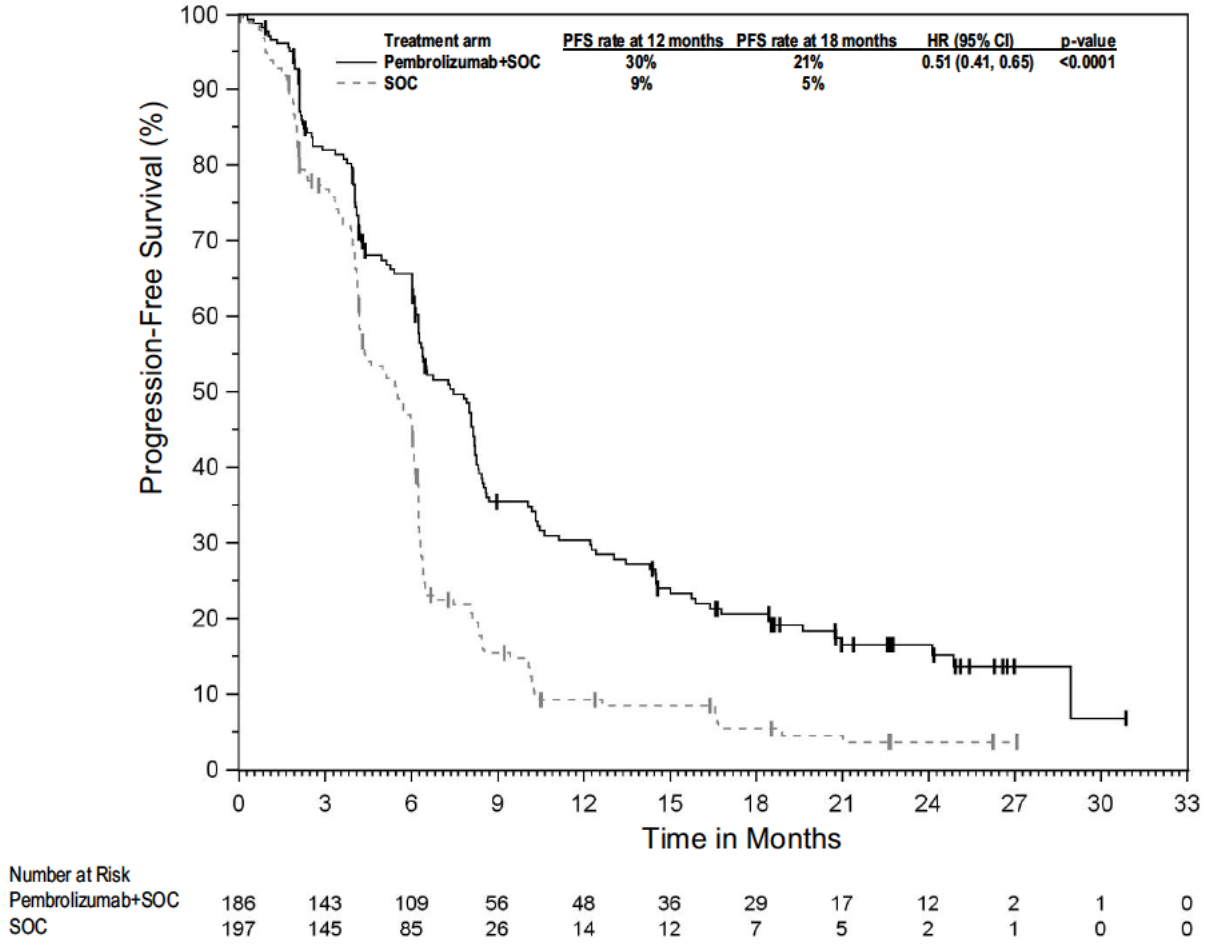
Figure 26: Kaplan-Meier curve for progression-free survival by treatment arm in KEYNOTE-590 with PD-L1 expression (CPS ≥ 10)



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 bw every 2 weeks, 2 to 10 mg/kg bw 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 bw 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 bw 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 bw 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 bw 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 bw, which produced exposure multiples of 19 and 94 times the exposure in humans at doses of 10 and 2 mg/kg bw, 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)

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial
3 years.

After reconstitution
From a microbiological point of view, the reconstituted or diluted solution should be used immediately. The reconstituted or diluted solution must not be frozen. If not used immediately, chemical and physical in-use stability of KEYTRUDA has been demonstrated for 96 hours at 2°C to 8°C. This 96-hour total hold from reconstitution may include up to 6 hours at room temperature (at or below 25°C). If refrigerated, the vials and/or intravenous bags must be allowed to come to room temperature prior to use.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).

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

6.5 Nature and contents of container

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

Each carton contains one vial.

6.6 Special precautions for disposal and other handling

Preparation and administration

- Prior to reconstitution, the vial of lyophilised powder can be out of refrigeration (temperatures at or below 25°C) for up to 24 hours.
- Aseptically add 2.3 mL of water for injections to yield a 25 mg/mL (pH 5.2-5.8) solution of KEYTRUDA. Each vial contains an excess fill of 10 mg (0.4 mL) to ensure the recovery of 50 mg of KEYTRUDA per vial. After reconstitution, 1 mL of concentrate contains 25 mg of pembrolizumab.
- To avoid foaming, deliver the water along the walls of the vial and not directly on the lyophilised powder.
- Slowly swirl the vial to allow reconstitution of the lyophilised powder. Allow up to 5 minutes for the bubbles to clear. Do not shake the vial.
- Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration. Reconstituted KEYTRUDA is a clear to slightly opalescent, colourless to slightly yellow solution. Discard the vial if visible particles are observed.
- Withdraw the required volume up to 2 mL (50 mg) of KEYTRUDA and transfer into an intravenous bag containing sodium chloride 9 mg/mL (0.9%) or glucose 50 mg/mL (5%) to prepare a diluted solution with a final concentration ranging from 1 to 10 mg/mL. Mix diluted solution by gentle inversion.
- From a microbiological point of view, the reconstituted or diluted solution should be used immediately. The reconstituted or diluted solution must not be frozen. If not used immediately, chemical and physical in-use stability of KEYTRUDA has been demonstrated for 96 hours at 2°C to 8°C. This 96-hour total hold from reconstitution may include up to 6 hours at room temperature (at or below 25°C). If refrigerated, the vials and/or intravenous bags must be allowed to come to room temperature prior to use. 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

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1024/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 July 2015
Date of latest renewal: 24 March 2020

10. DATE OF REVISION OF THE TEXT

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

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.

Oesophageal carcinoma
KEYTRUDA, in combination with platinum and fluoropyrimidine based chemotherapy, is indicated for the first-line treatment of patients with locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastroesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 10 (see section 5.1).

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
If specified in the indication, patient selection for treatment with KEYTRUDA based on the tumour expression of PD-L1 should be 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 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 (bw) (up to a maximum of 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**	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*

Immune-related adverse reactions	Severity	Treatment modification
combination with axitinib with liver enzyme elevations, see dosing guidelines following this table.	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 oesophageal carcinoma; 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, vasculitis, cholangitis sclerosing, gastritis and cystitis noninfective (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 has been assessed in a comparative study (KEYNOTE-361). In KEYNOTE-361, a higher number of deaths within 6 months of treatment initiation followed by a long-term survival benefit was observed with pembrolizumab monotherapy compared to chemotherapy (see section 5.1). No specific factor(s) associated with early deaths could be identified. Physicians should consider the delayed onset of pembrolizumab effect before initiating treatment in patients with urothelial carcinoma who are considered eligible for carboplatin-based combination chemotherapy. KEYNOTE-052 also included 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).

Use of pembrolizumab for first-line treatment of patients with oesophageal carcinoma
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).

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.

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

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

4.7 Effects on ability to drive and use machines

Pembrolizumab 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 bw every 3 weeks, 200 mg every 3 weeks, or 10 mg/kg bw 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 1,437 patients with NSCLC, HNSCC, or oesophageal carcinoma receiving 200 mg, 2 mg/kg bw or 10 mg/kg bw 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 nausea (55%), anaemia (51%), fatigue (39%), constipation (37%), decreased appetite (34%), diarrhoea (33%), neutropenia (29%), and vomiting (28%). Incidences of Grades 3-5 adverse reactions in patients with NSCLC were 67% for pembrolizumab combination therapy and 66% for chemotherapy alone, in patients with HNSCC were 85% for pembrolizumab combination therapy and 84% for chemotherapy plus cetuximab, and in patients with oesophageal carcinoma were 86% for pembrolizumab combination therapy and 83% for chemotherapy alone.

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			
Very common		pneumonia	
Common	pneumonia		pneumonia
Blood and lymphatic system disorders			
Very common	anaemia	anaemia, neutropenia, thrombocytopenia	
Common	thrombocytopenia, neutropenia, lymphopenia	febrile neutropenia, leukopenia, lymphopenia	anaemia, neutropenia, leukopenia, thrombocytopenia
Uncommon	leukopenia, eosinophilia	eosinophilia	lymphopenia, eosinophilia
Rare	immune thrombocytopenia, haemolytic anaemia, pure red cell aplasia, haemophagocytic lymphohistiocytosis		
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]	hypothyroidism	hyperthyroidism, hypothyroidism[b]
Common	hyperthyroidism, thyroiditis[c]	hyperthyroidism[d]	hypophysitis[f], thyroiditis[c], adrenal insufficiency[e]
Uncommon	adrenal insufficiency[e], hypophysitis[f]	hypophysitis[f], adrenal insufficiency[e], thyroiditis[c]	

	Monotherapy	Combination with chemotherapy	Combination with axitinib
Metabolism and nutrition disorders			
Very common	decreased appetite	hyponatraemia, hypokalaemia, decreased appetite	decreased appetite
Common	hyponatraemia, hypokalaemia, hypocalcaemia	hypocalcaemia	hypokalaemia, hyponatraemia, hypocalcaemia
Uncommon	type 1 diabetes mellitus[g]	type 1 diabetes mellitus	type 1 diabetes mellitus[g]
Psychiatric disorders			
Very common		insomnia	
Common	insomnia		insomnia
Nervous system disorders			
Very common	headache	dizziness, neuropathy peripheral, headache	headache, dysgeusia
Common	dizziness, neuropathy peripheral, lethargy, dysgeusia	dysgeusia, lethargy	dizziness, lethargy, neuropathy peripheral
Uncommon	epilepsy	encephalitis, epilepsy	myasthenic syndrome[k]
Rare	encephalitis[h], Guillain-Barré syndrome[i], myelitis[j], myasthenic syndrome[k], meningitis (aseptic)[l]	Guillain-Barré syndrome	
Eye disorders			
Common	dry eye	dry eye	dry eye
Uncommon	uveitis[m]		uveitis[m]
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	myocarditis[n], pericardial effusion	myocarditis
Rare		pericarditis	
Vascular disorders			
Very common			hypertension
Common	hypertension	vasculitis[o], hypertension	
Rare	vasculitis		
Respiratory, thoracic and mediastinal disorders			
Very common	dyspnoea, cough	dyspnoea, cough	dyspnoea, cough, dysphonia
Common	pneumonitis[p]	pneumonitis[p]	pneumonitis[p]
Gastrointestinal disorders			
Very common	diarrhoea, abdominal pain[q], nausea, vomiting, constipation	nausea, diarrhoea, vomiting, abdominal pain[q], constipation	diarrhoea, abdominal pain[q], nausea, vomiting, constipation
Common	colitis[r], dry mouth	colitis[r], dry mouth, gastritis	colitis[r], dry mouth, gastritis
Uncommon	pancreatitis[s], gastritis, gastrointestinal ulceration[t]	pancreatitis[s], gastrointestinal ulceration[t]	pancreatitis[s], gastrointestinal ulceration[t]

	Monotherapy	Combination with chemotherapy	Combination with axitinib
Rare	small intestinal perforation		
Hepatobiliary disorders			
Common		hepatitis[u]	hepatitis[u]
Uncommon	hepatitis[u]		
Rare	cholangitis sclerosing	cholangitis sclerosing	
Skin and subcutaneous tissue disorders			
Very common	rash[v], pruritus[w]	rash[v], alopecia, pruritus[w]	palmar-plantar erythrodysaesthesia syndrome, rash[v], pruritus[w]
Common	severe skin reactions[x], erythema, dermatitis, dry skin, vitiligo[y], eczema, alopecia, dermatitis acneiform	severe skin reactions[x], dry skin, erythema, dermatitis	severe skin reactions[x], dermatitis acneiform, dermatitis, dry skin, alopecia, eczema, erythema
Uncommon	psoriasis, lichenoid keratosis[z], papule, hair colour changes	psoriasis, vitiligo[y], eczema, dermatitis acneiform, papule, lichenoid keratosis	hair colour changes, lichenoid keratosis, papule, psoriasis, vitiligo[y]
Rare	toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema nodosum	hair colour changes	
Musculoskeletal and connective tissue disorders			
Very common	musculoskeletal pain[aa], arthralgia	musculoskeletal pain[aa], arthralgia	musculoskeletal pain[aa], arthralgia, pain in extremity
Common	pain in extremity, myositis[bb], arthritis[cc]	myositis[bb], pain in extremity, arthritis[cc]	myositis[bb], arthritis[cc], tenosynovitis[dd]
Uncommon	tenosynovitis[dd]	tenosynovitis[dd]	Sjogren's syndrome
Rare	Sjogren's syndrome	Sjogren's syndrome	
Renal and urinary disorders			
Common		acute kidney injury	acute kidney injury, nephritis[ee]
Uncommon	nephritis[ee]	nephritis[ee]	
Rare	cystitis noninfective		
General disorders and administration site conditions			
Very common	fatigue, asthenia, oedema[ff], pyrexia	fatigue, asthenia, pyrexia, oedema[ff]	fatigue, asthenia, pyrexia
Common	influenza-like illness, chills	influenza-like illness, chills	oedema[ff], influenza-like illness, chills
Investigations			
Very common		blood creatinine increased	alanine aminotransferase increased, aspartate aminotransferase increased, blood creatinine increased

	Monotherapy	Combination with chemotherapy	Combination with axitinib
Common	aspartate aminotransferase increased, alanine aminotransferase increased, hypercalcaemia, blood alkaline phosphatase increased, blood bilirubin increased, blood creatinine increased	aspartate aminotransferase increased, hypercalcaemia, alanine aminotransferase increased, blood alkaline phosphatase increased, blood bilirubin increased	blood alkaline phosphatase increased, hypercalcaemia, blood bilirubin increased
Uncommon	amylase 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. hyperthyroidism (Basedow's disease)
e. adrenal insufficiency (Addison's disease, adrenocortical insufficiency acute, secondary adrenocortical insufficiency)
f. hypophysitis (hypopituitarism)
g. type 1 diabetes mellitus (diabetic ketoacidosis)
h. encephalitis (autoimmune encephalitis)
i. Guillain Barré syndrome (axonal neuropathy and demyelinating polyneuropathy)
j. myelitis (including transverse myelitis)
k. myasthenic syndrome (myasthenia gravis, including exacerbation)
l. meningitis aseptic (meningitis, meningitis non infective)
m. uveitis (chorioretinitis, iritis and iridocyclitis)
n. myocarditis (autoimmune myocarditis)
o. vasculitis (central nervous system vasculitis)
p. pneumonitis (interstitial lung disease and organising pneumonia)
q. abdominal pain (abdominal discomfort, abdominal pain upper and abdominal pain lower)
r. colitis (colitis microscopic, enterocolitis, enterocolitis haemorrhagic, autoimmune colitis, and immune mediated enterocolitis)
s. pancreatitis (autoimmune pancreatitis and pancreatitis acute)
t. gastrointestinal ulceration (gastric ulcer and duodenal ulcer)
u. hepatitis (autoimmune hepatitis, immune mediated hepatitis, drug induced liver injury and acute hepatitis)
v. rash (rash erythematous, rash follicular, rash macular, rash maculo papular, rash papular, rash pruritic, rash vesicular and genital rash)
w. pruritus (urticaria, urticaria papular and pruritus genital)
x. 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)
y. vitiligo (skin depigmentation, skin hypopigmentation and hypopigmentation of the eyelid)
z. lichenoid keratosis (lichen planus and lichen sclerosus)
aa. musculoskeletal pain (musculoskeletal discomfort, back pain, musculoskeletal stiffness, musculoskeletal chest pain and torticollis)
bb. myositis (myalgia, myopathy, necrotising myositis, polymyalgia rheumatica and rhabdomyolysis)
cc. arthritis (joint swelling, polyarthritis and joint effusion)
dd. tenosynovitis (tendonitis, synovitis and tendon pain)
ee. 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)
ff. 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: 33.0% for neutrophils decreased, 25.5% for lymphocytes decreased, 20.3% for haemoglobin decreased, 19.3% for leucocytes decreased, 13.9% for sodium decreased, 10.8% for platelets decreased, 9.7% for phosphate decreased, 8.4% for potassium decreased, 7.6% for glucose increased, 3.9% for AST increased, 3.8% for potassium increased, 3.7% for calcium decreased, 3.6% for ALT increased, 3.1% for creatinine increased, 3.0% for albumin decreased, 2.2% for calcium increased, 1.6% for alkaline phosphatase increased, 1.2% for bilirubin increased, 0.8% for glucose decreased, and 0.4% 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 listed in Appendix V.

4.9 Overdose

There is no information on overdose with pembrolizumab.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

Clinical efficacy and safety
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 bw every 3 weeks, and 400 mg every 6 weeks (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 bw 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 bw every 3 weeks n=277	Pembrolizumab 10 mg/kg bw every 2 weeks n=279	Ipilimumab 3 mg/kg bw every 3 weeks n=278
OS			
Number (%) of patients with event	119 (43%)	122 (44%)	142 (51%)
Hazard ratio* (95% CI)	0.68 (0.53, 0.86)	0.68 (0.53, 0.87)	---
p-Value†	< 0.001	< 0.001	---
Median in months (95% CI)	Not reached (24, NA)	Not reached (22, NA)	16 (14, 22)
PFS			
Number (%) of patients with event	183 (66%)	181 (65%)	202 (73%)
Hazard ratio* (95% CI)	0.61 (0.50, 0.75)	0.61 (0.50, 0.75)	---
p-Value†	< 0.001	< 0.001	---
Median in months (95% CI)	4.1 (2.9, 7.2)	5.6 (3.4, 8.2)	2.8 (2.8, 2.9)
Best 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

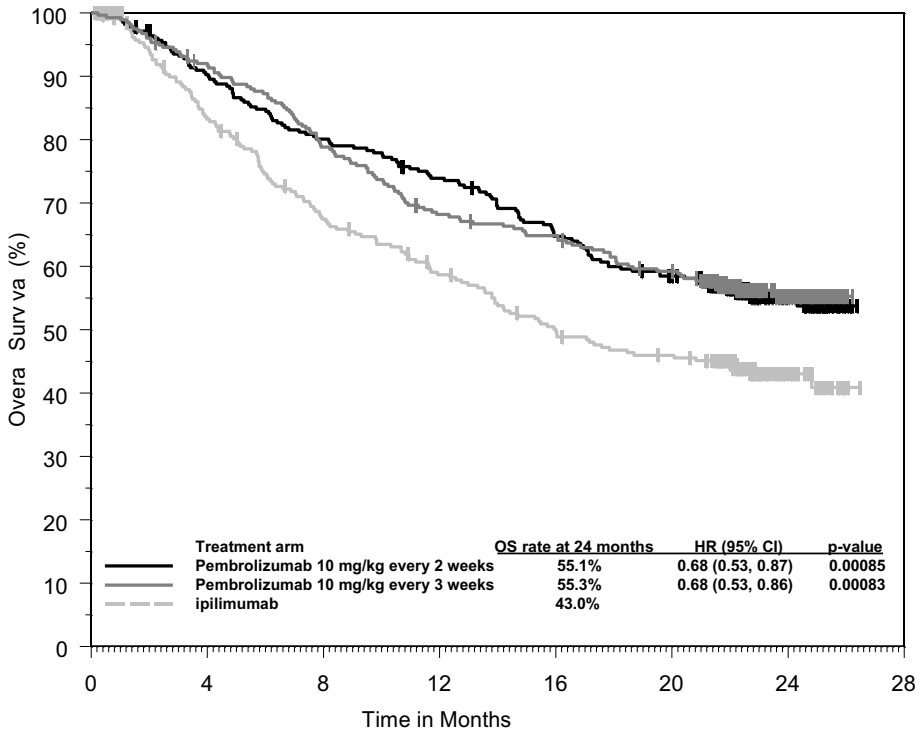
† Based on stratified log rank test

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

§ Based on Kaplan Meier estimation

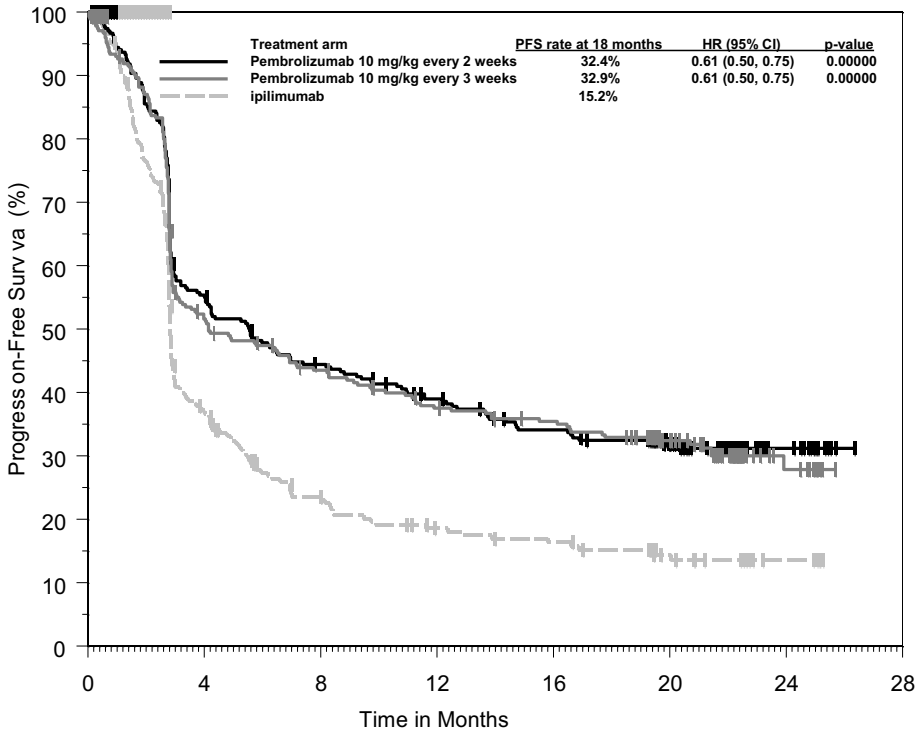
NA = not available

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 bw (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 bw or 10 mg/kg bw 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.

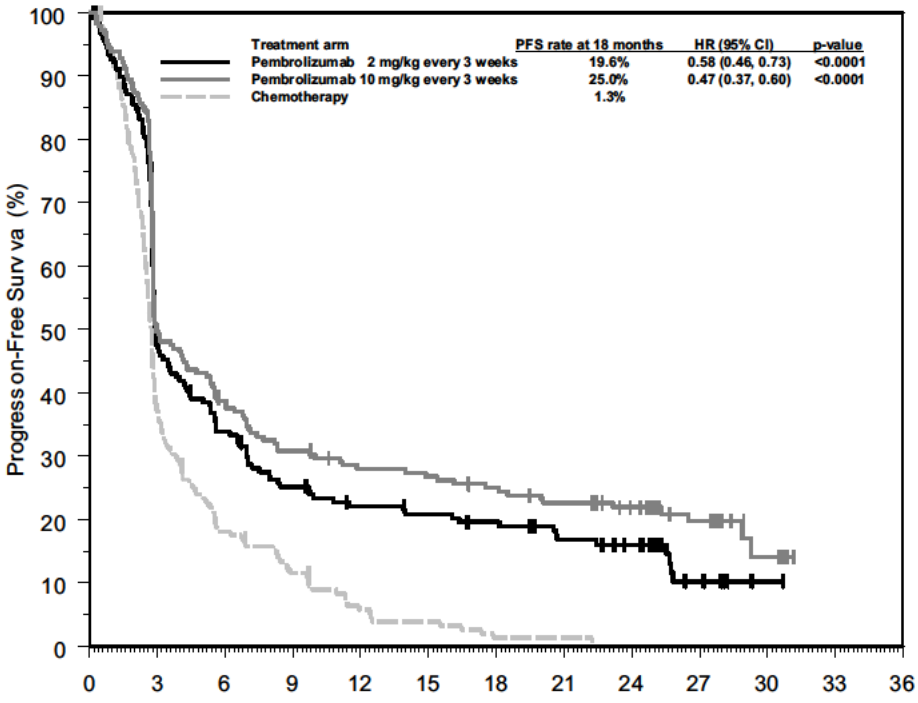
The primary efficacy outcome measures were PFS as assessed by IRO using RECIST version 1.1 and OS. Secondary efficacy outcome measures were ORR and response duration. Table 4 summarises key efficacy measures at the final analysis in patients previously treated with ipilimumab, and the Kaplan-Meier curve 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 bw every 3 weeks n=180	Pembrolizumab 10 mg/kg bw every 3 weeks n=181	Chemotherapy n=179
PFS			
Number (%) of patients with event	150 (83%)	144 (80%)	172 (96%)
Hazard ratio* (95% CI)	0.58 (0.46, 0.73)	0.47 (0.37, 0.60)	---
p-Value†	< 0.001	< 0.001	---
Median in months (95% CI)	2.9 (2.8, 3.8)	3.0 (2.8, 5.2)	2.8 (2.6, 2.8)
OS			
Number (%) of patients with event	123 (68%)	117 (65%)	128 (72%)
Hazard ratio* (95% CI)	0.86 (0.67, 1.10)	0.74 (0.57, 0.96)	---
p-Value†	0.1173	0.0106‡	---
Median in months (95% CI)	13.4 (11.0, 16.4)	14.7 (11.3, 19.5)	11.0 (8.9, 13.8)
Best 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)



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

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

The safety and efficacy of pembrolizumab for patients with advanced melanoma were investigated in an uncontrolled, open-label study, KEYNOTE-001. Efficacy was evaluated for 276 patients from two defined cohorts, one which included patients previously treated with ipilimumab (and if BRAF V600 mutation-positive, with a BRAF or MEK inhibitor) and the other which included patients naïve to treatment with ipilimumab. Patients were randomly assigned to receive pembrolizumab at a dose of 2 mg/kg bw every 3 weeks or 10 mg/kg bw 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 bw 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 bw 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 bw 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 bw every 3 weeks in patients previously treated with ipilimumab n=89**	**Pembrolizumab 2 mg/kg bw 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 bw of pembrolizumab every 3 weeks were similar to those seen in patients who received 2 mg/kg bw 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 bw every 3 weeks (n=136)**	**Chemotherapy (n=137)**	**Pembrolizumab 2 mg/kg bw 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 bw every 2 or 3 weeks (pooled)**	**Ipilimumab (n=170)**	**Pembrolizumab 10 mg/kg bw every 2 or 3 weeks (pooled)**	**Ipilimumab (n=55)**	**Pembrolizumab 10 mg/kg bw 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 bw every 3 weeks	Chemotherapy	Pembrolizumab 2 mg/kg bw 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 bw every 2 or 3 weeks (pooled)	Ipilimumab	Pembrolizumab 10 mg/kg bw 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 secondary outcome measures were distant metastasis-free survival (DMFS) and OS in the whole population and in the population with PD-L1 positive tumours. OS was not formally assessed at the time of these analyses. The study initially demonstrated a statistically significant improvement in RFS (HR 0.57; 98.4% CI 0.43, 0.74; p-Value < 0.0001) for patients randomised to the pembrolizumab arm compared with placebo at its pre-specified interim analysis. Updated efficacy results with a median follow-up time of 45.5 months are summarised in Table 10 and Figures 4 and 5.

Table 10: Efficacy results in KEYNOTE-054

Endpoint	**KEYTRUDA 200 mg every 3 weeks n=514**	**Placebo n=505**
RFS		
Number (%) of patients with event	203 (40%)	288 (57%)
Median in months (95% CI)	NR	21.4 (16.3, 27.0)
Hazard ratio* (95% CI)	0.59 (0.49, 0.70)	
DMFS		
Number (%) of patients with event	173 (34%)	245 (49%)
Median in months (95% CI)	NR	40.0 (27.7, NR)
Hazard ratio* (95% CI)	0.60 (0.49, 0.73)	
p-Value (stratified log-rank)	< 0.0001	

* Based on the stratified Cox proportional hazard model
NR = not reached

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

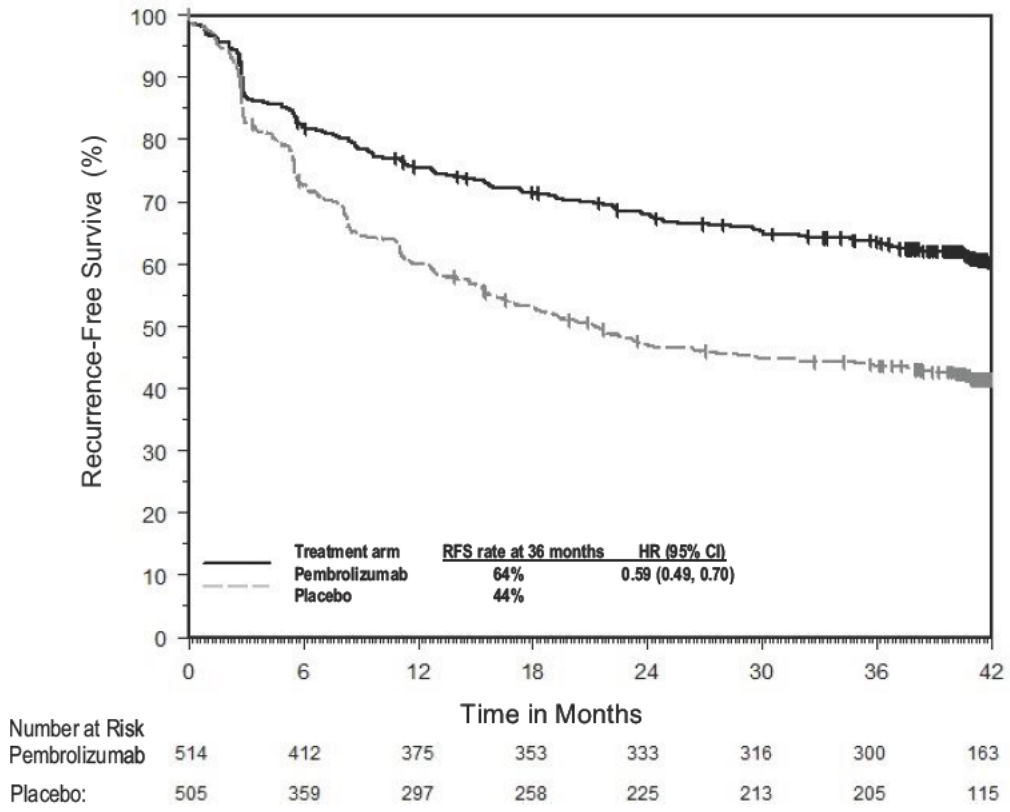
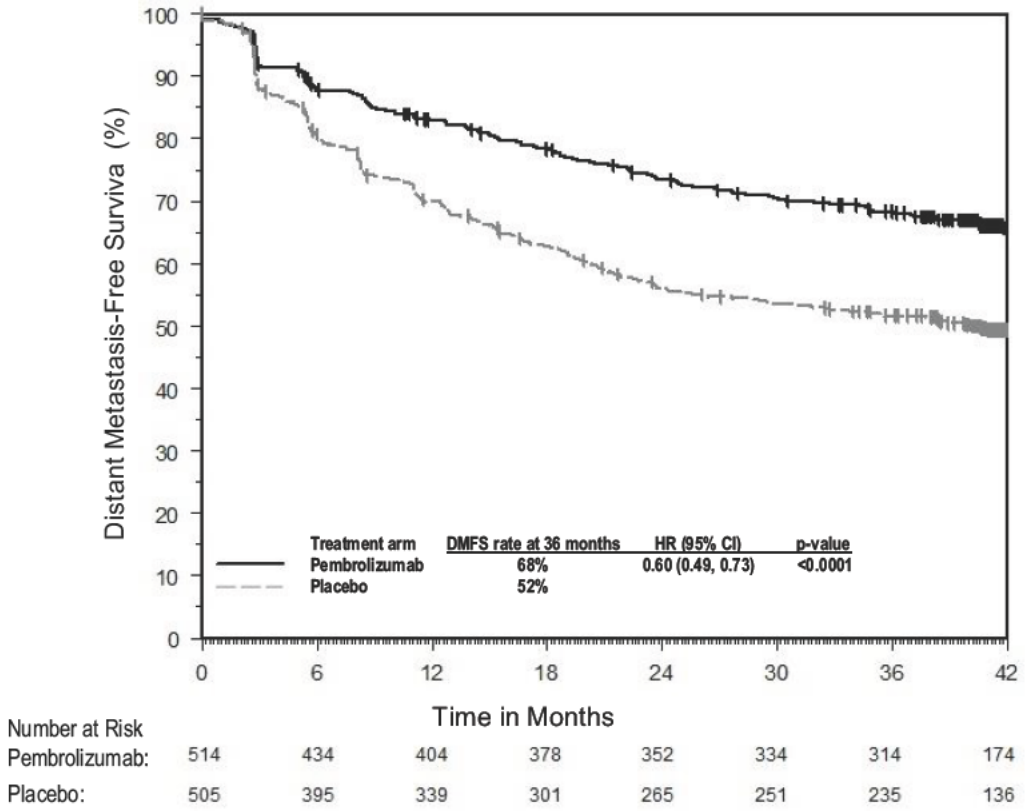


Figure 5: Kaplan-Meier curve for distant metastasis-free survival by treatment arm in KEYNOTE-054 (intent to treat population)



RFS and DMFS benefit was consistently demonstrated across subgroups, including tumour PD-L1 expression, BRAF mutation status, and stage of disease (using AJCC 7th edition). These results were consistent when reclassified in a post-hoc analysis according to the current AJCC 8th edition staging system.

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 11 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 11: 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 6: Kaplan-Meier curve for progression-free survival by treatment arm in KEYNOTE-024 (intent to treat population)

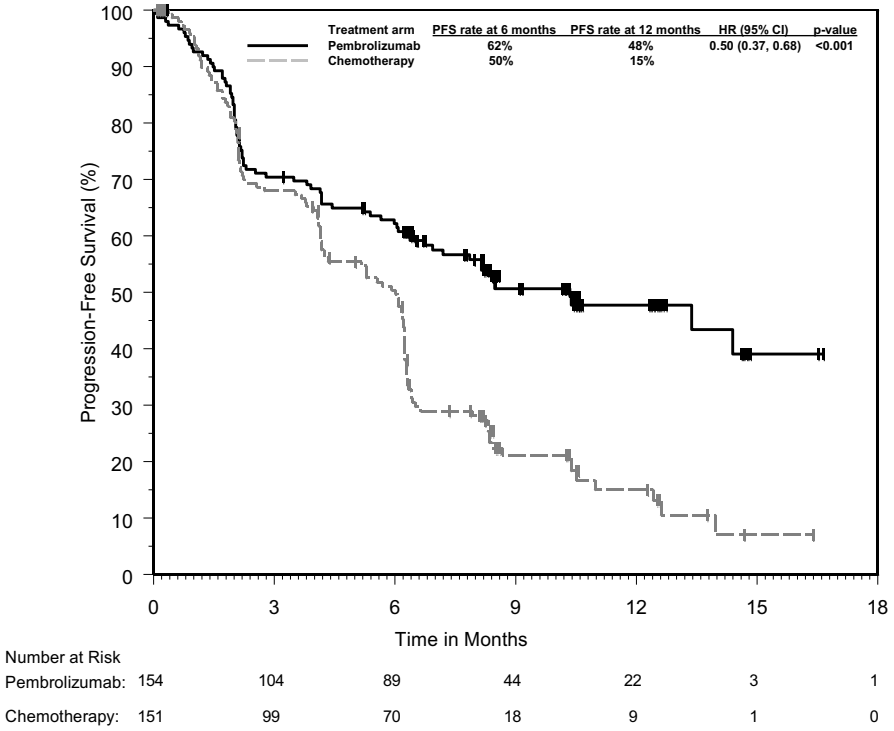
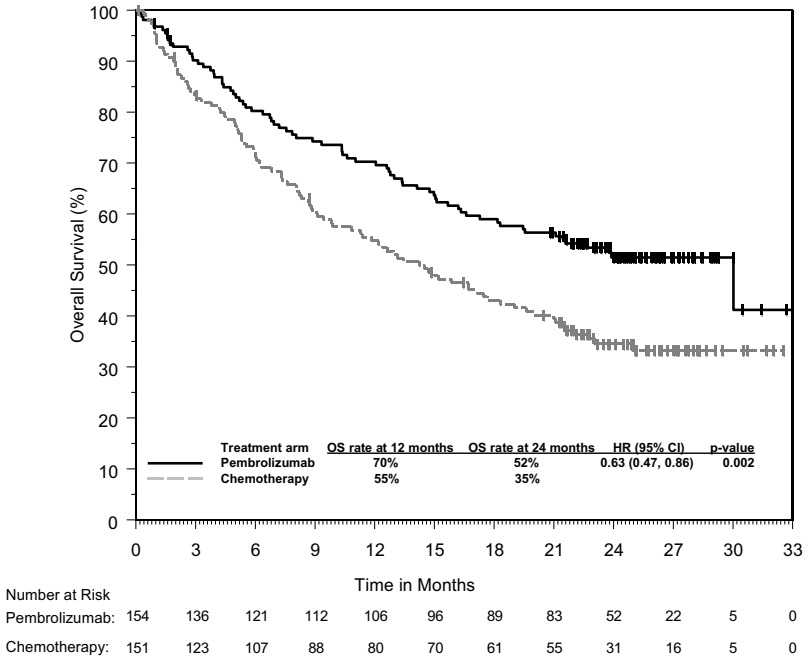


Figure 7: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-024 (intent to treat population)



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 12 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 8.

Table 12: Efficacy results (PD-L1 TPS ≥ 50%) in KEYNOTE-042

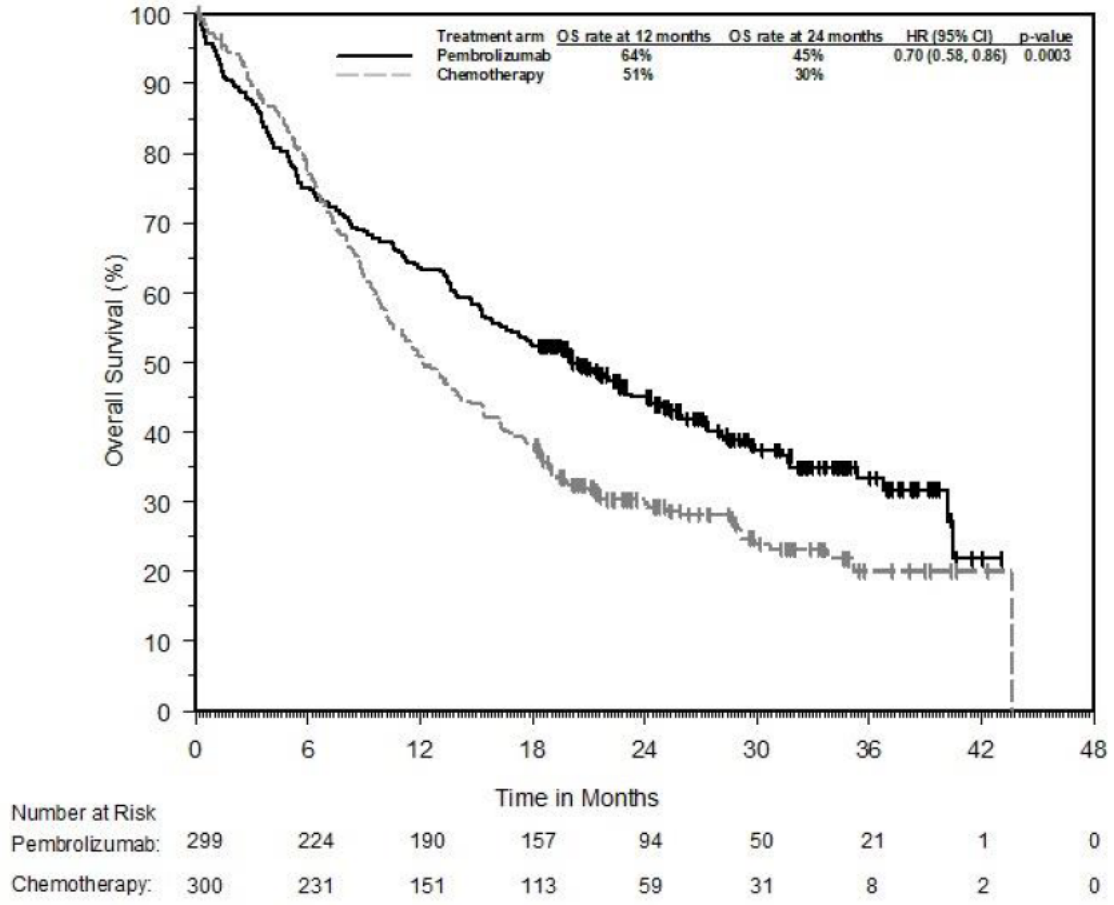
Endpoint	**Pembrolizumab 200 mg every 3 weeks n=299**	**Chemotherapy n=300**
OS		
Number (%) of patients with event	180 (60%)	220 (73%)
Hazard ratio* (95% CI)	0.70 (0.58, 0.86)	
p-Value†	0.0003	
Median in months (95% CI)	20.0 (15.9, 24.2)	12.2 (10.4, 14.6)
PFS		
Number (%) of patients with event	238 (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 8: 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 13 summarises key efficacy measures and Figures 9 and 10 show the Kaplan-Meier curves for OS and PFS based on the final analysis with a median follow-up of 18.8 months.

Table 13: 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 9: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-189 (intent to treat population)

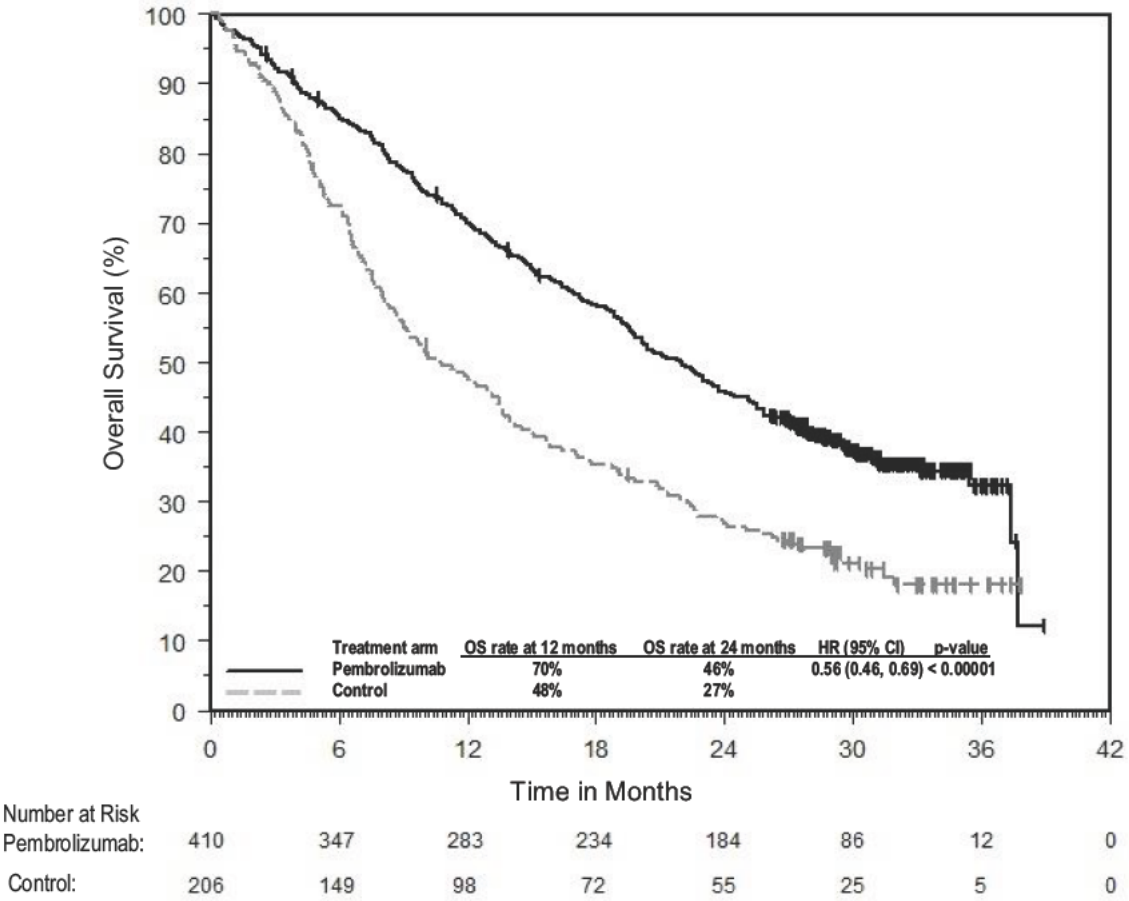
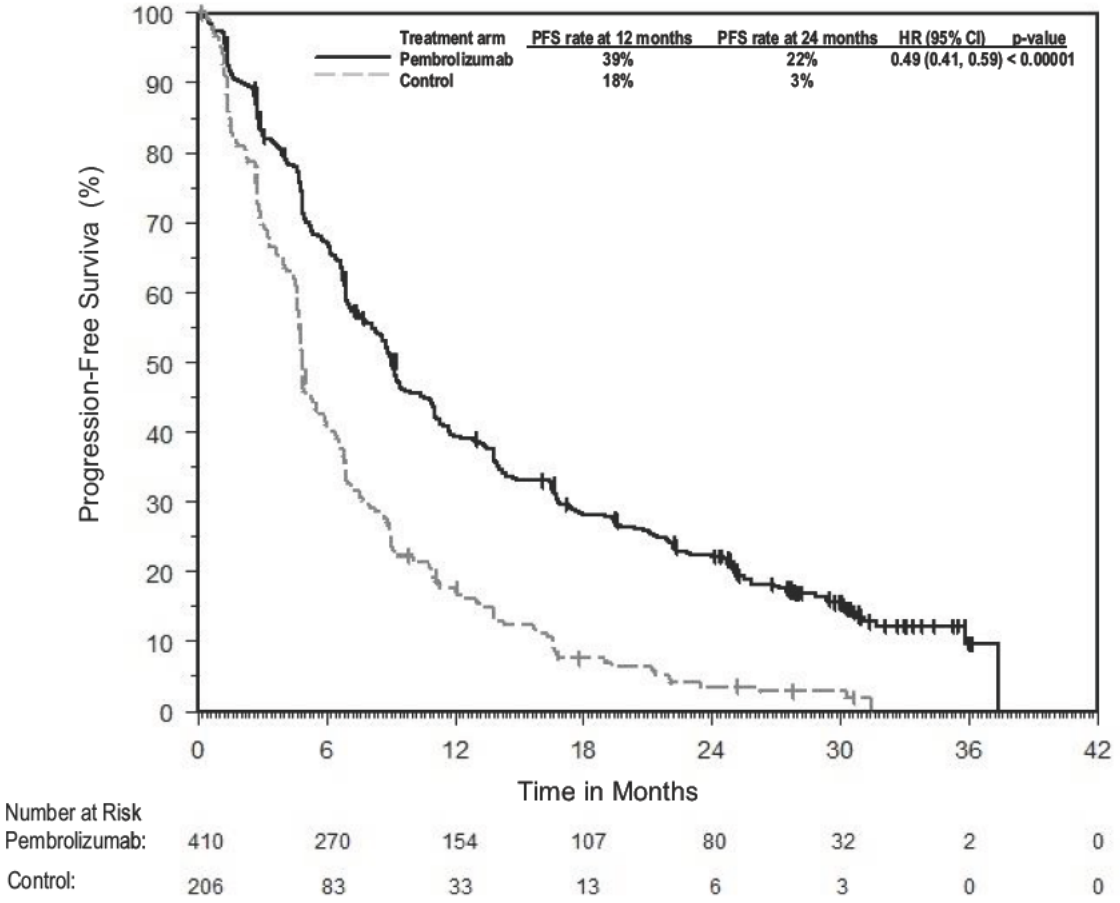


Figure 10: Kaplan-Meier curve for progression-free survival by treatment arm in KEYNOTE-189 (intent to treat population)



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 14).

Table 14: 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 15 summarises key efficacy measures and Figures 11 and 12 show the Kaplan-Meier curves for OS and PFS based on the final analysis with a median follow-up of 14.3 months.

Table 15: 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 11: Kaplan-Meier Curve for Overall Survival in KEYNOTE-407

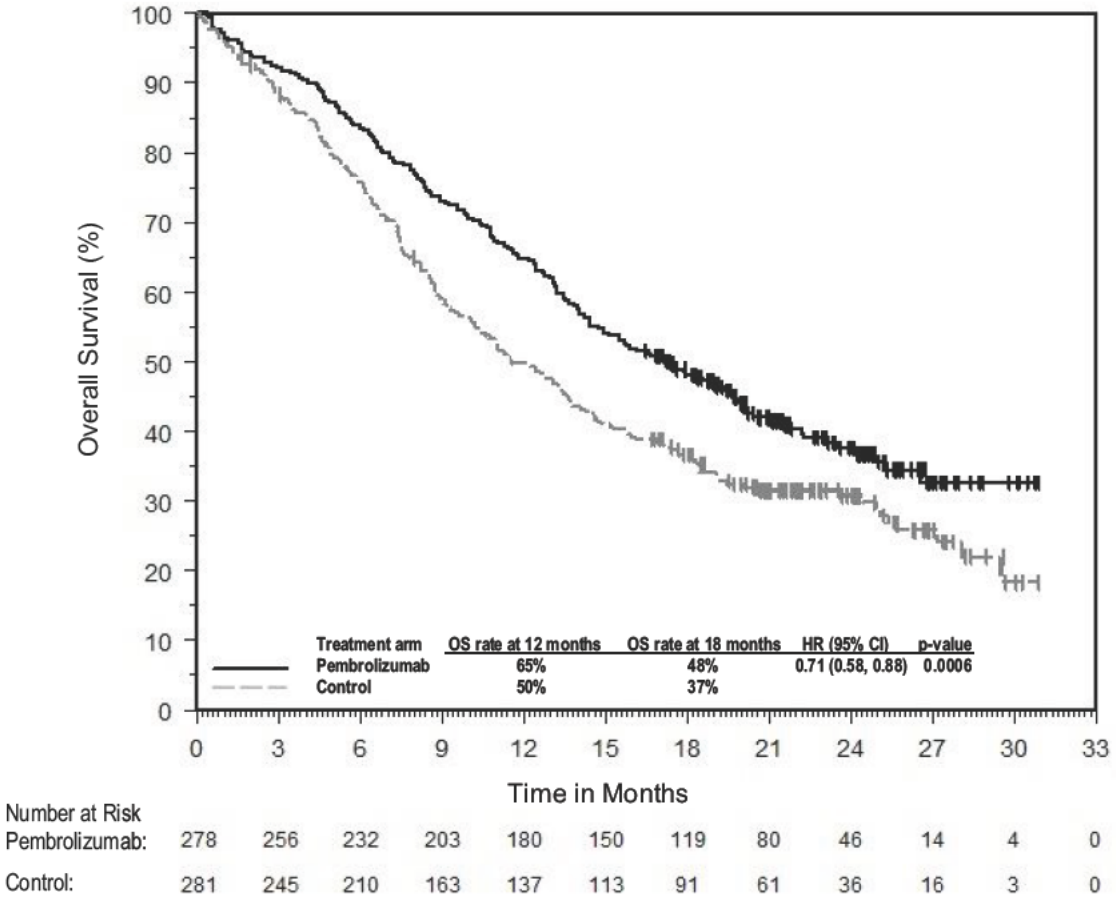
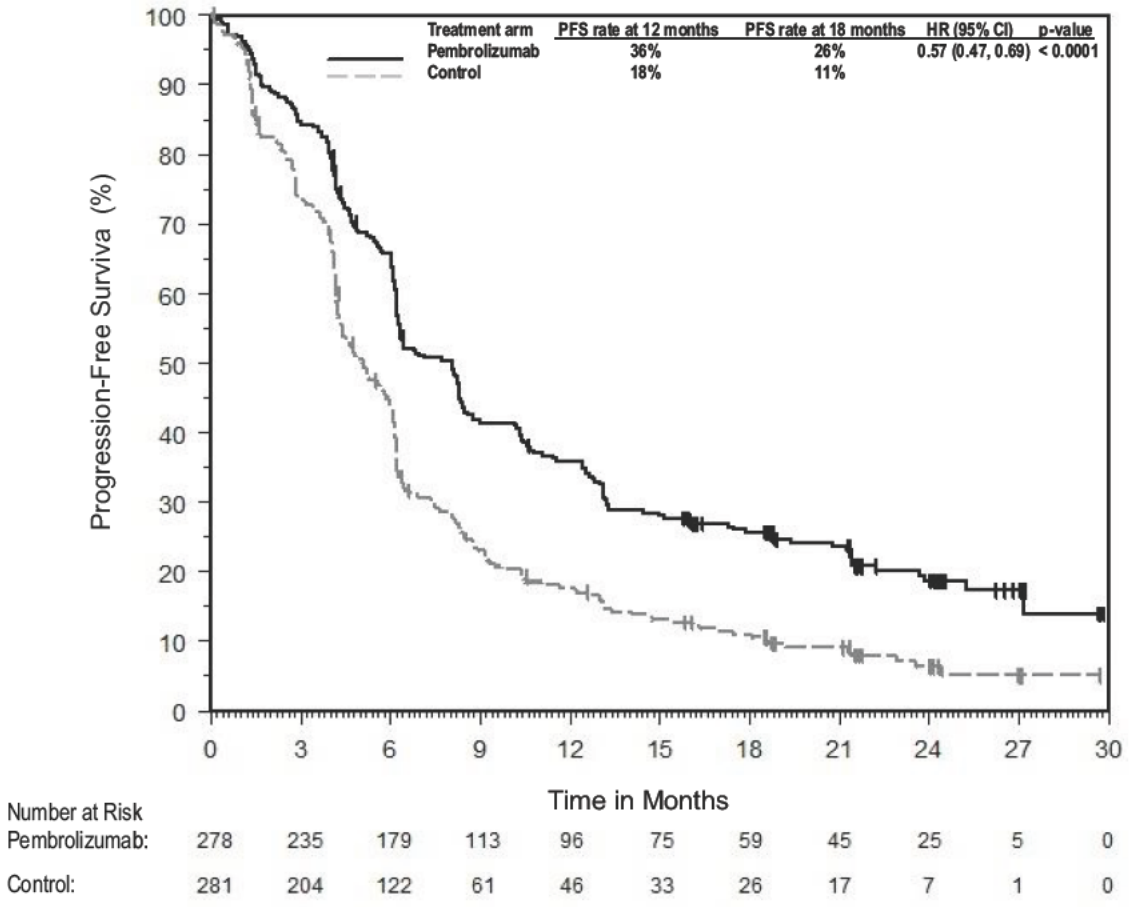


Figure 12: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-407



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 16).

Table 16: 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 bw (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 17 summarises key efficacy measures for the entire population (TPS ≥ 1%) and for the patients with TPS ≥ 50%, and Figure 13 shows the Kaplan-Meier curve for OS (TPS ≥ 1%), based on a final analysis with median follow-up of 42.6 months.

Table 17: Response to pembrolizumab 2 or 10 mg/kg bw every 3 weeks in previously treated patients with NSCLC in KEYNOTE-010

Endpoint	Pembrolizumab 2 mg/kg bw every 3 weeks	Pembrolizumab 10 mg/kg bw 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

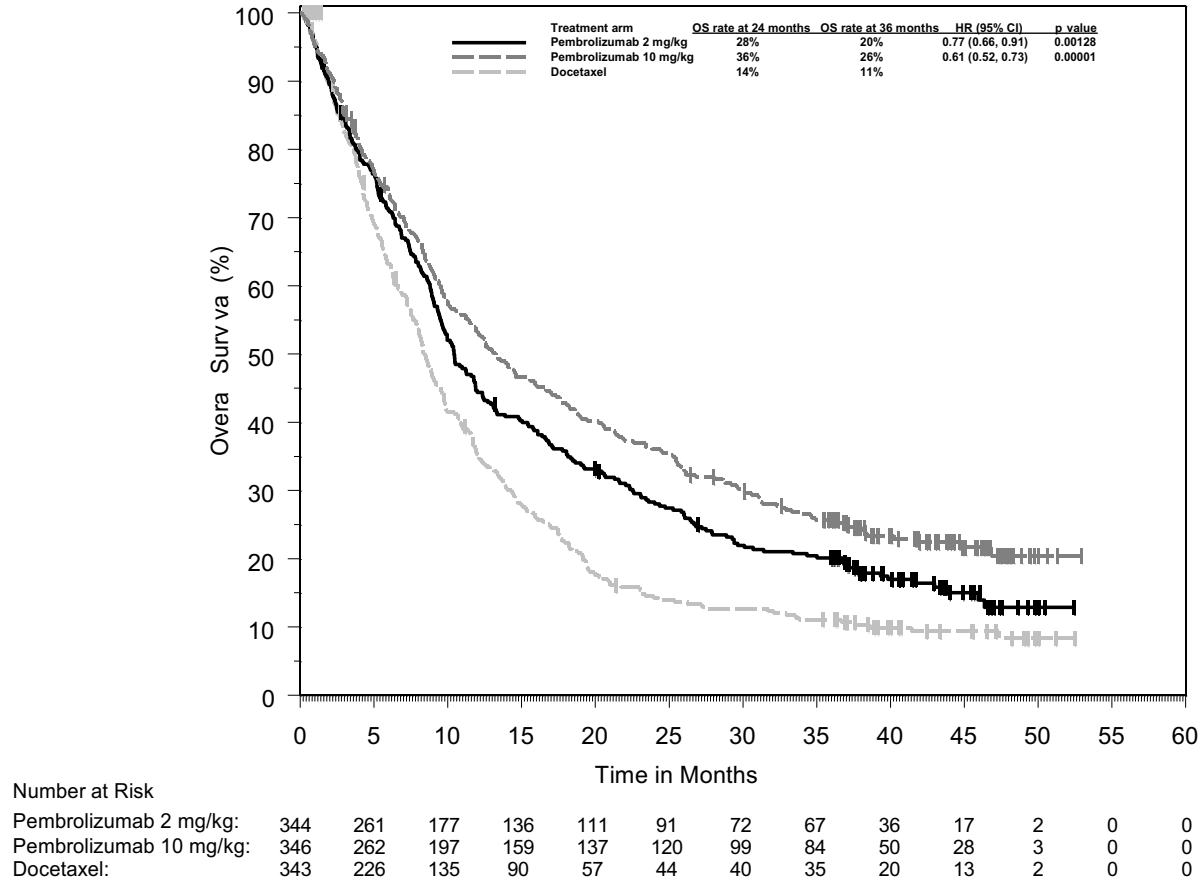
† Based on stratified log rank test

‡ 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 13: 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 bw and 10 mg/kg bw 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 bw 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.

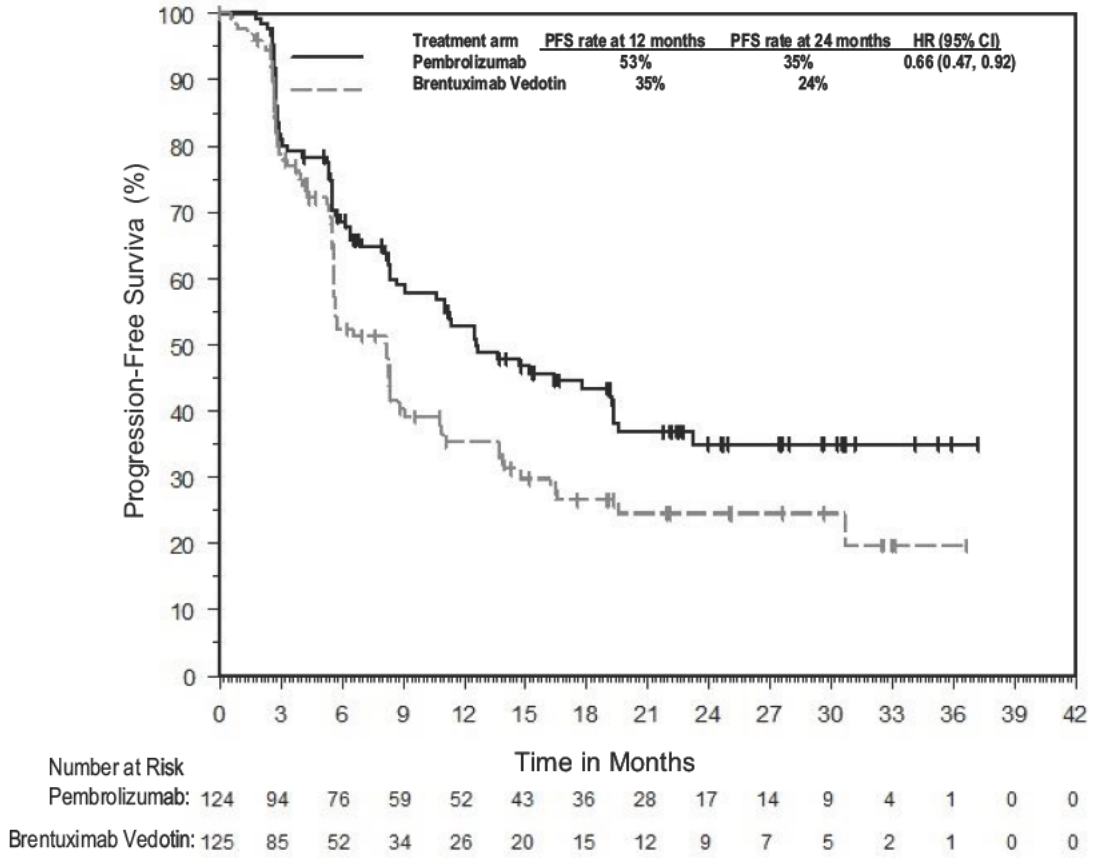
The primary efficacy outcome was PFS and the secondary efficacy outcome measure was ORR, both assessed by BICR according to the 2007 revised International Working Group (IWG) criteria. The additional primary efficacy outcome measure, OS, was not formally assessed at the time of the analysis. In the ITT 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 18 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 14.

Table 18: 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 bw 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 14: 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 bw 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 19.

Table 19: 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 bw 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%

[a] 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.

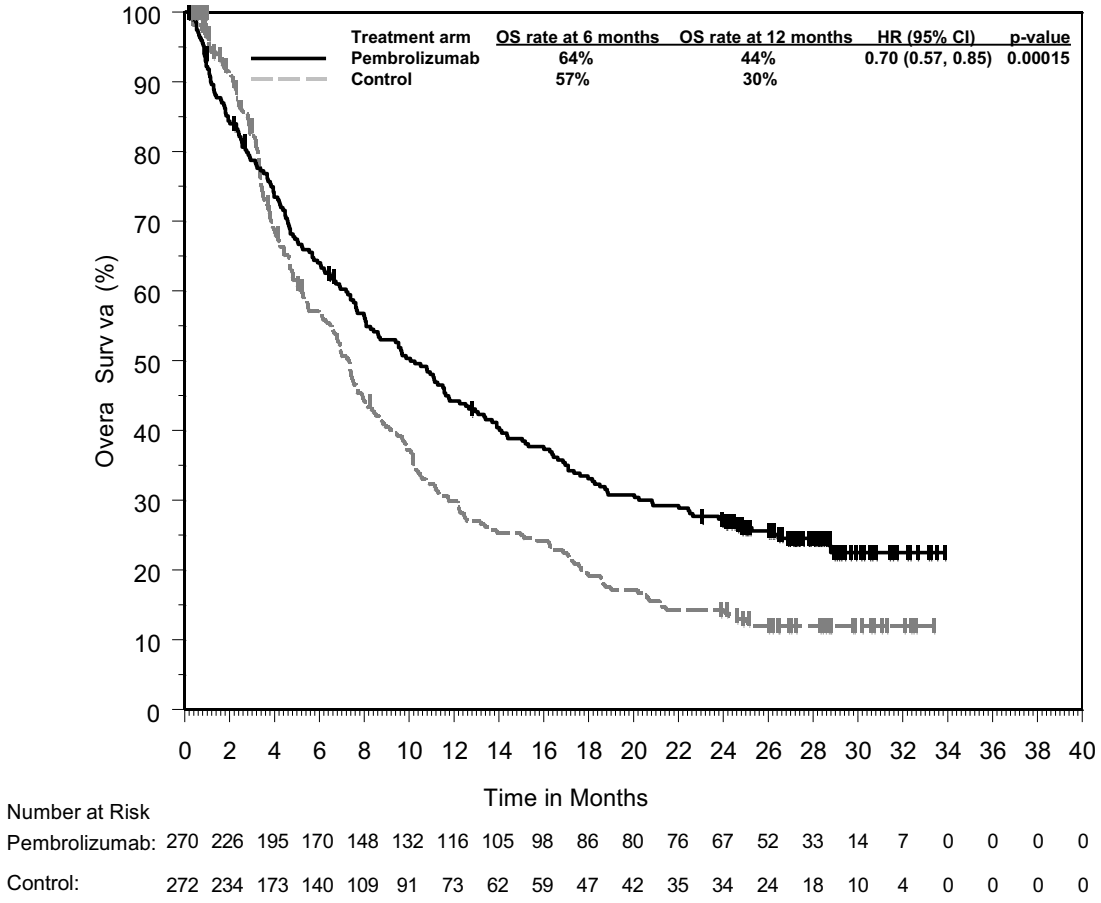
The primary efficacy outcomes were OS and PFS as assessed by BICR using RECIST v1.1. Secondary outcome measures were ORR (as assessed by BICR using RECIST v1.1) and duration of response. Table 20 summarises the key efficacy measures for the ITT population at the final analysis. The Kaplan-Meier curve based on the final analysis for OS is shown in Figure 15. 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 20: 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 15: 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 21).

Table 21: 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 patients ineligible for cisplatin-containing chemotherapy

The safety and efficacy of pembrolizumab were investigated in KEYNOTE-052, a multicentre, open-label study for the treatment of locally advanced or metastatic urothelial carcinoma in patients

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

Among 370 patients with urothelial carcinoma who were not eligible for cisplatin-containing chemotherapy baseline characteristics were: median age 74 years (82% age 65 or older); 77% male; and 89% White and 7% Asian. Eighty-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 22 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 22: 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 23).

Table 23: 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 a Phase III, randomised, controlled, open-label clinical study of pembrolizumab with or without platinum-based combination chemotherapy (i.e. either cisplatin or carboplatin with gemcitabine) versus chemotherapy as first-line treatment in subjects with advanced or metastatic urothelial carcinoma. Results of KEYNOTE-361 for pembrolizumab in combination with chemotherapy did not show statistically significant improvement in PFS as assessed by BICR using RECIST 1.1 (HR 0.78; 95% CI: 0.65, 0.93; p=0.0033), and OS (HR 0.86; 95% CI: 0.72, 1.02; p=0.0407) versus chemotherapy alone. Per the pre-specified hierarchical testing order no formal tests for statistical significance of pembrolizumab versus chemotherapy could be performed. The key efficacy results of pembrolizumab monotherapy in patients for whom carboplatin rather than cisplatin was selected by the investigator as the better choice of chemotherapy were consistent with KEYNOTE-052 results. Efficacy results in patients whose tumours express PD-L1 with CPS ≥ 10 were similar to the overall population for whom carboplatin was selected as the choice of chemotherapy. See Table 24 and Figures 16 and 17.

Table 24: Response to pembrolizumab 200 mg every 3 weeks or chemotherapy in patients with previously untreated urothelial carcinoma for whom carboplatin rather than cisplatin was selected by the investigator as the better choice of chemotherapy in KEYNOTE-361

Endpoint	Pembrolizumab n=170	Chemotherapy n=196	Pembrolizumab CPS ≥ 10 n=84	Chemotherapy CPS ≥ 10 n=89
Objective response rate*				
ORR %, (95% CI)	28% (21.1, 35.0)	42% (34.8, 49.1)	30% (20.3, 40.7)	46% (35.4, 57.0)
Complete response	10%	11%	12%	18%
Partial response	18%	31%	18%	28%
Response duration*				
Median in months (range)	NR (3.2+, 36.1+)	6.3 (1.8+, 33.8+)	NR (4.2, 36.1+)	8.3 (2.1+, 33.8+)
% with duration ≥ 12 months†	57%	30%	63%	38%
PFS*				
Median in months (95% CI)	3.2 (2.2, 5.5)	6.7 (6.2, 8.1)	3.9 (2.2, 6.8)	7.9 (6.1, 9.3)
12-month PFS rate	25%	24%	26%	31%
OS				
Median in months (95% CI)	14.6 (10.2, 17.9)	12.3 (10.0, 15.5)	15.6 (8.6, 19.7)	13.5 (9.5, 21.0)
12-month OS rate	54%	51%	57%	54%

* Assessed by BICR using RECIST 1.1

† Based on Kaplan Meier estimation

Figure 16: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-361 (intent to treat population, choice of carboplatin)

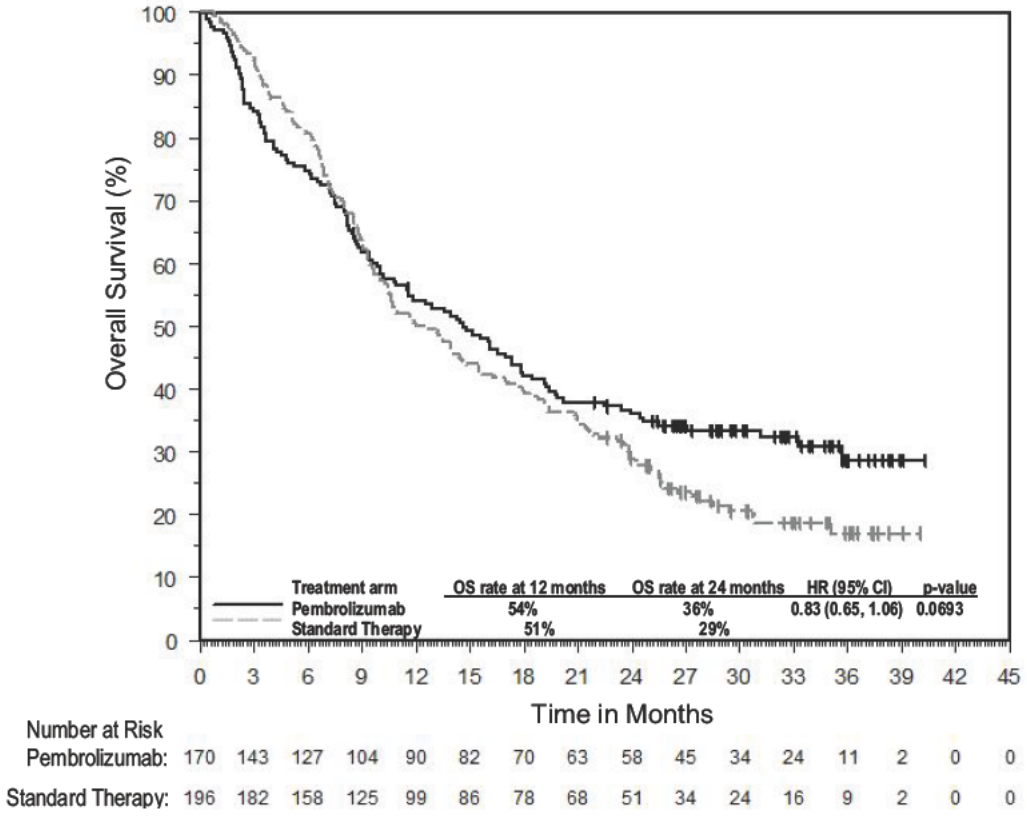
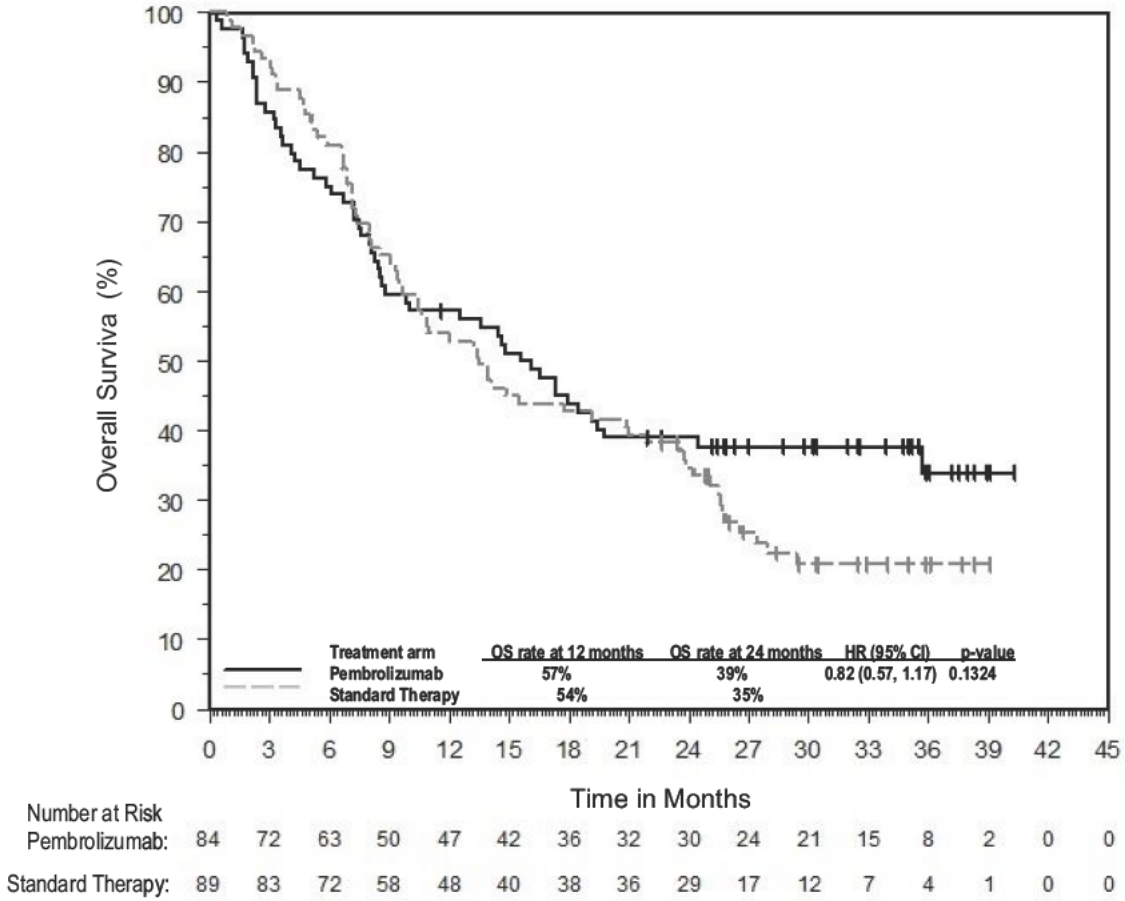


Figure 17: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-361 (patients with PD-L1 expression CPS ≥ 10, intent to treat population, choice of carboplatin)



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/m2 every 3 weeks, and 5-FU 1,000 mg/m2/d 4 days continuous every 3 weeks (maximum of 6 cycles of platinum and 5-FU)
- Cetuximab 400 mg/m2 load then 250 mg/m2 once weekly, carboplatin AUC 5 mg/mL/min every 3 weeks or cisplatin 100 mg/m2 every 3 weeks, and 5-FU 1,000 mg/m2/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 18 and 19.

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

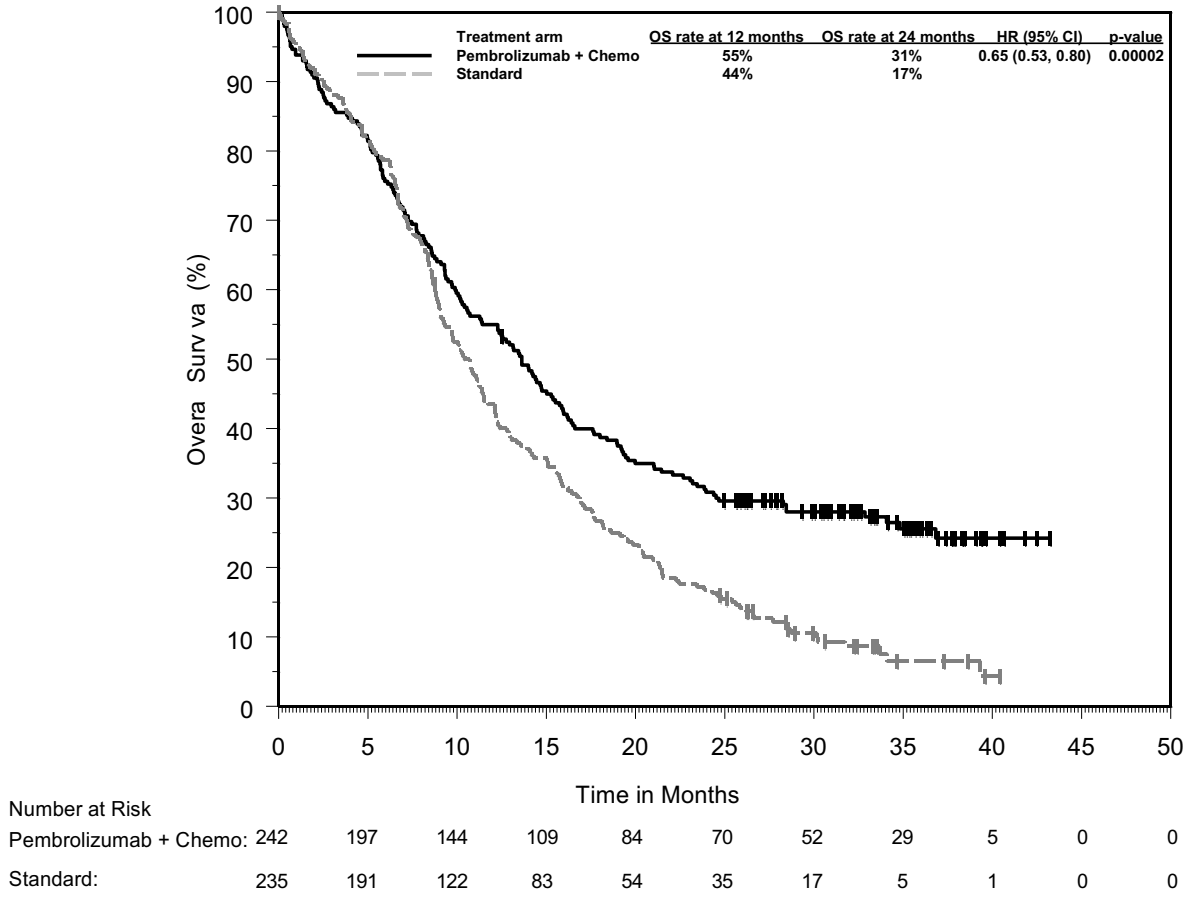
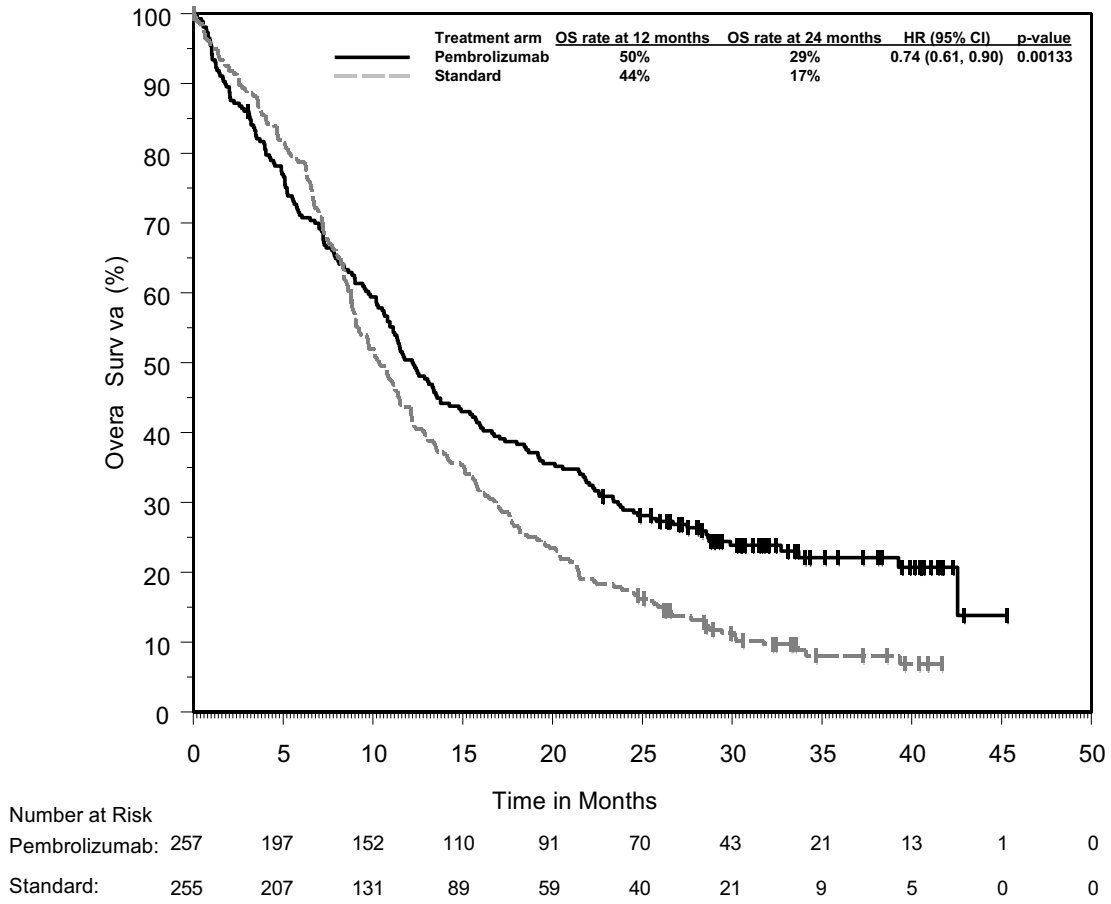


Table 26: Efficacy results for pembrolizumab as monotherapy in KEYNOTE-048 with PD-L1 expression (CPS ≥ 1)

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 19: 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)

Endpoint	Pembrolizumab + Platinum Chemotherapy + 5-FU n=126	Standard Treatment* n=110	Pembrolizumab Monotherapy n=133	Standard Treatment* n=122
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^{TM} 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.

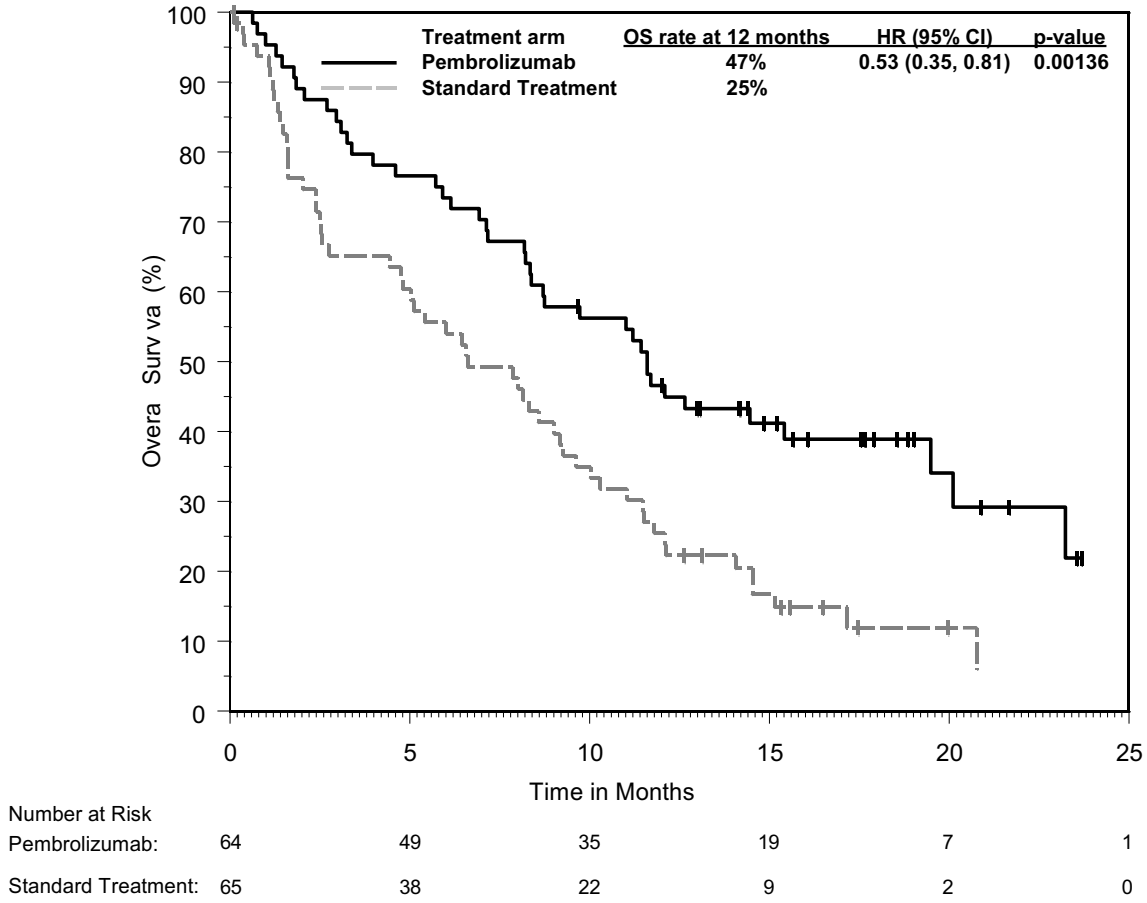
The primary efficacy outcome was OS in the ITT population. The initial analysis resulted in a HR for OS of 0.82 (95% CI: 0.67, 1.01) with a one-sided p-Value of 0.0316. The median OS was 8.4 months for pembrolizumab compared to 7.1 months for standard treatment. Table 29 summarises the key efficacy measures for the TPS ≥ 50% population. The Kaplan-Meier curve for OS for the TPS ≥ 50% population is shown in Figure 20.

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 20: 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.

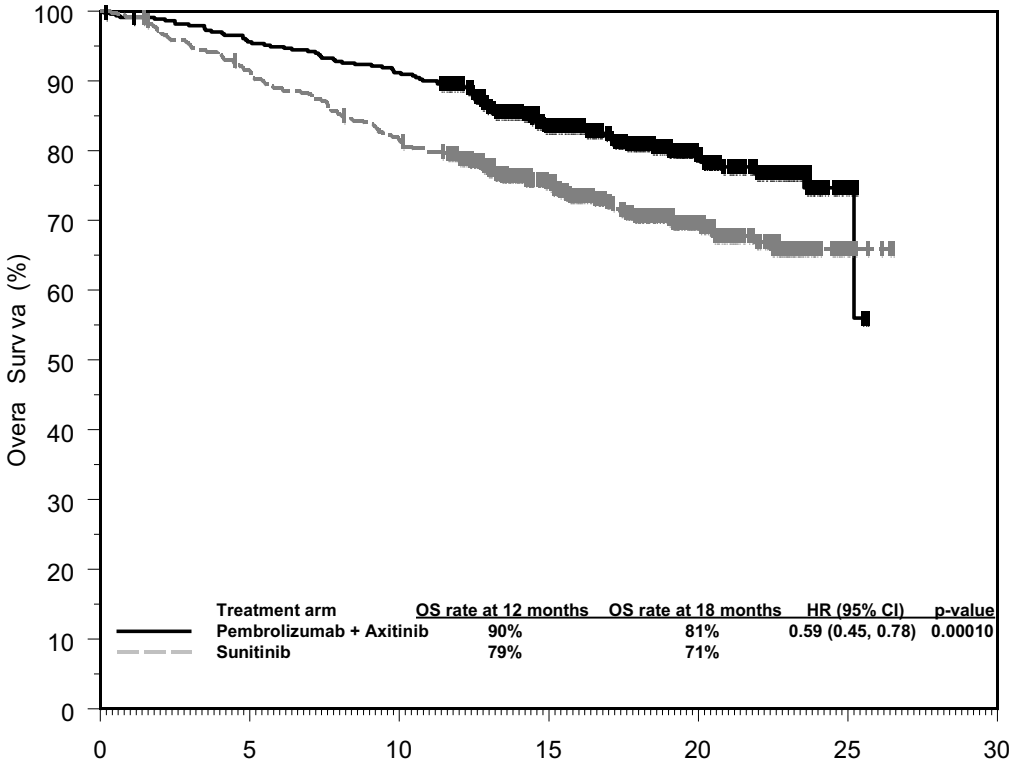
The primary efficacy outcome measures were OS and PFS (as assessed by BICR using RECIST 1.1). Secondary efficacy outcome measures were ORR and response duration, as assessed by BICR using RECIST 1.1. The median follow-up time was 12.8 months (range: 0.1 to 21.5 months). Table 30 summarises key efficacy 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 21 and 22.

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

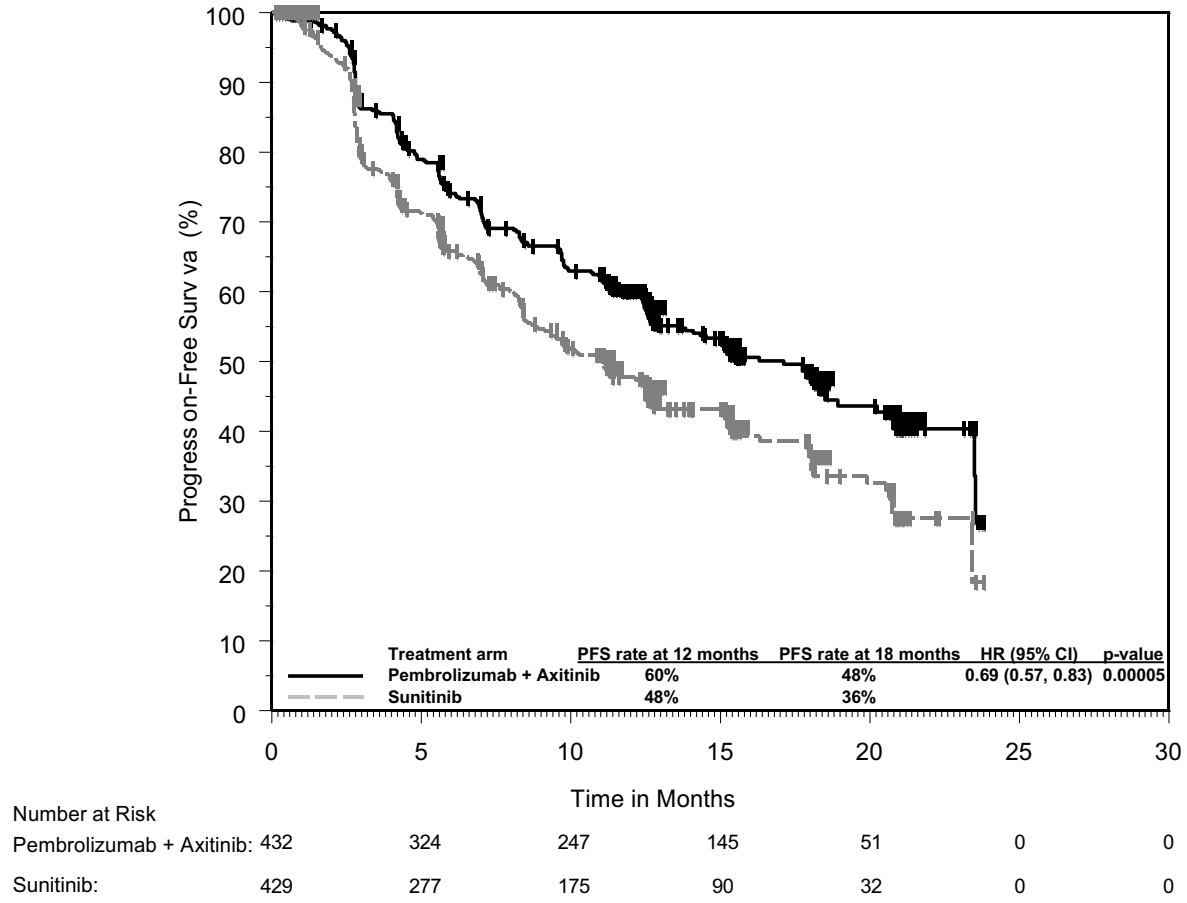
Figure 21: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-426 (intent to treat population)*



Number at Risk							
Pembrolizumab + Axitinib:	432	411	392	275	133	9	0
Sunitinib:	429	389	346	230	111	6	0

*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 22: 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)

Endpoint	Pembrolizumab + Axitinib N = 432	Sunitinib N = 429	Pembrolizumab + Axitinib vs. Sunitinib
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 bw 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 bw 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 23 and 24.

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

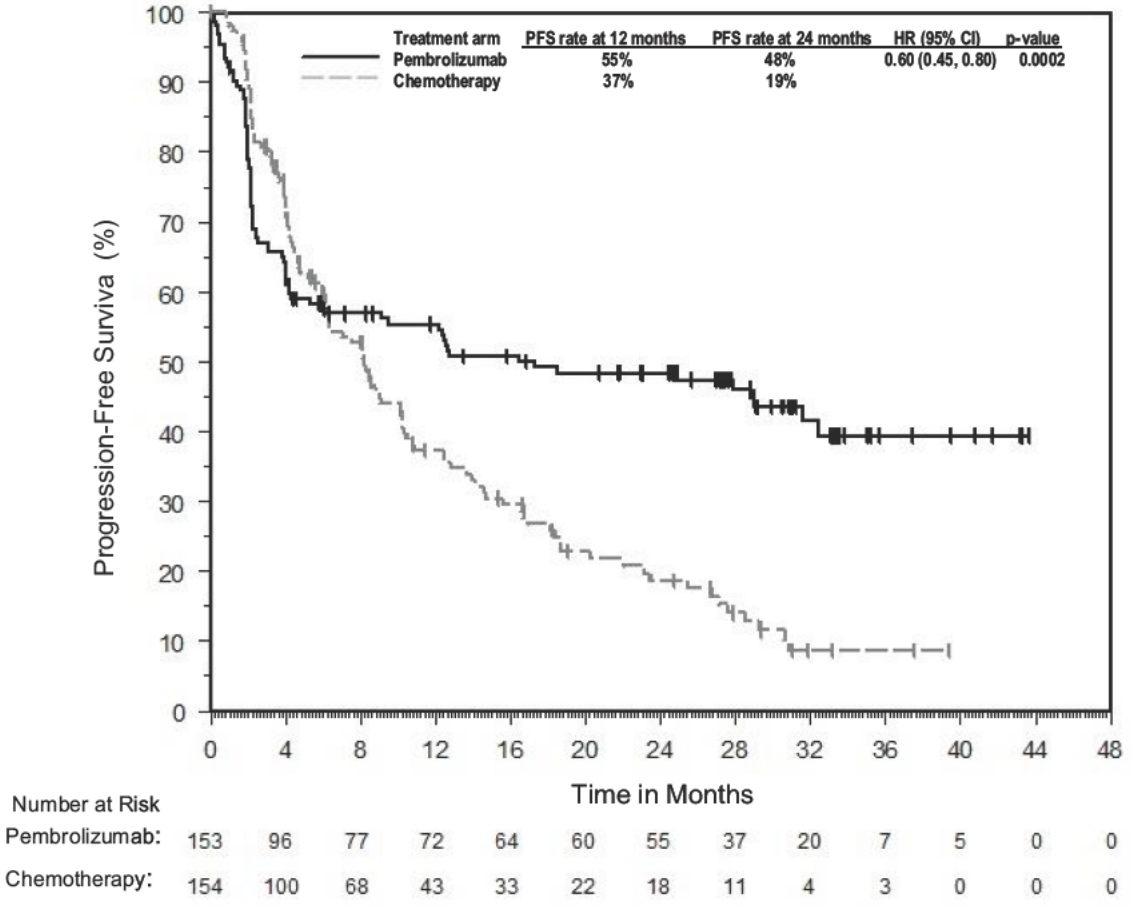
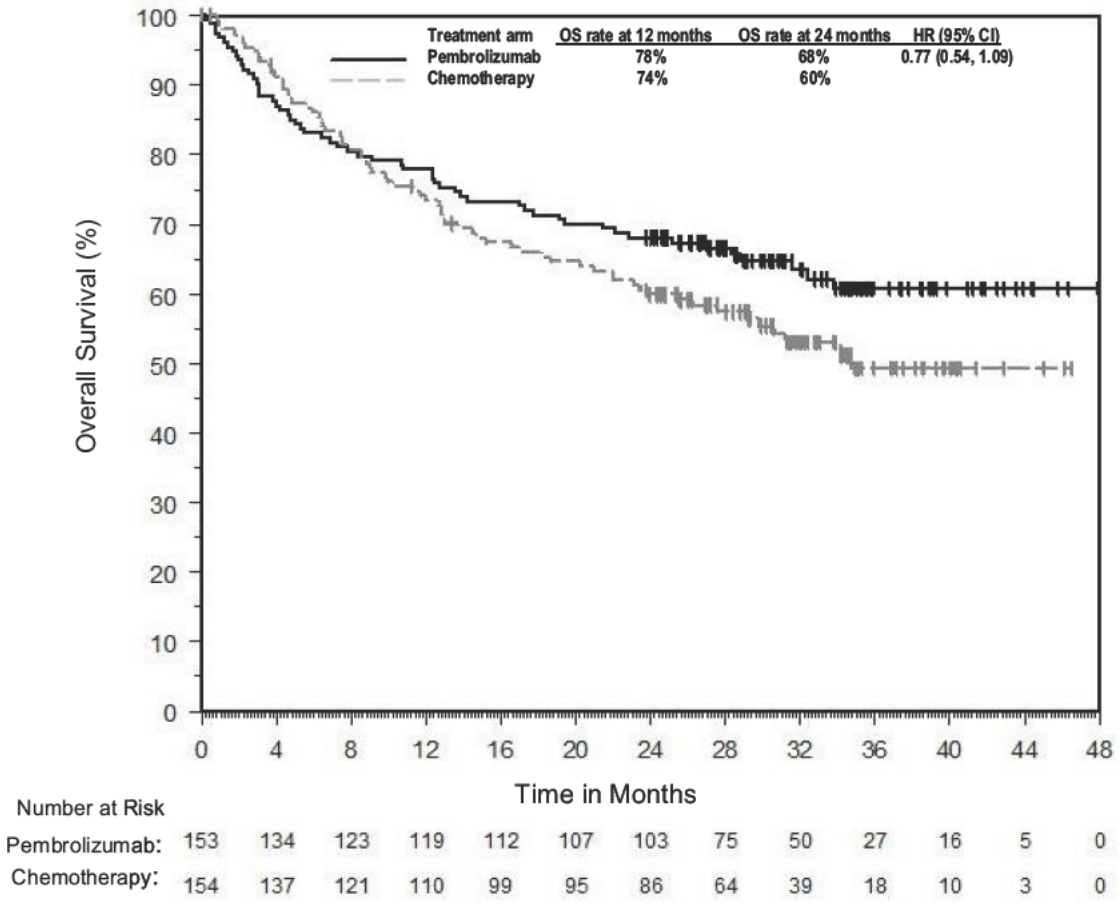


Figure 24: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-177 (intent to treat population)



Oesophageal Carcinoma

KEYNOTE-590: Controlled study of combination therapy in oesophageal carcinoma patients naïve to treatment

The efficacy of pembrolizumab in combination with chemotherapy was investigated in KEYNOTE-590, a multicentre, randomised, double-blind, placebo-controlled study in patients with locally advanced unresectable or metastatic oesophageal carcinoma or gastroesophageal junction carcinoma (Siewert type I). Patients with active autoimmune disease, a medical condition that required immunosuppression, or known HER-2 positive GEJ adenocarcinoma patients were ineligible for the study. Randomisation was stratified by tumour histology (squamous cell carcinoma vs. adenocarcinoma), geographic region (Asia vs. ex-Asia), and ECOG performance status (0 vs. 1).

Patients were randomised (1:1) to one of the following treatment arms:

- Pembrolizumab 200 mg on Day 1 of each three-week cycle in combination with cisplatin 80 mg/m^2 IV on Day 1 of each three-week cycle for up to six cycles and 5-FU 800 mg/m^2 IV per day on Day 1 to Day 5 of each three-week cycle, or per local standard for 5-FU administration.
- Placebo on Day 1 of each three-week cycle in combination with cisplatin 80 mg/m^2 IV on Day 1 of each three-week cycle for up to six cycles and 5-FU 800 mg/m^2 IV per day on Day 1 to Day 5 of each three-week cycle, or per local standard for 5-FU administration.

Treatment with pembrolizumab or chemotherapy continued until unacceptable toxicity or disease progression or a maximum of 24 months. Patients randomised to pembrolizumab were permitted to continue beyond the first RECIST v1.1-defined disease progression if clinically stable until the first radiographic evidence of disease progression was confirmed at least 4 weeks later with repeat imaging. Assessment of tumour status was performed every 9 weeks.

Among the 749 patients in KEYNOTE-590, 383 (51%) had tumours that expressed PD-L1 with a CPS ≥ 10 based on the PD-L1 IHC 22C3 pharmDx™ Kit. The baseline characteristics of these 383 patients were: median age of 63 years (range: 28 to 89), 41% age 65 or older; 82% male; 34% White and 56% Asian; 43% and 57% had an ECOG performance status of 0 and 1, respectively. Ninety-three percent had M1 disease. Seventy-five percent had a tumour histology of squamous cell carcinoma, and 25% had adenocarcinoma.

The primary efficacy outcome measures were OS and PFS as assessed by the investigator according to RECIST 1.1 in squamous cell histology, CPS ≥ 10, and in all patients. The study demonstrated a statistically significant improvement in OS and PFS for all pre-specified study populations. In all patients randomised to pembrolizumab in combination with chemotherapy, compared to chemotherapy the OS HR was 0.73 (95% CI 0.62-0.86) and the PFS HR was 0.65 (95% CI 0.55-0.76). Secondary efficacy outcome measures were ORR and DoR, according to RECIST 1.1 as assessed by the investigator. Table 33 summarises key efficacy measures from the pre-specified analysis in patients whose tumours expressed PD-L1 with a CPS ≥ 10 in KEYNOTE-590 performed at a median follow-up time of 13.5 months (range: 0.5 to 32.7 months). The Kaplan-Meier curve for OS and PFS are shown in Figures 25 and 26.

Table 33: Efficacy Results for pembrolizumab plus chemotherapy in KEYNOTE-590 with PD-L1 expression (CPS ≥ 10)

Endpoint	Pembrolizumab Cisplatin Chemotherapy 5-FU n=186	Standard Treatment* n=197
OS		
Number (%) of patients with event	124 (66.7%)	165 (83.8%)
Median in months† (95% CI)	13.5 (11.1, 15.6)	9.4 (8.0, 10.7)
Hazard ratio‡ (95% CI)	0.62 (0.49, 0.78)	
p-Value§	< 0.0001	
PFS¶		
Number (%) of patients with event	140 (75.3)	174 (88.3)
Median in months† (95% CI)	7.5 (6.2, 8.2)	5.5 (4.3, 6.0)
Hazard ratio‡ (95% CI)	0.51 (0.41, 0.65)	
p-Value§	< 0.0001	
Objective response rate¶		
Objective response rate§ (95% CI)	51.1 (43.7, 58.5)	26.9 (20.8, 33.7)
Complete response	5.9%	2.5%
Partial response	45.2%	24.4%
p-Value#	< 0.0001	
Response duration¶, Þ		
Median in months (range)	10.4 (1.9, 28.9+)	5.6 (1.5+, 25.0+)
% with duration ≥ 6 months†	80.2%	47.7%
% with duration ≥ 12 months†	43.7%	23.2%
% with duration ≥ 18 months†	33.4%	10.4%

* Cisplatin and 5 FU
† Based on Kaplan Meier estimation
‡ Based on the stratified Cox proportional hazard model
§ One sided p Value based on log rank test stratified by geographic region (Asia versus Rest of the World) and tumour histology (Adenocarcinoma versus Squamous Cell Carcinoma) and ECOG performance status (0 versus 1)
¶ Assessed by investigator using RECIST 1.1
# One sided p Value for testing. H0: difference in % = 0 versus H1: difference in % > 0
Þ Best objective response as confirmed complete response or partial response.

A total of 32 patients aged ≥ 75 years for PD-L1 CPS ≥ 10 were enrolled in KEYNOTE-590 (18 in the pembrolizumab combination and 14 in the control). Data about efficacy and safety of pembrolizumab in combination with chemotherapy are too limited in this patient population.

Figure 25: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-590 with PD-L1 expression (CPS ≥ 10)

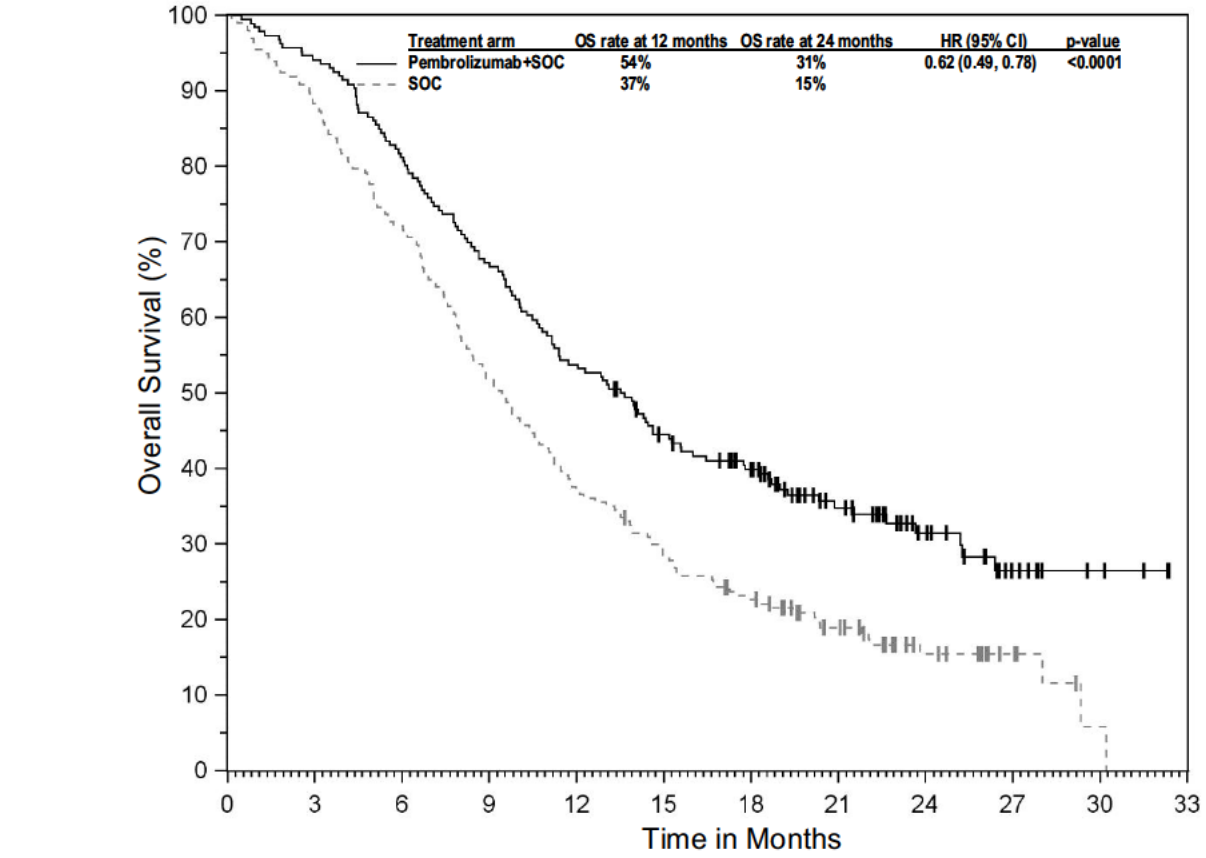
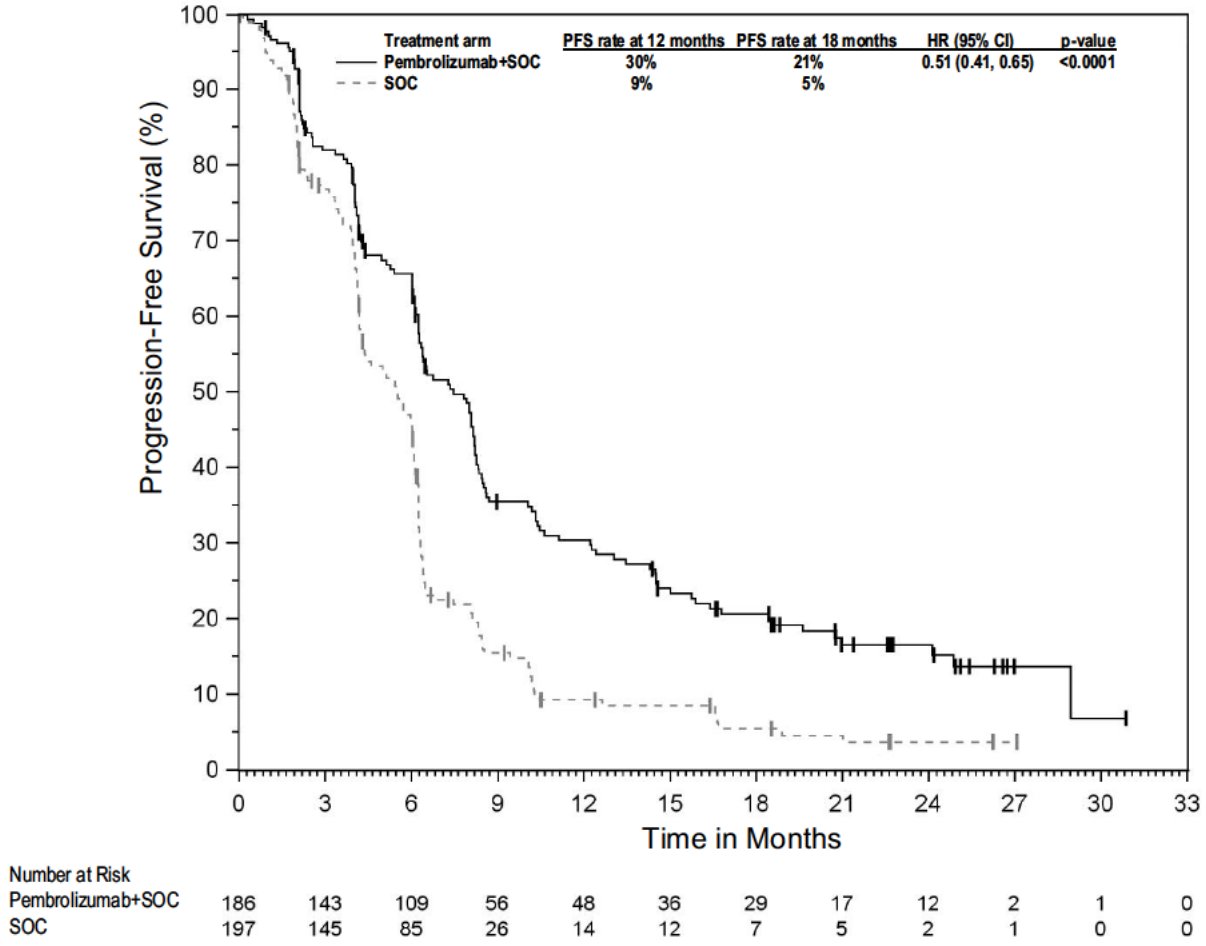


Figure 26: Kaplan-Meier curve for progression-free survival by treatment arm in KEYNOTE-590 with PD-L1 expression (CPS ≥ 10)



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 bw every 2 weeks, 2 to 10 mg/kg bw 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 bw 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 bw 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 bw 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 bw 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 bw, which produced exposure multiples of 19 and 94 times the exposure in humans at doses of 10 and 2 mg/kg bw, 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 2ºC to 8ºC. 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 2ºC to 8ºC. 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

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1024/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 July 2015
Date of latest renewal: 24 March 2020

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

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

Name and address of the manufacturers of the biological active substance

AstraZeneca Pharmaceuticals LP
Frederick Manufacturing Center (FMC)
633 Research Court
Frederick, Maryland 21703
U.S.

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

MSD Biotech B.V.
Vollenhovermeer 2
5347 JV Oss
The Netherlands

Boehringer Ingelheim Fremont, Inc. (BIF)
6701 Kaiser Drive
Fremont, California 94555
U.S.

Name and address of the manufacturers responsible for batch release

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

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

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

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

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

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

The educational programme is aimed at increasing the awareness of patients and/or their caregivers on the signs and symptoms relevant to the early recognition/identification of the potential immune-related adverse reactions (irARs).

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

The patient educational material should contain:
- Patient Information Brochure
- The patient alert card

The Patient Information Brochure and patient alert card shall contain the following key elements:
- Description of the main signs or symptoms of the irARs and the importance of notifying their treating physician immediately if symptoms occur
- The importance of not attempting to self-treat any symptoms without consulting their healthcare professional first
- The importance of carrying the patient alert card at all times and to show it at all medical visits to healthcare professionals other than the prescriber (e.g. emergency healthcare professionals).

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

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

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

Description	Due date
1. Post-authorisation efficacy study (PAES): The MAH should submit the final study report for study P087, A Phase II Clinical Trial of MK-3475 (Pembrolizumab) in Subjects with Relapsed or Refractory (R/R) Classical Hodgkin Lymphoma (cHL) – Final Study Report	3Q 2021
2. Post-authorisation efficacy study (PAES): The MAH should submit the final study report for study P204: A Phase III, Randomised, Open-label, Clinical Trial to Compare Pembrolizumab with Brentuximab Vedotin in Subjects with Relapsed or Refractory Classical Hodgkin Lymphoma – Final Study Report	4Q 2025
3. The value of biomarkers to predict the efficacy of pembrolizumab should be further explored, specifically: Additional biomarkers other than PD-L1 expression status by Immunohistochemistry (IHC) (e.g. PD-L2, RNA signature, etc.) predictive of pembrolizumab efficacy should be investigated together with more information regarding the pattern of expression of PD-L1 obtained in the ongoing HNSCC study (KN040) and resected Stage II melanoma adjuvant study (KN716): • Genomic analyses using whole exome sequencing and/or RNAseq (e.g. Nanostring RNA gene signature) • IHC staining for PD-L2 • Data on RNA and proteomic serum profiling	 4Q 2021 4Q 2024
4. Post-authorisation efficacy study (PAES) the MAH should submit the final study report of RFS/DMFS and OS data for study KN054: a Phase III Clinical Trial of Pembrolizumab (MK-3475) in Subjects with complete resection of high-risk Stage III melanoma – Final Study Report	4Q 2023
5. Post-authorisation efficacy study (PAES): The MAH should submit the final study report for study P426: A Phase III Randomised, Open-label Study to Evaluate Efficacy and Safety of Pembrolizumab (MK-3475) in combination with Axitinib versus Sunitinib Monotherapy as a First-line Treatment for Locally Advanced or Metastatic Renal Cell Carcinoma (mRCC)	3Q 2021
6. Post-authorisation efficacy study (PAES): The MAH should submit the final study report for study KN177: A Phase III study evaluating the efficacy and safety of pembrolizumab monotherapy versus globally-accepted SOC therapies for CRC in participants with locally confirmed dMMR or MSI-H unresectable or metastatic CRC who have not received prior chemotherapy for unresectable or metastatic CRC	3Q 2021

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

KEYTRUDA 50 mg powder for concentrate for solution for infusion
pembrolizumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

powder for concentrate for solution for infusion
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

The reconstituted vials and/or diluted intravenous bags may be stored for a cumulative time of up to 96 hours in a refrigerator (2°C – 8°C).

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C).

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

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

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

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

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

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

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

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not shake.

8. EXPIRY DATE

EXP

The diluted solution may be stored for up to 96 hours in a refrigerator (2°C – 8°C).

9. SPECIAL STORAGE CONDITIONS

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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

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

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

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

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

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

KEYTRUDA 50 mg powder for concentrate for solution for infusion
pembrolizumab

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

What is in this leaflet

1. What KEYTRUDA is and what it is used for
2. What you need to know before you are given KEYTRUDA
3. How you are given KEYTRUDA
4. Possible side effects
5. How to store KEYTRUDA
6. Contents of the pack and other information

1. What KEYTRUDA is and what it is used for

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

KEYTRUDA is used in adults to treat:
- a kind of skin cancer called melanoma
- a kind of lung cancer called non-small cell lung cancer
- a kind of cancer called classical Hodgkin lymphoma
- a kind of cancer called bladder cancer (urothelial carcinoma)
- a kind of head and neck cancer called head and neck squamous cell carcinoma
- a kind of kidney cancer called renal cell carcinoma
- a kind of cancer called colon or rectal cancer that is determined to be microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)
- a kind of cancer called oesophageal carcinoma.

KEYTRUDA is used in children and adolescents aged 3 years and older to treat:
- a kind of cancer called classical Hodgkin lymphoma.

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

People get KEYTRUDA after they have had surgery to remove melanoma to help prevent their cancer from coming back (adjuvant therapy).

KEYTRUDA may be given in combination with other anti-cancer medicines. It is important that you also read the package leaflets for these other medicines. If you have any questions about these medicines, ask your doctor.

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

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

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

Before you get KEYTRUDA, tell your doctor if you:
- have an autoimmune disease (a condition where the body attacks its own cells)
- have pneumonia or inflammation of your lungs (called pneumonitis)
- were previously given ipilimumab, another medicine for treating melanoma, and experienced serious side effects because of that medicine
- had an allergic reaction to other monoclonal antibody therapies
- have or have had chronic viral infection of the liver, including hepatitis B (HBV) or hepatitis C (HCV)
- have human immunodeficiency virus (HIV) infection or acquired immune deficiency syndrome (AIDS)
- have liver damage
- have kidney damage
- have had a solid organ transplant or a bone marrow (stem cell) transplant that used donor stem cells (allogeneic)

When you get KEYTRUDA, you can have some serious side effects. These side effects can sometimes become life-threatening and can lead to death. These side effects may happen anytime during treatment or even after your treatment has ended. You may experience more than one side effect at the same time.

If you have any of the following conditions, call or see your doctor right away. Your doctor may give you other medicines in order to prevent more severe complications and reduce your symptoms. Your doctor may withhold the next dose of KEYTRUDA or stop your treatment with KEYTRUDA.
- inflammation of the lungs, which may include shortness of breath, chest pain or coughing
- inflammation of the intestines, which may include diarrhoea or more bowel movements than usual, black, tarry, sticky stools or stools with blood or mucus, severe stomach pain or tenderness, nausea, vomiting
- inflammation of the liver, which may include nausea or vomiting, feeling less hungry, pain on the right side of stomach, yellowing of skin or whites of eyes, dark urine or bleeding or bruising more easily than normal
- inflammation of the kidneys, which may include changes in the amount or colour of your urine
- inflammation of hormone glands (especially the thyroid, pituitary and adrenal glands), which may include rapid heartbeat, weight loss, increased sweating, weight gain, hair loss, feeling cold, constipation, deeper voice, muscle aches, dizziness or fainting, headaches that will not go away or unusual headache
- type 1 diabetes, which may include feeling more hungry or thirsty than usual, need to urinate more often or weight loss
- inflammation of the eyes, which may include changes in eyesight
- inflammation in the muscles, which may include muscle pain or weakness
- inflammation of the heart muscle, which may include shortness of breath, irregular heartbeat, feeling tired, or chest pain
- inflammation of the pancreas, which may include abdominal pain, nausea and vomiting
- inflammation of the skin, which may include rash, itching, skin blistering, peeling or sores, and/or ulcers in mouth or in lining of nose, throat, or genital area
- an immune disorder that can affect the lungs, skin, eyes and/or lymph nodes (sarcoidosis)
- inflammation of the brain, which may include confusion, fever, memory problems or seizures (encephalitis)
- pain, numbness, tingling, or weakness in the arms or legs; bladder or bowel problems including needing to urinate more frequently, urinary incontinence, difficulty urinating and constipation (myelitis)
- inflammation and scarring of the bile ducts, which may include pain in the upper right part of the stomach, swelling of the liver or spleen, fatigue, itching, or yellowing of the skin or the whites of eyes (cholangitis sclerosing)

- inflammation of the stomach (gastritis)
- infusion reactions, which may include shortness of breath, itching or rash, dizziness or fever

Complications, including graft-versus-host-disease (GVHD), in people with bone marrow (stem cell) transplant that uses donor stem cells (allogeneic). These complications can be severe and can lead to death. They may occur if you had this kind of transplant in the past or if you get it in the future. Your doctor will monitor you for signs and symptoms, which may include skin rash, liver inflammation, abdominal pain, or diarrhoea.

Children and adolescents
Do not give KEYTRUDA to children under 18 years of age, except for children with classical Hodgkin lymphoma aged 3 years and older.

Other medicines and KEYTRUDA
Tell your doctor
- If you are taking other medicines that make your immune system weak. Examples of these may include corticosteroids, such as prednisone. These medicines may interfere with the effect of KEYTRUDA. However, once you are treated with KEYTRUDA, your doctor may give you corticosteroids to reduce the side-effects that you may have with KEYTRUDA. Corticosteroids may also be given to you before receiving KEYTRUDA in combination with chemotherapy to prevent and/or treat nausea, vomiting, and other side effects caused by chemotherapy.
- If you are taking, have recently taken or might take any other medicines.

Pregnancy
- You must not use KEYTRUDA if you are pregnant unless your doctor specifically recommends it.
- If you are pregnant, think you may be pregnant or are planning to have a baby, tell your doctor.
- KEYTRUDA can cause harm or death to your unborn baby.
- If you are a woman who could become pregnant, you must use adequate birth control while you are being treated with KEYTRUDA and for at least 4 months after your last dose.

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

Driving and using machines
KEYTRUDA has a minor effect on your ability to drive or use machines. Feeling dizzy, tired or weak are possible side effects of KEYTRUDA. Do not drive or use machines after you have been given KEYTRUDA unless you are sure you are feeling well.

3. How you are given KEYTRUDA

KEYTRUDA will be given to you in a hospital or clinic under the supervision of a doctor experienced in cancer treatment.
- The recommended dose of KEYTRUDA in adults is either 200 mg every 3 weeks or 400 mg every 6 weeks.
- The recommended dose of KEYTRUDA in children and adolescents aged 3 years and older with classical Hodgkin lymphoma, is 2 mg/kg bodyweight (up to a maximum of 200 mg) every 3 weeks.
- Your doctor will give you KEYTRUDA through an infusion into your vein (intravenous) for about 30 minutes.
- Your doctor will decide how many treatments you need.

If you miss an appointment to get KEYTRUDA
- Call your doctor right away to reschedule your appointment.

- It is very important that you do not miss a dose of this medicine.

If you stop receiving KEYTRUDA
Stopping your treatment may stop the effect of the medicine. Do not stop treatment with KEYTRUDA unless you have discussed this with your doctor.

If you have any further questions about your treatment, ask your doctor.

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

4. Possible side effects

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

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

The following side effects have been reported with pembrolizumab alone:

Very common (may affect more than 1 in 10 people)
- decrease in the number of red blood cells
- reduced thyroid gland activity
- feeling less hungry
- headache
- shortness of breath; cough
- diarrhoea; stomach pain; nausea; vomiting; constipation
- itching; skin rash
- pain in muscle and bones; joint pain
- feeling tired; unusual tiredness or weakness; swelling; fever

Common (may affect up to 1 in 10 people)
- lung infection
- decrease in the number of platelets (bruising or bleeding more easily); decrease in the number of white blood cell (neutrophils; lymphocytes)
- reactions related to the infusion of the medicine
- overactive thyroid gland activity; hot flush; inflammation of the thyroid
- decreased sodium, potassium, or calcium in the blood
- trouble sleeping
- dizziness; inflammation of the nerves causing numbness, weakness, tingling or burning pain of the arms and legs; lack of energy; change in your sense of taste
- dry eye
- abnormal heart rhythm
- high blood pressure
- inflammation of the lungs
- inflammation of the intestines; dry mouth
- red raised rash sometimes with blisters; patches of skin which have lost colour; inflammation of the skin; dry, itchy skin; hair loss; acne-like skin problem
- muscle pain, aches or tenderness; pain in arms or legs; joint pain with swelling
- chills; flu-like illness
- increased liver enzyme levels in the blood; increased calcium in the blood; abnormal kidney function test

Uncommon (may affect up to 1 in 100 people)
- a decreased number of white blood cells (leukocytes and eosinophils)
- an immune disorder that can affect the lungs, skin, eyes and/or lymph nodes (sarcoidosis)

- inflammation of the pituitary gland situated at the base of the brain; decreased secretion of hormones produced by the adrenal glands
- type 1 diabetes
- seizure
- inflammation of the eyes; eye pain, irritation, itchiness or redness; uncomfortable sensitivity to light; seeing spots
- inflammation of the heart muscle, which may present as shortness of breath, irregular heartbeat, feeling tired, or chest pain
- inflammation of the covering of the heart; accumulation of fluid around the heart
- inflammation of the pancreas
- inflammation of the stomach
- a sore that develops on the inside lining of your stomach or upper part of your small intestine
- inflammation of the liver
- thickened, sometimes scaly, skin growth; hair colour changes; small skin bumps, lumps or sores
- inflammation of the sheath that surrounds tendons
- inflammation of the kidneys
- increased level of amylase, an enzyme that breaks down starch

Rare (may affect up to 1 in 1,000 people)
- inflammation response against platelets or red blood cells; feeling weak, lightheaded, short of breath or if your skin looks pale (signs of low level of red blood cells, possibly due to a type of anaemia called pure red cell aplasia); a condition called haemophagocytic lymphohistiocytosis, where the immune system makes too many infection fighting cells called histiocytes and lymphocytes that may cause various symptoms
- inflammation of the brain, which may present as confusion, fever, memory problems or seizures (encephalitis)
- a temporary inflammation of the nerves that causes pain, weakness, and paralysis in the extremities; a condition in which the muscles become weak and tire easily
- pain, numbness, tingling, or weakness in the arms or legs; bladder or bowel problems including needing to urinate more frequently, urinary incontinence, difficulty urinating and constipation (myelitis)
- inflammation of the membrane around the spinal cord and brain, which may present as neck stiffness, headache, fever, eye sensitivity to light, nausea or vomiting (meningitis)
- inflammation of the blood vessels
- a hole in the small intestines
- inflammation of the bile ducts
- tender red bumps under the skin
- itching, skin blistering, peeling or sores, and/or ulcers in mouth or in lining of nose, throat, or genital area (toxic epidermal necrolysis or Stevens-Johnson syndrome)
- disease in which the immune system attacks the glands that make moisture for the body, such as tears and saliva (Sjogren's syndrome)
- inflammation of the bladder. Signs and symptoms may include frequent and/or painful urination, urge to pass urine, blood in urine, pain or pressure in lower abdomen

The following side effects have been reported in clinical studies with pembrolizumab in combination with chemotherapy:

Very common (may affect more than 1 in 10 people)
- lung infection
- decrease in the number of red blood cells
- decreased number of white blood cells; decrease in the number of platelets (bruising or bleeding more easily)
- decreased thyroid gland activity
- decreased sodium or potassium in the blood; feeling less hungry
- trouble sleeping
- dizziness; inflammation of the nerves causing numbness, weakness, tingling or burning pain of the arms and legs; headache

- shortness of breath; cough
- nausea; diarrhoea; vomiting; stomach pain; constipation
- skin rash; itching; hair loss
- pain in the muscles and bones; joint pain
- unusual tiredness or weakness; swelling; fever
- abnormal kidney function test

Common (may affect up to 1 in 10 people)
- decreased number of white blood cells (neutrophils) with a fever
- reaction related to the infusion of the medicine
- increased thyroid gland activity
- decreased calcium in the blood
- change in your sense of taste; feeling tired
- dry eye
- abnormal heart rhythm
- inflammation of the blood vessels; high blood pressure
- inflammation of the lungs
- inflammation of the intestines; dry mouth; inflammation of the stomach
- inflammation of the liver
- red raised rash, sometimes with blisters; inflammation of the skin
- muscle pain, aches or tenderness; joint pain with swelling; pain in arms or legs
- sudden kidney damage
- flu-like illness; chills
- increased blood levels of a liver enzyme known as aspartate aminotransferase; increased calcium in the blood; increased blood levels of a liver enzyme known as alanine aminotransferase; increased blood levels of a liver enzyme known as alkaline phosphatase; increased bilirubin in the blood

Uncommon (may affect up to 1 in 100 people)
- a decreased number of white blood cells (eosinophils)
- inflammation of the pituitary gland situated at the base of the brain; inflammation of the thyroid; decreased secretion of hormones produced by the adrenal glands
- type 1 diabetes
- inflammation of the brain; seizure
- inflammation of the heart muscle, which may present as shortness of breath, irregular heartbeat, feeling tired, or chest pain; accumulation of fluid around the heart
- inflammation of the pancreas
- a sore that develops on the inside lining of your stomach or upper part of your small intestine
- thickened, sometimes scaly, skin growth; patches of skin that have lost colour; acne-like skin problem; dry, itchy skin; small skin bumps, lumps or sores
- inflammation of the sheath that surrounds tendons
- inflammation of the kidneys
- increased level of amylase, an enzyme that breaks down starch

Rare (may affect up to 1 in 1,000 people)
- condition known as Guillain- Barré syndrome, which causes muscle weakness on both sides of the body, and can be severe
- inflammation of the covering of the heart
- inflammation of the bile ducts
- hair colour changes
- disease in which the immune system attacks the glands that make moisture for the body, such as tears and saliva (Sjogren's syndrome)

The following side effects have been reported in clinical studies with pembrolizumab in combination with axitinib:

Very common (may affect more than 1 in 10 people)
- thyroid gland problems
- feeling less hungry
- headache; change in your sense of taste
- high blood pressure
- shortness of breath; cough; hoarseness
- diarrhoea; stomach pain; nausea; vomiting; constipation
- blisters or rash on palms of hands or soles of feet; skin rash; itching
- feeling tired; unusual tiredness or weakness; fever
- increased liver enzyme levels in the blood; abnormal kidney function test
- pain in the muscles and bones; joint or muscle pain, aches or tenderness; pain in arms or legs

Common (may affect up to 1 in 10 people)
- lung infection
- decrease in the number of red blood cells; decreased number of white blood cells (neutrophils, leukocytes); decrease in the number of platelets (bruising or bleeding more easily)
- reaction related to the infusion of the medicine
- inflammation of the pituitary gland situated at the base of the brain; inflammation of the thyroid; decreased secretion of hormones produced by the adrenal glands
- decreased potassium, sodium or calcium in the blood
- trouble sleeping
- dizziness; lack of energy; inflammation of the nerves causing numbness, weakness, tingling or burning pain of the arms and legs
- dry eye
- abnormal heart rhythm
- inflammation of the lungs
- inflammation of the intestines; dry mouth; inflammation of the stomach
- red raised rash, sometimes with blisters; acne-like skin problem; inflammation of the skin; dry, itchy skin; hair loss
- inflammation of the liver
- muscle pain, aches or tenderness; joint or muscle pain with swelling; inflammation of the sheath that surrounds tendons
- sudden kidney damage; inflammation of the kidneys
- swelling; flu-like illness; chills
- increased calcium in the blood; increased liver enzyme levels in the blood

Uncommon (may affect up to 1 in 100 people)
- decreased number of white blood cells (lymphocytes and eosinophils)
- type 1 diabetes
- a condition in which the muscles become weak and tire easily
- inflammation of the heart muscle, which may present as shortness of breath, irregular heartbeat, feeling tired, or chest pain
- inflammation of the eyes; eye pain, irritation, itchiness or redness; uncomfortable sensitivity to light; seeing spots
- inflammation of the pancreas
- a sore that develops on the inside lining of your stomach or upper part of your small intestine
- hair colour changes; thickened, sometimes scaly, skin growth; small skin bumps, lumps or sores; patches of skin that have lost colour
- increased level of amylase, an enzyme that breaks down starch
- disease in which the immune system attacks the glands that make moisture for the body, such as tears and saliva (Sjogren's syndrome)

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

5. How to store KEYTRUDA

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

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

Store in a refrigerator (2°C – 8°C).

From a microbiological point of view, the reconstituted or diluted solution should be used immediately. The reconstituted or diluted solution must not be frozen. If not used immediately, chemical and physical in-use stability of KEYTRUDA has been demonstrated for 96 hours at 2°C to 8°C. This 96-hour total hold from reconstitution may include up to 6 hours at room temperature (at or below 25°C). If refrigerated, the vials and/or intravenous bags must be allowed to come to room temperature prior to use.

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

6. Contents of the pack and other information

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

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

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

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

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2031 BN Haarlem
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Manufacturer
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

Other sources of information

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

The following information is intended for healthcare professionals only:

Preparation and administration

- Prior to reconstitution, the vial of lyophilised powder can be out of refrigeration (temperatures at or below 25°C) for up to 24 hours.
- Aseptically add 2.3 mL of water for injections to yield a 25 mg/mL (pH 5.2-5.8) solution of KEYTRUDA. Each vial contains an excess fill of 10 mg (0.4 mL) to ensure the recovery of 50 mg of KEYTRUDA per vial. After reconstitution, 1 mL of concentrate contains 25 mg of pembrolizumab.
- To avoid foaming, deliver the water along the walls of the vial and not directly on the lyophilised powder.
- Slowly swirl the vial to allow reconstitution of the lyophilised powder. Allow up to 5 minutes for the bubbles to clear. Do not shake the vial.
- Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration. Reconstituted KEYTRUDA is a clear to slightly opalescent, colourless to slightly yellow solution. Discard the vial if visible particles are observed.
- Withdraw the required volume up to 2 mL (50 mg) of KEYTRUDA and transfer into an intravenous bag containing sodium chloride 9 mg/mL (0.9%) or glucose 50 mg/mL (5%) to prepare a diluted solution with a final concentration ranging from 1 to 10 mg/mL. Mix diluted solution by gentle inversion.
- From a microbiological point of view, the reconstituted or diluted solution should be used immediately. The reconstituted or diluted solution must not be frozen. If not used immediately, chemical and physical in-use stability of KEYTRUDA has been demonstrated for 96 hours at 2°C to 8°C. This 96-hour total hold from reconstitution may include up to 6 hours at room temperature (at or below 25°C). If refrigerated, the vials and/or intravenous bags must be allowed to come to room temperature prior to use. 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.

Package leaflet: Information for the patient

KEYTRUDA 25 mg/mL concentrate for solution for infusion
pembrolizumab

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

What is in this leaflet

1. What KEYTRUDA is and what it is used for
2. What you need to know before you are given KEYTRUDA
3. How you are given KEYTRUDA
4. Possible side effects
5. How to store KEYTRUDA
6. Contents of the pack and other information

1. What KEYTRUDA is and what it is used for

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

KEYTRUDA is used in adults to treat:
- a kind of skin cancer called melanoma
- a kind of lung cancer called non-small cell lung cancer
- a kind of cancer called classical Hodgkin lymphoma
- a kind of cancer called bladder cancer (urothelial carcinoma)
- a kind of head and neck cancer called head and neck squamous cell carcinoma.
- a kind of kidney cancer called renal cell carcinoma
- a kind of cancer called colon or rectal cancer that is determined to be microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)
- a kind of cancer called oesophageal carcinoma.

KEYTRUDA is used in children and adolescents aged 3 years and older to treat:
- a kind of cancer called classical Hodgkin lymphoma.

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

People get KEYTRUDA after they have had surgery to remove melanoma to help prevent their cancer from coming back (adjuvant therapy).

KEYTRUDA may be given in combination with other anti-cancer medicines. It is important that you also read the package leaflets for these other medicines. If you have any questions about these medicines, ask your doctor.

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

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

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

Before you get KEYTRUDA, tell your doctor if you:
- have an autoimmune disease (a condition where the body attacks its own cells)
- have pneumonia or inflammation of your lungs (called pneumonitis)
- were previously given ipilimumab, another medicine for treating melanoma, and experienced serious side effects because of that medicine
- had an allergic reaction to other monoclonal antibody therapies
- have or have had chronic viral infection of the liver, including hepatitis B (HBV) or hepatitis C (HCV)
- have human immunodeficiency virus (HIV) infection or acquired immune deficiency syndrome (AIDS)
- have liver damage
- have kidney damage
- have had a solid organ transplant or a bone marrow (stem cell) transplant that used donor stem cells (allogeneic)
-

When you get KEYTRUDA, you can have some serious side effects. These side effects can sometimes become life-threatening and can lead to death. These side effects may happen anytime during treatment or even after your treatment has ended. You may experience more than one side effect at the same time.

If you have any of the following conditions, call or see your doctor right away. Your doctor may give you other medicines in order to prevent more severe complications and reduce your symptoms. Your doctor may withhold the next dose of KEYTRUDA or stop your treatment with KEYTRUDA.
- inflammation of the lungs, which may include shortness of breath, chest pain or coughing
- inflammation of the intestines, which may include diarrhoea or more bowel movements than usual, black, tarry, sticky stools or stools with blood or mucus, severe stomach pain or tenderness, nausea, vomiting
- inflammation of the liver, which may include nausea or vomiting, feeling less hungry, pain on the right side of stomach, yellowing of skin or whites of eyes, dark urine or bleeding or bruising more easily than normal
- inflammation of the kidneys, which may include changes in the amount or colour of your urine
- inflammation of hormone glands (especially the thyroid, pituitary and adrenal glands), which may include rapid heartbeat, weight loss, increased sweating, weight gain, hair loss, feeling cold, constipation, deeper voice, muscle aches, dizziness or fainting, headaches that will not go away or unusual headache
- type 1 diabetes, which may include feeling more hungry or thirsty than usual, need to urinate more often or weight loss
- inflammation of the eyes, which may include changes in eyesight
- inflammation in the muscles, which may include muscle pain or weakness
- inflammation of the heart muscle, which may include shortness of breath, irregular heartbeat, feeling tired, or chest pain
- inflammation of the pancreas, which may include abdominal pain, nausea and vomiting
- inflammation of the skin, which may include rash, itching, skin blistering, peeling or sores, and/or ulcers in mouth or in lining of nose, throat, or genital area
- an immune disorder that can affect the lungs, skin, eyes and/or lymph nodes (sarcoidosis)
- inflammation of the brain, which may include confusion, fever, memory problems or seizures (encephalitis)
- pain, numbness, tingling, or weakness in the arms or legs; bladder or bowel problems including needing to urinate more frequently, urinary incontinence, difficulty urinating and constipation (myelitis)
- inflammation and scarring of the bile ducts, which may include pain in the upper right part of the stomach, swelling of the liver or spleen, fatigue, itching, or yellowing of the skin or the whites of eyes (cholangitis sclerosing)

- inflammation of the stomach (gastritis)
- infusion reactions, which may include shortness of breath, itching or rash, dizziness or fever

Complications, including graft-versus-host-disease (GVHD), in people with bone marrow (stem cell) transplant that uses donor stem cells (allogeneic). These complications can be severe and can lead to death. They may occur if you had this kind of transplant in the past or if you get it in the future. Your doctor will monitor you for signs and symptoms, which may include skin rash, liver inflammation, abdominal pain, or diarrhoea.

Children and adolescents
Do not give KEYTRUDA to children under 18 years of age, except for children with classical Hodgkin lymphoma aged 3 years and older.

Other medicines and KEYTRUDA
Tell your doctor
- If you are taking other medicines that make your immune system weak. Examples of these may include corticosteroids, such as prednisone. These medicines may interfere with the effect of KEYTRUDA. However, once you are treated with KEYTRUDA, your doctor may give you corticosteroids to reduce the side-effects that you may have with KEYTRUDA. Corticosteroids may also be given to you before receiving KEYTRUDA in combination with chemotherapy to prevent and/or treat nausea, vomiting, and other side effects caused by chemotherapy.
- If you are taking, have recently taken or might take any other medicines.

Pregnancy
- You must not use KEYTRUDA if you are pregnant unless your doctor specifically recommends it.
- If you are pregnant, think you may be pregnant or are planning to have a baby, tell your doctor.
- KEYTRUDA can cause harm or death to your unborn baby.
- If you are a woman who could become pregnant, you must use adequate birth control while you are being treated with KEYTRUDA and for at least 4 months after your last dose.

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

Driving and using machines
KEYTRUDA has a minor effect on your ability to drive or use machines. Feeling dizzy, tired or weak are possible side effects of KEYTRUDA. Do not drive or use machines after you have been given KEYTRUDA unless you are sure you are feeling well.

3. How you are given KEYTRUDA

KEYTRUDA will be given to you in a hospital or clinic under the supervision of a doctor experienced in cancer treatment.
- The recommended dose of KEYTRUDA in adults is either 200 mg every 3 weeks or 400 mg every 6 weeks.
- The recommended dose of KEYTRUDA in children and adolescents aged 3 years and older with classical Hodgkin lymphoma, is 2 mg/kg bodyweight (up to a maximum of 200 mg) every 3 weeks.
- Your doctor will give you KEYTRUDA through an infusion into your vein (intravenous) for about 30 minutes.
- Your doctor will decide how many treatments you need.

If you miss an appointment to get KEYTRUDA
- Call your doctor right away to reschedule your appointment.

- It is very important that you do not miss a dose of this medicine.

If you stop receiving KEYTRUDA
Stopping your treatment may stop the effect of the medicine. Do not stop treatment with KEYTRUDA unless you have discussed this with your doctor.

If you have any further questions about your treatment, ask your doctor.

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

4. Possible side effects

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

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

The following side effects have been reported with pembrolizumab alone:

Very common (may affect more than 1 in 10 people)
- decrease in the number of red blood cells
- reduced thyroid gland activity
- feeling less hungry
- headache
- shortness of breath; cough
- diarrhoea; stomach pain; nausea; vomiting; constipation
- itching; skin rash
- pain in muscle and bones; joint pain
- feeling tired; unusual tiredness or weakness; swelling; fever

Common (may affect up to 1 in 10 people)
- lung infection
- decrease in the number of platelets (bruising or bleeding more easily); decrease in the number of white blood cell (neutrophils; lymphocytes)
- reactions related to the infusion of the medicine
- overactive thyroid gland activity; hot flush; inflammation of the thyroid
- decreased sodium, potassium, or calcium in the blood
- trouble sleeping
- dizziness; inflammation of the nerves causing numbness, weakness, tingling or burning pain of the arms and legs; lack of energy; change in your sense of taste
- dry eye
- abnormal heart rhythm
- high blood pressure
- inflammation of the lungs
- inflammation of the intestines; dry mouth
- red raised rash sometimes with blisters; patches of skin which have lost colour; inflammation of the skin; dry, itchy skin; hair loss; acne-like skin problem
- muscle pain, aches or tenderness; pain in arms or legs; joint pain with swelling
- chills; flu-like illness
- increased liver enzyme levels in the blood; increased calcium in the blood; abnormal kidney function test

Uncommon (may affect up to 1 in 100 people)
- a decreased number of white blood cells (leukocytes and eosinophils)
- an immune disorder that can affect the lungs, skin, eyes and/or lymph nodes (sarcoidosis)

- inflammation of the pituitary gland situated at the base of the brain; decreased secretion of hormones produced by the adrenal glands
- type 1 diabetes
- seizure
- inflammation of the eyes; eye pain, irritation, itchiness or redness; uncomfortable sensitivity to light; seeing spots
- inflammation of the heart muscle, which may present as shortness of breath, irregular heartbeat, feeling tired, or chest pain
- inflammation of the covering of the heart; accumulation of fluid around the heart
- inflammation of the pancreas
- inflammation of the stomach
- a sore that develops on the inside lining of your stomach or upper part of your small intestine
- inflammation of the liver
- thickened, sometimes scaly, skin growth; hair colour changes; small skin bumps, lumps or sores
- inflammation of the sheath that surrounds tendons
- inflammation of the kidneys
- increased level of amylase, an enzyme that breaks down starch

Rare (may affect up to 1 in 1,000 people)
- inflammation response against platelets or red blood cells; feeling weak, lightheaded, short of breath or if your skin looks pale (signs of low level of red blood cells, possibly due to a type of anaemia called pure red cell aplasia); a condition called haemophagocytic lymphohistiocytosis, where the immune system makes too many infection fighting cells called histiocytes and lymphocytes that may cause various symptoms
- inflammation of the brain, which may present as confusion, fever, memory problems or seizures (encephalitis)
- a temporary inflammation of the nerves that causes pain, weakness, and paralysis in the extremities; a condition in which the muscles become weak and tire easily
- pain, numbness, tingling, or weakness in the arms or legs; bladder or bowel problems including needing to urinate more frequently, urinary incontinence, difficulty urinating and constipation (myelitis)
- inflammation of the membrane around the spinal cord and brain, which may present as neck stiffness, headache, fever, eye sensitivity to light, nausea or vomiting (meningitis)
- inflammation of the blood vessels
- a hole in the small intestines
- inflammation of the bile ducts
- tender red bumps under the skin
- itching, skin blistering, peeling or sores, and/or ulcers in mouth or in lining of nose, throat, or genital area (toxic epidermal necrolysis or Stevens-Johnson syndrome)
- disease in which the immune system attacks the glands that make moisture for the body, such as tears and saliva (Sjogren's syndrome)
- inflammation of the bladder. Signs and symptoms may include frequent and/or painful urination, urge to pass urine, blood in urine, pain or pressure in lower abdomen

The following side effects have been reported in clinical studies with pembrolizumab in combination with chemotherapy:

Very common (may affect more than 1 in 10 people)
- lung infection
- decrease in the number of red blood cells
- decreased number of white blood cells; decrease in the number of platelets (bruising or bleeding more easily)
- decreased thyroid gland activity
- decreased sodium or potassium in the blood; feeling less hungry
- trouble sleeping
- dizziness; inflammation of the nerves causing numbness, weakness, tingling or burning pain of the arms and legs; headache

- shortness of breath; cough
- nausea; diarrhoea; vomiting; stomach pain; constipation
- skin rash; itching; hair loss
- pain in the muscles and bones; joint pain
- unusual tiredness or weakness; swelling; fever
- abnormal kidney function test

Common (may affect up to 1 in 10 people)
- decreased number of white blood cells (neutrophils) with a fever
- reaction related to the infusion of the medicine
- increased thyroid gland activity
- decreased calcium in the blood
- change in your sense of taste; feeling tired
- dry eye
- abnormal heart rhythm
- inflammation of the blood vessels; high blood pressure
- inflammation of the lungs
- inflammation of the intestines; dry mouth; inflammation of the stomach
- inflammation of the liver
- red raised rash, sometimes with blisters; inflammation of the skin
- muscle pain, aches or tenderness; joint pain with swelling; pain in arms or legs
- sudden kidney damage
- flu-like illness; chills
- increased blood levels of a liver enzyme known as aspartate aminotransferase; increased calcium in the blood; increased blood levels of a liver enzyme known as alanine aminotransferase; increased blood levels of a liver enzyme known as alkaline phosphatase; increased bilirubin in the blood

Uncommon (may affect up to 1 in 100 people)
- a decreased number of white blood cells (eosinophils)
- inflammation of the pituitary gland situated at the base of the brain; inflammation of the thyroid; decreased secretion of hormones produced by the adrenal glands
- type 1 diabetes
- inflammation of the brain; seizure
- inflammation of the heart muscle, which may present as shortness of breath, irregular heartbeat, feeling tired, or chest pain; accumulation of fluid around the heart
- inflammation of the pancreas
- a sore that develops on the inside lining of your stomach or upper part of your small intestine
- thickened, sometimes scaly, skin growth; patches of skin that have lost colour; acne-like skin problem; dry, itchy skin; small skin bumps, lumps or sores
- inflammation of the sheath that surrounds tendons
- inflammation of the kidneys
- increased level of amylase, an enzyme that breaks down starch

Rare (may affect up to 1 in 1,000 people)
- condition known as Guillain- Barré syndrome, which causes muscle weakness on both sides of the body, and can be severe
- inflammation of the covering of the heart
- inflammation of the bile ducts
- hair colour changes
- disease in which the immune system attacks the glands that make moisture for the body, such as tears and saliva (Sjogren's syndrome)

The following side effects have been reported in clinical studies with pembrolizumab in combination with axitinib:

Very common (may affect more than 1 in 10 people)
- thyroid gland problems
- feeling less hungry
- headache; change in your sense of taste
- high blood pressure
- shortness of breath; cough; hoarseness
- diarrhoea; stomach pain; nausea; vomiting; constipation
- blisters or rash on palms of hands or soles of feet; skin rash; itching
- feeling tired; unusual tiredness or weakness; fever
- increased liver enzyme levels in the blood; abnormal kidney function test
- pain in the muscles and bones; joint or muscle pain, aches or tenderness; pain in arms or legs

Common (may affect up to 1 in 10 people)
- lung infection
- decrease in the number of red blood cells; decreased number of white blood cells (neutrophils, leukocytes); decrease in the number of platelets (bruising or bleeding more easily)
- reaction related to the infusion of the medicine
- inflammation of the pituitary gland situated at the base of the brain; inflammation of the thyroid; decreased secretion of hormones produced by the adrenal glands
- decreased potassium, sodium or calcium in the blood
- trouble sleeping
- dizziness; lack of energy; inflammation of the nerves causing numbness, weakness, tingling or burning pain of the arms and legs
- dry eye
- abnormal heart rhythm
- inflammation of the lungs
- inflammation of the intestines; dry mouth; inflammation of the stomach
- red raised rash, sometimes with blisters; acne-like skin problem; inflammation of the skin; dry, itchy skin; hair loss
- inflammation of the liver
- muscle pain, aches or tenderness; joint or muscle pain with swelling; inflammation of the sheath that surrounds tendons
- sudden kidney damage; inflammation of the kidneys
- swelling; flu-like illness; chills
- increased calcium in the blood; increased liver enzyme levels in the blood

Uncommon (may affect up to 1 in 100 people)
- decreased number of white blood cells (lymphocytes and eosinophils)
- type 1 diabetes
- a condition in which the muscles become weak and tire easily
- inflammation of the heart muscle, which may present as shortness of breath, irregular heartbeat, feeling tired, or chest pain
- inflammation of the eyes; eye pain, irritation, itchiness or redness; uncomfortable sensitivity to light; seeing spots
- inflammation of the pancreas
- a sore that develops on the inside lining of your stomach or upper part of your small intestine
- hair colour changes; thickened, sometimes scaly, skin growth; small skin bumps, lumps or sores; patches of skin that have lost colour
- increased level of amylase, an enzyme that breaks down starch
- disease in which the immune system attacks the glands that make moisture for the body, such as tears and saliva (Sjogren's syndrome)

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

5. How to store KEYTRUDA

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

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

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

From a microbiological point of view, the product, once diluted, should be used immediately. The diluted solution must not be frozen. If not used immediately, chemical and physical in-use stability of KEYTRUDA has been demonstrated for 96 hours at 2ºC to 8ºC. 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.

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

6. Contents of the pack and other information

What KEYTRUDA contains
The active substance is pembrolizumab.

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

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

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

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Merck Sharp & Dohme B.V.
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

Other sources of information

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

The following information is intended for healthcare professionals only:

Preparation and administration 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 2ºC to 8ºC. 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.

CTD 第 1 部

1.7　同種同効品一覧表

各製品の最新の添付文書を参照のこと。

MSD 株式会社

1.7　同種同効品一覧表

申請薬剤であるペムブロリズマブ（遺伝子組換え）（MK-3475）の添付文書（案）並びにその同種同効品の添付文書（2021年9月30日時点の最新版）の概要を以下のとおり示す。

[表 1.7-1]：シスプラチン、ドキソルビシン塩酸塩
[表 1.7-2]：パクリタキセル、ドセタキセル水和物

表 1.7-1 同種同効品一覧（シスプラチン、ドキソルビシン塩酸塩）

販売名	キイトルーダ®点滴静注100mg	ランダ®注10mg/20mL、ランダ®注25mg/50mL、ランダ®注50mg/100mL	アドリアシン®注用10、アドリアシン®注用50
一般名	ペムブロリズマブ（遺伝子組換え）	シスプラチン	ドキソルビシン塩酸塩
会社名	MSD 株式会社	日本化薬株式会社	サンドファーマ株式会社
効能又は効果	○　悪性黒色腫 ○　切除不能な進行・再発の非小細胞肺癌 ○　再発又は難治性の古典的ホジキンリンパ腫 ○　がん化学療法後に増悪した根治切除不能な尿路上皮癌 ○　がん化学療法後に増悪した進行・再発の高頻度マイクロサテライト不安定性（MSI-High）を有する固形癌（標準的な治療が困難な場合に限る） ○　根治切除不能又は転移性の腎細胞癌 ○　再発又は遠隔転移を有する頭頸部癌 ○　がん化学療法後に増悪した PD-L1陽性の根治切除不能な進行・再発の食道扁平上皮癌 ○　治癒切除不能な進行・再発の高頻度マイクロサテライト不安定性（MSI-High）を有する結腸・直腸癌 ○　PD-L1陽性のホルモン受容体陰性かつ HER2陰性の手術不能又は再発乳癌 ○　<u>がん化学療法後に増悪した切除不能な進行・再発の子宮体癌</u>	○シスプラチン通常療法 睾丸腫瘍、膀胱癌、腎盂・尿管腫瘍、前立腺癌、卵巣癌、頭頸部癌、非小細胞肺癌、食道癌、子宮頸癌、神経芽細胞腫、胃癌、小細胞肺癌、骨肉腫、胚細胞腫瘍（精巣腫瘍、卵巣腫瘍、性腺外腫瘍）、悪性胸膜中皮腫、胆道癌 以下の悪性腫瘍に対する他の抗悪性腫瘍剤との併用療法 悪性骨腫瘍、子宮体癌（術後化学療法、転移・再発時化学療法）、再発・難治性悪性リンパ腫、小児悪性固形腫瘍（横紋筋肉腫、神経芽腫、肝芽腫その他肝原発悪性腫瘍、髄芽腫等） ○M-VAC 療法 尿路上皮癌	◇ドキソルビシン塩酸塩通常療法 下記諸症の自覚的及び他覚的症状の緩解 悪性リンパ腫、肺癌、消化器癌（胃癌、胆のう・胆管癌、膵臓癌、肝癌、結腸癌、直腸癌等）、乳癌、膀胱腫瘍、骨肉腫 以下の悪性腫瘍に対する他の抗悪性腫瘍剤との併用療法 乳癌（手術可能例における術前、あるいは術後化学療法）、子宮体癌（術後化学療法、転移・再発時化学療法）、悪性骨・軟部腫瘍、悪性骨腫瘍、多発性骨髄腫、小児悪性固形腫瘍（ユーイング肉腫ファミリー腫瘍、横紋筋肉腫、神経芽腫、網膜芽腫、肝芽腫、腎芽腫等） ◇M-VAC 療法 尿路上皮癌
添付文書改訂日	-	2021年4月	2021年9月

下線：今回の申請案

表 1.7-2 同種同効品一覧（パクリタキセル、ドセタキセル水和物）

販売名	タキソール®注射液30mg、タキソール®注射液100mg	タキソテール®点滴静注用80mg、タキソテール®点滴静注用20mg
一般名	パクリタキセル	ドセタキセル水和物
会社名	ブリストル・マイヤーズ スクイブ株式会社	サノフィ株式会社
効能又は効果	卵巣癌，非小細胞肺癌，乳癌，胃癌，子宮体癌，再発又は遠隔転移を有する頭頸部癌，再発又は遠隔転移を有する食道癌，血管肉腫，進行又は再発の子宮頸癌，再発又は難治性の胚細胞腫瘍（精巣腫瘍，卵巣腫瘍，性腺外腫瘍）	○乳癌 ○非小細胞肺癌 ○胃癌 ○頭頸部癌 ○卵巣癌 ○食道癌 ○子宮体癌 ○前立腺癌
添付文書改訂日	2021年7月	2021年9月

CTD 第 1 部

1.8　添付文書（案）

最新の添付文書を参照のこと。

MSD 株式会社

添付文書（案）

20XX年X月改訂（第X版、効能変更、用法及び用量変更）
2021年8月改訂（第6版、効能変更、用法及び用量変更）

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貯　法：2～8℃保存、凍結を避けること
有効期間：24箇月

—抗悪性腫瘍剤—
ヒト化抗ヒトPD-1モノクローナル抗体
ペムブロリズマブ（遺伝子組換え）製剤

キイトルーダ®点滴静注100mg

KEYTRUDA® Injection 100mg

生物由来製品
劇薬
処方箋医薬品：注意－医師等の処方箋により使用すること

最適使用推進ガイドライン対象品目
（一部）条件付き早期承認品目

MSD

1. 警告
1.1 本剤は、緊急時に十分対応できる医療施設において、がん化学療法に十分な知識・経験を持つ医師のもとで、本剤の使用が適切と判断される症例についてのみ投与すること。また、治療開始に先立ち、患者又はその家族に本剤の有効性及び危険性を十分説明し、同意を得てから投与すること。
1.2 間質性肺疾患があらわれ、死亡に至った症例も報告されているので、初期症状（息切れ、呼吸困難、咳嗽等）の確認及び胸部X線検査の実施等、観察を十分に行うこと。また、異常が認められた場合には本剤の投与を中止し、副腎皮質ホルモン剤の投与等の適切な処置を行うこと。［8.2、9.1.2、11.1.1参照］

2. 禁忌（次の患者には投与しないこと）
本剤の成分に対し過敏症の既往歴のある患者

3. 組成・性状

3.1 組成

販売名	キイトルーダ®点滴静注100 mg
有効成分	ペムブロリズマブ（遺伝子組換え）注1)
分量／容量注2)（1バイアル中）	100 mg／4 mL
添加剤	L-ヒスチジン（1.2 mg）、L-ヒスチジン塩酸塩水和物（6.8 mg）、精製白糖（280 mg）、ポリソルベート80（0.8 mg）

注1）本剤は遺伝子組換え技術により、チャイニーズハムスター卵巣細胞を用いて製造される。マスター・セル・バンクの凍結保存用溶液中に、ウシ胎児血清を使用している。
注2）本剤は注射液吸引時の損失を考慮して、過量充填されているので、実充填量は106.25 mg／4.25 mLである。

3.2 製剤の性状

販売名	キイトルーダ®点滴静注100 mg
剤形	注射剤（バイアル）
pH	5.2～5.8
浸透圧比	約0 9（生理食塩液対比）
性状	無色～微黄色で澄明～乳白色の液

4. 効能又は効果

○ 悪性黒色腫
○ 切除不能な進行・再発の非小細胞肺癌
○ 再発又は難治性の古典的ホジキンリンパ腫
○ がん化学療法後に増悪した根治切除不能な尿路上皮癌
○ がん化学療法後に増悪した進行・再発の高頻度マイクロサテライト不安定性（MSI-High）を有する固形癌（標準的な治療が困難な場合に限る）注)
○ 根治切除不能又は転移性の腎細胞癌
○ 再発又は遠隔転移を有する頭頸部癌
○ がん化学療法後に増悪したPD-L1陽性の根治切除不能な進行・再発の食道扁平上皮癌
○ 治癒切除不能な進行・再発の高頻度マイクロサテライト不安定性（MSI-High）を有する結腸・直腸癌
○ PD-L1陽性のホルモン受容体陰性かつHER2陰性の手術不能又は再発乳癌
○ がん化学療法後に増悪した切除不能な進行・再発の子宮体癌

注）条件付き早期承認対象

5. 効能又は効果に関連する注意

〈悪性黒色腫〉
5.1 臨床試験に組み入れられた患者の病期等について、「17. 臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で、適応患者の選択を行うこと。［17.1.4参照］
〈切除不能な進行・再発の非小細胞肺癌〉
5.2 本剤の術後補助療法における有効性及び安全性は確立していない。
5.3 本剤を単独で投与する場合には、PD-L1の発現が確認された患者に投与すること。PD-L1を発現した腫瘍細胞が占める割合（TPS）について、「17. 臨床成績」の項の内容を熟知すること。十分な経験を有する病理医又は検査施設において、承認された体外診断用医薬品又は医療機器を用いること。なお、承認された体外診断用医薬品又は医療機器に関する情報については、以下のウェブサイトから入手可能である：
https://www.pmda.go.jp/review-services/drug-reviews/review-information/cd/0001 html
［17.1.7-17.1.9参照］
5.4 臨床試験に組み入れられた患者の *EGFR* 遺伝子変異又は *ALK* 融合遺伝子の有無等について、「17. 臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で、適応患者の選択を行うこと。［17.1.5、17.1.7-17.1.9参照］
〈再発又は難治性の古典的ホジキンリンパ腫〉
5.5 臨床試験に組み入れられた患者の前治療歴等について、「17. 臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で、適応患者の選択を行うこと。
［17.1.10参照］
〈がん化学療法後に増悪した根治切除不能な尿路上皮癌〉
5.6 本剤の一次治療における有効性及び安全性は確立していない。
5.7 臨床試験に組み入れられた患者の前治療歴等について、「17. 臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で、適応患者の選択を行うこと。
［17.1.11参照］
5.8 本剤の手術の補助療法としての有効性及び安全性は確立していない。
〈がん化学療法後に増悪した進行・再発の MSI-High を有する固形癌（標準的な治療が困難な場合に限る）〉
5.9 十分な経験を有する病理医又は検査施設における検査により、MSI-High が確認された進行・再発の固形癌患者に投与すること。検査にあたっては、承認された体外診断用医薬品又は医療機器を用いること。なお、承認された体外診断用医薬品又は医

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療機器に関する情報については、以下のウェブサイトから入手可能である：
https://www.pmda.go.jp/review-services/drug-reviews/review-information/cd/0001.html
5.10 結腸・直腸癌以外の固形癌の場合、本剤の一次治療における有効性及び安全性は確立していない。また、二次治療において標準的な治療が可能な場合にはこれらの治療を優先すること。
5.11 本剤の手術の補助療法における有効性及び安全性は確立していない。
5.12 臨床試験に組み入れられた患者の癌腫等について、「17. 臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で、本剤以外の治療の実施についても慎重に検討し、適応患者の選択を行うこと。[17.1.12、17.1.13参照]
〈根治切除不能又は転移性の腎細胞癌〉
5.13 本剤の術後補助療法における有効性及び安全性は確立していない。
〈再発又は遠隔転移を有する頭頸部癌〉
5.14 本剤の術後補助療法における有効性及び安全性は確立していない。
5.15 本剤単独投与の延命効果は、PD-L1発現率（CPS）により異なる傾向が示唆されている。CPSについて、「17. 臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で、適応患者の選択を行うこと。[17.1.15参照]
5.16 「17. 臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で、適応患者の選択を行うこと。[17.1.15参照]
〈がん化学療法後に増悪したPD-L1陽性の根治切除不能な進行・再発の食道扁平上皮癌〉
5.17 本剤の一次治療における有効性及び安全性は確立していない。
5.18 本剤の手術の補助療法における有効性及び安全性は確立していない。
5.19 PD-L1発現率（CPS）について、「17.臨床成績」の項の内容を熟知し、十分な経験を有する病理医又は検査施設における検査により、PD-L1の発現が確認された患者に投与すること。検査にあたっては、承認された体外診断用医薬品又は医療機器を用いること。なお、承認された体外診断用医薬品又は医療機器に関する情報については、以下のウェブサイトから入手可能である：
https://www.pmda.go.jp/review-services/drug-reviews/review-information/cd/0001.html
[17.1.16参照]
〈治癒切除不能な進行・再発の MSI-High を有する結腸・直腸癌〉
5.20 十分な経験を有する病理医又は検査施設における検査により、MSI-Highが確認された患者に投与すること。検査にあたっては、承認された体外診断用医薬品又は医療機器を用いること。なお、承認された体外診断用医薬品又は医療機器に関する情報については、以下のウェブサイトから入手可能である：
https://www.pmda.go.jp/review-services/drug-reviews/review-information/cd/0001.html
5.21 本剤の術後補助療法における有効性及び安全性は確立していない。
〈PD-L1陽性のホルモン受容体陰性かつ HER2陰性の手術不能又は再発乳癌〉
5.22 本剤の術前・術後薬物療法としての有効性及び安全性は確立していない。
5.23 PD-L1発現率（CPS）について、「17.臨床成績」の項の内容を熟知し、十分な経験を有する病理医又は検査施設における検査により、PD-L1の発現が確認された患者に投与すること。検査にあたっては、承認された体外診断用医薬品又は医療機器を用いること。なお、承認された体外診断用医薬品又は医療機器に関する情報については、以下のウェブサイトから入手可能である：
https://www.pmda.go.jp/review-services/drug-reviews/review-information/cd/0001.html
[17.1.18参照]
〈がん化学療法後に増悪した切除不能な進行・再発の子宮体癌〉
5.24 本剤の一次治療における有効性及び安全性は確立していない。
5.25 本剤の術後補助療法における有効性及び安全性は確立していない。
5.26 「17. 臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で、適応患者の選択を行うこと。[17.1.19参照]

6. 用法及び用量
〈悪性黒色腫〉
通常、成人には、ペムブロリズマブ（遺伝子組換え）として、1回200 mg を3週間間隔又は1回400 mg を6週間間隔で30分間かけて点滴静注する。ただし、術後補助療法の場合は、投与期間は12ヵ月間までとする。
〈切除不能な進行・再発の非小細胞肺癌、再発又は難治性の古典的ホジキンリンパ腫、がん化学療法後に増悪した根治切除不能な尿路上皮癌、がん化学療法後に増悪した進行・再発の MSI-High を有する固形癌（標準的な治療が困難な場合に限る）、再発又は遠隔転移を有する頭頸部癌、がん化学療法後に増悪した PD-L1陽性の根治切除不能な進行・再発の食道扁平上皮癌、治癒切除不能な進行・再発の MSI-High を有する結腸・直腸癌〉
通常、成人には、ペムブロリズマブ（遺伝子組換え）として、1回200 mg を3週間間隔又は1回400 mg を6週間間隔で30分間かけて点滴静注する。
〈根治切除不能又は転移性の腎細胞癌〉
アキシチニブとの併用において、通常、成人には、ペムブロリズマブ（遺伝子組換え）として、1回200 mg を3週間間隔又は1回400 mg を6週間間隔で30分間かけて点滴静注する。
〈PD-L1陽性のホルモン受容体陰性かつ HER2陰性の手術不能又は再発乳癌〉
他の抗悪性腫瘍剤との併用において、通常、成人には、ペムブロリズマブ（遺伝子組換え）として、1回200 mg を3週間間隔又は1回400 mg を6週間間隔で30分間かけて点滴静注する。
〈がん化学療法後に増悪した切除不能な進行・再発の子宮体癌〉
レンバチニブメシル酸塩との併用において、通常、成人には、ペムブロリズマブ（遺伝子組換え）として、1回200 mg を3週間間隔又は1回400 mg を6週間間隔で30分間かけて点滴静注する。

7. 用法及び用量に関連する注意
〈切除不能な進行・再発の非小細胞肺癌〉
7.1 本剤を他の抗悪性腫瘍剤と併用する場合、併用する他の抗悪性腫瘍剤は「17. 臨床成績」の項の内容を熟知し選択すること。[17.1.5、17.1.6参照]
〈再発又は遠隔転移を有する頭頸部癌〉
7.2 本剤の用法及び用量は「17. 臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で、選択すること。[17.1.15参照]
〈PD-L1陽性のホルモン受容体陰性かつ HER2陰性の手術不能又は再発乳癌〉
7.3 併用する他の抗悪性腫瘍剤は「17. 臨床成績」の項の内容を熟知し選択すること。[17.1.18参照]
〈悪性黒色腫、再発又は難治性の古典的ホジキンリンパ腫、がん化学療法後に増悪した根治切除不能な尿路上皮癌、がん化学療法後に増悪した進行・再発の MSI-High を有する固形癌（標準的な治療が困難な場合に限る）、がん化学療法後に増悪した PD-L1陽性の根治切除不能な進行・再発の食道扁平上皮癌、治癒切除不能な進行・再発の MSI-High を有する結腸・直腸癌〉

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7.4 他の抗悪性腫瘍剤との併用について、有効性及び安全性は確立していない。
〈効能共通〉
7.5 本剤投与により副作用が発現した場合には、下表を参考に、本剤を休薬又は中止すること。

副作用	程度	処置
間質性肺疾患	Grade 2の場合	Grade 1以下に回復するまで、本剤を休薬する。12週間を超える休薬後もGrade 1以下まで回復しない場合には、本剤を中止する。
	Grade 3以上又は再発性のGrade 2の場合	本剤を中止する。
大腸炎／下痢	Grade 2又は3の場合	Grade 1以下に回復するまで、本剤を休薬する。12週間を超える休薬後もGrade 1以下まで回復しない場合には、本剤を中止する。
	Grade 4又は再発性のGrade 3の場合	本剤を中止する。
肝機能障害	• AST若しくはALTが基準値上限の3～5倍又は総ビリルビンが基準値上限の1.5～3倍に増加した場合 • 腎細胞癌患者における初回発現時では、AST又はALTが基準値上限の3倍以上10倍未満に増加し、かつ総ビリルビンが基準値上限の2倍未満の場合	Grade 1以下に回復するまで、本剤を休薬する。12週間を超える休薬後もGrade 1以下まで回復しない場合には、本剤を中止する。
	• AST若しくはALTが基準値上限の5倍超又は総ビリルビンが基準値上限の3倍超に増加した場合 • 肝転移がある患者では、AST又はALTが治療開始時にGrade 2で、かつベースラインから50%以上の増加が1週間以上持続する場合 • 腎細胞癌患者における初回発現時では、AST若しくはALTが基準値上限の10倍以上、又は3倍超かつ総ビリルビンが基準値上限の2倍以上に増加した場合	本剤を中止する。
腎機能障害	Grade 2の場合	Grade 1以下に回復するまで、本剤を休薬する。12週間を超える休薬後もGrade 1以下まで回復しない場合には、本剤を中止する。
	Grade 3以上の場合	本剤を中止する。
内分泌障害	• Grade 2以上の下垂体炎 • 症候性の内分泌障害（甲状腺機能低下症を除く） • Grade 3以上の甲状腺機能障害 • Grade 3以上の高血糖 • 1型糖尿病	Grade 1以下に回復するまで、本剤を休薬する。12週間を超える休薬後もGrade 1以下まで回復しない場合には、本剤の中止を検討する。
Infusion reaction	Grade 2の場合	本剤の投与を直ちに中止する。1時間以内に回復する場合には、投与速度を50%減速して再開する。
	Grade 3以上の場合又は再発性のGrade 2の場合	本剤を直ちに中止し、再投与しない。
上記以外の副作用	• Grade 4又は再発性のGrade 3の副作用 • Grade 3以上の心筋炎、脳炎、ギラン・バレー症候群 • 副作用の処置としての副腎皮質ホルモン剤をプレドニゾロン換算で10 mg/日相当量以下まで12週間以内に減量できない場合 • 12週間を超える休薬後もGrade 1以下まで回復しない場合	以下の場合を除き、本剤を中止する。再発又は難治性の古典的ホジキンリンパ腫患者においてGrade 4の血液毒性が発現した場合は、Grade 1以下に回復するまで本剤を休薬する。

Gradeは NCI-CTCAE（Common Terminology Criteria for Adverse Events）v4.0に準じる。

8. 重要な基本的注意
8.1 本剤のT細胞活性化作用により、過度の免疫反応に起因すると考えられる様々な疾患や病態があらわれることがある。観察を十分に行い、異常が認められた場合には、過度の免疫反応による副作用の発現を考慮し、適切な鑑別診断を行うこと。過度の免疫反応による副作用が疑われる場合には、副腎皮質ホルモン剤の投与等を考慮すること。また、本剤投与終了後に重篤な副作用があらわれることがあるので、本剤投与終了後も観察を十分に行うこと。
8.2 間質性肺疾患があらわれることがあるので、初期症状（息切れ、呼吸困難、咳嗽等）の確認及び胸部X線検査の実施等、観察を十分に行うこと。また、必要に応じて胸部CT、血清マーカー等の検査を実施すること。[1.2、9.1.2、11.1.1参照]
8.3 甲状腺機能障害、下垂体機能障害及び副腎機能障害があらわれることがあるので、内分泌機能検査（TSH、遊離T3、遊離T4、ACTH、血中コルチゾール等の測定）を定期的に行うこと。また、必要に応じて画像検査等の実施も考慮すること。[11.1.7-11.1.9参照]
8.4 劇症肝炎、肝不全、肝機能障害、肝炎、硬化性胆管炎があらわれることがあるので、肝機能検査を定期的（特にアキシチニブとの併用投与時は頻回）に行い、患者の状態を十分に観察すること。[11.1.6参照]
8.5 1型糖尿病があらわれることがあるので、口渇、悪心、嘔吐等の症状の発現や血糖値の上昇に十分注意すること。[11.1.10参照]
8.6 腎障害があらわれることがあるので、腎機能検査を定期的に行い、患者の状態を十分に観察すること。[11.1.11参照]
8.7 筋炎、横紋筋融解症があらわれることがあるので、筋力低下、筋肉痛、CK上昇、血中及び尿中ミオグロビン上昇等の観察を十分に行うこと。[11.1.13参照]
8.8 重症筋無力症があらわれることがあるので、筋力低下、眼瞼下垂、呼吸困難、嚥下障害等の観察を十分に行うこと。[11.1.14参照]
8.9 心筋炎があらわれることがあるので、胸痛、CK上昇、心電図異常等の観察を十分に行うこと。[11.1.15参照]
8.10 ぶどう膜炎（虹彩炎及び虹彩毛様体炎を含む）等の重篤な眼障害があらわれることがあるので、眼の異常の有無を定期的に確認すること。また、眼の異常が認められた場合には、速やかに医療機関を受診するよう患者を指導すること。[11.2参照]

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9. 特定の背景を有する患者に関する注意
9.1 合併症・既往歴等のある患者
9.1.1 自己免疫疾患の合併又は慢性的若しくは再発性の自己免疫疾患の既往歴のある患者
免疫関連の副作用が発現又は増悪するおそれがある。
9.1.2 間質性肺疾患のある患者又はその既往歴のある患者
間質性肺疾患が発現又は増悪するおそれがある。［1.2、8.2、11.1.1参照］
9.1.3 臓器移植歴（造血幹細胞移植歴を含む）のある患者
本剤の投与により移植臓器に対する拒絶反応又は移植片対宿主病が発現するおそれがある。
9.1.4 結核の感染又は既往を有する患者
結核を発症するおそれがある。［11.1.19参照］
9.4 生殖能を有する者
妊娠する可能性のある女性には、本剤の投与中及び本剤投与後一定期間、適切な避妊法を用いるよう指導すること。［9.5参照］
9.5 妊婦
妊婦又は妊娠している可能性のある女性には、治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。本剤を用いた生殖発生毒性試験は実施されていない。妊娠マウスに抗 PD-1抗体又は抗 PD-L1抗体を投与すると、流産率が増加することが報告されていることから、妊娠中の女性に対する本剤の投与は、胎児に対して有害な影響を及ぼす可能性がある。また、ヒト IgG は母体から胎児へ移行することが知られている。［9.4参照］
9.6 授乳婦
治療上の有益性及び母乳栄養の有益性を考慮し、授乳の継続又は中止を検討すること。本剤のヒト母乳中への移行に関するデータはないが、ヒト IgG は母乳中に移行することが知られている。
9.7 小児等
小児等を対象とした臨床試験は実施していない。
9.8 高齢者
患者の状態を十分に観察しながら慎重に投与すること。一般に生理機能が低下している。

11. 副作用
次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど、適切な処置を行うこと。
11.1 重大な副作用
11.1.1 間質性肺疾患（3.8%）
［1.2、8.2、9.1.2参照］
11.1.2 大腸炎（2.1%）、小腸炎（0.1%未満）、重度の下痢（2.1%）
腸炎から穿孔、イレウスに至る例が報告されている。持続する下痢、腹痛、血便等の症状が認められた場合には、本剤の投与中止等の適切な処置を行うこと。
11.1.3 中毒性表皮壊死融解症（Toxic Epidermal Necrolysis：TEN）（頻度不明）、皮膚粘膜眼症候群（Stevens-Johnson 症候群）（0.1%未満）、多形紅斑（0.1%）
11.1.4 類天疱瘡（0.1%未満）
水疱、びらん等が認められた場合には、皮膚科医と相談すること。
11.1.5 神経障害
末梢性ニューロパチー（2.1%）、ギラン・バレー症候群（0.1%未満）等の神経障害があらわれることがある。
11.1.6 劇症肝炎、肝不全、肝機能障害、肝炎、硬化性胆管炎
劇症肝炎（頻度不明）、肝不全（0.1%未満）、AST、ALT、γ-GTP、Al-P、ビリルビン等の上昇を伴う肝機能障害（13.0%）、肝炎（1.1%）、硬化性胆管炎（0.1%未満）があらわれることがある。［8.4参照］
11.1.7 甲状腺機能障害
甲状腺機能低下症（14.1%）、甲状腺機能亢進症（5.4%）、甲状腺炎（1.1%）等の甲状腺機能障害があらわれることがある。［8.3参照］
11.1.8 下垂体機能障害
下垂体炎（0.5%）、下垂体機能低下症（0.2%）等の下垂体機能障害があらわれることがある。［8.3参照］
11.1.9 副腎機能障害
副腎機能不全（0.6%）等の副腎機能障害があらわれることがある。［8.3参照］
11.1.10 1型糖尿病
1型糖尿病（劇症1型糖尿病を含む）（0.3%）があらわれ、糖尿病性ケトアシドーシスに至るおそれがある。1型糖尿病が疑われた場合には、本剤の投与を中止し、インスリン製剤の投与等の適切な処置を行うこと。［8.5参照］
11.1.11 腎障害
腎不全（1.5%）、尿細管間質性腎炎（0.2%）、糸球体腎炎（0.1%未満）等の腎障害があらわれることがある。［8.6参照］
11.1.12 膵炎（0.3%）
11.1.13 筋炎（0.2%）、横紋筋融解症（頻度不明）
［8.7参照］
11.1.14 重症筋無力症（0.1%）
重症筋無力症によるクリーゼのため急速に呼吸不全が進行することがあるので、呼吸状態の悪化に十分注意すること。［8.8参照］
11.1.15 心筋炎（0.1%）
［8.9参照］
11.1.16 脳炎（0.1%未満）、髄膜炎（0.2%）
11.1.17 重篤な血液障害
免疫性血小板減少性紫斑病（頻度不明）、溶血性貧血（頻度不明）、赤芽球癆（頻度不明）、無顆粒球症（頻度不明）等の重篤な血液障害があらわれることがある。
11.1.18 血球貪食症候群（頻度不明）
11.1.19 結核（0.1%未満）
［9.1.4参照］
11.1.20 Infusion reaction（1.5%）
アナフィラキシーを含む Infusion reaction が認められた場合には、本剤の投与中止等の適切な処置を行うとともに、症状が回復するまで患者の状態を十分に観察すること。
11.2 その他の副作用

	10%以上	1～10%未満	1%未満	頻度不明
血液及びリンパ系障害	貧血	好中球減少、血小板減少、白血球減少、リンパ球減少、発熱性好中球減少症	好酸球増加症	
耳及び迷路障害			耳鳴	
内分泌障害		血中 TSH 増加	血中 TSH 減少	
眼障害		流涙増加、眼乾燥	霧視、ぶどう膜炎[注)]、虹彩毛様体炎[注)]、虹彩炎[注)]	フォークト・小柳・原田症候群
胃腸障害	悪心、下痢	嘔吐、便秘、口内炎、口内乾燥、腹痛、上腹部痛、消化不良	口腔内痛、胃炎、嚥下障害、胃食道逆流性疾患、鼓腸、腹部膨満	
一般・全身障害及び投与部位の状態	疲労	無力症、発熱、粘膜の炎症、末梢性浮腫、倦怠感、悪寒、インフルエンザ様疾患	胸痛、疼痛、浮腫	
感染症及び寄生虫症		肺炎	結膜炎、尿路感染、口腔カンジダ症、上気道感染	
代謝及び栄養障害	食欲減退	低マグネシウム血症、低ナトリウム血症、低カリウ	リパーゼ増加、低カルシウム血症、低リン酸	

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		ム血症、高血糖、脱水	血症、高トリグリセリド血症、高カリウム血症、アミラーゼ増加、血中コレステロール増加、高尿酸血症	
筋骨格系及び結合組織障害		関節痛、筋肉痛、四肢痛、背部痛、筋痙縮	関節炎、筋力低下、筋骨格痛、骨痛、筋骨格硬直	
精神・神経障害		頭痛、味覚異常、浮動性めまい、末梢性感覚ニューロパチー、錯感覚	不眠症、嗜眠	
腎及び尿路障害		蛋白尿、血中クレアチニン増加		
呼吸器、胸郭及び縦隔障害		呼吸困難、発声障害、咳嗽、鼻出血	口腔咽頭痛、しゃっくり、鼻漏、胸水、労作性呼吸困難	
皮膚及び皮下組織障害	そう痒症、発疹	脱毛症、手掌・足底発赤知覚不全症候群、皮膚乾燥、斑状丘疹状皮疹、尋常性白斑、紅斑	ざ瘡様皮膚炎、湿疹、皮膚炎、そう痒性皮疹、皮膚色素減少、じん麻疹、皮膚病変、斑状皮疹、寝汗、乾癬、多汗症、光線過敏性反応、丘疹、毛髪変色	
血管障害		高血圧	低血圧、ほてり、潮紅	
その他		体重減少	血中LDH増加、体重増加、サルコイドーシス	

注）［8.10参照］

14. 適用上の注意

14.1 薬剤調製前の注意

14.1.1 凍結を避け、バイアルを振盪しないこと。

14.1.2 バイアルを常温に戻し、希釈前に保存する場合には、遮光で、25℃以下で24時間以内に使用すること。［20. 参照］

14.1.3 調製前に、粒子状物質や変色の有無を目視により確認すること。微粒子が認められる場合には、バイアルを廃棄すること。

14.2 薬剤調製時の注意

14.2.1 必要量（4 mL以内）をバイアルから抜き取り、日局生理食塩液又は日局5%ブドウ糖注射液の点滴バッグに注入し、最終濃度を1～10 mg/mLとする。点滴バッグをゆっくり反転させて混和すること。過度に振盪すると、半透明から白色のタンパク質性の粒子がみられることがある。不溶性異物が認められる場合は使用しないこと。バイアル中の残液は廃棄すること。

14.2.2 希釈液は凍結させないこと。

14.2.3 本剤は保存料を含まない。希釈液をすぐに使用せず保管する場合には、希釈から投与終了までの時間を、25℃以下で6時間以内又は2～8℃で96時間以内とすること。希釈液を冷所保存した場合には、投与前に点滴バッグを常温に戻すこと。

14.3 薬剤投与時の注意

14.3.1 本剤の投与にあたっては、インラインフィルター（0.2～5 μm）を使用すること。

14.3.2 同一の点滴ラインを使用して他の薬剤を併用同時投与しないこと。

15. その他の注意

15.1 臨床使用に基づく情報

15.1.1 国内外の臨床試験において、本剤に対する抗体の産生が報告されている。

15.1.2 臨床試験において、本剤による治療後に同種造血幹細胞移植が実施された症例で、重篤な移植片対宿主病等の移植関連合併症が認められた。

16. 薬物動態

16.1 血中濃度

16.1.1 単回投与

国内第Ⅰ相試験（KEYNOTE-011試験）で、日本人の進行性固形がん患者に本剤2又は10 mg/kgを単回静脈内持続投与[注)]したときの、血清中濃度推移を図1に、薬物動態パラメータを表1に示す。クリアランス及び分布容積の幾何平均値は用量間（2及び10 mg/kg）で概して同様であった。

図1　日本人患者の血清中濃度推移
（平均±標準偏差）（KEYNOTE-011試験）

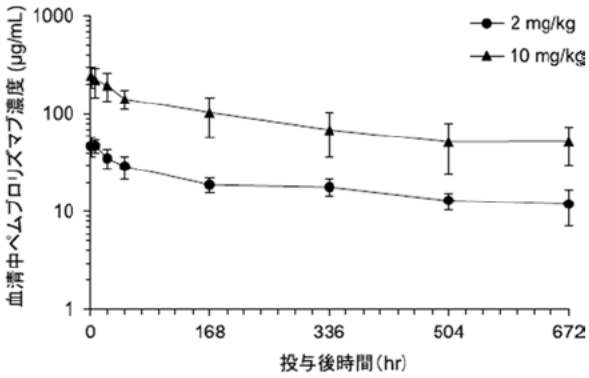


表1　本剤2又は10 mg/kgを単回投与したときの薬物動態パラメータの要約統計量（KEYNOTE-011試験）

	C_{max} (μg/mL)	T_{max}† (day)	$AUC_{0\text{-}28\ day}$ (μg day/mL)	$t_{1/2}$ (day)	CL (mL/day/kg)	Vz (mL/kg)
本剤2 mg/kg (3例)	47 4 (18 6)	0 223 (0 00208-0 233)	507 (20 0)	18 4 (56 1) ‡	2 46 (44 7)	65 3 (21 3)
本剤10 mg/kg (7例)	250 (23 2)	0 00903 (0 000694-0 232)	2219 (32 4)	18 1 (68 4) ‡	2 93 (56 5)	76 5 (34 4)

幾何平均（幾何変動係数［%］）

†：中央値（範囲）

‡：T_{last}を超える$t_{1/2}$を有する患者1例を平均値に含む

16.1.2 反復投与

〈悪性黒色腫〉

国内第Ⅰ相試験（KEYNOTE-041試験）で、日本人の根治切除不能な悪性黒色腫患者に本剤2 mg/kgを3週間間隔で反復静脈内持続投与[注)]したときの、初回（サイクル1）及び投与後21週（サイクル8）の血清中濃度推移を図2に、サイクル1及びサイクル8の薬物動態パラメータを表2に示す。サイクル8における、本剤のトラフ濃度及び$AUC_{0\text{-}21\ day}$の幾何平均は、それぞれ24.5 μg/mL及び797 μg·day/mLであった。本剤のトラフ濃度はサイクル8（21週）までにおおむね定常状態に到達した。

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図２　日本人患者のサイクル１及びサイクル８の
血清中濃度推移（平均±標準偏差）（KEYNOTE-041 試験）

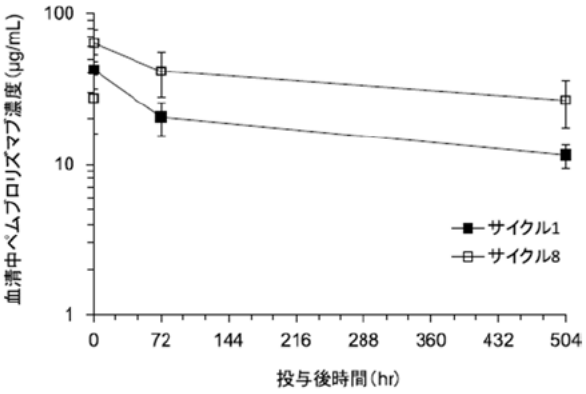


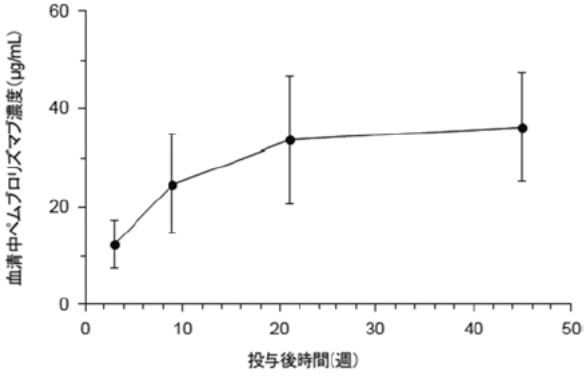
表２　本剤２mg/kg を３週間間隔で投与したときの
薬物動態パラメータの要約統計量（KEYNOTE-041 試験）

	C_{max} (μg/mL)	C_{trough} (μg/mL)	$AUC_{0\text{-}21\ day}$ (μg day /mL)	CL (mL/day/kg)
サイクル1 (42例)	40 9 (28 1)	11 3†‡ (19 0)	393† (18 2)	NA
サイクル8 (28例)	61 8 (24 5)	24 5§‖ (48 8)	797§ (32 4)	2 51§ (32 4)

幾何平均（幾何変動係数［%］）
†：41例
‡：サイクル2投与前の血清中濃度
§：25例
‖：サイクル9投与前の血清中濃度
NA：該当なし

〈切除不能な進行・再発の非小細胞肺癌〉
国際共同第Ⅲ相試験（KEYNOTE-024試験）で、PD-L1陽性の切除不能な進行・再発の非小細胞肺癌患者（薬物動態解析対象152例、日本人21例を含む）に、本剤200 mg を3週間間隔で反復静脈内持続投与したときの、日本人及び外国人患者における血清中トラフ濃度推移を図3に示す。初回（サイクル1）の C_{max} の幾何平均（幾何変動係数）は67.5 μg/mL（23%）で、投与後21週（サイクル8）のトラフ濃度†の幾何平均（幾何変動係数）は30.6 μg/mL（50%）であった。
†：サイクル8投与前の血清中濃度

図３　日本人及び外国人患者の血清中トラフ濃度推移
（平均±標準偏差）（KEYNOTE-024 試験）



16.1.3 母集団薬物動態解析
本剤200 mg を3週間間隔（Q3W）又は400 mg を6週間間隔（Q6W）で投与したときの母集団薬物動態解析に基づく薬物動態パラメータと海外第Ⅰ相試験（KEYNOTE-555試験）にて本剤400 mg を Q6W で投与したときの実測値に基づく薬物動態パラメータを比較した結果は、表3のとおりであった。母集団薬物動態解析には、国際共同第Ⅱ／Ⅲ相試験（KEYNOTE-010試験）、国際共同第Ⅲ相試験（KEYNOTE-024試験）、海外第Ⅰ相試験（KEYNOTE-001試験）、海外第Ⅱ相試験（KEYNOTE-002 試験）及び海外第Ⅲ相試験（KEYNOTE-006試験）に組み入れられた患者2,993例のデータ（うち日本人は83例）を含む。

表３　本剤投与後の薬物動態パラメータの要約

	用法・用量	C_{max} (μg/mL)	C_{avg} (μg/mL)	C_{trough} (μg/mL)
サイクル1	200 mg Q3W†	59 1 (58 5, 59 7)	27 9 (27 7, 28 1)	18 1‡ (17 8, 18 3)
	400 mg Q6W†	123 (122, 124)	32 4 (32 0, 32 7)	10 6‡ (10 4, 10 8)
	400 mg Q6W（実測値）	136 0§ (135 6, 136 4)	NA	14 9‖ (14 4, 15 4)
定常状態	200 mg Q3W†	92 8 (91 7, 94 1)	50 4 (49 8, 51 0)	30 9 (30 5, 31 4)
	400 mg Q6W†	148 (146, 149)	50 7 (50 1, 51 3)	20 3 (19 8, 20 9)

†：2,993例×100回のシミュレーションにより算出した幾何平均値の中央値（2 5%点, 97 5%点）
C_{avg}：平均血清中濃度
‡：サイクル2 投与前の血清中濃度
§：56例の幾何平均値（95%信頼区間）
‖：41例の幾何平均値（95%信頼区間）
NA：該当なし

16.8 その他
本剤の有効性及び安全性に対する曝露－反応解析の結果、本剤200 mg を Q3W で投与した際と本剤400 mg を Q6W で投与した際の有効性及び安全性に明確な差異はないと予測された。

注）本剤の承認用法及び用量は、通常、成人には、ペムブロリズマブ（遺伝子組換え）として、1回200 mg を3週間間隔又は1回400 mg を6週間間隔で30分間かけて点滴静注する。

17. 臨床成績
17.1 有効性及び安全性に関する試験
〈悪性黒色腫〉
17.1.1 国内第Ⅰ相試験（KEYNOTE-041試験）
化学療法歴のない又はイピリムマブを含まない2レジメンまでの化学療法歴を有する根治切除不能な悪性黒色腫患者42例（有効性解析対象37例）を対象に、本剤2 mg/kg 3週間間隔投与[注1)]の有効性及び安全性が検討された。なお、画像評価で疾患進行が認められた場合に、疾患進行を示す症状が認められない等の臨床的に安定している患者では、次回以降の画像評価で疾患進行が認められるまで本剤の投与を継続することが可能とされた。主要評価項目である奏効率［RECIST ガイドライン1.1版に基づく中央判定による完全奏効（CR）又は部分奏効（PR）］は、24%（95%信頼区間：12～41）であった。安全性解析対象例42例中34例（81.0%）に副作用が認められた。主な副作用（10%以上）は、そう痒症6例（14.3%）、斑状丘疹状皮疹6例（14.3%）及び倦怠感5例（11.9%）であった。

17.1.2 海外第Ⅱ相試験（KEYNOTE-002試験）
イピリムマブによる治療歴を有する根治切除不能な悪性黒色腫患者を対象に、本剤2 mg/kg 3週間間隔投与[注1)]及び10 mg/kg 3週間間隔投与[注1)]の有効性及び安全性が、化学療法（ダカルバジン、テモゾロミド、カルボプラチン、パクリタキセル又はカルボプラチン＋パクリタキセル）を対照として検討された。なお、画像評価で疾患進行が認められた場合に、疾患進行を示す症状が認められない等の臨床的に安定している患者では、次回以降の画像評価で疾患進行が認められるまで本剤の投与を継続することが可能とされた。主要評価項目は全生存期間（OS）及び無増悪生存期間（PFS）とされ、本剤は化学療法と比較して、PFS を有意に延長した（表1、図1及び図2）[1)]。
本剤2 mg/kg 3週間間隔投与[注1)]の安全性解析対象例178例中

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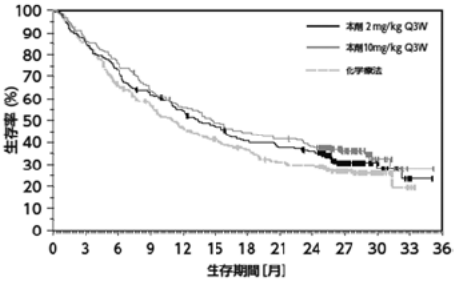
121例（68.0%）、及び本剤10 mg/kg 3週間間隔投与[注1)]の安全性解析対象例179例中133例（74.3%）に副作用が認められた。主な副作用（10%以上）は、本剤2 mg/kgの3週間間隔投与[注1)]で疲労40例（22.5%）、そう痒症37例（20.8%）及び発疹21例（11.8%）、本剤10 mg/kgの3週間間隔投与[注1)]で疲労52例（29.1%）、そう痒症42例（23.5%）、下痢19例（10.6%）及び発疹18例（10.1%）であった。

表1　有効性成績（KEYNOTE-002試験）

		本剤2 mg/kg Q3W (180例)	本剤10 mg/kg Q3W (181例)	化学療法 (179例)
OS	中央値［月］ (95%信頼区間)	13 4 (11 0, 16 4)	14 7 (11 3, 19 5)	11 0 (8 9, 13 8)
	ハザード比‡ (95%信頼区間)	0 86 (0 67, 1 10)	0 74 (0 57, 0 96)	—
	P値§	0 1173	0 0106	
PFS†	中央値［月］ (95%信頼区間)	2 9 (2 8, 3 8)	2 9 (2 8, 4 7)	2 7 (2 5, 2 8)
	ハザード比‡ (95%信頼区間)	0 57 (0 45, 0 73)	0 50 (0 39, 0 64)	—
	P値§	<0 0001	<0 0001	

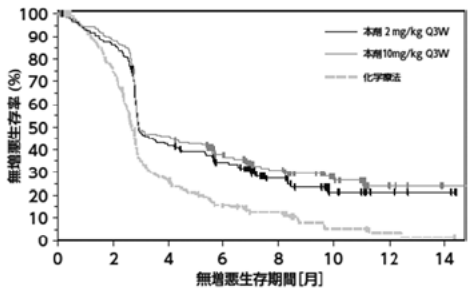
†：RECIST ガイドライン1 1版に基づく独立した放射線科医及び腫瘍専門医による評価
‡：層別Cox比例ハザードモデルによる化学療法との比較
§：層別ログランク検定
Q3W：3週間間隔投与

図1　OSのKaplan-Meier曲線（KEYNOTE-002試験）



at risk数							
本剤2 mg/kg Q3W	180	131	95	70	61	11	0
本剤10mg/kg Q3W	181	138	99	79	67	12	0
化学療法	179	115	80	60	48	9	0

図2　PFSのKaplan-Meier曲線（KEYNOTE-002試験）



at risk数							
本剤2 mg/kg Q3W	180	153	74	53	26	9	4	2
本剤10mg/kg Q3W	181	158	82	55	39	15	5	1
化学療法	179	128	43	22	15	4	2	1

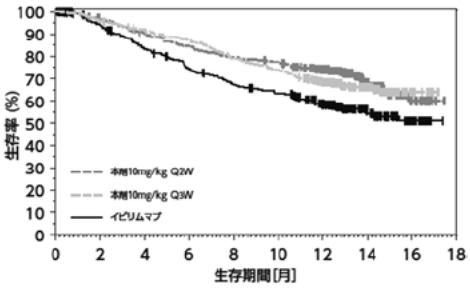
17.1.3 海外第Ⅲ相試験（KEYNOTE-006試験）
イピリムマブによる治療歴のない又はイピリムマブを含まない1レジメンまでの化学療法歴を有する根治切除不能な悪性黒色腫患者を対象に、本剤10 mg/kg 3週間間隔投与[注1)]及び10 mg/kg 2週間間隔投与[注1)]の有効性及び安全性が、イピリムマブを対照として検討された。なお、画像評価で疾患進行が認められた場合に、疾患進行を示す症状が認められない等の臨床的に安定している患者では、次回以降の画像評価で疾患進行が認められるまで本剤の投与を継続することが可能とされた。主要評価項目は全生存期間（OS）及び無増悪生存期間（PFS）とされ、本剤はイピリムマブと比較して、OS及びPFSを有意に延長した（表2、図3及び図4）[2)]。
本剤10 mg/kg 3週間間隔投与[注1)]の安全性解析対象例277例中202例（72.9%）、及び本剤10 mg/kg 2週間間隔投与[注1)]の安全性解析対象例278例中221例（79.5%）に副作用が認められた。主な副作用（10%以上）は、本剤10 mg/kg 3週間間隔投与[注1)]で疲労53例（19.1%）、下痢40例（14.4%）、そう痒症39例（14.1%）、発疹37例（13.4%）、関節痛32例（11.6%）、悪心31例（11.2%）、無力症31例（11.2%）及び尋常性白斑31例（11.2%）、本剤10 mg/kg 2週間間隔投与[注1)]で疲労58例（20.9%）、下痢47例（16.9%）、発疹41例（14.7%）、そう痒症40例（14.4%）、無力症32例（11.5%）及び悪心28例（10.1%）であった。

表2　有効性成績（KEYNOTE-006試験）

		本剤10 mg/kg Q3W (277例)	本剤10 mg/kg Q2W (279例)	イピリムマブ (278例)
OS†	中央値［月］ (95%信頼区間)	NE (NE, NE)	NE (NE, NE)	NE (13, NE)
	ハザード比‡ (95%信頼区間)	0 69 (0 52, 0 90)	0 63 (0 47, 0 83)	—
	P値§	0 00358	0 00052	
PFS‖¶	中央値［月］ (95%信頼区間)	4 1 (2 9, 6 9)	5 5 (3 4, 6 9)	2 8 (2 8, 2 9)
	ハザード比‡ (95%信頼区間)	0 58 (0 47, 0 72)	0 58 (0 46, 0 72)	—
	P値§	<0 00001	<0 00001	

†：中間解析時のデータ：2015年3月3日カットオフ
‡：層別Cox比例ハザードモデルによるイピリムマブとの比較
§：層別ログランク検定
‖：RECIST ガイドライン1 1版に基づく独立した放射線科医及び腫瘍専門医による評価
¶：中間解析時のデータ：2014年9月3日カットオフ
Q3W：3週間間隔投与、Q2W：2週間間隔投与、NE：Not Estimated

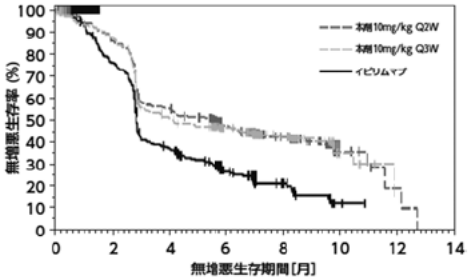
図3　OSのKaplan-Meier曲線（KEYNOTE-006試験）



at risk数										
本剤10mg/kg Q2W	279	266	248	233	219	212	177	67	19	0
本剤10mg/kg Q3W	277	266	251	238	215	202	158	71	18	0
イピリムマブ	278	242	212	188	169	157	117	51	17	0

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図 4　PFS の Kaplan-Meier 曲線（KEYNOTE-006 試験）



at risk数								
本剤10mg/kg Q2W	279	231	147	98	49	7	2	0
本剤10mg/kg Q3W	277	235	133	95	53	7	1	1
イピリムマブ	278	186	88	42	18	2	0	0

17.1.4 国際共同第Ⅲ相試験（EORTC-1325-MG／KEYNOTE-054試験）

完全切除後のステージⅢ［ⅢA 期（リンパ節転移1mm 超）、ⅢB 期及びⅢC 期］の悪性黒色腫患者（日本人15例を含む）を対象に、術後補助療法として本剤200 mg 3週間間隔投与の有効性及び安全性が、プラセボを対照として検討された。全患者集団で、本剤はプラセボと比較して、主要評価項目である無再発生存期間（RFS）を有意に延長した（表3及び図5）。

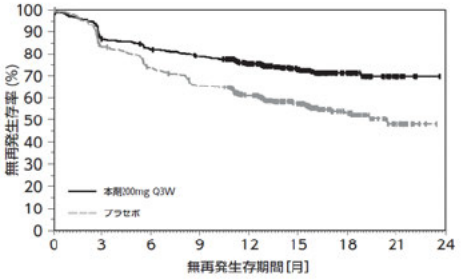
安全性解析対象例509例中396例（77.8%）（日本人9例中5例を含む）に副作用が認められた。主な副作用（10%以上）は、疲労143例（28 1%）、下痢94例（18.5%）、そう痒症85例（16.7%）、甲状腺機能低下症73例（14 3%）、悪心58例（11.4%）及び関節痛51例（10.0%）であった。［5.1参照］

表 3　有効性成績（EORTC-1325-MG／KEYNOTE-054 試験）

		本剤200 mg Q3W (514例)	プラセボ (505例)
RFS†	中央値［月］ (95%信頼区間)	NE (NE, NE)	20 4 (16 2, NE)
	ハザード比‡ (98%信頼区間)	0 57 (0 43, 0 74)	–
	P 値§	<0 0001	

†：中間解析時のデータ：2017年10月2日カットオフ
‡：層別 Cox 比例ハザードモデルによるプラセボとの比較
§：層別ログランク検定
Q3W：3週間間隔投与、NE：Not Estimated

図 5　RFS の Kaplan-Meier 曲線
（EORTC-1325-MG／KEYNOTE-054 試験）



at risk数									
本剤200mg Q3W	514	438	413	392	313	182	73	15	0
プラセボ	505	415	363	323	264	157	60	15	0

注1）悪性黒色腫の場合、本剤の承認用法及び用量は、通常、成人には、ペムブロリズマブ（遺伝子組換え）として、1回200 mg を3週間間隔又は1回400 mg を6週間間隔で30分間かけて点滴静注する。ただし、術後補助療法の場合は、投与期間は12ヵ月間までとする。

〈切除不能な進行・再発の非小細胞肺癌〉

17.1.5 国際共同第Ⅲ相試験（KEYNOTE-189試験）

化学療法歴のない、*EGFR* 遺伝子変異陰性及び *ALK* 融合遺伝子陰性の切除不能な進行・再発の非扁平上皮非小細胞肺癌患者616例（日本人10例を含む）を対象に、本剤200 mg、ペメトレキセドナトリウム水和物及びプラチナ製剤の併用療法3週間間隔投与の有効性及び安全性が、プラセボ、ペメトレキセドナトリウム水和物及びプラチナ製剤の併用療法を対照とした二重盲検試験で検討された。両群とも、プラチナ製剤（シスプラチン又はカルボプラチン）は担当医師が患者ごとに選択し、投与は最大4コースまでとした。なお、画像評価で疾患進行が認められた場合に、疾患進行を示す症状が認められない等の臨床的に安定している患者では、次回以降の画像評価で疾患進行が認められるまで本剤とペメトレキセドナトリウム水和物の併用投与を継続することが可能とされた。主要評価項目は全生存期間（OS）及び無増悪生存期間（PFS）とされ、本剤、ペメトレキセドナトリウム水和物及びプラチナ製剤の併用療法はプラセボ、ペメトレキセドナトリウム水和物及びプラチナ製剤の併用療法と比較して、OS 及び PFS を有意に延長した（表4、図6及び図7）[3)]。

安全性解析対象例405例中372例（91.9%）（日本人4例中3例を含む）に副作用が認められた。主な副作用（20%以上）は、悪心187例（46.2%）、貧血154例（38.0%）、疲労134例（33.1%）、好中球減少症101例（24.9%）及び食欲減退84例（20.7%）であった。［5.4、7.1参照］

表 4　有効性成績（KEYNOTE-189 試験）

		本剤200 mg Q3W、ペメトレキセドナトリウム水和物及びプラチナ製剤[注2)] (410例)	プラセボ、ペメトレキセドナトリウム水和物及びプラチナ製剤[注3)] (206例)
OS†	中央値［月］ (95%信頼区間)	NE (NE, NE)	11 3 (8 7, 15 1)
	ハザード比‡ (95%信頼区間)	0 49 (0 38, 0 64)	–
	P 値§	<0 00001	
PFS†‖	中央値［月］ (95%信頼区間)	8 8 (7 6, 9 2)	4 9 (4 7, 5 5)
	ハザード比‡ (95%信頼区間)	0 52 (0 43, 0 64)	–
	P 値§	<0 00001	

†：中間解析時のデータ：2017年11月8日カットオフ
‡：層別 Cox 比例ハザードモデルによるプラセボ、ペメトレキセドナトリウム水和物及びプラチナ製剤の併用療法との比較
§：層別ログランク検定
‖：RECIST ガイドライン1 1版に基づく盲検下独立中央判定
Q3W：3週間間隔投与、NE：Not Estimated

注2）本剤200 mg、ペメトレキセドナトリウム水和物500 mg/m²、シスプラチン75 mg/m² 又はカルボプラチン AUC 5 mg·min/mL 相当量の順に Q3W（各コースの1日目に投与）で4コース投与後、本剤200 mg 及びペメトレキセドナトリウム水和物500 mg/m² を Q3W で投与した。

注3）プラセボ、ペメトレキセドナトリウム水和物500 mg/m²、シスプラチン75 mg/m² 又はカルボプラチン AUC 5 mg·min/mL 相当量の順に Q3W（各コースの1日目に投与）で4コース投与後、プラセボ及びペメトレキセドナトリウム水和物500 mg/m² を Q3W で投与した。

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