SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

KEYTRUDA® Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE

Each vial contains 100 mg pembrolizumab in 4 mL solution (25 mg/mL).

Contains 280 mg sucrose.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Sterile solution for infusion.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Melanoma

KEYTRUDA is indicated for the treatment of patients with unresectable or metastatic melanoma.

KEYTRUDA is indicated for the adjuvant treatment of adult and paediatric (12 years and older) patients with Stage IIB, IIC or III Melanoma who have undergone complete resection.

Non-Small Cell Lung Carcinoma

KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of patients with metastatic non-squamous non-small cell lung carcinoma (NSCLC), with no EGFR or ALK genomic tumour aberrations.

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

KEYTRUDA, as monotherapy is indicated for the first-line treatment of patients with metastatic non-small cell lung carcinoma (NSCLC) of squamous and non-squamous histology whose tumours express PD-L1 with a ≥ 50 % tumour proportion score (TPS) as determined by a validated test, with no EGFR or ALK genomic tumour aberrations.

KEYTRUDA, as monotherapy is indicated as second-line treatment or greater for the treatment of patients with advanced non-small cell lung carcinoma (NSCLC) whose tumours express PD-L1 with a ≥ 1 % TPS as determined by a validated test and who have already been treated with platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have been treated for these aberrations before receiving treatment with KEYTRUDA (see section 4.2).

KEYTRUDA as monotherapy is indicated for the first-line treatment of patients with locally advanced or metastatic non-small cell lung carcinoma (NSCLC) whose tumours express PD-L1 with a ≥ 1 % tumour proportion score (TPS) as determined by a validated test, with no EGFR or ALK genomic tumour aberrations.

Head and Neck Cancer

KEYTRUDA, as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, is indicated for the first-line treatment of patients with metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC).

KEYTRUDA, as monotherapy, is indicated for the treatment of patients with metastatic or unresectable recurrent HNSCC with disease progression on or after platinum-containing chemotherapy.

Classical Hodgkin Lymphoma

KEYTRUDA is indicated for the treatment of adult and paediatric patients with relapsed or refractory classical Hodgkin Lymphoma (cHL).

Urothelial Carcinoma

KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 [combined positive score (CPS) ≥ 10] as determined by a validated test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.

KEYTRUDA is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have received platinum-containing chemotherapy.

Renal Cell Carcinoma

KEYTRUDA, in combination with axitinib, is indicated for the first-line treatment of patients with advanced renal cell carcinoma (RCC).

KEYTRUDA, in combination with lenvatinib, is indicated for the first-line treatment of patients with advanced renal cell carcinoma (RCC).

KEYTRUDA, as monotherapy, is indicated for the adjuvant treatment of patients with RCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.

Colorectal Cancer

KEYTRUDA is indicated for the first-line treatment of patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer (CRC).

Triple-Negative Breast Cancer

KEYTRUDA is indicated for the treatment of patients with high-risk early-stage triple-negative breast cancer (TNBC) in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery.

KEYTRUDA, in combination with chemotherapy, is indicated for the treatment of patients with locally recurrent unresectable or metastatic triple-negative breast cancer (TNBC) whose tumours express PD-L1 (CPS ≥10) as determined by a validated test.

Oesophageal Cancer

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 gastro-oesophageal junction.

Endometrial Carcinoma

KEYTRUDA, in combination with lenvatinib, is indicated for the treatment of patients with advanced endometrial carcinoma who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.

Cervical Cancer

KEYTRUDA, in combination with chemotherapy with or without bevacizumab, is indicated for the treatment of patients with persistent, recurrent, or metastatic cervical cancer.

KEYTRUDA, as monotherapy, is indicated for the treatment of patients with recurrent or metastatic cervical cancer whose tumours express PD-L1 (CPS ≥ 1) as determined by a validated test, with disease progression on or after chemotherapy.

Microsatellite Instability-High Cancer

KEYTRUDA is indicated for the treatment of patients with advanced microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) cancer, as determined by a validated test, who have received prior therapy.

4.2 Posology and method of administration

General

Patient selection

If specified in the indication, select patients for treatment with KEYTRUDA based on the presence of positive PD-L1 expression, MSI-H or dMMR tumour status, or TMB-H tumour status (see section 4.1).

PD-L1 expression should be evaluated using the PD-L1 IHC 22C3 pharmDx™ Kit or equivalent.

MSI or MMR tumour status should be evaluated using a validated test.

TMB-H tumour status should be evaluated using the FoundationOne® CDx assay or equivalent.

Recommended Dosing

KEYTRUDA is administered as an intravenous infusion over 30 minutes.

The recommended dose of KEYTRUDA in adults is either:

- 200 mg every 3 weeks or
- 400 mg every 6 weeks.

In cHL, the recommended dose of KEYTRUDA in paediatric patients is 2 mg/kg (up to a maximum of 200 mg), administered as an intravenous infusion over 30 minutes every 3 weeks.

For use in combination, see the prescribing information for the concomitant therapies. When administering KEYTRUDA as part of a combination with intravenous chemotherapy, KEYTRUDA should be administered first.

For RCC patients treated with KEYTRUDA in combination with axitinib, see the prescribing information regarding dosing of axitinib. When used in combination with KEYTRUDA, dose escalation of axitinib above the initial 5 mg dose may be considered at intervals of six weeks or longer.

For endometrial carcinoma and RCC patients treated with KEYTRUDA in combination with lenvatinib, the recommended initial dose of lenvatinib is 20 mg orally once daily until disease progression or unacceptable toxicity.

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

For the adjuvant treatment of melanoma, KEYTRUDA should be administered for up to one year or until disease recurrence or unacceptable toxicity.

Dose modifications

No dose reductions of KEYTRUDA are recommended. Withhold or discontinue KEYTRUDA to manage adverse reactions as described in **Table 1**.

Table 1: Recommended Dose Modifications (see section 4.4)

Adverse reactions	Severity	Dose modification
Immune-mediated pneumonitis	Moderate (Grade 2)	Withhold until adverse reactions recover to Grades 0-1*
	Severe or life-threatening (Grades 3 or 4) or recurrent moderate (Grade 2)	Permanently discontinue
Immune-mediated colitis	Moderate or severe (Grades 2 or 3)	Withhold until adverse reactions recover to Grades 0-1*
	Life-threatening (Grade 4) or recurrent severe (Grade 3)	Permanently discontinue
Immune-mediated nephritis	Moderate (Grade 2)	Withhold until adverse reactions recover to Grades 0-1*
	Severe or life-threatening (Grades 3 or 4)	Permanently discontinue
Immune-mediated endocrinopathies	Severe or life-threatening (Grades 3 or 4)	Withhold until adverse reactions recover to Grades 0-1* For patients with severe (Grade 3) or life-threatening

		(Grade 4) endocrinopathy that improves to Grade 2 or lower and is controlled with hormone replacement, continuation of KEYTRUDA may be considered
Immune-mediated hepatitis For liver enzyme elevations in RCC patients treated with combination therapy with axitinib, see dosing guidelines following this table.	Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 to 5 times upper limit of normal (ULN) or total bilirubin > 1,5 to 3 times ULN	Withhold until adverse reactions recover to Grades 0-1*
	AST or ALT > 5 times ULN or total bilirubin > 3 times ULN	Permanently discontinue
	For patients with liver metastases who begin treatment with moderate (Grade 2) elevation of AST or ALT, if AST or ALT increases ≥ 50 % relative to baseline and lasts ≥ 1 week	Permanently discontinue
Immune-mediated skin reactions or Stevens-Johnson	Severe skin reactions (Grade 3) or suspected SJS or TEN	Withhold until adverse reactions recover to Grades 0-

syndrome (SJS) or toxic epidermal necrolysis (TEN)		1*
	Severe skin reactions (Grade 4) or confirmed SJS or TEN	Permanently discontinue
Other immune-mediated adverse reactions	Based on severity and type of reaction (Grade 2 or Grade 3)	Withhold until adverse reactions recover to Grades 0-1*
	Severe or life-threatening (Grades 3 or 4) myocarditis, encephalitis or Guillain-Barré syndrome	Permanently discontinue
	Life-threatening (Grade 4) or recurrent severe (Grade 3)	Permanently discontinue
Infusion-related reactions	Severe or life-threatening (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 corticosteroid dosing cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks or a treatment-related toxicity does not resolve to Grades 0-1 within 12 weeks after last dose of KEYTRUDA, then KEYTRUDA should be permanently discontinued.

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

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, withhold both KEYTRUDA and axitinib until these adverse reactions recover to Grades 0-1. Consider corticosteroid therapy. Consider rechallenge with a single drug or sequential rechallenge with both drugs after recovery. If rechallenging with axitinib, consider dose reduction as per the axitinib prescribing information.
- If ALT or AST ≥ 10 times ULN or > 3 times ULN with concurrent total bilirubin ≥ 2 times ULN, permanently discontinue both KEYTRUDA and axitinib and consider corticosteroid therapy.

When administering KEYTRUDA in combination with lenvatinib, interrupt one or both or dose reduce or discontinue lenvatinib to manage adverse reactions as appropriate. No dose reductions are recommended for KEYTRUDA.

For recommendations for management of adverse reactions of lenvatinib, refer to the prescribing information for lenvatinib. Recommended dose reductions for lenvatinib when used to treat endometrial carcinoma or RCC are shown in the below table. For information on median dose and median duration of exposure of lenvatinib in RCC see section 5.1.

Recommended Dose Reductions of Lenvatinib for Adverse Reactions

Indication	Starting dose	First Dose Reduction To	Second Dose Reduction To	Third Dose Reduction To
Endometrial carcinoma	20 mg orally once daily	14 mg once daily	10 mg once daily	8 mg once daily
RCC	20 mg orally once daily	14 mg once daily	10 mg once daily	8 mg once daily

Lenvatinib Dose Modifications for Severe Renal Impairment

The recommended dosage of lenvatinib for patients with endometrial carcinoma or RCC and severe renal impairment (creatinine clearance < 30 mL/min calculated by Cockcroft-Gault equation using actual body weight) is 10 mg orally once daily. For additional information regarding renal toxicity with lenvatinib, refer to the prescribing information for lenvatinib.

Lenvatinib Dose Modifications for Severe Hepatic Impairment

The recommended dosage of lenvatinib for patients with endometrial carcinoma or RCC and severe hepatic impairment (Child-Pugh C) is 10 mg orally once daily. For additional information regarding hepatotoxicity with lenvatinib, refer to the prescribing information for lenvatinib.

Preparation and administration

- Protect from light. Do not freeze. Do not shake.
- Equilibrate the vial of KEYTRUDA to room temperature.
- Prior to dilution, the vial of liquid can be out of refrigeration (at or below 25 °C) for up to 24 hours.
- Parenteral medicine products should be inspected visually for particulate matter and discolouration prior to administration. 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 4 mL (100 mg) of KEYTRUDA and transfer into an intravenous bag containing 0,9 % sodium chloride or 5 % glucose (dextrose), to prepare a diluted solution with a final concentration ranging from 1 to 10 mg/mL. Mix diluted solution by gentle inversion.
- Do not freeze the infusion solution.

- The product does not contain a preservative. The diluted product should be used immediately. If not used immediately, diluted solutions of KEYTRUDA solutions may be stored at room temperature for a cumulative time of up to 6 hours. Diluted solutions of KEYTRUDA may also be stored under refrigeration at 2 to 8 °C; however, the total time from dilution of KEYTRUDA to completion of infusion should not exceed 96 hours. If refrigerated, allow the vials and/or IV bags to come to room temperature prior to use.
- Translucent to white proteinaceous particles may be seen in the diluted solution.
- Administer infusion solution intravenously over 30 minutes using a sterile, non-pyrogenic, low-protein binding 0,2 to 5 µm in-line or add-on filter.
- Do not co-administer other medicines through the same infusion line.
- Discard any unused portion left in the vial.

Special populations

Paediatric patients

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.

Elderly patients

No overall differences in safety or efficacy were reported between elderly patients (65 years and over) and younger patients (less than 65 years). No dose adjustment is necessary in this population (see sections 4.4 and 5.2).

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 or moderate hepatic impairment. KEYTRUDA has not been studied in patients with severe hepatic impairment (see sections 4.4 and 5.2).

4.3 Contraindications

KEYTRUDA is contraindicated in patients with hypersensitivity to pembrolizumab or any of the inactive ingredients listed in section 6.1.

Pregnancy and Lactation (see section 4.6).

4.4 Special warnings and precautions for use

Immune-mediated adverse reactions

Immune-mediated adverse reactions, including severe and fatal cases, have occurred in patients receiving KEYTRUDA. Immune-mediated adverse reactions can occur after discontinuation of treatment. Excluding cases involving the endocrine system whose management often required permanent hormone replacement therapy, approximately 1/3 of immune-mediated adverse reactions did not resolve with interruptions of KEYTRUDA, administration of corticosteroids and/or supportive case. Immune-mediated adverse reactions affecting more than one body system can occur simultaneously.

For suspected immune-mediated adverse reactions, ensure adequate evaluation to confirm aetiology or exclude other causes. Based on the severity of the adverse reaction, withhold KEYTRUDA and administer corticosteroids. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Based on limited data from clinical studies in patients whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered. Restart KEYTRUDA if the adverse reaction remains at Grade 1 or less following corticosteroid taper. If another episode of a severe adverse reaction occurs, permanently discontinue KEYTRUDA. (See sections 4.2 and 4.4 above.)

Immune-mediated pneumonitis

Pneumonitis (including fatal cases) has been reported in patients receiving KEYTRUDA (see section 4.8). Monitor patients for signs and symptoms of pneumonitis. If pneumonitis is suspected, evaluate with radiographic imaging and exclude other causes. Administer corticosteroids for Grade 2 or greater events (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper), withhold KEYTRUDA for moderate (Grade 2) pneumonitis, and permanently discontinue KEYTRUDA for severe (Grade 3), life-threatening (Grade 4) or recurrent moderate (Grade 2) pneumonitis. (See sections 4.2 and 4.4 above.)

Immune-mediated colitis

Colitis has been reported in patients receiving KEYTRUDA (see section 4.8). Monitor patients for signs and symptoms of colitis and exclude other causes. Administer corticosteroids for Grade 2 or greater events (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper), withhold KEYTRUDA for moderate (Grade 2) or severe (Grade 3) colitis, and

permanently discontinue KEYTRUDA for life-threatening (Grade 4) colitis. (See sections 4.2 and 4.4 above.)

Immune-mediated hepatitis

Hepatitis has been reported in patients receiving KEYTRUDA (see section 4.8). Monitor patients 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 exclude other causes. Administer corticosteroids (initial dose of 0,5 to 1 mg/kg/day [for Grade 2 events] and 1 to 2 mg/kg/day [for Grade 3 or greater events] prednisone or equivalent followed by a taper) and, based on severity of liver enzyme elevations, withhold or discontinue KEYTRUDA. (See sections 4.2 and 4.4 above.)

Immune-mediated nephritis

Nephritis has been reported in patients receiving KEYTRUDA (see section 4.8). Monitor patients for changes in renal function and exclude other causes. Administer corticosteroids for Grade 2 or greater events (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper), withhold KEYTRUDA for moderate (Grade 2), and permanently discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) nephritis. (See sections 4.2 and 4.4 above.)

Immune-mediated endocrinopathies

Adrenal insufficiency (primary and secondary) has been reported in patients receiving KEYTRUDA. Hypophysitis has also been reported in patients receiving KEYTRUDA (see section 4.8). Monitor patients for signs and symptoms of adrenal insufficiency and hypophysitis (including hypopituitarism) and exclude other causes. Administer corticosteroids to treat adrenal

insufficiency and other hormone replacement as clinically indicated, withhold KEYTRUDA for moderate (Grade 2), withhold or discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency or hypophysitis. (See sections 4.2 and 4.4 above.)

Type 1 diabetes mellitus, including diabetic ketoacidosis, has been reported in patients receiving KEYTRUDA (see section 4.8). Monitor patients for hyperglycaemia or other signs and symptoms of diabetes. Administer insulin for type 1 diabetes and withhold KEYTRUDA in cases of severe hyperglycaemia until metabolic control is achieved.

Thyroid disorders including hyperthyroidism, hypothyroidism and thyroiditis, have been reported in patients receiving KEYTRUDA and can occur at any time during treatment; therefore, monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and clinical signs and symptoms of thyroid disorders. Hypothyroidism may be managed with replacement therapy without treatment interruption and without corticosteroids. Hyperthyroidism may be managed symptomatically. Withhold or discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) hyperthyroidism. (See sections 4.2 and 4.4 above.)

For patients with severe (Grade 3) or life-threatening (Grade 4) endocrinopathy that improves to Grade 2 or lower and is controlled with hormone replacement, continuation of KEYTRUDA may be considered.

Severe skin reactions

Immune-mediated severe skin reactions have been reported in patients treated with KEYTRUDA. Monitor patients for suspected severe skin reactions and exclude other causes. Based on the severity of the adverse reaction, withhold or permanently discontinue KEYTRUDA and administer corticosteroids (see section 4.2).

Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some with fatal outcome, have been reported in patients treated with KEYTRUDA. For signs or symptoms of SJS or TEN, withhold KEYTRUDA and refer the patient for specialised care for assessment and treatment. If SJS or TEN is confirmed, permanently discontinue KEYTRUDA (see section 4.2).

Other immune-mediated adverse reactions

The following additional clinically significant, immune-mediated adverse reactions were reported in less than 1 % of patients treated with KEYTRUDA: uveitis, myositis, Guillain-Barré syndrome, pancreatitis, encephalitis, sarcoidosis, myasthenic syndrome/myasthenia gravis (including exacerbation), myelitis vasculitis and hypoparathyroidism. The following was reported in other clinical studies with KEYTRUDA or in post-marketing use: myocarditis, sclerosing cholangitis and optic neuritis.

Some of these immune-mediated adverse reactions have been severe.

Transplant-related adverse reactions

Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with KEYTRUDA. Treatment with KEYTRUDA may increase the risk of rejection in solid organ transplant recipients.

Acute graft-versus-host-disease (GVHD), including fatal GVHD, after treatment with KEYTRUDA has been reported in patients with a history of allogeneic haematopoietic stem cell transplant (HSCT). Patients who experienced GVHD after their transplant procedure may be at increased risk for GVHD after treatment with KEYTRUDA. Consider the benefit of treatment with KEYTRUDA versus the risk of possible GVHD in patients with a history of allogeneic HSCT.

Elevated liver enzymes when KEYTRUDA is given in combination with axitinib for RCC

When KEYTRUDA 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). Monitor liver enzymes before initiation of and periodically throughout treatment. Consider more frequent monitoring of liver enzymes as compared to when the drugs are used in monotherapy. Follow medical management guidelines for both drugs. (See section 4.2 and the prescribing information for axitinib.)

Increased mortality in patients with multiple myeloma when KEYTRUDA is added to a thalidomide analogue and dexamethasone

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

Infusion-related reactions

Severe infusion reactions including hypersensitivity and anaphylaxis have been reported in 6 (0,2 %) of 2 799 patients receiving KEYTRUDA in KEYNOTE-001, KEYNOTE-002, KEYNOTE-006 and KEYNOTE-010. For severe infusion reactions, stop infusion and permanently discontinue KEYTRUDA (see section 4.2). Patients with mild or moderate infusion reaction may continue to receive KEYTRUDA with close monitoring; pre-medication with antipyretic and antihistamine may be considered.

Contains sucrose which may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5 Interaction with other medicine products and other forms of interaction

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

The use of systemic corticosteroids or immunosuppressants before starting KEYTRUDA should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of KEYTRUDA. However, systemic corticosteroids or other immunosuppressants can be used after starting KEYTRUDA to treat immune-mediated adverse reactions (see section 4.4). Corticosteroids can also be used as premedication, when KEYTRUDA is used in combination with chemotherapy, as anti-emetic prophylaxis and/or to alleviate chemotherapy-related adverse reactions.

4.6 Fertility, pregnancy and lactation

Pregnancy

KEYTRUDA should not be used during pregnancy and lactation (see section 4.3).

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. These results indicate a potential risk, based on its mechanism of action, that administration of KEYTRUDA during pregnancy could cause foetal harm, including increased rates of abortion or stillbirth. Human IgG4 (immunoglobulin) is known to cross the placental barrier and pembrolizumab is an IgG4; therefore, pembrolizumab has the potential to be transmitted from the mother to the developing

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

Breastfeeding

Mothers should not breastfeed their infants while receiving KEYTRUDA or for 4 months after the last dose (see section 4.3).

Fertility

There are no effects of pembrolizumab on male reproductive organs in the 1-month and 6-month repeat-dose toxicity studies in Cynomologus monkeys. There are no data in humans on the effect of KEYTRUDA on male fertility.

4.7 Effects on ability to drive and use machines

KEYTRUDA may influence the ability to drive and use machines. Patients should not drive and use machines until they know how treatment with KEYTRUDA affects them (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 frequencies included below and in Table 2 are based on all reported adverse drug reactions, regardless of the investigator assessment of causality.

Pembrolizumab in monotherapy (see section 4.2)

The safety of KEYTRUDA as monotherapy has been evaluated in 6 185 patients with advanced melanoma, resected Stage III melanoma (adjuvant therapy), NSCLC, cHL, urothelial carcinoma, HNSCC or CRC across four doses (2 mg/kg every 3 weeks, 200 mg every 3 weeks or 10 mg/kg every 2 or 3 weeks) in clinical studies. 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 KEYTRUDA 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).

Pembrolizumab in combination with chemotherapy (see section 4.2)

The safety of pembrolizumab in combination with chemotherapy has been evaluated in 2 033 patients with NSCLC, HNSCC, oesophageal carcinoma or TNBC receiving 200 mg, 2 mg/kg or 10 mg/kg pembrolizumab every 3 weeks, in clinical studies. In this patient population, the most frequent adverse reactions were anaemia (52 %), nausea (52 %), fatigue (37 %), constipation (34 %), neutropenia (33 %), diarrhoea (32 %), decreased appetite (30 %) 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, and in patients with TNBC were 78 % for pembrolizumab combination therapy and 74 % for chemotherapy alone.

Pembrolizumab in combination with tyrosine kinase inhibitor (TKI) (see section 4.2)

The safety of pembrolizumab in combination with axitinib or lenvatinib in advanced RCC, and in combination with lenvatinib in advanced EC has been evaluated in a total of 1 456 patients with advanced RCC or advanced EC receiving 200 mg pembrolizumab every 3 weeks with either axitinib 5 mg twice daily or lenvatinib 20 mg once daily in clinical studies, as appropriate. In these patient population, the most frequent adverse reactions were diarrhoea (58 %), hypertension (54 %), hypothyroidism (46 %), fatigue (41 %), decreased appetite (40 %), nausea (40 %), arthralgia (30 %), vomiting (28 %), weight decreased (28 %), dysphonia (28 %), abdominal pain (28 %), proteinuria (27 %), palmar-plantar erythrodysaesthesia syndrome (26 %), rash (26 %), stomatitis (25 %), constipation (25 %), musculoskeletal pain (23 %), headache (23 %) and cough (21 %). Grades 3-5 adverse reactions in patients with RCC were 80 % for pembrolizumab in combination with either axitinib or lenvatinib and 71 % for sunitinib alone. In patients with EC, Grades 3-5 adverse reactions were 89 % for pembrolizumab in combination with lenvatinib and 73 % for chemotherapy alone.

Tabulated summary of adverse reactions

Adverse reactions observed in clinical studies with KEYTRUDA as monotherapy or in combination with chemotherapy or other anti-tumour medicines or reported from post-marketing use of KEYTRUDA are listed in **Table 2**. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1 000 to < 1/100), rare (≥ 1/10 000 to < 1/1 000), very rare (< 1/10 000) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness. Adverse reactions known to occur with pembrolizumab or combination therapy components 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.

For additional safety information when pembrolizumab is administered in combination, refer to the prescribing information for the respective combination therapy components.

Table 2: Adverse reactions in patients treated with pembrolizumab†

	Monotherapy	**In combination with chemotherapy**	**In combination with axitinib or lenvatinib**
Infections and Infestations			
Very common			urinary tract infection
Common	pneumonia	pneumonia	pneumonia
Blood and lymphatic system disorders			
Very common	anaemia	neutropenia, anaemia, thrombocytopenia, leukopenia	anaemia
Common	thrombocytopenia, neutropenia lymphopenia	febrile neutropenia, lymphopenia	neutropenia, thrombocytopenia, lymphopenia, leukopenia
Uncommon	leukopenia, immune thrombocytopenia, eosinophilia	eosinophilia	eosinophilia
Rare	haemophagocytic	haemolytic anaemia,	

	lymphohistiocytosis, haemolytic anaemia, pure red cell aplasia	immune thrombocytopenia	
Immune system disorders			
Common	infusion-related reaction*	infusion-related reaction*	infusion-related reaction*
Uncommon	sarcoidosis		
Rare		sarcoidosis	
Not known	solid organ transplant rejection		
Endocrine disorders			
Very common	hypothyroidism*	hypothyroidism*	hypothyroidism
Common	hyperthyroidism	adrenal insufficiency*, thyroiditis*, hyperthyroidism*	adrenal insufficiency*, hyperthyroidism, thyroiditis*
Uncommon	adrenal insufficiency*, hypophysitis*, thyroiditis*	hypophysitis*	hypophysitis*
Rare	hypoparathyroidism	hypoparathyroidism	hypoparathyroidism
Metabolism and nutrition disorders			
Very common	decreased appetite	hypokalaemia, decreased appetite	decreased appetite
Common	hyponatraemia,	hyponatraemia,	hyponatraemia,

	hypokalaemia, hypocalcaemia	hypocalcaemia	hypokalaemia, hypocalcaemia
Uncommon	type 1 diabetes mellitus*	type 1 diabetes mellitus*	type 1 diabetes mellitus*
Psychiatric disorders			
Very common		insomnia	
Common	insomnia		insomnia
Nervous system disorders			
Very common	headache	neuropathy peripheral, headache, dizziness, dysgeusia	headache, dysgeusia
Common	dizziness, neuropathy peripheral, lethargy, dysgeusia	lethargy	dizziness, neuropathy peripheral, lethargy
Uncommon	myasthenic syndrome*, epilepsy	encephalitis*, epilepsy	myasthenic syndrome*, encephalitis*
Rare	encephalitis*, Guillain-Barré syndrome*, encephalitis, myelitis*, optic neuritis, meningitis (aseptic)*	Guillain-Barré syndrome*, myasthenic syndrome	optic neuritis
Eye disorders			

Common	dry eye	dry eye	dry eye
Uncommon	uveitis*		uveitis*
Rare	Vogt-Koyanagi-Harada syndrome	uveitis*	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*, pericardial effusion, pericarditis	myocarditis, pericardial effusion
Vascular disorders			
Very common			hypertension
Common	hypertension	hypertension	
Uncommon		vasculitis*	vasculitis*
Rare	vasculitis*		
Respiratory, thoracic and mediastinal disorders			
Very common	dyspnoea, cough	dyspnoea, cough	dyspnoea, cough
Common	pneumonitis*	pneumonitis*	pneumonitis*
Gastrointestinal disorders			
Very common	diarrhoea, abdominal pain*, nausea, vomiting, constipation	nausea, diarrhoea, vomiting, abdominal pain*, constipation	diarrhoea, abdominal pain*, nausea, vomiting, constipation

Common	colitis*, dry mouth	colitis*, gastritis, dry mouth	colitis*, pancreatitis*, gastritis, dry mouth
Uncommon	pancreatitis*, gastritis, gastrointestinal ulceration*	pancreatitis*, gastrointestinal ulceration*	gastrointestinal ulceration*
Rare	small intestinal performation	small intestinal performation	small intestinal performation
Hepatobiliary disorders			
Common	hepatitis*	hepatitis*	hepatitis*
Rare	cholangitis sclerosing	cholangitis sclerosing*	
Skin and subcutaneous tissue disorders			
Very common	pruritus*, rash*	alopecia, rash*, pruritus*	rash*, pruritus*
Common	severe skin reactions*, erythema, dermatitis, dry skin, vitiligo*, eczema, alopecia, dermatitis acneiform	severe skin reactions*, erythema, dermatitis acneiform, dermatitis, dry skin, eczema	severe skin reactions*, dermatitis, dry skin, erythema, dermatitis acneiform, alopecia
Uncommon	psoriasis, lichenoid keratosis*, papule, hair colour changes	psoriasis, lichenoid keratosis*, vitiligo*, papule	eczema, lichenoid keratosis*, psoriasis, vitiligo*, papule, hair colour changes
Rare	Stevens-Johnson	Stevens-Johnson	toxic epidermal

	syndrome, erythema nodosum, toxic epidermal necrolysis	syndrome, erythema nodosum, hair colour changes	necrolysis, Stevens-Johnson syndrome
Musculoskeletal and connective tissue disorders			
Very common	musculoskeletal pain*, arthralgia	arthralgia, musculoskeletal pain*, myositis*	arthralgia, musculoskeletal pain*, myositis*, pain in extremity
Common	myositis*, pain in extremity, arthritis*	pain in extremity, arthritis*	arthritis*
Uncommon	tenosynovitis*	tenosynovitis*	tenosynovitis*
Rare	Sjogren's syndrome	Sjogren's syndrome	Sjogren's syndrome
Renal and urinary disorders			
Common		acute kidney injury	nephritis*
Uncommon	nephritis*	nephritis*, cystitis noninfective	
Rare	cystitis noninfective		cystitis noninfective
General disorders and administration site conditions			
Very common	fatigue, asthenia, oedema*, pyrexia	fatigue, asthenia, pyrexia, oedema*	fatigue, asthenia, oedema*, pyrexia
Common	influenza-like illness, chills	influenza-like illness, chills	influenza-like illness, chills

Investigations			
Very common		alanine aminotransferase increased, aspartate aminotransferase increased	lipase increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood creatinine increased
Common	alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, hypercalcaemia, blood bilirubin increased, blood creatinine increased	blood creatinine increased, blood alkaline phosphatase increased, hypercalcaemia, blood bilirubin increased	amylase increased, blood bilirubin increased, blood alkaline phosphatase increased, hypercalcaemia,
Uncommon	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:

- infusion-related reactions (drug hypersensitivity, anaphylactic reaction, anaphylactoid reaction, hypersensitivity, infusion-related hypersensitivity reaction, cytokine release syndrome and serum sickness)
- hypothyroidism (myxoedema and immune-mediated hypothyroidism)
- adrenal insufficiency (Addison's disease, adrenocortical insufficiency acute, secondary adrenocortical insufficiency)
- thyroiditis, (autoimmune thyroiditis, thyroid disorder and thyroiditis acute)
- hyperthyroidism (Basedow's disease)
- hypophysitis (hypopituitarism, lymphocytic hypophysitis)
- type 1 diabetes mellitus (diabetic ketoacidosis)
- myasthenic syndrome (myasthenia gravis, including exacerbation)
- encephalitis (autoimmune encephalitis, noninfective encephalitis)
- Guillain-Barré syndrome (axonal neuropathy and demyelinating polyneuropathy)
- myelitis (including transverse myelitis)
- meningitis aseptic (meningitis, meningitis non-infective)
- uveitis (chorioretinitis, iritis and iridocyclitis)
- myocarditis (autoimmune myocarditis)
- vasculitis (central nervous system vasculitis, aortitis, giant cell arteritis)
- pneumonitis (interstitial lung disease, organising pneumonia, immune-mediated pneumonitis and immune-mediated lung disease)
- abdominal pain (abdominal discomfort, abdominal pain upper and abdominal pain lower)

- colitis (colitis microscopic, enterocolitis, enterocolitis haemorrhagic, autoimmune colitis and immune-mediated enterocolitis)
- pancreatitis (autoimmune pancreatitis, and pancreatitis acute and immune-mediated pancreatitis)
- gastrointestinal ulceration (gastric ulcer and duodenal ulcer)
- hepatitis (autoimmune hepatitis, immune-mediated hepatitis, drug induced liver injury and acute hepatitis)
- cholangitis sclerosing (immune-mediated cholangitis)
- pruritus (urticaria, urticaria popular and pruritus genital)
- rash (rash erythematous, rash follicular, rash macular, rash maculo-papular, rash papular, rash pruritic, rash vesicular and genital rash)
- severe skin reactions (dermatitis exfoliative generalised, exfoliative rash, pemphigus and Grade ≥ 3 of the following: acute febrile neutrophilic dermatosis, contusion, decubitus ulcer, dermatitis bullous, 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)
- vitiligo (skin depigmentation, skin hypopigmentation and hypopigmentation of the eyelid)
- lichenoid keratosis (lichen planus and lichen sclerosus)
- musculoskeletal pain (musculoskeletal discomfort, back pain, musculoskeletal stiffness, musculoskeletal chest pain and torticollis)
- myositis (myalgia, myopathy, necrotising myositis, polymyalgia rheumatica and rhabdomyolysis)

- arthritis (joint swelling, polyarthritis, joint effusion, autoimmune arthritis and immune-mediated arthritis)
- tenosynovitis (tendonitis, synovitis and tendon pain)
- 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)
- 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 KEYTRUDA across four doses (2 mg/kg every 3 weeks, 10 mg/kg every 2 or 3 weeks or 200 mg every 3 weeks). The management guidelines for these adverse reactions are described in section 4.4.

Immune-related adverse reactions (see section 4.4)

Pneumonitis: Pneumonitis occurred in 324 (4,2 %) patients, including Grade 2, 3, 4 or 5 cases in 143 (1,9 %), 81 (1,1 %), 19 (0,2 %) and 9 (0,1 %) patients, respectively, receiving KEYTRUDA. The median time to onset of pneumonitis was 3,9 months (range 2 days to 27,2 months). The median duration was 2,0 months (range 1 day to 51,0+ months). Pneumonitis occurred more frequently in patients with a history of prior thoracic radiation (8,1 %) than in patients who did not receive prior thoracic radiation (3,9 %). Pneumonitis led to discontinuation of KEYTRUDA in 131 (1,7 %) patients. Pneumonitis resolved in 190 patients, 6 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.

Colitis: Colitis occurred in 158 (2,1 %) patients, including Grade 2, 3 or 4 cases in 49 (0,6 %), 82 (1,1%) and 6 (0,1 %) patients, respectively, receiving KEYTRUDA. The median time to onset of colitis was 4,3 months (range 2 days to 24,3 months). The median duration was 1,1 months (range 1 day to 45,2 months). Colitis led to discontinuation of KEYTRUDA in 48 (0,6 %) patients. Colitis resolved in 130 patients, 2 with sequelae. In patients with CRC treated with KEYTRUDA as monotherapy (n=153), the incidence of colitis was 6,5 % (all Grades) with 2,0 % Grade 3 and 1,3 % Grade 4.

Hepatitis: Hepatitis occurred in 80 (1,0 %) patients, including Grade 2, 3 or 4 cases in 12 (0,2 %), 55 (0,7 %) and 8 (0,1 %) patients, respectively, receiving KEYTRUDA. The median time to onset of hepatitis was 3,5 months (range 8 days to 26,3 months). The median duration was 1,3 months (range 1 day to 20,9+ months). Hepatitis led to discontinuation of KEYTRUDA in 37 (0,5 %) patients. Hepatitis resolved in 60 patients.

Nephritis: Nephritis occurred in 37 (0,5 %) patients, including Grade 2, 3 or 4 cases in 11 (0,1 %), 19 (0,2 %) and 2 (< 0,1 %) patients, respectively, receiving KEYTRUDA as monotherapy. The median time to onset of nephritis was 4,2 months (range 12 days to 21,4 months). The median duration was 3,3 months (range 6 days to 28,2+ months). Nephritis led to

discontinuation of pembrolizumab in 17 (0,2 %) patients. Nephritis resolved in 20 patients, 5 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.

Endocrinopathies: Adrenal insufficiency occurred in 74 (1,0 %) patients, including Grade 2, 3 or 4 cases in 34 (0,4 %), 31 (0,4 %) and 4 (0,1 %) patients, respectively, receiving pembrolizumab. The median time to onset of adrenal insufficiency was 5,4 months (range 1 day to 23,7 months). The median duration was not reached (range 3 days to 40,1+ months). Adrenal insufficiency led to discontinuation of KEYTRUDA in 13 (0,2 %) patients. Adrenal insufficiency resolved in 17 patients, 11 with sequelae.

Hypophysitis occurred in 52 (0,7 %) patients, including Grade 2, 3 or 4 cases in 23 (0,3 %), 24 (0,3 %) and 1 (< 0,1 %) patients, respectively, receiving KEYTRUDA. 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 48,1+ months). Hypophysitis led to discontinuation of KEYTRUDA in 14 (0,2 %) patients. Hypophysitis resolved in 15 patients, 8 with sequelae.

Hyperthyroidism occurred in 394 (5,2 %) patients, including Grade 2 or 3 cases in 108 (1,4 %) and 9 (0,1 %) patients, respectively, receiving KEYTRUDA. The median time to onset of hyperthyroidism was 1,4 months (range 1 day to 23,2 months). The median duration was 1,6 months (range 4 days to 43,1+ months). Hyperthyroidism led to discontinuation of KEYTRUDA in 4 (0,1 %) patients. Hyperthyroidism resolved in 315 (79,9 %) patients, 11 with sequelae. In patients with RCC and melanoma treated with pembrolizumab monotherapy in the adjuvant setting (n=1,480), the incidence of hyperthyroidism was 10,9 %, the majority of which were Grade 1 or 2.

Hypothyroidism occurred in 939 (12,3 %) patients, including Grade 2 or 3 cases in 687 (9,0 %) and 8 (0,1 %) patients, respectively, receiving KEYTRUDA. 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 63,0+ months). Hypothyroidism led to discontinuation of pembrolizumab in 6 (0,1 %) patients. Hypothyroidism resolved in 200 (21,3 %) patients, 16 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 KEYTRUDA as monotherapy (n=909), the incidence of hypothyroidism was 16,1 % (all Grades) with 0,3 % Grade 3. In patients with HNSCC treated with KEYTRUDA 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. In patients treated with pembrolizumab in combination with axitinib or lenvatinib (n=1 456), the incidence of hypothyroidism was 46,2 % (all Grades) with 0,8 % Grade 3 or 4. In patients with RCC and melanoma treated with pembrolizumab monotherapy in the adjuvant setting (n=1 480), the incidence of hypothyroidism was 17,7 %, the majority of which were Grade 1 or 2.

Skin adverse reactions: Immune-related severe skin reactions occurred in 130 (1,7 %) patients, including Grade 2, 3, 4 or 5 cases in 11 (0,1 %), 103 (1,3 %), 1 (< 0,1 %) and 1 (< 0,1 %) patients, respectively, receiving KEYTRUDA. The median time to onset of severe skin reactions was 3,0 months (range 2 days to 25,5 months). The median duration was 1,9 months (range 1 day to 47,1+ months). Severe skin reactions led to discontinuation of KEYTRUDA in 18 (0,2 %) patients. Severe skin reactions resolved in 93 patients, 2 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: 9,4 % for lymphocytes decreased, 7,4 % for sodium decreased, 5,8 % for haemoglobin decreased, 5,3 % for phosphate decreased, 5,3 % for glucose increased, 3,3 % for ALT increased, 3,1 % for AST increased, 2,6 % for alkaline phosphatase increased, 2,3 % for potassium decreased, 2,1 % for potassium increased, 1,9 % for neutrophils decreased, 1,8 % for platelets decreased, 1,8 % for calcium increased, 1,7 % for bilirubin increased, 1,5 % for calcium decreased, 1,4 % for albumin decreased, 1,3 % for creatinine increased, 1,2 % for glucose decreased, 0,8 % for leucocytes decreased, 0,7 % for magnesium increased, 0,5 % for sodium increased, 0,4 % for haemoglobin increased and 0,2 % for magnesium decreased.

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: 44,0 % for neutrophils decreased, 29,4 % for leucocytes decreased, 26,9 % for lymphocytes decreased, 22,1 % for haemoglobin decreased, 13,2 % for platelets decreased, 11,0 % for sodium decreased, 7,7 % for phosphate decreased, 6,8 % for potassium decreased, 6,8 % for ALT increased, 6,1 % for glucose increased, 5,6 % for AST increased, 3,5 % for calcium decreased, 3,2 % for potassium increased, 2,9 % for creatinine increased, 2,2 % for albumin decreased, 2,1 % for alkaline phosphatase increased, 2,0 % for bilirubin increased, 2,0 % for calcium increased, 1,3 % for prothrombin INR increased, 1,2 % for glucose decreased and 0,5 % for sodium increased.

In patients treated with pembrolizumab in combination with axitinib or lenvatinib, the proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 23,0 % for lipase increased (not measured in patients treated with pembrolizumab and axitinib), 12,0 % for lymphocyte decreased, 11,4 % for sodium decreased, 11,2 % for amylase increased, 11,2 % for triglycerides increased, 10,4 % for ALT increased, 8,9 % for AST increased, 7,8 % for glucose increased, 7,3 % for phosphorus decreased, 6,8 % for phosphate decreased, 6,1 % for potassium decreased, 5,1 % for potassium increased, 4,5 % for cholesterol increased, 4,4 % for creatinine increased, 4,2 % for haemoglobin decreased, 4,0 % for magnesium decreased, 3,5 % for neutrophils decreased, 3,1 % for alkaline phosphatase increased, 3,0 % for platelets decreased, 2,8 % for bilirubin increased, 2,2 % for calcium decreased, 1,7 % for white blood cells decreased, 1,6 % for magnesium increased, 1,5 % for prothrombin INR increased, 1,4 % for glucose decreased, 1,2 % for albumin decreased, 1,2 % for calcium increased, 0,4 % for sodium increased and 0,1 % for haemoglobin increased.

Paediatric population

The safety of pembrolizumab as monotherapy has been evaluated in 161 paediatric patients aged 6 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 KEYTRUDA. 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. Long-term safety data of pembrolizumab in adolescents with Stage IIB, IIC and III melanoma treated in the adjuvant setting are currently unavailable.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the **6.04 Adverse Drug Reaction Reporting Form**, found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

In overdose, side effects will be exaggerated and exacerbated. Treatment is symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A.30.1 Biologicals - Antibodies

Mechanism of action

Pembrolizumab 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. Pembrolizumab 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.

The anti-angiogenic effect of Lenvatinib (multi-TKI) in combination with the immune-stimulatory effect of pembrolizumab (anti-PD-1) results in a tumour microenvironment with greater T-cell activation to help overcome primary and acquired resistance to immunotherapy and may improve tumour responses compared to either treatment alone. In preclinical murine models, PD-1 plus TKI inhibitors have demonstrated enhanced anti-tumour activity compared to either agent alone.

Clinical efficacy and safety

Based on the modeling of dose/exposure relationships for efficacy and safety for pembrolizumab, there are no clinically significant differences in efficacy and safety between the doses of 200 mg every 3 weeks or 2 mg/kg 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	Pembrolizumab	Ipilimumab

	10 mg/kg bw every 3 weeks n=277	10 mg/kg bw every 2 weeks n=279	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)

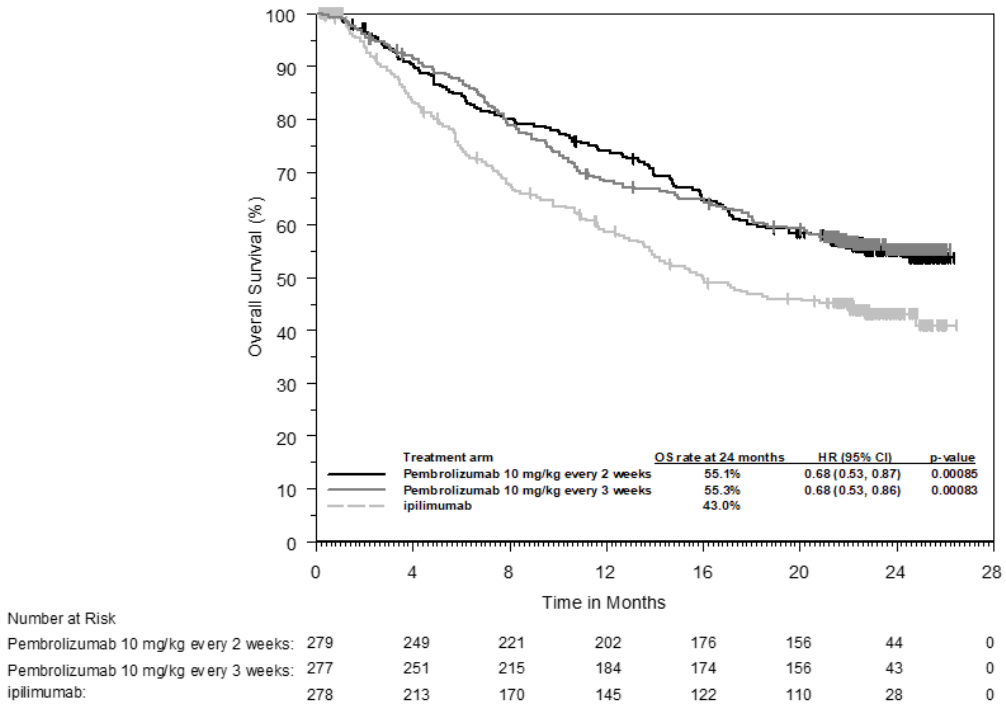
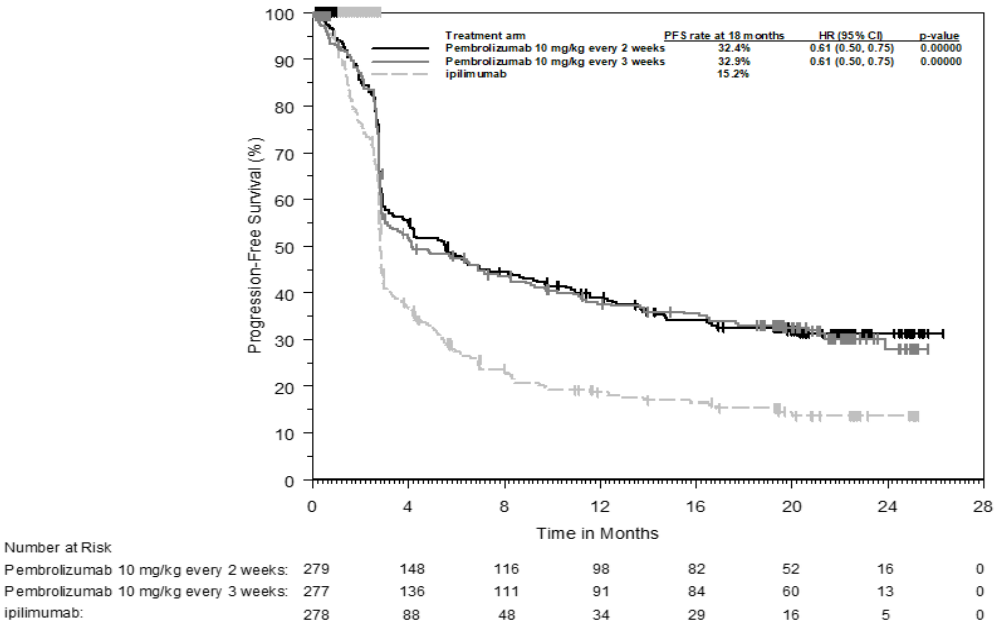


Figure 2: Kaplan-Meier curve for progression-free survival by treatment arm in KEYNOTE-006 (intent to treat population)



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

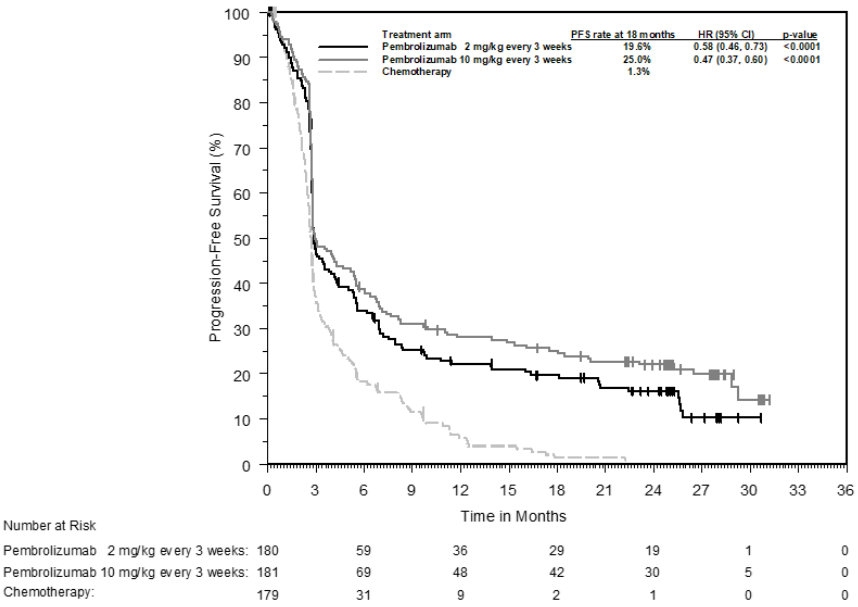
[†]Based on stratified log-rank test

[‡]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)



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	Pembrolizumab 2 mg/kg bw

	every 3 weeks in patients previously treated with ipilimumab n=89	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	0,50 (0,39, 0,66)	---	0,79 (0,50, 1,25)	---

ratio* (95 % CI)				
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	0,68 (0,52, 0,88)	---	0,70 (0,40, 1,22)	---	0,66 (0,41, 1,04)	---

Hazard ratio* (95 % CI)						
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-716: Placebo-controlled study for the adjuvant treatment of patients with resected Stage IIB or IIC melanoma

The efficacy of pembrolizumab was evaluated in KEYNOTE-716, a multicentre, randomised, double-blind, placebo-controlled study in patients with resected Stage IIB or IIC melanoma. A total of 976 patients were randomised (1:1) to receive pembrolizumab 200 mg every three weeks (or the paediatric [12 to 17 years old] dose of 2 mg/kg intravenously [up to a maximum of 200 mg] every three weeks) (n=487) or placebo (n=489), for up to one year or until disease recurrence or unacceptable toxicity. Randomisation was stratified by American Joint Committee on Cancer (AJCC) 8th edition T stage. 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 were ineligible. Patients underwent imaging every six months from randomisation through the 4th year, and then once in year 5 from randomisation or until recurrence, whichever came first.

Among the 976 patients, the baseline characteristics were: median age of 61 years (range 16-87; 39 % age 65 or older; 2 adolescent patients [one per treatment arm]); 60 % male; and ECOG PS of 0 (93 %) and 1 (7 %). Sixty-four percent had Stage IIB and 35 % had Stage IIC.

The primary efficacy outcome measure was investigator-assessed recurrence-free survival (RFS) in the whole population, 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. OS was not formally assessed at the time of this analysis. The study initially demonstrated a statistically significant improvement in RFS (HR 0,65; 95 % CI 0,46, 0,92; p-Value=0,00658) for patients randomised to the pembrolizumab arm compared with placebo at its pre-specified interim analysis. Results reported from the pre-specified final analysis for RFS at a median follow-up of 20,5 months are summarised in **Table 10** and Figure 4. Updated RFS results at a median follow-up of 26,9 months were consistent with the final analysis for RFS for patients randomised to the pembrolizumab arm compared with placebo (HR 0,64; 95 % CI 0,50, 0,84). DMFS results are reported from the interim analysis for DMFS at a median follow-up of 26,9 months in **Table 10** and Figure 5.

Table 10: Efficacy results in KEYNOTE-716

Endpoint	**Pembrolizumab** **200 mg every 3 weeks** **n=48**	**Placebo** **n=489**
RFS		
Number (%) of patients with event	72 (15 %)	115 (24 %)
Median in months (95 % CI)	NR (NR, NR)	NR (29,9, NR)
Hazard ratio* (95 % CI)	0,61 (0,45, 0,82	
p-Value (stratified log-rank)†	0,00046	
DMFS		

Number (%) of patients with event	63 (13 %)	95 (19 %)
Median in months (95 % CI)	NR (NR, NR)	NR (NR, NR)
Hazard ratio* (95 % CI)	0,64 (0,47, 0,88)	
p-Value (stratified log-rank)	0,00292	
*Based on the stratified Cox proportional hazard model †Nominal p-Value based on log-rank test stratified by American Joint Committee on Cancer (AJCC) 8th edition T stage NR = not reached		

Figure 4: Kaplan-Meier curve for recurrence-free survival by treatment arm in KEYNOTE-716 (intent to treat population)

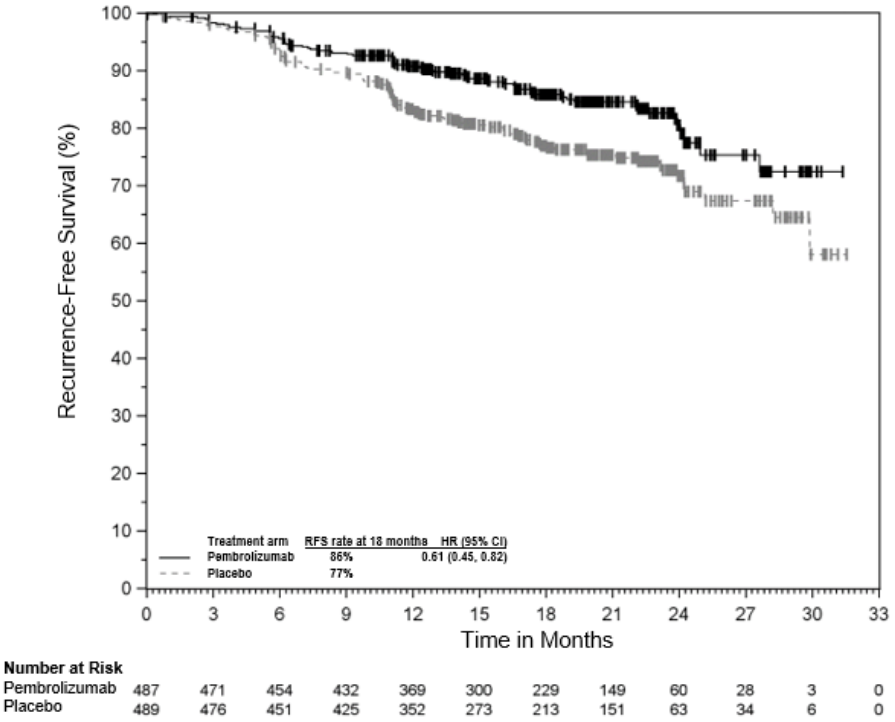
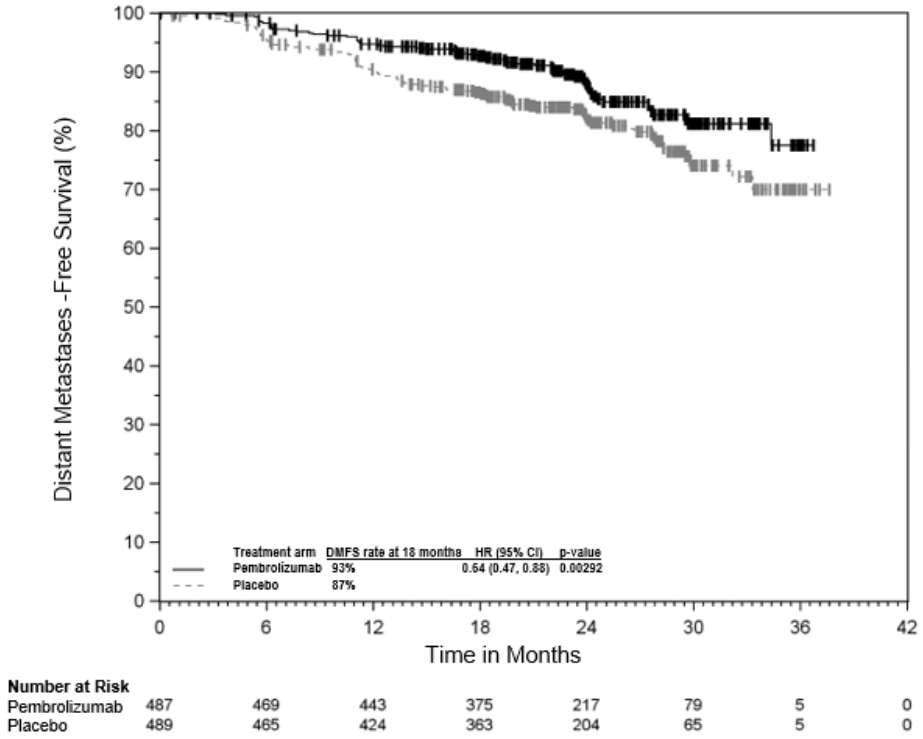


Figure 5: Kaplan-Meier curve for distant metastasis-free survival by treatment arm in KEYNOTE-716 (intent to treat population)



KEYNOTE-054: Placebo-controlled study for the adjuvant treatment of patients with completely resected Stage III 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 11** and Figures 6 and 7.

Table 11: Efficacy results in KEYNOTE-054

Endpoint	Pembrolizumab 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 6: Kaplan-Meier curve for recurrence-free survival by treatment arm in KEYNOTE-054 (intent to treat population)

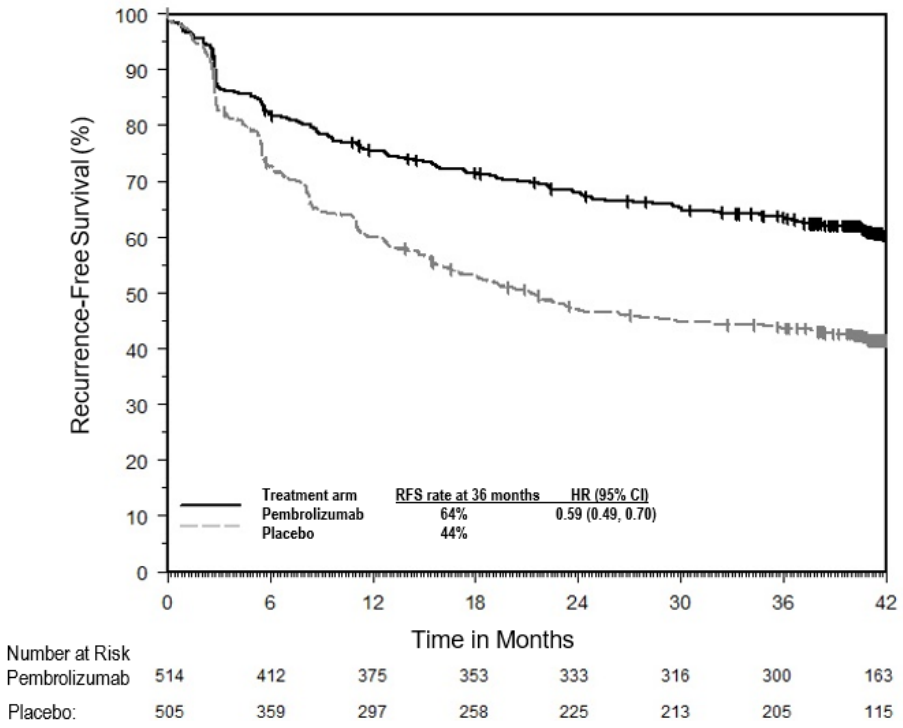
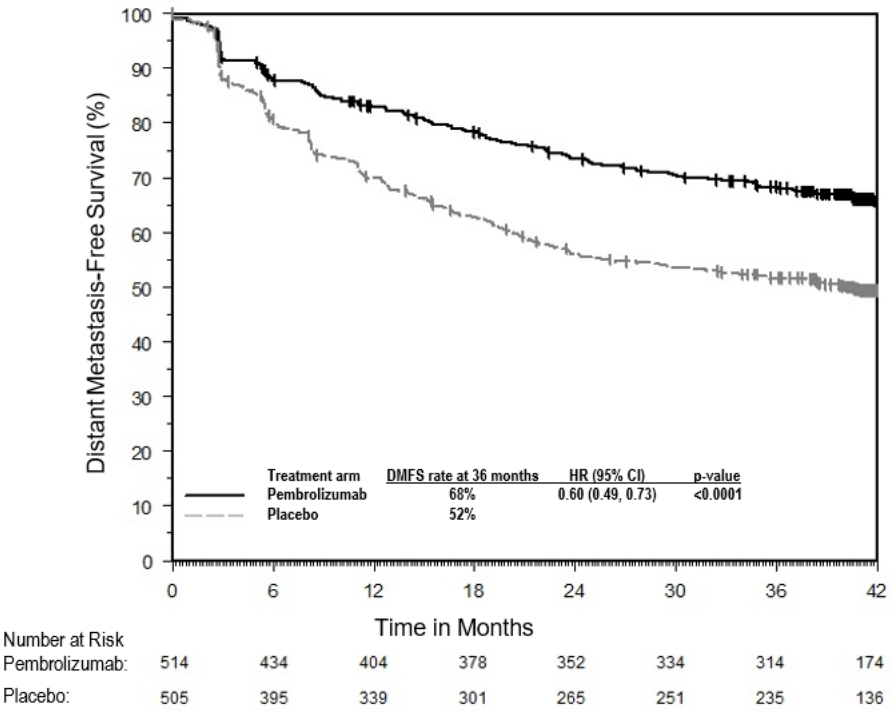


Figure 7: Kaplan-Meier curve for distant metastasis-free survival by treatment arm in KEYNOTE-054 (intent to treat population)



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 12** summarises key efficacy measures for the entire intent to treat (ITT) population. PFS and ORR results are reported from an interim analysis at a median follow-up of 11 months. OS results are reported from the final analysis at a median follow-up of 25 months.

Table 12: Efficacy results in KEYNOTE-024

Endpoint	Pembrolizumab 200 mg every 3 weeks n=154	Chemotherapy n=151
PFS		
Number (%) of patients with event	73 (47 %)	116 (77 %)
Hazard ratio* (95 % CI)	0,50 (0,37, 0,68)	
p-Value†	< 0,001	
Median in months (95 % CI)	10,3 (6,7, NA)	6,0 (4,2, 6,2)
OS		
Number (%) of patients with event	73 (47 %)	96 (64 %)
Hazard ratio* (95 % CI)	0,63 (0,47, 0,86)	
p-Value†	0,002	
Median in months (95 % CI)	30,0 (18,3, NA)	14,2 (9,8, 19,0)
Objective response rate		
ORR % (95 % CI)	45 % (37, 53)	28 % (21, 36)
Complete response %	4 %	1 %
Partial response %	41 %	27 %
Response duration‡		
Median in months (range)	Not reached (1,9+, 14,5+)	6,3 (2,1+, 12,6+)

% with duration ≥ 6 months	88 %§	59 %¶

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

†Based on stratified log-rank test

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

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

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

NA = not available

Figure 8: Kaplan-Meier curve for progression-free survival by treatment arm in KEYNOTE-024 (intent to treat population)

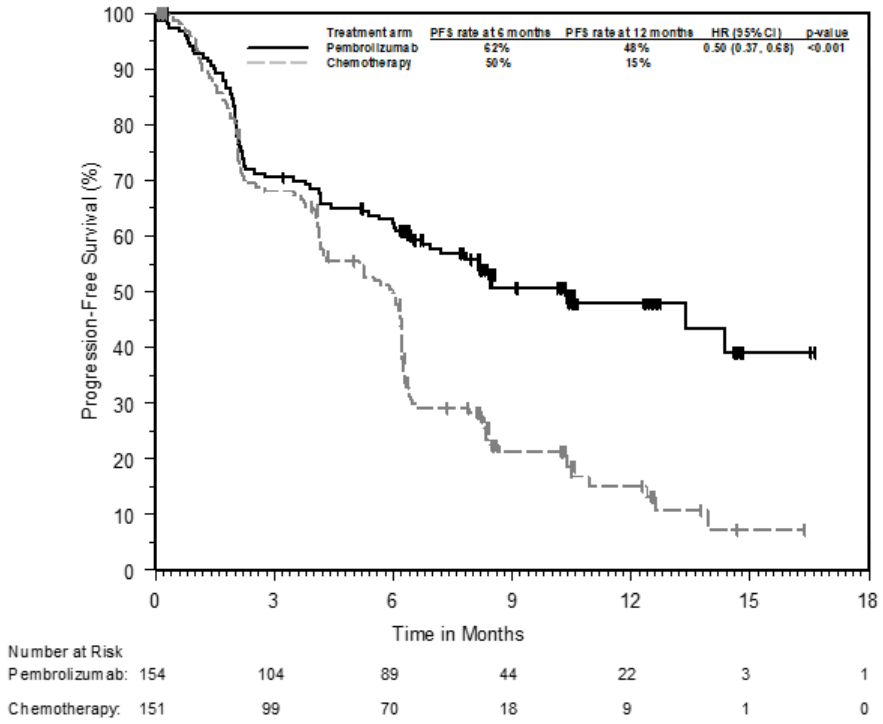
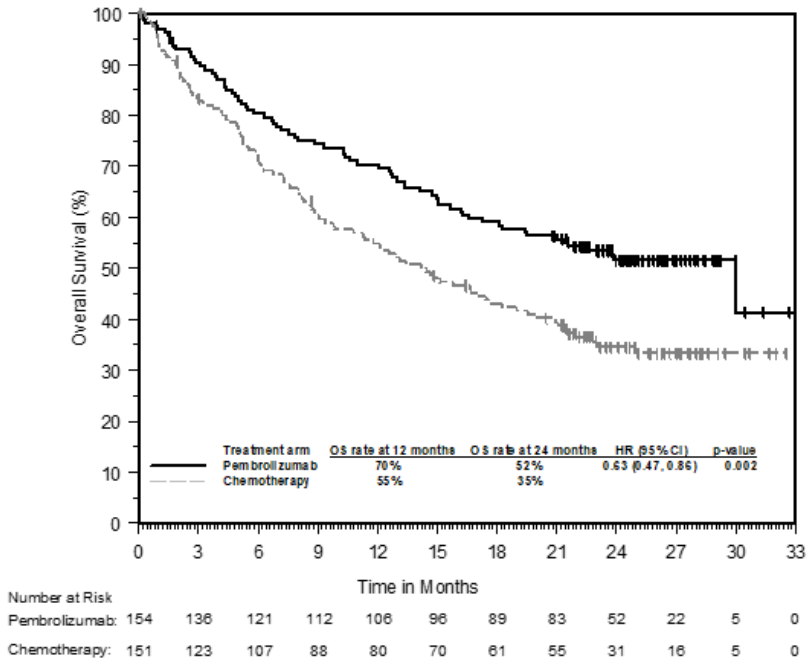


Figure 9: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-024 (intent to treat population)



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

KEYNOTE-042: Controlled study of NSCLC patients naïve to treatment

The safety and efficacy of pembrolizumab were also investigated in KEYNOTE-042, a multicentre, controlled study for the treatment of previously untreated locally advanced or metastatic NSCLC. The study design was similar to that of KEYNOTE-024, except that patients had PD-L1 expression with a ≥ 1 % TPS based on the PD-L1 IHC 22C3 pharmDx™ Kit. Patients

were randomised (1:1) to receive pembrolizumab at a dose of 200 mg every 3 weeks (n=637) or investigator's choice platinum-containing chemotherapy (n=637; including pemetrexed+carboplatin or paclitaxel+carboplatin. Patients with non-squamous NSCLC could receive pemetrexed maintenance.). Assessment of tumour status was performed every 9 weeks for the first 45 weeks, and every 12 weeks thereafter.

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

The primary efficacy outcome measure was OS. Secondary efficacy outcome measures were PFS and ORR (as assessed by BICR using RECIST 1.1). The study demonstrated a statistically significant improvement in OS for patients whose tumours expressed PD-L1 TPS ≥ 1 % randomised to pembrolizumab monotherapy compared to chemotherapy (HR 0,82; 95 % CI 0,71, 0,93 at the final analysis) and in patients whose tumours expressed PD-L1 TPS ≥ 50 % randomised to pembrolizumab monotherapy compared to chemotherapy. **Table 13** summarises key efficacy measures for the TPS ≥ 50 % population at the final analysis performed at a median follow-up of 15,4 months. The Kaplan-Meier curve for OS for the TPS ≥ 50 % population based on the final analysis is shown in Figure 10.

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

Endpoint	Pembrolizumab	Chemotherapy

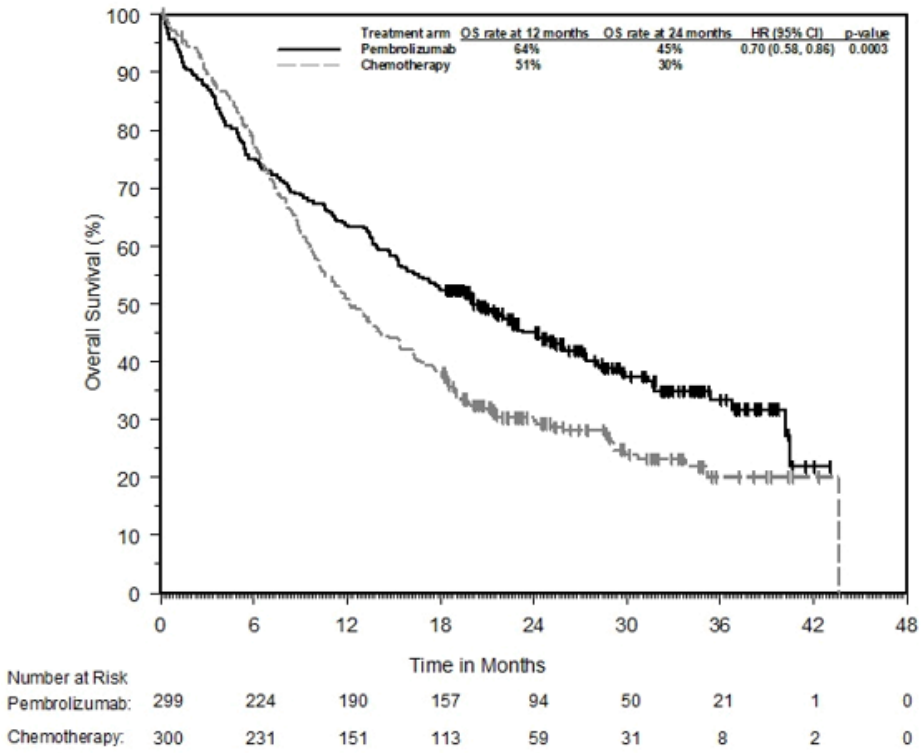
	200 mg every 3 weeks n=299	n=300
OS		
Number (%) of patients with event	180 (60 %)	220 (73 %)
Hazard ratio* (95 % CI)	0,70 (0,58, 0,86)	
p-Value†	0,0003	
Median in months (95 % CI)	20,0 (15,9, 24,2)	12,2 (10,4, 14,6)
PFS		
Number (%) of patients with event	238 (80 %)	250 (83 %)
Hazard ratio* (95 % CI)	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 10: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-042 (patients with PD-L1 expression TPS ≥ 50 %, intent to treat population)



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

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

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

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

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

receiving placebo plus chemotherapy who experienced independently-verified progression of disease were offered pembrolizumab as monotherapy.

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

The primary efficacy outcome measures were OS and PFS (as assessed by BICR using RECIST 1.1). Secondary efficacy outcome measures were ORR and response duration, as assessed by BICR using RECIST 1.1. **Table 14** summarises key efficacy measures and Figures 11 and 12 show the Kaplan-Meier curves for OS and PFS based on the final analysis with a median follow-up of 18,8 months.

Table 14: Efficacy results in KEYNOTE-189

Endpoint	Pembrolizumab + Pemetrexed + Platinum Chemotherapy n=410	Placebo + Pemetrexed + Platinum Chemotherapy n=206
OS[*]		
Number (%) of patients with event	258 (63 %)	163 (79 %)
Hazard ratio[†] (95 % CI)	0,56 (0,46, 0,69)	
p-Value[‡]	< 0,00001	
Median in months (95 % CI)	22,0	10,6

	(19,5, 24,5)	(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 11: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-189 (intent to treat population)

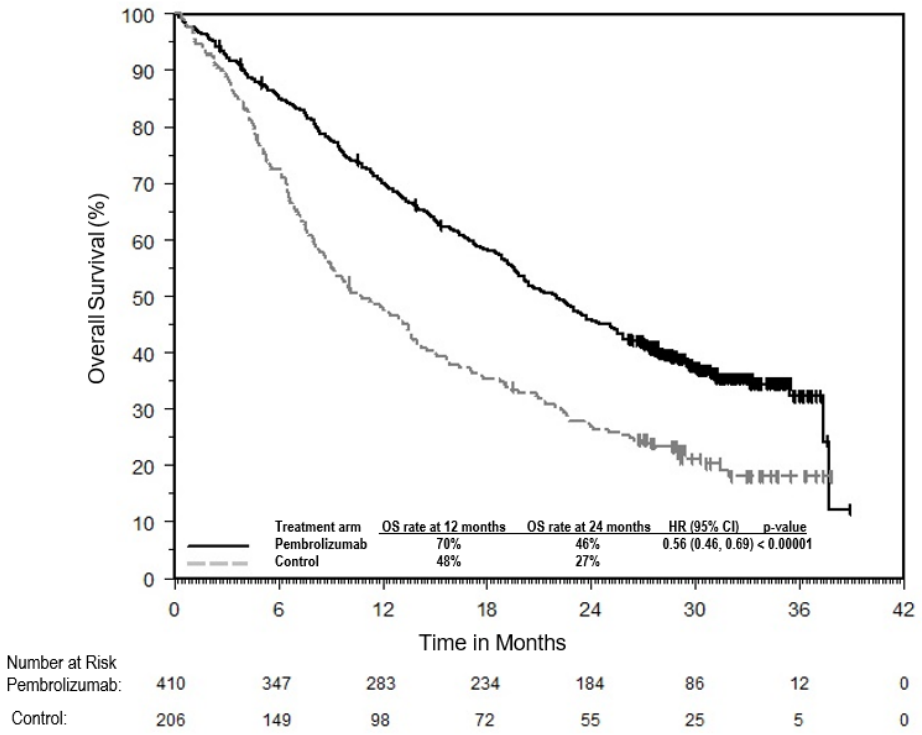
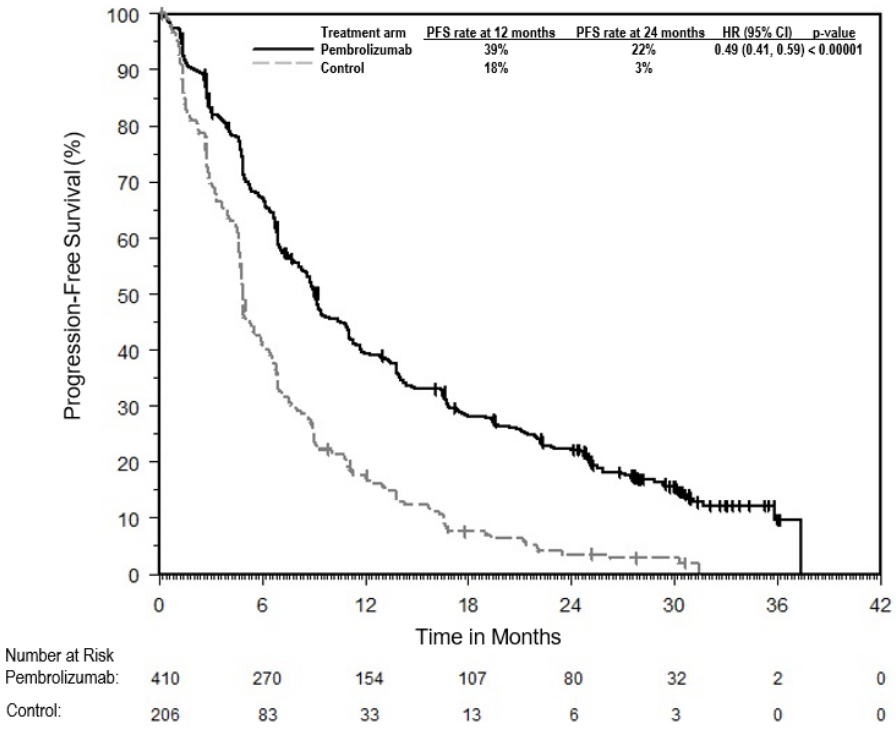


Figure 12: Kaplan-Meier curve for progression-free survival by treatment arm in KEYNOTE-189 (intent to treat population)



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

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

Endpoint	Pembrolizumab combination therapy	Chemotherapy	Pembrolizumab combination therapy	Chemotherapy	Pembrolizumab combination therapy	Chemotherapy
	TPS < 1 %		TPS 1 to 49 %		TPS ≥ 50 %	

OS Hazard ratio† (95 % CI)	0,51 (0,36, 0,71)		0,66 (0,46, 0,96)		0,59 (0,40, 0,86)	
PFS Hazard ratio† (95 % CI)	0,67 (0,49, 0,93)		0,53 (0,38, 0,74)		0,35 (0,25, 0,49)	
ORR %	33 %	14 %	50 %	21 %	62 %	26 %
*Based on final analysis †Hazard ratio (pembrolizumab combination therapy compared to chemotherapy) based on the stratified Cox proportional hazard model						

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

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

The efficacy of pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel was investigated in Study KEYNOTE-407, a randomised, double-blind, multicentre, placebo-controlled study. The key eligibility criteria for this study were metastatic squamous NSCLC, regardless of tumour PD-L1 expression status, and no prior systemic treatment for

metastatic disease. Patients with autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Randomisation was stratified by tumour PD-L1 expression (TPS < 1 % [negative] vs. TPS ≥ 1 %), investigator's choice of paclitaxel or nab-paclitaxel and geographic region (East Asia vs. non-East Asia). Patients were randomised (1:1) to one of the following treatment arms via intravenous infusion:

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

Treatment with pembrolizumab or placebo continued until RECIST 1.1-defined progression of disease as determined by BICR, unacceptable toxicity or a maximum of 24 months. Administration of pembrolizumab was permitted beyond RECIST-defined disease progression if the patient was clinically stable and deriving clinical benefit as determined by the investigator. Patients in the placebo arm were offered pembrolizumab as a single agent at the time of disease progression.

Assessment of tumour status was performed every 6 weeks through Week 18, every 9 weeks through Week 45 and every 12 weeks thereafter.

A total of 559 patients were randomised. The study population characteristics were: median age of 65 years (range: 29 to 88); 55 % age 65 or older; 81 % male; 77 % White; ECOG performance status of 0 (29 %) and 1 (71 %); and 8 % with treated brain metastases at baseline. Thirty-five percent had tumour PD-L1 expression TPS < 1 % [negative]; 19 % were East Asian; and 60 % received paclitaxel.

The primary efficacy outcome measures were OS and PFS (as assessed by BICR using RECIST 1.1). Secondary efficacy outcome measures were ORR and response duration, as assessed by BICR using RECIST 1.1. **Table 16** summarises key efficacy measures and Figures 13 and 14 show the Kaplan-Meier curves for OS and PFS based on the final analysis with a median follow-up of 14,3 months.

Table 16: Efficacy Results in KEYNOTE-407

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

Median in months (95 % CI)	8,0 (6,3, 8,4)	5,1 (4,3, 6,0)
Hazard ratio† (95 % CI)	0,57 (0,47, 0,69)	
p-Value‡	< 0,0001	
Objective response rate		
ORR % (95 % CI)	63 % (57, 68)	38 % (33, 44)
Complete response %	2,2 %	3,2 %
Partial response %	60 %	35 %
p-Value§	< 0,0001	
Response duration		
Median duration of response in months (range)	8,8 (1,3+, 28,4+)	4,9 (1,3+, 28,3+)
% with duration ≥ 12 months¶	38 %	25 %

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

†Based on the stratified Cox proportional hazard model

‡Based on stratified log-rank test

§Based on method by Miettinen and Nurminen

¶Based on Kaplan-Meier estimation

Figure 13: Kaplan-Meier Curve for Overall Survival in KEYNOTE-407

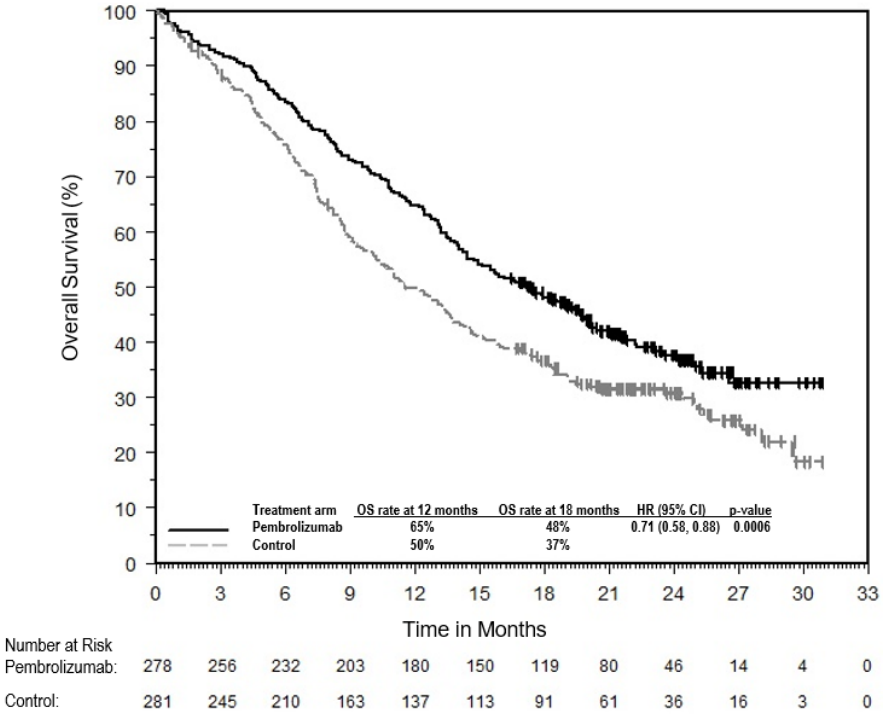
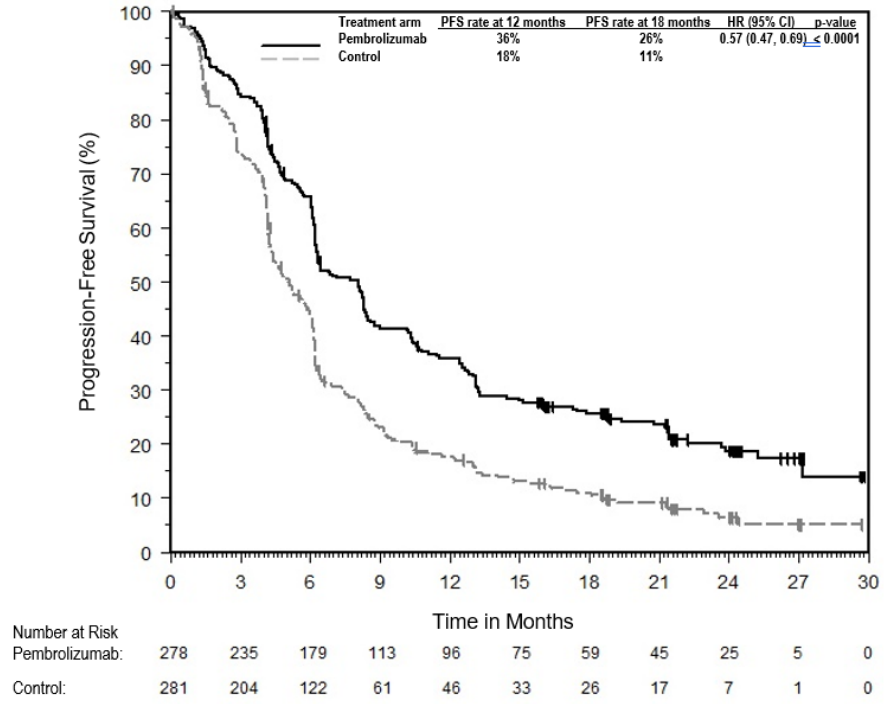


Figure 14: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-407



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

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

Endpoint	Pembrolizumab combinati	Chemotherapy	Pembrolizumab combinati	Chemotherapy	Pembrolizumab combinati	Chemotherapy

	on therapy		on therapy		on therapy	
	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 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 18** summarises key efficacy measures for the entire population (TPS ≥ 1 %) and for the-patients with TPS ≥ 50 %, and Figure 15 shows the Kaplan-Meier curve for OS (TPS ≥ 1 %), based on a final analysis with median follow-up of 42,6 months.

Table 18: Response to pembrolizumab 2 or 10 mg/kg 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	107 (77 %)	115 (76 %)	138 (91 %)

patients with event			
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

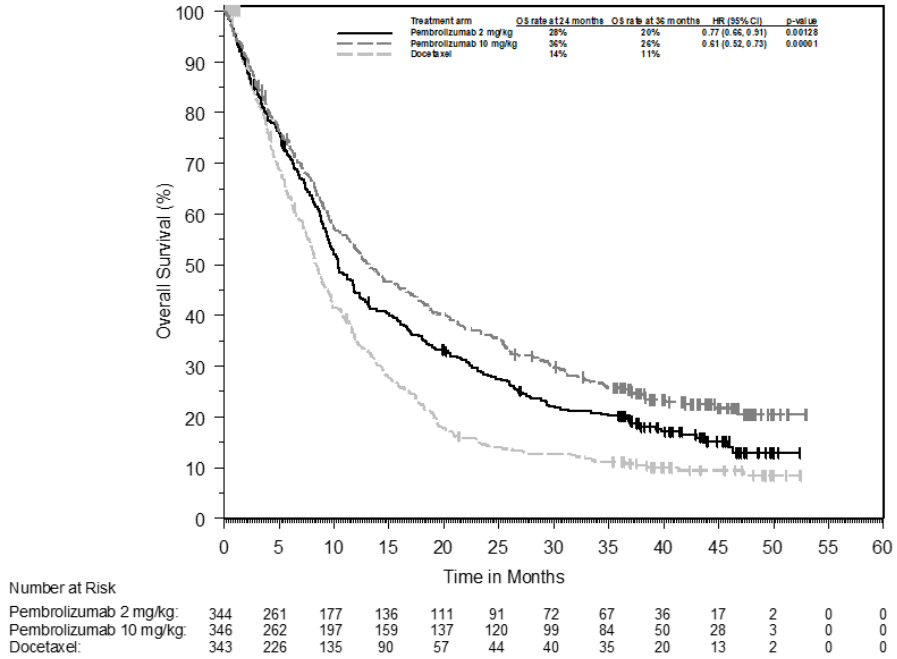
‡Assessed by BICR using RECIST 1.1

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



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)

KEYNOTE-204 was a randomised, open-label, active-controlled trial 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 trial. Randomisation was stratified by prior auto-SCT (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 intravenously every 3 weeks

Patients received pembrolizumab 200 mg intravenously every 3 weeks until unacceptable toxicity or documented disease progression. Disease assessment was performed every 12 weeks. The major efficacy outcome measures were PFS and ORR as assessed by BICR according to the 2007 revised International Working Group (IWG) criteria.

Among KEYNOTE-204 patients, the baseline characteristics were median age 35 years (16 % age 65 or older); 57 % male; 77 % White; and 61 % and 38 % had an ECOG performance status 0 and 1, respectively. The median number of prior lines of therapy administered for the treatment of cHL was 2 (range 1 to 11). Forty-two percent were refractory to the last prior

therapy and 29 % had primary refractory disease. Thirty-seven percent had undergone prior auto-HSCT, 5 % had received prior BV, and 39 % had prior radiation therapy.

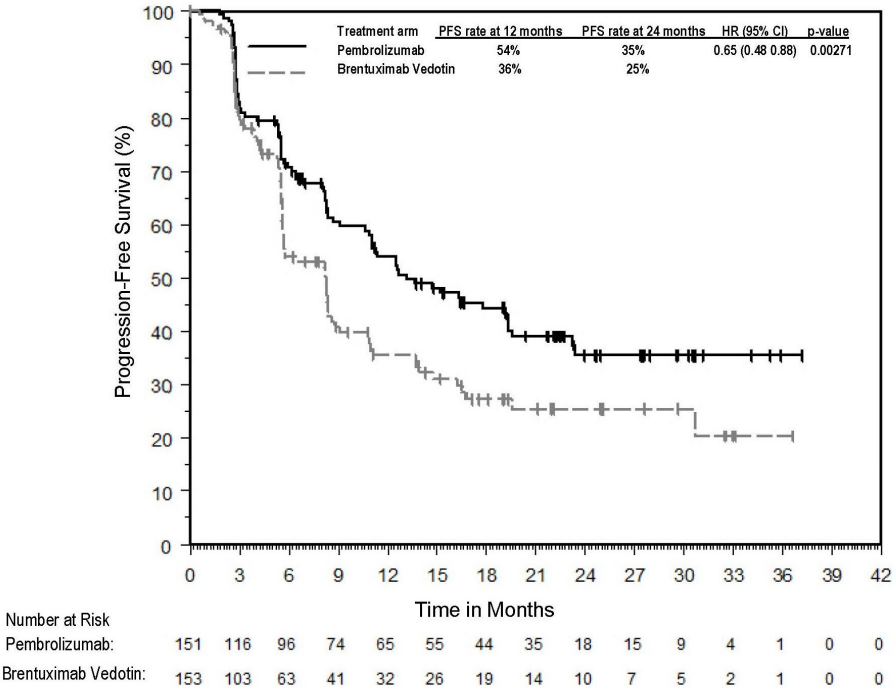
The median follow-up time for 151 patients treated with pembrolizumab was 24,9 months (range: 1,8 to 42,0 months). Efficacy results are summarised in **Table 19**.

Table 19: Efficacy Results in Patients with Refractory or Relapsed Classical Hodgkin Lymphoma

Endpoint	**Pembrolizumab** **200 mg every 3 weeks** **n=151**	**Brentuximab vedotin** **1,8 mg/kg every 3 weeks** **n=153**
PFS		
Number (%) of patients with event	81 (54 %)	88 (58 %)
Median in months (95 % CI)	13,2 (10,9, 19,4)	8,3 (5,7, 8,8)
Hazard ratio* (95 % CI)	0,65 (0,48, 0,88)	
p-Value†	0,0027	
Objective response rate		
ORR‡ % (95 % CI)	66 % (57,4, 73,1)	54 % (46,0, 62,3)
Complete response	25 %	24 %
Partial response	41 %	30 %
p-Value§	0,0225	
Response duration		
Median in months (range)	20,7 (0,0+, 33,2+)	13,8 (0,0+, 33,9+)

Number (%¶) of patients with duration ≥ 6 months	66 (80 %)	34 (60 %)
Number (%¶) of patients with duration ≥ 12 months	48 (62 %)	23 (50 %)
Number (%¶) of patients with duration ≥ 24 months	11 (47 %)	7 (43 %)
*Based on the stratified Cox proportional hazard model †Based on stratified log-rank test ‡Based on patients with best overall response as complete response or partial response §Based on Miettinen and Nurminen method stratified by prior auto-SCT and disease status ¶Based on Kaplan-Meier estimation		

Figure 16: Kaplan-Meier curve for progression-free survival in KEYNOTE-204



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 BV (HR 0,40; 95 % CI: 0,22-0,74). Over 24 weeks of follow-up, patients treated with pembrolizumab had an improvement in global health status/QoL compared to BV which showed a decline (difference in Least Square (LS) means=8,60; 95 % CI: 3,89, 13,31; nominal two-sided p=0,0004). These results should be interpreted in the context of the open-label study design and therefore taken cautiously.

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

The efficacy of pembrolizumab was investigated in 241 patients with refractory classical Hodgkin lymphoma or who have relapsed after 3 or more prior lines of therapy, enrolled in two

multicenter, non-randomised, open-label studies (KEYNOTE-013 and KEYNOTE-087). Both studies included patients regardless of PD-L1 expression. Patients with active, non-infectious pneumonitis, an allogeneic hematopoietic stem cell transplant within the past 5 years (or greater than 5 years but with GVHD), active autoimmune disease or a medical condition that required immunosuppression were ineligible for either trial. Patients received pembrolizumab 10 mg/kg every 2 weeks (n=31) or 200 mg every 3 weeks (n=210) until unacceptable toxicity or documented disease progression. Response was assessed using the revised lymphoma criteria by PET CT scans, with the first planned post-baseline assessment at Week 12. The major efficacy outcome measures (ORR, CRR and duration of response) were assessed by blinded independent central review according to the 2007 revised International Working Group (IWG) criteria. Secondary efficacy outcome measures were PFS and OS.

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

Among KEYNOTE-087 patients, the baseline characteristics were median age 35 years (9 % age 65 or older); 54 % male; 88 % White; and 49 % and 51 % had an ECOG performance status 0 and 1, respectively. The median number of prior lines of therapy administered for the treatment of cHL was 4 (range 1 to 12). Eighty-one percent were refractory to at least one prior therapy, including 34 % who were refractory to first-line therapy. Sixty-one percent of patients had received Auto-SCT, 38 % were transplant ineligible; 17 % had no prior brentuximab vedotin

use; and 37 % of patients had prior radiation therapy. Efficacy results are summarised in **Table 20**.

Table 20: Efficacy Results in Patients with Refractory or Relapsed Classical Hodgkin Lymphoma

	KEYNOTE-013	KEYNOTE-087
Endpoint	**n=31**	**n=210**
Objective response rate[*]		
ORR % (95 % CI)	58 % (39,1, 75,5)	71 % (64, 77)
Complete remission	19 %	28 %
Partial remission	39 %	43 %
Response duration[*]		
Median in months (range)	Not reached (0,0+, 26,1+)[†]	16,6 (0,0+, 39,1+)[‡]
% with duration ≥ 6-months	80 %[§]	74 %[¶]
% with duration ≥ 12-months	70 %[#]	59 %[Þ]
Time to response		
Median in months (range)	2,8 (2,4, 8,6)[†]	2,8 (2,1, 16,5)[‡]
PFS[*]		
Median in months (95 % CI)	11,4 (4,9, 27,8)	13,6 (11,1, 16,7)
6-month PFS rate	66 %	72 %
9-month PFS rate	---	61 %
12-month PFS rate	48 %	52 %
OS		

6-month OS rate	100 %	99,5 %
12-month OS rate	87,1 %	96,1 %

*Assessed by blinded independent central review according to the 2007 revised International Working Group (IWG) criteria

†Based on patients (n=18) with a response by independent review

‡Based on patients (n=149) with a response by independent review

§Based on Kaplan-Meier estimation; includes 9 patients with responses of 6 months or longer

¶Based on Kaplan-Meier estimation; includes 84 patients with responses of 6 months or longer

#Based on Kaplan-Meier estimation; includes 7 patients with responses of 12 months or longer

ÞBased on Kaplan-Meier estimation; includes 60 patients with responses of 12 months or longer

The improved benefit as assessed by ORR, CRR and response duration in the KEYNOTE-087 population was accompanied by overall improvements in health-related quality of life (HRQoL) as assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and the European Quality of Life Five Dimensions Questionnaire (EQ-5D). Relative to subjects with stable disease or progressive disease, subjects with a complete or partial response had the largest improvement and the highest proportion with a 10 point or greater increase in their EORTC QLQ-C30 global health status/QoL score, as well as, had the largest improvement in their EQ-5D utility and VAS scores from baseline to Week 12.

Urothelial carcinoma

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

The safety and efficacy of pembrolizumab were evaluated in KEYNOTE-045, a multicentre, open-label, randomised (1:1), controlled study for the treatment of locally advanced or metastatic urothelial carcinoma in patients with disease progression on or after platinum-containing chemotherapy. Patients must have received first-line platinum-containing regimen for locally advanced/metastatic disease or as neoadjuvant/adjuvant treatment, with recurrence/progression ≤ 12 months following completion of therapy. Patients were randomised (1:1) to receive either pembrolizumab 200 mg every 3 weeks (n=270) or investigator's choice of any of the following chemotherapy regimens all given intravenously every 3 weeks (n=272): paclitaxel 175 mg/m^2 (n=84), docetaxel 75 mg/m^2 (n=84) or vinflunine 320 mg/m^2 (n=87). Patients were treated with pembrolizumab until unacceptable toxicity or disease progression. Treatment could continue beyond progression if the patient was clinically stable and was considered to be deriving clinical benefit by the investigator. Patients without disease progression could be treated for up to 24 months. The study excluded patients with autoimmune disease, a medical condition that required immunosuppression and patients with more than 2 prior lines of systemic chemotherapy for metastatic urothelial carcinoma. Patients with an ECOG performance status of 2 had to have a haemoglobin ≥ 10 g/dL, could not have liver metastases, and must have received the last dose of their last prior chemotherapy regimen ≥ 3 months prior to enrolment. Assessment of tumour status was performed at 9 weeks after the first dose, then every 6 weeks through the first year, followed by every 12 weeks thereafter. Among the 542 randomised patients in KEYNOTE-045, baseline characteristics were: median age 66 years (range: 26 to 88), 58 % age 65 or older; 74 % male; 72 % White and 23 % Asian; 56 % ECOG performance status of 1 and 1 % ECOG performance status of 2; and 96 % M1 disease and 4 % M0 disease. Eighty-seven percent of patients had visceral metastases, including 34 % with liver metastases. Eighty-six percent had a primary tumour in the lower tract

and 14 % had a primary tumour in the upper tract. Fifteen percent of patients had disease progression following prior platinum-containing neoadjuvant or adjuvant chemotherapy. Twenty-one percent had received 2 prior systemic regimens in the metastatic setting. Seventy-six percent of patients received prior cisplatin, 23 % had prior carboplatin, and 1 % was treated with other platinum-based regimens.

The primary efficacy outcomes were OS and PFS as assessed by BICR using RECIST v1.1. Secondary outcome measures were ORR (as assessed by BICR using RECIST v1.1) and duration of response. **Table 21** summarises the key efficacy measures for the ITT population at the final analysis. The Kaplan-Meier curve based on the final analysis for OS is shown in Figure 17. The study demonstrated statistically significant improvements in OS and ORR for patients randomised to pembrolizumab as compared to chemotherapy. There was no statistically significant difference between pembrolizumab and chemotherapy with respect to PFS.

Table 21: Response to pembrolizumab 200 mg every 3 weeks in patients with urothelial carcinoma previously treated with chemotherapy in KEYNOTE-045

Endpoint	Pembrolizumab 200 mg every 3 weeks n=270	Chemotherapy n=272
OS		
Number (%) of patients with event	200 (74 %)	219 (81 %)
Hazard ratio* (95 % CI)	0,70 (0,57, 0,85)	
p-Value†	< 0,001	

Median in months (95 % CI)	10,1 (8,0, 12,3)	7,3 (6,1, 8,1)
PFS‡		
Number (%) of patients with event	233 (86 %)	237 (87 %)
Hazard ratio* (95 % CI)	0,96 (0,79, 1,16)	
p-Value†	0,313	
Median in months (95 % CI)	2,1 (2,0, 2,2)	3,3 (2,4, 3,6)
Objective response rate‡		
ORR % (95 % CI)	21 % (16, 27)	11 % (8, 15)
p-Value§	< 0,001	
Complete response	9 %	3 %
Partial response	12 %	8 %
Stable disease	17 %	34 %
Response duration‡,¶		
Median in months (range)	Not reached (1,6+, 30,0+)	4,4 (1,4+, 29,9+)
Number (%#) of patients with duration ≥ 6 months	46 (84 %)	8 (47 %)
Number (%#) of patients with duration ≥ 12 months	35 (68 %)	5 (35 %)
*Hazard ratio (pembrolizumab compared to chemotherapy) based on the stratified Cox proportional hazard model †Based on stratified log-rank test		

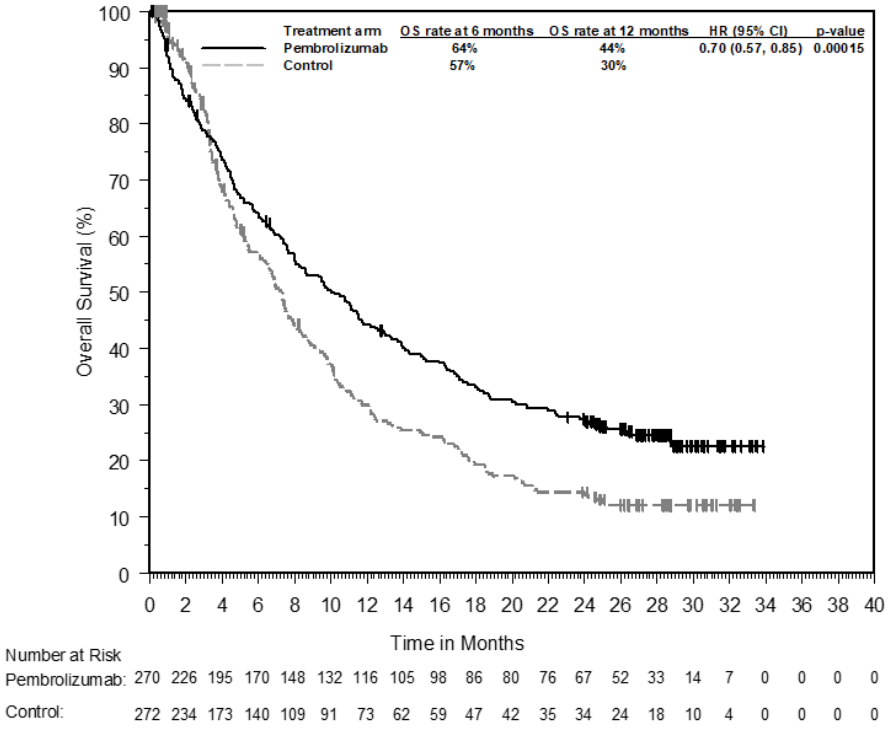
‡Assessed by BICR using RECIST 1.1

§Based on method by Miettinen and Nurminen

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

#Based on Kaplan-Meier estimation

Figure 17: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-045 (intent to treat population)



An analysis was performed in KEYNOTE-045 in patients who had PD-L1 CPS < 10 [pembrolizumab: n=186 (69 %) vs. chemotherapy: n=176 (65 %)] or ≥ 10 [pembrolizumab: n=74 (27 %) vs. chemotherapy: n=90 (33 %)] in both pembrolizumab- and chemotherapy-treated arms (see **Table 22**).

Table 22: OS by PD-L1 Expression

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

*Based on final analysis

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

Patient-reported outcomes (PROs) were assessed using EORTC QLQ-C30. A prolonged time to deterioration in EORTC QLQ-C30 global health status/QoL was observed for patients treated with pembrolizumab compared to investigator's choice chemotherapy (HR 0,70; 95 % CI 0,55-0,90). Over 15 weeks of follow-up, patients treated with pembrolizumab had stable global health status/QoL, while those treated with investigator's choice chemotherapy had a decline in global health status/QoL. These results should be interpreted in the context of the open-label study design and therefore taken cautiously.

KEYNOTE-052: Open-label study in urothelial carcinoma 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 23** summarises the key efficacy measures for the study population at the final analysis based on a median follow-up time of 11,4 months (range: 0,1, 41,2 months) for all patients.

Table 23: Response to pembrolizumab 200 mg every 3 weeks in patients with urothelial carcinoma ineligible for cisplatin-containing chemotherapy in KEYNOTE-052

Endpoint	n=370
Objective response rate*	
ORR %, (95 % CI)	29 % (24, 34)
Disease control rate†	47 %
Complete response	9 %
Partial response	20 %
Stable disease	18 %
Response duration	
Median in months (range)	30,1 (1,4+, 35,9+)
% with duration ≥ 6-months	81 %‡
Time to response	
Median in months (range)	2,1 (1,3, 9,0)
PFS*	
Median in months (95 % CI)	2,2 (2,1, 3,4)
6-month PFS rate	33 %
12-month PFS rate	22 %
OS	
Median in months (95 % CI)	11,3 (9,7, 13,1)
6-month OS rate	67 %
12-month OS rate	47 %
*Assessed by BICR using RECIST 1.1	

†Based on best response of stable disease or better

‡Based on Kaplan-Meier estimates; includes 84 patients with response of 6 months or longer

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

Table 24: ORR and OS by PD-L1 Expression

Endpoint	**CPS < 10** **N=251**	**CPS ≥ 10** **N=110**
Objective response rate*		
ORR %, (95 % CI)	20 % (16, 26)	47 % (38, 57)
OS		
Median in months (95 % CI)	10 (8, 12)	19 (12, 29)
12-month OS rate	41 %	61 %
*BICR using RECIST 1.1		

Head and Neck Squamous Cell Carcinoma

KEYNOTE-048: Controlled study of monotherapy and combination therapy in HNSCC

The efficacy of pembrolizumab was investigated in Study KEYNOTE-048, a multicenter, randomised, open-label, active-controlled study in patients with metastatic or recurrent HNSCC who had not previously received systemic therapy for recurrent or metastatic disease and who were considered incurable by local therapies. Patients with 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 %) based on the PD-L1 IHC 22C3 pharmDx™ Kit, HPV status (positive or negative) and ECOG PS (0 vs. 1). Patients were randomised 1:1:1 to one of the following treatment arms:

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

Treatment with pembrolizumab continued until RECIST 1.1-defined progression of disease as determined by the investigator, unacceptable toxicity or a maximum of 24 months. Administration of pembrolizumab was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Assessment of tumour status was performed at Week 9 and then every 6 weeks for the first year, followed by every 9 weeks through 24 months.

A total of 882 patients were randomised; 301 patients to the pembrolizumab monotherapy arm, 281 patients to the pembrolizumab plus chemotherapy arm, and 300 patients to the standard treatment arm. The study population characteristics were: median age of 61 years (range: 20 to 94); 36 % age 65 or older; 83 % male; 73 % White and 20 % Asian; 61 % ECOG PS of 1; and 79 % were former/current smokers. Disease characteristics were: 22 % HPV positive, 85 %, 43 %, and 23 % had PD-L1 expression defined as CPS ≥ 1, CPS ≥ 20, and TPS ≥ 50 %,

respectively, and 95 % had Stage IV disease (Stage IVa 19 %, Stage IVb 6 % and Stage IVc 70 %).

The primary efficacy outcome measures were OS and PFS (assessed by BICR according to RECIST 1.1). ORR, as assessed by BICR according to RECIST 1.1, was a secondary outcome measure. The trial demonstrated a statistically significant improvement in OS for patients randomised to pembrolizumab in combination with chemotherapy compared to standard treatment. OS for patients randomised to pembrolizumab monotherapy was non-inferior compared to standard treatment. **Tables 25** and **26** and Figures 18 and 19 describe key efficacy results for pembrolizumab in KEYNOTE-048.

Table 25: Efficacy results for pembrolizumab plus chemotherapy in KEYNOTE-048

Endpoint	**Pembrolizumab Platinum Chemotherapy 5-FU n=281**	**Standard Treatment* n=278**
OS		
Number (%) of patients with event	197 (70 %)	223 (80 %)
Median in months (95 % CI)	13,0 (10,9, 14,7)	10,7 (9,3, 11,7)
Hazard ratio† (95 % CI)	0,77 (0,63, 0,93)	
p-Value‡	0,0033	
PFS		
Number (%) of patients with	244 (87 %)	253 (91 %)

event		
Median in months (95 % CI)	4,9 (4,7, 6,0)	5,1 (4,9, 6,0)
Hazard ratio† (95 % CI)	0,92 (0,77, 1,10)	
p-Value‡	0,1697	
ORR		
Objective response rate§ (95 % CI)	36 % (30,0, 41,5)	36 % (30,7, 42,3)
Complete response	6 %	3 %
Partial response	30 %	33 %
p-Value¶	0,5740	
Duration of Response		
Median in months (range)	6,7 (1,6+, 30,4+)	4,3 (1,2+, 27,9+)
% with duration ≥ 6 months	54 %	37 %

*Cetuximab, platinum and 5-FU

†Based on the stratified Cox proportional hazard model

‡Based on stratified log-rank test

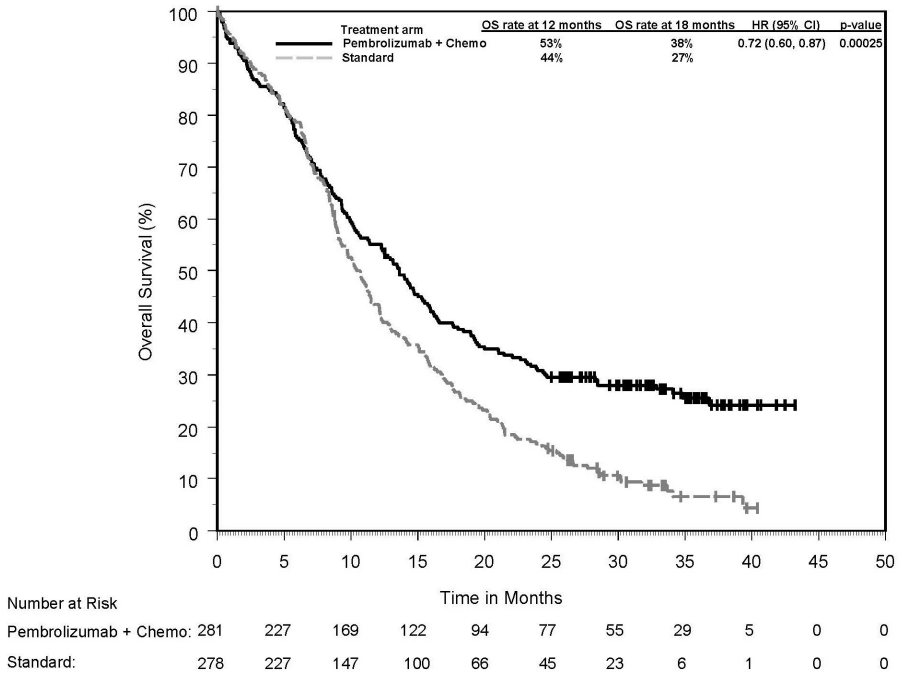
§Response: Best objective response as confirmed complete response or partial response

¶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)

In KEYNOTE-048, OS HRs for patients randomised to pembrolizumab in combination with chemotherapy, compared with cetuximab in combination with chemotherapy, were similar for all populations regardless of PD-L1 expression in a pre-specified interim analysis: ITT (HR 0,77, 95 % CI: 0,63, 0,93), CPS ≥ 1 (HR 0,71, 95 % CI: 0,57, 0,88), CPS ≥ 20 (HR 0,69, 95 % CI: 0,51,

0,94). The OS HRs at final analysis with a median follow-up of 11,4 months were similar to those obtained at the pre-specified interim analysis and in addition, demonstrated a statistically significant improvement in OS for the subgroup of patients with PD-L1 CPS ≥ 1 and CPS ≥ 20: ITT (0,72, 95 % CI: 0,60, 0,87), CPS ≥ 1 (0,65, 95 % CI: 0,53, 0,80), CPS ≥ 20 (0,60, 95 % CI: 0,45, 0,82).

Figure 18: Kaplan-Meier curve for overall survival for pembrolizumab plus chemotherapy in KEYNOTE-048*



*Median follow-up of 11.4 months at protocol-specified final analysis.

Table 26: Efficacy results for pembrolizumab as monotherapy in KEYNOTE-048

Endpoint	Pembrolizumab n=301	Standard Treatment*

		n=300
OS		
Number (%) of patients with event	213 (71 %)	240 (80 %)
Median in months (95 % CI)	11,6 (10,5, 13,6)	10,7 (9,3, 11,7)
Hazard ratio† (95 % CI)	0,85 (0,71, 1,03)	
p-Value‡	0,00014	
PFS		
Number (%) of patients with event	269 (89 %)	270 (90 %)
Median in months (95 % CI)	2,3 (2,2, 3,3)	5,2 (4,9, 6,0)
Hazard ratio† (95 % CI)	1,32 (1,11, 1,57)	
p-Value§	0,9992	
ORR		
Objective response rate§ % (95 % CI)	17 % (12,9, 21,7)	36 % (30,6, 41,7)
Complete response	5 %	3 %
Partial response	12 %	33 %
p-Value#	1,0000	
Duration of Response		
Median in months (range)	20,9 (1,5+, 34,8+)	4,5 (1,2+, 30,6+)
% with duration ≥ 6 months	76 %	39 %
*Cetuximab, platinum and 5-FU		

†Based on the stratified Cox proportional hazard model

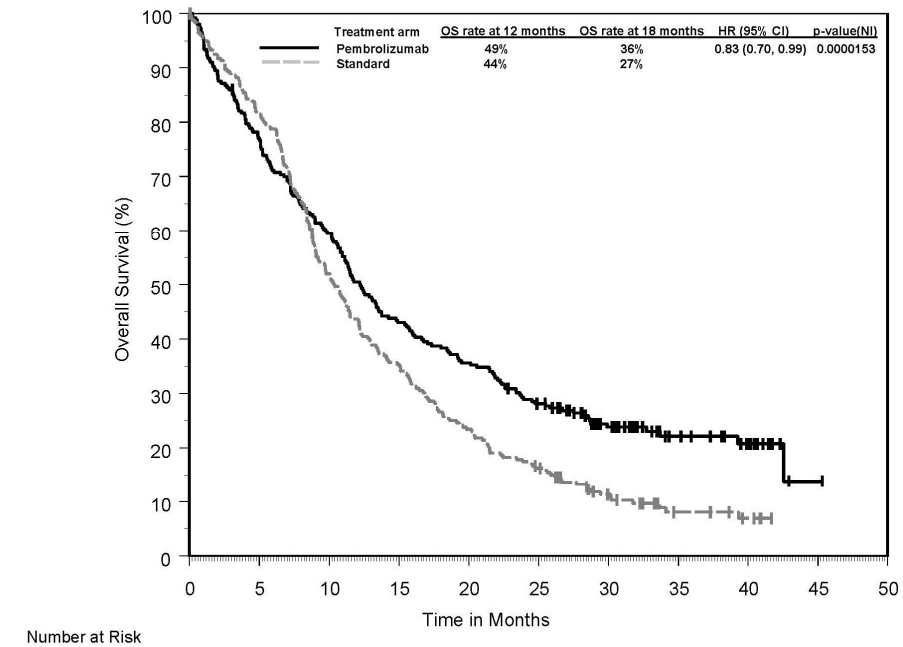
‡Non-inferiority p-Value

§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



*Median follow-up of 11.2 months at protocol-specified final analysis.

Additional OS analyses based on PD-L1 expression (CPS ≥ 1 and CPS ≥ 20) were performed in KEYNOTE-048. The trial demonstrated a statistically significant improvement in OS for patients

randomised to pembrolizumab monotherapy compared to standard treatment for PD-L1 expression CPS ≥ 1 and CPS ≥ 20. OS for patients who had PD-L1 CPS ≥ 1 or CPS ≥ 20 for pembrolizumab monotherapy compared to standard treatment is summarised in **Table 27**.

Table 27: OS by PD-L1 Expression

	CPS ≥ 1		**CPS ≥ 20**	
	Pembrolizumab n=257	**Standard Treatment* n=255**	**Pembrolizumab n=133**	**Standard Treatment* n=122**
Number of events (%)	177 (69 %)	206 (81 %)	82 (62 %)	95 (78 %)
Median in months (95 % CI)	12,3 (10,8, 14,9)	10,3 (9,0, 11,5)	14,9 (11,6, 21,5)	10,7 (8,8, 12,8)
Hazard ratio† (95 % CI)	0,78 (0,64, 0,96)		0,61 (0,45, 0,83)	
p-Value‡	0,0085		0,0007	

*Cetuximab, platinum and 5-FU

†Hazard ratio (compared to standard treatment) based on the stratified Cox proportional hazard model

‡Based on stratified log-rank test

The final OS analysis was performed for patients with CPS ≥ 1 with a median follow-up of 11,4 months from the pre-specified interim analysis. Median OS was 12,3 months (95 % CI: 10,8, 14,3) for pembrolizumab as a single agent and 10,3 months (95 % CI: 9,0, 11,5) for cetuximab in combination with chemotherapy, with an HR of 0,74 (95 % CI: 0,61, 0,90).

The final OS analysis was performed for patients with CPS ≥ 20 with a median follow-up of 12,2 months from the pre-specified interim analysis. Median OS was 14,8 months (95 % CI: 11,5, 20,6) for pembrolizumab as a single agent and 10,7 months (95 % CI: 8,8, 12,8) for cetuximab in combination with chemotherapy, with an HR of 0,58 (95 % CI: 0,44, 0,78).
In an exploratory subgroup analysis for patients with CPS 1-19 HNSCC, the median OS was 10,8 months (95 % CI: 9,0, 12,6) for pembrolizumab as a single agent and 10,1 months (95 % CI: 8,7, 12,1) for cetuximab in combination with chemotherapy, with an HR of 0,90 (95 % CI: 0,68, 1,18). The final OS analysis was performed for patients with CPS 1-19 with a median follow-up of 10,3 months. At the final analysis, the median OS was 10,8 months (95 % CI: 9,0, 12,6) for pembrolizumab as a single agent and 10,1 months (95 % CI: 8,7, 12,1) for cetuximab in combination with chemotherapy, with an HR of 0,86 (95 % CI: 0,66, 1,12).

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

The efficacy of pembrolizumab was investigated in KEYNOTE-040, a multicenter, open-label, randomised, active-controlled study for the treatment of recurrent or metastatic HNSCC in patients with disease progression who received prior platinum-containing chemotherapy. The study excluded patients with 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. Patients were stratified by PD-L1 expression, 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). Patients were treated with pembrolizumab for up to 24 months or 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. 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 randomised patients in KEYNOTE-040, the baseline characteristics included: median age 60 years (33 %, age 65 or older); 83 % male; 84 % White, 6 % Asian, and 2 % Black; and 28 % and 72 % with an ECOG performance status 0 or 1, respectively. Disease characteristics were: HPV positive (24 %) and PD-L1 expression defined as CPS ≥ 1 (78 %) and TPS ≥ 50 % (26 %). Seventy-one percent (71 %) of patients had M1 disease and the majority had Stage IV disease (Stage IV 33 %, Stage IVa 11 %, Stage IVb 5 % and Stage IVc 45 %). Fifteen percent (15 %) 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. Secondary efficacy outcome measures were PFS, ORR and duration of response (as assessed by BICR using RECIST 1.1) and OS (PD-L1 CPS ≥ 1). Efficacy measures for KEYNOTE-040 are summarised in **Table 28** and the Kaplan-Meier curve for OS is shown in Figure 20.

Table 28: Efficacy Results in KEYNOTE-040

Endpoint	Pembrolizumab 200 mg every 3 weeks n=247	Standard Treatment* n=248

OS		
Number (%) of patients with event	181 (73 %)	207 (84 %)
Hazard ratio† (95 % CI)	0,80 (0,65, 0,98)	
p-Value‡	0,016	
Median in months (95 % CI)	8,4 (6,4, 9,4)	6,9 (5,9, 8,0)
PFS§		
Number (%) of patients with event	218 (88 %)	224 (90 %)
Hazard ratio† (95 % CI)	0,96 (0,79, 1,16)	
p-Value‡	0,325	
Median in months (95 % CI)	2,1 (2,1, 2,3)	2,3 (2,1, 2,8)
Rate (%) at 6 months	25,6 (20,3, 31,2)	20 (15,1, 25,3)
Overall Response Rate§		
ORR (95 % CI)	15 % (10,4, 19,6)	10 % (6,6, 14,5)
p-Value¶	0,061	
Complete response	2 %	0,4 %
Partial response	13 %	10 %
Stable disease	23 %	26 %
Response duration§,#		
Median in months (range)	18,4 (2,7, 18,4)	5 (1,4+, 18,8)
Number (%Þ) of patients with duration ≥ 6 months	16 (72 %)	6 (47 %)

*Methotrexate, docetaxel and 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

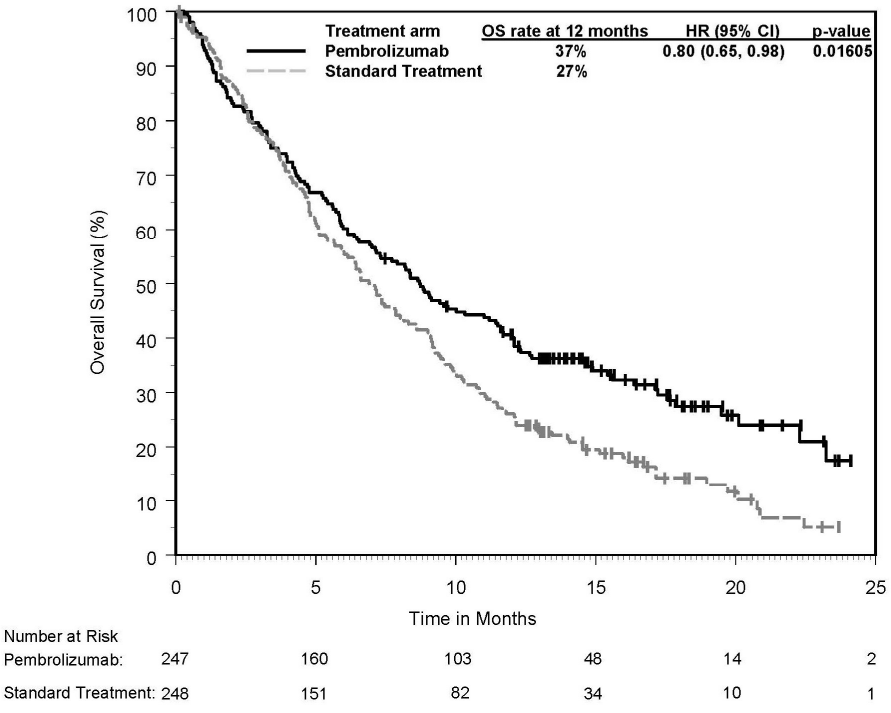
§Assessed by BICR using RECIST 1.1

¶Based on method by Miettinen and Nurminen

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

ÞBased on Kaplan-Meier estimation

Figure 20: Kaplan-Meier curve for overall survival in KEYNOTE-040



Renal cell carcinoma

KEYNOTE-426: Controlled study of combination therapy with axitinib 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.

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 study demonstrated a statistically significant improvement in OS (HR 0,53; 95 % CI 0,38, 0,74; p-Value=0,00005) and PFS (HR 0,69; 95 % CI 0,56, 0,84; p-Value=0,00012) for patients randomised to the pembrolizumab combination arm compared with sunitinib at its pre-specified interim analysis. **Table 29** summarises key efficacy measures and Figures 21 and 22 show the Kaplan-Meier curves for OS and PFS based on the final analysis with a median follow-up time of 37,7 months.

Table 29: Efficacy Results in KEYNOTE-426

Endpoint	**Pembrolizumab** **Axitinib** **n=432**	**Sunitinib** **n=429**
OS		
Number (%) of patients with events	193 (45 %)	225 (52 %)
Median in months (95 % CI)	45,7 (43,6, NA)	40,1 (34,3, 44,2)
Hazard ratio* (95 % CI)	0,73 (0,60, 0,88)	

p-Value†	0,00062	
PFS‡		
Number (%) of patients with events	286 (66 %)	301 (70 %)
Median in months (95 % CI)	15,7 (13,6, 20,2)	11,1 (8,9, 12,5)
Hazard ratio* (95 % CI)	0,68 (0,58, 0,80)	
p-Value†	< 0,00001	
Objective response rate		
ORR§ % (95 % CI)	60 (56, 65)	40 (35, 44)
Complete response	10 %	3 %
Partial response	50 %	36 %
p-Value¶	< 0,0001	
Response duration		
Median in months (range)	236, (1,4+, 43,4+)	15,3 (2,3, 42,8+)
Number (%#) of patients with duration ≥ 30 months	87 (45 %)	29 (32 %)

*Based on the stratified Cox proportional hazard model

†Nominal p-Value 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

¶Nominal p-Value based on Miettinen and Nurminen method stratified by IMDC risk group and geographic region. At the pre-specified interim analysis of ORR (median follow-up time of 12,8 months), statistically significant superiority was achieved for ORR comparing pembrolizumab plus axitinib with sunitinib p-Value < 0,0001

#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)

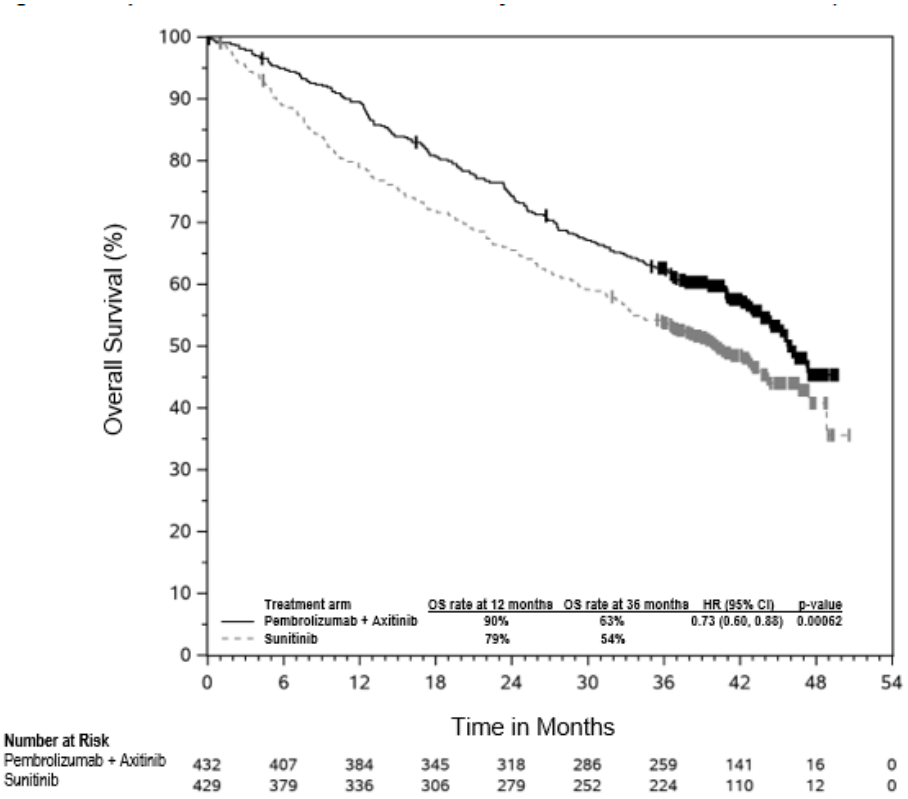
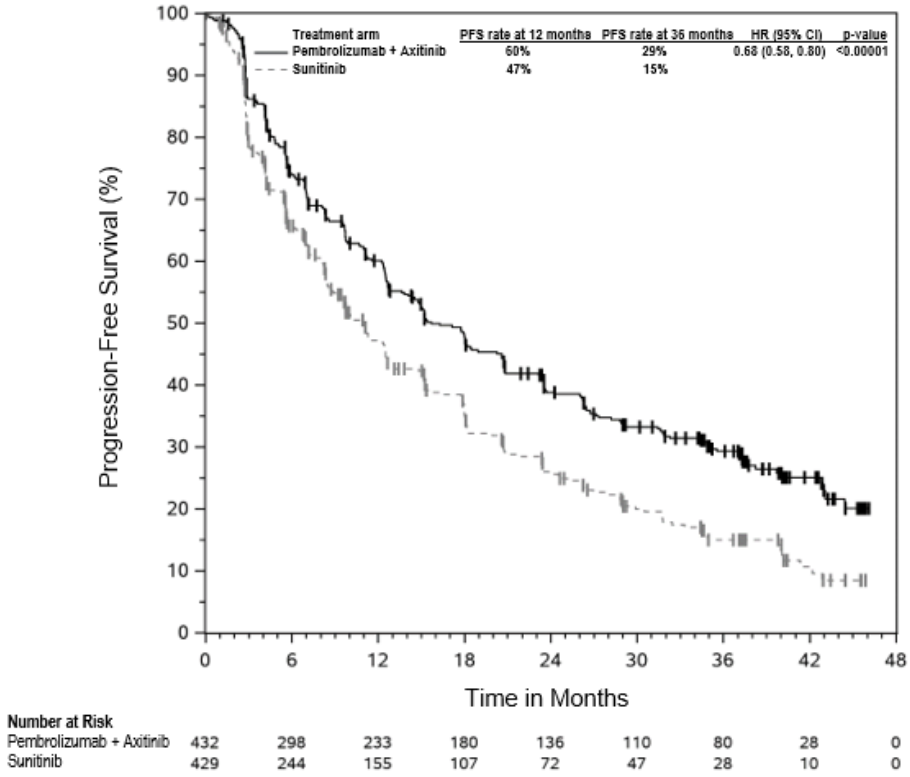


Figure 22: Kaplan-Meier curve for progression-free survival by treatment arm in KEYNOTE-426 (intent to treat population)



Subgroup analyses 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 %)].
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.
At the pre-specified interim analysis, for the IMDC risk category, the OS hazard ratio (HR) for patients randomised to the pembrolizumab combination arm compared with sunitinib in the favourable risk group was 0,64 (95 % CI 0,24, 1,68), for the intermediate risk group the OS HR was 0,53 (95 % CI 0,35, 0,82), and for the poor risk group the OS HR was 0,43 (95 % CI 0,23,

0,81). The PFS HR (95 % CI) for the favourable, intermediate and poor risk groups were 0,81 (0,53, 1,24), 0,69 (0,53, 0,90) and 0.58 (0,35, 0,94), respectively. The ORR difference (95 % CI) for the favourable, intermediate and poor risk groups were 17,0 % (5,3, 28,4), 25,5 % (16,7, 33,9) and 31,5 % (15,7, 46,2), respectively.

Table 30 summarises the efficacy measures by IMDC risk category based on the final OS analysis at a median follow-up of 37,7 months.

Table 30: 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	95,6 (90,5, 98,0)	94,6 (89,0, 97,4)	1,17 (0,76, 1,80)
Intermediate	90,7 (86,2, 93,8)	77,6 (71,8, 82,3)	0,67 (0,52, 0,86)
Poor	69,6 (55,8, 79,9)	45,1 (31,2, 58,0)	0,51 (0,32, 0,81)
PFS	**Median (95 % CI), months**		**PFS HR (95 % CI)**
Favourable	20,7 (15,2, 28,9)	17,8 (12,5, 20,7)	0,76 (0,56, 1,03)
Intermediate	15,3 (12,5, 20,8)	9,7 (8,0, 12,4)	0,69 (0,55, 0,86)
Poor	4,9 (2,8, 12,4)	2,9 (2,7, 4,2)	0,53 (0,33, 0,84)
Confirmed ORR	**% (95 % CI)**		**ORR difference, % (95 % CI)**
Favourable	68,8 (60,4, 76,4)	50,4 (41,5, 59,2)	18,5 (6,7, 29,7)
Intermediate	60,5 (54,0, 66,8)	39,8 (33,7, 46,3)	20,7 (11,8, 29,2)

Poor	39,3 (26,5, 53,2)	11,5 (4,4, 23,4)	27,7 (11,7, 42,8)

*n (%) for favourable, intermediate and poor risk categories for pembrolizumab/axitinib vs. sunitinib were: 138 (32 %) vs. 131 (31 %); 238 (55 %) vs. 246 (57 %); 56 (13 %) vs. 52 (12 %), respectively

KEYNOTE-581: Controlled study of combination therapy with lenvatinib in RCC patients naïve to treatment

The efficacy of pembrolizumab in combination with lenvatinib was investigated in KEYNOTE-581, a multicentre, open-label, randomised study conducted in 1 069 patients with advanced RCC with clear cell component including other histological features such as sarcomatoid and papillary in the first-line setting. Patients were enrolled regardless of PD-L1 tumour expression status. The study excluded patients with active autoimmune disease or a medical condition that required immunosuppression. Randomisation was stratified by geographic region (North America versus Western Europe versus “Rest of the World”) and Memorial Sloan Kettering Cancer Center (MSKCC) prognostic groups (favourable versus intermediate versus poor). Patients were randomised (1:1:1) to one of the following treatment arms:

- pembrolizumab 200 mg intravenously every 3 weeks up to 24 months in combination with lenvatinib 20 mg orally once daily.
- lenvatinib 18 mg orally once daily in combination with everolimus 5 mg orally once daily.
- sunitinib 50 mg orally once daily for 4 weeks then off treatment for 2 weeks.

Treatment continued until unacceptable toxicity or disease progression as determined by the investigator and confirmed by BICR using RECIST 1.1. Administration of pembrolizumab with lenvatinib was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered by the investigator to be deriving clinical benefit. Pembrolizumab

was continued for a maximum of 24 months; however, treatment with lenvatinib could be continued beyond 24 months. The median average daily dose for lenvatinib was 14 mg. The median duration of exposure to lenvatinib was 16,1 months. Assessment of tumour status was performed at baseline and then every 8 weeks.

Among the study population (355 patients in the pembrolizumab with lenvatinib arm and 357 in the sunitinib arm), the baseline characteristics were: median age of 62 years (range: 29 to 88 years), 41 % age 65 or older; 74 % male; 75 % White, 21 % Asian, 1 % Black and 2 % other races; 17 % and 83 % of patients had a baseline KPS of 70 to 80 and 90 to 100, respectively; patient distribution by IMDC risk categories was 33 % favourable, 56 % intermediate and 10 % poor, and by MSKCC prognostic groups was 27 % favourable, 64 % intermediate and 9 % poor. Metastatic disease was present in 99 % of the patients and locally advanced disease was present in 1 %. Common sites of metastases in patients were lung (69 %), lymph node (46 %) and bone (26 %).

The primary efficacy outcome measure was PFS based on BICR using RECIST 1.1. Key secondary efficacy outcome measures included OS and ORR. The study demonstrated statistically significant improvements in PFS, OS and ORR in patients randomised to pembrolizumab in combination with lenvatinib compared with sunitinib. The median survival follow-up time was 26,5 months. The median duration of treatment for pembrolizumab plus lenvatinib was 17,0 months. Efficacy results for KEYNOTE-581 are summarised in **Table 31** and Figures 23 and 24. PFS results were consistent across pre-specified subgroups, MSKCC prognostic groups and PD-L1 tumour expression status. Efficacy results by MSKCC prognostic group are summarised in **Table 32**.

Table 31: Efficacy Results in KEYNOTE-581

Endpoint	Pembrolizumab 200 mg every 3 weeks and Lenvatinib n=355	Sunitinib n=357
PFS*		
Number of patients with event (%)	160 (45 %)	205 (57 %)
Median in months (95 % CI)	23,9 (20,8, 27,7)	9,2 (6,0, 11,0)
Hazard ratio† (95 % CI)	0,39 (0,32, 0,49)	
p-Value‡	< 0,0001	
OS		
Number of patients with event (%)	80 (23 %)	101 (28 %)
Median in months (95 % CI)	NR (33,6, NR)	NR (NR, NR)
Hazard ratio† (95 % CI)	0,66 (0,49, 0,88)	
p-Value‡	0,0049	
Objective response rate		
ORR§ (95 % CI)	71 % (66, 76)	36 % (31, 41)
Complete response	16 %	4 %
Partial response	55 %	32 %
p-Value¶	< 0,0001	
Response duration#		
Median in months (range)	26 (1,6+, 36,8+)	15 (1,6+, 33,2+)

*The primary analysis of PFS included censoring for new anti-cancer treatment. Results for PFS with and without censoring for new anti-cancer treatment were consistent.

[†]Based on the stratified Cox proportional hazard model

[‡]Two-sided based on stratified log-rank test

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

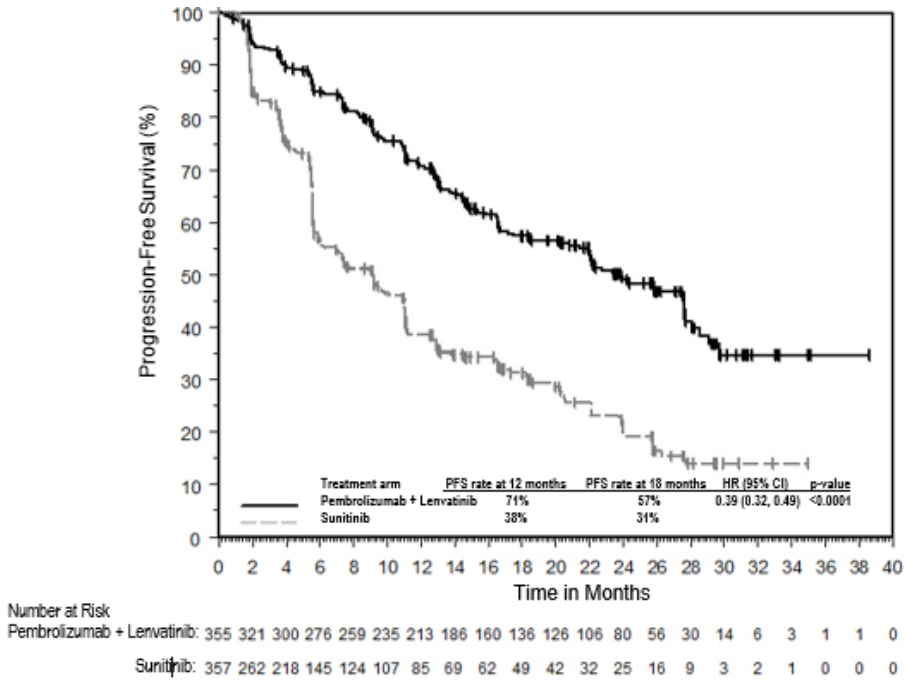
[¶]Nominal two-sided p-Value based on the stratified Cochran-Mantel-Haenszel (CMH) test. At the earlier pre-specified final analysis of ORR (median follow-up time of 17,3 months), statistically significant superiority was achieved for ORR comparing pembrolizumab plus lenvatinib with sunitinib, (odds ratio: 3,84 [95 % CI: 2,81, 5,26], p-Value < 0,0001).

[#]Based on Kaplan-Meier estimates

NR = not reached

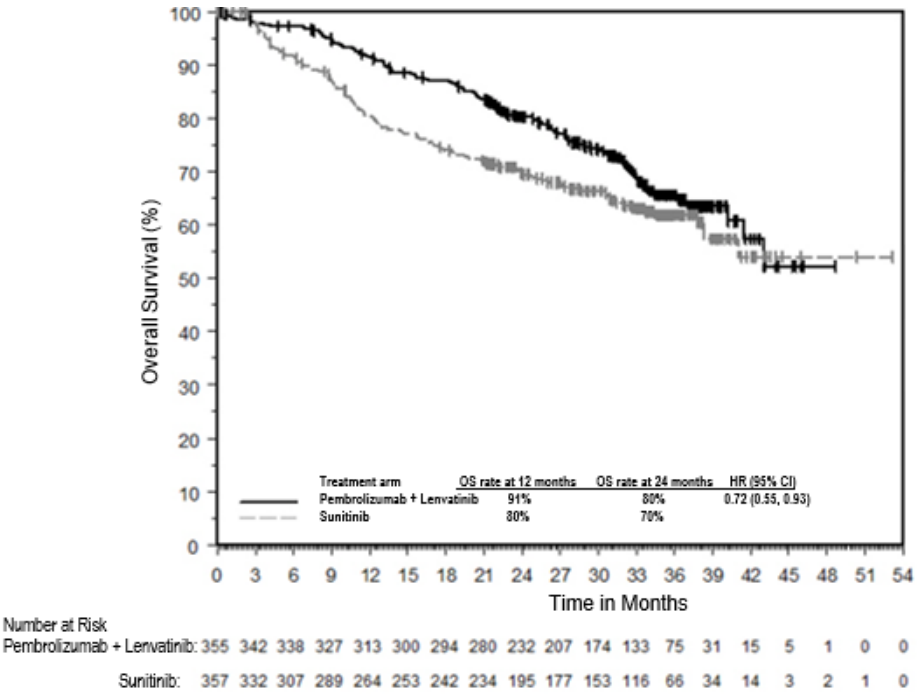
The primary OS analysis was not adjusted to account for subsequent therapies.

Figure 23: Kaplan-Meier curve for progression-free survival by treatment arm in KEYNOTE-581



An updated OS analysis was performed when patients receiving pembrolizumab and lenvatinib or sunitinib had a median survival follow-up of 33,4 months. The hazard ratio was 0,72 (95 % CI 0,55, 0,93) with 105/355 (30 %) deaths in the combination arm and 122/357 (34 %) deaths in the sunitinib arm. This updated OS analysis was not adjusted to account for subsequent therapies.

Figure 24: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-581



The KEYNOTE-581 study was not powered to evaluate efficacy of individual subgroups. **Table 32** summarises the efficacy measures by MSKCC prognostic group from the pre-specified primary analysis and the updated OS analysis.

Table 32: Efficacy Results in KEYNOTE-581 by MSKCC Prognostic Group

	Pembrolizumab + Lenvatinib (N=355)		**Sunitinib (N=357)**		**Pembrolizumab + Lenvatinib vs. Sunitinib**
	Number of Patients	**Number of Events**	**Number of Patients**	**Number of Events**	
Progression-Free Survival (PFS) by IRC*					**PFS HR (95 % CI)**

Favourable	96	39	97	60	0,36 (0,23, 0,54)
Intermediate	227	101	228	126	0,44 (0,34, 0,58)
Poor	32	20	32	19	0,18 (0,08, 0,42)
Overall Survival (OS)*					**OS HR (95 % CI)**
Favourable†	96	11	97	13	0,86 (0,38, 1,92)
Intermediate	227	57	228	73	0,66 (0,47, 0,94)
Poor	32	12	32	15	0,50 (0,23, 1,08)
Updated OS‡					**OS HR (95 % CI)**
Favourable†	96	17	97	17	1,00 (0,51, 1,96)
Intermediate	227	74	228	87	0,71 (0,52, 0,97)
Poor	32	14	32	18	0,50 (0,25, 1,02)

*Median follow-up: 26,5 months (data cutoff – 28 August 2020)

†Interpretation of HR is limited by the low number of events (24/193 and 34/193)

‡Median follow-up: 33,4 months (data cutoff – 31 March 2021)

KEYNOTE-564: Placebo-controlled study for the adjuvant treatment of patients with resected RCC

The efficacy of pembrolizumab was investigated as adjuvant therapy for RCC in KEYNOTE-564, a multicentre, randomised, double-blind, placebo-controlled study in 994 patients with increased risk of recurrence defined as intermediate-high or high risk or M1 with no evidence of disease (NED). The intermediate-high risk category included: pT2 with Grade 4 or sarcomatoid features; pT3, any Grade without nodal involvement (N0) or distant metastases (M0). The high risk category included: pT4, any Grade N0 and M0; any pT, any Grade with nodal involvement and M0. The M1 NED category included patients with metastatic disease who had undergone

complete resection of primary and metastatic lesions. Patients must have undergone a partial nephroprotective or radical complete nephrectomy (and complete resection of solid, isolated, soft tissue metastatic lesion(s) in M1 NED participants) with negative surgical margins ≥ 4 weeks prior to the time of screening. The study excluded patients with active autoimmune disease or a medical condition that required immunosuppression. Patients with RCC with clear cell component were randomised (1:1) to receive pembrolizumab 200 mg every 3 weeks (n=496) or placebo (n=498) for up to 1 year until disease recurrence or unacceptable toxicity. Randomisation was stratified by metastasis status (M0, M1 NED), and within M0 group, further stratified by ECOG PS (0,1), and geographic region (US, non-US). Starting from randomisation, patients underwent imaging every 12 weeks for the first 2 years, then every 16 weeks from year 3 to 5, and then every 24 weeks annually.

Among the 994 patients, the baseline characteristics were: median age of 60 years (range: 25 to 84), 33 % age 65 or older; 71 % male; and 85 % ECOG PS of 0 and 15 % ECOG PS of 1. Ninety-four percent were N0; 83 % had no sarcomatoid features; 86 % were pT2 with Grade 4 or sarcomatoid features or pT3; 8 % were pT4 or with nodal involvement; and 6 % were M1 NED. Baseline characteristics and demographics were generally comparable between the pembrolizumab and placebo arms.

The primary efficacy outcome measure was investigator-assessed disease-free survival (DFS). The key secondary outcome measure was OS. At the pre-specified interim analysis with a median follow-up time of 23,9 months, the study demonstrated a statistically significant improvement in DFS (HR 0,68; 95 % CI 0,53, 0,87; p-Value = 0,0010) for patients randomised to the pembrolizumab arm compared with placebo. Updated efficacy results with a median follow-up time of 29,7 months are summarised in **Table 33** and Figure 25.

Table 33: Efficacy results in KEYNOTE-564

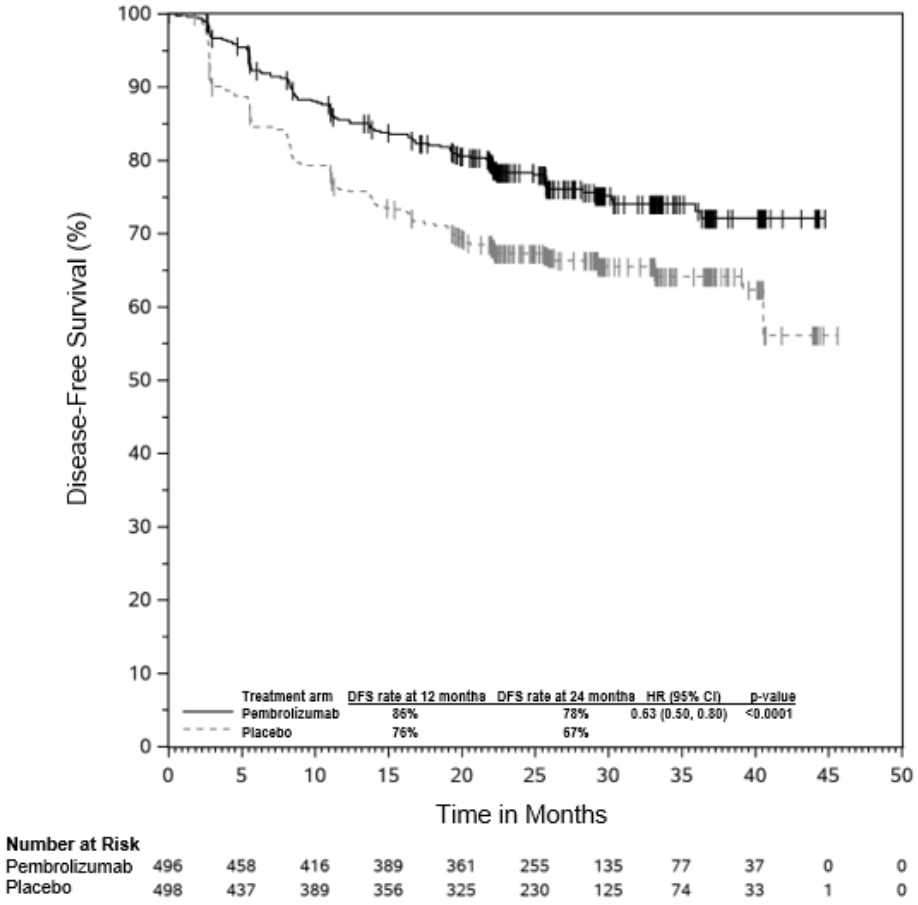
Endpoint	Pembrolizumab 200 mg every 3 weeks n=496	Placebo n=498
DFS		
Number (%) of patients with event	114 (23 %)	169 (34 %)
Median in months (95 % CI)	NR	NR
Hazard ratio* (95 % CI)	0,63 (0,50, 0,80)	
p-Value†	< 0,0001	

*Based on the stratified Cox proportional hazard model

†Nominal p-Value based on stratified log-rank test

NR = not reached

Figure 25: Kaplan-Meier curve for disease-free survival by treatment arm in KEYNOTE-564 (intent to treat population)



At the time of the updated analysis, the DFS hazard ratio (95 % CI) was 0,68 (0,52, 0,89) in the subgroup of patients with M0-intermediate-high risk of recurrence, 0,60 (0,33, 1,10) in the subgroup of patients with M0-high risk of recurrence, and 0,28 (0,12, 0,66) in the subgroup of patients with M1 NED. OS results were not yet mature with 23 deaths out of 496 patients in the pembrolizumab arm and 43 deaths out of 498 patients in the placebo arm.

MSI-H or dMMR cancers

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 (mismatch repair) 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. The study demonstrated a statistically significant improvement in PFS (HR 0,60; 95 % CI 0,45, 0,80; p-Value 0,0002) for patients randomised to the pembrolizumab arm compared with chemotherapy at the pre-specified final analysis for PFS. There was no statistically significant difference between pembrolizumab and chemotherapy in the final OS analysis in which 60 % of the patients who had been randomised to receive chemotherapy had crossed over to receive subsequent anti-PD-1/PD-L1 therapies including pembrolizumab. **Table 34** summarises the key efficacy measures and Figures 26 and 27 show the Kaplan Meier curves for updated PFS and OS based on the final analysis with a median follow-up time of 38,1 months (range: 0,2 to 58,7 months).

Table 34: Efficacy Results in KEYNOTE-177

Endpoint	Pembrolizumab	Chemotherapy

	200 mg every 3 weeks n=153	n=154
PFS*		
Number (%) of patients with event	86 (56 %)	117 (76 %)
Median in months (95 % CI)	16,5 (5,4, 38,1)	8,2 (6,1, 10,2)
Hazard ratio† (95 % CI)	0,59 (0,45, 0,79)	
p-Value‡	0,0001	
OS§		
Number (%) of patients with event	62 (41 %)	78 (51 %)
Median in months (95 % CI)	NR (49,2, NR)	36,7 (27,6, NR)
Hazard ratio† (95 % CI)	0,74 (0,53, 1,03)	
p-Value§	0,0359	
Objective response rate		
ORR (95 % CI)	45 % (37,1, 53,3)	33 % (25,8, 41,1)
Complete response	13 %	4 %
Partial response	32 %	29 %
Response duration		
Median in months (range)	NR (2,3+, 53,5+)	10,6 (2,8, 48,3+)
% of patients with duration ≥ 24 months¶	84 %	34 %
*With additional 12 months of follow-up after the pre-specified final analysis for PFS.		

†Based on Cox regression model

‡p-Value is nominal.

¶Based on Kaplan-Meier estimation

NR = not reached

Figure 26: Kaplan-Meier Curve for Progression-free Survival by Treatment Arm in KEYNOTE-177 (intent to treat population)

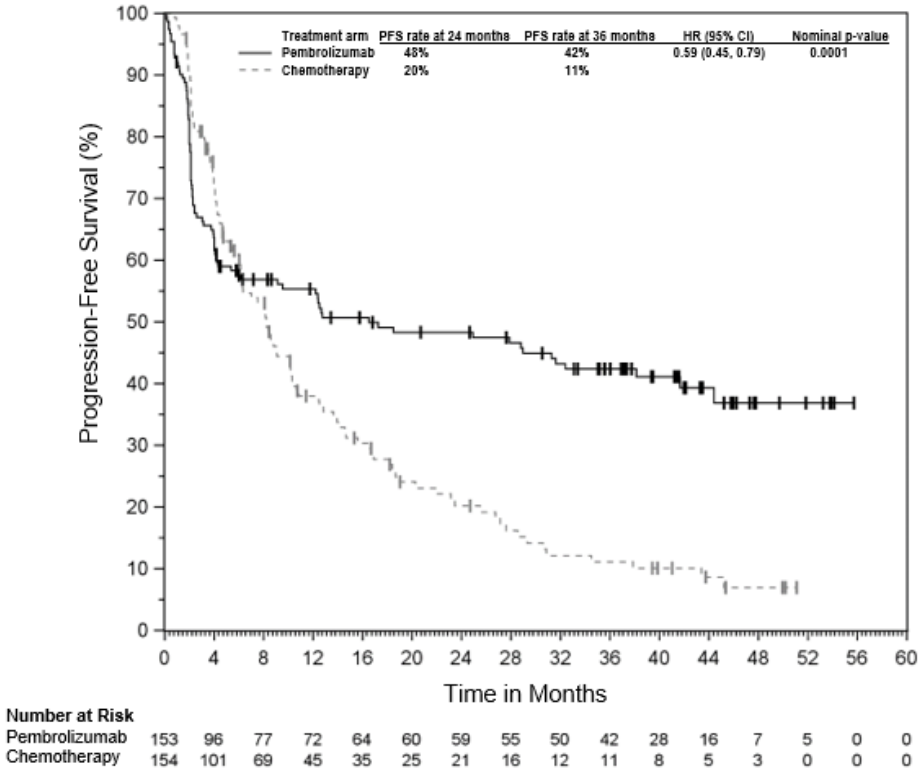
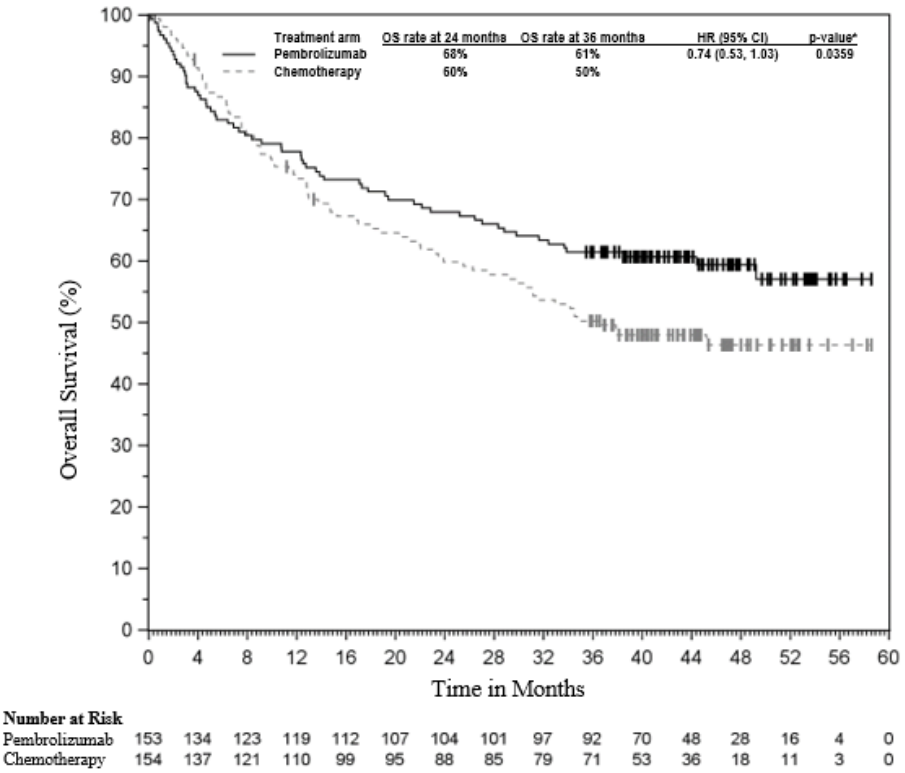


Figure 27: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-177 (intent to treat population)



*Not statistically significant after adjustment for multiplicity

KEYNOTE-164: Open-label study in patients with unresectable or metastatic MSI-H or dMMR CRC who have received prior therapy

The efficacy of pembrolizumab was investigated in KEYNOTE-164, a multicentre, non-randomised, open-label, multi-cohort Phase II study that enrolled patients with unresectable or metastatic MSI-H or dMMR CRC that progressed following prior fluoropyrimidine-based therapy in combination with irinotecan and/or oxaliplatin.

Patients received pembrolizumab 200 mg every 3 weeks until unacceptable toxicity or disease progression. Clinically stable patients with initial evidence of disease progression were permitted to remain on treatment until disease progression was confirmed. Patients without

disease progression were treated for up to 24 months (up to 35 cycles). Assessment of tumour status was performed every 9 weeks.

Among the 124 patients enrolled in KEYNOTE-164, the baseline characteristics were: median age 56 years (35 % age 65 or older); 56 % male; 68 % White, 27 % Asian; 41 % and 59 % had an ECOG performance status of 0 and 1, respectively. Twelve percent of patients had BRAF mutations and 36 % had RAS mutations; 39 % and 34 % were undetermined for BRAF and RAS mutations, respectively. Ninety-seven percent of the patients had M1 disease and 3 % had M0 disease (locally advanced unresectable). Seventy-six percent of patients received 2 or more prior lines of therapy.

The primary efficacy outcome measure was ORR as assessed by BICR using RECIST 1.1. Secondary efficacy outcome measures included response duration, PFS and OS. The median follow-up time in months was 37,3 (range: 0,1 to 65,2). Efficacy results are summarised in **Table 35**.

Table 35: Efficacy results in KEYNOTE-164

Endpoint	**n=124**
Objective response* rate	
ORR % (95 % CI)	34 % (25,6, 42,9)
Complete response	10 %
Partial response	24 %
Response duration*	
Median in months (range)	NR (4,4, 58,5+)
% with duration ≥ 36 months#	92 %

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

#Based on Kaplan-Meier estimation

+Denotes there is no progressive disease by the time of last disease assessment

NR = not reached

Objective responses were observed regardless of BRAF or RAS mutation status.

Non-colorectal cancers

KEYNOTE-158: Open-label study in patients with unresectable or metastatic MSI-H or dMMR endometrial, gastric, small intestine or biliary cancer who have received prior therapy

The efficacy of pembrolizumab was investigated in 355 patients with unresectable or metastatic MSI-H or dMMR non-CRC solid tumours enrolled in a multicentre, non-randomised, open-label Phase II study (KEYNOTE-158), including patients with endometrial, gastric, small intestine or biliary cancer. MSI or MMR tumour status was determined prospectively using PCR or IHC, respectively.

Patients received pembrolizumab 200 mg every 3 weeks until unacceptable toxicity or disease progression. Clinically stable patients with initial evidence of disease progression were permitted to remain on treatment until disease progression was confirmed. Patients without disease progression were treated for up to 24 months (up to 35 cycles). Assessment of tumour status was performed every 9 weeks through the first year, then every 12 weeks thereafter.

Among the 83 patients with endometrial cancer, the baseline characteristics were: median age of 64 years (range: 42 to 86), 46 % age 65 or older; 84 % White, 6 % Asian and 4 % Black; and

ECOG PS 0 (46 %) and 1 (54 %). Ninety-eight percent of the patients had M1 disease and 2 % had M0 disease. Forty-seven percent of patients received 2 or more prior lines of therapy.

Among the 51 patients with gastric cancer, the baseline characteristics were: median age 67 years (range: 41 to 89); 57 % age 65 or older; 65 % male, 63 % White, 28 % Asian; and ECOG PS 0 (45 %) and 1 (55 %). All patients had M1 disease. Forty-five percent of patients received 2 or more prior lines of therapy.

Among the 27 patients with small intestinal cancer, the baseline characteristics were: median age 58 years (range: 21 to 77); 33 % age 65 or older; 63 % male, 81 % White, 11 % Asian; and ECOG PS 0 (56 %) and 1 (44 %). Ninety-six percent of patients had M1 disease and 4 % M0 disease. Thirty-seven percent of patients received 2 or more prior lines of therapy. All patients had a tumour histology of adenocarcinoma.

Among the 22 patients with biliary cancer, the baseline characteristics were: median age 61 years (range: 40 to 77); 41 % age 65 or older; 73 % male, 91 % White, 9 % Asian; ECOG PS 0 (45 %) and 1 (55 %); and 82 % M1 disease and 18 % M0 disease. Forty-one percent of patients received 2 or more prior lines of therapy.

The primary efficacy outcome measure was ORR as assessed by BICR using RECIST 1.1. Secondary efficacy outcome measures included response duration, PFS and OS. The median follow-up time in months was 21,9 (range: 1,5 to 64,0) for endometrial, 13,9 (range: 1,1 to 66,9) for gastric, 29,1 (4,2 to 67,7) for small intestine and 19,4 (range: 1,1 to 60,8) for biliary cancer. Efficacy results are summarised in **Table 36**.

Table 36: Efficacy results in KEYNOTE-158

Endpoint	Endometrial	Gastric	Small Intestine	Biliary

	n=83	n=51	n=27	n=22
Objective response* rate				
ORR % (95 % CI)	51 % (39,4, 61,8)	37 % (24,1, 51,9)	56 % (35,3, 74,5)	41 % (20,7, 63,6)
Complete response	16 %	14 %	15 %	14 %
Partial response	35 %	24 %	41 %	27 %
Response duration*				
Median in months (range)	NR (2,9, 60,4+)	NR (6,2, 63,0+)	NR (3,7+, 57,3+)	30.6 (6,2, 46,0+)
% with duration ≥ 12 months#	85 %	90 %	93 %	89 %
% with duration ≥ 36 months#	60 %	81 %	73 %	42 %

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

Based on Kaplan-Meier estimation

+Denotes there is no progressive disease by the time of last disease assessment

NR = not reached

Oesophageal carcinoma

KEYNOTE-590: First-line treatment of locally advanced unresectable or metastatic Oesophageal Cancer/Gastro-oesophageal Junction

The efficacy of pembrolizumab was investigated in KEYNOTE-590, a multicenter, randomised, placebo-controlled trial that enrolled 749 patients as a first-line treatment in patients with locally advanced unresectable or metastatic carcinoma of the oesophagus and gastro-oesophageal junction. All patients were required to have tumour specimens for PD-L1 testing at a central laboratory; PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx™ Kit. Patients with active autoimmune disease, a medical condition that required immunosuppression or known HER-2 positive GEJ adenocarcinoma patients were ineligible. 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; all study medications were administered via intravenous infusion:

- 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, for up to 24 months.
- 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, for up to 24 months.

Treatment with pembrolizumab or chemotherapy continued until unacceptable toxicity or disease progression. 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. Patients treated with pembrolizumab without disease progression could be treated for up to 24

months. Assessment of tumour status was performed every 9 weeks. The major efficacy outcome measures were OS and PFS as assessed by the investigator according to RECIST v1.1. Secondary efficacy outcome measures were ORR and DoR, according to RECIST v1.1, as assessed by the investigator.

The baseline characteristics were: median age of 63 years (range: 27 to 94), 43 % age 65 or older; 83 % male; 37 % White and 53 % Asian; 40 % had an ECOG PS of 0 and 60 % had an ECOG PS of 1. Ninety-one percent had M1 disease and 9 % had M0 disease. Seventy-three percent had a tumour histology of squamous cell carcinoma and 27 % had adenocarcinoma.

Pembrolizumab, in combination with chemotherapy, demonstrated a statistically significant and clinically meaningful improvement in OS and PFS when compared to chemotherapy (cisplatin and 5-FU) in previously untreated participants with locally advanced unresectable or metastatic carcinoma of the oesophagus or gastro-oesophageal junction. The investigator-assessed results were consistent with BICR.

Table 37 summarises the key efficacy measures for KEYNOTE-590. The Kaplan-Meier curves for OS and PFS are shown in Figures 28 and 29.

Table 37: Efficacy Results in Patients with Locally Advanced Unresectable or Metastatic Oesophageal Cancer in KEYNOTE-590

Endpoint	Pembrolizumab 200 mg every 3 weeks Cisplatin 5-FU n=373	Placebo Cisplatin 5-FU n=376

OS		
Number (%) of patients with event	262 (70 %)	309 (82 %)
Median in months* (95 % CI)	12,4 (10,5, 14,0)	9,8 (8,8, 10,8)
Hazard ratio† (95 % CI)	0,73 (0,62, 0,86)	
p-Value (stratified log-rank)	< 0,0001	
PFS‡		
Number (%) of patients with event	297 (79,6 %)	333 (88,6 %)
Median in months* (95 % CI)	6,3 (6,2, 6,9)	5,8 (5,0, 6,0)
Hazard ratio† (95 % CI)	0,65 (0,55, 0,76)	
p-Value (stratified log-rank)	< 0,0001	
Objective response rate‡		
ORR % (95 % CI)	45 % (39,9, 50,2)	29,3 % (24,7, 34,1)
Complete response rate	6,4 %	2,4 %
Partial response rate	38,6 %	26,9 %
p-Value (Miettinen-Nurminen)	< 0,0001	
Response duration‡,§		
Median duration of response in months (range)	8,3 (1,2+, 31,0+)	6,0 (1,5+, 25,0+)
% with duration ≥ 6 months*	73,5 %	50,4 %
% with duration ≥ 12 months*	38,6 %	17,8 %
% with duration ≥ 18 months*	29,4 %	7,7 %
*Based on Kaplan-Meier estimation †Based on the stratified Cox proportional hazard model		

‡Assessed by investigator using RECIST 1.1

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

Figure 28: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-590

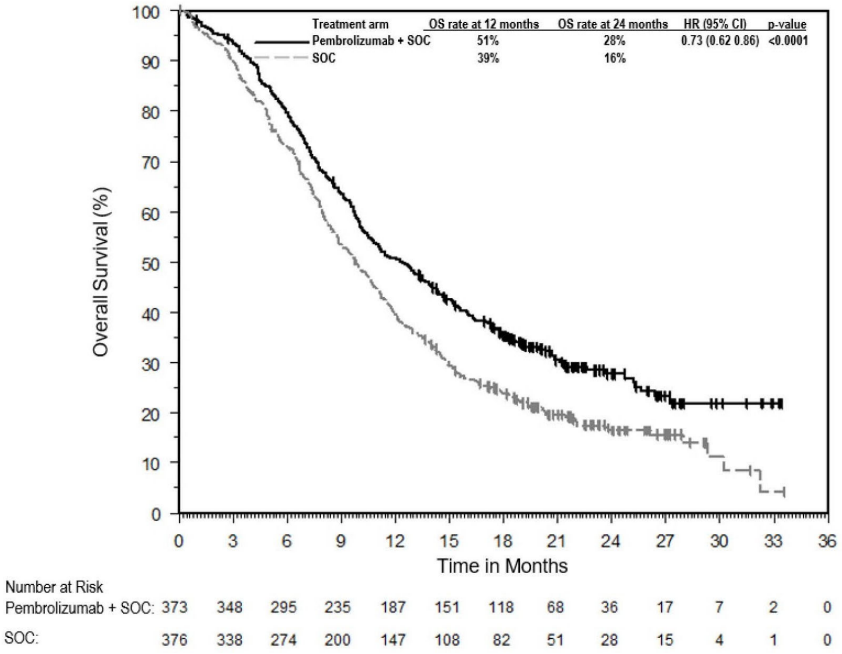
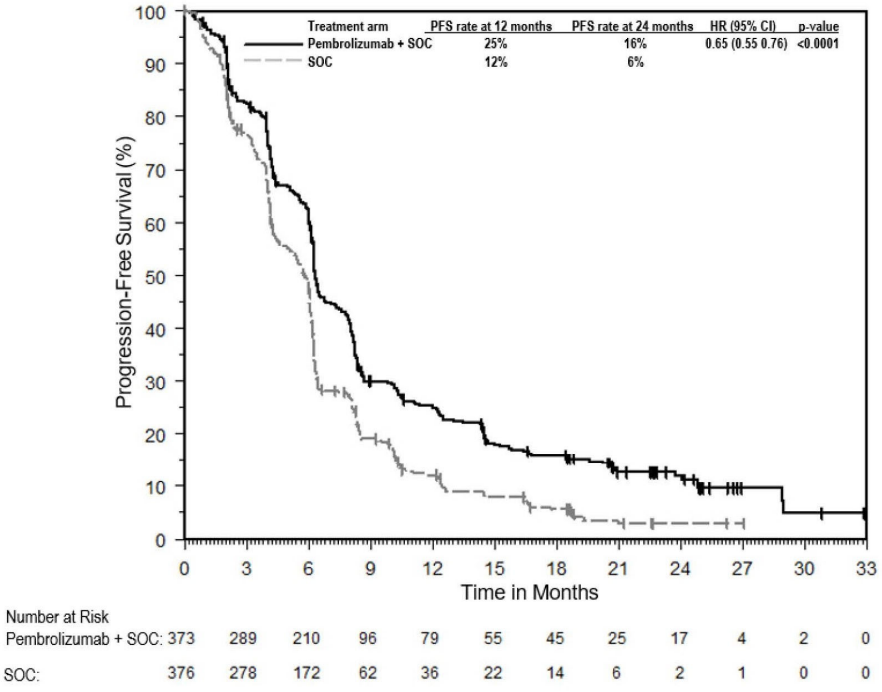


Figure 29: Kaplan-Meier curve for progression-free survival by treatment arm in KEYNOTE-590



Triple-negative breast cancer

KEYNOTE-522: Controlled study of neoadjuvant and adjuvant therapy in patients with locally advanced, inflammatory or early-stage triple-negative breast cancer at high risk of recurrence

The efficacy of pembrolizumab in combination with chemotherapy as neoadjuvant treatment and then continued as monotherapy as adjuvant treatment after surgery was investigated in the randomised, double-blind, multicentre, placebo-controlled study KEYNOTE-522. If indicated, patients received adjuvant radiation therapy prior to or concurrent with adjuvant pembrolizumab or placebo. The key eligibility criteria for this study were locally advanced, inflammatory or early-stage TNBC at high risk of recurrence (tumour size > 1 cm but ≤ 2 cm in diameter with nodal involvement or tumour size > 2 cm in diameter regardless of nodal involvement), regardless of tumour PD-L1 expression. Patients with active autoimmune disease that required systemic

therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible for the study. Randomisation was stratified by nodal status (positive vs. negative), tumour size (T1/T2 vs. T3/T4) and choice of carboplatin (dosed every 3 weeks vs. weekly). Patients were randomised (2:1) to receive either pembrolizumab or placebo via intravenous infusion:

- Four cycles of neoadjuvant pembrolizumab 200 mg every 3 weeks or placebo on Day 1 of cycles 1-4 of treatment regimen in combination with:
  - Carboplatin
    - AUC 5 mg/mL/min every 3 weeks on Day 1 of cycles 1-4 of treatment regimen or AUC 1,5 mg/mL/min every week on Day 1, 8 and 15 of cycles 1-4 of treatment regimen and
  - Paclitaxel 80 mg/m^2 every week on Day 1, 8 and 15 of cycles 1-4 of treatment regime
- Followed by four additional cycles of neoadjuvant pembrolizumab 200 mg every 3 weeks or placebo on Day 1 of cycles 5-8 of treatment regimen in combination with:
  - Doxorubicin 60 mg/m^2 or epirubicin 90 mg/m^2 every 3 weeks on Day 1 of cycles 5-8 of treatment regimen and
  - Cyclophosphamide 600 mg/m^2 every 3 weeks on Day 1 of cycles 5-8 of treatment regimen
- Following surgery, 9 cycles of adjuvant pembrolizumab 200 mg every 3 weeks or placebo were administered.

Treatment with pembrolizumab or placebo continued until completion of the treatment (17 cycles), disease progression that precludes definitive surgery, disease recurrence in the adjuvant phase or unacceptable toxicity.

A total of 1 174 patients were randomised. The study population characteristics were: median age of 49 years (range: 22 to 80); 11 % age 65 or older; 99,9 % female; 64 % White; 20 % Asian, 5 % Black and 2 % American Indian or Alaska Native; ECOG performance status of 0 (87 %) and 1 (13 %); 56 % were pre-menopausal status and 44 % were post-menopausal status; 7 % were primary Tumour 1 (T1), 68 % T2, 19 % T3 and 7 % T4; 49 % were nodal involvement 0 (N0), 40 % N1, 11 % N2 and 0,2 % N3; 1,4 % of patients had inflammatory breast cancer; 75 % of patients were overall Stage II and 25 % were Stage III.

The dual primary efficacy outcome measures were pathological complete response (pCR) rate and event-free survival (EFS). pCR was defined as absence of invasive cancer in the breast and lymph nodes (ypT0/Tis ypN0) and was assessed by the blinded local pathologist at the time of definitive surgery. EFS was defined as the time from randomisation to the first occurrence of any of the following events: progression of disease that precludes definitive surgery, local or distant recurrence, second primary malignancy or death due to any cause. The study demonstrated a statistically significant improvement in pCR rate difference at its pre-specified primary analysis (n=602), the pCR rates were 64,8 % (95 % CI: 59,9 %, 69,5 %) in the pembrolizumab arm and 51,2 % (95 % CI: 44,1 %, 58,3 %) in the placebo arm, with a treatment difference of 13,6 % (95 % CI: 5,4 %, 21,8 %; p-Value 0,00055). The study also demonstrated a statistically significant improvement in EFS at its pre-specified analysis. A secondary efficacy outcome measure was OS. At the time of EFS analysis, OS results were not yet mature (45 % of the required events for final analysis). At a pre-specified interim analysis, the median follow-up time for all patients was 37,8 months (range: 2,7-48 months). **Table 38** summarises key efficacy measures from the pre-specified analyses. The Kaplan-Meier curve for EFS and OS are shown in Figures 30 and 31.

Table 38: Efficacy results in KEYNOTE-522

Endpoint	Pembrolizumab with Chemotherapy/Pembrolizumab	Placebo with Chemotherapy/Placebo
pCR (ypT0/Tis ypN0)[*]	**n=669**	**n=333**
Number of patients with pCR	428	182
pCR Rate (%), (95 % CI)	64,0 (60,2, 67,6)	54,7 (49,1, 60,1)
Treatment difference (%) estimate (95 % CI)[†]	9,2 (2,8, 15,6)	
p-Value[‡]	0,00221	
EFS[§]	**n=784**	**n=390**
Number (%) of patients with event	123 (15,7 %)	93 (23,8 %)
24 month EFS rate (95 % CI)	87,8 (85,3, 89,9)	81,0 (76,8, 84,6)
Hazard ratio (95 % CI)[¶]	0,63 (0,48, 0,82)	
p-Value[#]	0,00031	
OS[Þ]		
Number (%) of patients with event	80 (10,2 %)	55 (14,1 %)
24-month OS rate (95 % CI)	92,3 (90,2, 94,0)	91,0 (87,7, 93,5)
Hazard ratio (95 % CI)[¶]	0,72 (0,51, 1,02)	

[*]Based on a pre-specified pCR final analysis (compared to a significance level of 0,0028)

[†]Based on Miettinen and Nurminen method stratified by nodal status, tumour size and choice of

carboplatin

‡One-sided p-Value for testing. H0: difference in % = 0 versus H1: difference in % > 0

§Based on a pre-specified EFS interim analysis (compared to a significance level of 0,0052)

¶Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by nodal status, tumour size and choice of carboplatin

#One-sided p-Value based on log-rank test stratified by nodal status, tumour size and choice of carboplatin

ÞOS results at interim analysis did not meet the pre-specified efficacy boundary of 0,00085861 for statistical significance.

Figure 30: Kaplan-Meier curve for event-free survival by treatment arm in KEYNOTE-522 (intent to treat population)

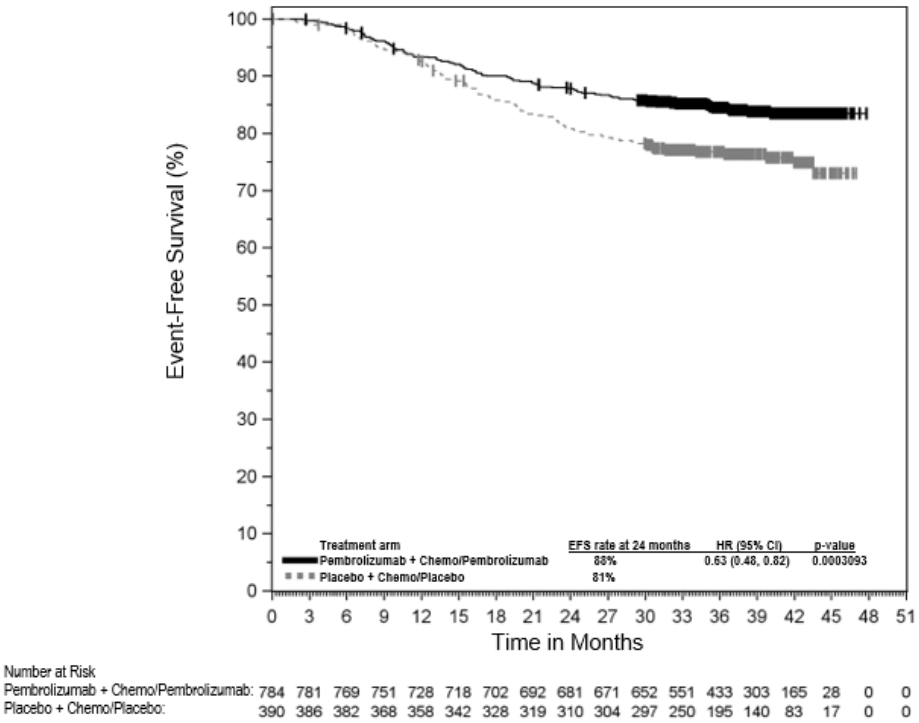
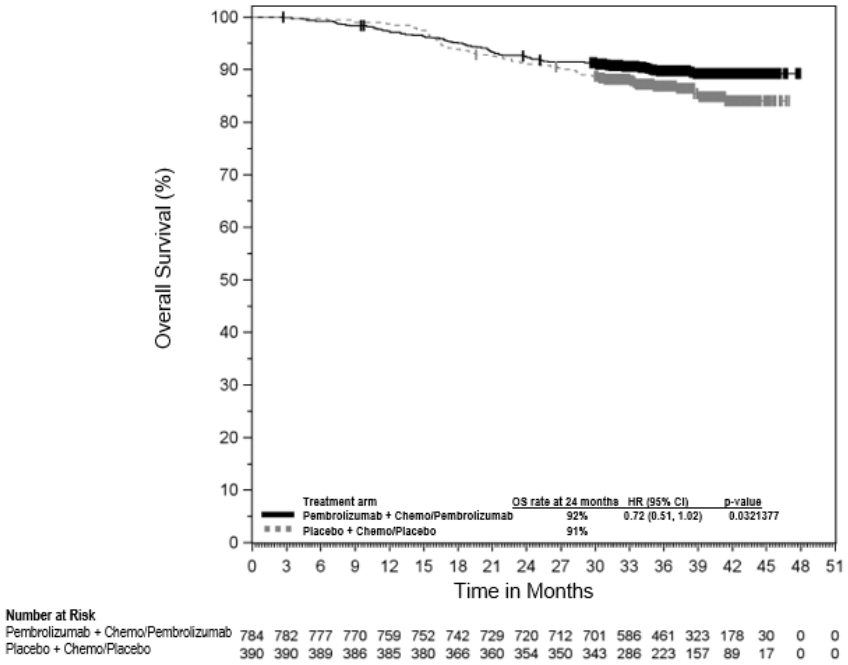


Figure 31: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-522 (intent to treat population)



KEYNOTE-355: Controlled study of combination therapy in TNBC patients previously untreated for metastatic disease

The efficacy of pembrolizumab in combination with paclitaxel, nab-paclitaxel, or gemcitabine and carboplatin was investigated in KEYNOTE-355, a randomised, double-blind, multicentre, placebo-controlled study. Key eligibility criteria were locally recurrent unresectable or metastatic TNBC, regardless of tumour PD-L1 expression, not previously treated with chemotherapy in the advanced setting. Patients with active autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Randomisation was stratified by chemotherapy treatment (paclitaxel or nab-paclitaxel

vs. gemcitabine and carboplatin), tumour PD-L1 expression (CPS ≥ 1 vs. CPS < 1), and prior treatment with the same class of chemotherapy in the neoadjuvant setting (yes vs. no). Patients were randomised (2:1) to one of the following treatment arms via intravenous infusion:

- Pembrolizumab 200 mg on Day 1 every 3 weeks in combination with nab-paclitaxel 100 mg/m^2 on Days 1, 8 and 15 every 28 days, or paclitaxel 90 mg/m^2 on Days 1, 8 and 15 every 28 days, or gemcitabine 1 000 mg/m^2 and carboplatin AUC 2 mg/mL/min on Days 1 and 8 every 21 days.
- Placebo on Day 1 every 3 weeks in combination with nab-paclitaxel 100 mg/m^2 on Days 1, 8 and 15 every 28 days, or paclitaxel 90 mg/m^2 on Days 1, 8 and 15 every 28 days, or gemcitabine 1 000 mg/m^2 and carboplatin AUC 2 mg/mL/min on Days 1 and 8 every 21 days.

Treatment with pembrolizumab or placebo, both in combination with chemotherapy, continued until RECIST 1.1-defined progression of disease as determined by the investigator, unacceptable toxicity or a maximum of 24 months. Chemotherapy could continue per standard of care. 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. Assessment of tumour status was performed at Weeks 8, 16 and 24, then every 9 weeks for the first year, and every 12 weeks thereafter.

Among the 847 patients randomised in KEYNOTE-355, 636 (75 %) had tumours that expressed PD-L1 with a CPS ≥ 1 and 323 (38 %) had tumour PD-L1 expression CPS ≥ 10 based on the PD-L1 IHC 22C3 pharmDx™ Kit. The baseline characteristics of the 323 patients with tumour PD-L1 expression CPS ≥ 10 included: median age of 53 years (range: 22 to 83); 20 % age 65 or older; 100 % female; 69 % White, 20 % Asian and 5 % Black; ECOG performance status of 0

(61 %) and 1 (39 %); 67 % were post-menopausal status; 3 % had a history of brain metastases; and 20 % had disease-free interval of < 12 months.

The dual primary efficacy outcome measures were PFS as assessed by BICR using RECIST 1.1 and OS. Secondary efficacy outcome measures were ORR and response duration as assessed by BICR using RECIST 1.1. The study demonstrated a statistically significant improvement in PFS at its pre-specified interim analysis (HR 0,65; 95 % CI 0,49, 0,86; p-Value 0,0012) and OS at final analysis for patients with tumour PD-L1 expression CPS ≥ 10 randomised to the pembrolizumab in combination with chemotherapy arm compared with placebo in combination with chemotherapy. **Table 39** summarises key efficacy measures and Figures 32 and 33 show the Kaplan-Meier curves for PFS and OS based on the final analysis with a median follow-up time of 20,2 months (range: 0,3 to 53,1 months) for patients with tumour PD-L1 expression CPS ≥ 10.

Table 39: Efficacy Results in KEYNOTE-355 patients with CPS ≥ 10

Endpoint	Pembrolizumab with chemotherapy* n=220	Placebo with chemotherapy* n=103
PFS†		
Number (%) of patients with event	144 (65 %)	81 (79 %)
Hazard ratio‡ (95 % CI)	0,66 (0,50, 0,88)	
p-Value§	0,0018	
Median in months (95 % CI)	9,7 (7,6, 11,3)	5,6 (5,3, 7,5)
OS		

Number (%) of patients with event	155 (70 %)	84 (82 %)
Hazard ratio‡ (95 % CI)	0,73 (0,55, 0,95)	
p-Value¶	0,0093	
Median in months (95 % CI)	23,0 (19,0, 26,3)	16,1 (12,6, 18,8)
Objective response rate†		
ORR % (95 % CI)	53 % (46, 60)	41 % (31, 51)
Complete response	17 %	14 %
Partial response	36 %	27 %
Response duration†		
Median in months (range)	12,8 (1,6+, 45,9+)	7,3 (1,5, 46,6+)
% with duration ≥ 6 months#	82 %	60 %
% with duration ≥ 12 months#	56 %	38 %

*Chemotherapy: paclitaxel, nab-paclitaxel or gemcitabine and carboplatin

†Assessed by BICR using RECIST 1.1

‡Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by chemotherapy on study (taxane vs. gemcitabine and carboplatin) and prior treatment with same class of chemotherapy in the neoadjuvant setting (yes vs. no)

§Nominal p-Value based on log-rank test stratified by chemotherapy on study (taxane vs. gemcitabine and carboplatin) and prior treatment with same class of chemotherapy in the neoadjuvant setting (yes vs. no). At the pre-specified interim analysis of PFS (median follow-up time of 19,2 months), statistically significant superiority was achieved for PFS comparing pembrolizumab/chemotherapy with placebo/chemotherapy p-Value 0,0012

¶One-sided p-Value based on log-rank test stratified by chemotherapy on study (taxane vs.

gemcitabine and carboplatin) and prior treatment with same class of chemotherapy in the neoadjuvant setting (yes vs. no). OS results met the pre-specified efficacy boundary of 0,0113 for statistical significance.

#From product-limit (Kaplan-Meier) method for censored data

+Denotes there is no progressive disease by the time of last disease assessment

Figure 32: Kaplan-Meier curve for progression-free survival by treatment arm in KEYNOTE-355 patients with PD-L1 expression (CPS ≥ 10)

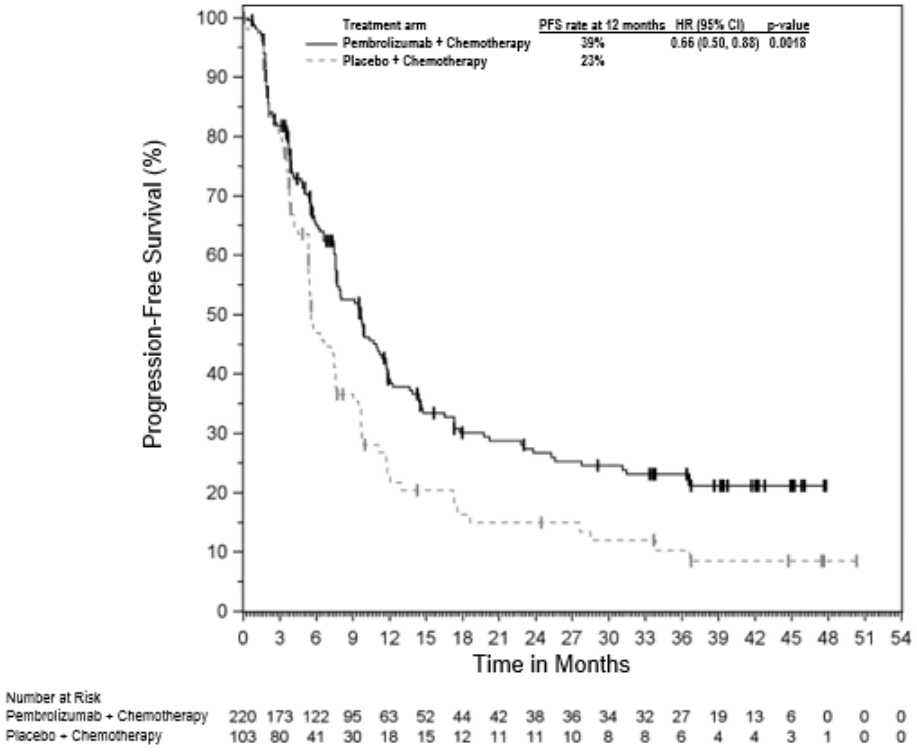
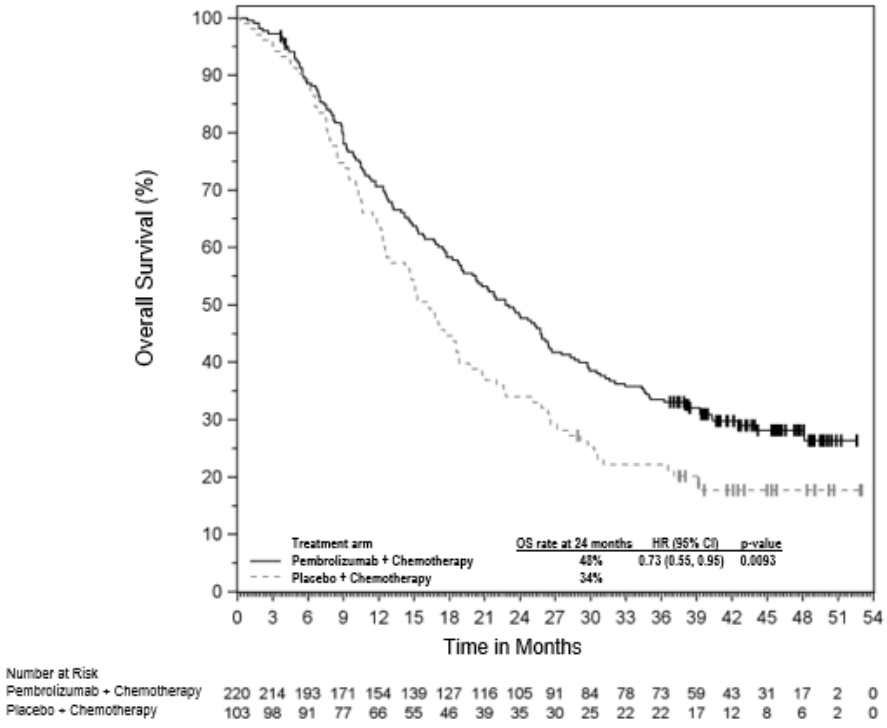


Figure 33: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-355 patients with PD-L1 expression (CPS ≥ 10)



Endometrial carcinoma

KEYNOTE-775: Controlled study of combination therapy in advanced EC patients previously treated with systemic chemotherapy

The efficacy of pembrolizumab in combination with lenvatinib was investigated in KEYNOTE-775, a randomised, multicentre, open-label, active-controlled study conducted in patients with advanced EC who had been previously treated with at least one prior platinum-based chemotherapy regimen in any setting, including in the neoadjuvant and adjuvant settings. Participants may have received up to 2 platinum-containing therapies in total, as long as one was given in the neoadjuvant or adjuvant treatment setting. The study excluded patients with endometrial sarcoma, carcinosarcoma, pre-existing Grade ≥ 3 fistula, uncontrolled BP (> 150/90 mmHg), significant cardiovascular impairment or event within previous 12 months, or patients

who had active autoimmune disease or a medical condition that required immunosuppression. Randomisation was stratified by MMR status (dMMR or pMMR [mismatch repair proficient]) using a validated IHC test. The pMMR stratum was further stratified by ECOG performance status, geographic region and history of pelvic radiation. Patients were randomised (1:1) to one of the following treatment arms:

- pembrolizumab 200 mg intravenously every 3 weeks in combination with lenvatinib 20 mg orally once daily.
- investigator's choice consisting of either doxorubicin 60 mg/m^2 every 3 weeks or paclitaxel 80 mg/m^2 weekly, 3 weeks on/1 week off.

Treatment with pembrolizumab and lenvatinib continued until RECIST v1.1-defined progression of disease as verified by BICR, unacceptable toxicity or for pembrolizumab, a maximum of 24 months. Administration of study treatment was permitted beyond RECIST-defined disease progression if the treating investigator considered the patient to be deriving clinical benefit and the treatment was tolerated. A total of 121/411 (29 %) of the pembrolizumab and lenvatinib-treated patients received continued study therapy beyond RECIST-defined disease progression. The median duration of the post-progression therapy was 2,8 months. Assessment of tumour status was performed every 8 weeks.

A total of 827 patients were enrolled and randomised to pembrolizumab in combination with lenvatinib (n=411) or investigator's choice of doxorubicin (n=306) or paclitaxel (n=110). The baseline characteristics of these patients were: median age of 65 years (range: 30 to 86), 50 % age 65 or older; 61 % White, 21 % Asian and 4 % Black; ECOG PS of 0 (59 %) or 1 (41 %), and 84 % with pMMR tumour status and 16 % with dMMR tumour status. The histologic subtypes were endometrioid carcinoma (60 %), serous (26 %), clear cell carcinoma (6 %), mixed (5 %) and other (3 %). All 827 of these patients received prior systemic therapy for EC: 69 % had one,

28 % had two and 3 % had three or more prior systemic therapies. 37 % of patients received only prior neoadjuvant or adjuvant therapy.

The primary efficacy outcome measures were OS and PFS (as assessed by BICR using RECIST 1.1). Secondary efficacy outcome measures included ORR, as assessed by BICR using RECIST 1.1. The median follow-up time was 11,4 months (range: 0,3 to 26,9 months). Efficacy results by MMR subgroups were consistent with overall study results. Efficacy measures are summarised in **Table 40** and Kaplan-Meier curves for OS and PFS are shown in Figures 34 and 35, respectively.

Table 40: Efficacy results in KEYNOTE-775

Endpoint	**Pembrolizumab 200 mg every 3 weeks Lenvatinib n=411**	**Chemotherapy*** **n=416**
OS		
Number (%) of patients with event	188 (46 %)	245 (59 %)
Median in months (95 % CI)	18,3 (15,2, 20,5)	11,4 (10,5, 12,9)
Hazard ratio† (95 % CI)	0,62 (0,51, 0,75)	
p-Value‡	< 0,0001	
PFS		
Number (%) of patients with event	281 (68 %)	286 (69 %)
Median in months (95 % CI)	7,2 (5,7, 7,6)	3,8 (3,6, 4,2)
Hazard ratio† (95 % CI)	0,56 (0,47, 0,66)	

p-Value‡	< 0,0001	
Objective response rate		
ORR§ (95 % CI)	32 % (27, 37)	15 % (11, 18)
Complete response %	7 %	3 %
Partial response %	25 %	12 %
p-Value¶	< 0,0001	
Response duration		
Median in months# (range)	14,4 (1,6+, 23,7+)	5,7 (0,0+, 24,2+)

*Doxorubicin or Paclitaxel

†Based on the stratified Cox regression model

‡One-sided p-Value 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 MMR Status, ECOG performance status, geographic region and history of pelvic radiation

#Based on Kaplan-Meier estimation

Figure 34: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-775 (intent to treat population)

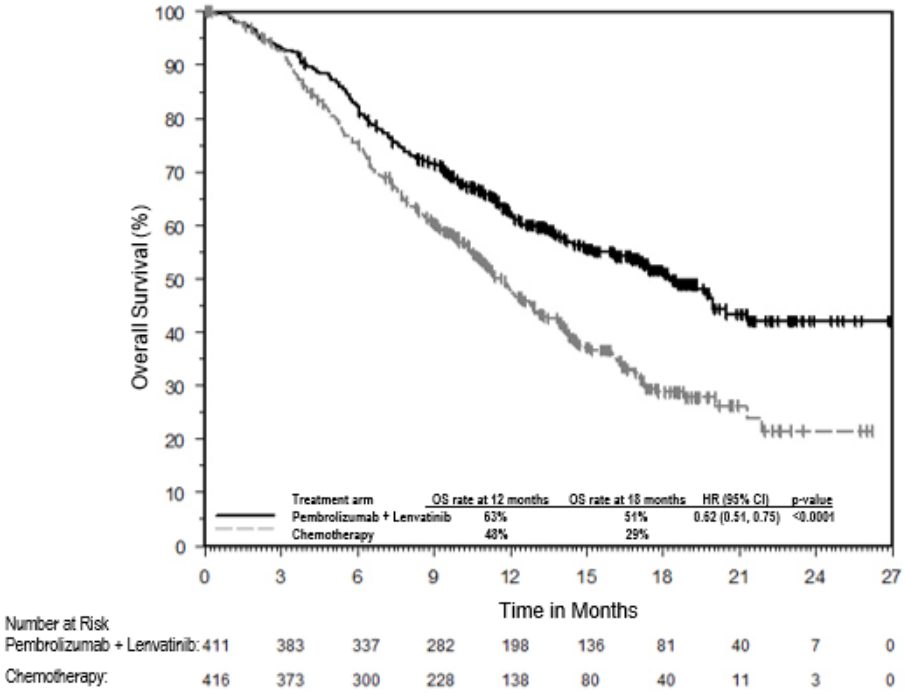
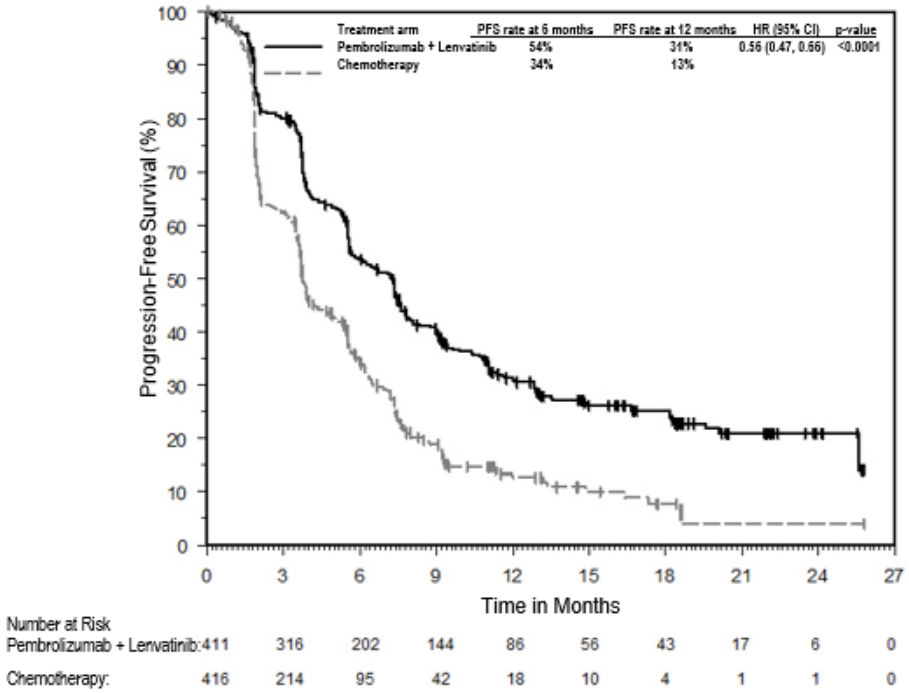


Figure 35: Kaplan-Meier curve for progression free-survival by treatment arm in KEYNOTE-775 (intent to treat population)



For pMMR patients (n=697), the OS HR was 0,68 (95 % CI: 0,56, 0,84), p=0,0001, one-sided; with median OS of 17,4 months for pembrolizumab and lenvatinib versus 12,0 months for chemotherapy. For dMMR patients (n=130), there was no formal hypothesis testing; the OS HR was 0,37 (95 % CI: 0,22, 0,62) with median OS not reached for pembrolizumab and lenvatinib versus 8,6 months for chemotherapy.

Cervical cancer

KEYNOTE-826: Controlled study of combination therapy in patients with persistent, recurrent or metastatic cervical cancer

The efficacy of pembrolizumab in combination with paclitaxel and cisplatin or paclitaxel and carboplatin, with or without bevacizumab, was investigated in KEYNOTE-826, a multicentre, randomised, double-blind, placebo-controlled study that enrolled 617 patients with persistent, recurrent or first-line metastatic cervical cancer who had not been treated with chemotherapy

except when used concurrently as a radio-sensitising agent. Patients were enrolled regardless of tumour PD-L1 expression status. Patients with autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Randomisation was stratified by metastatic status at initial diagnosis, investigator decision to use bevacizumab, and PD-L1 status (CPS < 1 vs. CPS 1 to < 10 vs. CPS ≥ 10). Patients were randomised (1:1) to one of the two treatment groups:

- Treatment Group 1: Pembrolizumab 200 mg plus chemotherapy with or without bevacizumab
- Treatment Group 2: Placebo plus chemotherapy with or without bevacizumab

The investigator selected one of the following four treatment regimens prior to randomisation:

1. Paclitaxel 175 mg/m^2 + cisplatin 50 mg/m^2
2. Paclitaxel 175 mg/m^2 + cisplatin 50 mg/m^2 + bevacizumab 15 mg/kg
3. Paclitaxel 175 mg/m^2 + carboplatin AUC 5 mg/mL/min
4. Paclitaxel 175 mg/m^2 + carboplatin AUC 5 mg/mL/min + bevacizumab 15 mg/kg

All study medications were administered as an intravenous infusion. All study treatments were administered on Day 1 of each 3-week treatment cycle. Cisplatin could be administered on Day 2 of each 3-week treatment cycle. The option to use bevacizumab was by investigator choice prior to randomisation. Treatment with pembrolizumab continued until RECIST v1.1-defined progression of disease, 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 9 weeks for the first year, followed by every 12 weeks thereafter.

Of the 617 enrolled patients, 548 patients (89 %) had tumours expressing PD-L1with a CPS ≥ 1 based on the PD-L1 IHC 22C3 pharmDx™ Kit. Among these 548 enrolled patients with tumours expressing PD-L1, 273 patients were randomised to pembrolizumab in combination with chemotherapy with or without bevacizumab, and 275 patients were randomised to placebo in combination with chemotherapy with or without bevacizumab. The baseline characteristics of these 548 patients were: median age of 51 years (range: 22 to 82), 16 % age 65 or older; 59 % White, 18 % Asian and 1 % Black; 37 % Hispanic or Latino; 56 % and 43 % ECOG performance status of 0 or 1, respectively; 63 % received bevacizumab as study treatment; 21 % with adenocarcinoma and 5 % with adenosquamous histology; for patients with persistent or recurrent disease with or without distant metastases, 39 % had received prior chemoradiation only and 17 % had received prior chemoradiation plus surgery.

The primary efficacy outcome measures were OS and PFS as assessed by investigator according to RECIST v1.1. Secondary efficacy outcome measures were ORR and duration of response, according to RECIST v1.1, as assessed by investigator. The study demonstrated statistically significant improvements in OS and PFS for patients randomised to pembrolizumab in combination with chemotherapy with or without bevacizumab compared to placebo in combination with chemotherapy with or without bevacizumab at a pre-specified interim analysis in the overall population. The median follow-up time was 17,2 months (range: 0,3 to 29,4 months). **Table 41** summarises key efficacy measures for patients whose tumours expressed PD-L1 with a CPS ≥ 1 in KEYNOTE-826 from the pre-specified interim analysis. The Kaplan-Meier curves for OS and PFS are shown in Figures 36 and 37.

Table 41: Efficacy results in KEYNOTE-826 for patients with PD-L1 expression (CPS ≥ 1)

Endpoint	Pembrolizumab 200 mg every 3 weeks plus Chemotherapy* with or without bevacizumab n=273	Placebo plus Chemotherapy* with or without bevacizumab n=275
OS		
Number (%) of patients with event	118 (43 %)	154 (56 %)
Median in months (95 % CI)	NR (19,8, NR)	16,3 (14,5, 19,4)
Hazard ratio† (95 % CI)	0,64 (0,50, 0,81)	
p-Value‡	0,0001	
PFS		
Number (%) of patients with event	157 (58 %)	198 (72 %)
Median in months (95 % CI)	10,4 (9,7, 12,3)	8,2 (6,3, 8,5)
Hazard ratio† (95 % CI)	0,62 (0,50, 0,77)	
p-Value§	< 0,0001	
Objective response rate		
ORR¶ % (95 % CI)	68 % (62, 74)	50 % (44, 56)
Complete response	23 %	13 %
Partial response	45 %	37 %
Duration of response		
Median in months (range)	18,0 (1,3+, 24,2+)	10,4 (1,5+, 22,0+)

% with duration ≥ 12 months[#]	56	46

[*]Chemotherapy (paclitaxel and cisplatin or paclitaxel and carboplatin)

[†]Based on the stratified Cox proportional hazard model

[‡]Based on stratified log-rank test (compared to an alpha boundary of 0,00549)

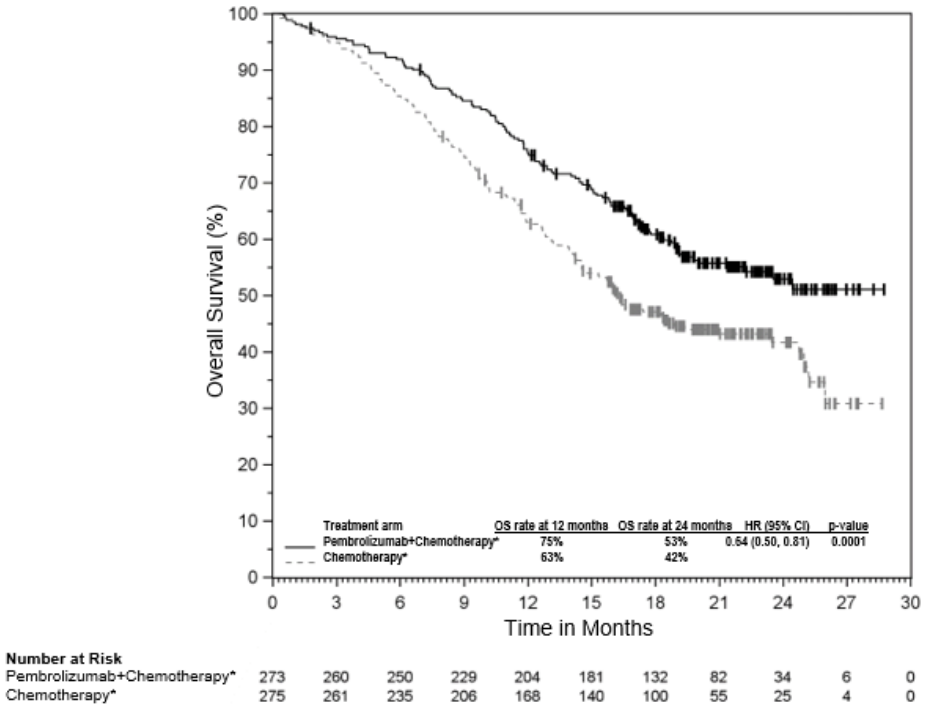
[§]Based on stratified log-rank test (compared to an alpha boundary of 0,00144)

[¶]Response: Best objective response as confirmed complete response or partial response

[#]Based on Kaplan-Meier estimation

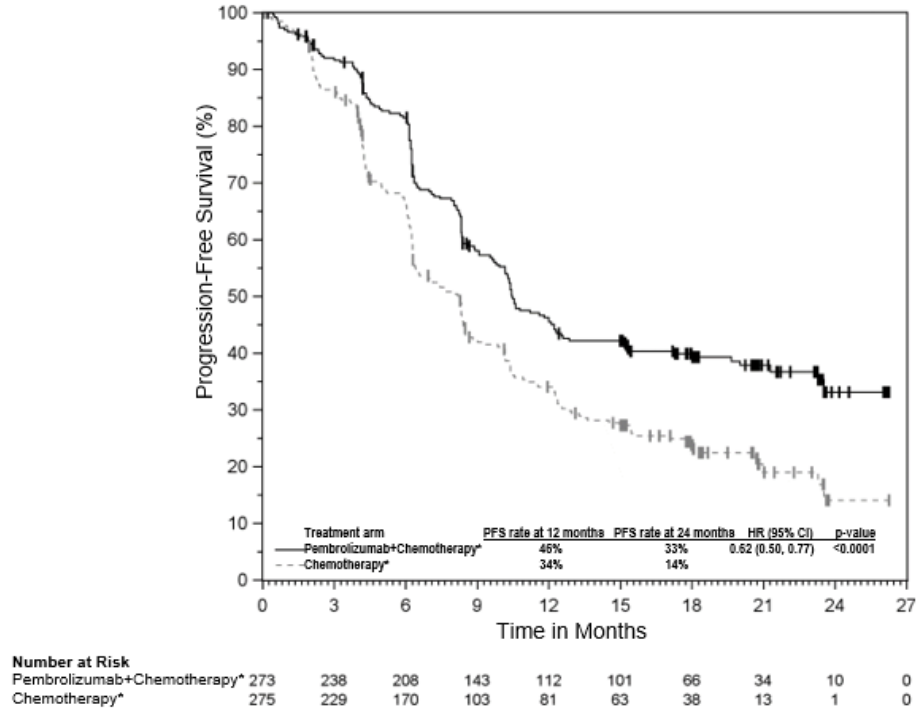
NR = not reached

Figure 36: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-826 patients with PD-L1 expression (CPS ≥ 1)



*Chemotherapy (paclitaxel and cisplatin or paclitaxel and carboplatin) with or without bevacizumab

Figure 37: Kaplan-Meier curve for progression free survival by treatment arm in KEYNOTE-826 patients with PD-L1 expression (CPS ≥ 1)



*Chemotherapy (paclitaxel and cisplatin or paclitaxel and carboplatin) with or without bevacizumab

Elderly population

No overall differences in safety were observed in patients ≥ 75 years of age compared to younger patients receiving pembrolizumab monotherapy. Based on limited safety data from patients ≥ 75 years of age, when administrated in combination with chemotherapy,

pembrolizumab showed less tolerability in patients ≥ 75 years of age compared to younger patients. For efficacy data in patients ≥ 75 years of age please refer to the relevant section of each indication.

Paediatric population

In KEYNOTE-051, 161 paediatric patients (62 children aged 9 months to < 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 bw 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.

5.2 Pharmacokinetic properties

The pharmacokinetics of pembrolizumab was studied in 2 993 patients with various cancers who received doses in the range of 1 to 10 mg/kg every 2 weeks, 2 to 10 mg/kg every 3 weeks or 200 mg every 3 weeks.

Absorption

Pembrolizumab is administered via the IV route and therefore is immediately and completely bioavailable.

Distribution

Consistent with a limited extravascular distribution, the volume of distribution of pembrolizumab at steady-state is small (6 litres; coefficient of variation [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 clearance (CV%) is approximately 23 % lower [geometric mean, 195 mL/day (40 %)] after achieving maximal change at steady state compared with the first dose (252 mL/day [CV%: 37 %]); this decrease in clearance with time is not considered clinically important. The geometric mean value (CV%) for the terminal half-life ($t_{½}$) is 22 days (32 %) at steady-state.

Linearity/non-linearity

Steady-state concentrations of pembrolizumab were reached by 16 weeks of repeated dosing with an every 3-week regimen and the systemic accumulation was 2,1-fold. The peak concentration (C_{max}), trough concentration (C_{min}) and area under the plasma concentration versus time curve at steady-state (AUC_{ss}) of pembrolizumab increased dose proportionally in the dose range of 2 to 10 mg/kg every 3 weeks.

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 to 94 years), gender, race, mild or moderate renal impairment, mild or moderate 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 analysis in patients with mild (GFR < 90 and ≥ 60 mL/min/1,73 m^2) or moderate (GFR < 60 and ≥ 30 mL/min/1,73 m^2) renal impairment compared to patients with normal (GFR ≥ 90 mL/min/1,73 m^2) renal function. No clinically important differences in the clearance of pembrolizumab were found between patients with mild or moderate renal

impairment and patients with normal renal function. KEYTRUDA has not been studied in patients with severe (GFR < 30 and ≥ 15 mL/min/1,73 m^2) renal impairment (see section 4.2).

Hepatic impairment

The effect of hepatic impairment on the clearance of pembrolizumab was evaluated by population pharmacokinetic analysis in patients with mild hepatic impairment (total bilirubin (TB) 1,0 to 1,5 x ULN or AST > ULN as defined using the National Cancer Institute criteria of hepatic dysfunction) compared to patients with normal hepatic function (TB and AST ≤ ULN). No clinically important differences in the clearance of pembrolizumab were found between patients with mild hepatic impairment and normal hepatic function. KEYTRUDA has not been studied in patients with moderate (TB > 1,5 to 3 x ULN and any AST) or severe (TB > 3 x ULN and any AST) hepatic impairment.

Immunogenicity

Among 1,8 % of patients receiving KEYTRUDA who tested positive for anti-pembrolizumab antibodies, there was no evidence of an altered pharmacokinetic or safety profile.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Inactive ingredients: L-histidine, L-histidine hydrochloride monohydrate, sucrose, polysorbate 80 (EA433) and water for injection.

6.2 Incompatibilities

In the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3 Shelf-life

Unopened vial: 24 months.

6.4 Special precautions for storage

Store vials in a refrigerator at 2 to 8 °C in the original carton to protect from light. Do not freeze.

Do not shake.

For storage conditions after dilution see section 4.2.

6.5 Nature and contents of container

KEYTRUDA is supplied in a 10 mL clear type 1 glass vial with a grey rubber stopper and an aluminium seal with a dark blue coloured flip-off cap as a single vial in a carton.

7 HOLDER OF CERTIFICATE OF REGISTRATION

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

8 REGISTRATION NUMBER

50/30.1/0957

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29 September 2017

10 DATE OF REVISION OF THE TEXT

22 November 2023

Namibia Only	
Registration Number	19/26/0113
Scheduling Status	NS2

Botswana Only	
Registration Number	BOT2203817
Scheduling Status	S2