Applicant: MSD (Pty) Ltd
APPROVED PROFESSIONAL INFORMATION
Keytruda Solution for Infusion

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.

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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.

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KEYTRUDA is indicated for the treatment of patients with resectable Stage II, IIIA, or IIIB (T3 4N2) NSCLC in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment.

KEYTRUDA as monotherapy is indicated for the adjuvant treatment of patients with Stage IB (T2a ≥ 4 cm), II, or IIIA NSCLC who have undergone complete resection.

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.

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.

Colorectal Cancer

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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 chemotherapy, followed by KEYTRUDA as monotherapy, is indicated for the treatment of patients with primary advanced or recurrent endometrial carcinoma.

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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.

Gastric Cancer

KEYTRUDA, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of patients with locally advanced unresectable or metastatic gastric or gastro-oesophageal junction (GEJ) adenocarcinoma.

KEYTRUDA, in combination with trastuzumab, fluoropyrimidine and platinum-containing chemotherapy, is indicated for the first-line treatment of patients with locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction (GEJ) adenocarcinoma, whose tumours express PD-L1 [Combined Positive Score (CPS) ≥ 1] as determined by a validated test.

Biliary Tract Carcinoma

KEYTRUDA, in combination with chemotherapy, is indicated for the treatment of patients with locally advanced unresectable or metastatic biliary tract carcinoma (BTC).

Cervical Cancer

KEYTRUDA, in combination with chemoradiotherapy (CRT), is indicated for the treatment of patients with high-risk, locally advanced 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.

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, or MSI-H or dMMR 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.

Because subclonal dMMR mutations and microsatellite instability may arise in high-grade gliomas during temozolomide therapy, it is recommended to test for MSI-H and dMMR in the primary tumour specimens obtained prior to initiation of temozolomide chemotherapy in patients with high-grade gliomas.

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.

For melanoma and 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, NSCLC or RCC KEYTRUDA should be administered for up to one year or until disease recurrence or unacceptable toxicity.

For the neoadjuvant and adjuvant treatment of resectable NSCLC, patients should be treated with neoadjuvant KEYTRUDA in combination with chemotherapy for 12 weeks or until disease progression that precludes definitive surgery or unacceptable toxicity, followed by adjuvant treatment with KEYTRUDA as monotherapy for 39 weeks or until disease recurrence or unacceptable toxicity.

For the neoadjuvant and adjuvant treatment of high-risk early-stage TNBC, patients should be treated with neoadjuvant KEYTRUDA in combination with chemotherapy for 8 doses of 200 mg every 3 weeks or 4 doses of 400 mg every 6 weeks or until disease progression that precludes definitive surgery or unacceptable toxicity, followed by adjuvant treatment with KEYTRUDA as monotherapy for 9 doses of 200 mg every 3 weeks or 5 doses of 400 mg every 6 weeks or until disease recurrence or unacceptable toxicity. Patients who experience disease progression that precludes definitive surgery or unacceptable toxicity related to KEYTRUDA as neoadjuvant treatment in combination with chemotherapy should not receive KEYTRUDA monotherapy as adjuvant treatment.

Dose modifications

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

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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	Permanently discontinue

	(Grade 2) elevation of AST or ALT, if AST or ALT increases ≥ 50 % relative to baseline and lasts ≥ 1 week	
Immune-mediated skin reactions or Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Severe skin reactions (Grade 3) or suspected SJS or TEN	Withhold until adverse reactions recover to Grades 0-1*
	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 melanoma or 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-mediated 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 in KEYNOTE-001, KEYNOTE-002, KEYNOTE-006 and KEYNOTE-010: uveitis, myositis, Guillain-Barré syndrome, pancreatitis, encephalitis, sarcoidosis, myasthenic syndrome/myasthenia gravis (including exacerbation), myelitis vasculitis, hypoparathyroidism, gastritis, haemolytic aneamia and pericarditis. The following were reported in other clinical studies with KEYTRUDA or in post-marketing use: myocarditis, sclerosing cholangitis, optic neuritis and exocrine pancreatic insufficiency.

Cases of these immune-mediated adverse reactions, some of which were severe, have been reported in clinical trials or in post-marketing use.

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

KEYTRUDA is most commonly associated with immune-mediated adverse reactions. Most of these, including severe reactions, resolved following initiation of appropriate medical therapy or withdrawal of KEYTRUDA (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.

KEYTRUDA in monotherapy (see section 4.2)

The safety of KEYTRUDA as monotherapy has been evaluated in 7,631 patients across tumour types and across four doses (2 mg/kg bw 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 8,5 months (range: 1 day to 39 months) and the most frequent adverse reactions with KEYTRUDA were fatigue (31 %), diarrhoea (22 %), and nausea (20 %). The majority of adverse

reactions reported for monotherapy were of Grades 1 or 2 severity. The most serious adverse reactions were immune-related adverse reactions and severe infusion-related reactions (see section 4.4). The incidences of immune-mediated adverse reactions were 37 % all Grades and 9 % for Grades 3-5 for KEYTRUDA monotherapy in the adjuvant setting and 25 % all Grades and 6 % for Grades 3-5 in the metastatic setting. No new immune-mediated adverse reactions were identified in the adjuvant setting.

KEYTRUDA in combination with chemotherapy or chemoradiotherapy (CRT) (see section 4.2)

The safety of KEYTRUDA in combination with chemotherapy or CRT has been evaluated in 6 093 patients across tumour types receiving 200 mg, 2 mg/kg bw or 10 mg/kg bw KEYTRUDA every 3 weeks, in clinical studies. In this patient population, the most frequent adverse reactions were anaemia (53 %), nausea (52 %), diarrhoea (36 %), fatigue (35 %), constipation (32 %), vomiting (28 %), neutrophil count decreased (28 %), and decreased appetite (27 %). Incidences of Grades 3-5 adverse reactions in patients with NSCLC were 69 % for KEYTRUDA combination therapy and 61 % for chemotherapy alone in patients with HNSCC were 85 % for KEYTRUDA combination therapy and 84 % for chemotherapy plus cetuximab, and in patients with oesophageal carcinoma were 86 % for KEYTRUDA combination therapy and 83 % for chemotherapy alone, and in patients with TNBC were 80 % for KEYTRUDA combination therapy and 77 % for chemotherapy alone in patients with cervical cancer were 77 % for KEYTRUDA combination therapy (chemotherapy with or without bevacizumab or in combination with CRT and 71 % for chemotherapy, with or without bevacizumab or CRT alone, in patients

with gastric cancer were 74 % for KEYTRUDA combination therapy (chemotherapy with or without trastuzumab) and 68 % for chemotherapy with or without trastuzumab, and in patients with biliary tract carcinoma were 85 % for KEYTRUDA combination therapy and 84 % for chemotherapy alone, and in patients with EC were 59 % for pembrolizumab combination therapy and 46 % for chemotherapy alone.

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

The safety of KEYTRUDA 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 KEYTRUDA 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 KEYTRUDA in combination with either axitinib or lenvatinib and 71 % for sunitinib alone. In patients with EC, Grades 3-5 adverse reactions were 89 % for KEYTRUDA 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 CRT 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 or chemoradiotherapy**	**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	anaemia, neutropenia, thrombocytopenia	anaemia
Common	thrombocytopenia, neutropenia, lymphopenia	febrile neutropenia, leukopenia, lymphopenia	neutropenia, thrombocytopenia, lymphopenia, leukopenia
Uncommon	leukopenia, immune thrombocytopenia, eosinophilia	haemolytic anaemia*, eosinophilia	eosinophilia
Rare	haemolytic anaemia*, haemophagocytic lymphohistiocytosis, 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*, hyperthyroidism*, thyroiditis*	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, hypokalaemia, hypocalcaemia	hyponatraemia, hypocalcaemia	hyponatraemia, 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	headache, dysgeusia
Common	dizziness, neuropathy peripheral, lethargy, dysgeusia	dysgeusia, lethargy	dizziness, neuropathy peripheral, lethargy
Uncommon	myasthenic syndrome*, epilepsy	encephalitis*, epilepsy	myasthenic syndrome*, encephalitis*
Rare	Guillain-Barré syndrome*, encephalitis, myelitis*, optic neuritis, meningitis (aseptic)*	myasthenic syndrome, Guillain-Barré syndrome*,optic neuritis, meningitis (aseptic)	optic neuritis
Eye disorders			
Common	dry eye	dry eye	dry eye
Uncommon	uveitis*	uveitis*	uveitis*
Rare	Vogt-Koyanagi-Harada syndrome		Vogt-Koyanagi-Harada syndrome
Cardiac disorders			

Common	cardiac arrhythmia‡ (including atrial fibrillation)	cardiac arrhythmia‡ (including atrial fibrillation)	cardiac arrhythmia‡ (including atrial fibrillation)
Uncommon	myocarditis, pericarditis*, pericardial effusion	myocarditis*, pericarditis*, pericardial effusion	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	diarrhoea, nausea, 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	exocrine pancreatic insufficiency, small intestinal perforation, coeliac disease	exocrine pancreatic insufficiency, small intestinal perforation, coeliac disease	small intestinal perforation
Not known			exocrine pancreatic insufficiency, coeliac disease
Hepatobiliary disorders			
Common	hepatitis*	hepatitis*	hepatitis*
Rare	cholangitis sclerosing	cholangitis sclerosing*	
Skin and subcutaneous tissue disorders			
Very common	pruritus*, rash*	alopecia, pruritus*, rash*	rash*, pruritus*
Common	severe skin reactions*, erythema, dermatitis, dry skin, vitiligo*, eczema,	severe skin reactions*, dermatitis, erythema, dry skin,	severe skin reactions*, dermatitis, dry skin, erythema,

	alopecia, dermatitis acneiform	dermatitis acneiform, eczema	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 syndrome, erythema nodosum, toxic epidermal necrolysis	Stevens-Johnson syndrome, erythema nodosum, hair colour changes	toxic epidermal necrolysis, Stevens-Johnson syndrome
Musculoskeletal and connective tissue disorders			
Very common	musculoskeletal pain*, arthralgia	musculoskeletal pain*, arthralgia	arthralgia, musculoskeletal pain*, myositis*, pain in extremity
Common	myositis*, pain in extremity, arthritis*	myositis*, 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, blood creatinine increased	lipase increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood creatinine increased
Common	alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase	blood bilirubin increased, blood alkaline phosphatase increased, hypercalcaemia	amylase increased, blood bilirubin increased, blood alkaline phosphatase increased, hypercalcaemia

	increased, hypercalcaemia, blood bilirubin increased, blood creatinine increased		
Uncommon	amylase increased	amylase increased	

†Adverse reaction frequencies presented in Table 2 may not be fully attributable to KEYTRUDA 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:

- haemolytic anaemia (autoimmune haemolytic anaemia and Coombs negative haemolytic anaemia)
- infusion-related reactions (drug hypersensitivity, anaphylactic reaction, anaphylactoid reaction, hypersensitivity, infusion-related hypersensitivity reaction, cytokine release syndrome and serum sickness)
- sarcoidosis (cutaneous sarcoidosis and pulmonary sarcoidosis)
- hypothyroidism (myxoedema and immune-mediated hypothyroidism and autoimmune hypothyroidism)
- adrenal insufficiency (Addison's disease, adrenocortical insufficiency acute, and secondary adrenocortical insufficiency)

- thyroiditis, (autoimmune thyroiditis, silent thyroiditis, thyroid disorder thyroiditis acute, and immune-mediated thyroiditis)
- hyperthyroidism (Graves' disease)
- hypophysitis (hypopituitarism and lymphocytic hypophysitis)
- type 1 diabetes mellitus (diabetic ketoacidosis)
- myasthenic syndrome (myasthenia gravis, including exacerbation)
- encephalitis (autoimmune encephalitis, and noninfective encephalitis)
- Guillain-Barré syndrome (axonal neuropathy and demyelinating polyneuropathy)
- myelitis (including transverse myelitis)
- meningitis aseptic (meningitis and meningitis non-infective)
- uveitis (chorioretinitis, iritis and iridocyclitis)
- myocarditis (autoimmune myocarditis)
- pericarditis (autoimmune pericarditis, pleuropericarditis and myopericarditis)
- vasculitis (central nervous system vasculitis, aortitis and giant cell arteritis)
- pneumonitis (interstitial lung disease, organising pneumonia, immune-mediated pneumonitis, immune-mediated lung disease and autoimmune 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)
- gastritis (gastritis erosive, gastritis haemorrhagic, and immune-mediated gastritis)
- 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 exfoliative rash, pemphigus and Grade ≥ 3 of the following: cutaneous vasculitis, dermatitis bullous, dermatitis exfoliative, dermatitis exfoliative generalised, erythema multiforme, lichen planus, oral lichen planus, pemphigoid, pruritus, pruritus genital, rash, rash erythematous, rash maculo-papular, rash pruritic, rash pustular, 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, immune-mediated nephritis, tubulointerstitial nephritis and renal failure, renal failure acute, or acute kidney injury with evidence of nephritis, nephrotic syndrome, glomerulonephritis, glomerulonephritis membranous and glomerulonephritis acute)
- oedema (oedema peripheral, generalised oedema, fluid overload, fluid retention, eyelid oedema and lip oedema, face oedema, localised oedema and periorbital oedema

Adverse events occurring in patients with resectable NSCLC receiving KEYTRUDA in combination with platinum-containing chemotherapy, given as neoadjuvant treatment and continued as monotherapy adjuvant treatment in KEYNOTE-671, were generally similar to those occurring in patients in other clinical trials across tumour types receiving KEYTRUDA in combination with chemotherapy.

Description of selected adverse reactions

Data for the following immune-mediated adverse reactions are based on patients who received KEYTRUDA across four doses (2 mg/kg bw every 3 weeks, 10 mg/kg bw every 2 or 3 weeks or 200 mg every 3 weeks) in clinical studies (see section 5.1). The management guidelines for these adverse reactions are described in section 4.4.

Immune-mediated 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 196 patients, 6 with sequelae. In patients with NSCLC, pneumonitis occurred in 206 (6,1 %), including Grade 2, 3, 4 or 5 cases in 92 (2,7 %), 56 (1,7 %), 16 (0,5 %) and 9 (0,3 %), respectively. In patients with locally advanced or metastatic 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 132 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 29,9+ 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 KEYTRUDA in 17 (0,2 %) patients. Nephritis resolved in 25 patients, 5 with sequelae. In patients with non-squamous NSCLC treated with KEYTRUDA 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 KEYTRUDA. 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 28 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 23 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 326 (82,7 %) patients, 11 with sequelae. In patients with melanoma, NSCLC and RCC treated with KEYTRUDA monotherapy in the adjuvant setting (n=2,060), the incidence of hyperthyroidism was 11,0 %, 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 KEYTRUDA in 6 (0,1 %) patients. Hypothyroidism resolved in 216 (23,0 %) 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 KEYTRUDA 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 melanoma, NSCLC and RCC

treated with KEYTRUDA monotherapy in the adjuvant setting (n=2 060), the incidence of hypothyroidism was 18,5 %, the majority of which were Grade 1 or 2.

Skin adverse reactions: Immune-mediated 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 2,8 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 95 patients, 2 with sequelae 2.
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 KEYTRUDA monotherapy, the proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 9,9 % for lymphocytes decreased, 7,3 % for sodium decreased, 5,7 % for haemoglobin decreased, 4,6 % for glucose increased, 4,5 % for phosphate decreased 3,1 % for ALT increased, 2,9 % for AST increased, 2,6 % for alkaline phosphatase increased, 2,2 % for potassium decreased, 2,1 % for

neutrophils decreased, 1,7 % for bilirubin increased, 1,7 % for platelets decreased, 1,7 % for potassium increased, 1,6 % for calcium increased, 1,4 % for albumin decreased, 1,3 % for calcium decreased, 1,2 % for creatinine increased, 0,8 % for leukocytes decreased, 0,8 % for magnesium increased, 0,6 % for glucose decreased, 0,2 % for magnesium decreased, and 0,2 % for sodium increased.

In patients treated with KEYTRUDA in combination with chemotherapy or CRT, the proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 37,8 % for neutrophils decreased, 31,1 % for lymphocytes decreased, 24,7 % for leukocytes decreased, 20,7 % for haemoglobin decreased, 12,5 % for platelets decreased, 9,3 % for sodium decreased, 7,9 % for potassium decreased, 7,3 % for phosphate decreased, 5,5 % for glucose increased, 5,2 % for ALT increased, 4,7 % for AST increased, 3,5 % for calcium decreased, 3,2 % for bilirubin increased, 3,0 % for creatinine increased, 3,0 % for potassium increased, 2,4 % for alkaline phosphatase increased, 2,3 % for albumin decreased, 1,6 % for calcium increased, 0,9 % for glucose decreased, and 0,4 % for sodium increased.

In patients treated with KEYTRUDA 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), 12,3 % 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, 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 neutrophils decreased, 3,1 % for

alkaline phosphatase increased, 3,0 % for platelets decreased, 2,8 % for bilirubin increased, 2,2 % for calcium decreased, 2,2 % for magnesium increased, 1,7 % for leukocytes decreased, 1,5 % for magnesium decreased, 1,5 % for prothrombin INR increased, 1,4 % for glucose decreased, 1,2 % for albumin decreased, 1,0 % for calcium increased, 0,4 % for sodium increased and 0,1 % for haemoglobin increased.

Paediatric population

The safety of KEYTRUDA as monotherapy has been evaluated in 161 paediatric patients aged 9 months to 17 years with advanced melanoma, lymphoma or PD-L1 positive advanced, relapsed or refractory solid tumours at 2 mg/kg bw 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 KEYTRUDA 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 requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

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)

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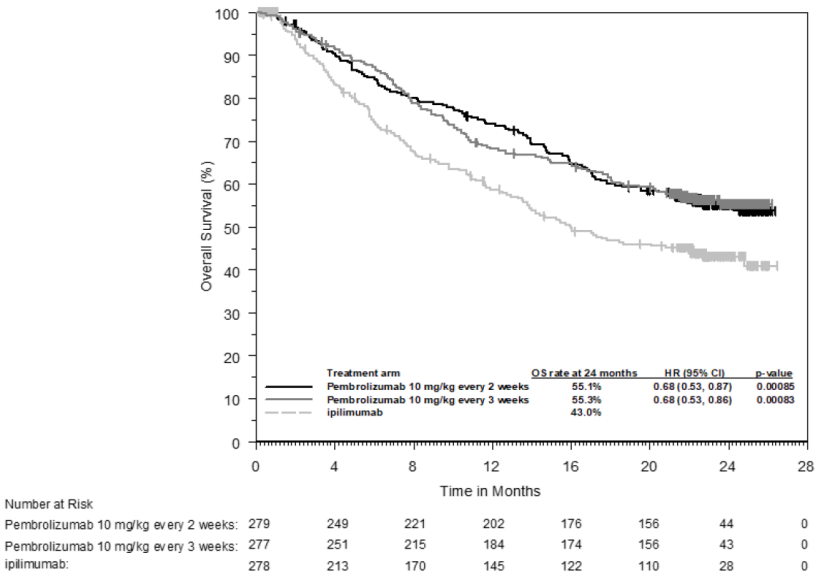
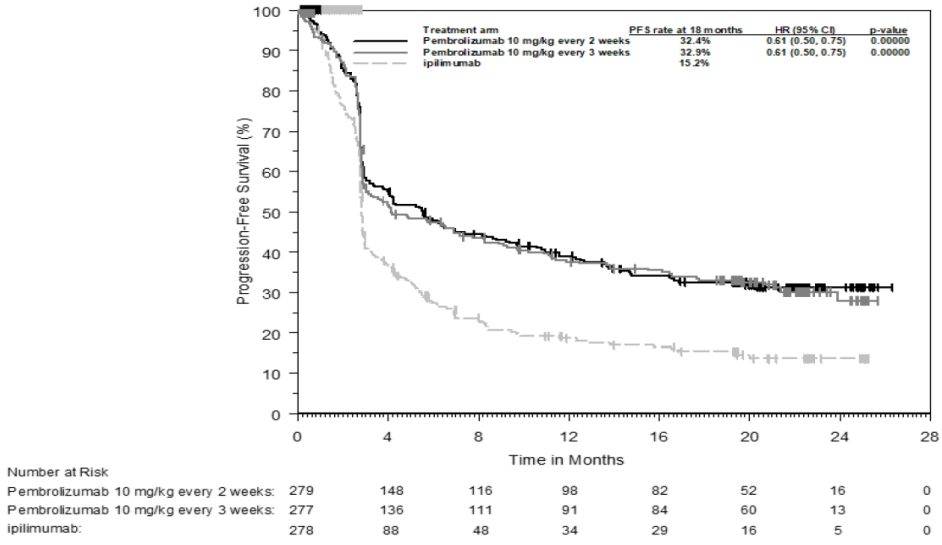


Figure 2: Kaplan-Meier curve for progression-free survival by treatment arm in KEYNOTE-006 (intent to treat population)



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-mediated 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

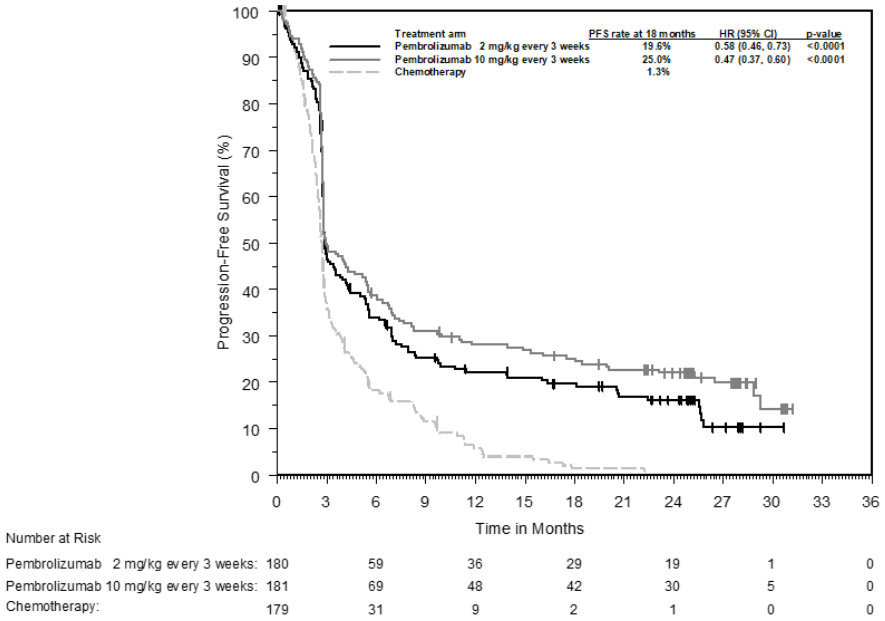
†Based on stratified log-rank test

‡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.

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Table 5: Efficacy results in KEYNOTE-001

Endpoint	Pembrolizumab 2 mg/kg bw every 3 weeks in patients previously treated with ipilimumab n=89	Pembrolizumab 2 mg/kg bw every 3 weeks in patients naïve to treatment with ipilimumab n=51
Best objective response* by IRO†		
ORR %, (95 % CI)	26 % (17, 36)	35 % (22, 50)
Complete response	7 %	12 %
Partial response	19 %	24 %
Disease control rate %‡	48 %	49 %
Response duration§		
Median in months (range)	30,5 (2,8+, 30,6+)	27,4 (1,6+, 31,8+)
% ongoing at 24 months¶	75 %	71 %
PFS		
Median in months (95 % CI)	4,9 (2,8, 8,3)	4,7 (2,8, 13,8)
PFS rate at 12 months	34 %	38 %
OS		
Median in months (95 % CI)	18,9 (11, not available)	28,0 (14, not available)
OS rate at 24 months	44 %	56 %

*Includes patients without measurable disease at baseline by independent radiology

†IRO = Integrated radiology and oncologist assessment using RECIST 1.1

‡Based on best response of stable disease or better

§Based on patients with a confirmed response by independent review, starting from the date the response was first recorded; n=23 for patients previously treated with ipilimumab; n=18 for patients naïve to treatment with ipilimumab

¶Based on Kaplan-Meier estimation

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

Sub-population analyses

BRAF mutation status in melanoma

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

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

	BRAF wild type	BRAF mutant with prior BRAF treatment

Endpoint	Pembrolizumab 2 mg/kg bw every 3 weeks (n=136)	Chemotherapy (n=137)	Pembrolizumab 2 mg/kg bw every 3 weeks (n=44)	Chemotherapy (n=42)
PFS Hazard ratio* (95 % CI)	0,50 (0,39, 0,66)	---	0,79 (0,50, 1,25)	---
OS Hazard ratio* (95 % CI)	0,78 (0,58, 1,04)	---	1,07 (0,64, 1,78)	---
ORR %	26 %	6 %	9 %	0 %

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

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

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

	BRAF wild type		BRAF mutant without prior BRAF treatment		BRAF mutant with prior BRAF treatment	
Endpoint	Pembrolizumab 10 mg/kg bw every 2 or 3 weeks (pooled)	Ipilimumab (n=170)	Pembrolizumab 10 mg/kg bw every 2 or 3 weeks (pooled)	Ipilimumab (n=55)	Pembrolizumab 10 mg/kg bw every 2 or 3 weeks (pooled)	Ipilimumab (n=52)

PFS Hazard ratio* (95 % CI)	0,61 (0,49, 0,76)	---	0,52 (0,35, 0,78)	---	0,76 (0,51, 1,14)	---
OS Hazard ratio* (95 % CI)	0,68 (0,52, 0,88)	---	0,70 (0,40, 1,22)	---	0,66 (0,41, 1,04)	---
ORR %	38 %	14 %	41 %	15 %	24 %	10 %
*Hazard ratio (pembrolizumab compared to ipilimumab) based on the stratified Cox proportional hazard model						

PD-L1 status in melanoma

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

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

Endpoint	**Pembrolizumab 2 mg/kg bw every 3 weeks**	**Chemotherapy**	**Pembrolizumab 2 mg/kg bw every 3 weeks**	**Chemotherapy**
	PD-L1 positive		**PD-L1 negative**	
PFS Hazard ratio* (95 % CI)	0,55 (0,40, 0,76)	---	0,81 (0,50, 1,31)	---

OS Hazard ratio* (95 % CI)	0,90 (0,63, 1,28)	---	1,18 (0,70, 1,99)	---
ORR %	25 %	4 %	10 %	8 %
*Hazard ratio (pembrolizumab compared to chemotherapy) based on the stratified Cox proportional hazard model				

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

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

Endpoint	**Pembrolizumab 10 mg/kg bw every 2 or 3 weeks (pooled)**	**Ipilimumab**	**Pembrolizumab 10 mg/kg bw every 2 or 3 weeks (pooled)**	**Ipilimumab**
	PD-L1 positive		**PD-L1 negative**	
PFS Hazard ratio* (95 % CI)	0,53 (0,44, 0,65)	---	0,87 (0,58, 1,30)	---
OS Hazard ratio* (95 % CI)	0,63 (0,50, 0,80)	---	0,76 (0,48, 1,19)	---
ORR %	40 %	14 %	24 %	13 %

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

Ocular melanoma

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

KEYNOTE-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 occurred 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 analysisThe 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. Updated RFS results at a median follow-up of 38,5 months were consistent with the final analysis for RFS for patients randomised to the pembrolizumab arm compared with placebo (HR 0,62; 95 % CI 0,49, 0,79) (see Figure 4). The study demonstrated a statistically significant improvement in DMFS (HR 0,64; 95 % CI 0,47, 0,88; p-Value = 0,00292) for patients randomised to the pembrolizumab arm compared with placebo at its pre specified interim analysis at a median follow-up of 26,9 months. Results reported from the pre-specified final analysis for DMFS at a median follow-up time of 38,5 months are summarised in Table 10 and Figure 5.

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Table 10: Efficacy results in KEYNOTE-716

Endpoint	Pembrolizumab 200 mg every 3 weeks n=487	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	74 (15,2 %)	119 (24,3 %)
Median in months (95 % CI)	NR (NR, NR)	NR (NR, NR)
Hazard ratio* (95 % CI)	0,59 (0,44, 0,79)	

*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)

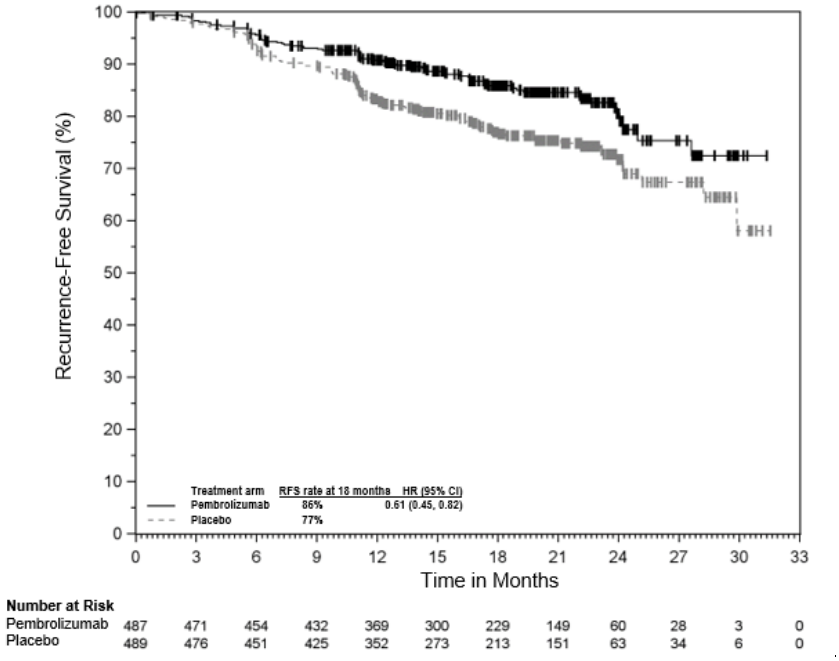
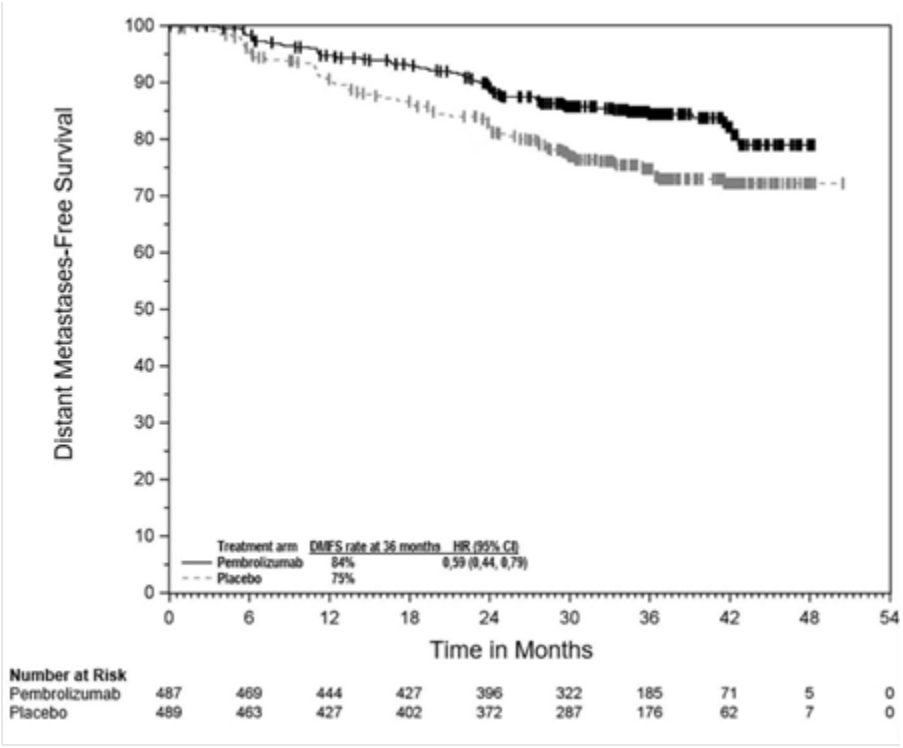


Figure 5: Kaplan-Meier curve for distant metastasis-free survival by treatment arm in KEYNOTE-716 (intent to treat population)



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)

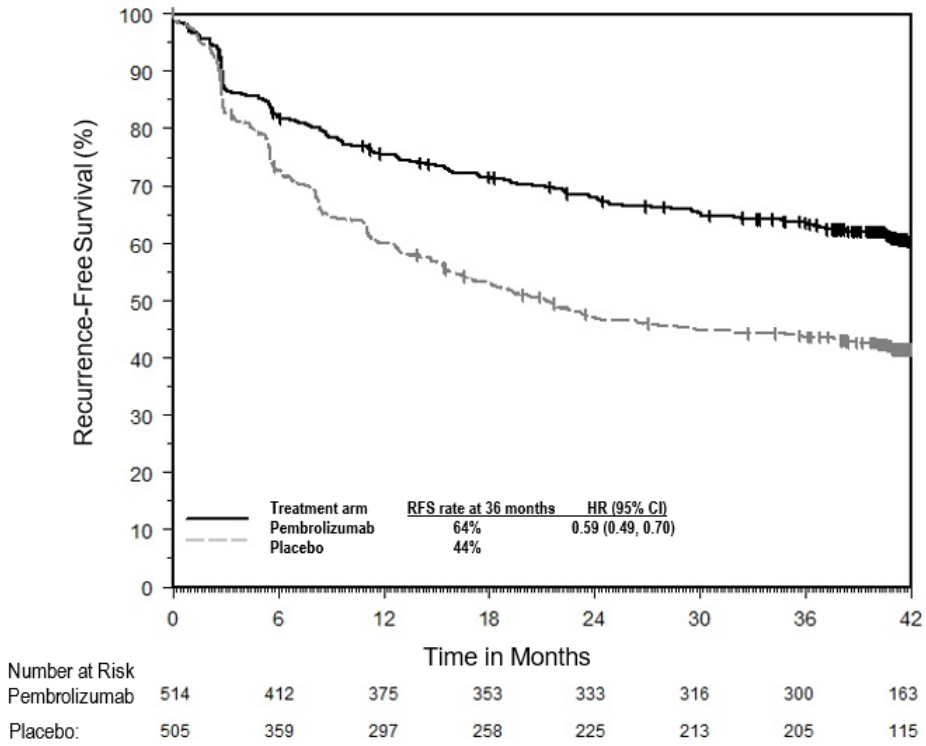
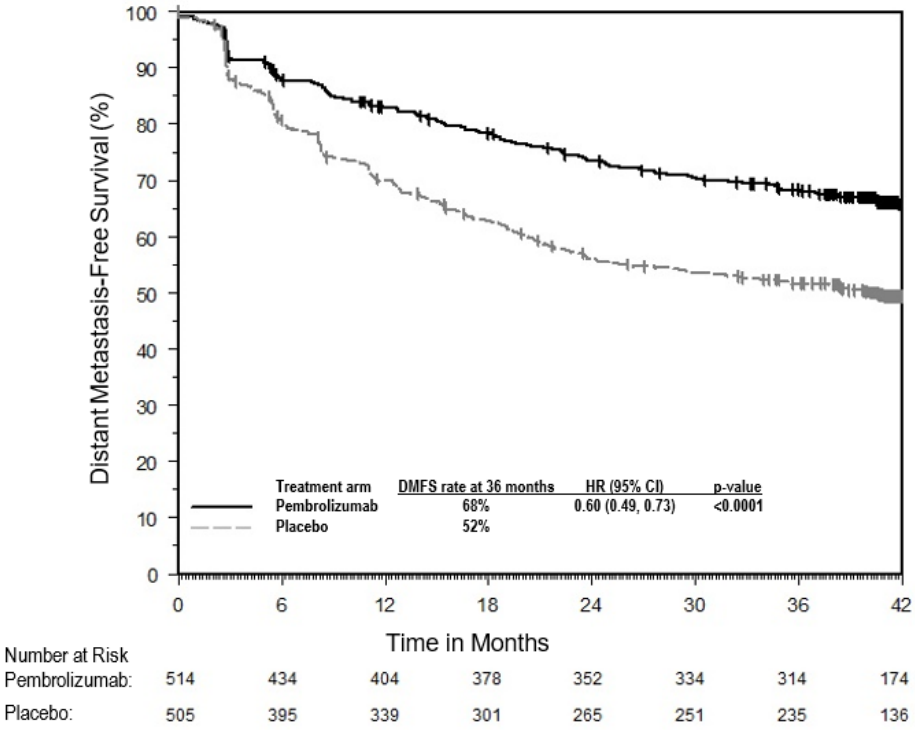


Figure 7: Kaplan-Meier curve for distant metastasis-free survival by treatment arm in KEYNOTE-054 (intent to treat population)



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)

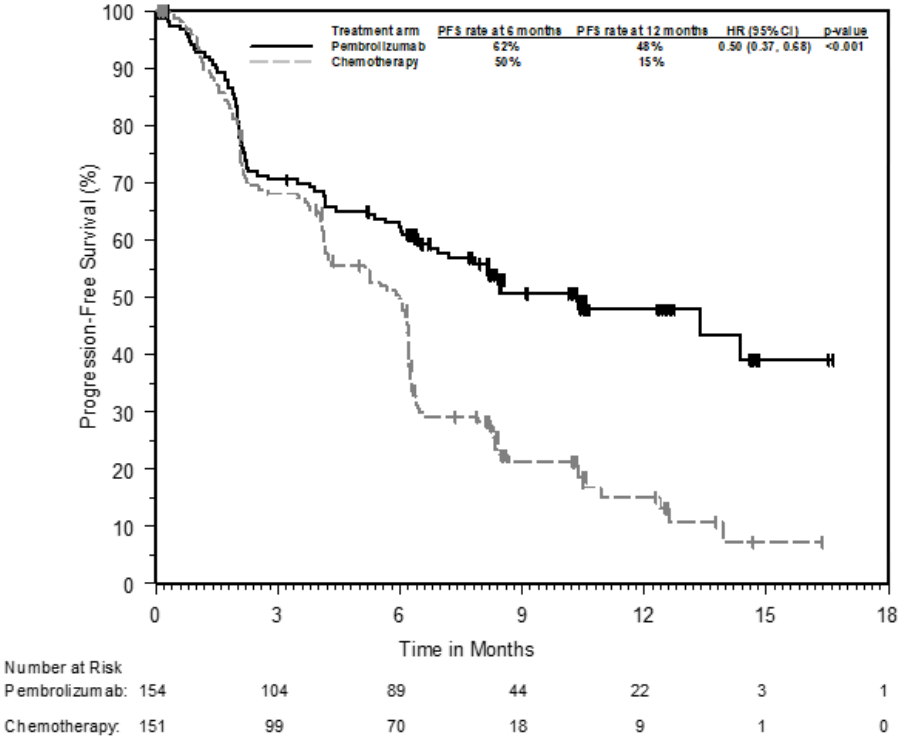
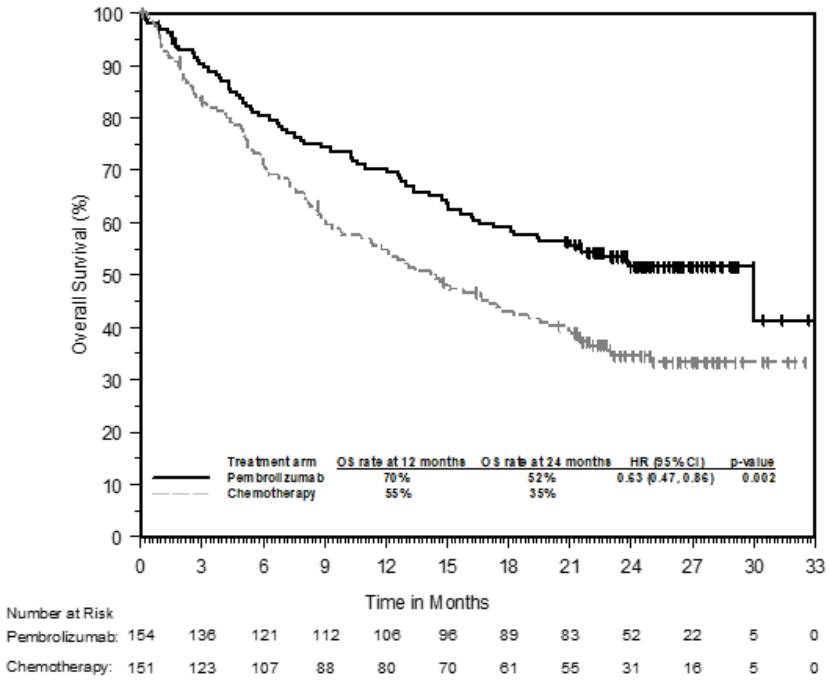


Figure 9: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-024 (intent to treat population)



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

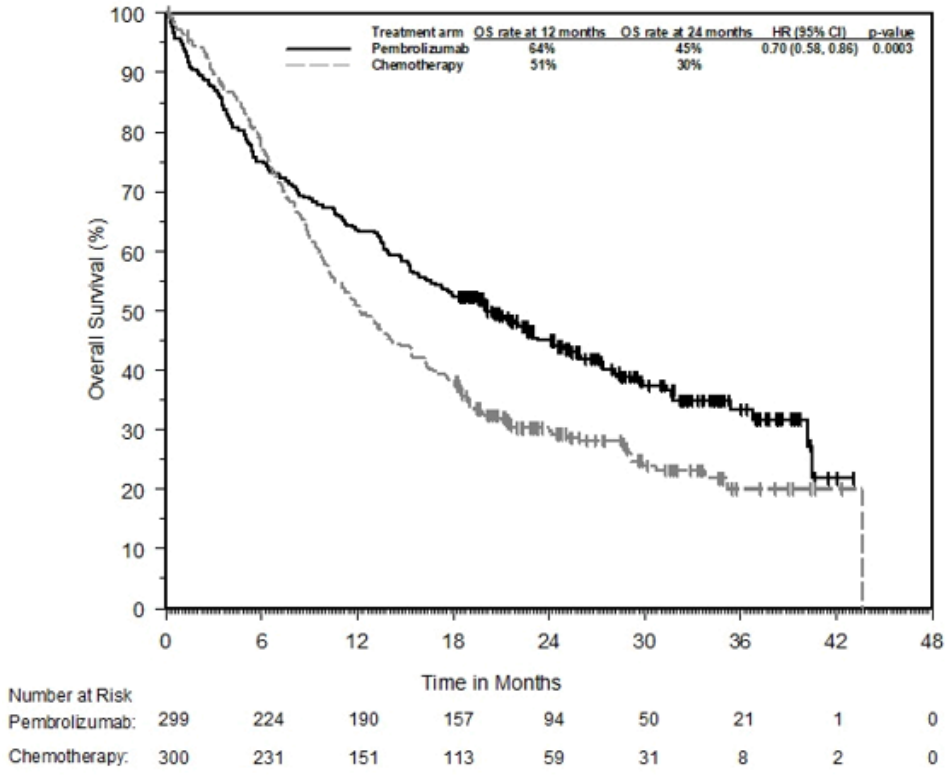
Endpoint	**Pembrolizumab 200 mg every 3 weeks n=299**	**Chemotherapy n=300**
OS		
Number (%) of patients with event	180 (60 %)	220 (73 %)
Hazard ratio* (95 % CI)	0,70 (0,58, 0,86)	
p-Value†	0,0003	
Median in months (95 % CI)	20,0 (15,9, 24,2)	12,2 (10,4, 14,6)
PFS		
Number (%) of patients with event	238 (80 %)	250 (83 %)
Hazard ratio* (95 % CI)	0,84 (0,70, 1,01)	
Median in months (95 % CI)	6,5 (5,9, 8,5)	6,4 (6,2, 7,2)
Objective response rate		
ORR % (95 % CI)	39 % (34, 45)	32 % (27, 38)
Complete response	1 %	0,3 %
Partial response	38 %	32 %
Response duration‡		
Median in months (range)	22,0 (2,1+, 36,5+)	10,8 (1,8+, 30,4+)
% with duration ≥ 18 months	57 %	34 %

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

†Based on stratified log-rank test

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

Figure 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 (19,5, 24,5)	10,6 (8,7, 13,6)
PFS		
Number (%) of patients with event	337 (82 %)	197 (96 %)
Hazard ratio† (95 % CI)	0,49 (0,41, 0,59)	
p-Value‡	< 0,00001	
Median in months (95 % CI)	9,0 (8,1, 10,4)	4,9 (4,7, 5,5)
Objective response rate		
ORR§ % (95 % CI)	48 % (43, 53)	20 % (15, 26)
Complete response %	1,2 %	0,5 %
Partial response %	47 %	19 %
p-Value¶	< 0,0001	

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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)

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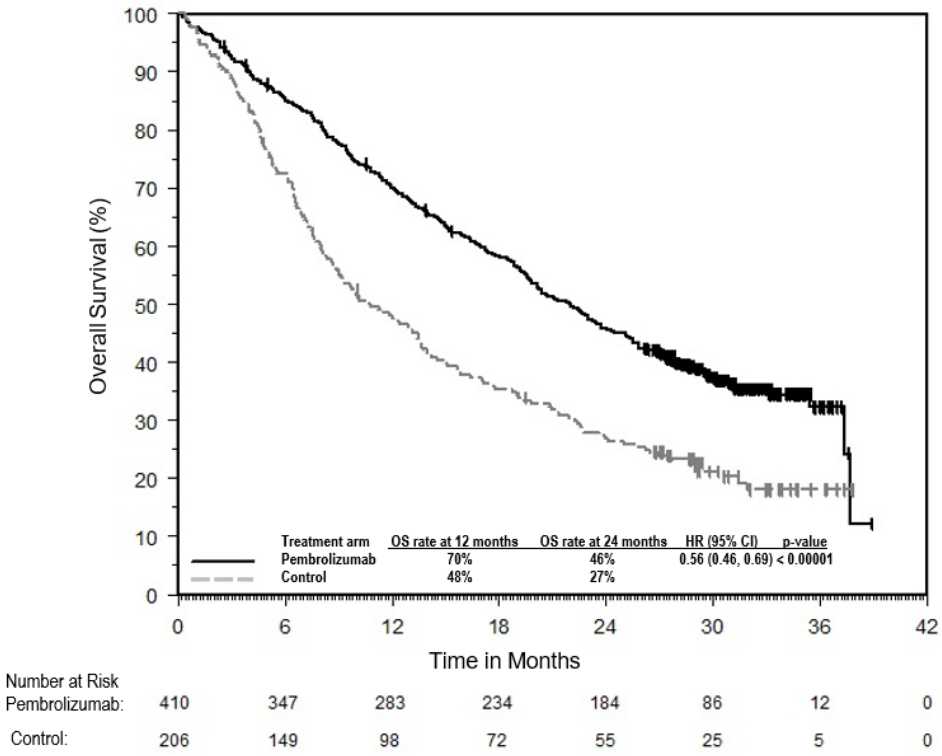
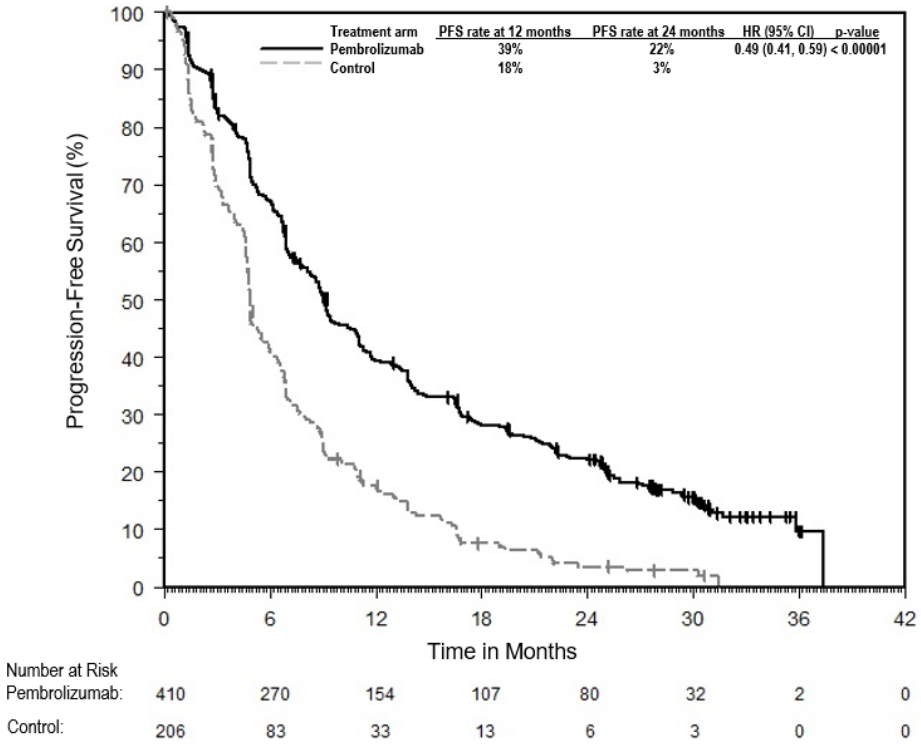


Figure 12: Kaplan-Meier curve for progression-free survival by treatment arm in KEYNOTE-189 (intent to treat population)



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 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)	0,51 (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	Placebo Carboplatin

	Paclitaxel/Nab-paclitaxel n=278	**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

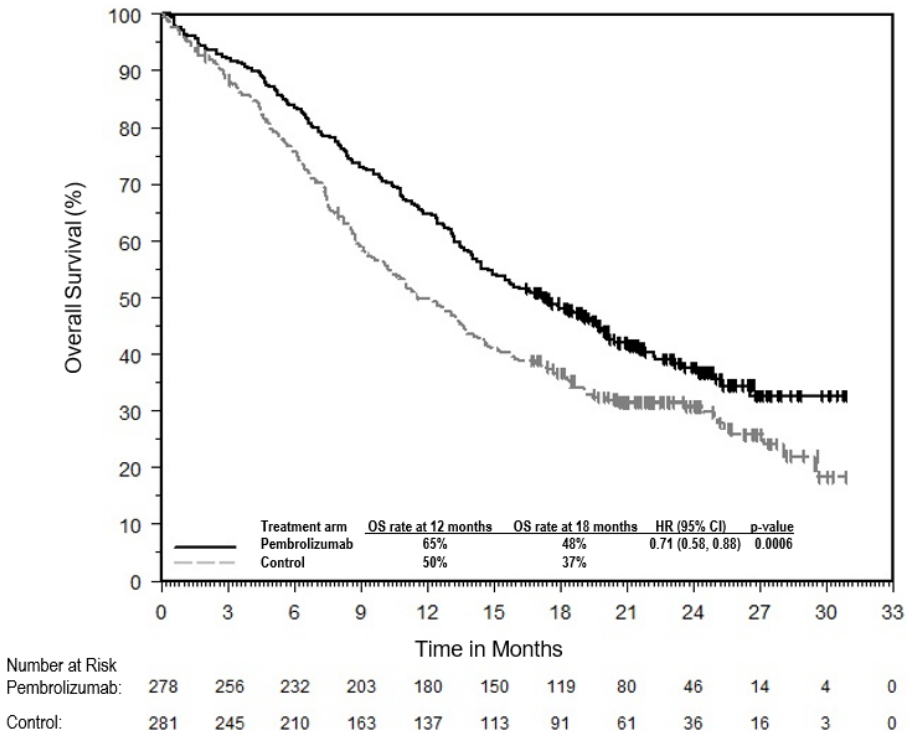


Figure 14: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-407

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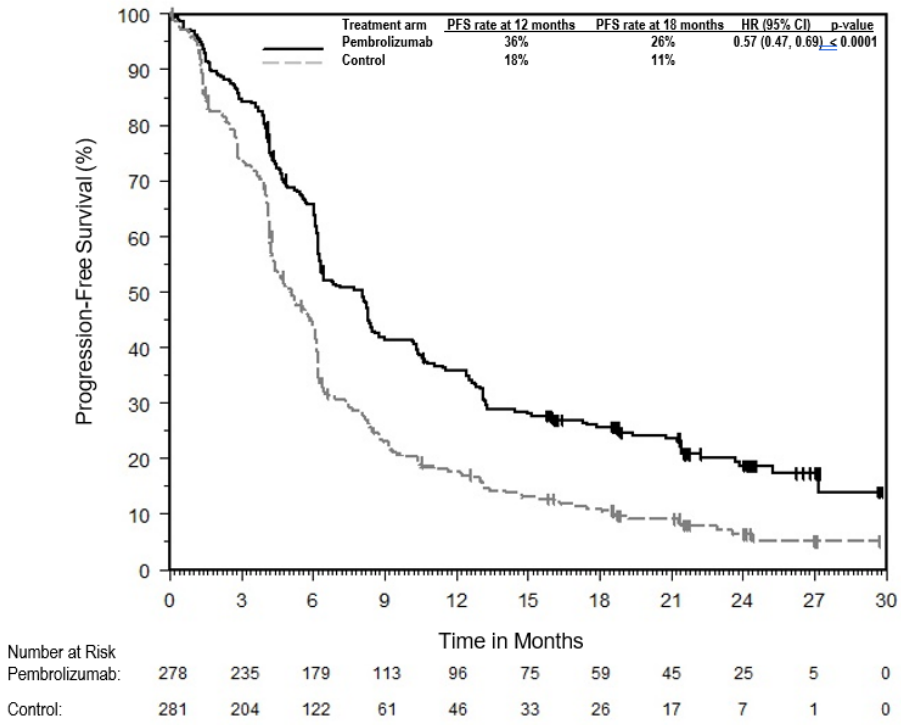


An analysis was performed in KEYNOTE-407 in patients who had PD-L1 TPS < 1 % [pembrolizumab plus chemotherapy arm: n=95 (34 %) vs. placebo plus chemotherapy arm: n=99 (35 %)], TPS 1 % to 49 % [pembrolizumab plus chemotherapy arm: n=103 (37 %) vs. placebo plus chemotherapy arm: n=104 (37 %)] or TPS ≥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

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

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

*Based on final analysis

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

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

Data about efficacy 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 patients with event	107 (77 %)	115 (76 %)	138 (91 %)
Hazard ratio* (95 % CI)	0,59 (0,45, 0,77)	0,53 (0,41, 0,70)	---
p-Value†	< 0,001	< 0,001	---
Median in months (95 % CI)	5,3 (4,1, 7,9)	5,2 (4,1, 8,1)	4,2 (3,8, 4,7)
Objective response rate‡			
ORR % (95 % CI)	32 % (24, 40)	32 % (25, 41)	9 % (5, 14)
Complete response %	4 %	4 %	0 %
Partial response %	27 %	28 %	9 %

Response duration‡,§			
Median in months (range)	Not reached (2,8, 44,0+)	37,5 (2,0+, 49,3+)	8,1 (2,6, 16,8)
% ongoing¶	55 %	47 %	8 %

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

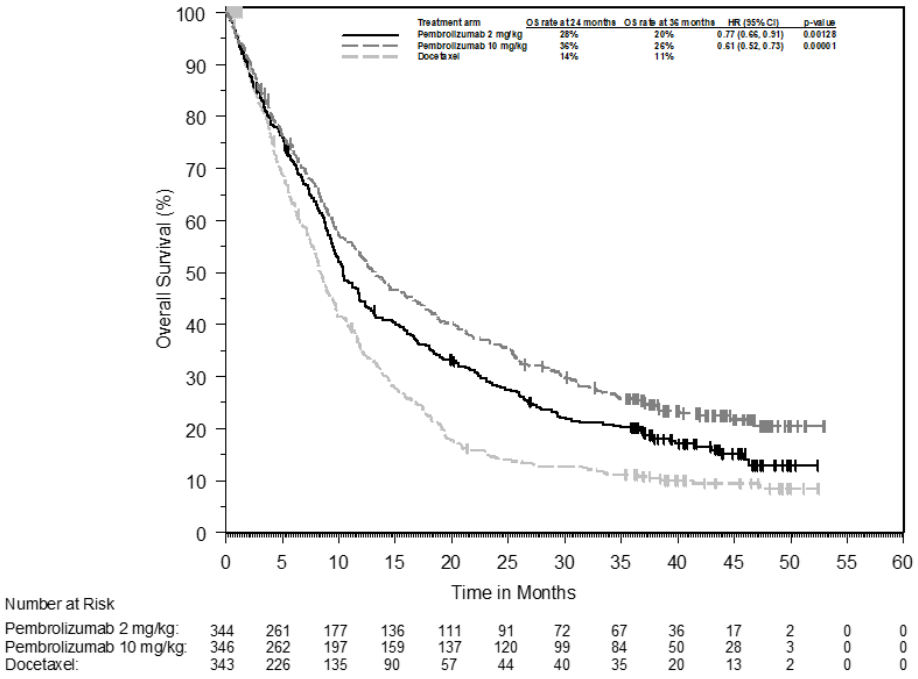
†Based on stratified log-rank test

‡Assessed by BICR using RECIST 1.1

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

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

Figure 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.

KEYNOTE-671: Controlled trial for the neoadjuvant and adjuvant treatment of patients with resectable NSCLC

The efficacy of pembrolizumab in combination with platinum-containing chemotherapy given as neoadjuvant treatment and continued as monotherapy adjuvant treatment was investigated in KEYNOTE-671, a multicentre, randomised, double-blind, placebo-controlled trial. Key eligibility criteria were previously untreated and resectable Stage II, IIIA, or IIIB (N2) NSCLC by AJCC 8th edition, 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. Randomisation was stratified by stage (II vs. III), tumour PD-L1 expression (TPS ≥ 50 % or < 50 %), histology (squamous vs. non-squamous) and geographic region (East Asia vs. non-East Asia).

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

- Treatment Arm A: neoadjuvant pembrolizumab 200 mg on Day 1 in combination with cisplatin 75 mg/m^2 and either pemetrexed 500 mg/m^2 on Day 1 or gemcitabine 1 000 mg/m^2 on Days 1 and 8 of each 21-day cycle for up to 4 cycles. Following surgery, pembrolizumab 200 mg was administered every 3 weeks for up to 13 cycles.
- Treatment Arm B: neoadjuvant placebo on Day 1 in combination with cisplatin 75 mg/m^2 and either pemetrexed 500 mg/m^2 on Day 1 or gemcitabine 1 000 mg/m^2 on Days 1 and 8 of each 21-day cycle for up to 4 cycles. Following surgery, placebo was administered every 3 weeks for up to 13 cycles.

All study medications were administered via intravenous infusion. Treatment with pembrolizumab or placebo continued until completion of the treatment (17 cycles), disease progression that precluded definitive surgery, disease recurrence in the adjuvant phase, disease progression for those who did not undergo surgery or had incomplete resection and entered the adjuvant phase, or unacceptable toxicity. Assessment of tumour status was performed at baseline, Week 7, and Week 13 in the neoadjuvant phase and within 4 weeks prior to the start of the adjuvant phase. Following the start of the adjuvant phase, assessment of tumour status was performed every 16 weeks through the end of Year 3, and then every 6 months thereafter. The primary efficacy outcome measures were OS and investigator-assessed event-free survival (EFS). Secondary efficacy outcome measures were pathological complete response (pCR) rate and major pathological response (mPR) rate as assessed by blinded independent pathology review (BIPR).

A total of 797 patients in KEYNOTE-671 were randomised: 397 patients to the pembrolizumab arm and 400 to the placebo arm. Baseline characteristics were: median age of 64 years (range: 26 to 83), 45 % age 65 or older; 71 % male; 61 % White, 31 % Asian, and 2,0 % Black. Sixty-three percent and 37 % had ECOG performance of 0 or 1, respectively; 30 % had Stage II and 70 % had Stage III disease; 33 % had TPS ≥ 50 % and 67 % had TPS < 50 %; 43 % had tumours with squamous histology and 57 % had tumours with non-squamous histology; 31% were from the East Asian region.

Eighty-one percent of patients in the pembrolizumab in combination with platinum-containing chemotherapy arm had definitive surgery compared to 76 % of patients in the platinum-containing chemotherapy arm.

The trial demonstrated statistically significant improvements in OS and EFS for patients randomised to pembrolizumab in combination with platinum-containing chemotherapy followed by pembrolizumab monotherapy compared with patients randomised to placebo in combination with platinum-containing chemotherapy followed by placebo alone. OS efficacy results with a median follow-up time of 29,8 months (range: 0,4 to 62,0 months) are summarised in Table 19 and Figure 16. EFS, pCR, and mPR efficacy results with a median follow-up time of 21,4 months (range: 0,4 to 50,6 months) are summarised in Table 19.

Table 19: Efficacy Results in KEYNOTE-671

Endpoint	**Pembrolizumab with chemotherapy/Pembrolizumab n=397**	**Placebo with chemotherapy/Placebo n=400**
OS		
Number of patients with event (%)	110 (28 %)	144 (36 %)
Median in months* (95 % CI)	NR (NR, NR)	52,4 (45,7, NR)
Hazard ratio† (95 % CI)	0,72 (0,56, 0,93)	
p-Value‡	0,00517	
EFS		
Number of patients with event (%)	139 (35 %)	205 (51 %)
Median in months* (95 % CI)	NR (34,1, NR)	17,0 (14,3, 22,0)
Hazard ratio† (95 % CI)	0,58 (0,46, 0,72)	

p-Value‡	< 0,0001	
pCR		
Number of patients with pCR	72	16
pCR Rate (%), (95 % CI)	18,1 (14,5, 22,3)	4,0 (2,3, 6,4)
Treatment difference estimate (%), (95 % CI)§	14,2 (10,1, 18,7)	
p-Value	< 0,0001	
mPR		
Number of patients with mPR	120	44
mPR Rate (%), (95 % CI)	30,2 (25,7, 35,0)	11,0 (8,1, 14,5)
Treatment difference estimate (%), (95 % CI)§	19,2 (13,9, 24,7)	
p-Value	< 0,0001	

*Based on Kaplan-Meier estimates

†Based on Cox regression model with treatment as a covariate stratified by stage, tumour PD-L1 expression, histology, and geographic region

‡Based on stratified log-rank test

§Based on Miettinen and Nurminen method stratified by stage, tumour PD-L1 expression, histology, and geographic region

NR = not reached

The final EFS analysis was performed at a median duration of follow-up of 29,8 months after 422 patient events (174 for the pembrolizumab arm and 248 for the placebo arm). Median EFS was 47,2 months (95 % CI: 32,9, NR) for the pembrolizumab arm and 18,3 months (95 % CI: 14,8, 22,1) for the placebo arm. The EFS HR was 0,59 (95 % CI: 0,48, 0,72). See Figure 17.

Figure 16: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-671 (Intent to Treat Population)

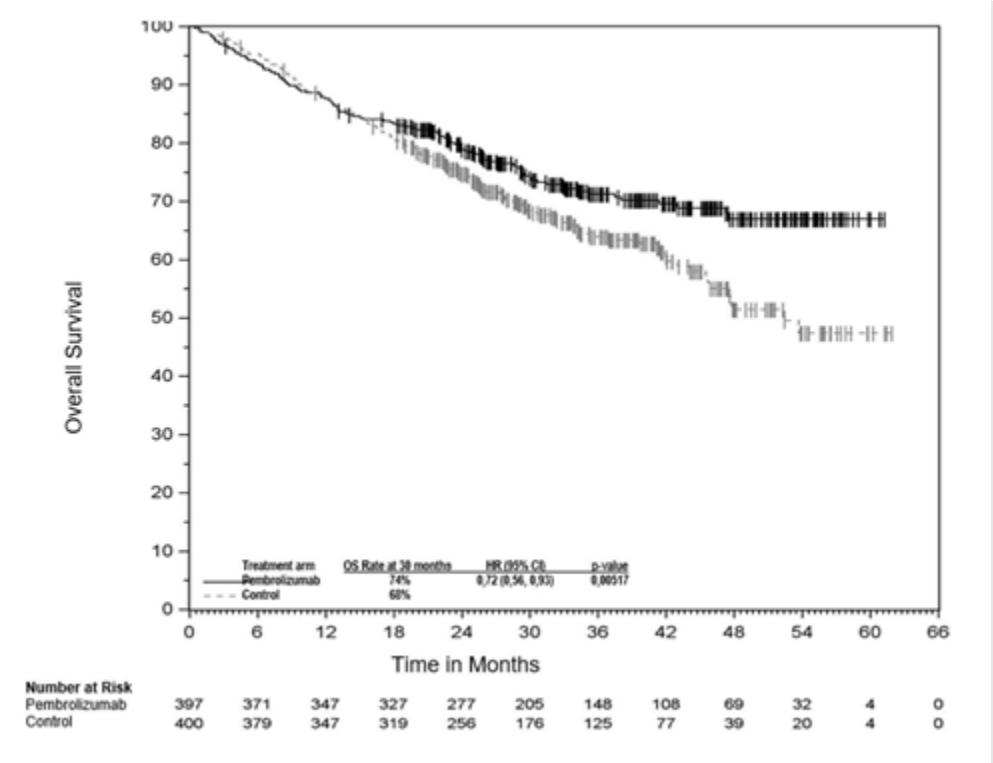
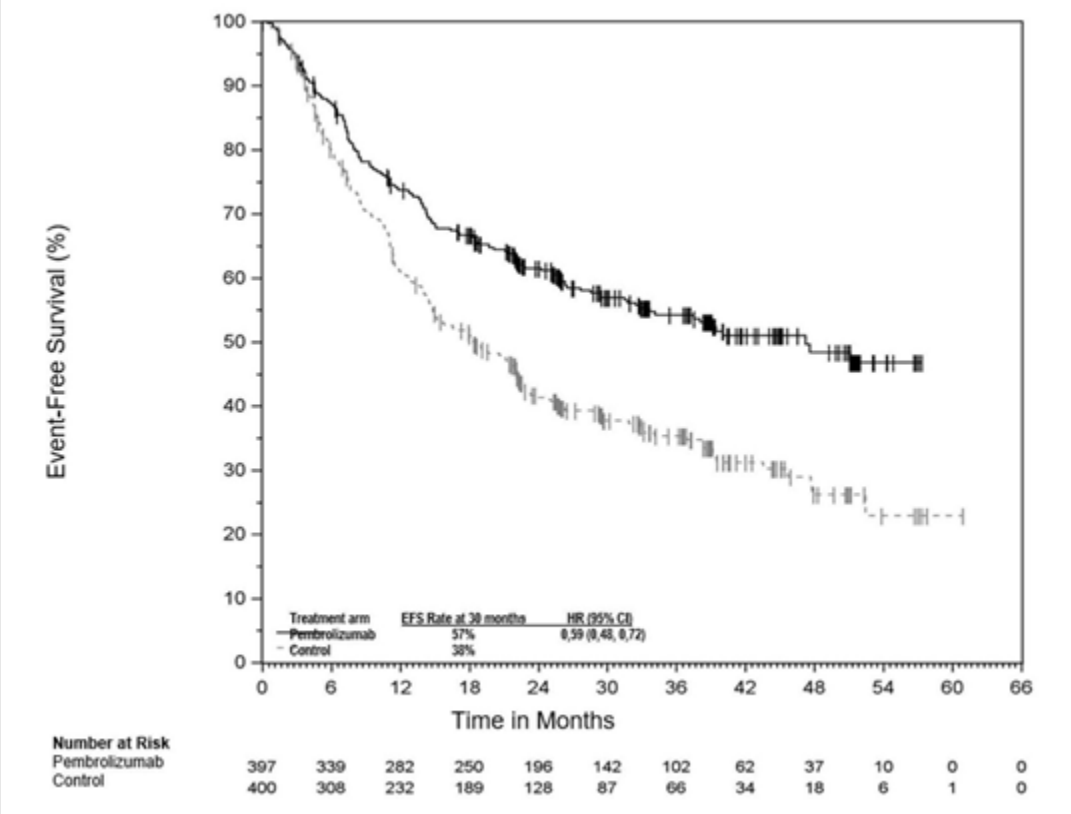


Figure 17: Kaplan-Meier Curve for Event-Free Survival by Treatment Arm in KEYNOTE-671 (Intent to Treat Population)



KEYNOTE-091: Placebo-controlled study for the adjuvant treatment of patients with resected NSCLC

The efficacy of pembrolizumab was investigated in KEYNOTE-091, a multicentre, randomised, triple-blind, placebo-controlled trial. Key eligibility criteria were completely resected stage IB (T2a ≥ 4 cm), II or IIIA NSCLC by AJCC 7th edition, regardless of tumour PD-L1 expression status, no prior neoadjuvant radiotherapy and/or neoadjuvant chemotherapy, and no prior or planned adjuvant radiotherapy for the current malignancy. Patients may or may not have received adjuvant chemotherapy. 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 4 cycles of adjuvant chemotherapy were ineligible. Randomisation was stratified by stage (IB vs. II vs. IIIA), adjuvant chemotherapy (no adjuvant chemotherapy vs. adjuvant chemotherapy), PD-L1 status (TPS < 1 % [negative] vs. TPS 1-49 % vs. TPS ≥ 50 %), and geographic region (Western Europe vs. Eastern Europe vs. Asia vs. Rest of World). Patients were randomised (1:1) to receive pembrolizumab 200 mg or placebo intravenously every 3 weeks.

Treatment continued until RECIST 1.1-defined disease recurrence as determined by the investigator, unacceptable toxicity, or approximately one year (18 doses). Patients underwent imaging every 12 weeks after the first dose of pembrolizumab for the first year, then every 6 months for years 2 to 3, and then annually up to the end of year 5. After year 5, imaging is performed as per local standard of care.

Among the 1 177 patients in KEYNOTE-091 (590 patients in the pembrolizumab arm and 587 in the placebo arm), baseline characteristics were: median age of 65 years (range: 31 to 87), 53 % age 65 or older; 68 % male; and 77 % White, 18 % Asian. Sixty-one percent and 39 % had ECOG performance of 0 or 1, respectively. Fourteen percent had stage IB (T2a ≥ 4 cm), 57 % had stage II, and 29 % had stage IIIA disease. Forty percent had tumour PD-L1 expression TPS < 1 % [negative], 32 % had TPS 1-49 %, 28 % had TPS ≥ 50 %, and 86 % received adjuvant chemotherapy. Fifty-one percent were from Western Europe.

The primary efficacy outcome measures were investigator-assessed disease-free survival (DFS) in the overall population and in the population with tumour PD-L1 expression TPS ≥ 50 %, where DFS was defined as the time between the date of randomisation and the date of first recurrence (local/regional recurrence, distant metastasis), a second malignancy, or death,

whichever occurred first. Secondary efficacy outcome measures were investigator-assessed DFS in the population with tumour PD-L1 expression TPS ≥ 1 %, and OS in the overall population and in the populations with tumour PD-L1 expression TPS ≥ 50 % and TPS ≥ 1 %.

The trial demonstrated a statistically significant improvement in DFS in the overall population at a pre-specified interim analysis for patients randomised to the pembrolizumab arm compared to patients randomised to the placebo arm. At the time of analysis, OS results were not mature (18 % with events in the overall population). The median follow-up time was 32,4 months (range: 0,6 to 68 months). Efficacy results are summarised in Table 20 and Figure 18.

Table 20: Efficacy Results in KEYNOTE-091

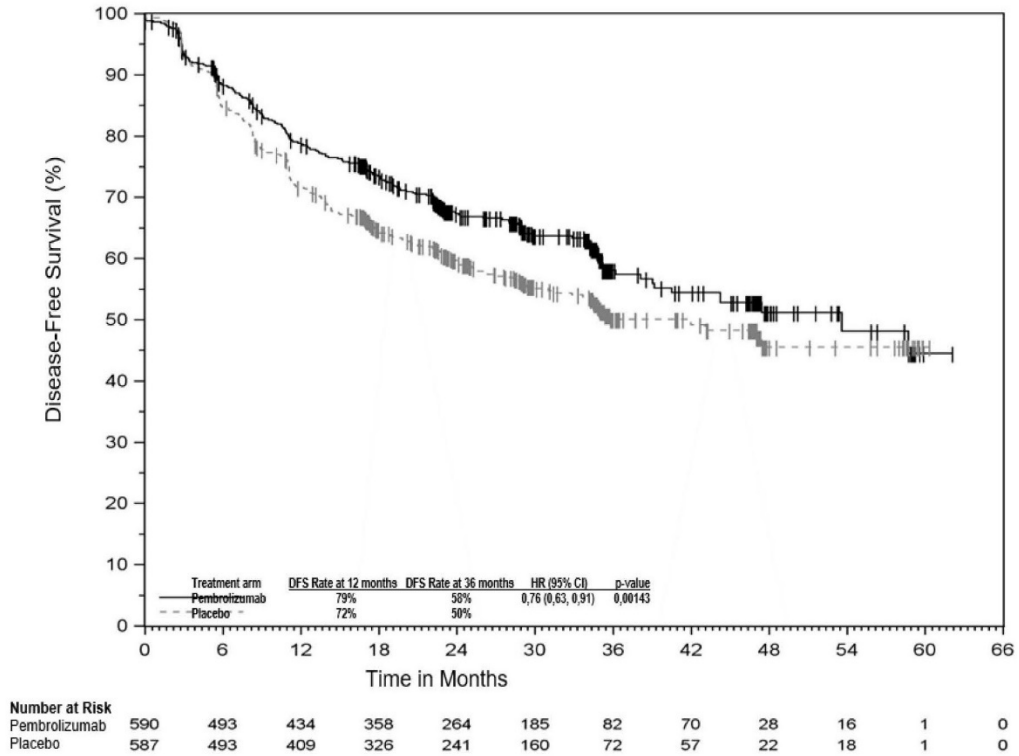
Endpoint	**Pembrolizumab 200 mg every 3 weeks n=590**	**Placebo n=587**
DFS (Overall)		
Number (%) of patients with event	212 (36 %)	260 (44 %)
Hazard ratio* (95 % CI)	0,76 (0,63, 0,91)	
p-Value†	0,0014	
Median in months (95 % CI)	53,6 (39,2, NR)	42,0 (31,3, NR)

*Based on the multivariate Cox regression model

†Based on the permutation test with multivariate Cox regression model

NR = not reached

Figure 18: Kaplan-Meier Curve for Disease-Free Survival by Treatment Arm in KEYNOTE-091 (Overall Intent to Treat Population)



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.

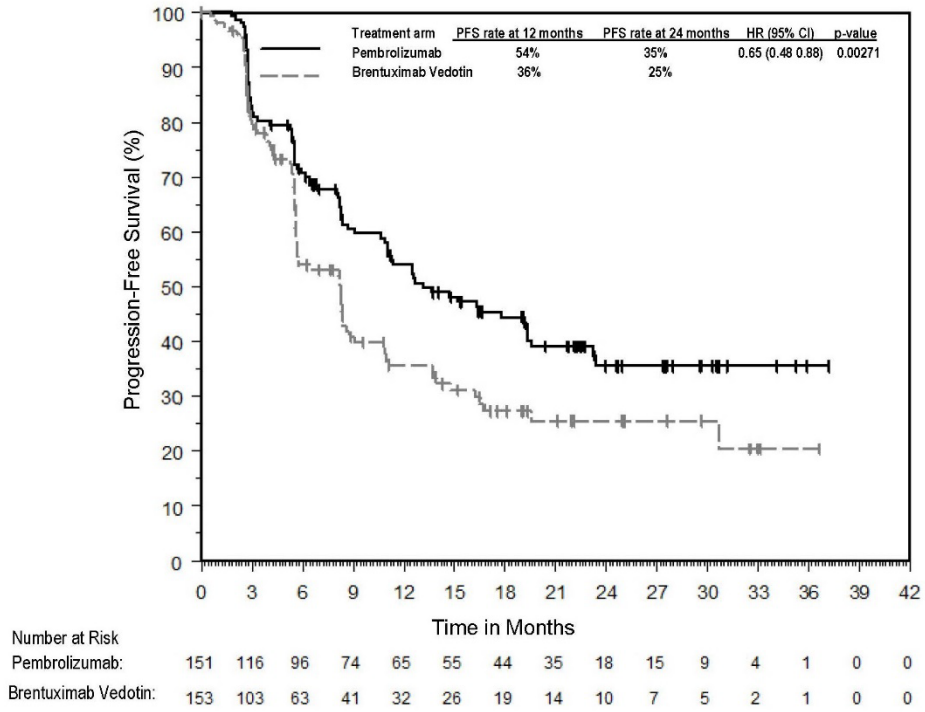
The median follow-up time for 151 patients treated with pembrolizumab was 24,9 months (range: 1,8 to 42,0 months). Efficacy results are summarised in Table 21.

Table 21: 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 19: 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 multicentre, 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 22.

Table 22: Efficacy Results in Patients with Refractory or Relapsed Classical Hodgkin Lymphoma

	KEYNOTE-013	KEYNOTE-087
Endpoint	**n=31**	**n=210**

Applicant: MSD (Pty) Ltd
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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 Organisation 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 23 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 20. 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 23: 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)

Applicant: MSD (Pty) Ltd
APPROVED PROFESSIONAL INFORMATION
Keytruda Solution for Infusion

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

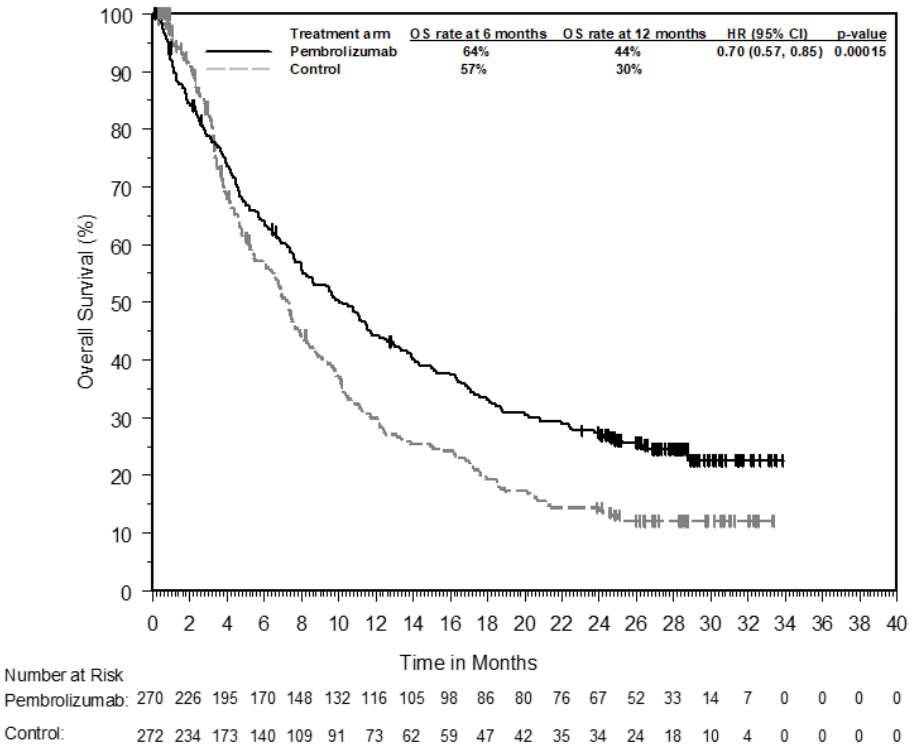
‡Assessed by BICR using RECIST 1.1

§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 20: 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 24).

Table 24: 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 25 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 25: 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 26).

Table 26: 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		

Gastric Cancer

KEYNOTE-859: Controlled trial of combination therapy in HER2-negative gastric cancer patients naïve to treatment

The efficacy of pembrolizumab in combination with fluoropyrimidine and platinum chemotherapy was investigated in KEYNOTE-859, a multicentre, randomised, double-blind, placebo-controlled trial that enrolled 1 579 patients with HER2-negative advanced gastric or gastro-oesophageal junction (GEJ) adenocarcinoma regardless of PD-L1 expression status, who had not previously received systemic therapy for metastatic disease. Patients with an autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Randomisation was stratified by PD-L1 expression (CPS ≥ 1 or < 1), chemotherapy regimen (5-FU plus cisplatin [FP] or capecitabine plus oxaliplatin [CAPOX]), and geographic region (Europe/Israel/North America/Australia, Asia or Rest of the World). Patients were randomised (1:1) to one of the following treatment arms; all study medications, except oral capecitabine, were administered as an intravenous infusion for every 3-week cycle:

- Pembrolizumab 200 mg, investigator's choice of combination chemotherapy of cisplatin 80 mg/m^2 and 5-FU 800 mg/m^2/day for 5 days (FP) or oxaliplatin 130 mg/m^2 and capecitabine 1 000 mg/m^2 bid for 14 days (CAPOX) for up to 35 cycles. Pembrolizumab was administered prior to chemotherapy on Day 1 of each cycle.

- Placebo, investigator's choice of combination chemotherapy of cisplatin 80 mg/m^2 and 5-FU 800 mg/m^2/day for 5 days (FP) or oxaliplatin 130 mg/m^2 and capecitabine 1 000 mg/m^2 bid for 14 days (CAPOX) for up to 35 cycles. Placebo was administered prior to chemotherapy on Day 1 of each cycle.

Treatment with pembrolizumab and chemotherapy or placebo and chemotherapy continued until RECIST v1.1-defined progression of disease as determined by BICR, unacceptable toxicity, or a maximum of 24 months. Treatment 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 every 6 weeks. The primary efficacy outcome measure was OS. Additional secondary efficacy outcome measures included PFS, ORR, and DOR as assessed by BICR using RECIST v1.1.

The population characteristics were: median age of 62 years (range: 21 to 86), 39 % age 65 or older; 68 % male; 55 % White and 34 % Asian; 37 % ECOG PS of 0 and 63 % ECOG PS of 1. Ninety-seven percent of patients had metastatic disease (stage IV) and 3 % had locally advanced unresectable disease. Seventy-eight percent had tumours that expressed PD-L1 with a CPS ≥ 1 and 5 % (n=74) of patients had tumours that were MSI-H. Eighty-six percent of patients received CAPOX.

A statistically significant improvement in OS, PFS and ORR was demonstrated in patients randomised to pembrolizumab in combination with chemotherapy compared with placebo in combination with chemotherapy. Efficacy results are summarised in Table 27.

Table 27: Efficacy Results for KEYNOTE-859

Endpoint	**Pembrolizumab 200 mg every 3 weeks FP or CAPOX n=790**	**Placebo FP or CAPOX n=789**
OS		
Number (%) of patients with event	603 (76)	666 (84)
Median in months* (95 % CI)	12,9 (11,9,14,0)	11,5 (10,6,12,1)
Hazard ratio† (95 % CI)	0,78 (0,70, 0,87)	
p-Value (stratified log-rank)‡	< 0,0001	
PFS		
Number (%) of patients with event	572 (72)	608 (77)
Median in months* (95 % CI)	6,9 (6,3, 7,2)	5,6 (5,5, 5,7)
Hazard ratio† (95 % CI)	0,76 (0,67, 0,85)	
p-Value (stratified log-rank)‡	< 0,0001	
Objective Response Rate		
ORR§ (95 % CI)	51 % (47,7, 54,8)	42 % (38,5, 45,5)
Complete response rate	9 %	6 %

Partial response rate	42 %	36 %
Difference (95 % CI)	9 % (4,4, 14,1)	
p-Value¶	0,00009	
Response Duration	n=405	n=331
Median in months (range)	8,0 (1,2+ - 41,5+)	5,7 (1,3+ - 34,7+)
% with duration ≥ 12 months*	39 %	26 %
% with duration ≥ 24 months*	27 %	13 %

*Based on Kaplan-Meier estimation

†Based on the stratified Cox proportional hazard model

‡One-sided p-Value based on stratified log-rank test

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

¶One-sided p-Value based on stratified Miettinen & Nurminen method

Figure 21: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-859

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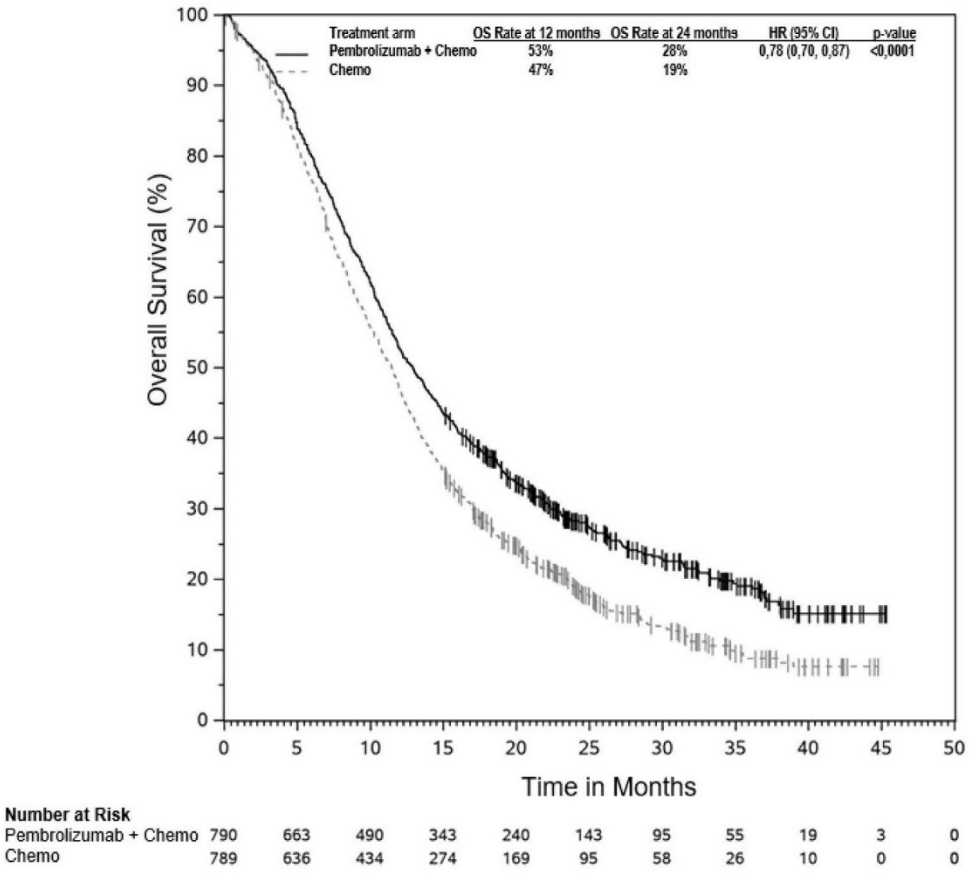
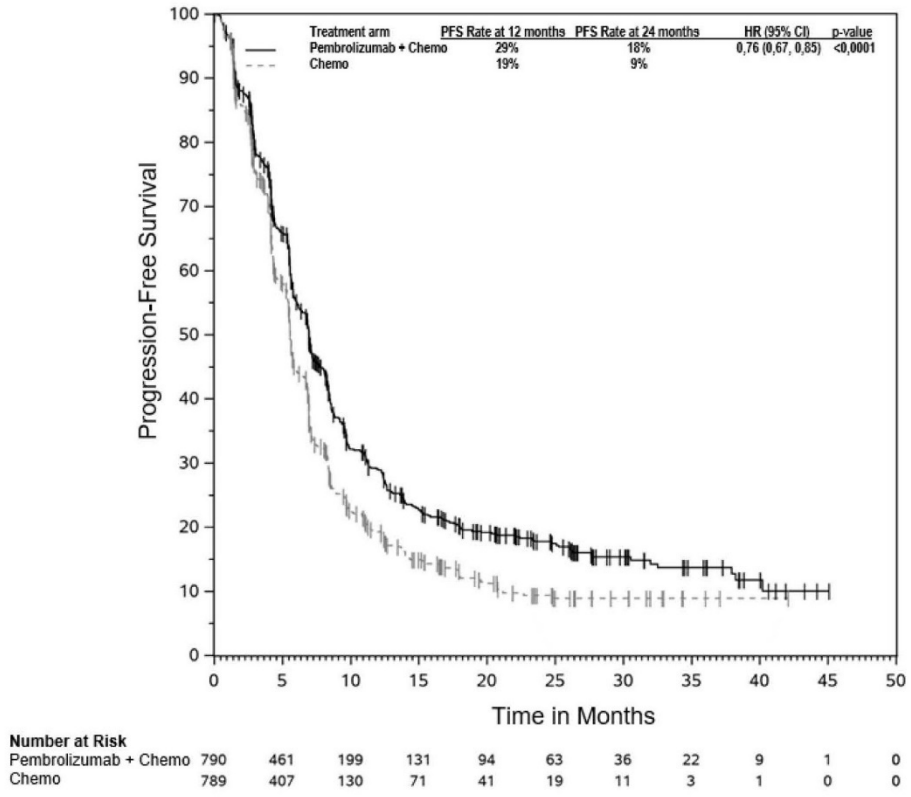


Figure 22: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-859



KEYNOTE-811: First-line treatment of locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction (GEJ) adenocarcinoma

The efficacy of pembrolizumab in combination with trastuzumab plus fluoropyrimidine and platinum chemotherapy was investigated in KEYNOTE-811, a multicentre, randomised, double-blind, placebo-controlled trial that enrolled 698 patients with HER2-positive advanced gastric or gastro-oesophageal junction (GEJ) adenocarcinoma regardless of PD-L1 expression status, who had not previously received systemic therapy for metastatic disease. Patients with an autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Randomisation was stratified by PD-

L1 expression (CPS ≥ 1 or < 1), chemotherapy regimen (5-FU plus cisplatin [FP] or capecitabine plus oxaliplatin [CAPOX]), and geographic region (Europe/Israel/North America/Australia, Asia or Rest of the World). Patients were randomised (1:1) to one of the following treatment arms; all study medications, except oral capecitabine, were administered as an intravenous infusion for every 3-week cycle:

- Pembrolizumab 200 mg, trastuzumab 8 mg/kg on first infusion and 6 mg/kg in subsequent cycles, followed by investigator's choice of combination chemotherapy of cisplatin 80 mg/m^2 for up to 6 cycles and 5-FU 800 mg/m^2/day for 5 days (FP) or oxaliplatin 130 mg/m^2 up to 6-8 cycles and capecitabine 1 000 mg/m^2 bid for 14 days (CAPOX). Pembrolizumab was administered prior to trastuzumab and chemotherapy on Day 1 of each cycle.
- Placebo, trastuzumab 8 mg/kg on first infusion and 6 mg/kg in subsequent cycles, followed by investigator's choice of combination chemotherapy of cisplatin 80 mg/m^2 for up to 6 cycles and 5-FU 800 mg/m^2/day for 5 days (FP) or oxaliplatin 130 mg/m^2 up to 6-8 cycles and capecitabine 1 000 mg/m^2 bid for 14 days (CAPOX). Placebo was administered prior to trastuzumab and chemotherapy on Day 1 of each cycle.

Treatment with pembrolizumab, trastuzumab and chemotherapy or placebo, trastuzumab and chemotherapy continued until RECIST v1.1-defined progression of disease as determined by BICR, unacceptable toxicity, or a maximum of 24 months. Treatment 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 every 6 weeks.

Among the 698 patients randomised in KEYNOTE-811, 594 (85 %) had tumours that expressed PD-L1 with a CPS ≥ 1. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx™ kit. The population characteristics of these 594 patients were: median age of 63 years (range: 19 to 85), 43 % age 65 or older; 80 % male; 63 % White, 33 % Asian, and 0,7 % Black; 42 % ECOG PS of 0 and 58 % ECOG PS of 1. Ninety-eight percent of patients had metastatic disease (stage IV) and 2 % had locally advanced unresectable disease. Ninety-five percent (n=562) had tumours that were not MSI-H, 1 % (n=8) had tumours that were MSI-H, and in 4 % (n=24) the status was not known. Eighty-five percent of patients received CAPOX.

The primary efficacy outcome measures were PFS, based on BICR using RECIST 1.1, and OS. Secondary efficacy outcome measures included ORR and DoR, based on BICR using RECIST 1.1.

At the first interim analysis conducted on the first 264 patients randomised in the overall population (133 patients in the pembrolizumab arm and 131 in the placebo arm), a statistically significant improvement was observed in the objective response rate (74,4 % vs 51,9 %, representing a 22,7 % difference; 95 % CI (11,2, 33,7); p-Value 0,00006).

At the second interim analysis in the overall population, a statistically significant improvement in PFS (HR 0,72, 95 % CI 0,60, 0,87; p-Value 0,0002) was demonstrated in patients randomised to pembrolizumab in combination with trastuzumab and chemotherapy compared with placebo in combination with trastuzumab and chemotherapy. At the time of this analysis in the overall population, there was no statistically significant difference with respect to OS.

Efficacy results at the second interim analysis for the pre-specified subgroup of patients whose tumours expressed PD-L1 with a CPS ≥ 1 are summarised in Table 28 and Figures 23 and 24.

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Table 28: Efficacy Results for KEYNOTE-811 with PD-L1 Expression CPS ≥ 1

Endpoint	Pembrolizumab 200 mg every 3 weeks Trastuzumab Fluoropyrimidine and Platinum Chemotherapy n=298	Placebo Trastuzumab Fluoropyrimidine and Platinum Chemotherapy n=296
PFS		
Number (%) of patients with event	199 (67 %)	215 (73 %)
Median in months (95 % CI)	10,8 (8,5, 12,5)	7,2 (6,8, 8,4)
Hazard ratio* (95 % CI)	0,7 (0,58, 0,85)	
p-Value†	0,0001	
OS		
Number (%) of patients with event	167 (56 %)	183 (61,8 %)
Median in months (95 % CI)	20,5 (18,2, 24,3)	15,6 (13,5, 18,6)
Hazard ratio* (95 % CI)	0,79 (0,64, 0,98)	
p-Value†	0,0143	
Objective Response Rate		
ORR‡ (95 % CI)	73 % (67,7, 78,1)	58 % (52,6, 64,1)

Complete response rate	14 %	10 %
Partial response rate	59 %	49 %
Difference (95 % CI)[§]	15 % (7, 22)	
p-Value[§]	0,00008	
Response Duration	n=218	n=173
Median in months (range)	11,3 (1,1+, 40,1+)	9,5 (1,4+, 38,3+)
% with duration ≥ 6 months[¶]	75 %	67 %
% with duration ≥ 12 months[¶]	49 %	41 %

*Based on the unstratified Cox proportional hazard model

[†]Based on unstratified log-rank test; p-value is nominal p-value

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

[§]Based on unstratified Miettinen and Nurminen method; p-value is nominal p-value

[¶]Based on Kaplan-Meier estimation

Figure 23: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-811 (CPS ≥ 1)

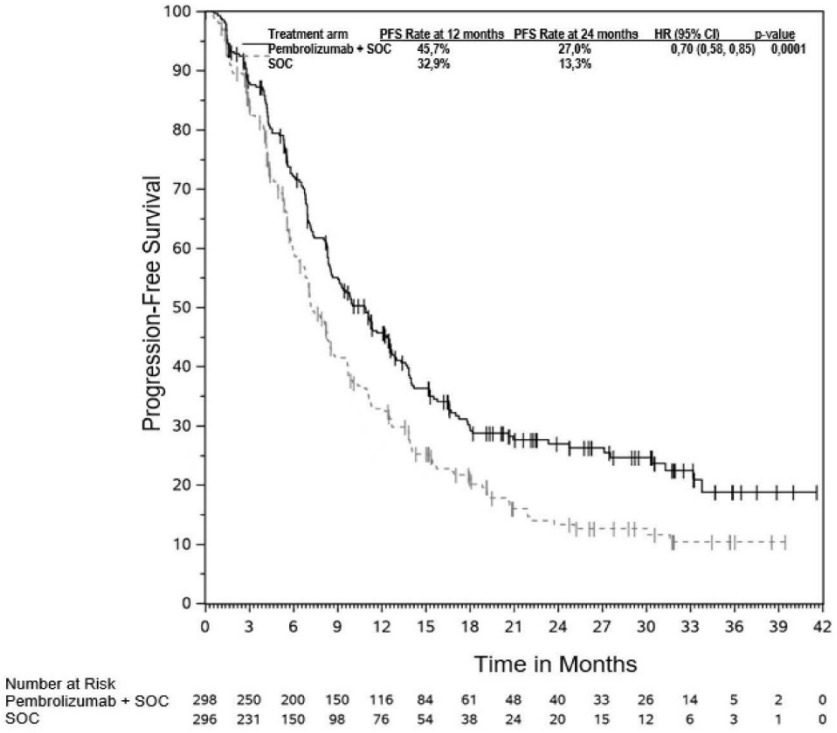
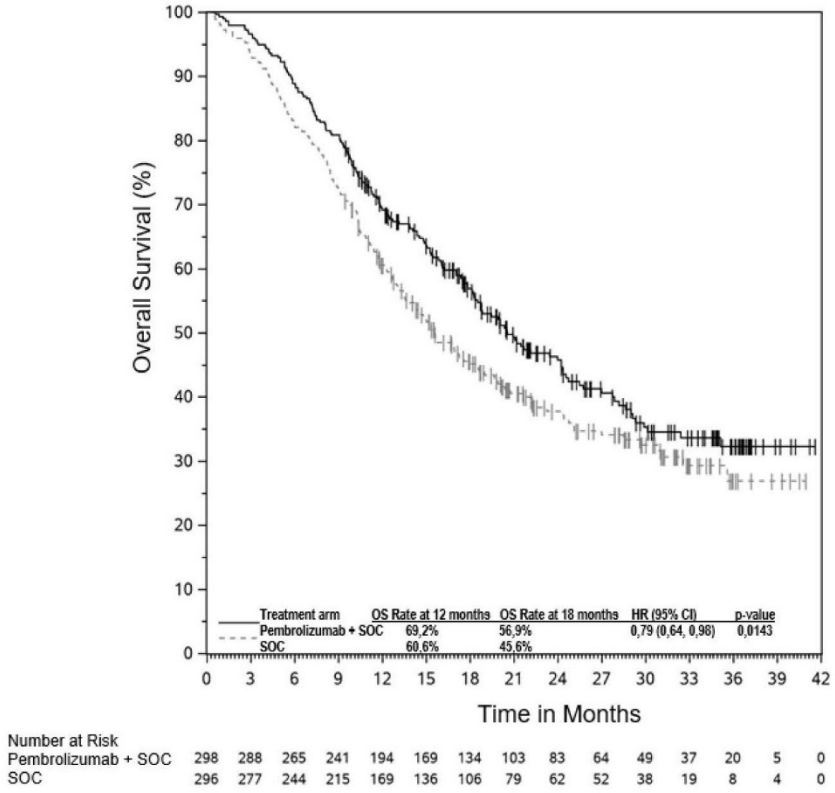


Figure 24: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-811 (CPS ≥ 1)



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 multicentre, 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 29 and 30 and Figures 25 and 26 describe key efficacy results for pembrolizumab in KEYNOTE-048.

Table 29: 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 event	244 (87 %)	253 (91 %)
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

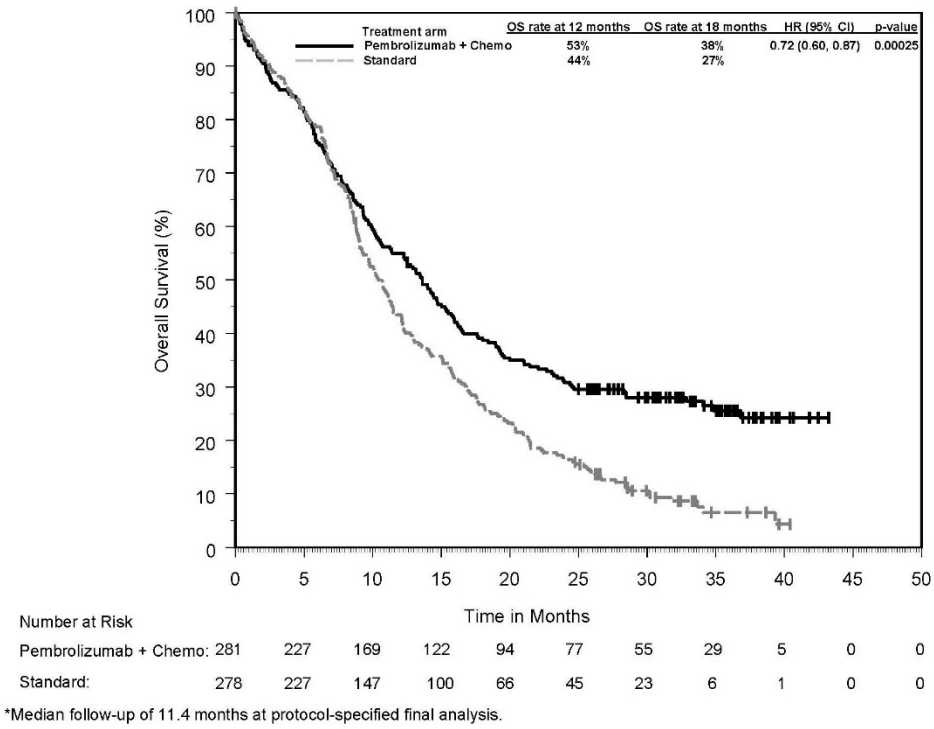
‡Based on stratified log-rank test

§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 25: 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 30: 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

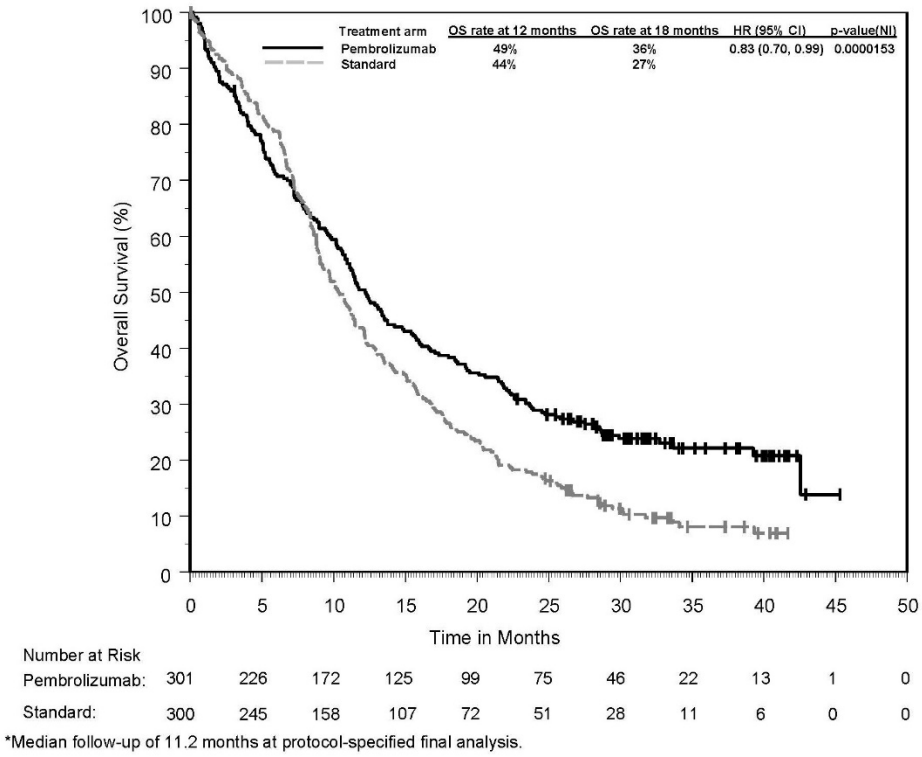
‡Non-inferiority p-Value

§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 26: 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 31.

Table 31: 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 multicentre, 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 32 and the Kaplan-Meier curve for OS is shown in Figure 27.

Table 32: 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

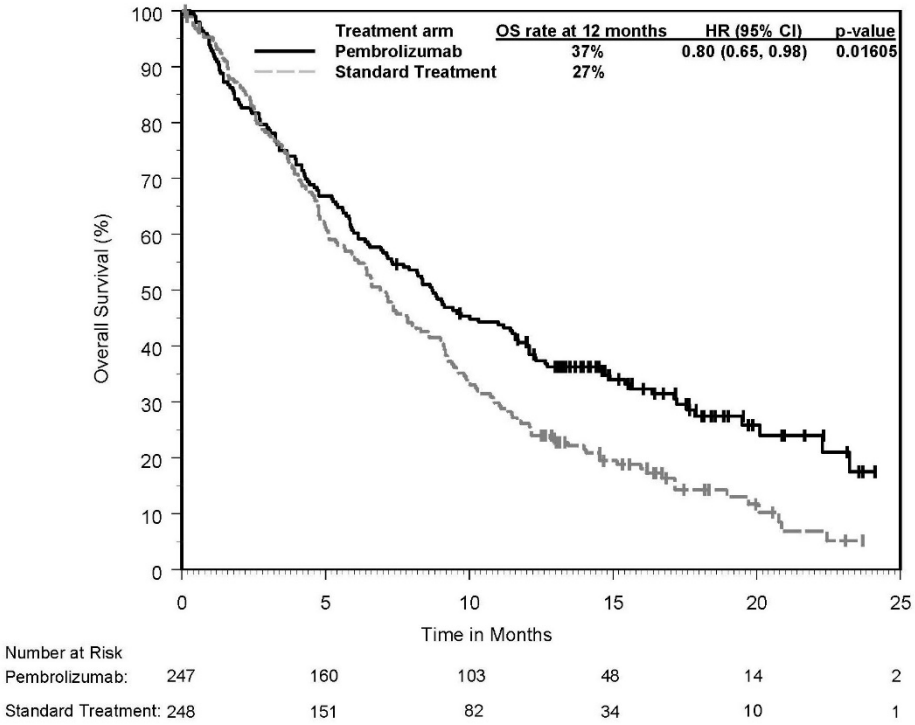
[§]Assessed by BICR using RECIST 1.1

[¶]Based on method by Miettinen and Nurminen

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

[Þ]Based on Kaplan-Meier estimation

Figure 27: 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 33 summarises key efficacy measures and Figures 28 and 29 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 33: 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

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Figure 28: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-426 (intent to treat population)

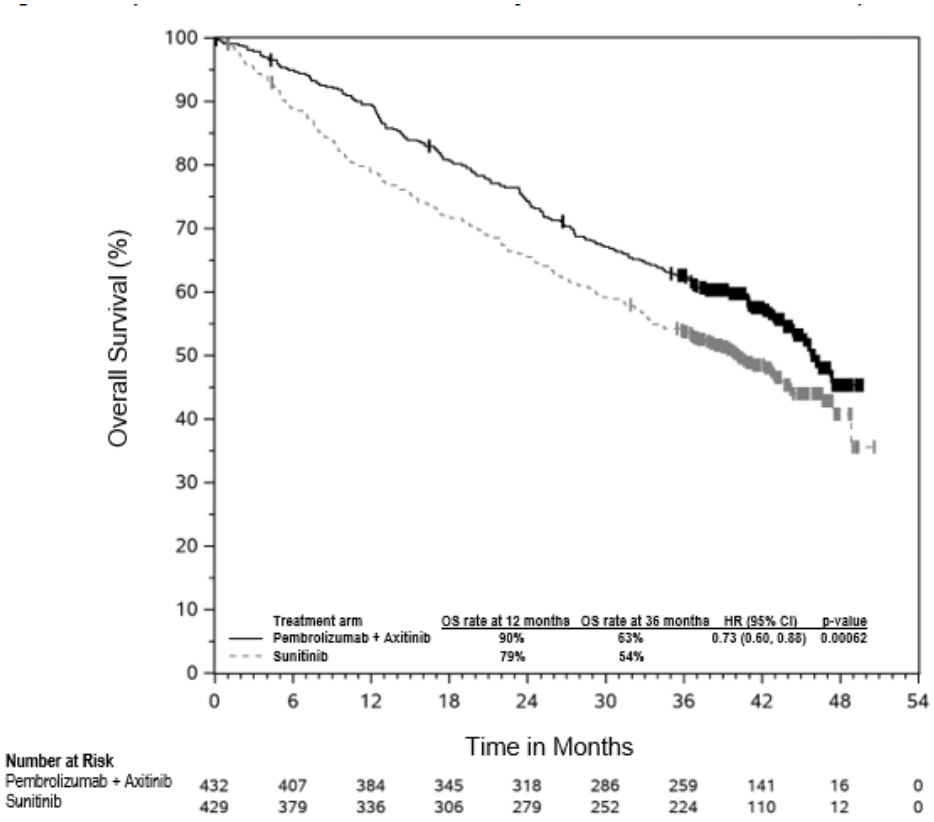
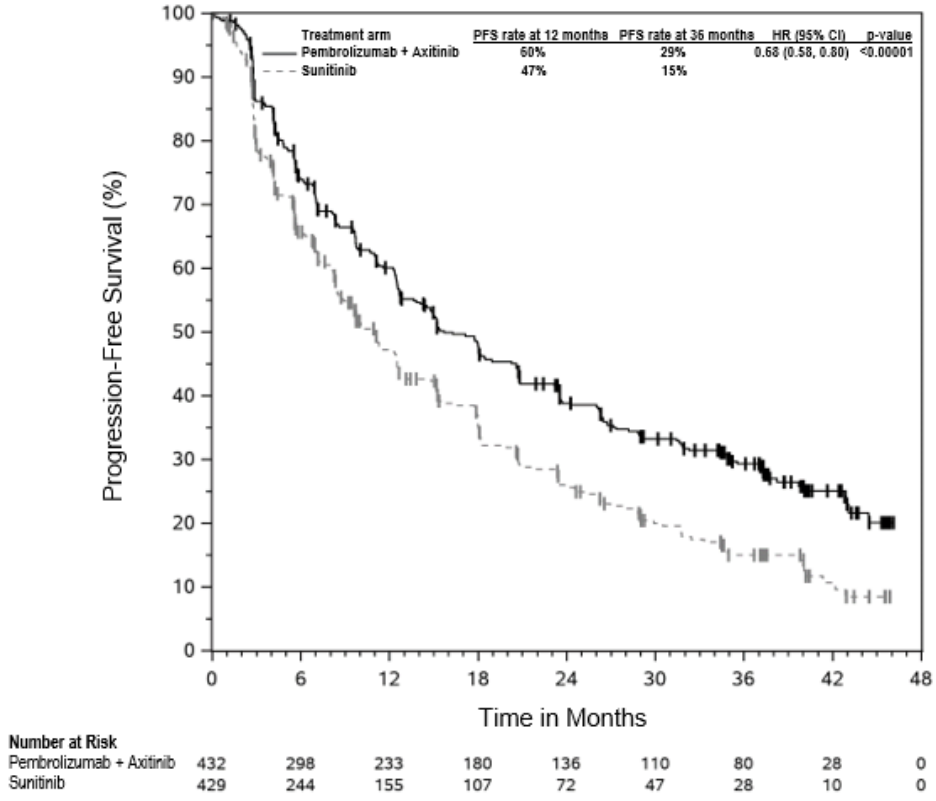


Figure 29: Kaplan-Meier curve for progression-free survival by treatment arm in KEYNOTE-426 (intent to treat population)



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

Table 34: 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 (CLEAR): 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 (CLEAR), 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 Centre (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 (HR 0,39; 95 % CI 0,32, 0,49; p-Value < 0,0001), OS (HR 0,66; 95 % CI 0,49, 0,88; p-Value 0,0049), and ORR (71 %; 95 % CI 66, 76) vs. (36 %;

95 % CI 31, 41); p-Value < 0,0001 in patients randomised to pembrolizumab in combination with lenvatinib compared with sunitinib at the pre-specified interim analysis, with median survival follow-up time of 26,5 months and median duration of treatment for pembrolizumab plus lenvatinib of 17,0 months.The primary OS analysis was not adjusted to account for subsequent therapies.

Efficacy results for KEYNOTE-581(CLEAR) at the protocol-specified final analysis with median follow-up time of 49,4 months are summarised in Table 35 and Figures 30 and 31. 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 35.

Table 35: Efficacy Results in KEYNOTE-581 (CLEAR)

Endpoint	**Pembrolizumab 200 mg every 3 weeks and Lenvatinib n=355**	**Sunitinib n=357**
PFS*		
Number of patients with event (%)	207 (58 %)	214 (60 %)
Median in months (95 % CI)	23,9 (20,8, 27,7)	9,2 (6,0, 11,0)
Hazard ratio† (95 % CI)	0,47 (0,38, 0,57)	
p-Value‡	< 0,0001	
OS		
Number of patients with event (%)	149 42 %)	159 (45 %)

Median in months (95 % CI)	57,7 (33,648,7, NR)	54,3 (40,9, NR)
Hazard ratio† (95 % CI)	0,79 (0,63, 0,99)	
p-Value‡	0,0424	
Objective response rate		
ORR§ (95 % CI)	71 % (66,6, 76,0)	37 % (31,7, 41,7)
Complete response	18 %	45 %
Partial response	53 %	32 %
p-Value¶	< 0,0001	
Response duration#		
Median in months (range)	26,7 (1,64+, 55,92+)	14,7 (1,64+, 54,08+)

*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

‡Nominal p-Value, 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 final OS analysis was not adjusted to account for subsequent therapies, with 195/357 (54,6 %) patients in the sunitinib arm and 56/355 (15,8 %) patients in the pembrolizumab plus lenvatinib arm receiving subsequent anti-PD-1/PD-L1 therapy.

Figure 30: Kaplan-Meier curve for progression-free survival by treatment arm in KEYNOTE-581

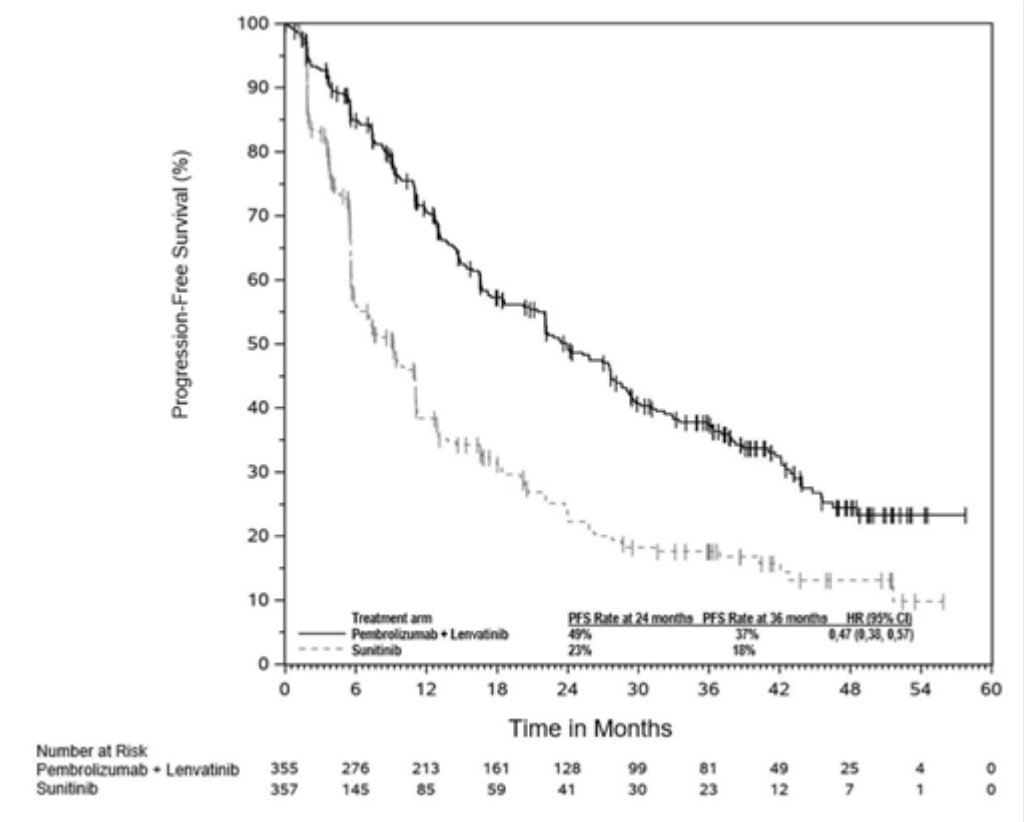
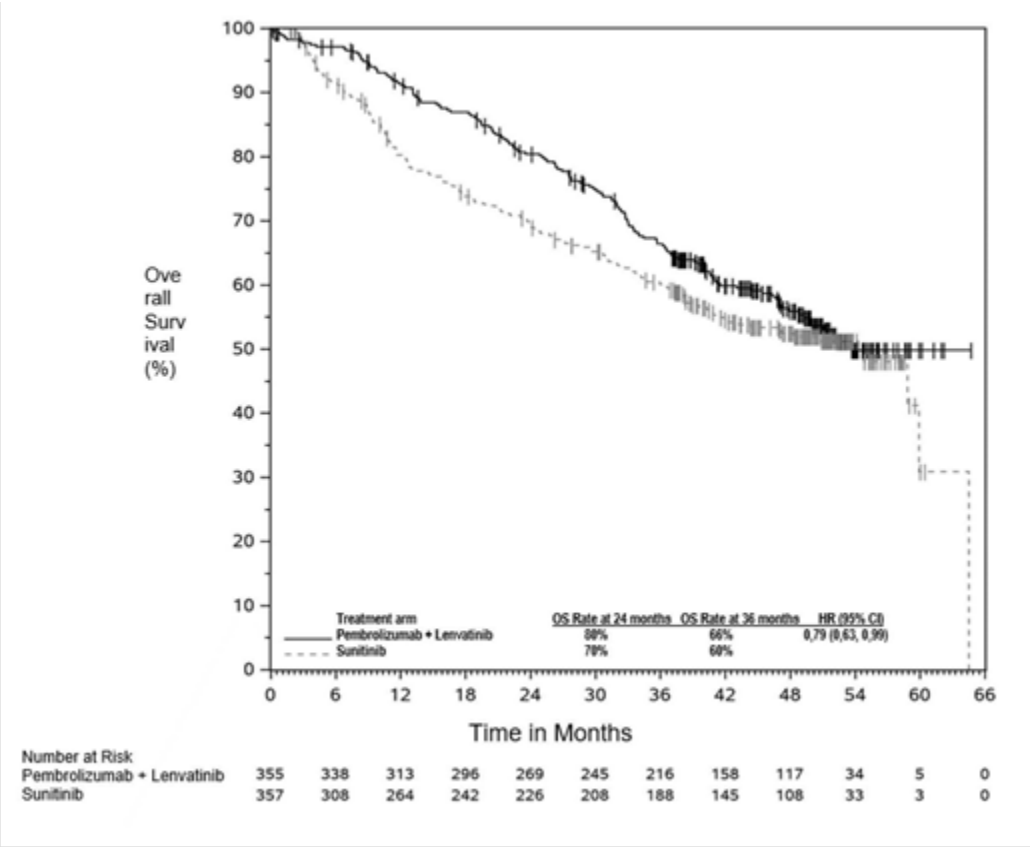


Figure 31: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-581



The KEYNOTE-581 (CLEAR) study was not powered to evaluate efficacy of individual subgroups.

Subgroup analyses were performed by MSKCC prognostic group.

Table 36 summarises the efficacy measures by MSKCC prognostic group based on final OS analysis at median follow-up of 49,4 months.

Table 36: Efficacy Results in KEYNOTE-581 (CLEAR) 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 BIRC*					**PFS HR (95 % CI)**
Favourable	96	56	97	65	0,46 (0,32, 0,67)
Intermediate	227	129	228	130	0,51 (0,40, 0,65)
Poor	32	22	32	19	0,18 (0,08, 0,42)
Overall Survival (OS)*					**OS HR (95 % CI)**
Favourable†	96	27	97	31	0,89 (0,53, 1,50)
Intermediate	227	104	228	108	0,81 (0,62, 1,06)
Poor	32	18	32	20	0,59 (0,31, 1,12)
*Median follow-up: 49,4 months (data cutoff – 31 July 2022)					

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. The study demonstrated statistically significant

improvements in OS and DFS for patients randomised to the pembrolizumab arm compared with placebo. At the pre-specified interim analysis with a median follow-up time of 23,9 months, the DFS (HR was 0,68; 95 % CI 0,53, 0,87; p-Value = 0,0010. Efficacy results with a median follow-up time of 55,8 months are summarised in Table 37 and Figure 32 and Figure 33.

Table 37: Efficacy results in KEYNOTE-564

Endpoint	**Pembrolizumab 200 mg every 3 weeks n=496**	**Placebo n=498**
DFS		
Number (%) of patients with event	174 (35 %)	224 (45 %)
Median in months (95 % CI)	NR (NR, NR)	NR (54,9, NR)
Hazard ratio* (95 % CI)	0,72 (0,59, 0,87)	
OS		
Number (%) of patients with event	55 (11 %)	86 (17 %)
Median in months (95 % CI)	NR (NR, NR)	NR (NR, NR)
p-Value†	0,0024	

*Based on the stratified Cox proportional hazard model

One-sided p-Value based on stratified log-rank test

NR = not reached

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Figure 32: Kaplan-Meier curve for disease-free survival by treatment arm in KEYNOTE-564 (intent to treat population)

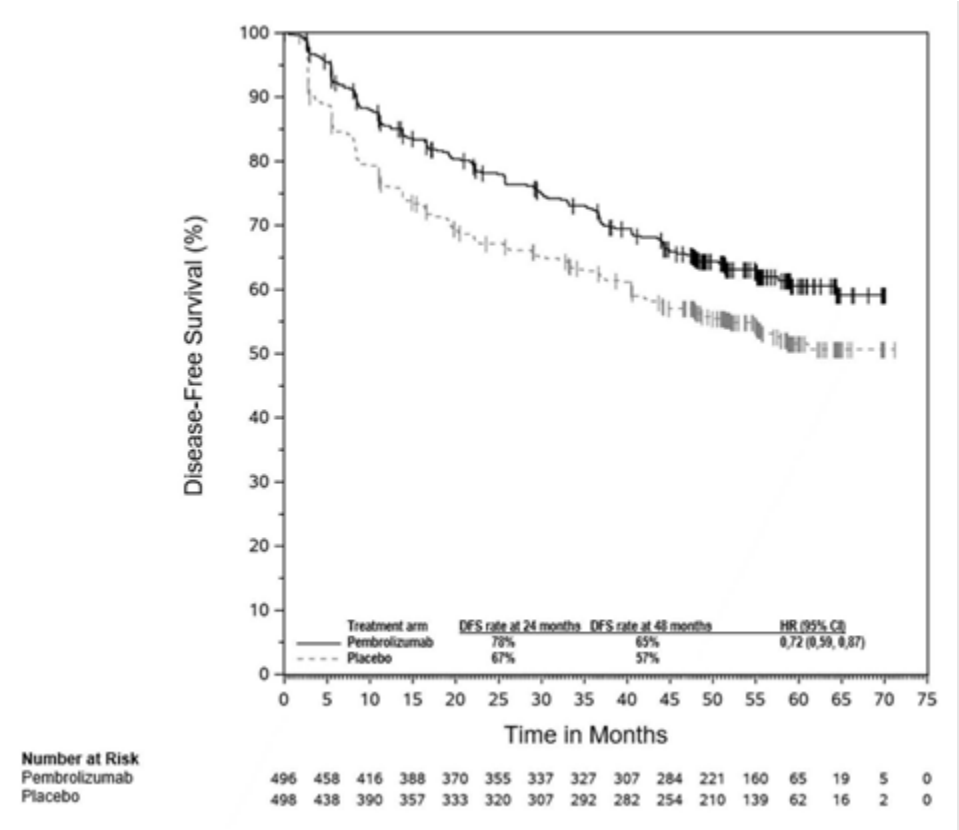
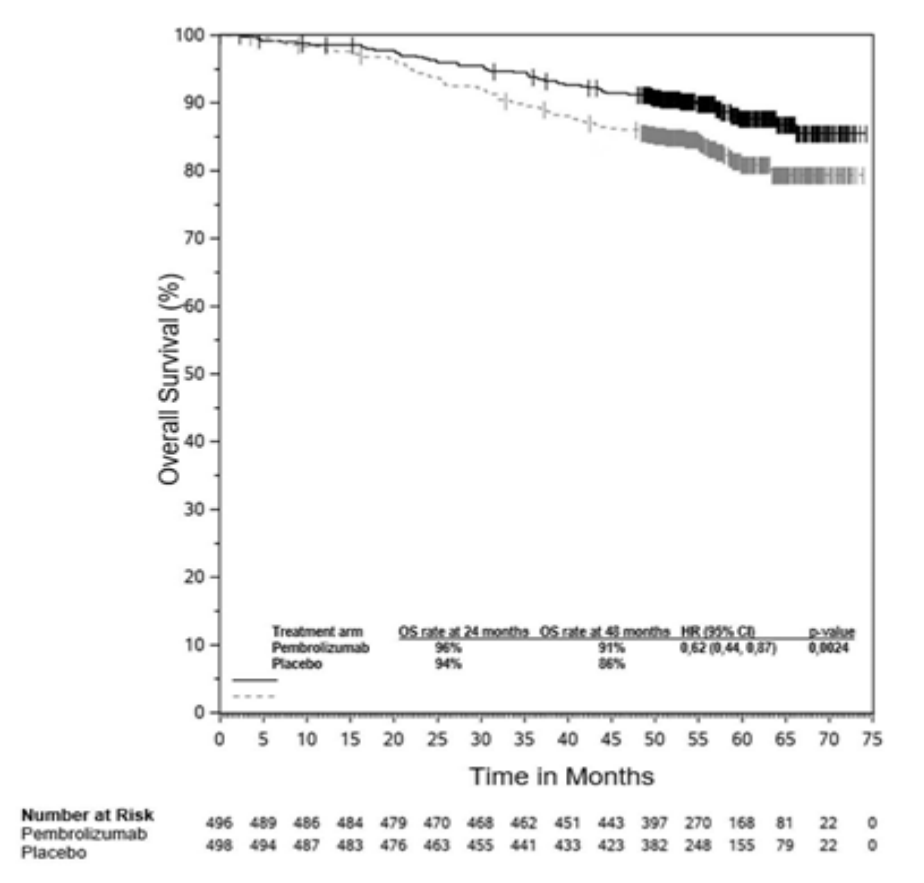


Figure 33: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-564 (intent to treat population)



At the time of an updated analysis (median follow-up time of 55,8 months), the DFS hazard ratio (95 % CI) was 0,76 (0,61, 0,95) in the subgroup of patients with M0-intermediate-high risk of recurrence, (0,61 (0,35, 1,08) in the subgroup of patients with M0-high risk of recurrence, and (0,40 (0,20, 0,81) in the subgroup of patients with M1 NED. The OS HR (95 % CI) was 0,59 (0,40, 0,87) in the subgroup of patients with M0-intermediate-high risk of recurrence, 0,78 (0,32, 1,93) in the subgroup of patients with M0-high risk of recurrence, and 0,51 (0,15, 1,75) in the subgroup of patients with M1 NED.

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 38 summarises the key efficacy measures and Figures 34 and 35 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 38: Efficacy Results in KEYNOTE-177

Endpoint	**Pembrolizumab 200 mg every 3 weeks n=153**	**Chemotherapy 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 34: Kaplan-Meier Curve for Progression-free Survival by Treatment Arm in KEYNOTE-177 (intent to treat population)

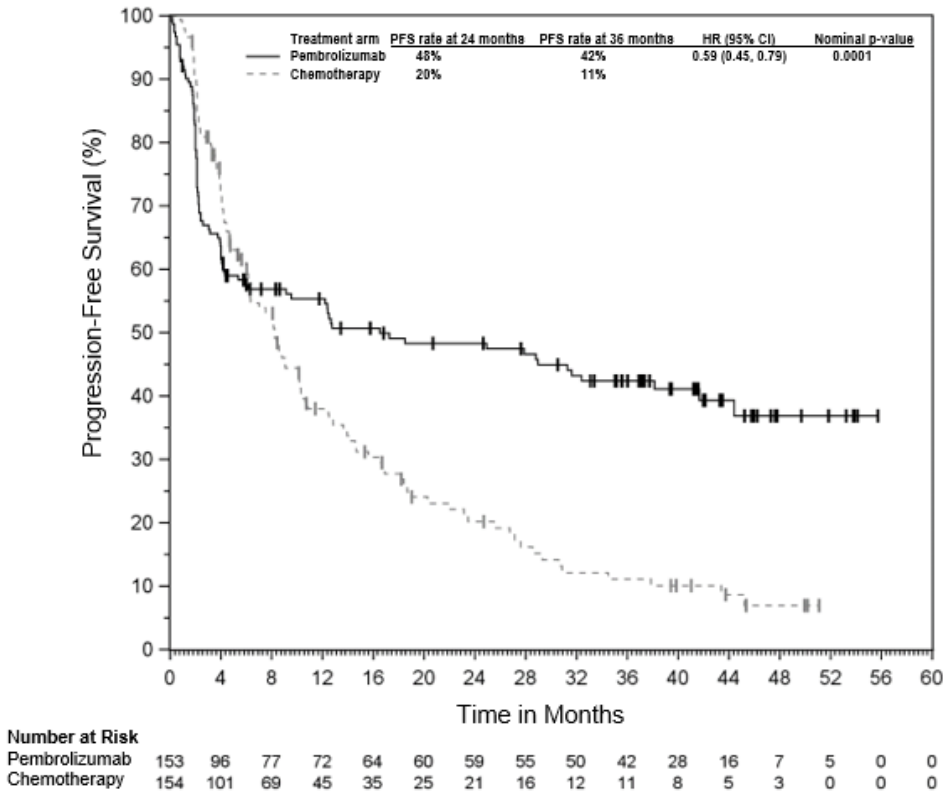
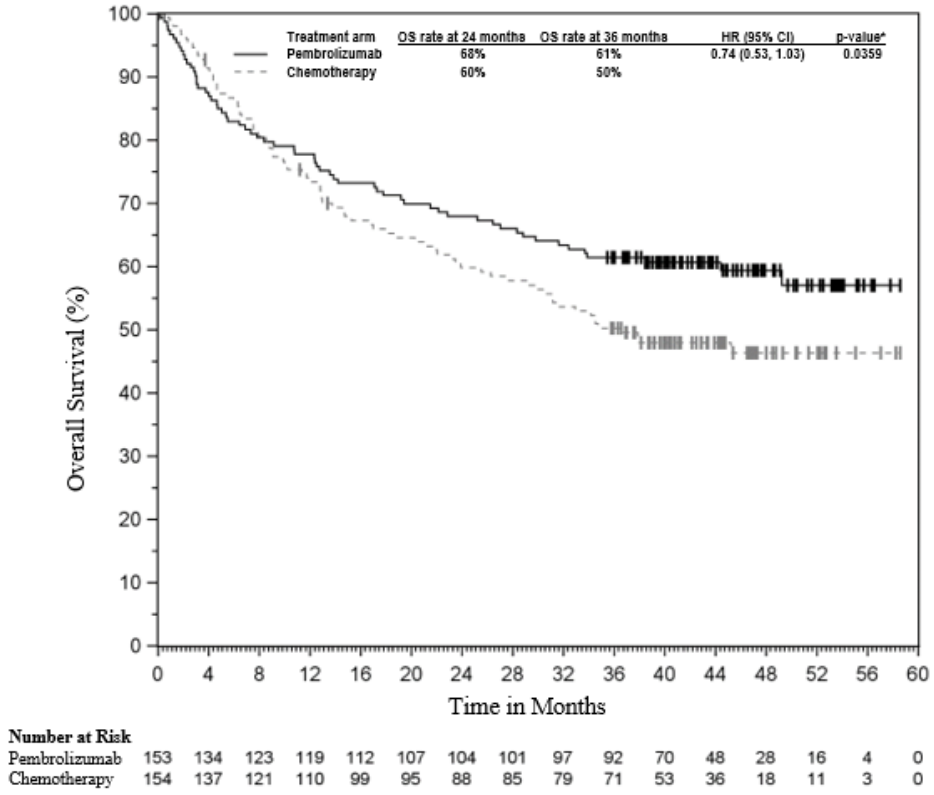


Figure 35: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-177 (intent to treat population)



*Not statistically significant after adjustment for multiplicity

Non-colorectal cancers

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

The efficacy of pembrolizumab was investigated in 497 patients with MSI-H or dMMR cancer enrolled in a two multicentre, non-randomised, open-label multi-cohort Phase II studies (KEYNOTE-164 and KEYNOTE-158). Regardless of histology, MSI or MMR tumour status was determined using polymerase chain reaction (PCR) or immunohistochemistry (IHC), respectively. Efficacy was evaluated in 124 patients enrolled in KEYNOTE-164 with advanced

MSI-H or dMMR colorectal cancer (CRC) that progressed following treatment with a fluoropyrimidine, oxaliplatin and irinotecan. Efficacy was also evaluated in 373 patients enrolled in KEYNOTE-158 with advanced MSI-H or dMMR non-colorectal cancer (non-CRC) who had disease progression following prior therapy. Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible for either trial.

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.Treatment with pembrolizumab could be reinitiated for subsequent disease progression and administered for up to 1 year. Assessment of tumour status was performed every 9 weeks through the first year, then every 12 weeks thereafter. The major efficacy outcome measures were ORR and duration of response according to RECIST 1.1.

Among the 497 patients with MSI-H cancer, the baseline characteristics were: median age of 60 years (36 % age 65 or older); 44 % male; 78 % White, 14 % Asian; and ECOG PS 0 (45 %) and 1 (55 %). Ninety-two percent of the patients had M1 disease and 4 % had M0 disease. Thirty-seven percent of patients had one and 61 % had two or more prior lines of therapy.

Table 39: Efficacy Results for Patients with MSI-H Cancer

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Endpoint	**n=497**
Objective Response Rate*	
ORR %, (95 % CI)	34 % (30, 38)
Complete response	11 %
Partial response	23 %
Stable disease	18 %
Disease control rate†	52 %
Response Duration*	
Median in months (range)	63,2 (1,9+, 63,9+)
% with duration ≥ 36-months	75 %‡
Time to Response	
Median in months (range)	2,2 (1,3, 49,3)
PFS*	
Median in months (95 % CI)	4,0 (2,4, 4,2)
6-month PFS rate	44 %
24-month PFS rate	30 %
OS	
Median in months (95 % CI)	23,8 (18,9, 29,5)
12-month OS rate	63 %
24-month OS rate	50 %

*Assessed by BICR using RECIST 1.1

†Based on best response of stable disease or better

‡Based on Kaplan-Meier estimates; includes 65 patients with response of 36 months or longer

+Denotes ongoing response

Table 40: Efficacy Results for CRC and Non-CRC

Endpoint	**CRC** **n=124**	**Non-CRC*** **N=373**
Objective Response Rate†		
ORR %, (95 % CI)	34 % (26, 43)	34 % (29, 39)
Response Duration†		
Median in months (range)	Not reached (4,4, 58,5+)	63,2 (1,9+, 63,9+)

*Includes tumour type (n): endometrial (94), gastric (51), small intestinal (27), ovarian (25), cholangiocarcinoma (22), pancreatic (22), brain (21), sarcoma (14), breast (13), neuroendocrine (11), cervical (11), prostate (8), adrenocortical (7), mesothelioma (7), thyroid (7), small cell lung (6), urothelial (6), salivary (5), renal cell (4), anal (3), HNSCC (1), nasopharyngeal (1), retroperitoneal (1), testicular (1), vaginal (1), vulvar (1), appendiceal adenocarcinoma, NOS (1), hepatocellular carcinoma (1), and carcinoma of unknown origin (1).

†Assessed by BICR using RECIST 1.1

+Denotes ongoing response

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 multicentre, 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 41 summarises the key efficacy measures for KEYNOTE-590. The Kaplan-Meier curves for OS and PFS are shown in Figures 36 and 37.

Table 41: 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	

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

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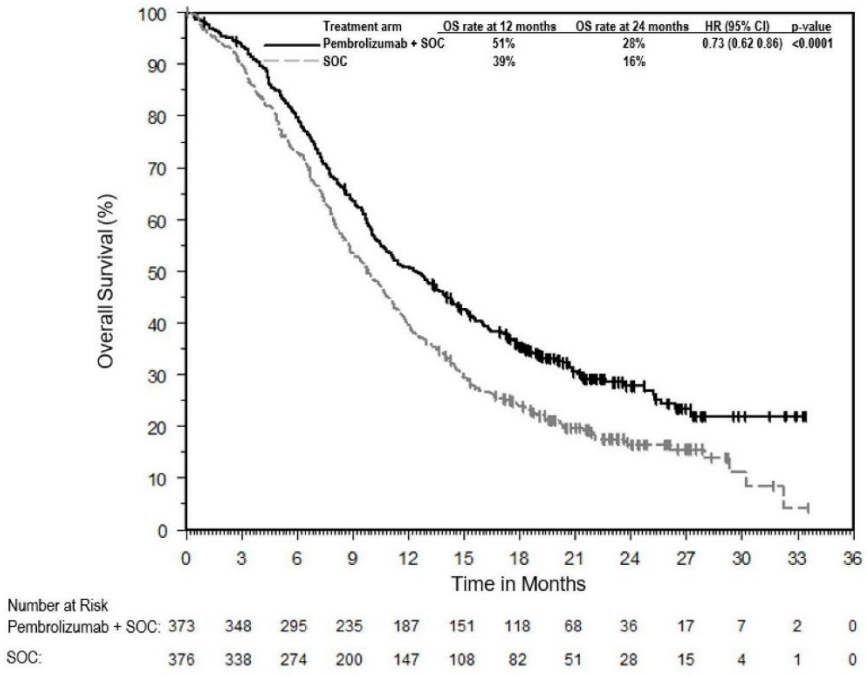
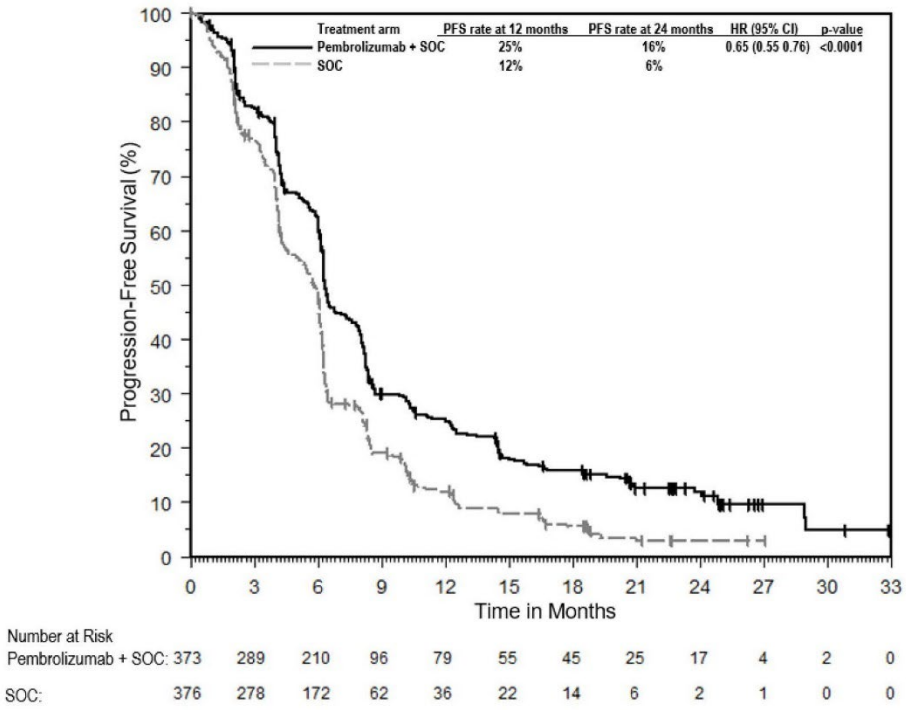


Figure 37: Kaplan-Meier curve for progression-free survival by treatment arm in KEYNOTE-590



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 42 summarises key efficacy measures from the pre-specified analyses. The Kaplan-Meier curve for EFS and OS are shown in Figures 38 and 39.

Table 42: 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

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

Figure 38: Kaplan-Meier curve for event-free survival by treatment arm in KEYNOTE-522 (intent to treat population)

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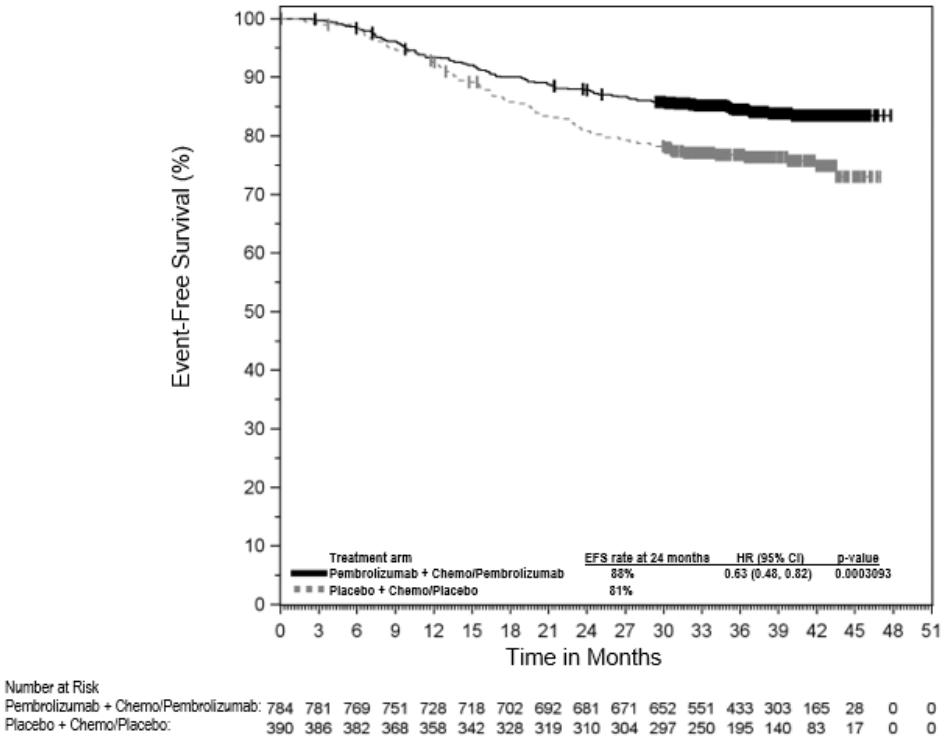
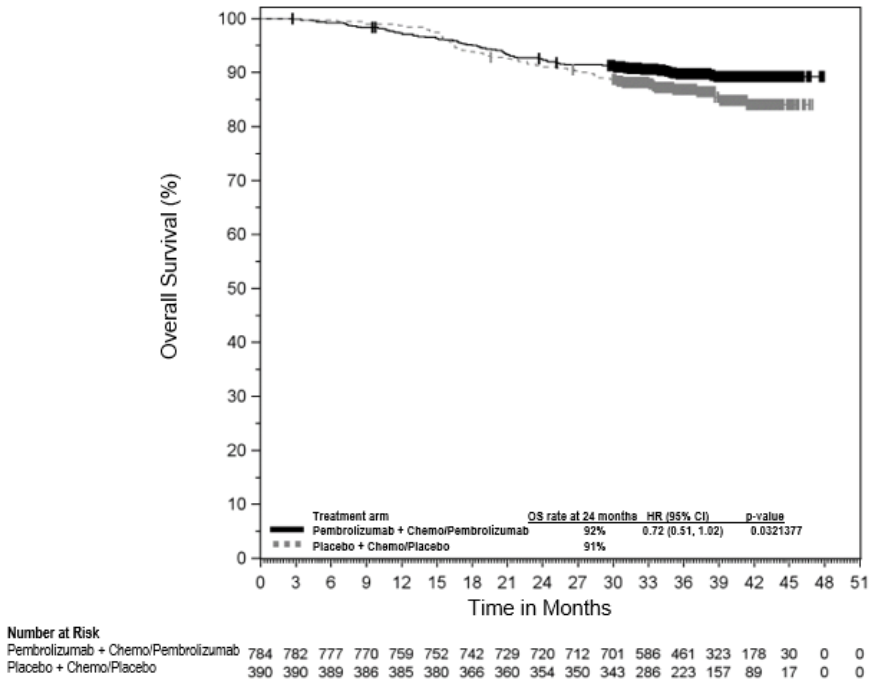


Figure 39: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-522 (intent to treat population)



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 43 summarises key efficacy measures and Figures 40 and 41 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 43: 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)

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

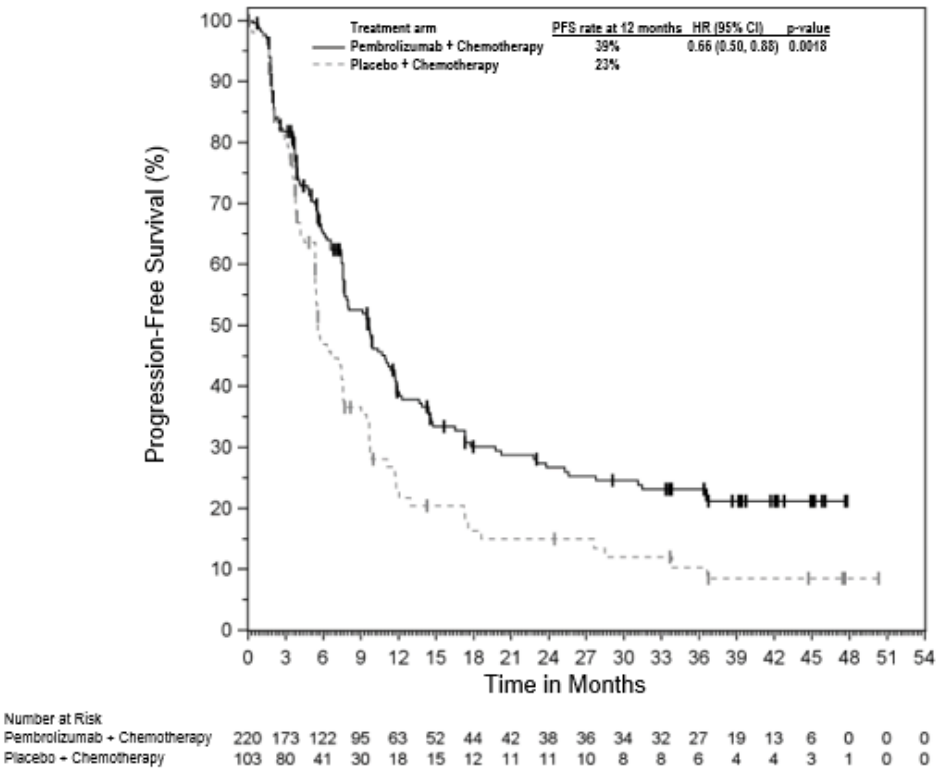
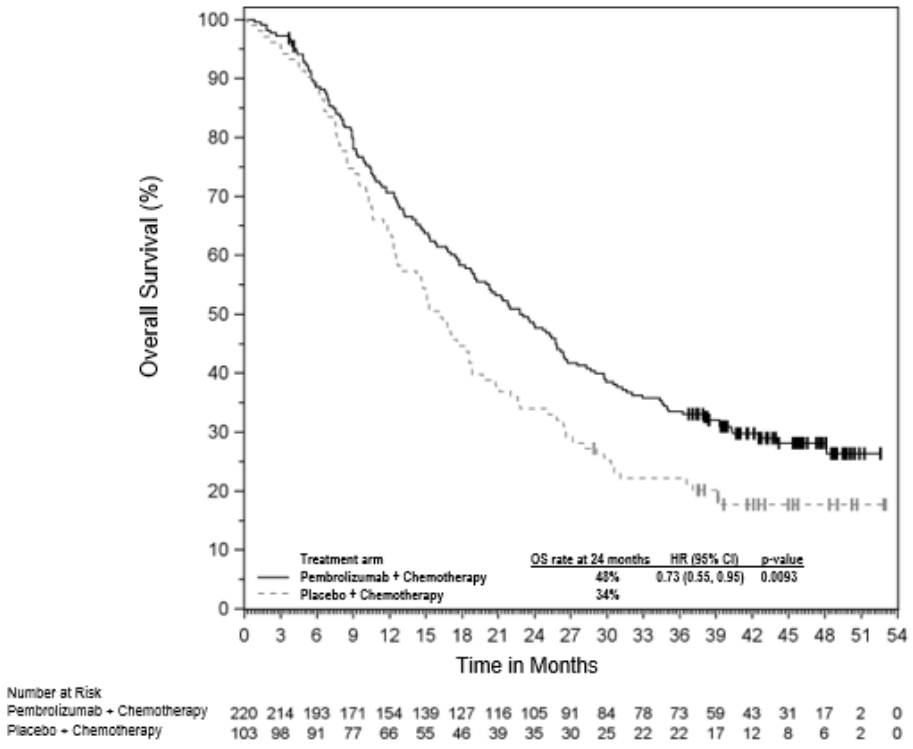


Figure 41: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-355 patients with PD-L1 expression (CPS ≥ 10)



Endometrial carcinoma

KEYNOTE-868/NRG-GY018: Controlled trial of combination therapy for treatment of patients with primary advanced or EC

The efficacy of pembrolizumab in combination with paclitaxel and carboplatin was investigated in KEYNOTE-868, a multicentre, randomised, double-blind, placebo-controlled trial in 810 patients with advanced or recurrent endometrial carcinoma including those with with dMMR and pMMR tumours. Patients had not received prior systemic therapy or had received prior chemotherapy in the adjuvant setting. Patients who had received prior adjuvant chemotherapy were eligible if their chemotherapy-free interval was at least 12 months.

Patients with endometrial sarcoma, including carcinosarcoma, or patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible. Randomisation was stratified according to MMR status, ECOG PS (0 or 1 vs. 2), and prior adjuvant chemotherapy. Patients were randomised (1:1) to one of the following treatment arms:

- Pembrolizumab 200 mg every 3 weeks, paclitaxel 175 mg/m^2 and carboplatin AUC 5 mg/mL/min for 6 cycles, followed by pembrolizumab 400 mg every 6 weeks for up to 14 cycles.
- Placebo every 3 weeks, paclitaxel 175 mg/m^2 and carboplatin AUC 5 mg/mL/min for 6 cycles, followed by placebo every 6 weeks for up to 14 cycles.

All study medications were administered as an intravenous infusion on Day 1 of each treatment cycle. Treatment continued until disease progression, unacceptable toxicity, or a maximum of 20 cycles (up to approximately 24 months). Patients with measurable disease who had RECIST-defined stable disease or partial response at the completion of cycle 6 were permitted to continue receiving paclitaxel and carboplatin with pembrolizumab or placebo for up to 10 cycles as determined by the investigator. Assessment of tumour status was performed every 9 weeks for the first 9 months and then every 12 weeks thereafter.

Among the 810 randomised patients, 222 (27 %) had dMMR tumour status and 588 (73 %) had pMMR tumour status.

The dMMR population characteristics were: median age of 66 years (range: 37 to 86), 55 % age 65 or older; 79 % White, 9 % Black, and 3 % Asian; 5 % Hispanic or Latino; 64 % ECOG PS of 0, 33 % ECOG PS of 1, and 3 % ECOG PS of 2; 61 % had recurrent disease and 39 % had primary or persistent disease; 5 % received prior adjuvant chemotherapy and 43 % received

prior radiotherapy. The histologic subtypes were endometrioid carcinoma (24 % grade 1, 43 % grade 2, 14 % grade 3), adenocarcinoma NOS (11 %), and other (8 % including dedifferentiated/undifferentiated, serous, and mixed epithelial).

The pMMR population characteristics were: median age of 66 years (range: 29 to 94), 54 % age 65 or older; 72 % White, 16 % Black, and 5 % Asian; 6 % Hispanic or Latino; 67 % ECOG PS of 0, 30 % ECOG PS of 1, and 3 % ECOG PS of 2; 56 % had recurrent disease and 44 % had primary or persistent disease; 26 % received prior adjuvant chemotherapy and 41 % received prior radiotherapy. The histologic subtypes were endometrioid carcinoma (17 % grade 1, 19 % grade 2, 16 % grade 3), serous (26 %), adenocarcinoma NOS (10 %), clear cell carcinoma (7 %), and other (5 % including mixed epithelial and dedifferentiated/undifferentiated).

The primary efficacy outcome measure was PFS as assessed by the investigator according to RECIST 1.1. Secondary efficacy outcome measures included OS, ORR, and DoR. The trial demonstrated statistically significant improvements in PFS for patients randomised to pembrolizumab in combination with chemotherapy compared to placebo in combination with chemotherapy in both the dMMR and pMMR populations. The median follow-up time was 13.6 months (range: 0,6 to 39,4 months) and 8,7 months (range: 0,1 to 37,2 months) in the dMMR and pMMR populations, respectively. OS endpoint was not formally assessed within multiplicity control. OS maturity was 12,2 % in the dMMR population and 16,8 % in the pMMR population.

Among the patients who had been randomised to receive placebo in combination with chemotherapy and discontinued from the study, 55 % from the dMMR population and 45 % from the pMMR population subsequently received post-study therapies that incorporated

anti-PD-1/PD-L1 therapy. Table 44 and Figures 42 and 43 summarise the efficacy results for KEYNOTE-868 by MMR status.

Table 44: Efficacy Results in KEYNOTE-868

Endpoint	dMMR Population		pMMR Population	
	Pembrolizumab with chemotherapy* n=110	Placebo with chemotherapy* n=112	Pembrolizumab with chemotherapy* n=294	Placebo with chemotherapy* n=294
PFS				
Number (%) of patients with event	29 (26 %)	60 (54 %)	95 (32 %)	138 (47 %)
Median in months (95 % CI)	NR (30,7, NR)	8,3 (6,5, 12,3)	13,1 (10,6, 19,5)	8,7 (8,4, 11,0)
Hazard ratio† (95 % CI)	0,34 (0,22, 0,53)		0,57 (0,44, 0,74)	
p-Value‡	< 0,0001		< 0,0001	
OS				
Number (%) of patients with event	10 (9 %)	17 (15 %)	45 (15 %)	54 (18 %)
Median in months (95 % CI)	NR (NR, NR)	NR (NR, NR)	28,0 (21,4, NR)	27,4 (19,5, NR)
Hazard ratio† (95 % CI)	0,55 (0,25, 1,19)		0,79 (0,53, 1,17)	
p-Value§	0,0617		0,1157	

*Chemotherapy (paclitaxel and carboplatin)

†Based on the stratified Cox proportional hazard model

‡Based on stratified log-rank test (compared to an alpha boundary of 0,00207 for dMMR and 0,00116 for pMMR)

§Nominal p-Value; no multiplicity adjustment

NR=not reached

Figure 42: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-868 (dMMR Population)

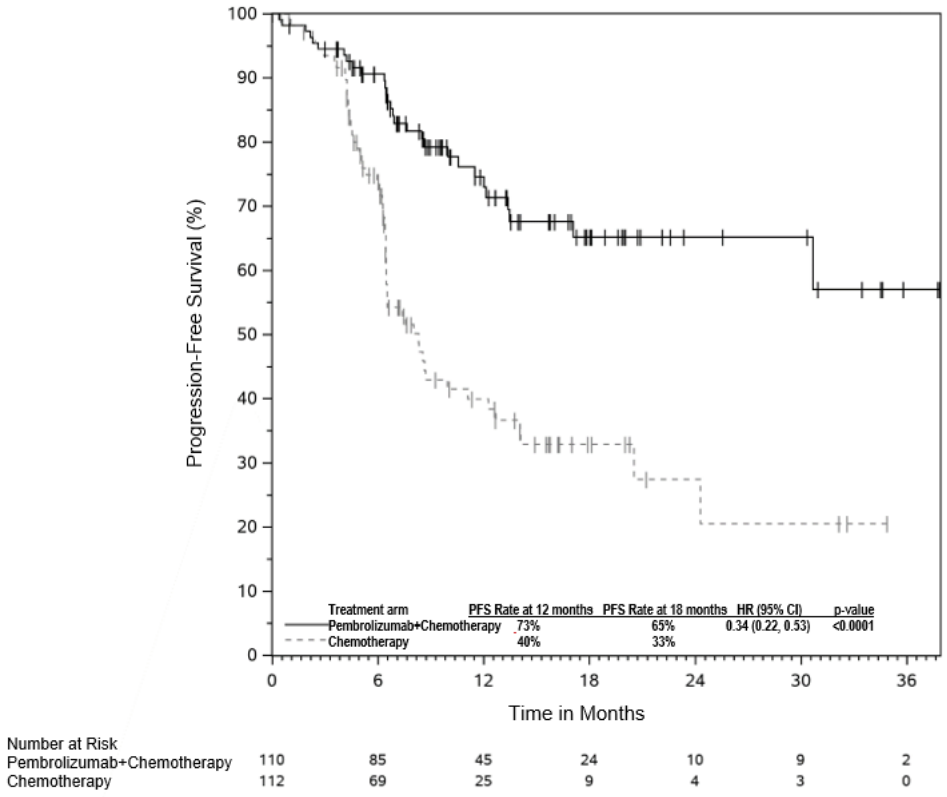
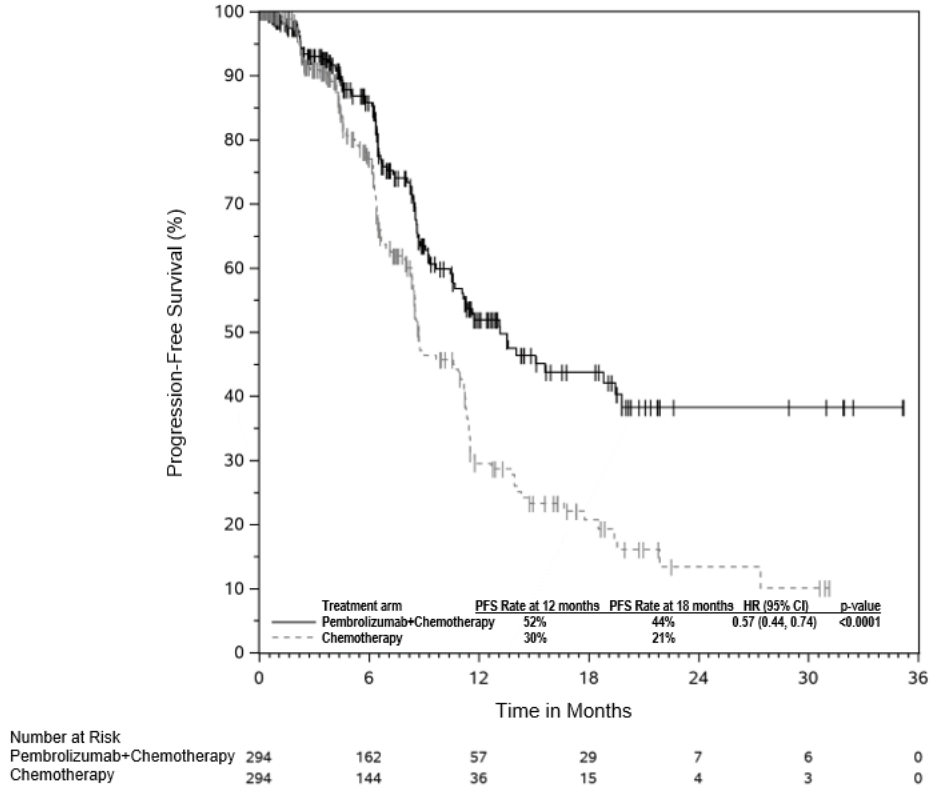


Figure 43: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-868 (pMMR Population)



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 45 and Kaplan-Meier curves for OS and PFS are shown in Figures 44 and 45, respectively.

Table 45: 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 44: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-775 (intent to treat population)

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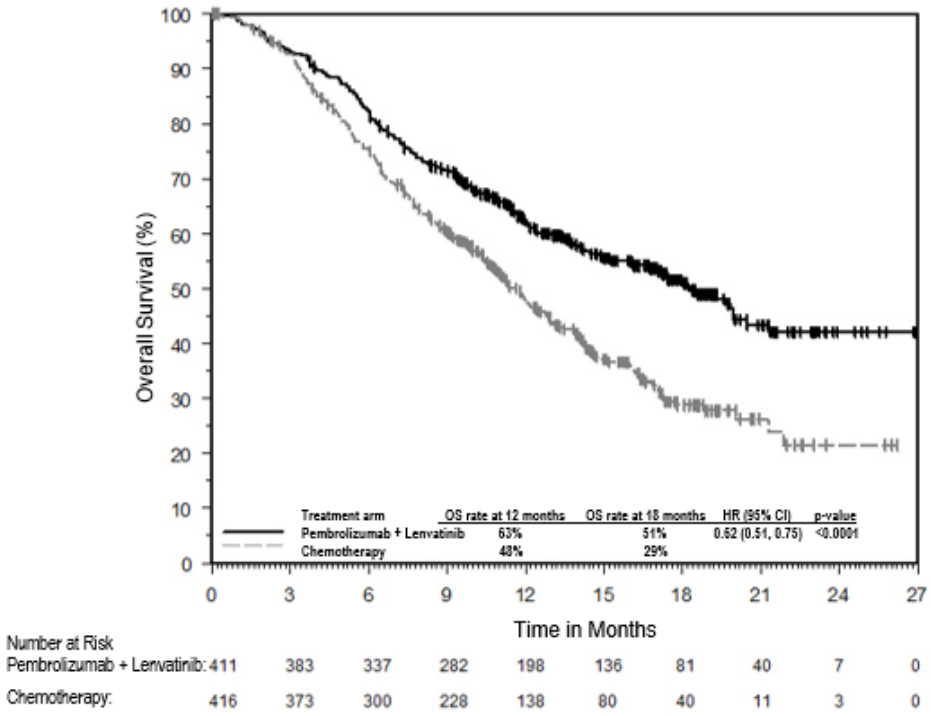
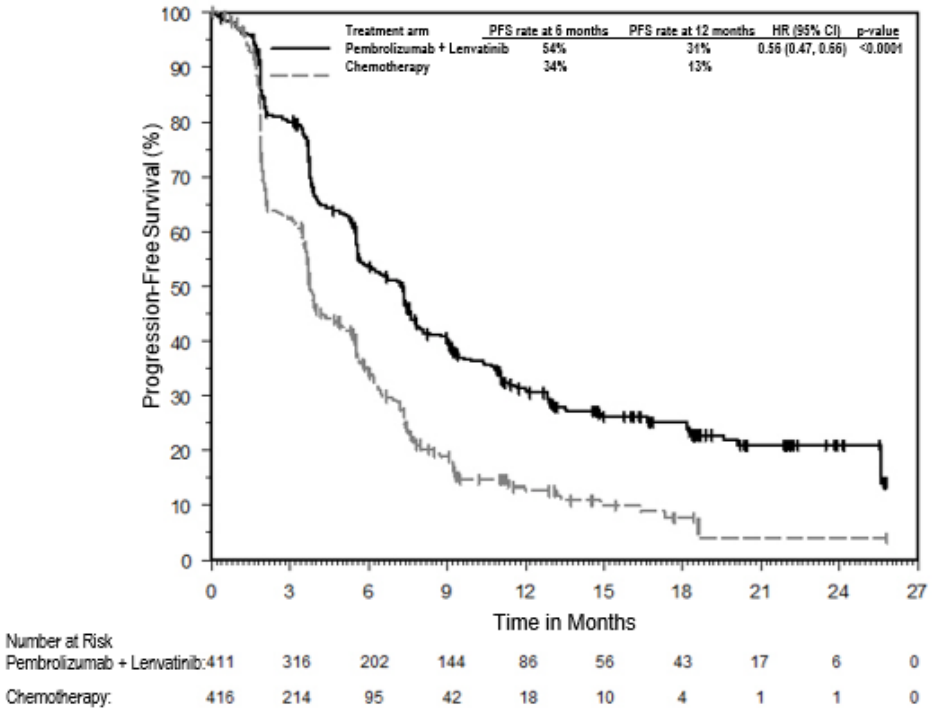


Figure 45: Kaplan-Meier curve for progression-free survival by treatment arm in KEYNOTE-775 (intent to treat population)



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.

KEYNOTE-966: Controlled trial of combination therapy in patients with locally advanced unresectable or metastatic biliary tract carcinoma

The efficacy of pembrolizumab in combination with gemcitabine and cisplatin was investigated in KEYNOTE-966, a multicentre, randomised, double-blind, placebo-controlled trial that enrolled

1 069 patients with locally advanced unresectable or metastatic BTC, who had not received prior systemic therapy in the advanced disease setting. 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 region (Asia vs. non-Asia), locally advanced vs. metastatic, and site of origin (gallbladder, intrahepatic or extrahepatic cholangiocarcinoma).

Patients were randomised (1:1) to one of the two treatment groups:

- Pembrolizumab 200 mg on Day 1 plus gemcitabine 1 000 mg/m^2 and cisplatin 25 mg/m^2 on Day 1 and Day 8 every 3 weeks.
- Placebo on Day 1 plus gemcitabine 1 000 mg/m^2 and cisplatin 25 mg/m^2 on Day 1 and Day 8 every 3 weeks

All study medications were administered via intravenous infusion. Treatment was continued until unacceptable toxicity or disease progression. For pembrolizumab, treatment was continued for a maximum of 35 cycles, or approximately 24 months. For cisplatin, treatment could be administered for a maximum of 8 cycles and for gemcitabine, treatment could be continued beyond 8 cycles.

Administration of pembrolizumab with chemotherapy was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered by the investigator to be deriving clinical benefit. Assessment of tumour status was performed at baseline and then every 6 weeks through 54 weeks, followed by every 12 weeks thereafter.

The study population characteristics were median age of 64 years (range: 23 to 85), 47 % age 65 or older; 52 % male; 49 % White, 46 % Asian; 46 % ECOG PS of 0 and 54 % ECOG PS of 1; 31 % of patients had a history of hepatitis B infection, and 3 % had a history of hepatitis C infection.

The primary efficacy outcome measure was OS and the secondary efficacy measures were PFS, ORR and DOR as assessed by BICR according to RECIST v1.1.

Table 46 and Figures 46 and 47 summarise the efficacy results for KEYNOTE-966.

Table 46: Efficacy Results in Patients with BTC in KEYNOTE-966

Endpoint	**Pembrolizumab 200 mg every 3 weeks with gemcitabine/cisplatin n=533**	**Placebo with gemcitabine/cisplatin n=536**
OS*		
Number (%) of patients with event	414 (78 %)	443 (83 %)
Median in months (95 % CI)	12,7 (11,5, 13,6)	10,9 (9,9, 11,6)
Hazard ratio† (95 % CI)	0,83 (0,72, 0,95)	
p-Value‡	0,0034	
PFS§		

Number (%) of patients with event	361 (68 %)	391 (73 %)
Median in months (95 % CI)	6,5 (5,7, 6,9)	5,6 (5,1, 6,6)
Hazard ratio† (95 % CI)	0,86 (0,75, 1,00)	
p-Value‡	0,0225	
Objective Response Rate§		
ORR¶ (95 % CI)	28,7% (24,9, 32,8)	28,5% (24,8, 32,6)
Number (%) of complete responses	11 (2,1 %)	7 (1,3 %)
Number (%) of partial responses	142 (26,6 %)	146 (27,2 %)
p-Value#	0,4735	
Duration of Response*, Þ	n=156	n=152
Median in months (range)	8,3 (1,2+ - 33,0+)	6,8 (1,1+ - 30,0+)
% with duration ≥ 6 months	65 %	55 %
% with duration ≥ 12 months	38 %	27 %
% with duration ≥ 24 months	18 %	6 %

*Results at the pre-specified final OS analysis

†Based on the stratified Cox proportional hazard model

‡One-sided p-Value based on a stratified log-rank test

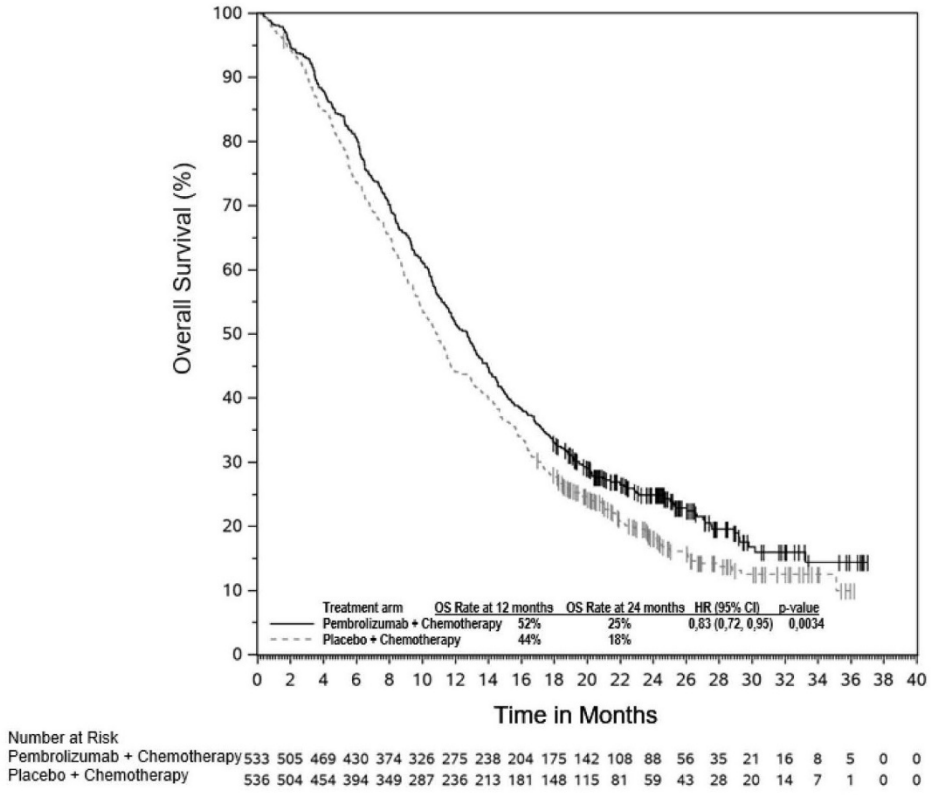
§Results at pre-specified interim analysis

¶Confirmed complete response or partial response

[#]One-sided p-Value based on the stratified Miettinen and Nurminen analysis

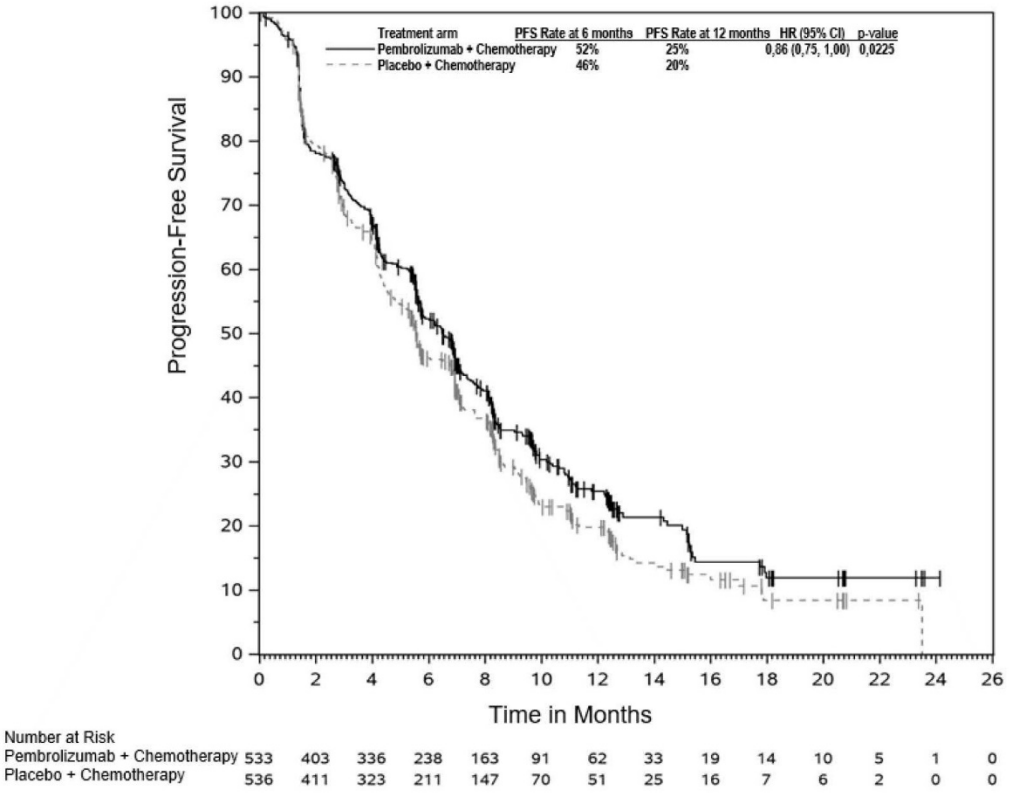
[Þ]Based on Kaplan-Meier estimate

Figure 46: Kaplan-Meier Curve for Overall Survival in KEYNOTE-966*



*Based on the pre-specified final OS analysis

Figure 47: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-966*



*Based on the pre-specified interim analysis data cut-off

From baseline to Week 18, pre-specified exploratory patient-reported outcomes (PROs) using the EORTC QLQ-C30 (global health status/quality of life, physical functioning, role functioning), EORTC QLQ-BIL21 (pain and jaundice scores), and EQ-5D-5L visual analog scale (VAS) for patients receiving pembrolizumab in combination with gemcitabine/cisplatin were similar to those treated with placebo and gemcitabine/cisplatin. From baseline to Week 18, health-related quality of life (HRQoL) was maintained when pembrolizumab was added to gemcitabine/cisplatin.

Cervical cancer

KEYNOTE-A18: Controlled trial of combination therapy with chemoradiotherapy in patients with high-risk, locally advanced cervical cancer

The efficacy of pembrolizumab in combination with cisplatin and external beam radiation therapy (EBRT) followed by brachytherapy (BT) was investigated in KEYNOTE-A18, a multicentre, randomised, double-blind, placebo-controlled trial that enrolled 1 060 patients with high-risk, locally advanced cervical cancer who had not previously received any definitive surgery, radiation, or systemic therapy for cervical cancer. Eligible patients included high-risk FIGO 2014 Stage IB2-IIB (tumour lesions > 4 cm or clinically visible lesions that have spread beyond the uterus but have not extended onto the pelvic wall or to the lower third of vagina) with node-positive disease , or Stage III-IVA (tumour involvement of the lower vagina with or without extension onto pelvic sidewall or hydronephrosis/non-functioning kidney or has spread to adjacent pelvic organs) with either node-positive or node-negative disease. 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 planned type of EBRT (Intensity-modulated radiation therapy [IMRT] or volumetric modulated arc therapy [VMAT] vs. non-IMRT and non-VMAT), stage at screening of cervical cancer (FIGO 2014 Stage IB2-IIB vs. Stage III-IVA), and planned total radiotherapy dose ([EBRT + BT dose] of < 70 Gy vs. ≥ 70 Gy as per equivalent dose [EQD2]). Patients were randomised (1:1) to one of two treatment arms:

- Pembrolizumab 200 mg IV every 3 weeks (5 cycles) concurrent with cisplatin 40 mg/m^2 IV weekly (5 cycles, an optional sixth infusion could be administered per local practice)

and radiotherapy (EBRT followed by BT), followed by Pembrolizumab 400 mg IV every 6 weeks (15 cycles)

- Placebo IV every 3 weeks (5 cycles) concurrent with cisplatin 40 mg/m^2 IV weekly (5 cycles, an optional sixth infusion could be administered per local practice), and radiotherapy (EBRT followed by BT), followed by placebo IV every 6 weeks (15 cycles)

Treatment continued until RECIST v1.1-defined progression of disease as determined by investigator or unacceptable toxicity. Treatment 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 every 12 weeks for the first two years, every 24 weeks in year 3, and then annually. The primary efficacy outcomes were PFS as assessed by investigator according to RECIST v1.1, or histopathologic confirmation, and OS.

Among the 1 060 patients enrolled in KEYNOTE-A18, the baseline characteristics were: median age of 50 years (range: 22 to 87); 13 % age 65 or older, 49 % White, 2 % Black, 29 % Asian; 32 % Hispanic or Latino; 73 % ECOG PS 0 and 27 % ECOG PS 1; 94 % with CPS ≥ 1; 44 % were FIGO 2014 Stage IB2-IIB, 56 % were FIGO 2014 Stage III-IVA, 83 % had positive pelvic and/or positive para-aortic lymph node(s), 17 % had neither positive pelvic nor para-aortic lymph node, 89 % IMRT or VMAT EBRT, 91 % ≥ 70 Gy (EQD2). Eighty-three percent had squamous cell carcinoma and 17 % had non-squamous histology.

The trial demonstrated statistically significant improvements in PFS and OS for patients randomised to pembrolizumab with CRT compared to placebo with CRT. Results reported from

the pre-specified interim analysis for PFS with a median follow-up time of 17 months (range: 0,9 to 31 months) are summarised in Table 47. Results reported from the pre-specified interim analysis for OS with a median follow-up of 28 months (range: 0,9 to 43 months) are summarised in Table 47 and Figures 48 and 49.

Table 47: Efficacy Results for Patients in KEYNOTE-A18

Endpoint	**Pembrolizumab 200 mg every 3 weeks and 400 mg every 6 weeks with CRT n=529**	**Placebo with CRT n=531**
OS*		
Number of patients with event (%)	75 (14 %)	109 (21 %)
Median in months (95 % CI)	NR (NR, NR)	NR (NR, NR)
24-month OS rate (95 % CI)	87 % (84, 90)	82 % (78, 85)
36-month OS rate (95 % CI)	83 % (78, 86)	75 % (70, 79)
Hazard ratio† (95 % CI)	0,67 (0,50, 0,90)	
p-Value‡	0,0040	
PFS by Investigator§		
Number of patients with event (%)	115 (22 %)	154 (29 %)
Median in months (95 % CI)	NR (NR, NR)	NR (NR, NR)
12-month PFS rate (95 % CI)	78 % (74, 82)	72 % (68, 76)

24-month PFS rate (95 % CI)	68 % (62, 73)	57 % (51, 63)
Hazard ratio† (95 % CI)	0,70 (0,55, 0,89)	
p-Value‡	0,0020	

*Based on a pre-specified interim OS analysis

†Based on the stratified Cox proportional hazard model

‡One-sided p-Value based on a stratified log-rank test

§Based on a pre-specified interim PFS analysis

CRT = Chemoradiotherapy

NR = Not reached

At the pre-specified interim OS analysis, the updated PFS hazard ratio in patients treated with pembrolizumab with CRT versus patients treated with placebo with CRT was 0,68 (95 % CI: 0,56, 0,84; nominal p=0,0002). The median PFS was not reached for either treatment arm. The updated PFS rates at 12 and 24 months were 80 % and 71 % in patients receiving pembrolizumab with CRT versus 73 % and 59 % in patients receiving placebo with CRT.

Figure 48: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-A18

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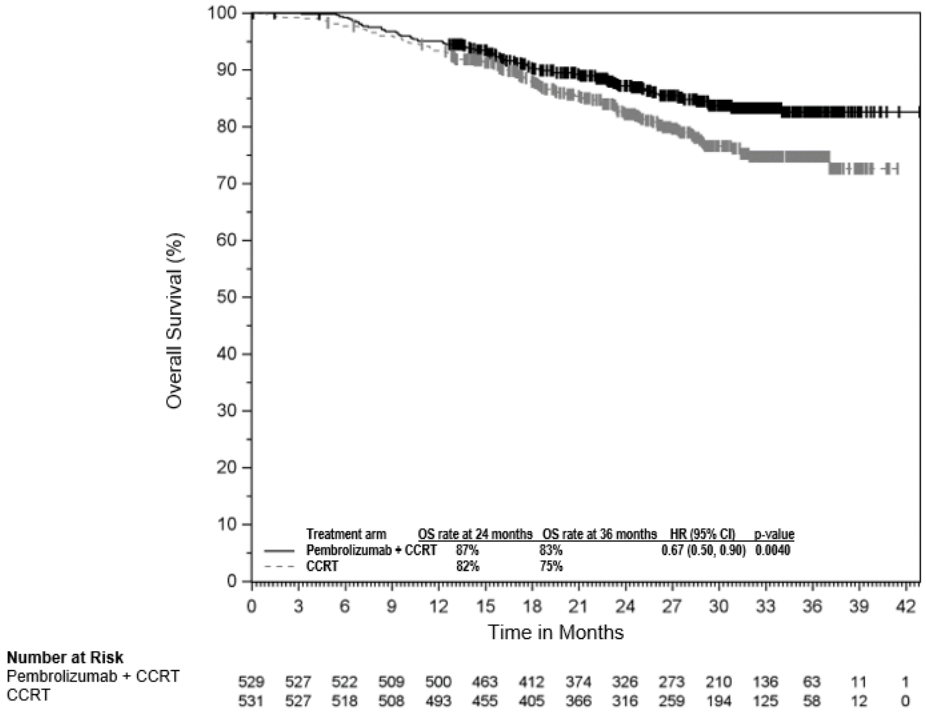
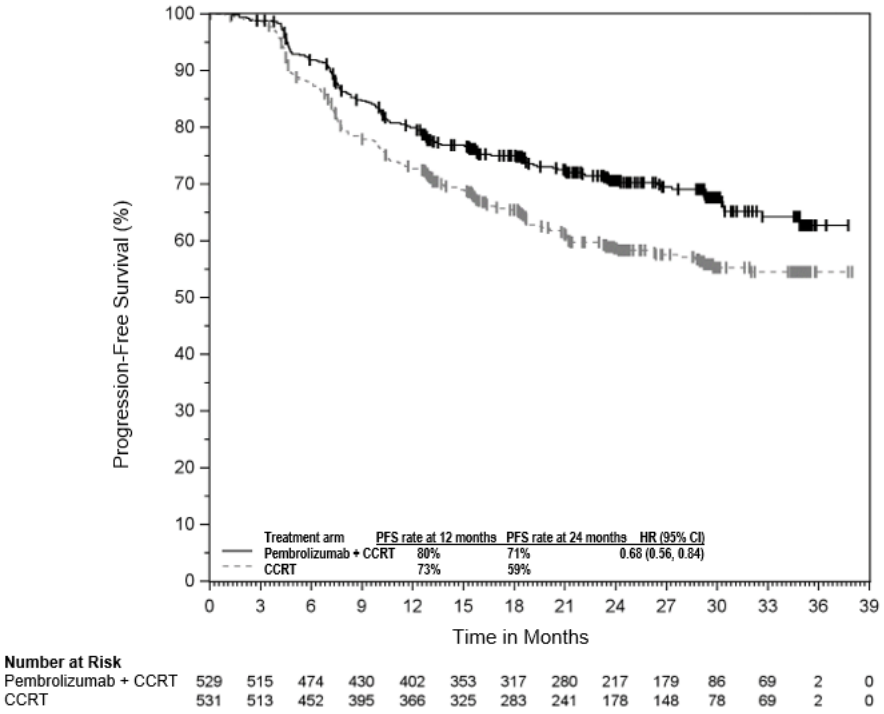


Figure 49: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-A18



***Based on pre-specified interim OS analysis**

Patient-reported outcomes (PROs) were assessed using EORTC QLQ-C30. Analyses of EORTC QLQ C30 global health status/QoL and physical functioning showed no clinically meaningful differences between participants treated with KEYTRUDA pembrolizumab plus CRT compared with placebo plus CRT. Similar percentages of patients treated with pembrolizumab plus CRT or placebo plus CRT experienced improved or stable scores on the EORTC QLQ-C30 global health status/QoL (81 % vs. 82 %) and physical functioning scales (81 % vs. 83 %).

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. 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 DoR, according to RECIST v1.1, as assessed by investigator.

The study population characteristics were: median age of 51 years (range: 22 to 82), 16 % age 65 or older; 58 % White, 18 % Asian and 1 % Black; 37 % Hispanic or Latino; 56 % and 43 % ECOG performance status of 0 or 1, 89 % with PD-L1 CPS ≥1; respectively; 63 % received bevacizumab as study treatment; 23 % 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 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).

Efficacy results are summarised in Table 48.

Table 48: Efficacy results in KEYNOTE-826 for patients with PD-L1 expression (CPS ≥ 1)

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Endpoint	Pembrolizumab 200 mg every 3 weeks plus Chemotherapy* with or without bevacizumab n=308	Placebo plus Chemotherapy* with or without bevacizumab n=309
OS		
Number (%) of patients with event	138 (45 %)	424,4 (56 %)
Median in months (95 % CI)	24,4 (19,2, NR)	16,5 (14,5, 19,4)
Hazard ratio† (95 % CI)	0,67 (0,54, 0,84)	
p-Value‡	0,0003	
PFS		
Number of patients with event (%)	180 (58 %)	226 (73 %)
Median in months (95 % CI)	10,4 (,1, 12,1)	8,2 (6,4, 8,4)
Hazard ratio† (95 % CI)	0,65 (0,53, 0,79)	
p-Value§	< 0,0001	
Objective response rate		
ORR¶ % (95 % CI)	66 % (60, 71)	51 % (45, 57)
Complete response	21 %	13 %
Partial response	45 %	38 %
Duration of response		

Median in months (range)	18,0 (1,3+, 24,2+)	10,4 (1,5+, 22,0+)
% of patients with duration ≥ 12 months[#]	55	46
% of patients with duration ≥18 months[#]	50	32

[*]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 0,00491)

[§]Based on stratified log-rank test (compared to an alpha boundary of 0,00128)

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

[#]Based on Kaplan-Meier estimation

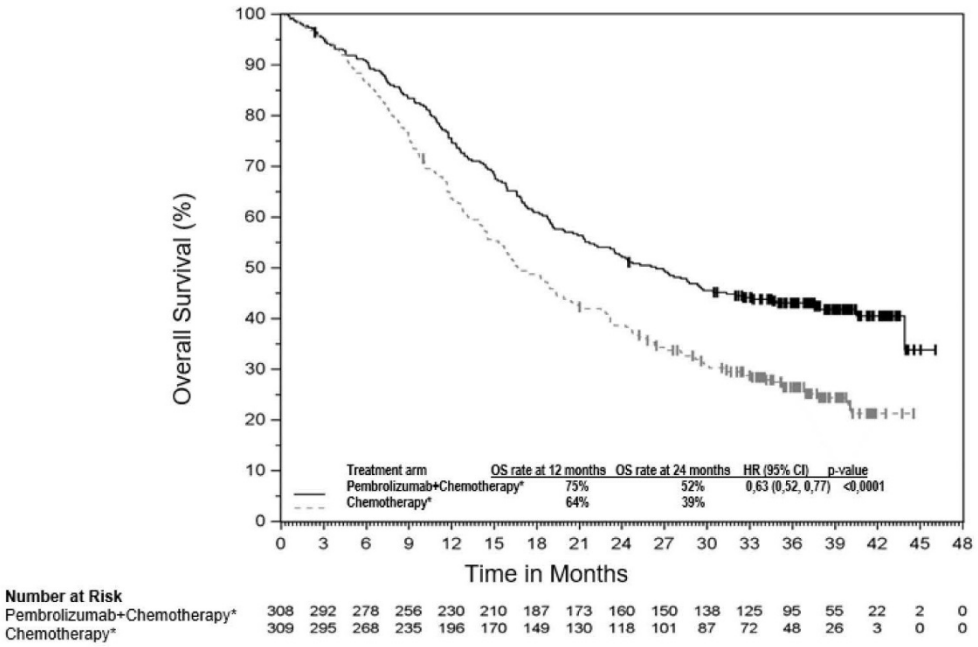
NR = not reached

The final OS analysis was performed at a median duration of follow-up of 20,6 months after 406 patient events (178 for pembrolizumab and 228 for placebo, both in combination with chemotherapy with or without bevacizumab). The median OS was 26,4 months (95 % CI: 21,3, 32,5) for pembrolizumab and 16,8 months (95 % CI: 14,6, 19,4) for placebo, both in combination with chemotherapy with or without bevacizumab. The OS HR was 0,63 (95 % CI: 0,52, 0.77; p < 0,0001). The final PFS analysis was performed based on 443 patient events (195 for pembrolizumab and 248 for placebo, both in combination with chemotherapy with or without bevacizumab). The median PFS was 10,4 months (95 % CI: 9,1, 12,2) for pembrolizumab and 8,2 months (95 % CI: 6,4, 8,4) for placebo, both in combination with chemotherapy with or

without bevacizumab. The PFS HR was 0,61 (95 % CI: 0,50, 0,74; p < 0,0001). See Figures 50 and 51.

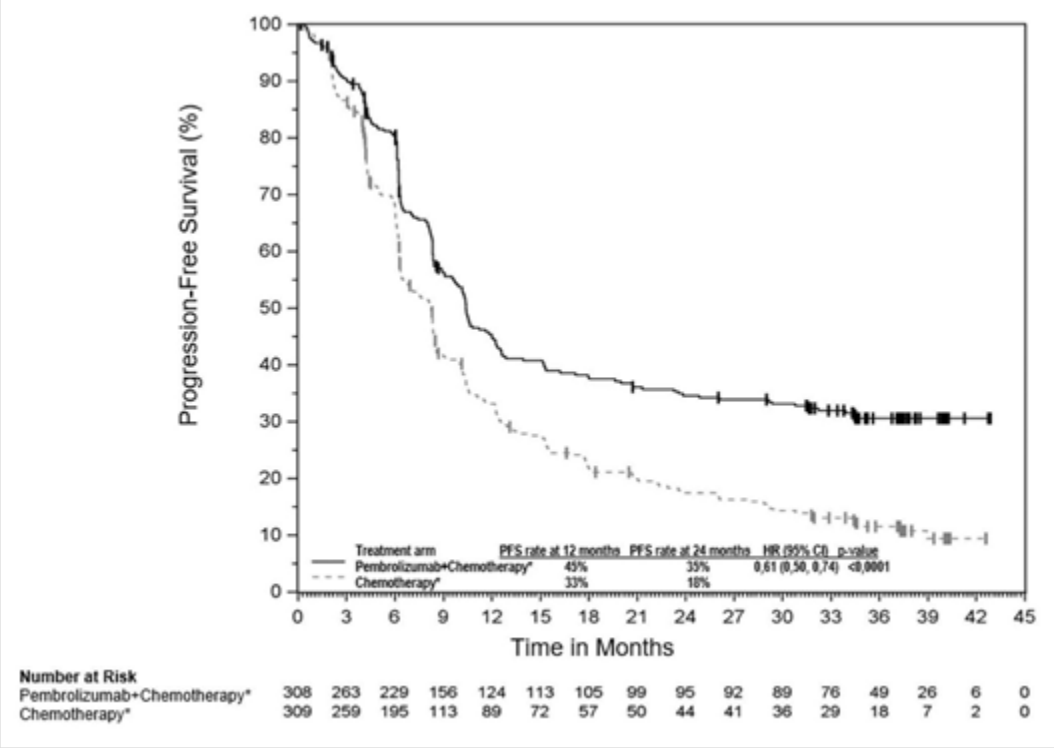
The ORR at the final analysis was 66% for pembrolizumab and 51 % for placebo, both in combination with chemotherapy with or without bevacizumab. The median duration of response was 18,0 months (range 1,3+, 40,9+) for pembrolizumab and 10,4 months (1,5+, 40,7+) for placebo, both in combination with chemotherapy with or without bevacizumab. The percentage of patients with ongoing responses based on Kaplan-Meier estimation was 47 % at 24 months or longer, in patients who received pembrolizumab, vs. 28 % in patients who received placebo, both in combination with chemotherapy with or without bevacizumab.

Figure 50: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-826 (Intent to Treat Population)



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

Figure 51: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-826 (Intent to Treat Population)



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

KEYNOTE-158: Open-label study in recurrent or metastatic cervical cancer patients previously treated with chemotherapy

The efficacy of pembrolizumab was investigated in 98 patients with recurrent or metastatic cervical cancer enrolled in a single cohort in KEYNOTE-158, a multicentre, non-randomised, open-label, multi-cohort trial. The trial excluded patients with autoimmune disease or a medical condition that required immunosuppression.

Patients received pembrolizumab at a dose of 200 mg every 3 weeks until unacceptable toxicity or documented 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 could be treated for up to 24 months. Assessment of tumour status was performed every 9 weeks for the first 12 months, and every 12 weeks thereafter. The major efficacy outcome measures were ORR according to RECIST 1.1, as assessed by blinded independent central review, and duration of response.

Among the 98 patients with cervical cancer, 77 (79 %) had tumours that expressed PD-L1 with a CPS ≥ 1 and received at least one line of chemotherapy for recurrent or metastatic disease. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx™ Kit. The baseline characteristics of these 77 patients were: median age 45 years (range: 27 to 75 years); 81 % White, 14 % Asian, 3 % Black; ECOG PS 0 (32 %) and 1 (68 %); 92 % had squamous cell carcinoma, 6 % adenocarcinoma, and 1 % adenosquamous histology; 95 % had M1 disease and 5 % had recurrent disease; 35 % had one and 65 % had two or more prior lines of therapy in the recurrent or metastatic setting.

No responses were observed in patients whose tumours did not have PD-L1 expression (CPS < 1) (n=15).

The median follow-up time in patients with PD-L1 (CPS ≥ 1) and who received at least one line of chemotherapy for recurrent or metastatic disease was 11,7 months. Efficacy results are summarised in Table 49.

Table 49: Efficacy Results for Patients with Cervical Cancer with PD-L1 Expression CPS ≥ 1

Endpoint	**n=77**
Best Overall Response*	
ORR %, (95 % CI)	14,3 % (7,4, 24,1)
Complete response	2,6 %
Partial response	11,7 %
Stable disease	16,9 %
Disease control rate†	31,2 %
Response Duration*	
Median in months (range)	Not reached (4,1, 18,6+)
% with duration ≥ 6 months	91 %‡
% with duration ≥ 12 months	80 %§
Time to Response	
Median in months (range)	2,2 (1,6, 4,1)

PFS*	
Median in months (95 % CI)	2,1 (2,1, 2,3)
6-month PFS rate	27 %
12-month PFS rate	20 %
OS	
6-month OS rate	82 %
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 10 patients with response of 6 months or longer

§Based on Kaplan-Meier estimates; includes 7 patients with response of 12 months or longer

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 and moderate hepatic impairment (total bilirubin (TB) 1,0 to 1,5 x ULN or AST > ULN and TB > 1,5 to 3 x ULN and any AST, respectively, 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 or moderate hepatic impairment and normal hepatic function. KEYTRUDA has not been studied in patients with or severe (TB > 3 x ULN and any AST) hepatic impairment (see section 4.2).

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

Applicant: MSD (Pty) Ltd
APPROVED PROFESSIONAL INFORMATION
Keytruda Solution for Infusion

50/30.1/0957

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29 September 2017

10 DATE OF REVISION OF THE TEXT

11 August 2025