutes.
KEYTRUDA must not be administered as an intravenous push or bolus injection.
For use in combination, see the SmPC for the concomitant therapies. When administering KEYTRUDA as part of a combination with intravenous chemotherapy, KEYTRUDA should be administered first.
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

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

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
Immune-related adverse reactions, including severe and fatal cases, have occurred in patients receiving pembrolizumab. 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 recovers to 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 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 or recurrent Grade 3 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 adrenal insufficiency, 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.

Adrenal insufficiency (primary and secondary) has been reported in patients receiving pembrolizumab. Hypophysitis has also been reported in patients receiving pembrolizumab (see section 4.8). Patients should be monitored for signs and symptoms of adrenal insufficiency and hypophysitis (including hypopituitarism) and other causes excluded. Corticosteroids to treat adrenal insufficiency and other hormone replacement should be administered as clinically indicated. Pembrolizumab should be withheld for Grade 2 adrenal insufficiency or hypophysitis until the event is controlled with hormone replacement. Pembrolizumab should be withheld or discontinued for Grades 3 or 4 adrenal insufficiency or symptomatic hypophysitis. 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 type 1 diabetes associated with Grade ≥ 3 hyperglycaemia or ketoacidosis 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. Hypothyroidism is more frequently reported in patients with HNSCC with prior radiation therapy. 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. Thyroid function and hormone levels should be monitored to ensure appropriate hormone replacement.

For patients with Grade 3 or Grade 4 endocrinopathies that improved to Grade 2 or lower and are controlled with hormone replacement, if indicated, continuation of pembrolizumab may be considered after corticosteroid taper, if needed. Otherwise treatment should be discontinued (see sections 4.2 and 4.8).

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 for Grade 3 skin reactions until recovery to Grade ≤ 1 or permanently discontinued for Grade 4 skin reactions, and corticosteroids should be administered (see section 4.2).

Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in patients receiving pembrolizumab (see section 4.8). For suspected 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 anti-cancer agents.

Other immune-related adverse reactions
The following additional clinically significant, immune-related adverse reactions have been reported in clinical studies or in post-marketing experience: uveitis, arthritis, myositis, myocarditis, pancreatitis, Guillain-Barré syndrome, myasthenic syndrome, haemolytic anaemia, sarcoidosis, encephalitis, myelitis and vasculitis (see sections 4.2 and 4.8).
Based on the severity and type of the adverse reaction, pembrolizumab should be withheld for Grade 2 or Grade 3 events and corticosteroids administered.
Pembrolizumab may be restarted within 12 weeks after last dose of KEYTRUDA if the adverse reaction recovers to 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.
For Grades 3 or 4 myocarditis, encephalitis or Guillain-Barré syndrome, pembrolizumab should be permanently discontinued (see sections 4.2 and 4.8).

Transplant-related adverse reactions
Solid organ transplant rejection
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 cHL 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 Grades 3 or 4 infusion reactions, infusion should be stopped and pembrolizumab permanently discontinued (see section 4.2). Patients with

Grades 1 or 2 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 carcinoma, 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 carcinoma for patients who are considered ineligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with CPS ≥ 10

The baseline and prognostic disease characteristics of the study population of KEYNOTE-052 included a proportion of patients eligible for a carboplatin-based combination, for whom the benefit is being assessed in a comparative study, and patients eligible for mono-chemotherapy, for whom no randomised data are available. In addition, 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.

Use of pembrolizumab for first-line treatment of patients with NSCLC

In general, the frequency of adverse reactions for pembrolizumab combination therapy is observed to be higher than for pembrolizumab monotherapy or chemotherapy alone, reflecting the contributions of each of these components (see sections 4.2 and 4.8). A direct comparison of pembrolizumab when used in combination with chemotherapy to pembrolizumab monotherapy is not available.

Physicians should consider the benefit/risk balance of the available treatment options (pembrolizumab monotherapy or pembrolizumab in combination with chemotherapy) before initiating treatment in previously untreated patients with NSCLC whose tumours express PD-L1.

In KEYNOTE-042, a higher number of deaths within 4 months of treatment initiation followed by a long-term survival benefit was observed with pembrolizumab monotherapy compared to chemotherapy (see section 5.1).

Efficacy and safety data from patients ≥ 75 years are limited. For patients ≥ 75 years, pembrolizumab combination therapy should be used with caution after careful consideration of the potential benefit/risk on an individual basis (see section 5.1).

Use of pembrolizumab for first-line treatment of patients with HNSCC

In general, the frequency of adverse reactions for pembrolizumab combination therapy is observed to be higher than for pembrolizumab monotherapy or chemotherapy alone, reflecting the contributions of each of these components (see section 4.8).

Physicians should consider the benefit/risk balance of the available treatment options (pembrolizumab monotherapy or pembrolizumab in combination with chemotherapy) before initiating treatment in patients with HNSCC whose tumours express PD-L1 (see section 5.1).

Use of pembrolizumab for adjuvant treatment of patients with melanoma

A trend toward increased frequency of severe and serious adverse reactions in patients ≥ 75 years was observed. Safety data of pembrolizumab in the adjuvant melanoma setting in patients ≥ 75 years are limited.

Use of pembrolizumab in combination with axitinib for first-line treatment of patients with RCC
When pembrolizumab is given with axitinib, higher than expected frequencies of Grades 3 and 4 ALT and AST elevations have been reported in patients with advanced RCC (see section 4.8). Liver enzymes should be monitored before initiation of and periodically throughout treatment. More frequent monitoring of liver enzymes as compared to when the medicines are used in monotherapy may be considered. Medical management guidelines for both medicines should be followed (see section 4.2 and refer to the SmPC for axitinib).

Use of pembrolizumab for first-line treatment of patients with MSI-H/dMMR CRC
In KEYNOTE-177, the hazard rates for overall survival events were greater for pembrolizumab compared with chemotherapy for the first 4 months of treatment, followed by a long-term survival benefit for pembrolizumab (see section 5.1).

Patients excluded from clinical studies
Patients with the following conditions were excluded from clinical studies: active CNS metastases; ECOG PS ≥ 2 (except for urothelial carcinoma and RCC); HIV infection, 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 studies 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 studies, therefore information is limited in patients with severe renal and moderate to severe hepatic impairment.
There are limited data on the safety and efficacy of KEYTRUDA in patients with ocular melanoma (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). Corticosteroids can also be used as premedication, when pembrolizumab is used in combination with chemotherapy, as antiemetic prophylaxis and/or to alleviate chemotherapy-related adverse reactions.

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 signalling 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.

Breastfeeding

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 breastfeeding or to discontinue pembrolizumab, taking into account the benefit of breastfeeding 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 has a minor influence on the ability to drive and use machines. In some patients, dizziness and fatigue have 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 as monotherapy has been evaluated in 6 185 patients with advanced melanoma, resected Stage III melanoma (adjuvant therapy), NSCLC, cHL, urothelial carcinoma, HNSCC or CRC 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. The frequencies included below and in Table 2 are based on all reported adverse drug reactions, regardless of the investigator assessment of causality. In this patient population, the median observation time was 7,6 months (range: 1 day to 47 months) and the most frequent adverse reactions with pembrolizumab were fatigue (32 %), nausea (21 %), and diarrhoea (21 %). The majority of adverse reactions reported for monotherapy were of Grades 1 or 2 severity. The most serious adverse reactions were immune-related adverse reactions and severe infusion-related reactions (see section 4.4).

The safety of pembrolizumab in combination with chemotherapy has been evaluated in 1 067 patients with NSCLC or HNSCC receiving 200 mg, 2 mg/kg or 10 mg/kg pembrolizumab every 3 weeks, in clinical studies. The frequencies included below and in Table 2 are based on all reported adverse drug reactions, regardless of the investigator assessment of causality. In this patient population, the most frequent adverse reactions were anaemia (50 %), nausea (50 %), fatigue (37 %), constipation (35 %), diarrhoea (30 %), neutropenia (30 %), decreased appetite (28 %) and vomiting (25 %). Incidences of

Grades 3-5 adverse reactions in patients with NSCLC were 67 % for pembrolizumab combination therapy and 66 % for chemotherapy alone and in patients with HNSCC were 85 % for pembrolizumab combination therapy and 84 % for chemotherapy plus cetuximab.
The safety of pembrolizumab in combination with axitinib has been evaluated in a clinical study of 429 patients with advanced RCC receiving 200 mg pembrolizumab every 3 weeks and 5 mg axitinib twice daily. In this patient population, the most frequent adverse reactions were diarrhoea (54 %), hypertension (45 %), fatigue (38 %), hypothyroidism (35 %), decreased appetite (30 %), palmar-plantar erythrodysaesthesia syndrome (28 %), nausea (28 %), ALT increased (27 %), AST increased (26 %), dysphonia (25 %), cough (21 %) and constipation (21 %). Incidences of Grades 3-5 adverse reactions were 76 % for pembrolizumab combination therapy and 71 % for sunitinib alone.

Tabulated list of adverse reactions
Adverse reactions observed in clinical studies of pembrolizumab as monotherapy or in combination with chemotherapy or other anti-tumour medicines or reported from post-marketing use of pembrolizumab are listed in Table 2. Adverse reactions known to occur with pembrolizumab, or chemotherapies given alone may occur during treatment with these medicinal products in combination, even if these reactions were not reported in clinical studies with combination therapy. 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); and 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*

	Monotherapy	**Combination with chemotherapy**	**Combination with axitinib**
Infections and infestations			
Common	pneumonia	pneumonia	pneumonia
Blood and lymphatic system disorders			
Very common	anaemia	anaemia, neutropenia, thrombocytopenia	
Common	thrombocytopenia, lymphopenia, neutropenia	febrile neutropenia, leukopenia, lymphopenia	anaemia, neutropenia, leukopenia, thrombocytopenia
Uncommon	leukopenia, eosinophilia		lymphopenia, eosinophilia
Rare	immune thrombocytopenia, haemolytic anaemia, pure red cell aplasia, haemophagocytic lymphohistiocytosis	eosinophilia	
Immune system disorders			
Common	infusion-related reaction[a]	infusion-related reaction[a]	infusion-related reaction[a]
Uncommon	sarcoidosis		
Not known	solid organ transplant rejection		
Endocrine disorders			

Very common	hypothyroidism[b]		hyperthyroidism, hypothyroidism[b]
Common	hyperthyroidism, thyroiditis[c]	hypothyroidism, hyperthyroidism	hypophysitis[e], thyroiditis[c], adrenal insufficiency[d]
Uncommon	adrenal insufficiency[d], hypophysitis[e],	hypophysitis[e], thyroiditis[c], adrenal insufficiency[d]	
Metabolism and nutrition disorders			
Very common	decreased appetite	hypokalaemia, decreased appetite	decreased appetite
Common	hyponatraemia, hypokalaemia, hypocalcaemia	hyponatraemia, hypocalcaemia	hypokalaemia, hyponatraemia, hypocalcaemia
Uncommon	type 1 diabetes mellitus[f]	type 1 diabetes mellitus	type 1 diabetes mellitus[f]
Psychiatric disorders			
Common	insomnia	insomnia	insomnia
Nervous system disorders			
Very common	headache	dizziness, headache, neuropathy peripheral, dysgeusia	headache, dysgeusia
Common	dizziness, neuropathy peripheral, lethargy, dysgeusia	lethargy	dizziness, lethargy, neuropathy peripheral
Uncommon	epilepsy	epilepsy	myasthenic syndrome[j]
Rare	encephalitis[g], Guillain-Barré syndrome[h], myelitis[i], myasthenic syndrome[j], meningitis (aseptic)[k]		
Eye disorders			
Common	dry eye	dry eye	dry eye
Uncommon	uveitis[l]		uveitis[l]
Rare	Vogt-Koyanagi-Harada syndrome		
Cardiac disorders			
Common	cardiac arrhythmia[†] (including atrial fibrillation)	cardiac arrhythmia[†] (including atrial fibrillation)	cardiac arrhythmia[†] (including atrial fibrillation)
Uncommon	myocarditis, pericardial effusion, pericarditis	pericardial effusion	myocarditis
Rare		myocarditis[m], pericarditis	
Vascular disorders			
Very common			hypertension
Common	hypertension	hypertension	
Uncommon		vasculitis	
Rare	vasculitis		

Respiratory, thoracic and mediastinal disorders			
Very common	dyspnoea, cough	dyspnoea, cough	dyspnoea, cough, dysphonia
Common	pneumonitis[n]	pneumonitis[n]	pneumonitis[n]
Gastrointestinal disorders			
Very common	diarrhoea, abdominal pain[o], nausea, vomiting, constipation	diarrhoea, nausea, vomiting, constipation, abdominal pain[o]	diarrhoea, abdominal pain[o], nausea, vomiting, constipation
Common	colitis[p], dry mouth	colitis[p], dry mouth	colitis[p], dry mouth
Uncommon	pancreatitis[q], gastrointestinal ulceration[r]	pancreatitis[q], gastrointestinal ulceration[r]	pancreatitis[q], gastrointestinal ulceration[r]
Rare	small intestinal perforation		
Hepatobiliary disorders			
Common			hepatitis[s]
Uncommon	hepatitis[s]	hepatitis[s]	
Skin and subcutaneous tissue disorders			
Very common	rash[t], pruritus[u]	rash[t], alopecia, pruritus[u]	palmar-plantar erythrodysaesthesia syndrome, rash[t], pruritus[u]
Common	severe skin reactions[v], erythema, dry skin, vitiligo[w], eczema, alopecia, dermatitis acneiform, dermatitis	severe skin reactions[v], erythema, dry skin	severe skin reactions[v], dermatitis acneiform, dermatitis, dry skin, alopecia, eczema, erythema
Uncommon	lichenoid keratosis[x], psoriasis, papule, hair colour changes	psoriasis, dermatitis acneiform, dermatitis, vitiligow, eczema	hair colour changes, lichenoid keratosis, papule, psoriasis, vitiligo[w]
Rare	toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema nodosum	hair colour changes, lichenoid keratosis, papule	
Musculoskeletal and connective tissue disorders			
Very common	musculoskeletal pain[y], arthralgia	musculoskeletal pain[y], arthralgia	musculoskeletal pain[y], arthralgia, pain in extremity
Common	pain in extremity, myositis[z], arthritis[aa]	myositis[z], pain in extremity, arthritis[aa]	myositis[z], arthritis[aa], tenosynovitis[bb]
Uncommon	tenosynovitis[bb]	tenosynovitis[bb]	Sjogren's syndrome
Rare	Sjogren's syndrome	Sjogren's syndrome	
Renal and urinary disorders			
Common		nephritis[cc], acute kidney injury	acute kidney injury, nephritis[cc]
Uncommon	nephritis[cc]		
General disorders and administration site conditions			

Very common	fatigue, asthenia, oedema[dd], pyrexia	fatigue, asthenia, pyrexia, oedema[dd]	fatigue, asthenia, pyrexia
Common	influenza-like illness, chills	chills, influenza-like illness	oedema[dd], influenza-like illness, chills
Investigations			
Very common		blood creatinine increased	alanine aminotransferase increased, aspartate aminotransferase increased, blood creatinine increased
Common	aspartate aminotransferase increased, alanine aminotransferase increased, hypercalcaemia, blood alkaline phosphatase increased, blood bilirubin increased, blood creatinine increased	hypercalcaemia, alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased	blood alkaline phosphatase increased, hypercalcaemia, blood bilirubin increased
Uncommon	amylase increased	blood bilirubin increased, amylase increased	amylase increased

[*]Adverse reaction frequencies presented in Table 2 may not be fully attributable to pembrolizumab alone but may contain contributions from the underlying disease or from other medicinal products used in a combination.

[†]Based upon a standard query including bradyarrhythmias and tachyarrhythmias.

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

[a] infusion-related reaction (drug hypersensitivity, anaphylactic reaction, anaphylactoid reaction, hypersensitivity and cytokine release syndrome)

[b] hypothyroidism (myxoedema)

[c] thyroiditis (autoimmune thyroiditis and thyroid disorder)

[d] adrenal insufficiency (Addison's disease, adrenocortical insufficiency acute, secondary adrenocortical insufficiency)

[e] hypophysitis (hypopituitarism)

[f] type 1 diabetes mellitus (diabetic ketoacidosis)

[g] encephalitis (autoimmune encephalitis)

[h] Guillain-Barré syndrome (axonal neuropathy and demyelinating polyneuropathy)

[i] myelitis (including transverse myelitis)

[j] myasthenic syndrome (myasthenia gravis, including exacerbation)

[k] meningitis aseptic (meningitis, meningitis non-infective)

[l] uveitis (chorioretinitis, iritis and iridocyclitis)

[m] myocarditis (autoimmune myocarditis)

[n] pneumonitis (interstitial lung disease and organising pneumonia)

[o] abdominal pain (abdominal discomfort, abdominal pain upper and abdominal pain lower)

[p] colitis (colitis microscopic, enterocolitis, enterocolitis haemorrhagic, autoimmune colitis and immune-mediated enterocolitis)
[q] pancreatitis (autoimmune pancreatitis and pancreatitis acute)
[r] gastrointestinal ulceration (gastric ulcer and duodenal ulcer)
[s] hepatitis (autoimmune hepatitis, immune-mediated hepatitis, drug induced liver injury and acute hepatitis)
[t] rash (rash erythematous, rash follicular, rash macular, rash maculo-papular, rash papular, rash pruritic, rash vesicular and genital rash)
[u] pruritus (urticaria, urticaria papular and pruritus genital)
[v] severe skin reactions (dermatitis bullous, dermatitis exfoliative generalised, exfoliative rash, pemphigus and Grade ≥ 3 of the following: acute febrile neutrophilic dermatosis, contusion, decubitus ulcer, dermatitis exfoliative, dermatitis psoriasiform, drug eruption, erythema multiforme, jaundice, lichen planus, oral lichen planus, pemphigoid, pruritus, pruritus genital, rash, rash erythematous, rash maculo-papular, rash pruritic, rash pustular, skin lesion, skin necrosis and toxic skin eruption)
[w] vitiligo (skin depigmentation, skin hypopigmentation and hypopigmentation of the eyelid)
[x] lichenoid keratosis (lichen planus and lichen sclerosus)
[y] musculoskeletal pain (musculoskeletal discomfort, back pain, musculoskeletal stiffness, musculoskeletal chest pain and torticollis)
[z] myositis (myalgia, myopathy, necrotising myositis, polymyalgia rheumatica and rhabdomyolysis)
[aa] arthritis (joint swelling, polyarthritis and joint effusion)
[bb] tenosynovitis (tendonitis, synovitis and tendon pain)
[cc] nephritis (autoimmune nephritis, tubulointerstitial nephritis and renal failure, renal failure acute or acute kidney injury with evidence of nephritis, nephrotic syndrome, glomerulonephritis and glomerulonephritis membranous)
[dd] oedema (oedema peripheral, generalised oedema, fluid overload, fluid retention, eyelid oedema and lip oedema, face oedema, localised 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 four doses (2 mg/kg every 3 weeks, 10 mg/kg every 2 or 3 weeks, or 200 mg every 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 286 (4,6 %) patients, including Grade 2, 3, 4 or 5 cases in 128 (2,1 %), 73 (1,2 %), 17 (0,3 %) and 9 (0,1 %) patients, respectively, receiving pembrolizumab. The median time to onset of pneumonitis was 3,5 months (range 2 days to 26,7 months). The median duration was 2,0 months (range 1 day to 33,0+ months). Pneumonitis occurred more frequently in patients with a history of prior thoracic radiation (8,2 %) than in patients who did not receive prior thoracic radiation (4,2 %). Pneumonitis led to discontinuation of pembrolizumab in 117 (1,9 %) patients. Pneumonitis resolved in 166 patients, 4 with sequelae.

In patients with NSCLC, pneumonitis occurred in 160 (5,7 %), including Grade 2, 3, 4 or 5 cases in 62 (2,2 %), 47 (1,7 %), 14 (0,5 %) and 10 (0,4 %), respectively. In patients with NSCLC, pneumonitis occurred in 8,9 % with a history of prior thoracic radiation. In patients with cHL, the incidence of pneumonitis (all Grades) ranged from 5,2 % to 10,8 % for cHL patients in KEYNOTE-087 (n=210) and KEYNOTE-204 (n=148), respectively.

Immune-related colitis

Colitis occurred in 121 (2,0 %) patients, including Grade 2, 3 or 4 cases in 35 (0,6 %), 67 (1,1 %) and 5 (0,1 %) patients, respectively, receiving pembrolizumab. The median time to onset of colitis was 4,7 months (range 7 days to 24,3 months). The median duration was 1,0 month (range 1 day to 12,4 months). Colitis led to discontinuation of pembrolizumab in 34 (0,5 %) patients. Colitis resolved in 99 patients, 2 with sequelae. In patients with CRC treated with pembrolizumab as monotherapy (n=153), the incidence of colitis was 6,5 % (all Grades) with 2,0 % Grade 3 and 1,3 % Grade 4.

Immune-related hepatitis
Hepatitis occurred in 61 (1,0 %) patients, including Grade 2, 3 or 4 cases in 8 (0,1 %), 41 (0,7 %) and 8 (0,1 %) patients, respectively, receiving pembrolizumab. The median time to onset of hepatitis was 3,8 months (range 8 days to 26,3 months). The median duration was 1,1 months (range 1 day to 20,9+ months). Hepatitis led to discontinuation of pembrolizumab in 24 (0,4 %) patients. Hepatitis resolved in 46 patients.

Immune-related nephritis
Nephritis occurred in 25 (0,4 %) patients, including Grade 2, 3 or 4 cases in 5 (0,1 %), 15 (0,2 %) and 2 (< 0,1 %) patients, respectively, receiving pembrolizumab as monotherapy. The median time to onset of nephritis was 5,1 months (range 12 days to 21,4 months). The median duration was 3,3 months (range 6 days to 19,6 months). Nephritis led to discontinuation of pembrolizumab in 10 (0,2 %) patients. Nephritis resolved in 15 patients, 4 with sequelae. In patients with non-squamous NSCLC treated with pembrolizumab in combination with pemetrexed and platinum chemotherapy (n=488), the incidence of nephritis was 1,4 % (all Grades) with 0,8 % Grade 3 and 0,4 % Grade 4.

Immune-related endocrinopathies
Adrenal insufficiency occurred in 52 (0,8 %) patients, including Grade 2, 3 or 4 cases in 23 (0,4 %), 21 (0,3 %) and 4 (0,1 %) patients, respectively, receiving pembrolizumab. The median time to onset of adrenal insufficiency was 5,5 months (range 1 day to 23,7 months). The median duration was not reached (range 3 days to 32,4+ months). Adrenal insufficiency led to discontinuation of pembrolizumab in 5 (0,1 %) patients. Adrenal insufficiency resolved in 18 patients, 5 with sequelae.
Hypophysitis occurred in 38 (0,6 %) patients, including Grade 2, 3 or 4 cases in 15 (0,2 %), 19 (0,3 %) and 1 (< 0,1 %) patients, respectively, receiving pembrolizumab. The median time to onset of hypophysitis was 5,9 months (range 1 day to 17,7 months). The median duration was 3,6 months (range 3 days to 30,4+ months). Hypophysitis led to discontinuation of pembrolizumab in 9 (0,1 %) patients. Hypophysitis resolved in 17 patients, 8 with sequelae.
Hyperthyroidism occurred in 261 (4,2 %) patients, including Grade 2 or 3 cases in 64 (1,0 %) and 7 (0,1 %) patients, respectively, receiving pembrolizumab. The median time to onset of hyperthyroidism was 1,4 months (range 1 day to 23.2 months). The median duration was 1,8 months (range 4 days to 27,6+ months). Hyperthyroidism led to discontinuation of pembrolizumab in 3 (< 0,1 %) patients. Hyperthyroidism resolved in 207 (79,3 %) patients, 5 with sequelae.
Hypothyroidism occurred in 699 (11,3 %) patients, including Grade 2 or 3 cases in 510 (8,2 %) and 7 (0,1 %) patients, respectively, receiving pembrolizumab. The median time to onset of hypothyroidism was 3,4 months (range 1 day to 25,9 months). The median duration was not reached (range 2 days to 53,9+ months). Two patients (< 0,1 %) discontinued pembrolizumab due to hypothyroidism. Hypothyroidism resolved in 171 (24,5 %) patients, 14 with sequelae. In patients with cHL (n=389) the incidence of hypothyroidism was 17 %, all of which were Grade 1 or 2. In patients with HNSCC treated with pembrolizumab as monotherapy (n=909), the incidence of hypothyroidism was 16,1 % (all Grades) with 0,3 % Grade 3. In patients with HNSCC treated with pembrolizumab in combination with platinum and 5-FU chemotherapy (n=276), the incidence of hypothyroidism was 15,2 %, all of which were Grade 1 or 2.

Immune-related skin adverse reactions
Immune-related severe skin reactions occurred in 102 (1,6 %) patients, including Grade 2, 3 or 5 cases in 11 (0,2 %), 77 (1,2 %) and 1 (< 0,1 %) patients, respectively, receiving pembrolizumab. The median time to onset of severe skin reactions was 3,5 months (range 3 days to 25,5 months). The median duration was 1,9 months (range 1 day to 33,0+ months). Severe skin reactions led to discontinuation of pembrolizumab in 13 (0,2 %) patients. Severe skin reactions resolved in 71 patients, 1 with sequelae. 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 cHL
Of 14 patients in KEYNOTE-013 who proceeded to allogeneic HSCT after treatment with pembrolizumab, 6 patients reported acute GVHD and 1 patient reported chronic GVHD, none of which were fatal. Two patients experienced hepatic VOD, one of which was fatal. One patient experienced engraftment syndrome post-transplant.
Of 32 patients in KEYNOTE-087 who proceeded to allogeneic HSCT after treatment with pembrolizumab, 16 patients reported acute GVHD and 7 patients reported chronic GVHD, two of which were fatal. No patients experienced hepatic VOD. No patients experienced engraftment syndrome post-transplant.
Of 14 patients in KEYNOTE-204 who proceeded to allogeneic HSCT after treatment with pembrolizumab, 8 patients reported acute GVHD and 3 patients reported chronic GVHD, none of which were fatal. No patients experienced hepatic VOD. One patient experienced engraftment syndrome post-transplant.

Elevated liver enzymes when pembrolizumab is combined with axitinib in RCC
In a clinical study of previously untreated patients with RCC receiving pembrolizumab in combination with axitinib, a higher than expected incidence of Grades 3 and 4 ALT increased (20 %) and AST increased (13 %) were observed. The median time to onset of ALT increased was 2,3 months (range: 7 days to 19,8 months). In patients with ALT ≥ 3 times ULN (Grades 2-4, n=116), ALT resolved to Grades 0-1 in 94 %. Fifty-nine percent of the patients with increased ALT received systemic corticosteroids. Of the patients who recovered, 92 (84 %) were rechallenged with either pembrolizumab (3 %) or axitinib (31 %) monotherapy or with both (50 %). Of these patients, 55 % had no recurrence of ALT > 3 times ULN, and of those patients with recurrence of ALT > 3 times ULN, all recovered. There were no Grade 5 hepatic events.

Laboratory abnormalities
In patients treated with pembrolizumab monotherapy, the proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 10,8 % for lymphocytes decreased, 8,3 % for sodium decreased, 6,4 % for haemoglobin decreased, 5,4 % for phosphate decreased, 5,0 % for glucose increased, 3,1 % for AST increased, 3,0 % for ALT increased, 2,7 % for alkaline phosphatase increased, 2,4 % for potassium decreased, 2,1 % for neutrophils decreased, 2,0 % for platelets decreased, 1,9 % for calcium increased, 1,9 % for potassium increased, 1,9 % for bilirubin increased, 1,6 % for albumin decreased, 1,5 % for calcium decreased, 1,5 % for creatinine increased, 0,9 % for leucocytes decreased, 0,7 % for magnesium increased, 0,6 % for glucose decreased, 0,2 % for magnesium decreased and 0,2 % for sodium increased.
In patients treated with pembrolizumab in combination with chemotherapy, the proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 26,7 % for neutrophils decreased, 23,9 % for lymphocytes decreased, 19,1 % for haemoglobin decreased, 17,9 % for leucocytes decreased, 12,2 % for platelets decreased, 10,2 % for sodium decreased, 8,9 % for phosphate decreased, 7,4 % for glucose increased, 6,5 % for potassium decreased, 3,3 % for creatinine increased, 3,1 % for ALT increased, 3,1 % for AST increased, 3,1 % for calcium decreased, 3,0 % for

potassium increased, 2,9 % for albumin decreased, 2,3 % for calcium increased, 1,2 % for alkaline phosphatase increased, 0,8 % for glucose decreased, 0,7 % for bilirubin increased and 0,3 % for sodium increased.
In patients treated with pembrolizumab in combination with axitinib, the proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 20,1 % for ALT increased, 13,2 % for AST increased, 10,8 % for lymphocytes decreased, 8,9 % for glucose increased, 7,8 % for sodium decreased, 6,4 % for phosphate decreased, 6,2 % for potassium increased, 4,3 % for creatinine increased, 3,6 % for potassium decreased, 2,1 % for bilirubin increased, 2,1 % for haemoglobin decreased, 1,7 % for alkaline phosphatase increased, 1,5 % for prothrombin INR increased, 1,4 % for leukocytes decreased, 1,4 % for platelets decreased, 1,2 % for activated partial thromboplastin time prolonged, 1,2 % for neutrophils decreased, 1,2 % for sodium increased, 0,7 % for calcium decreased, 0,7 % for calcium increased, 0,5 % for albumin decreased and 0,2 % for glucose decreased.

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 as monotherapy, 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.

Paediatric population
The safety of pembrolizumab as monotherapy has been evaluated in 161 paediatric patients aged 9 months to 17 years with advanced melanoma, lymphoma, or PD-L1 positive advanced, relapsed, or refractory solid tumours at 2 mg/kg every 3 weeks in the Phase I/II study KEYNOTE-051. The cHL population (n=22) included patients 11 to 17 years of age. The safety profile in paediatric patients was generally similar to that seen in adults treated with pembrolizumab. The most common adverse reactions (reported in at least 20 % of paediatric patients) were pyrexia (33 %), vomiting (30 %), headache (26 %), abdominal pain (22 %), anaemia (21 %), cough (21 %) and constipation (20 %). The majority of adverse reactions reported for monotherapy were of Grades 1 or 2 severity. Seventy-six (47,2 %) patients had 1 or more Grades 3 to 5 adverse reactions of which 5 (3,1 %) patients had 1 or more adverse reactions that resulted in death. The frequencies are based on all reported adverse drug reactions, regardless of the investigator assessment of causality.

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.

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

Pembrolizumab doses of 2 mg/kg every 3 weeks, 10 mg/kg every 3 weeks, and 10 mg/kg every 2 weeks were evaluated in melanoma or previously treated NSCLC clinical studies. Based on the modelling and simulation of dose/exposure relationships for efficacy and safety for pembrolizumab, there are no clinically significant differences in efficacy or safety among the doses of 200 mg every 3 weeks, 2 mg/kg every 3 weeks, and 400 mg every 6 weeks as monotherapy (see section 4.2).

Melanoma

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

The safety and efficacy of pembrolizumab were investigated in KEYNOTE-006, a multicentre, open-label, 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 objective 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*	0,68	0,68	---

(95 % CI)	(0,53, 0,86)	(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 objective 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

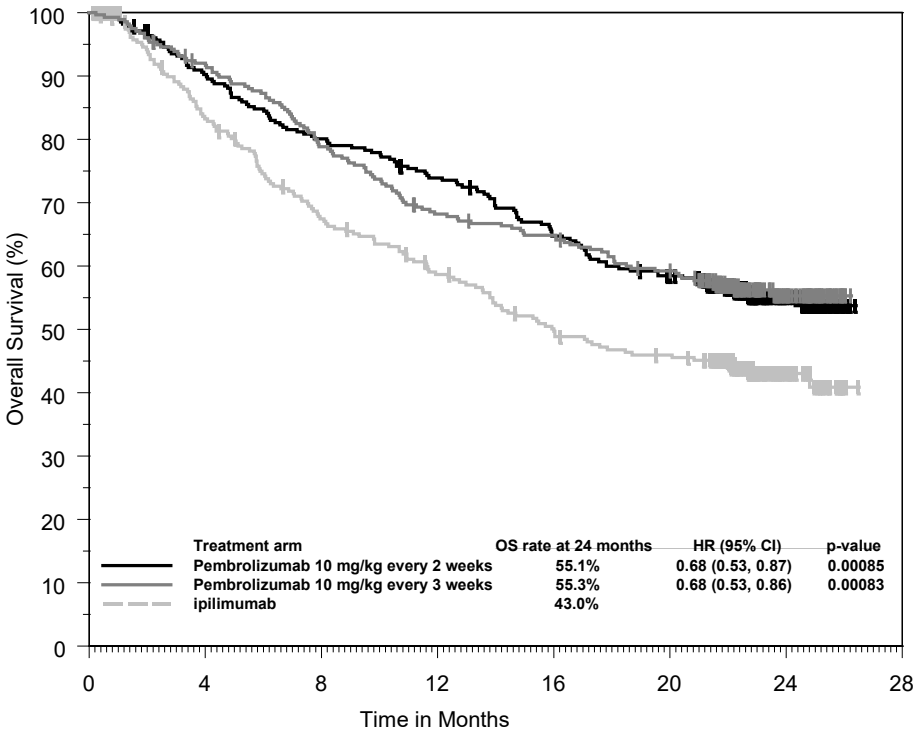
†Based on stratified log-rank test

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

§Based on Kaplan-Meier estimation

NA = not available

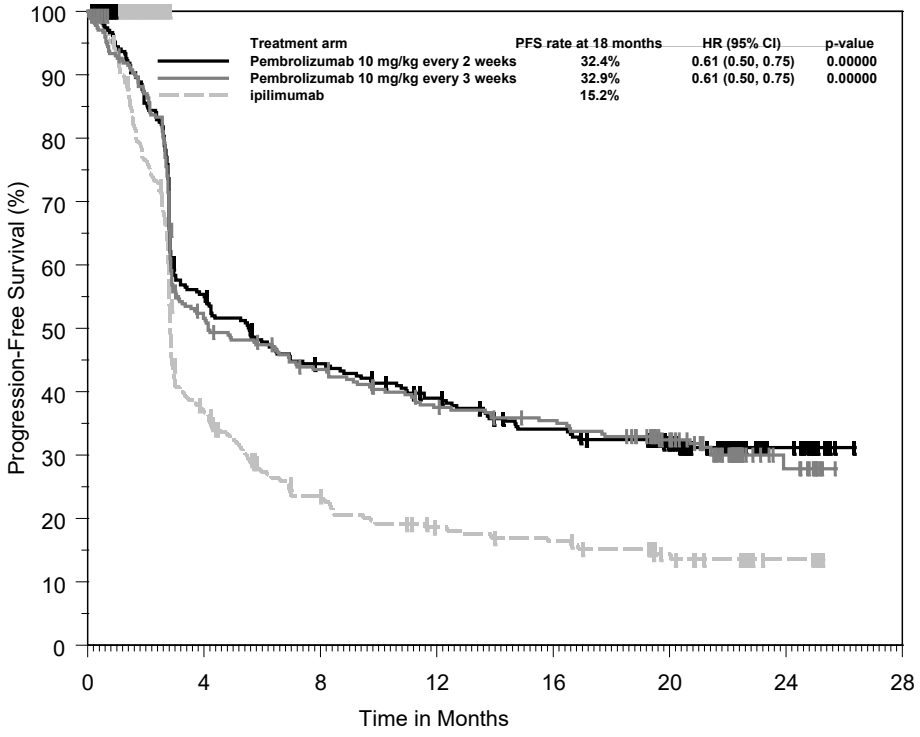
Figure 1: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-006 (intent to treat population)



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 study in melanoma patients previously treated with ipilimumab

The safety and efficacy of pembrolizumab were investigated in KEYNOTE-002, a multicentre, double-blind, 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*	0,86	0,74	---

(95 % CI)	(0,67, 1,10)	(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 objective 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

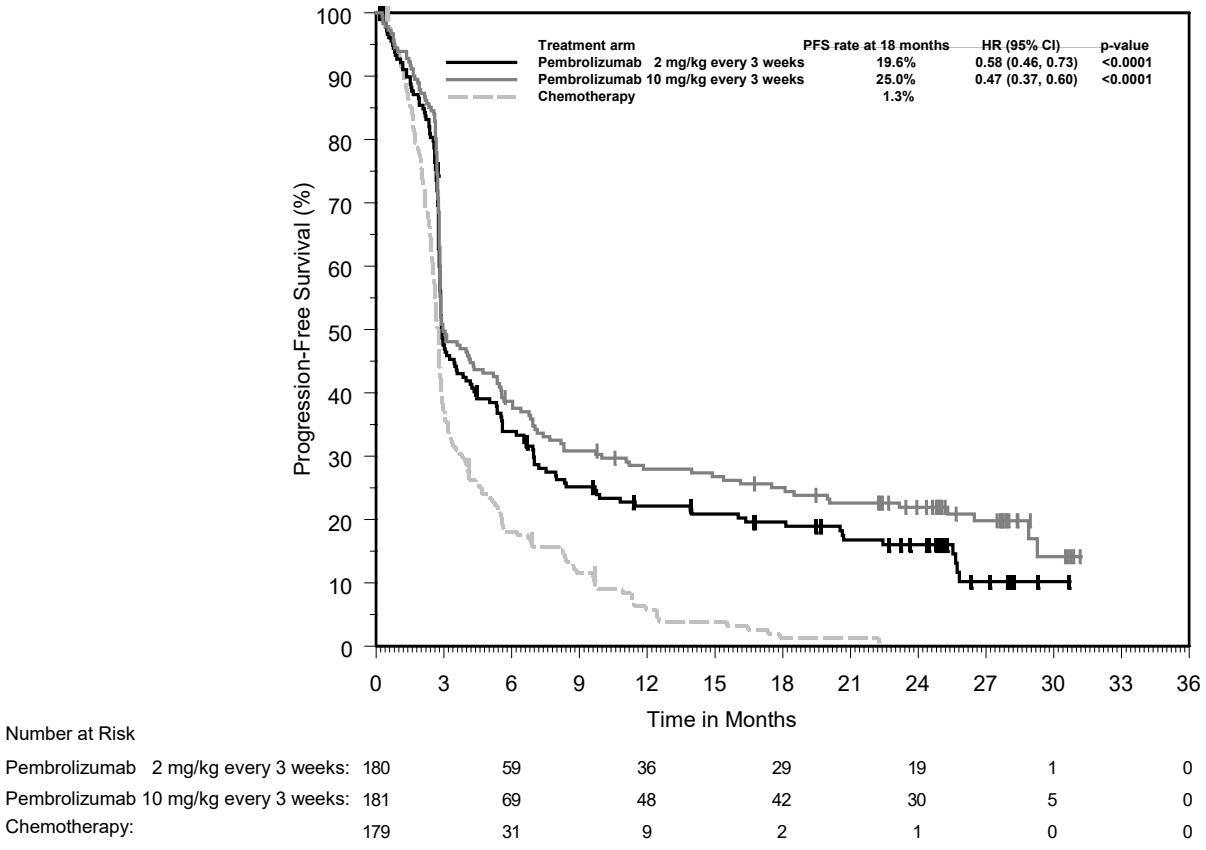
†Based on stratified log-rank test

‡Not statistically significant after adjustment for multiplicity

§Based on patients with a best objective 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)



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 a dose of 2 mg/kg 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 objective 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 2 mg/kg every 3 weeks (n=136)**	**Chemotherapy (n=137)**	**Pembrolizumab 2 mg/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 10 mg/kg every 2 or 3 weeks (pooled)**	**Ipilimumab (n=170)**	**Pembrolizumab 10 mg/kg every 2 or 3 weeks (pooled)**	**Ipilimumab (n=55)**	**Pembrolizumab 10 mg/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 relative to all viable tumour cells - MEL score) vs. PD-L1 negative. PD-L1 expression was tested retrospectively by immunohistochemistry (IHC) 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 summarises 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.

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

The efficacy of pembrolizumab was evaluated in KEYNOTE-054, a multicentre, randomised, double-blind, placebo-controlled study in patients with completely resected stage IIIA (> 1 mm lymph node metastasis), IIIB or IIIC melanoma. A total of 1 019 adult patients were randomised (1:1) to receive

pembrolizumab 200 mg every three weeks (n=514) or placebo (n=505), for up to one year until disease recurrence or unacceptable toxicity. Randomisation was stratified by American Joint Committee on Cancer (AJCC) 7th edition stage (IIIA vs. IIIB vs. IIIC 1-3 positive lymph nodes vs. IIIC ≥ 4 positive lymph nodes) and geographic region (North America, European countries, Australia and other countries as designated). Patients must have undergone lymph node dissection, and if indicated, radiotherapy within 13 weeks prior to starting treatment. Patients with active autoimmune disease or a medical condition that required immunosuppression or mucosal or ocular melanoma were ineligible. Patients who received prior therapy for melanoma other than surgery or interferon for thick primary melanomas without evidence of lymph node involvement were ineligible. Patients underwent imaging every 12 weeks after the first dose of pembrolizumab for the first two years, then every 6 months from year 3 to 5, and then annually.

Among the 1 019 patients, the baseline characteristics were: median age of 54 years (25 % age 65 or older); 62 % male; and ECOG PS of 0 (94 %) and 1 (6 %). Sixteen percent had stage IIIA; 46 % had stage IIIB; 18 % had stage IIIC (1-3 positive lymph nodes) and 20 % had stage IIIC (≥ 4 positive lymph nodes); 50 % were BRAF V600 mutation positive and 44 % were BRAF wild-type. PD-L1 expression was tested retrospectively by IHC assay with the 22C3 anti-PD-L1 antibody; 84 % of patients had PD-L1-positive melanoma (PD-L1 expression in ≥ 1 % of tumour and tumour-associated immune cells relative to all viable tumour cells). The same scoring system was used for metastatic melanoma (MEL score).

The primary efficacy outcome measures were investigator-assessed recurrence-free survival (RFS) in the whole population and in the population with PD-L1 positive tumours, where RFS was defined as the time between the date of randomisation and the date of first recurrence (local, regional or distant metastasis) or death, whichever occurs first. The study demonstrated a statistically significant improvement in RFS for patients randomised to the pembrolizumab arm compared with placebo at the pre-specified interim analysis. Efficacy results based on an additional seven months of follow-up are summarised in Table 10 and Figure 4.

Table 10: Efficacy results in KEYNOTE-054

Endpoint	**KEYTRUDA 200 mg every 3 weeks n=514**	**Placebo n=505**
Number (%) of patients with event	158 (31 %)	246 (49 %)
Median in months (95% CI)	NR	21,7 (17,1, NR)
Hazard ratio* (98% CI)	0,56 (0,44, 0,72)	
p-Value (stratified log-rank)	< 0,0001	
RFS at 6 months		
RFS rate	82 %	73 %
RFS at 12 months		
RFS rate	76 %	61 %
RFS at 18 months		
RFS rate	72 %	54 %

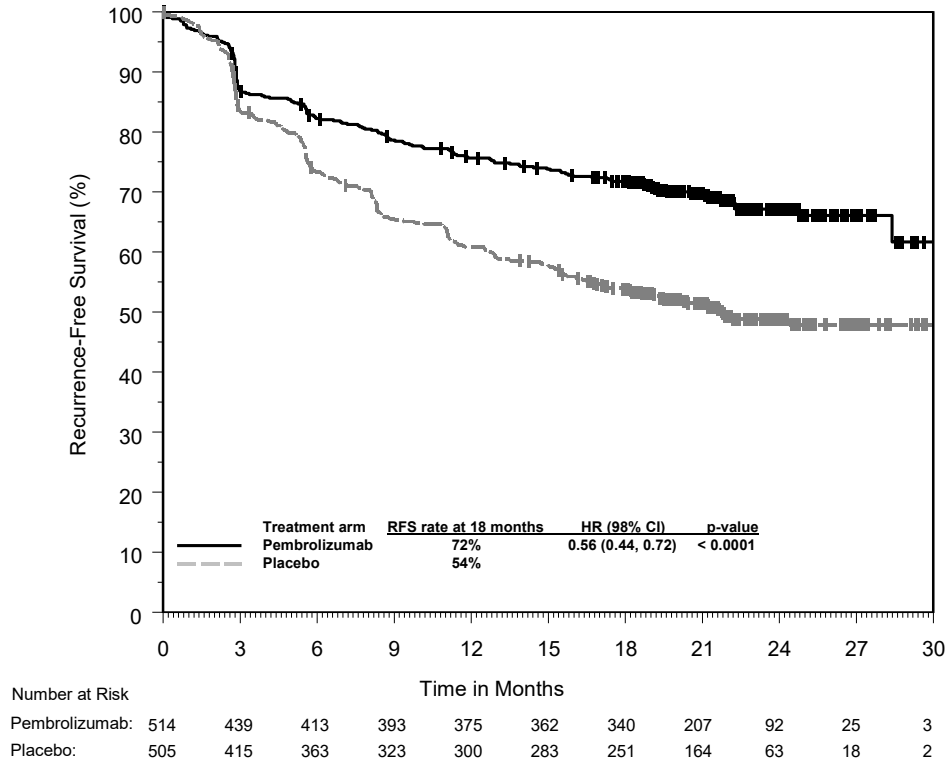
*Based on the stratified Cox proportional hazard model

NR = not reached

KEYNOTE-054 enrolled patients per AJCC 7th edition and a subgroup analysis of RFS per AJCC 8th edition was performed after the RFS study results were reported. A statistically significant improvement in RFS for patients randomised to the pembrolizumab arm compared with placebo was demonstrated in the overall population across resected stage III melanoma per AJCC 7th edition. Stage

IIIA melanoma according to the AJCC 8th edition identifies a patient population with a better prognosis compared to stage IIIA according to AJCC 7th edition. Per the AJCC 8th edition classification, a total of 82 subjects were classified as stage IIIA; 42 in the pembrolizumab arm and 40 in the placebo arm; with a total of 13 RFS events; 6 in the pembrolizumab arm and 7 in the placebo arm. There is limited data on subjects with stage IIIA according to AJCC 8th edition at the time of this RFS analysis.

Figure 4: Kaplan-Meier curve for recurrence-free survival by treatment arm in KEYNOTE-054 (intent to treat population)



While the analysis in patients with PD-L1 positive tumours was a co-primary endpoint, pre-defined subgroup analyses were performed in patients whose tumours were PD-L1 negative, BRAF mutation positive or negative. Table 11 summarises efficacy results by PD-L1 expression and BRAF mutation status.

Table 11: Efficacy results by PD-L1 expression and BRAF mutation status in KEYNOTE-054

Endpoint	**Pembrolizumab 200 mg every 3 weeks**	**Placebo**	**Pembrolizumab 200 mg every 3 weeks**	**Placebo**
	PD-L1 positive		**PD-L1 negative**	
	n=428	**n=425**	**n=59**	**n=57**
RFS Hazard ratio* (95 % CI)	0,54 (0,42, 0,69)	---	0,47 (0,26, 0,85)	---
RFS rate at 6 months	84 %	75 %	81 %	64 %
	BRAF mutation positive		**BRAF mutation negative**	
	n=245	**n=262**	**n=233**	**n=214**
RFS Hazard ratio* (95 % CI)	0,49 (0,36, 0,67)	---	0,64 (0,47, 0,87)	---
RFS rate at 6 months	83 %	73 %	80 %	72 %

*Based on the stratified Cox proportional hazard model

NSCLC

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

The safety and efficacy of pembrolizumab were investigated in KEYNOTE-024, a multicentre, open-label, controlled study for the treatment of previously untreated metastatic NSCLC. Patients had PD-L1 expression with a ≥ 50 % 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. Patients with non-squamous NSCLC 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 blinded independent central review (BICR) using RECIST 1.1. Secondary efficacy outcome measures were OS and ORR (as assessed by BICR using RECIST 1.1). Table 12 summarises key efficacy measures for the entire intent to treat (ITT) population. PFS and ORR results are reported from an interim analysis at a median follow-up of 11 months. OS results are reported from the final analysis at a median follow-up of 25 months.

Table 12: 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	73 (47 %)	96 (64 %)
Hazard ratio* (95 % CI)	0,63 (0,47, 0,86)	
p-Value†	0,002	
Median in months (95 % CI)	30.0 (18,3, NA)	14.2 (9,8, 19,0)
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 objective 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 5: Kaplan-Meier curve for progression-free survival by treatment arm in KEYNOTE-024 (intent to treat population)

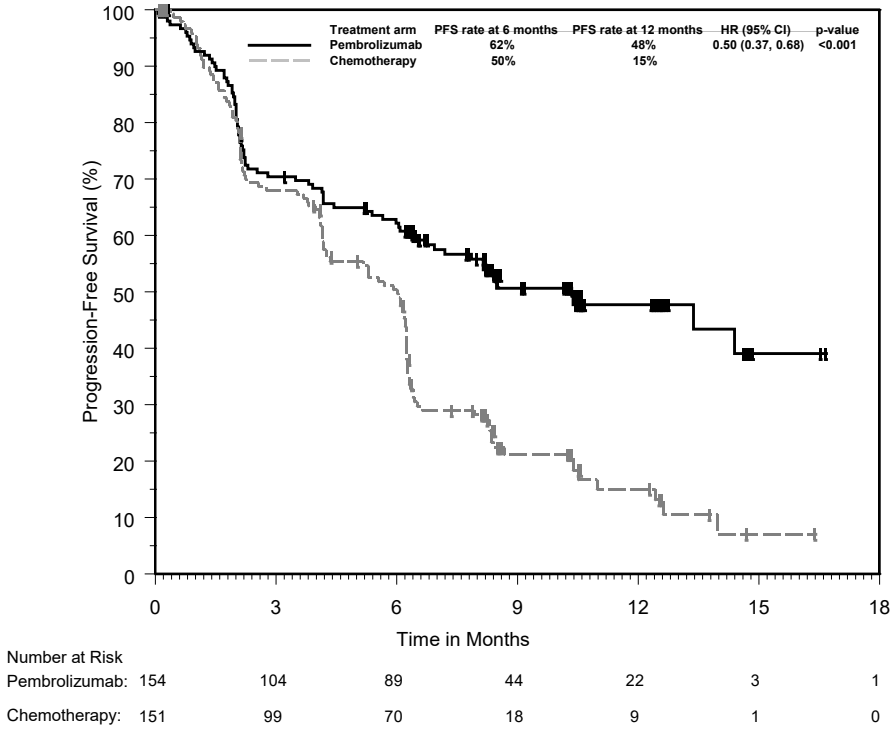
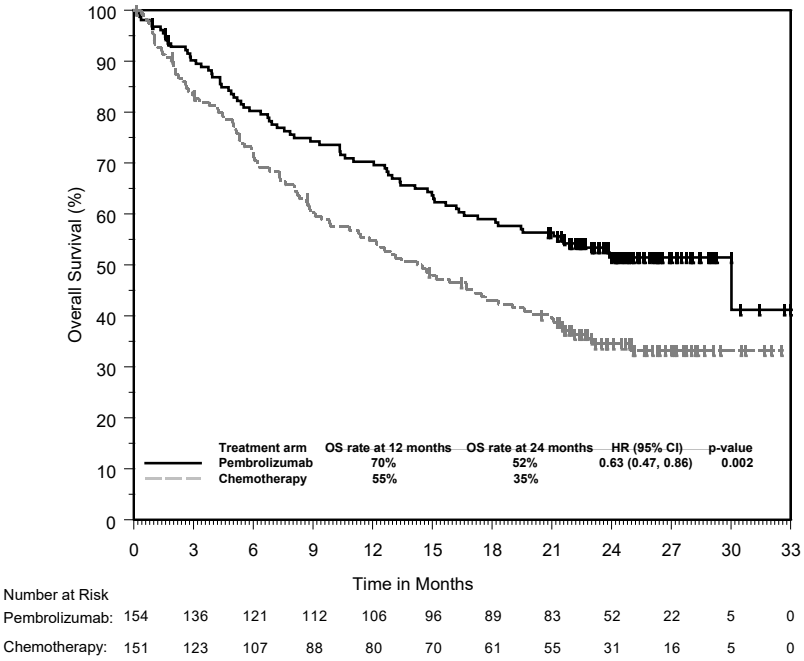


Figure 6: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-024 (intent to treat population)



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-042: Controlled study of NSCLC patients naïve to treatment

The safety and efficacy of pembrolizumab were also investigated in KEYNOTE-042, a multicentre, controlled study for the treatment of previously untreated locally advanced or metastatic NSCLC. The study design was similar to that of KEYNOTE-024, except that patients had PD-L1 expression with a ≥ 1 % 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=637) or investigator's choice platinum-containing chemotherapy (n=637; including pemetrexed + carboplatin or paclitaxel + carboplatin. Patients with non-squamous NSCLC could receive pemetrexed maintenance.). Assessment of tumour status was performed every 9 weeks for the first 45 weeks, and every 12 weeks thereafter.

Among the 1 274 patients in KEYNOTE-042, 599 (47 %) had tumours that expressed PD-L1 with TPS ≥ 50 % based on the PD-L1 IHC 22C3 pharmDx™ Kit. The baseline characteristics of these 599 patients included: median age 63 years (45 % age 65 or older); 69 % male; 63 % White and 32 % Asian; 17 % Hispanic or Latino; and ECOG performance status 0 and 1 in 31 % and 69 %, respectively. Disease characteristics were squamous (37 %) and non-squamous (63 %); stage IIIA (0,8 %); stage IIIB (9 %); stage IV (90 %); and treated brain metastases (6 %).

The primary efficacy outcome measure was OS. Secondary efficacy outcome measures were PFS and ORR (as assessed by BICR using RECIST 1.1). The study demonstrated a statistically significant improvement in OS for patients whose tumours expressed PD-L1 TPS ≥ 1 % randomised to pembrolizumab monotherapy compared to chemotherapy (HR 0,82; 95 % CI 0,71, 0,93 at the final analysis) and in patients whose tumours expressed PD-L1 TPS ≥ 50 % randomised to pembrolizumab monotherapy compared to chemotherapy. Table 13 summarises key efficacy measures for the TPS ≥ 50 % population at the final analysis performed at a median follow-up of 15,4 months. The Kaplan-Meier curve for OS for the TPS ≥ 50 % population based on the final analysis is shown in Figure 7.

Table 13: Efficacy results (PD-L1 TPS ≥ 50 %) in KEYNOTE-042

Endpoint	**Pembrolizumab 200 mg every 3 weeks**	**Chemotherapy n=300**

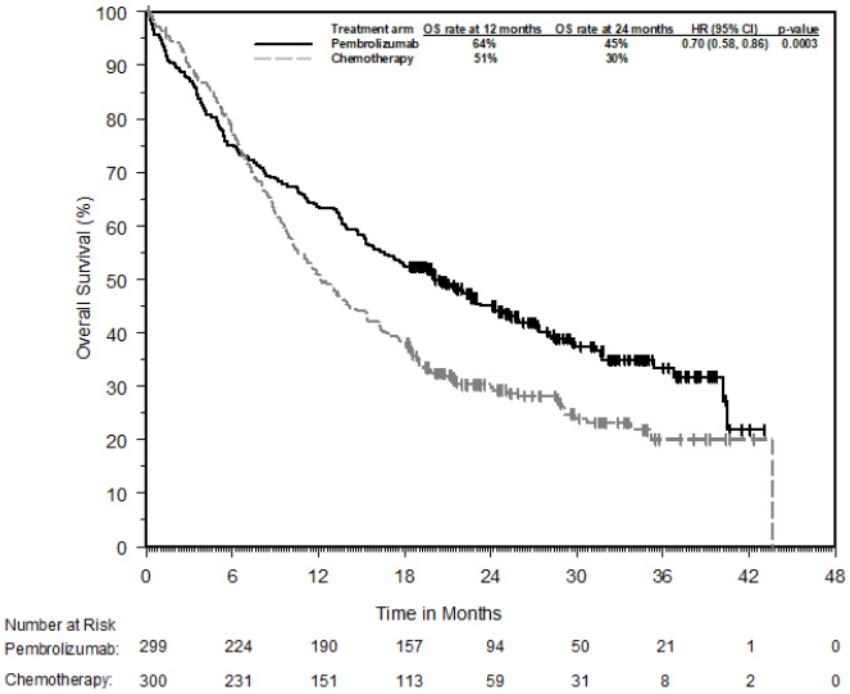
	n=299	
OS		
Number (%) of patients with event	180 (60 %)	220 (73 %)
Hazard ratio* (95 % CI)	0,70 (0,58, 0,86)	
p-Value†	0,0003	
Median in months (95 % CI)	20,0 (15,9, 24,2)	12,2 (10,4, 14,6)
PFS		
Number (%) of patients with event	238 (80 %)	250 (83 %)
Hazard ratio* (95 % CI)	0,84 (0,70, 1,01)	
Median in months (95 % CI)	6,5 (5,9, 8,5)	6,4 (6,2, 7,2)
Objective response rate		
ORR % (95 % CI)	39 % (34, 45)	32 % (27, 38)
Complete response %	1 %	0,3 %
Partial response %	38 %	32 %
Response duration‡		
Median in months (range)	22,0 (2,1+, 36,5+)	10,8 (1,8+, 30,4+)
% with duration ≥ 18 months	57 %	34 %

*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 objective response as confirmed complete or partial response

Figure 7: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-042 (patients with PD-L1 expression TPS ≥ 50 %, intent to treat population)



The results of a post-hoc exploratory subgroup analysis indicated a trend towards reduced survival benefit of pembrolizumab compared to chemotherapy, during both the first 4 months and throughout the entire duration of treatment, in patients who were never-smokers. However, due to the exploratory nature of this subgroup analysis, no definitive conclusions can be drawn.

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

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

- Pembrolizumab 200 mg with pemetrexed 500 mg/m^2 and investigator's choice of cisplatin 75 mg/m^2 or carboplatin AUC 5 mg/mL/min intravenously every 3 weeks for 4 cycles followed by pembrolizumab 200 mg and pemetrexed 500 mg/m^2 intravenously every 3 weeks (n=410)
- Placebo with pemetrexed 500 mg/m^2 and investigator's choice of cisplatin 75 mg/m^2 or carboplatin AUC 5 mg/mL/min intravenously every 3 weeks for 4 cycles followed by placebo and pemetrexed 500 mg/m^2 intravenously every 3 weeks (n=206)

Treatment with pembrolizumab continued until RECIST 1.1-defined progression of disease as determined by the investigator, unacceptable toxicity, or a maximum of 24 months. Administration of pembrolizumab was permitted beyond RECIST-defined disease progression by BICR or beyond discontinuation of pemetrexed if the patient was clinically stable and deriving clinical benefit as determined by the investigator. For patients who completed 24 months of therapy or had a complete response, treatment with pembrolizumab could be reinitiated for disease progression and administered for up to 1 additional year. Assessment of tumour status was performed at Week 6 and Week 12, followed by every 9 weeks thereafter. Patients receiving placebo plus chemotherapy who experienced independently verified progression of disease were offered pembrolizumab as monotherapy.

Among the 616 patients in KEYNOTE-189, baseline characteristics were: median age of 64 years (49 % age 65 or older); 59 % male; 94 % White and 3 % Asian; 43 % and 56 % ECOG performance status of 0 or 1 respectively; 31 % PD-L1 negative (TPS < 1 %); and 18 % with treated or untreated brain metastases at baseline.

The primary efficacy outcome measures were OS and PFS (as assessed by BICR using RECIST 1.1). Secondary efficacy outcome measures were ORR and response duration, as assessed by BICR using RECIST 1.1. Table 14 summarises key efficacy measures and Figures 8 and 9 show the Kaplan-Meier curves for OS and PFS based on the final analysis with a median follow-up of 18,8 months.

Table 14: Efficacy results in KEYNOTE-189

Endpoint	**Pembrolizumab + Pemetrexed + Platinum Chemotherapy n=410**	**Placebo + Pemetrexed + Platinum Chemotherapy n=206**
OS[*]		
Number (%) of patients with event	258 (63 %)	163 (79 %)
Hazard ratio[†] (95 % CI)	0,56 (0,46, 0,69)	
p-Value[‡]	< 0,00001	
Median in months (95 % CI)	22,0 (19,5, 24,5)	10,6 (8,7, 13,6)
PFS		
Number (%) of patients with event	337 (82 %)	197 (96 %)
Hazard ratio[†] (95 % CI)	0,49 (0,41, 0,59)	
p-Value[‡]	< 0,00001	

Median in months (95 % CI)	9,0 (8,1, 10,4)	4,9 (4,7, 5,5)
Objective response rate		
ORR[§] % (95 % CI)	48 % (43, 53)	20 % (15, 26)
Complete response %	1,2 %	0,5 %
Partial response %	47 %	19 %
p-Value[¶]	< 0,0001	
Response duration		
Median in months (range)	12,5 (1,1+, 34,9+)	7,1 (2,4, 27,8+)
% with duration ≥ 12 months[#]	53 %	27 %

[*]A total of 113 patients (57 %) who discontinued study treatment in the placebo plus chemotherapy arm crossed over to receive monotherapy pembrolizumab or received a checkpoint inhibitor as subsequent therapy

[†]Based on the stratified Cox proportional hazard model

[‡]Based on stratified log-rank test

[§]Based on patients with a best objective response as confirmed complete or partial response

[¶]Based on Miettinen and Nurminen method stratified by PD-L1 status, platinum chemotherapy and smoking status

[#]Based on Kaplan-Meier estimation

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

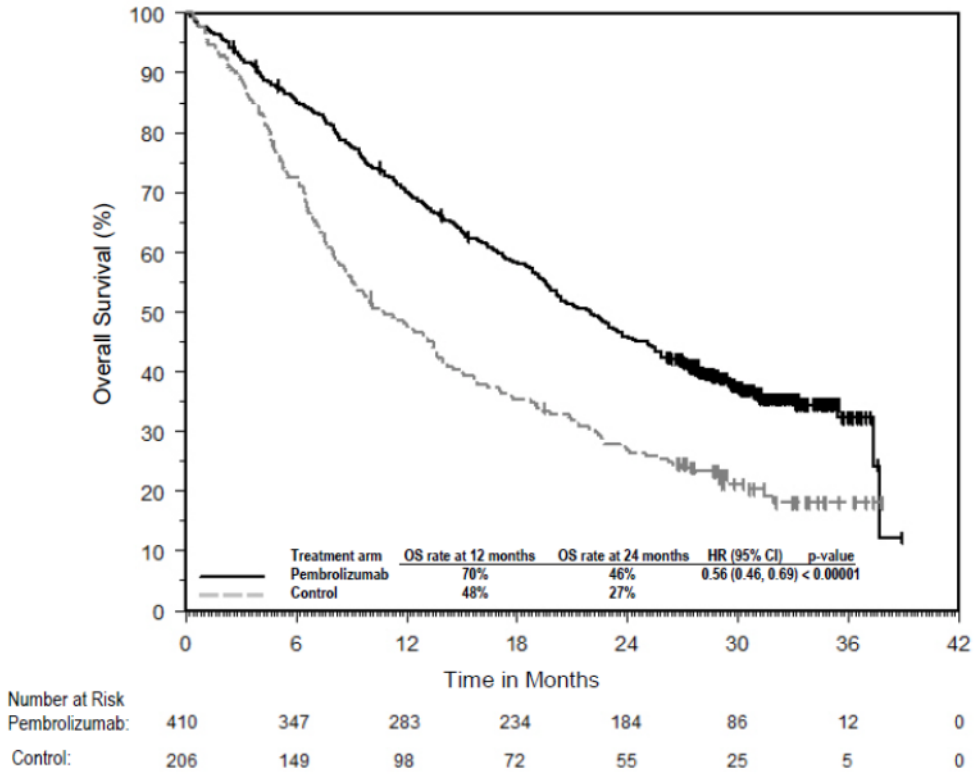
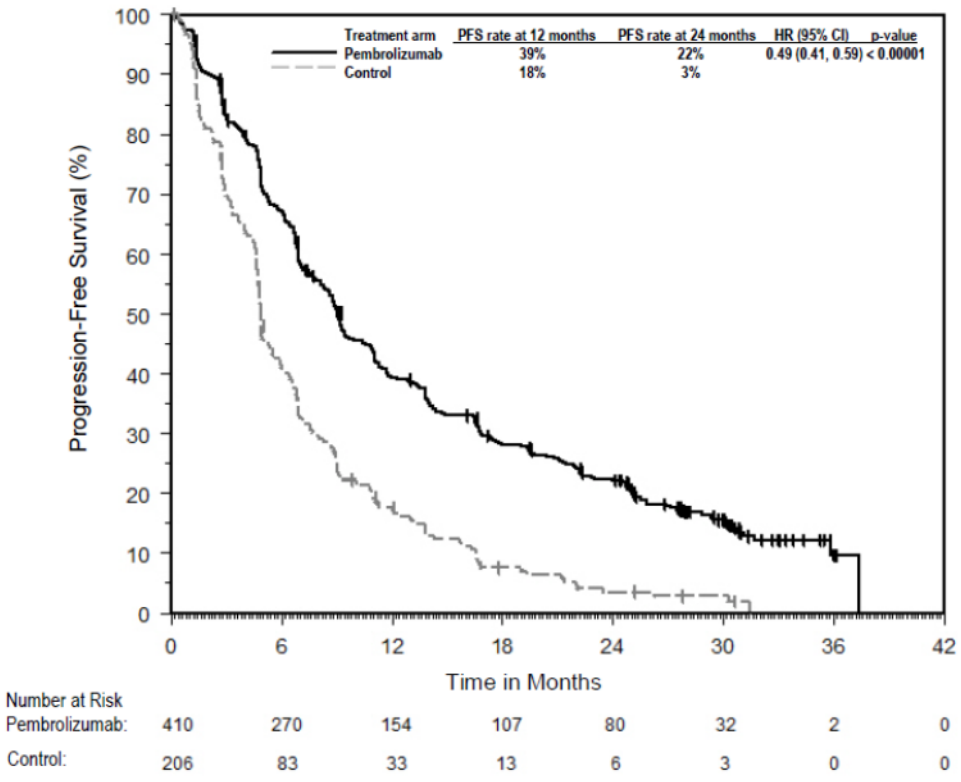


Figure 9: Kaplan-Meier curve for progression-free survival by treatment arm in KEYNOTE-189 (intent to treat population)



An analysis was performed in KEYNOTE-189 in patients who had PD-L1 TPS < 1 % [pembrolizumab combination: n=127 (31 %) vs. chemotherapy: n=63 (31 %)], TPS 1-49 % [pembrolizumab combination: n=128 (31 %) vs. chemotherapy: n=58 (28 %)] or ≥ 50 % [pembrolizumab combination: n=132 (32 %) vs. chemotherapy: n=70 (34 %)] (see Table 15).

Table 15: Efficacy results by PD-L1 Expression in KEYNOTE-189*

Endpoint	Pembrolizumab combination therapy	Chemotherapy	Pembrolizumab combination therapy	Chemotherapy	Pembrolizumab combination therapy	Chemotherapy
	TPS < 1 %		**TPS 1 to 49 %**		**TPS ≥ 50 %**	
OS Hazard ratio† (95 % CI)	0,51 (0,36, 0,71)		0,66 (0,46, 0,96)		0,59 (0,40, 0,86)	
PFS Hazard ratio† (95 % CI)	0,67 (0,49, 0,93)		0,53 (0,38, 0,74)		0,35 (0,25, 0,49)	
ORR %	33 %	14 %	50 %	21 %	62 %	26 %

*Based on final analysis

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

At final analysis, a total of 57 NSCLC patients aged ≥ 75 years were enrolled in study KEYNOTE-189 (35 in the pembrolizumab combination and 22 in the control). A HR=1,54 [95 % CI 0,76, 3,14] in OS and HR=1,12 [95 % CI 0,56, 2,22] in PFS for pembrolizumab combination vs. chemotherapy was reported within this study subgroup. Data about efficacy and safety of pembrolizumab in combination with platinum chemotherapy are limited in this patient population.

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

The efficacy of pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel was investigated in Study KEYNOTE-407, a randomised, double-blind, multicentre, placebo-controlled study. The key eligibility criteria for this study were metastatic squamous NSCLC,

regardless of tumour PD-L1 expression status, and no prior systemic treatment for metastatic disease. Patients with autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Randomisation was stratified by tumour PD-L1 expression (TPS < 1 % [negative] vs. TPS ≥ 1 %), investigator's choice of paclitaxel or nab-paclitaxel, and geographic region (East Asia vs. non-East Asia). Patients were randomised (1:1) to one of the following treatment arms via intravenous infusion:

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

Treatment with pembrolizumab or placebo continued until RECIST 1.1-defined progression of disease as determined by BICR, unacceptable toxicity, or a maximum of 24 months. Administration of pembrolizumab was permitted beyond RECIST-defined disease progression if the patient was clinically stable and deriving clinical benefit as determined by the investigator.
Patients in the placebo arm were offered pembrolizumab as a single agent at the time of disease progression.
Assessment of tumour status was performed every 6 weeks through Week 18, every 9 weeks through Week 45 and every 12 weeks thereafter.
A total of 559 patients were randomised. The study population characteristics were: median age of 65 years (range: 29 to 88); 55 % age 65 or older; 81 % male; 77% White; ECOG performance status of 0 (29 %) and 1 (71 %); and 8% with treated brain metastases at baseline. Thirty-five percent had tumour PD-L1 expression TPS < 1 % [negative]; 19 % were East Asian; and 60 % received paclitaxel.
The primary efficacy outcome measures were OS and PFS (as assessed by BICR using RECIST 1.1). Secondary efficacy outcome measures were ORR and response duration, as assessed by BICR using RECIST 1.1. Table 16 summarises key efficacy measures and Figures 10 and 11 show the Kaplan-Meier curves for OS and PFS based on the final analysis with a median follow-up of 14,3 months.

Table 16: Efficacy Results in KEYNOTE-407

Endpoint	**Pembrolizumab Carboplatin Paclitaxel/Nab-paclitaxel n=278**	**Placebo Carboplatin Paclitaxel/Nab-paclitaxel n=281**
OS[*]		
Number of events (%)	168 (60 %)	197 (70 %)
Median in months (95 % CI)	17,1 (14,4, 19,9)	11,6 (10,1, 13,7)
Hazard ratio[†] (95 % CI)	0,71 (0,58, 0,88)	
p-Value[‡]	0,0006	
PFS		
Number of events (%)	217 (78%)	252 (90%)
Median in months (95% CI)	8.0 (6.3, 8.4)	5.1 (4.3, 6.0)
Hazard ratio† (95% CI)	0.57 (0.47, 0.69)	
p-Value[‡]	< 0.0001	
Objective response rate		

ORR % (95 % CI)	63 % (57, 68)	38 % (33, 44)
Complete response %	2,2 %	3,2 %
Partial response %	60 %	35 %
p-Value[§]	< 0,0001	
Response duration		
Median duration of response in months (range)	8,8 (1,3+, 28,4+)	4,9 (1,3+, 28,3+)
% with duration ≥ 12 months[¶]	38 %	25 %

[*]A total of 138 patients (51 %) who discontinued study treatment in the placebo plus chemotherapy arm crossed over to receive monotherapy pembrolizumab or received a checkpoint inhibitor as subsequent therapy

[†]Based on the stratified Cox proportional hazard model

[‡]Based on stratified log-rank test

[§]Based on method by Miettinen and Nurminen

[¶]Based on Kaplan-Meier estimation

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

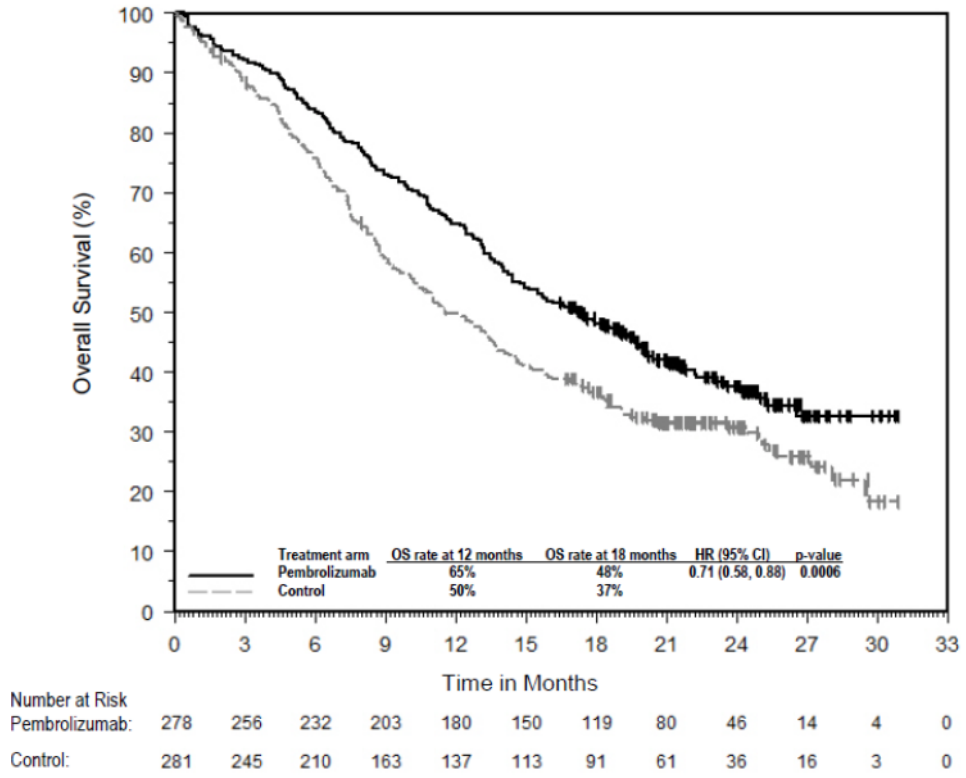
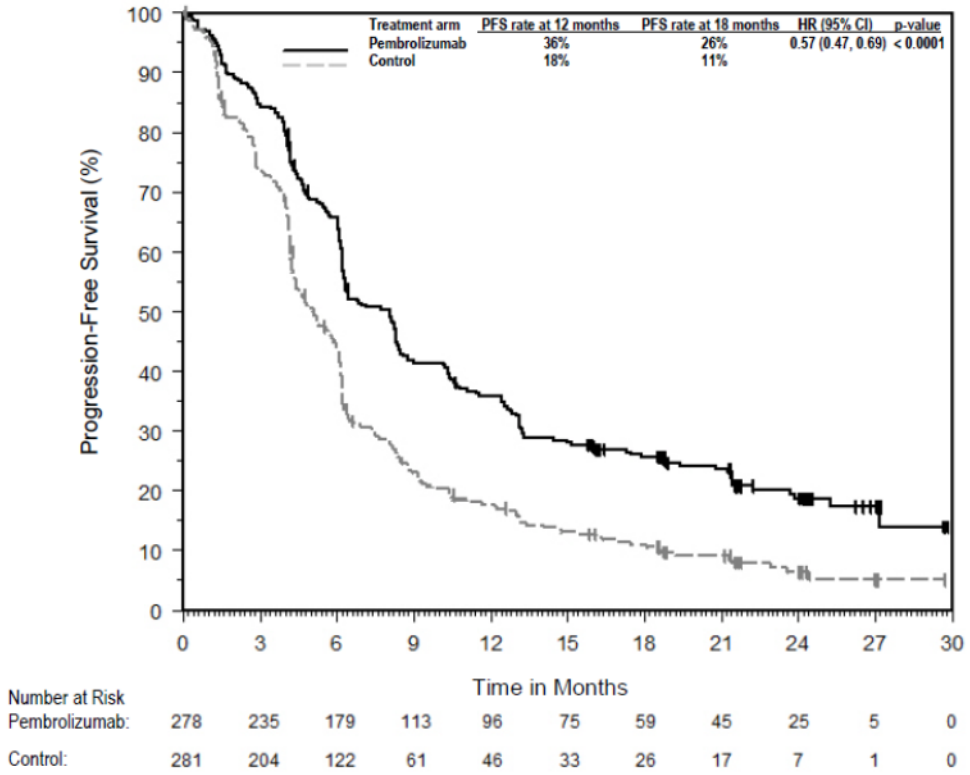


Figure 11: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-407



An analysis was performed in KEYNOTE-407 in patients who had PD-L1 TPS < 1 % [pembrolizumab plus chemotherapy arm: n=95 (34 %) vs. placebo plus chemotherapy arm: n=99 (35 %)], TPS 1 % to 49 % [pembrolizumab plus chemotherapy arm: n=103 (37 %) vs. placebo plus chemotherapy arm: n=104 (37 %)] or TPS ≥ 50 % [pembrolizumab plus chemotherapy arm: n=73 (26 %) vs. placebo plus chemotherapy arm: n=73 (26 %)] (see Table 17).

Table 17: Efficacy results by PD-L1 Expression in KEYNOTE-407*

Endpoint	Pembrolizumab combination therapy	Chemotherapy	Pembrolizumab combination therapy	Chemotherapy	Pembrolizumab combination therapy	Chemotherapy
	TPS < 1 %		**TPS 1 to 49 %**		**TPS ≥ 50 %**	
OS Hazard ratio† (95 % CI)	0,79 (0,56, 1,11)		0,59 (0,42, 0,84)		0,79 (0,52, 1,21)	
PFS Hazard ratio† (95 % CI)	0,67 (0,49, 0,91)		0,52 (0,38, 0,71)		0,43 (0,29, 0,63)	
ORR %	67 %	41 %	55 %	42 %	64 %	30 %

*Based on final analysis

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

At final analysis, a total of 65 NSCLC patients aged ≥ 75 years were enrolled in study KEYNOTE-407 (34 in the pembrolizumab combination and 31 in the control). An HR=0,81 [95 % CI 0,43, 1,55] in OS, an HR=0,61 [95 % CI 0,34, 1,09] in PFS, and an ORR of 62 % and 45 % for pembrolizumab combination vs. chemotherapy was reported within this study subgroup. Data about efficacy and safety of pembrolizumab in combination with platinum chemotherapy are limited in this patient population.

KEYNOTE-010: Controlled study 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 study 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 %); stage IIIA (2 %); stage IIIB (7 %); stage IV (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 BICR using RECIST 1.1. Secondary efficacy outcome measures were ORR and response duration. Table 18 summarises key efficacy measures for the entire population (TPS ≥ 1 %) and for the patients with TPS ≥ 50 %, and Figure 12 shows the Kaplan-Meier curve for OS (TPS ≥ 1 %), based on a final analysis with median follow-up of 42,6 months.

Table 18: 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	284 (83 %)	264 (76 %)	295 (86 %)
Hazard ratio[*] (95 % CI)	0,77 (0,66, 0,91)	0,61 (0,52, 0,73)	---
p-Value[†]	0,00128	< 0,001	---
Median in months (95 % CI)	10,4 (9,5, 11,9)	13,2 (11,2, 16,7)	8,4 (7,6, 9,5)
PFS[‡]			
Number (%) of patients with event	305 (89 %)	292 (84 %)	314 (92 %)
Hazard ratio[*] (95 % CI)	0,88 (0,75, 1,04)	0,75 (0,63, 0,89)	---
p-Value[†]	0,065	< 0,001	---
Median in months (95 % CI)	3,9 (3,1, 4,1)	4,0 (2,7, 4,5)	4,1 (3,8, 4,5)
Objective response rate[‡]			
ORR % (95 % CI)	20 % (16, 25)	21 % (17, 26)	9 % (6, 13)
Complete response %	2 %	3 %	0 %
Partial response %	18 %	18 %	9 %
Response duration[‡,§]			
Median in months (range)	Not reached (2,8, 46,2+)	37,8 (2,0+, 49,3+)	7,1 (1,4+, 16,8)
% ongoing[¶]	42 %	43 %	6 %
TPS ≥ 50 %			
Number of patients	139	151	152
OS			

Number (%) of patients with event	97 (70 %)	102 (68 %)	127 (84 %)
Hazard ratio* (95 % CI)	0,56 (0,43, 0,74)	0,50 (0,38, 0,65)	---
p-Value†	< 0,001	< 0,001	---
Median in months (95 % CI)	15,8 (10,8, 22,5)	18,7 (12,1, 25,3)	8,2 (6,4, 9,8)
PFS‡			
Number (%) of patients with event	107 (77 %)	115 (76 %)	138 (91 %)
Hazard ratio* (95 % CI)	0,59 (0,45, 0,77)	0,53 (0,41, 0,70)	---
p-Value†	< 0,001	< 0,001	---
Median in months (95 % CI)	5,3 (4,1, 7,9)	5,2 (4,1, 8,1)	4,2 (3,8, 4,7)
Objective response rate‡			
ORR % (95 % CI)	32 % (24, 40)	32 % (25, 41)	9 % (5, 14)
Complete response %	4 %	4 %	0 %
Partial response %	27 %	28 %	9 %
Response duration‡,§			
Median in months (range)	Not reached (2,8, 44,0+)	37,5 (2,0+, 49,3+)	8,1 (2,6, 16,8)
% ongoing¶	55 %	47 %	8 %

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

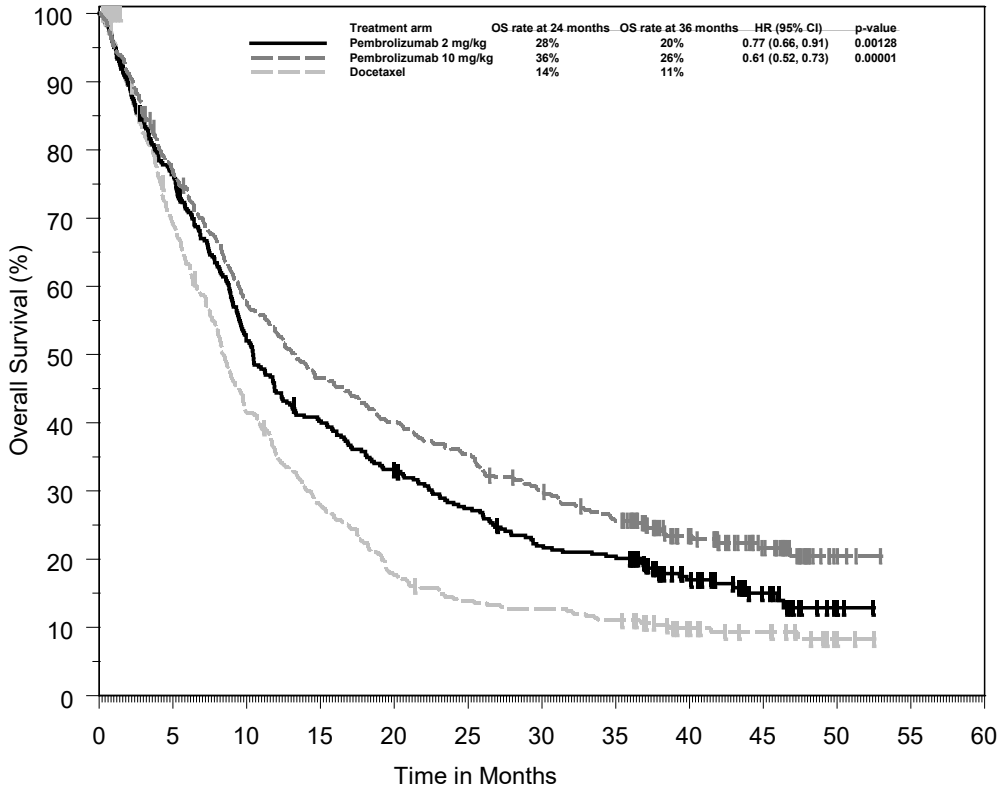
†Based on stratified log-rank test

‡Assessed by BICR using RECIST 1.1

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

¶Ongoing response includes all responders who at the time of analysis were alive, progression-free, did not initiate new anti-cancer therapies and had not been determined to be lost to follow-up

Figure 12: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-010 (patients with PD-L1 expression TPS ≥ 1 %, intent to treat population)



Number at Risk

Pembrolizumab 2 mg/kg:	344	261	177	136	111	91	72	67	36	17	2	0	0
Pembrolizumab 10 mg/kg:	346	262	197	159	137	120	99	84	50	28	3	0	0
Docetaxel:	343	226	135	90	57	44	40	35	20	13	2	0	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-204: Controlled study in patients with relapsed or refractory classical Hodgkin lymphoma (cHL)

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

- Pembrolizumab 200 mg intravenously every 3 weeks
- Brentuximab vedotin (BV) 1,8 mg/kg bodyweight intravenously every 3 weeks.

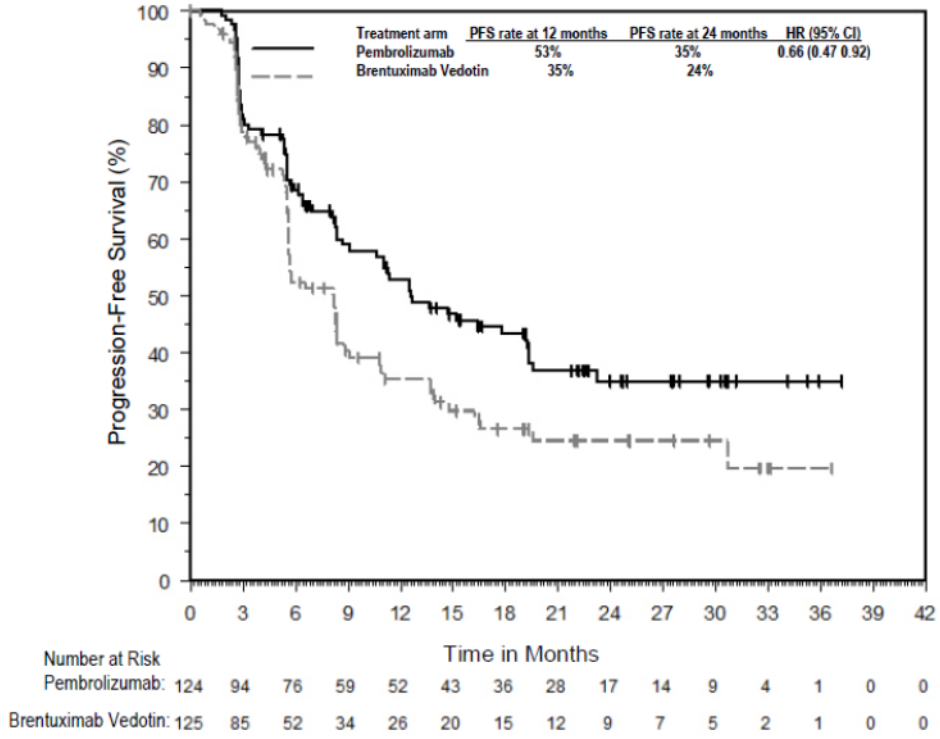
Patients received pembrolizumab 200 mg intravenously every 3 weeks until unacceptable toxicity or documented disease progression, or a maximum of 35 cycles. Limited data are currently available on response duration following pembrolizumab discontinuation at cycle 35. Response was assessed every 12 weeks, with the first planned post-baseline assessment at Week 12.
Among the 304 patients in KEYNOTE-204, there is a subpopulation consisting of 112 patients who failed a transplant before enrolling and 137 who failed 2 or more prior therapies and were ineligible for ASCT at the time of enrolment. The baseline characteristics of these 249 patients were: median age 34 years (11 % age 65 or older); 56 % male; 80 % White and 7 % Asian and 58 % and 41 % with an ECOG performance status 0 and 1, respectively. Approximately 30 % were refractory to frontline chemotherapy and ~ 45 % had received prior ASCT. Nodular sclerosis was the more represented cHL histological subtype (~ 81 %) and bulky disease, B symptoms and bone marrow involvement were present in approximately 21 %, 28 % and 4 % of patients, respectively.
The primary efficacy outcome was PFS and the secondary efficacy outcome measure was ORR, both assessed by BICR according to the 2007 revised International Working Group (IWG) criteria. The additional primary efficacy outcome measure, OS, was not formally assessed at the time of the analysis. In the ITT population, the median follow-up time for 151 patients treated with pembrolizumab was 24,9 months (range: 1,8 to 42,0 months). The initial analysis resulted in a HR for PFS of 0,65 (95 % CI: 0,48, 0,88) with a one-sided p value of 0,0027. The ORR was 66 % for pembrolizumab compared to 54 % for standard treatment with a p-value of 0,0225. Table 19 summarises the efficacy results in the subpopulation. Efficacy results in this subpopulation were consistent with the ITT population. The Kaplan-Meier curve for PFS for this subpopulation is shown in Figure 13.

Table 19: Efficacy results in cHL patients who failed a transplant before enrolling or who failed 2 or more prior therapies and were ineligible for ASCT in KEYNOTE-204

Endpoint	**Pembrolizumab 200 mg every 3 weeks n=124**	**Brentuximab vedotin 1,8 mg/kg every 3 weeks n=125**
PFS		
Number (%) of patients with event	68 (55 %)	75 (60 %)
Hazard ratio* (95 % CI)	0,66 (0,47, 0,92)	
Median in months (95 % CI)	12,6 (8,7, 19,4)	8,2 (5,6, 8,8)
Objective response rate		
ORR‡ % (95 % CI)	65 % (56,3, 73,6)	54 % (45,3, 63,3)
Complete response	27 %	22 %
Partial response	39 %	33 %
Stable disease	12 %	23 %
Response duration		
Median in months (range)	20,5 (0,0+, 33,2+)	11,2 (0,0+, 33,9+)
Number (%¶) of patients with duration ≥ 6 months	53 (80,8)	28 (61,2)
Number (%¶) of patients with duration ≥ 12 months	37 (61,7)	17 (49,0)

*Based on the stratified Cox proportional hazard model
‡Based on patients with a best overall response as complete or partial response
¶Based on Kaplan-Meier estimation

Figure 13: Kaplan-Meier curve for progression-free survival by treatment arm in cHL patients who failed a transplant before enrolling or who failed 2 or more prior therapies and were ineligible for ASCT in KEYNOTE-204



KEYNOTE-087 and KEYNOTE-013: Open-label studies in patients with relapsed or refractory 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 study. 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 34 % who were refractory to first line therapy. Sixty-one percent of patients had received ASCT, 38 % were transplant ineligible; 17 % had no prior brentuximab vedotin use; and 37 % of patients had prior radiation therapy. Disease subtypes were 81 % 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-four percent were refractory to at least one prior therapy, including 35 % who were refractory to first line therapy. Seventy-four percent of patients had received ASCT, 26 % were

transplant ineligible, and 45 % of patients had prior radiation therapy. Disease subtypes were 97 % nodular sclerosis and 3 % mixed cellularity.
The primary efficacy outcome measures (ORR and CRR) were assessed by BICR according to the IWG 2007 criteria. Secondary efficacy outcome measures were duration of response, PFS and OS. Response was assessed in KEYNOTE-087 and KEYNOTE-013 every 12 and 8 weeks, respectively, with the first planned post-baseline assessment at Week 12. Efficacy results are summarised in Table 20.

Table 20: 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)	71 % (64,3, 77,0)	58 % (39,1, 75,5)
Complete remission	28 %	19 %
Partial remission	43 %	39 %
Response duration[c]		
Median in months (range)	16,6 (0,0+, 39,1+)[d]	Not reached (0,0+, 45,6+)[e]
% with duration ≥ 6 months	74 %[f]	80 %[g]
% with duration ≥ 12 months	59 %[h]	70 %[i]
Time to response		
Median in months (range)	2,8 (2,1, 16,5)[d]	2,8 (2,4, 8,6)[e]
PFS[c]		
Number (%) of patients with event	133 (63 %)	19 (61 %)
Median in months (95 % CI)	13,6 (11,1, 16,7)	11,4 (4,9, 27,8)
9 month PFS rate	61 %	---
12 month PFS rate	52 %	48 %
24 month PFS rate	32 %	30 %
OS		
Number (%) of patients with event	33 (16 %)	6 (19 %)
12 month OS rate	96 %	87 %
24 month OS rate	91 %	87 %
36 month OS rate	86 %	81 %

Median follow-up time of 39,5 months
b Median follow-up time of 52,8 months
c Assessed by BICR according to the IWG 2007 criteria by PET CT scans
d Based on patients (n=149) 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 84 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 60 patients with responses of 12 months or longer
i Based on Kaplan-Meier estimation; includes 7 patients with responses of 12 months or longer

Safety and efficacy in elderly patients
Overall, 46 cHL patients ≥ 65 years were treated with pembrolizumab in studies KEYNOTE-087, KEYNOTE-013 and KEYNOTE-204. Data from these patients are too limited to draw any conclusion on safety or efficacy in this population.

Urothelial Carcinoma

KEYNOTE-045: Controlled study in urothelial carcinoma patients who have received prior platinum-containing chemotherapy

The safety and efficacy of pembrolizumab were evaluated in KEYNOTE-045, a multicentre, open-label, 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 pembrolizumab 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 carcinoma. Patients with an ECOG performance status of 2 had to have a haemoglobin ≥ 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 enrolment. 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 21 summarises the key efficacy measures for the ITT population at the final analysis. The Kaplan-Meier curve based on the final analysis for OS is shown in Figure 14. 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 21: 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	200 (74 %)	219 (81 %)
Hazard ratio* (95 % CI)	0,70 (0,57, 0,85)	
p-Value†	< 0,001	
Median in months (95 % CI)	10,1 (8,0, 12,3)	7,3 (6,1, 8,1)
PFS‡		

Number (%) of patients with event	233 (86 %)	237 (87 %)
Hazard ratio* (95 % CI)	0,96 (0,79, 1,16)	
p-Value†	0,313	
Median in months (95% CI)	2,1 (2,0, 2,2)	3,3 (2,4, 3,6)
Objective response rate‡		
ORR % (95 % CI)	21 % (16, 27)	11 % (8, 15)
p-Value§	< 0,001	
Complete response	9 %	3 %
Partial response	12 %	8 %
Stable disease	17 %	34 %
Response duration‡,¶		
Median in months (range)	Not reached (1,6+, 30,0+)	4,4 (1,4+, 29,9+)
Number (%#) of patients with duration ≥ 6 months	46 (84 %)	8 (47 %)
Number (%#) of patients with duration ≥ 12 months	35 (68 %)	5 (35 %)

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

†Based on stratified log-rank test

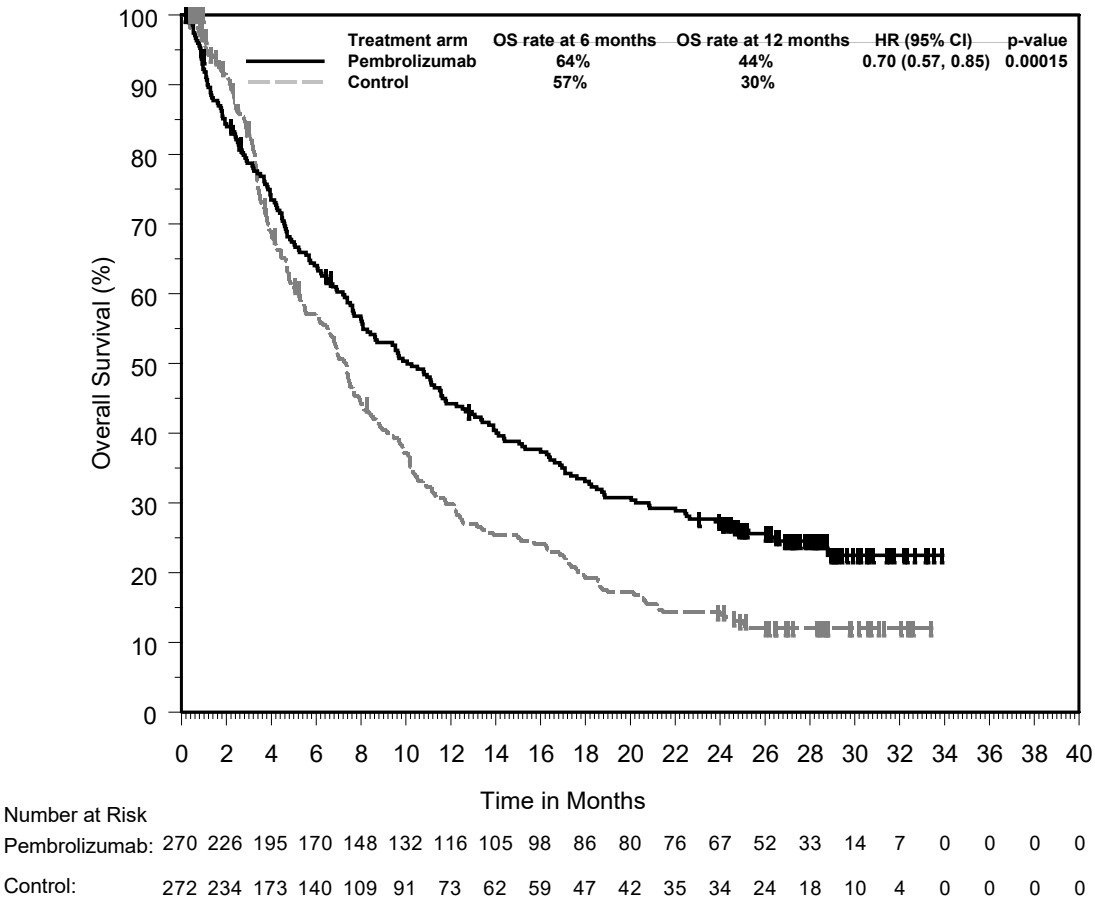
‡Assessed by BICR using RECIST 1.1

§Based on method by Miettinen and Nurminen

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

#Based on Kaplan-Meier estimation

Figure 14: 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 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 22).

Table 22: OS by PD-L1 Expression

PD-L1 Expression	Pembrolizumab	Chemotherapy	
	OS by PD-L1 Expression Number (%) of patients with event*		Hazard Ratio† (95 % CI)
CPS < 10	140 (75 %)	144 (82 %)	0,75 (0,59, 0,95)
CPS ≥ 10	53 (72 %)	72 (80 %)	0,55 (0,37, 0,81)

*Based on final analysis

†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 study in urothelial carcinoma patient's 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-eight percent had M1 disease and 12 % had M0 disease. Eighty-five percent of patients had visceral metastases, including 21 % with liver metastases. Reasons for cisplatin ineligibility included: baseline creatinine clearance of < 60 mL/min (50 %), ECOG performance status of 2 (32 %), ECOG performance status of 2 and baseline creatinine clearance of < 60 mL/min (9 %), and other (Class III heart failure, Grade 2 or greater peripheral neuropathy, and Grade 2 or greater hearing loss; 9 %). Ninety percent of patients were treatment naïve, and 10 % received prior adjuvant or neoadjuvant platinum-based chemotherapy. Eighty-one percent had a primary tumour in the lower tract, and 19 % of patients had a primary tumour in the upper tract.
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 23 summarises the key efficacy measures for the study population at the final analysis based on a median follow-up time of 11,4 months (range: 0,1, 41,2 months) for all patients.

Table 23: 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 % (24, 34)
Disease control rate†	47 %
Complete response	9 %
Partial response	20 %
Stable disease	18 %
Response duration	
Median in months (range)	30,1 (1,4+, 35,9+)
% with duration ≥ 6 months	81 %‡
Time to response	
Median in months (range)	2,1 (1,3, 9,0)
PFS*	
Median in months (95 % CI)	2,2 (2,1, 3,4)
6 month PFS rate	33 %
12 month PFS rate	22 %
OS	
Median in months (95 % CI)	11,3 (9,7, 13,1)
6 month OS rate	67 %
12 month OS rate	47 %

*Assessed by BICR using RECIST 1.1
†Based on best response of stable disease or better
‡Based on Kaplan-Meier estimates; includes 84-patients with response of 6 months or longer

An analysis was performed in KEYNOTE-052 in patients who had tumours that expressed PD-L1 with a CPS < 10 (n=251; 68 %) or ≥ 10 (n=110; 30 %) based on the PD-L1 IHC 22C3 pharmDx™ Kit (see Table 24).

Table 24: ORR and OS by PD-L1 Expression

Endpoint	**CPS < 10 n=251**	**CPS ≥ 10 n=110**
Objective response rate*		
ORR %, (95 % CI)	20 % (16, 26)	47 % (38, 57)
OS		
Median in months (95 % CI)	10 (8, 12)	19 (12, 29)
12 month OS rate	41 %	61 %

*BICR using RECIST 1.1

KEYNOTE-361 is an ongoing Phase III, randomised, controlled, open-label clinical study of pembrolizumab with or without platinum-based combination chemotherapy versus chemotherapy as first-line treatment in subjects with advanced or metastatic urothelial carcinoma. Preliminary data from an early review showed a reduced survival with pembrolizumab monotherapy in patients whose tumours express PD-L1 with a CPS < 10 compared with standard chemotherapy.
Based on a recommendation by an external Data Monitoring Committee, the accrual in the pembrolizumab monotherapy arm was stopped for patients whose tumours express PD-L1 with a CPS < 10. The pembrolizumab monotherapy arm remains open only to patients whose tumours express PD-L1 with a CPS ≥ 10. Subjects whose tumours express PD-L1 CPS < 10 already enrolled into the pembrolizumab monotherapy arm can continue treatment. Randomisation to the chemotherapy and the chemotherapy-pembrolizumab arms remains open.

Head and Neck Squamous Cell Carcinoma
KEYNOTE-048: Controlled study of monotherapy and combination therapy in HNSCC patients naïve to treatment in the recurrent or metastatic setting
The efficacy of pembrolizumab was investigated in KEYNOTE-048, a multicentre, randomised, open-label, active-controlled study in patients with histologically confirmed metastatic or recurrent HNSCC of the oral cavity, pharynx or larynx, who had not previously received systemic therapy for recurrent or metastatic disease and who were considered incurable by local therapies. Patients with nasopharyngeal carcinoma, active autoimmune disease that required systemic therapy within two years of treatment or a medical condition that required immunosuppression were ineligible for the study. Randomisation was stratified by tumour PD-L1 expression (TPS ≥ 50 % or < 50 %), HPV status (positive or negative), and ECOG PS (0 vs. 1). Patients were randomised 1:1:1 to one of the following treatment arms:

- Pembrolizumab 200 mg every 3 weeks
- Pembrolizumab 200 mg every 3 weeks, carboplatin AUC 5 mg/mL/min every 3 weeks or cisplatin 100 mg/m^2 every 3 weeks, and 5-FU 1 000 mg/m^2/d 4 days continuous every 3 weeks (maximum of 6 cycles of platinum and 5-FU)
- Cetuximab 400 mg/m^2 load then 250 mg/m^2 once weekly, carboplatin AUC 5 mg/mL/min every 3 weeks or cisplatin 100 mg/m^2 every 3 weeks, and 5-FU 1 000 mg/m^2/d 4 days continuous every 3 weeks (maximum of 6 cycles of platinum and 5-FU)

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

pembrolizumab was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Assessment of tumour status was performed at Week 9 and then every 6 weeks for the first year, followed by every 9 weeks through 24 months.

Among the 882 patients in KEYNOTE-048, 754 (85 %) had tumours that expressed PD-L1 with a CPS ≥ 1 based on the PD-L1 IHC 22C3 pharmDx™ Kit. The baseline characteristics of these 754 patients included: median age of 61 years (range: 20 to 94); 36 % age 65 or older; 82 % male; 74 % White and 19 % Asian; 61 % ECOG performance status of 1; and 77 % former/current smokers. Disease characteristics were: 21 % HPV positive and 95 % had stage IV disease (stage IVa 21 %, stage IVb 6 %, and stage IVc 69 %).

The primary efficacy outcome measures were OS and PFS (assessed by BICR according to RECIST 1.1). The study demonstrated a statistically significant improvement in OS for all patients randomised to pembrolizumab in combination with chemotherapy compared to standard treatment (HR 0.72; 95 % CI 0.60-0.87) and in patients whose tumours expressed PD-L1 CPS ≥ 1 randomised to pembrolizumab monotherapy compared to standard treatment. Tables 25 and 26 summarise key efficacy results for pembrolizumab in patients whose tumours expressed PD-L1 with a CPS ≥ 1 in KEYNOTE-048 at the final analysis performed at a median follow-up of 13 months for pembrolizumab in combination with chemotherapy and at a median follow-up of 11.5 months for pembrolizumab monotherapy. Kaplan-Meier curves for OS based on the final analysis are shown in Figures 15 and 16.

Table 25: Efficacy results for pembrolizumab plus chemotherapy in KEYNOTE-048 with PD-L1 expression (CPS ≥ 1)

Endpoint	**Pembrolizumab + Platinum Chemotherapy + 5-FU n=242**	**Standard Treatment* n=235**
OS		
Number (%) of patients with event	177 (73 %)	213 (91 %)
Median in months (95 % CI)	13,6 (10,7, 15,5)	10,4 (9,1, 11,7)
Hazard ratio† (95 % CI)	0,65 (0,53, 0,80)	
p-Value‡	0,00002	
PFS		
Number (%) of patients with event	212 (88 %)	221 (94 %)
Median in months (95 % CI)	5,1 (4,7, 6,2)	5,0 (4,8, 6,0)
Hazard ratio† (95 % CI)	0,84 (0,69, 1,02)	
p-Value‡	0,03697	
Objective response rate		
ORR§ % (95 % CI)	36 % (30,3, 42,8)	36 % (29,6, 42,2)
Complete response	7 %	3 %
Partial response	30 %	33 %
p-Value¶	0,4586	
Response duration		
Median in months (range)	6,7 (1,6+, 39,0+)	4,3 (1,2+, 31,5+)
% with duration ≥ 6 months	54 %	34 %

*Cetuximab, platinum, and 5-FU

†Based on the stratified Cox proportional hazard model

‡Based on stratified log-rank test

§Response: Best objective response as confirmed complete response or partial response

¶Based on Miettinen and Nurminen method stratified by ECOG (0 vs. 1), HPV status (positive vs. negative) and PD-L1 status (strongly positive vs. not strongly positive)

Figure 15: Kaplan-Meier curve for overall survival for pembrolizumab plus chemotherapy in KEYNOTE-048 with PD-L1 expression (CPS ≥ 1)

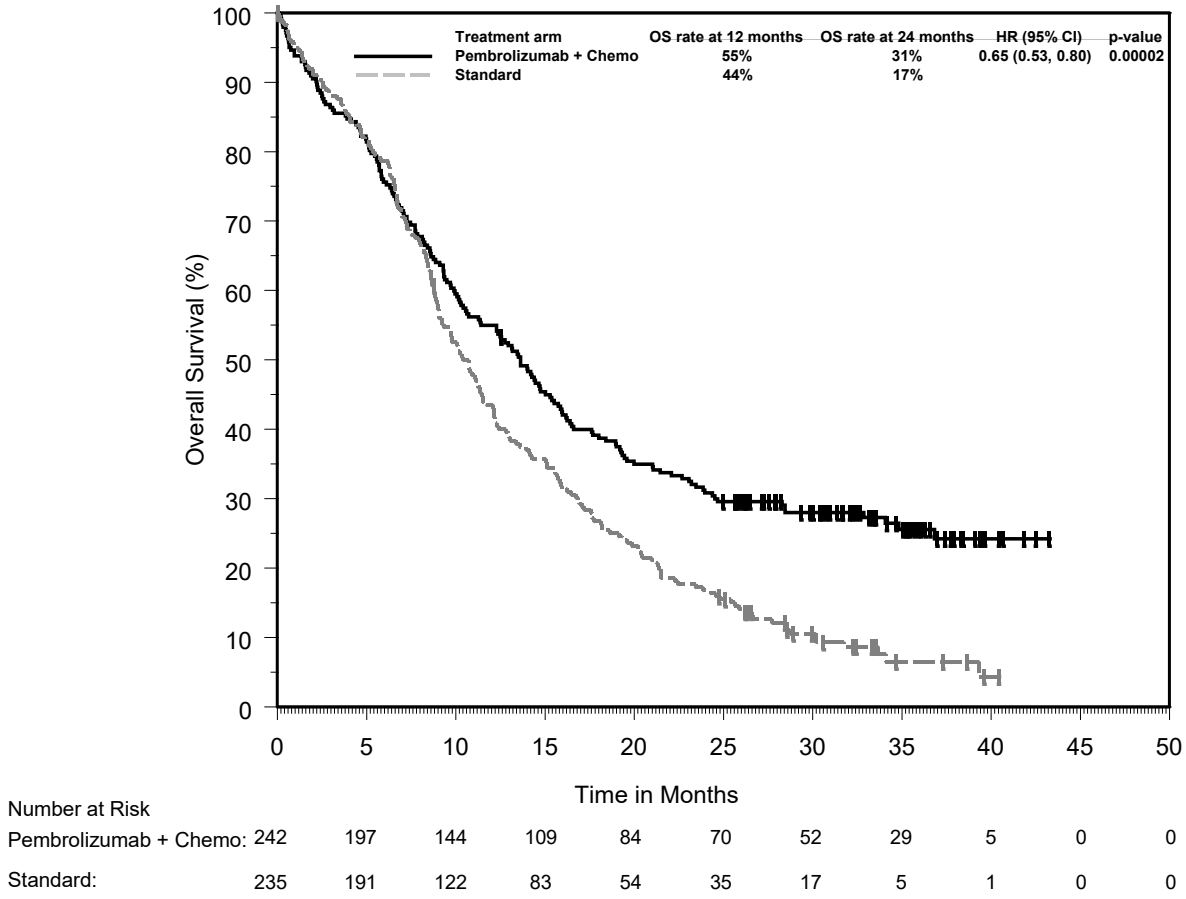


Table 26: Efficacy results for pembrolizumab as monotherapy in KEYNOTE-048 with PD-L1 expression (CPS ≥ 1)

Endpoint	**Pembrolizumab n=257**	**Standard Treatment* n=255**
OS		
Number (%) of patients with event	197 (77 %)	229 (90 %)
Median in months (95 % CI)	12,3 (10,8, 14,3)	10,3 (9,0, 11,5)
Hazard ratio† (95 % CI)	0,74 (0,61, 0,90)	
p-Value‡	0,00133	
PFS		
Number (%) of patients with event	228 (89 %)	237 (93 %)
Median in months (95 % CI)	3,2 (2,2, 3,4)	5,0 (4,8, 6,0)
Hazard ratio† (95 % CI)	1,13 (0,94, 1,36)	
p-Value‡	0,89580	
Objective response rate		
ORR§ % (95 % CI)	19,1 % (14,5, 24,4)	35 % (29,1, 41,1)
Complete response	5 %	3 %
Partial response	14 %	32 %

p-Value¶	1,0000	
Response duration		
Median in months (range)	23,4 (1,5+, 43,0+)	4,5 (1,2+, 38,7+)
% with duration ≥ 6 months	81 %	36 %

*Cetuximab, platinum, and 5-FU

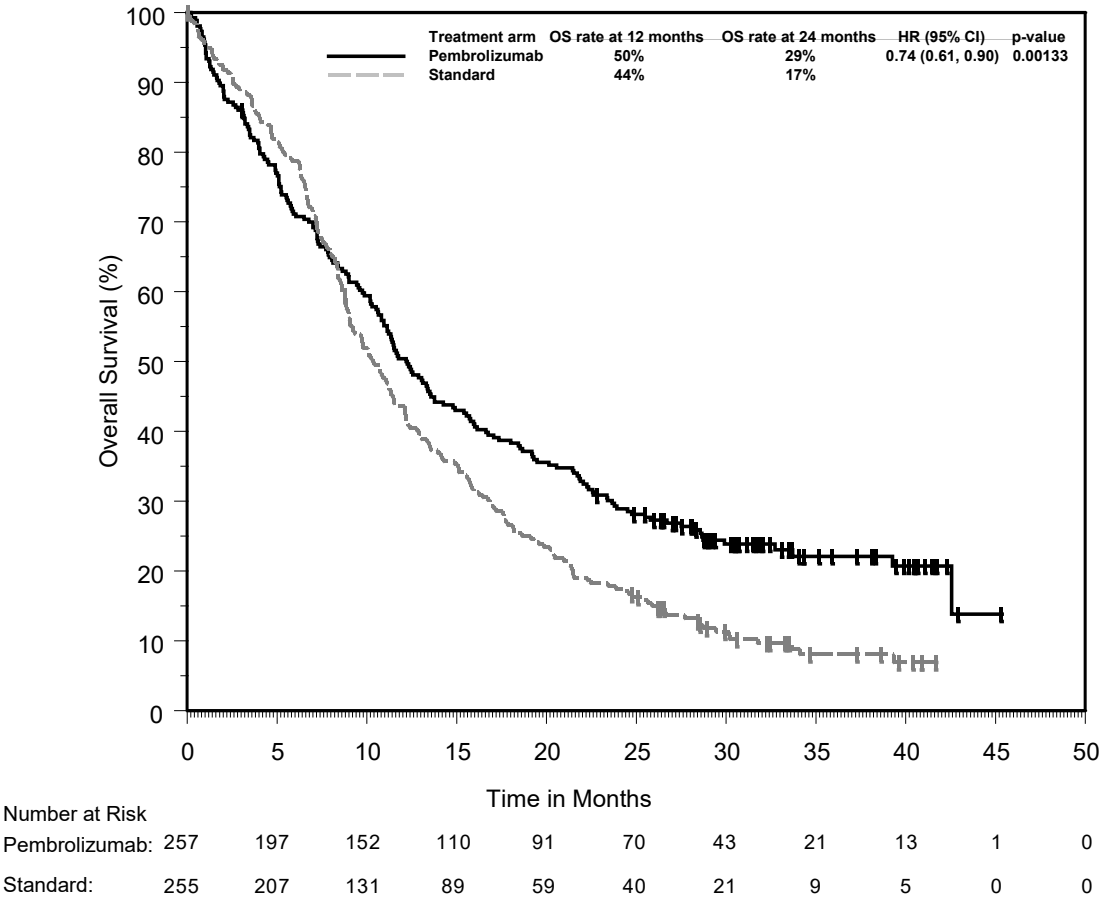
†Based on the stratified Cox proportional hazard model

‡Based on stratified log-rank test

§Response: Best objective response as confirmed complete response or partial response

¶Based on Miettinen and Nurminen method stratified by ECOG (0 vs. 1), HPV status (positive vs. negative) and PD-L1 status (strongly positive vs. not strongly positive)

Figure 16: Kaplan-Meier curve for overall survival for pembrolizumab as monotherapy in KEYNOTE-048 with PD-L1 expression (CPS ≥ 1)



An analysis was performed in KEYNOTE-048 in patients whose tumours expressed PD-L1 CPS ≥ 20 [pembrolizumab plus chemotherapy: n=126 (49 %) vs. standard treatment: n=110 (43 %) and pembrolizumab monotherapy: n=133 (52 %) vs. standard treatment: n=122 (48 %)] (see Table 27).

Table 27: Efficacy results for pembrolizumab plus chemotherapy and pembrolizumab as monotherapy by PD-L1 Expression in KEYNOTE-048 (CPS ≥ 20)

Endpoint	**Pembrolizumab + Platinum Chemotherapy + 5-FU n=126**	**Standard Treatment* n=110**	**Pembrolizumab Monotherapy n=133**	**Standard Treatment* n=122**
OS				

Number (%) of patients with event	84 (66,7)	98 (89,1)	94 (70,7)	108 (88,5)
Median in months (95 % CI)	14,7 (10,3, 19,3)	11,0 (9,2, 13,0)	14,8 (11,5, 20,6)	10,7 (8,8, 12,8)
Hazard ratio† (95 % CI)	0,60 (0,45, 0,82)		0,58 (0,44, 0,78)	
p-Value‡	0,00044		0,00010	
OS rate at 6 months (95 % CI)	74,6 (66,0, 81,3)	80,0 (71,2, 86,3)	74,4 (66,1, 81,0)	79,5 (71,2, 85,7)
OS rate at 12 months (95 % CI)	57,1 (48,0, 65,2)	46,1 (36,6, 55,1)	56,4 (47,5, 64,3)	44,9 (35,9, 53,4)
OS rate at 24 months (95 % CI)	35,4 (27,2, 43,8)	19,4 (12,6, 27,3)	35,3 (27,3, 43,4)	19,1 (12,7, 26,6)
PFS				
Number (%) of patients with event	106 (84,1)	104 (94,5)	115 (86,5)	114 (93,4)
Median in months (95 % CI)	5,8 (4,7, 7,6)	5,3 (4,9, 6,3)	3,4 (3,2, 3,8)	5,3 (4,8, 6,3)
Hazard ratio† (95 % CI)	0,76 (0,58, 1,01)		0,99 (0,76, 1,29)	
p-Value‡	0,02951		0,46791	
PFS rate at 6 months (95 % CI)	49,4 (40,3, 57,9)	47,2 (37,5, 56,2)	33,0 (25,2, 41,0)	46,6 (37,5, 55,2)
PFS rate at 12 months (95 % CI)	23,9 (16,7, 31,7)	14,0 (8,2, 21,3)	23,5 (16,6, 31,1)	15,1 (9,3, 22,2)
PFS rate at 24 months (95 % CI)	14,6 (8,9, 21,5)	5,0 (1,9, 10,5)	16,8 (10,9, 23,8)	6,1 (2,7, 11,6)
Objective response rate				
ORR§ % (95 % CI)	42,9 (34,1, 52,0)	38,2 (29,1, 47,9)	23,3 (16,4, 31,4)	36,1 (27,6, 45,3)
Response duration				
Number of responders	54	42	31	44
Median in months (range)	7,1 (2,1+, 39,0+)	4,2 (1,2+, 31,5+)	22,6 (2,7+, 43,0+)	4,2 (1,2+, 31,5+)

*Cetuximab, platinum, and 5-FU

†Based on the stratified Cox proportional hazard model

‡Based on stratified log-rank test

§Response: Best objective response as confirmed complete response or partial response

An exploratory subgroup analysis was performed in KEYNOTE-048 in patients whose tumours expressed PD-L1 CPS ≥ 1 to < 20 [pembrolizumab plus chemotherapy: n=116 (45 %) vs. standard treatment: n=125 (49 %) and pembrolizumab monotherapy: n=124 (48 %) vs. standard treatment: n=133 (52 %)] (see Table 28).

Table 28: Efficacy results for pembrolizumab plus chemotherapy and pembrolizumab as monotherapy by PD-L1 Expression in KEYNOTE-048 (CPS ≥ 1 to < 20)

Endpoint	Pembrolizumab + Platinum Chemotherapy + 5-FU n=116	Standard Treatment* n=125	Pembrolizumab Monotherapy n=124	Standard Treatment* n=133
OS				
Number (%) of patients with event	93 (80,2)	115 (92,0)	103 (83,1)	121 (91,0)
Median in months (95 % CI)	12,7 (9,4, 15,3)	9,9 (8,6, 11,5)	10,8 (9,0, 12,6)	10,1 (8,7, 12,1)
Hazard ratio† (95 % CI)	0,71 (0,54, 0,94)		0,86 (0,66, 1,12)	
OS rate at 6 months (95 % CI)	76,7 (67,9, 83,4)	77,4 (69,0, 83,8)	67,6 (58,6, 75,1)	78,0 (70,0, 84,2)
OS rate at 12 months (95 % CI)	52,6 (43,1, 61,2)	41,1 (32,4, 49,6)	44,0 (35,1, 52,5)	42,4 (33,9, 50,7)
OS rate at 24 months (95 % CI)	25,9 (18,3, 34,1)	14,5 (9,0, 21,3)	22,0 (15,1, 29,6)	15,9 (10,3, 22,6)
PFS				
Number (%) of patients with event	106 (91,4)	117 (93,6)	113 (91,1)	123 (92,5)
Median in months (95 % CI)	4,9 (4,2, 5,3)	4,9 (3,7, 6,0)	2,2 (2,1, 2,9)	4,9 (3,8, 6,0)
Hazard ratio† (95 % CI)	0,93 (0,71, 1,21)		1,25 (0,96, 1,61)	
PFS rate at 6 months (95 % CI)	40,1 (31,0, 49,0)	40,0 (31,2, 48,5)	24,2 (17,1, 32,0)	41,4 (32,8, 49,7)
PFS rate at 12 months (95 % CI)	15,1 (9,1, 22,4)	11,3 (6,4, 17,7)	17,5 (11,4, 24,7)	12,1 (7,2, 18,5)
PFS rate at 24 months (95 % CI)	8,5 (4,2, 14,7)	5,0 (1,9, 10,1)	8,3 (4,3, 14,1)	6,3 (2,9, 11,5)
Objective response rate				
ORR‡ % (95 % CI)	29,3 (21,2, 38,5)	33,6 (25,4, 42,6)	14,5 (8,8, 22,0)	33,8 (25,9,42,5)
Response duration				
Number of responders	34	42	18	45
Median in months (range)	5,6 (1,6+, 25,6+)	4,6 (1,4+, 31,4+)	NR (1,5+, 38,9+)	5,0 (1,4+, 38,7+)

*Cetuximab, platinum, and 5-FU

†Based on the stratified Cox proportional hazard model

‡Response: Best objective response as confirmed complete response or partial response

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

The safety and efficacy of pembrolizumab were investigated in KEYNOTE-040, a multicentre, open-label, randomised, controlled study for the treatment of histologically confirmed recurrent or metastatic HNSCC of the oral cavity, pharynx or larynx in patients who had disease progression on or after platinum-containing chemotherapy administered for recurrent or metastatic HNSCC or following platinum-containing chemotherapy administered as part of induction, concurrent, or adjuvant therapy, and were not amenable to local therapy with curative intent. Patients were stratified by PD-L1 expression (TPS ≥ 50 %), HPV status and ECOG performance status and then randomised (1:1) to receive either pembrolizumab 200 mg every 3 weeks (n=247) or one of three standard treatments (n=248): methotrexate 40 mg/m^2 once weekly (n=64), docetaxel 75 mg/m^2 once every 3 weeks (n=99), or cetuximab 400 mg/m^2 loading dose and then 250 mg/m^2 once weekly (n=71). Treatment could continue beyond progression if the patient was clinically stable and was considered to be deriving clinical benefit by the investigator. The study excluded patients with nasopharyngeal carcinoma, active autoimmune disease that required systemic therapy within 2 years of treatment, a medical condition that required immunosuppression, or who were previously treated with 3 or more systemic regimens for recurrent and/or metastatic HNSCC. Assessment of tumour status was performed at 9 weeks, then every 6 weeks through Week 52, followed by every 9 weeks through 24 months.

Among the 495 patients in KEYNOTE-040, 129 (26 %) had tumours that expressed PD-L1 with a TPS ≥ 50 % based on the PD-L1 IHC 22C3 pharmDx™ Kit. The baseline characteristics of these 129 patients included: median age 62 years (40 % age 65 or older); 81 % male; 78 % White, 11 % Asian, and 2 % Black; 23 % and 77 % with an ECOG performance status 0 or 1, respectively; and 19 % with HPV positive tumours. Sixty-seven percent (67 %) of patients had M1 disease and the majority had stage IV disease (stage IV 32 %, stage Iva 14 %, stage IVb 4 %, and stage IVc 44 %). Sixteen percent (16 %) had disease progression following platinum-containing neoadjuvant or adjuvant chemotherapy, and 84 % had received 1-2 prior systemic regimens for metastatic disease.

The primary efficacy outcome was OS in the ITT population. The initial analysis resulted in a HR for OS of 0,82 (95 % CI: 0,67, 1,01) with a one-sided p-value of 0,0316. The median OS was 8,4 months for pembrolizumab compared to 7,1 months for standard treatment. Table 29 summarises the key efficacy measures for the TPS ≥ 50 % population. The Kaplan-Meier curve for OS for the TPS ≥ 50 % population is shown in Figure 17.

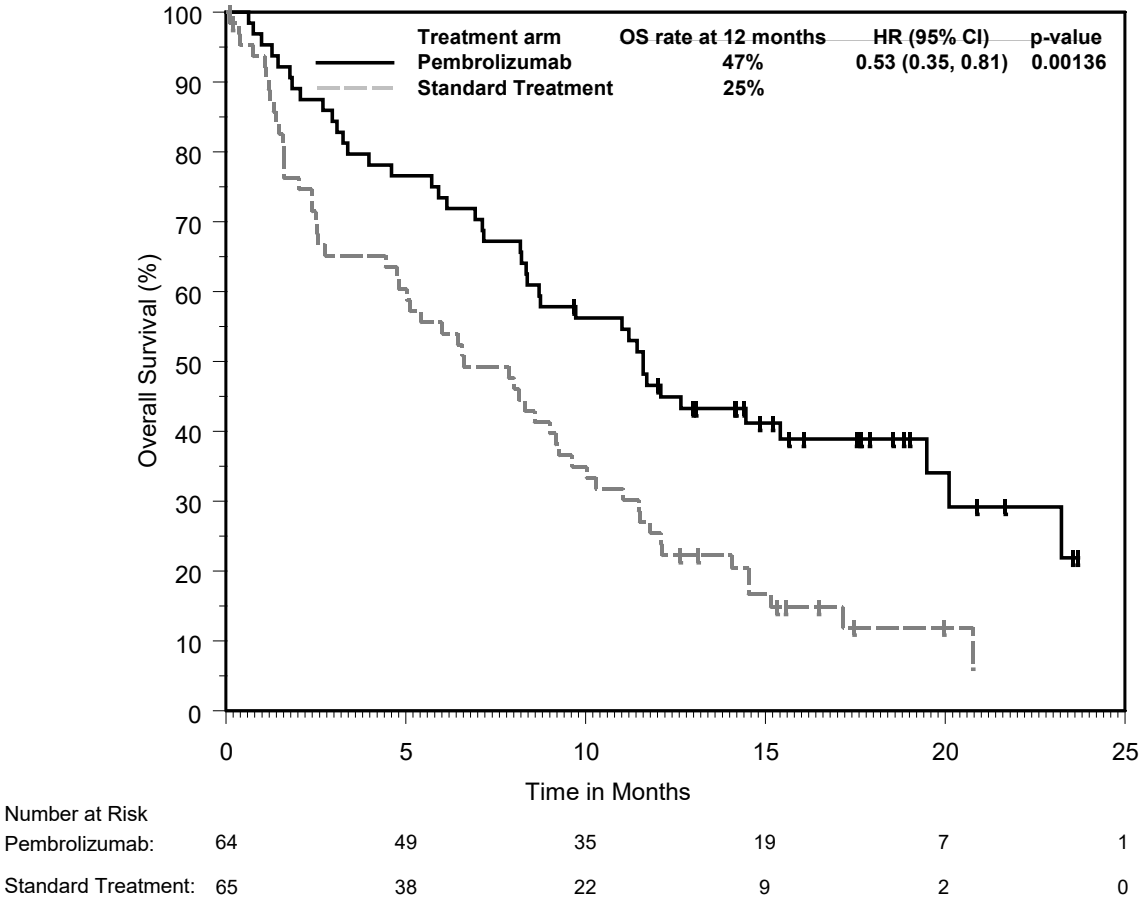
Table 29: Efficacy of pembrolizumab 200 mg every 3 weeks in HNSCC patients with TPS ≥ 50 % who were previously treated with platinum chemotherapy in KEYNOTE-040

Endpoint	**Pembrolizumab 200 mg every 3 weeks n=64**	**Standard Treatment* n=65**
OS		
Number (%) of patients with event	41 (64)	56 (86)
Hazard ratio† (95 % CI)	0,53 (0,35, 0,81)	
p-Value‡	0,001	
Median in months (95 % CI)	11,6 (8,3, 19,5)	6,6 (4,8, 9,2)
PFS§		
Number (%) of patients with event	52 (81)	58 (89)
Hazard ratio† (95 % CI)	0,58 (0,39, 0,86)	
p-Value‡	0,003	
Median in months (95 % CI)	3,5 (2,1, 6,3)	2,1 (2,0, 2,4)
Rate (%) at 6 months (95 % CI)	40,1 (28,1, 51,9)	17,1 (8,8, 27,7)

Objective response rate[§]		
ORR % (95 % CI)	26,6 (16,3, 39,1)	9,2 (3,5, 19,0)
p-Value[¶]	0,0009	
Complete response	5 %	2 %
Partial response	22 %	8 %
Stable disease	23 %	23 %
Response duration[§,#]		
Median in months (range)	Not reached (2,7, 13,8+)	6,9 (4,2, 18,8)
Number (%[Þ]) of patients with duration ≥ 6 months	9 (66)	2 (50)

[*]Methotrexate, docetaxel, or cetuximab
[†]Hazard ratio (pembrolizumab compared to standard treatment) based on the stratified Cox proportional hazard model
[‡]One-sided p-Value based on log-rank test
[§]Assessed by BICR using RECIST 1.1
[¶]Based on method by Miettinen and Nurminen
[#]Based on patients with a best objective response as confirmed complete or partial response
[Þ]Based on Kaplan-Meier estimation

Figure 17: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-040 patients with PD-L1 expression (TPS ≥ 50 %)



Renal cell carcinoma

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

The efficacy of pembrolizumab in combination with axitinib was investigated in KEYNOTE-426, a randomised, multicentre, open-label, active-controlled study conducted in patients with advanced RCC

with clear cell component, regardless of PD-L1 tumour expression status and International Metastatic RCC Database Consortium (IMDC) risk group categories. The study excluded patients with autoimmune disease or a medical condition that required immunosuppression. Randomisation was stratified by risk categories (favourable versus intermediate versus poor) and geographic region (North America versus Western Europe versus "Rest of the World"). Patients were randomised (1:1) to one of the following treatment arms:

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

Treatment with pembrolizumab and axitinib continued until RECIST v1.1-defined progression of disease as verified by BICR or confirmed by the investigator, unacceptable toxicity, or for pembrolizumab, a maximum of 24 months. Administration of pembrolizumab and axitinib was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Assessment of tumour status was performed at baseline, after randomisation at Week 12, then every 6 weeks thereafter until Week 54, and then every 12 weeks thereafter. Chemistry and haematology laboratory tests were performed at each cycle.

A total of 861 patients were randomised. The study population characteristics were: median age of 62 years (range: 26 to 90); 38 % age 65 or older; 73 % male; 79 % White and 16 % Asian; 80 % had a Karnofsky Performance Score (KPS) 90-100 and 20 % had KPS 70-80; patient distribution by IMDC risk categories was 31 % favourable, 56 % intermediate and 13 % poor.

The primary efficacy outcome measures were OS and PFS (as assessed by BICR using RECIST 1.1). Secondary efficacy outcome measures were ORR and response duration, as assessed by BICR using RECIST 1.1. The median follow-up time was 12,8 months (range: 0,1 to 21,5 months). Table 30 summarises key efficacy measures from the pre-specified interim analysis. The Kaplan-Meier curves for OS and PFS based on an additional four months of follow-up are shown in Figures 18 and 19.

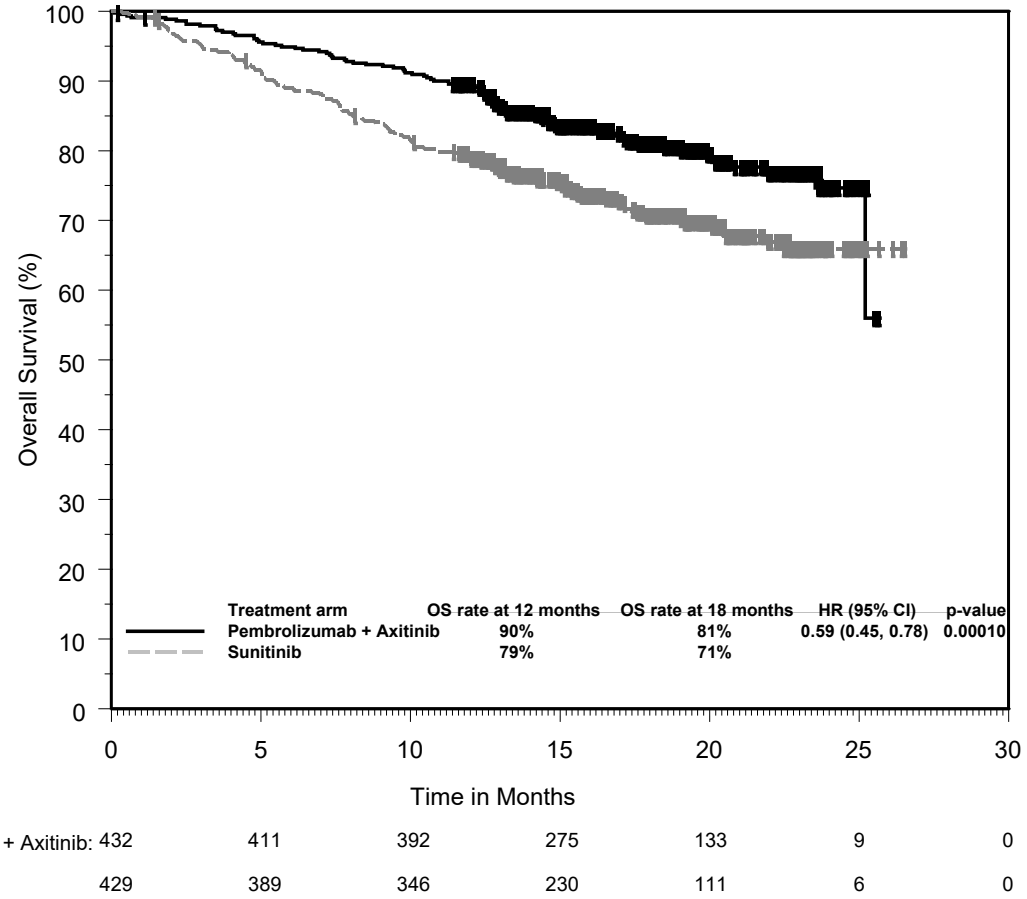
Table 30: Efficacy Results in KEYNOTE-426

Endpoint	**Pembrolizumab Axitinib n=432**	**Sunitinib n=429**
OS		
Number of events (%)	59 (14 %)	97 (23 %)
Median in months (95 % CI)	Not reached (NA, NA)	Not reached (NA, NA)
Hazard ratio* (95 % CI)	0,53 (0,38, 0,74)	
p-Value†	0,00005	
PFS‡		
Number of events (%)	183 (42 %)	213 (50 %)
Median in months (95 % CI)	15,1 (12,6, 17,7)	11,0 (8,7, 12,5)
Hazard ratio* (95 % CI)	0,69 (0,56, 0,84)	
p-Value†	0,00012	
Objective response rate		
ORR§ % (95 % CI)	59 (54, 64)	36 (31, 40)

Complete response	6 %	2 %
Partial response	53 %	34 %
p-Value¶	< 0,0001	
Response duration		
Median in months (range)	Not reached (1.4+, 18.2+)	15.2 (1.1+, 15.4+)
Number (%#) of patients with duration ≥ 6 months	161 (88 %)	84 (81 %)
Number (%#) of patients with duration ≥ 12 months	58 (71 %)	26 (62 %)

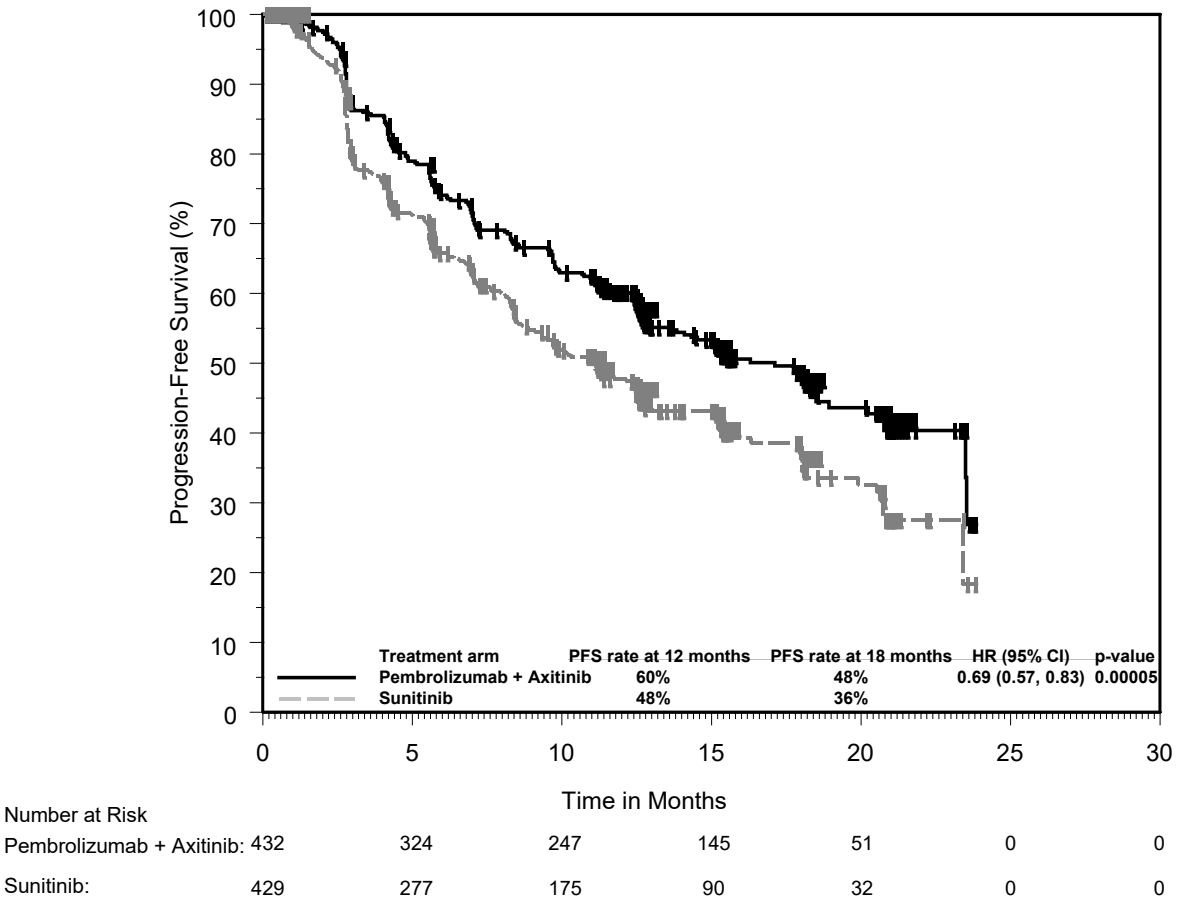
*Based on the stratified Cox proportional hazard model
†Based on stratified log-rank test
‡Assessed by BICR using RECIST 1.1
§Based on patients with a best objective response as confirmed complete or partial response
¶Based on Miettinen and Nurminen method stratified by IMDC risk group and geographic region
#Based on Kaplan-Meier estimation
NA = not available

Figure 18: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-426 (intent to treat population)*



*p-Value is nominal. See Table 30 for p-Value for inferential test of OS based on the pre-specified interim analysis, where statistical significance has been reached.

Figure 19: Kaplan-Meier curve for progression-free survival by treatment arm in KEYNOTE-426 (intent to treat population)*



*p-Value is nominal. See Table 30 for p-Value for inferential test of PFS based on the pre-specified interim analysis, where statistical significance has been reached.

Subgroup analyses by enrolment were performed in KEYNOTE-426 in patients with PD-L1 CPS ≥ 1 [pembrolizumab/axitinib combination: n=243 (56 %) vs. sunitinib: n=254 (59 %)]; CPS < 1 [pembrolizumab/axitinib combination: n=167 (39 %) vs. sunitinib: n=158 (37 %)], and in patients with IMDC risk categories of favourable [pembrolizumab/axitinib combination: n=138 (32 %) vs. sunitinib: n=131 (31 %)]; intermediate [pembrolizumab/axitinib combination: n=238 (55 %) vs. sunitinib: n=246 (57 %)]; and poor [pembrolizumab/axitinib combination: n=56 (13 %) vs. sunitinib: n=52 (12 %)]. OS and PFS benefits were observed regardless of PD-L1 expression level.
The KEYNOTE-426 study was not powered to evaluate efficacy of individual subgroups. Table 31 summarises the efficacy measures by IMDC risk category from the pre-specified interim analysis.

Table 31: Efficacy Results in KEYNOTE-426 by IMDC Risk Category

Endpoint	**Pembrolizumab + Axitinib n=432**	**Sunitinib n=429**	**Pembrolizumab + Axitinib vs. Sunitinib**
OS	**12 month OS rate, % (95 % CI)**		**OS HR (95 % CI)**
Favourable	95,2 (89,6, 97,9)	93,8 (87,4, 97,0)	0,64 (0,24, 1,68)
Intermediate	92,1 (84,7, 96,0)	76,7 (70,6, 81,8)	0,53 (0,35, 0,82)
Poor	70,3 (56,1, 80,7)	45,2 (30,0, 59,3)	0,43 (0,23, 0,81)
PFS	**Median (95 % CI), months**		**PFS HR (95 % CI)**
Favourable	17,7 (15,2, NA)	12,7 (11,5, NA)	0,81 (0,53, 1,24)
Intermediate	14,5 (12,4, 18,0)	9,5 (8,0, 12,5)	0,69 (0,53, 0,90)
Poor	4,9 (2,9, 12,4)	2,9 (2,7, 4,2)	0,58 (0,35, 0,94)
Confirmed ORR	**% (95 % CI)**		**ORR difference,**

			% (95 % CI)
Favourable	66,7 (58,1, 74,5)	49,6 (40,8, 58,5)	17,0 (5,3, 28,4)
Intermediate	59,2 (52,7, 65,5)	33,7 (27,9, 40,0)	25,5 (16,7, 33,9)
Poor	41,1 (28,1, 55,0)	9,6 (3,2, 21,0)	31,5 (15,7, 46,2)

NA = not available

An updated OS analysis was performed when patients had a median follow-up of 16,6 months (range: 0,1 to 26,3 months). At the time of this analysis, the hazard ratio in the overall population (95 % CI) was 0,59 (0,45, 0,78) with 84/432 (19,4 %) events in the combination arm and 122/429 (28,4 %) events in the sunitinib arm. The 12 month OS rate was 89,5 % (95 % CI 86,2, 92,1) for pembrolizumab in combination with axitinib and 78,8 % (95 % CI 74,7, 82,4) for sunitinib. The 18 month OS rate was 81,0 % (95 % CI 76,7, 84,6) for pembrolizumab in combination with axitinib and 70,7 % (95 % CI 65,8, 75,1) for sunitinib. For the IMDC risk category, the OS hazard ratio for the favourable risk group was 0,94 (95 % CI 0,43, 2,07), for the intermediate risk group the OS hazard ratio was 0,52 (95 % CI 0,36, 0,75), and for the poor risk group the OS hazard ratio was 0,50 (95 % CI 0,29, 0,87).

Colorectal Cancer

KEYNOTE-177: Controlled study in MSI-H or dMMR CRC patients naïve to treatment in the metastatic setting

The efficacy of pembrolizumab was investigated in KEYNOTE-177, a multicentre, randomised, open-label, active-controlled study that enrolled patients with previously untreated metastatic MSI-H or dMMR CRC. MSI or MMR tumour status was determined locally using polymerase chain reaction (PCR) or IHC, respectively. Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible.

Patients were randomised (1:1) to receive pembrolizumab 200 mg intravenously every 3 weeks or investigator's choice of the following chemotherapy regimens given intravenously every 2 weeks:

- mFOLFOX6 (oxaliplatin, leucovorin, and FU) or mFOLFOX6 in combination with either bevacizumab or cetuximab: Oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2 (or levoleucovorin 200 mg/m^2), and FU 400 mg/m^2 bolus on Day 1, then FU 2 400 mg/m^2 over 46-48 hours. Bevacizumab 5 mg/kg bodyweight on Day 1 or cetuximab 400 mg/m^2 on first infusion, then 250 mg/m^2 weekly.
- FOLFIRI (irinotecan, leucovorin and FU) or FOLFIRI in combination with either bevacizumab or cetuximab: Irinotecan 180 mg/m^2, leucovorin 400 mg/m^2 (or levoleucovorin 200 mg/m^2), and FU 400 mg/m^2 bolus on Day 1, then FU 2 400 mg/m^2 over 46-48 hours. Bevacizumab 5 mg/kg bodyweight on Day 1 or cetuximab 400 mg/m^2 on first infusion, then 250 mg/m^2 weekly.

Treatment with pembrolizumab continued until RECIST v1.1-defined progression of disease as determined by the investigator or unacceptable toxicity. Patients treated with pembrolizumab without disease progression could be treated for up to 24 months. Assessment of tumour status was performed every 9 weeks. Patients randomised to chemotherapy were offered pembrolizumab at the time of disease progression.

A total of 307 patients were enrolled and randomised to pembrolizumab (n=153) or chemotherapy (n=154). The baseline characteristics of these patients were: median age of 63 years (range: 24 to 93), 47 % age 65 or older; 50 % male; 75 % White and 16 % Asian; 52 % and 48 % had an ECOG performance status of 0 or 1, respectively. Mutation status: 25 % BRAF V600E, 24 % KRAS/NRAS.

For 143 patients treated with chemotherapy, 56 % received mFOLFOX6 with or without bevacizumab or cetuximab and 44 % received FOLFIRI with or without bevacizumab or cetuximab.
The primary efficacy outcome measures were PFS assessed by BICR according to RECIST v1.1 and OS. Secondary outcome measures were ORR and response duration. Table 32 summarises the key efficacy measures of the final analysis for PFS and the interim analysis of OS with a median follow-up time of 27,6 months (range: 0,2 to 48,3 months). The Kaplan-Meier curves for PFS and OS are shown in Figures 20 and 21.

Table 32: Efficacy Results in KEYNOTE-177

Endpoint	**Pembrolizumab 200 mg every 3 weeks n=153**	**Chemotherapy n=154**
PFS		
Number (%) of patients with event	82 (54 %)	113 (73 %)
Median in months (95 % CI)	16,5 (5,4, 32,4)	8,2 (6,1, 10,2)
Hazard ratio* (95% CI)	0,60 (0,45, 0,80)	
p-Value†	0,0002	
OS		
Number (%) of patients with event	56 (37 %)	69 (45 %)
Median in months (95 % CI)	NR (NR, NR)	34,8 (26,3, NR)
Hazard ratio* (95 % CI)	0,77 (0,54, 1,09)	
Objective response rate		
ORR (95 % CI)	44 % (35,8, 52,0)	33 % (25,8, 41,1)
Complete response rate	11 %	4 %
Partial response rate	33 %	29 %
Response duration		
Median in months (range)	NR (2,3+, 41,4+)	10,6 (2,8, 37,5+)
% of patients with duration ≥ 12 months‡	85 %	44 %

*Based on Cox regression model
†Based on log-rank test compared to a significance level of 0,0117
‡Based on Kaplan-Meier estimation
NR = not reached

Figure 20: Kaplan-Meier curve for progression-free survival by treatment arm in KEYNOTE-177 (intent to treat population)

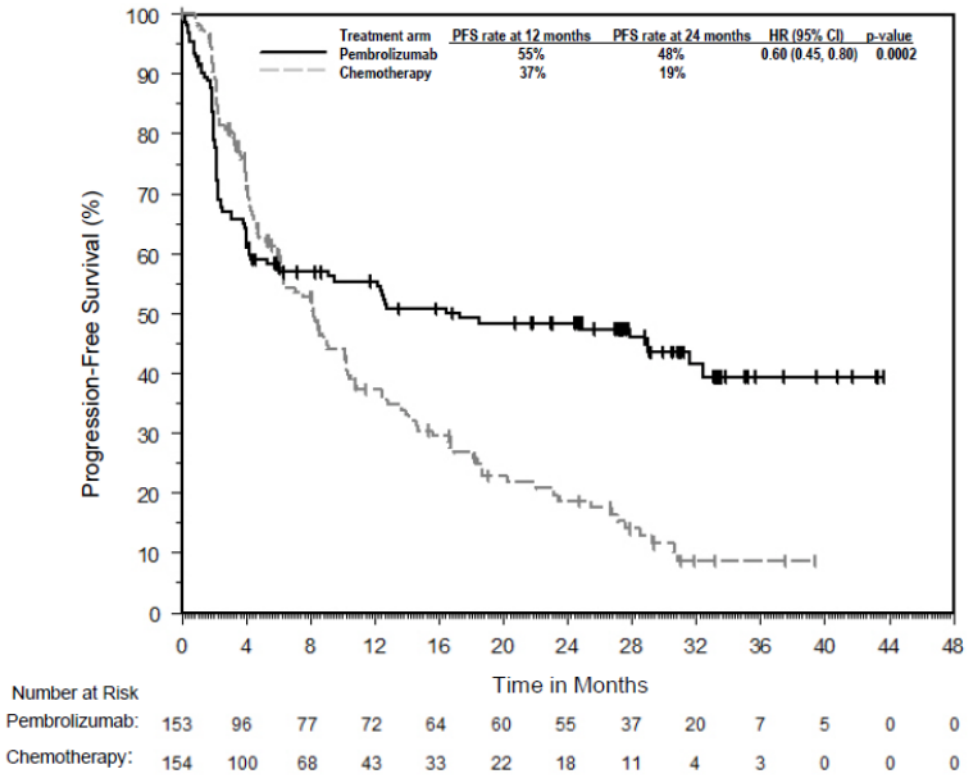
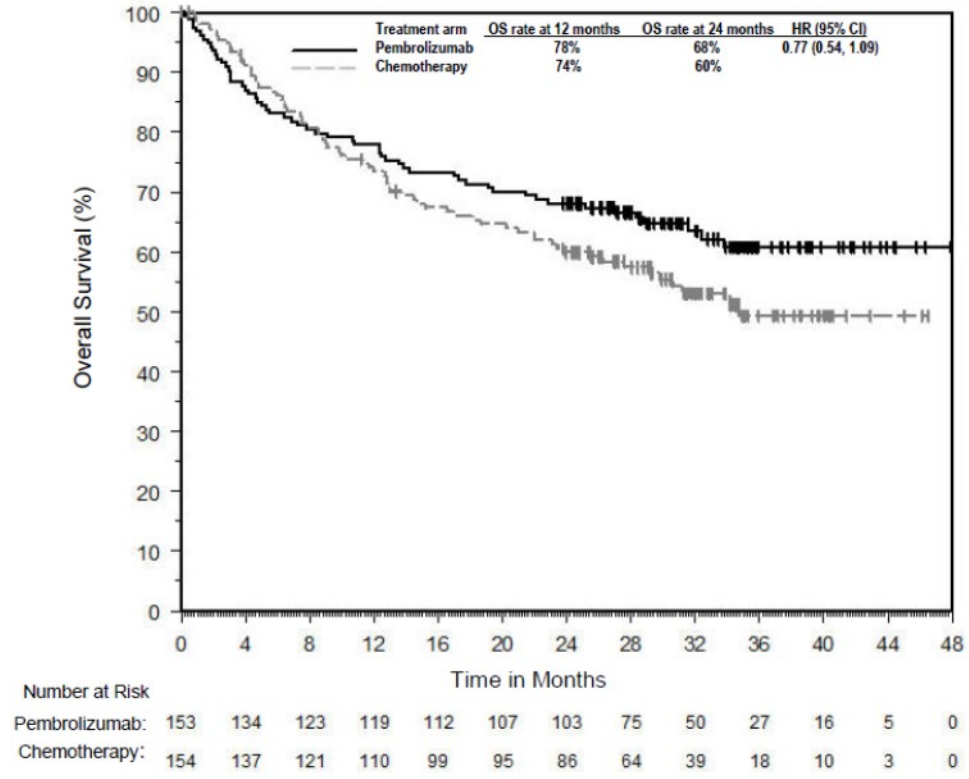


Figure 21: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-177 (intent to treat population)



Paediatric population

In KEYNOTE-051, 161 paediatric patients (62 children aged 9 months to less than 12 years and 99 adolescents aged 12 years to 17 years) with advanced melanoma or PD-L1 positive advanced, relapsed, or refractory solid tumours or lymphoma were administered pembrolizumab 2 mg/kg every 3 weeks. All patients received pembrolizumab for a median of 4 doses (range 1-35 doses), with 138

patients (85,7 %) receiving pembrolizumab for 2 doses or more. Participants were enrolled across 28 tumour types by primary diagnosis. The most common tumour types by histology were Hodgkin lymphoma (13,7 %), glioblastoma multiforme (9,3 %), neuroblastoma (6,2 %), osteosarcoma (6,2 %) and melanoma (5,6 %). Of the 161 patients, 137 were enrolled with solid tumours, 22 with Hodgkin lymphoma, and 2 with other lymphomas. In patients with solid tumours and other lymphomas, the ORR was 5,8 %, no patient had a complete response and 8 patients (5,8 %) had a partial response. In the Hodgkin lymphoma population (n=22), in patients aged 11 years to 17 years, the baseline characteristics were median age 15 years; 64 % male; 68 % White; 77 % had a Lansky/Karnofsky scale 90-100 and 23 % had scale 70-80. Eighty-six percent had two or more prior lines of therapy and 91 % had Stage 3 or higher. In these paediatric patients with cHL, the ORR assessed by BICR according to the IWG 2007 criteria was 54,5 %, 1 patient (4,5 %) had a complete response and 11 patients (50,0 %) had a partial response, and the ORR assessed by the Lugano 2014 criteria was 63,6 %, 4 patients (18,2 %) had a complete response and 10 patients (45,5 %) had a partial response.
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 Hodgkin lymphoma (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 weeks, 2 to 10 mg/kg every 3 weeks, or 200 mg every 3 weeks.

Absorption
Pembrolizumab is administered 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 (~6.0 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
Pembrolizumab CL is approximately 23 % lower (geometric mean, 195 mL/day [CV%: 40 %]) after achieving maximal change at steady-state compared with the first dose (252 mL/day [CV%: 37 %]); this decrease in CL with time is not considered clinically meaningful. The geometric mean value (CV%) for the terminal half-life is 22 days (32 %) at steady-state.

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. Steady-state concentrations of pembrolizumab were reached by 16 weeks of repeated dosing with an every 3 week regimen and the systemic accumulation was 2,1-fold. The median trough concentrations (C_{min}) at steady-state were approximately 22 mcg/mL at a dose of 2 mg/kg every 3 weeks and 29 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 794 mcg·day/mL at a dose of 2 mg/kg every 3 weeks and 1 053 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. Pembrolizumab exposure with weight-based dosing at 2 mg/kg every 3 weeks in paediatric patients (> 3 to 17 years) are comparable to those of adults at the same dose.

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 produced exposure multiples of 19 and 94 times the exposure in humans at doses of 10 and 2 mg/kg, respectively. The exposure multiple between the NOAEL and a human dose of 200 mg was 74.
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 signalling 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 (E433)
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 96 hours at 2 ºC to 8 ºC. This 96-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 or bromobutyl 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 96 hours at 2 ºC to 8 ºC. This 96-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. Translucent to white proteinaceous particles may be seen in diluted solution. 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

MSD (Pty) Ltd, 117 16th Road, Halfway House 1685, South Africa

8. NAME AND ADDRESS OF THE MANUFACTURER

MSD International GmbH T/A MSD Ireland (Carlow), Dublin Road, Carlow, Co. Carlow, Ireland

9. MARKETING AUTHORISATION NUMBER(S)

COUNTRY	
ETHIOPIA	07328/08996/NMR/2021
KENYA	
NIGERIA (NAFDAC Reg. No.)	
TANZANIA	
UGANDA	
ZAMBIA	
ZIMBABWE	

10. SCHEDULING STATUS

POM

R_x ONLY

ZIMBABWE SCHEDULING: TBA

11. DATE OF FIRST AUTHORISATION

COUNTRY	
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NIGERIA	
TANZANIA	
UGANDA	
ZAMBIA	
ZIMBABWE	

12. DATE OF REVISION OF THE TEXT

09 March 2021