1. NAME OF THE MEDICINAL PRODUCT

KEYTRUDA 25 mg/mL concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

Excipient with known effect

This medicinal product contains 0.2 mg of polysorbate 80 in each mL of concentrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Melanoma

KEYTRUDA as monotherapy is indicated for the treatment of adults and adolescents aged 12 years and older with advanced (unresectable or metastatic) melanoma.

KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults and adolescents aged 12 years and older with Stage IIB, IIC or III melanoma and who have undergone complete resection (see section 5.1).

Non-small cell lung carcinoma (NSCLC)

KEYTRUDA, in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment, is indicated for the treatment of resectable non-small cell lung carcinoma at high risk of recurrence in adults (for selection criteria, see section 5.1).

KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults with non-small cell lung carcinoma who are at high risk of recurrence following complete resection and platinum-based chemotherapy (for selection criteria, see section 5.1).

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

KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of metastatic non-squamous non-small cell lung carcinoma in adults whose tumours have no EGFR or ALK positive mutations.

KEYTRUDA, in combination with carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the first-line treatment of metastatic squamous non-small cell lung carcinoma in adults.

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

Malignant pleural mesothelioma (MPM)

KEYTRUDA, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of adults with unresectable non-epithelioid malignant pleural mesothelioma.

Classical Hodgkin lymphoma (cHL)

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

Urothelial carcinoma

KEYTRUDA, in combination with enfortumab vedotin, as neoadjuvant treatment and then continued after radical cystectomy as adjuvant treatment, is indicated for the treatment of adults with resectable muscle invasive bladder cancer (MIBC).

KEYTRUDA, in combination with enfortumab vedotin, is indicated for the first-line treatment of unresectable or metastatic urothelial carcinoma in adults.

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

KEYTRUDA as monotherapy is indicated for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with a combined positive score (CPS) ≥ 10 (see section 5.1).

Head and neck squamous cell carcinoma (HNSCC)

KEYTRUDA as monotherapy is indicated for the treatment of resectable locally advanced head and neck squamous cell carcinoma as neoadjuvant treatment, continued as adjuvant treatment in combination with radiation therapy with or without concomitant cisplatin and then as monotherapy in adults whose tumours express PD-L1 with a CPS ≥ 1.

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

KEYTRUDA as monotherapy is indicated for the treatment of recurrent or metastatic head and neck squamous cell carcinoma in adults whose tumours express PD-L1 with a ≥ 50% TPS and progressing on or after platinum-containing chemotherapy (see section 5.1).

Renal cell carcinoma (RCC)

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

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

KEYTRUDA as monotherapy is indicated for the adjuvant treatment of adults with renal cell carcinoma at increased risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions (for selection criteria, see section 5.1).

Microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) cancers

Colorectal cancer (CRC)
KEYTRUDA as monotherapy is indicated for adults with MSI-H or dMMR colorectal cancer in the following settings:

- first-line treatment of metastatic colorectal cancer;
- treatment of unresectable or metastatic colorectal cancer after previous fluoropyrimidine-based combination therapy.

Non-colorectal cancers
KEYTRUDA as monotherapy is indicated for the treatment of the following MSI-H or dMMR tumours in adults with:

- advanced or recurrent endometrial carcinoma, who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation;
- unresectable or metastatic gastric, small intestine, or biliary cancer, who have disease progression on or following at least one prior therapy.

Oesophageal carcinoma

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

Triple-negative breast cancer (TNBC)

KEYTRUDA, in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery, is indicated for the treatment of adults with locally advanced, or early-stage triple-negative breast cancer at high risk of recurrence (see section 5.1).

KEYTRUDA, in combination with chemotherapy, is indicated for the treatment of locally recurrent unresectable or metastatic triple-negative breast cancer in adults whose tumours express PD-L1 with a CPS ≥ 10 and who have not received prior chemotherapy for metastatic disease (see section 5.1).

Endometrial carcinoma (EC)

KEYTRUDA, in combination with carboplatin and paclitaxel, is indicated for the first-line treatment of primary advanced or recurrent endometrial carcinoma in adults who are candidates for systemic therapy.

KEYTRUDA, in combination with lenvatinib, is indicated for the treatment of advanced or recurrent endometrial carcinoma in adults who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation.

Cervical cancer

KEYTRUDA, in combination with chemoradiotherapy (external beam radiation therapy followed by brachytherapy), is indicated for the treatment of FIGO 2014 Stage III - IVA locally advanced cervical cancer in adults who have not received prior definitive therapy.

KEYTRUDA, in combination with chemotherapy with or without bevacizumab, is indicated for the treatment of persistent, recurrent, or metastatic cervical cancer in adults whose tumours express PD-L1 with a CPS ≥ 1.

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 locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1.

KEYTRUDA, in combination with fluoropyrimidine and platinum-containing chemotherapy, is indicated for the first-line treatment of locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction adenocarcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1 (see section 5.1).

Biliary tract carcinoma (BTC)

KEYTRUDA, in combination with gemcitabine and cisplatin, is indicated for the first-line treatment of locally advanced unresectable or metastatic biliary tract carcinoma in adults.

Ovarian Cancer

KEYTRUDA, in combination with paclitaxel, with or without bevacizumab, is indicated for the treatment of platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal carcinoma in adults whose tumours express PD-L1 with a CPS ≥ 1 and who have received one or two prior systemic treatment regimens.

4.2 Posology and method of administration

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

Patients receiving subcutaneous pembrolizumab can switch to intravenous pembrolizumab at their next scheduled dose. Patients receiving intravenous pembrolizumab can switch to subcutaneous pembrolizumab at their next scheduled dose.

PD-L1 testing

If specified in the indication, patient selection for treatment with KEYTRUDA based on the tumour expression of PD-L1 should be confirmed by a validated test (see sections 4.1, 4.4, 4.8 and 5.1).

MSI/MMR testing

If specified in the indication, patient selection for treatment with KEYTRUDA based on MSI-H/dMMR tumour status should be confirmed by a validated test (see sections 4.1 and 5.1).

Posology

The recommended dose of KEYTRUDA in adults is either 200 mg every 3 weeks or 400 mg every 6 weeks administered as an intravenous infusion over 30 minutes.

The recommended dose of KEYTRUDA as monotherapy in paediatric patients aged 3 years and older with cHL or patients aged 12 years and older with melanoma is 2 mg/kg bodyweight (bw) (up to a maximum of 200 mg), every 3 weeks administered as an intravenous infusion over 30 minutes.

For use in combination, see the Summary of Product Characteristics (SmPC) for the concomitant therapies.

Patients should be treated with KEYTRUDA until disease progression or unacceptable toxicity (and up to maximum duration of therapy if specified for an indication). Atypical responses (i.e., an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed. It is recommended to continue treatment for clinically stable patients with initial evidence of disease progression until disease progression is confirmed.

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

For the neoadjuvant and adjuvant treatment of resectable NSCLC, patients should be treated with neoadjuvant KEYTRUDA in combination with chemotherapy for 4 doses of 200 mg every 3 weeks or 2 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 13 doses of 200 mg every 3 weeks or 7 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.

For the neoadjuvant and adjuvant treatment of cisplatin-eligible MIBC, patients should be treated with neoadjuvant KEYTRUDA in combination with enfortumab vedotin for 4 doses of 200 mg every 3 weeks or for 2 doses of 400 mg every 6 weeks or until disease progression that precludes radical cystectomy or unacceptable toxicity, followed by adjuvant treatment with KEYTRUDA in combination with enfortumab vedotin for 13 doses of 200 mg every 3 weeks or 7 doses of 400 mg every 6 weeks or until disease recurrence or unacceptable toxicity.

For the neoadjuvant and adjuvant treatment of cisplatin-ineligible MIBC, patients should be treated with neoadjuvant KEYTRUDA in combination with enfortumab vedotin for 3 doses of 200 mg every 3 weeks or until disease progression that precludes radical cystectomy or unacceptable toxicity, followed by adjuvant treatment with KEYTRUDA in combination with enfortumab vedotin for 14 doses of 200 mg every 3 weeks or 7 doses of 400 mg every 6 weeks or until disease recurrence or unacceptable toxicity.

For the neoadjuvant and adjuvant treatment of resectable locally advanced HNSCC, patients should be treated with neoadjuvant KEYTRUDA as monotherapy for 2 doses of 200 mg every 3 weeks or 1 dose of 400 mg or until disease progression that precludes definitive surgery or unacceptable toxicity, followed by adjuvant treatment with KEYTRUDA in combination with radiation with or without concomitant cisplatin for 3 doses of 200 mg every 3 weeks or 2 doses of 400 mg every 6 weeks followed by KEYTRUDA as monotherapy for 12 doses of 200 mg every 3 weeks or 6 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 monotherapy as neoadjuvant treatment should not receive KEYTRUDA in combination with radiation with or without concomitant cisplatin as adjuvant treatment.

For the neoadjuvant and adjuvant treatment of 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.

For locally advanced cervical cancer, patients should be treated with KEYTRUDA concurrent with chemoradiotherapy, followed by KEYTRUDA as monotherapy. KEYTRUDA can be administered as either 200 mg every 3 weeks or 400 mg every 6 weeks until disease progression, unacceptable toxicity or up to 24 months.

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

Table 1: Recommended treatment modifications for KEYTRUDA

Immune-mediated adverse reactions	**Severity**	**Treatment modification**
Pneumonitis	Grade 2	Withhold until adverse reactions recover to Grades 0-1*
	Grades 3 or 4, or recurrent Grade 2	Permanently discontinue
Colitis	Grades 2 or 3	Withhold until adverse reactions recover to Grades 0-1*
	Grade 4 or recurrent Grade 3	Permanently discontinue
Nephritis	Grade 2 with creatinine > 1.5 to ≤ 3 times upper limit of normal (ULN)	Withhold until adverse reactions recover to Grades 0-1*
	Grade ≥ 3 with creatinine > 3 times ULN	Permanently discontinue
Endocrinopathies	Grade 2 adrenal insufficiency and hypophysitis	Withhold treatment until controlled by hormone replacement
	Grades 3 or 4 adrenal insufficiency or symptomatic hypophysitis Type 1 diabetes associated with Grade ≥ 3 hyperglycaemia (glucose > 250 mg/dL or > 13.9 mmol/L) or associated with ketoacidosis Hyperthyroidism Grade ≥ 3	Withhold until adverse reactions recover to Grades 0-1* For patients with Grade 3 or Grade 4 endocrinopathies that improved to Grade 2 or lower and are controlled with hormone replacement, if indicated, continuation of pembrolizumab may be considered after corticosteroid taper, if needed. Otherwise treatment should be discontinued.
	Hypothyroidism	Hypothyroidism may be managed with replacement therapy without treatment interruption.
Hepatitis **NOTE:** for RCC patients treated with **pembrolizumab in combination with axitinib** with	Grade 2 with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 to 5 times ULN or total bilirubin > 1.5 to 3 times ULN	Withhold until adverse reactions recover to Grades 0-1*

Immune-mediated adverse reactions	Severity	Treatment modification
liver enzyme elevations, see dosing guidelines following this table.	Grade ≥ 3 with AST or ALT > 5 times ULN or total bilirubin > 3 times ULN	Permanently discontinue
	In case of liver metastasis with baseline Grade 2 elevation of AST or ALT, hepatitis with AST or ALT increases ≥ 50% and lasts ≥ 1 week	Permanently discontinue
Skin reactions	Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold until adverse reactions recover to Grades 0-1*
	Grade 4 or confirmed SJS or TEN	Permanently discontinue
Other immune-mediated adverse reactions	Based on severity and type of reaction (Grade 2 or Grade 3)	Withhold until adverse reactions recover to Grades 0-1*
	Grades 3 or 4 myocarditis Grades 3 or 4 encephalitis Grades 3 or 4 Guillain-Barré syndrome	Permanently discontinue
	Grade 4 or recurrent Grade 3	Permanently discontinue
Myocarditis-myositis-myasthenia gravis overlap syndrome†	Grade 2	Withhold until adverse reactions recover to Grades 0-1*
	Grades 3 or 4	Permanently discontinue
Infusion-related reactions	Grades 3 or 4	Permanently discontinue

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

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

† Presenting as an overlap of either two or all three conditions. The most severe CTCAE grade of the individual events should be considered when assessing the recommended treatment modification for KEYTRUDA.

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

KEYTRUDA, as monotherapy or as combination therapy, should be permanently discontinued for Grade 4 or recurrent Grade 3 immune-mediated adverse reactions, unless otherwise specified in Table 1.

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

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

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

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

KEYTRUDA in combination with lenvatinib
When used in combination with lenvatinib, one or both medicines should be interrupted as appropriate. Lenvatinib should be withheld, dose reduced, or discontinued in accordance with the instructions in the lenvatinib SmPC for combination with pembrolizumab. No dose reductions are recommended for KEYTRUDA.

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

Special populations
Elderly
No dose adjustment is necessary in patients ≥ 65 years (see sections 4.4 and 5.1).

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

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

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

Method of administration

It is important to check the vial label to ensure that the correct formulation (intravenous or subcutaneous) is being prepared and administered to the patient as prescribed, to reduce the risk of medication errors.

KEYTRUDA concentrate for solution for infusion is for intravenous use only. KEYTRUDA concentrate for solution for infusion is not intended for subcutaneous administration.
KEYTRUDA concentrate for solution for infusion must be administered by infusion over 30 minutes. KEYTRUDA intravenous formulation must not be administered as an intravenous push or bolus injection.

KEYTRUDA concentrate for solution for infusion should not be substituted for or with subcutaneous pembrolizumab because they have different recommended dosages and routes of administration.

When administering KEYTRUDA as part of a combination with intravenous chemotherapy, KEYTRUDA should be administered first.

When administering KEYTRUDA as part of a combination with enfortumab vedotin, KEYTRUDA should be administered after enfortumab vedotin when given on the same day.

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

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

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

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

Pembrolizumab may be restarted within 12 weeks after last dose of KEYTRUDA if the adverse reaction recovers to Grade ≤ 1 and corticosteroid dose has been reduced to ≤ 10 mg prednisone or equivalent per day.

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

In patients with pre-existing autoimmune disease (AID), data from observational studies suggest that the risk of immune-mediated adverse reactions following immune-checkpoint inhibitor therapy may be increased as compared with the risk in patients without pre-existing AID. In addition, flares of the underlying AID were frequent, but the majority were mild and manageable.

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

Immune-mediated colitis
Colitis has been reported in patients receiving pembrolizumab (see section 4.8). Patients should be monitored for signs and symptoms of colitis, and other causes excluded. Corticosteroids should be administered for Grade ≥ 2 events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by

a taper); pembrolizumab should be withheld for Grade 2 or Grade 3 colitis, and permanently discontinued for Grade 4 or recurrent Grade 3 colitis (see section 4.2). The potential risk of gastrointestinal perforation should be taken into consideration.

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

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

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

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

Adrenal insufficiency (primary and secondary) has been reported in patients receiving pembrolizumab. Hypophysitis has also been reported in patients receiving pembrolizumab (see section 4.8). Patients should be monitored for signs and symptoms of adrenal insufficiency and hypophysitis (including hypopituitarism) and other causes excluded. Corticosteroids to treat adrenal insufficiency and other hormone replacement should be administered as clinically indicated. Pembrolizumab should be withheld for Grade 2 adrenal insufficiency or hypophysitis until the event is controlled with hormone replacement. Pembrolizumab should be withheld or discontinued for Grades 3 or 4 adrenal insufficiency or symptomatic hypophysitis. Continuation of pembrolizumab may be considered, after corticosteroid taper, if needed (see section 4.2). Pituitary function and hormone levels should be monitored to ensure appropriate hormone replacement.

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

Thyroid disorders, including hypothyroidism, hyperthyroidism and thyroiditis, have been reported in patients receiving pembrolizumab and can occur at any time during treatment. Hypothyroidism is more frequently reported in patients with HNSCC with prior radiation therapy. Patients should be monitored for changes in thyroid function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and clinical signs and symptoms of thyroid disorders. Hypothyroidism may be managed with replacement therapy without treatment interruption and without corticosteroids. Hyperthyroidism may be managed symptomatically. Pembrolizumab should be withheld for Grade ≥ 3 until recovery to Grade ≤ 1 hyperthyroidism. Thyroid function and hormone levels should be monitored to ensure appropriate hormone replacement.

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

Immune-mediated skin adverse reactions
Immune-mediated severe skin reactions have been reported in patients receiving pembrolizumab (see section 4.8). Patients should be monitored for suspected severe skin reactions and other causes should be excluded. Based on the severity of the adverse reaction, pembrolizumab should be withheld for Grade 3 skin reactions until recovery to Grade ≤ 1 or permanently discontinued for Grade 4 skin reactions, and corticosteroids should be administered (see section 4.2).

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

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

Other immune-mediated adverse reactions
The following additional clinically significant, immune-mediated adverse reactions have been reported in clinical studies or in post-marketing experience: uveitis, arthritis, myositis, myocarditis, pancreatitis, Guillain-Barré syndrome, myasthenic syndrome, haemolytic anaemia, sarcoidosis, encephalitis, myelitis, vasculitis, cholangitis sclerosing, gastritis, cystitis noninfective, hypoparathyroidism, pericarditis and myocarditis-myositis-myasthenia gravis overlap syndrome (see sections 4.2 and 4.8).

Based on the severity and type of the adverse reaction, pembrolizumab should be withheld for Grade 2 or Grade 3 events and corticosteroids administered.

Pembrolizumab may be restarted within 12 weeks after last dose of KEYTRUDA if the adverse reaction recovers to Grade ≤ 1 and corticosteroid dose has been reduced to ≤ 10 mg prednisone or equivalent per day.

Pembrolizumab must be permanently discontinued for any Grade 3 immune-mediated adverse reaction that recurs and for any Grade 4 immune-mediated adverse reaction.

For Grades 3 or 4 myocarditis, encephalitis or Guillain-Barré syndrome, pembrolizumab should be permanently discontinued (see sections 4.2 and 4.8).

Transplant-related adverse reactions

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

Complications of allogeneic Haematopoietic Stem Cell Transplant (HSCT)

Allogeneic HSCT after treatment with pembrolizumab
Cases of graft-versus-host-disease (GVHD) and hepatic veno-occlusive disease (VOD) have been observed in patients with cHL undergoing allogeneic HSCT after previous exposure to pembrolizumab. Until further data become available, careful consideration to the potential benefits of

HSCT and the possible increased risk of transplant-related complications should be made case by case (see section 4.8).

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

Infusion-related reactions
Severe infusion-related reactions, including hypersensitivity and anaphylaxis, have been reported in patients receiving pembrolizumab (see section 4.8). For Grades 3 or 4 infusion reactions, infusion should be stopped and pembrolizumab permanently discontinued (see section 4.2). Patients with Grades 1 or 2 infusion reaction may continue to receive pembrolizumab with close monitoring; premedication with antipyretic and antihistamine may be considered.

Use of pembrolizumab in combination with chemotherapy
Pembrolizumab in combination with chemotherapy should be used with caution in patients ≥ 75 years after careful consideration of the potential benefit/risk on an individual basis (see section 5.1).

Disease-specific precautions

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

Use of pembrolizumab in urothelial carcinoma for patients who are considered ineligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 with CPS ≥ 10
The baseline and prognostic disease characteristics of the study population of KEYNOTE-052 included a proportion of patients eligible for a carboplatin-based combination, for whom the benefit has been assessed in a comparative study (KEYNOTE-361). In KEYNOTE-361, a higher number of deaths within 6 months of treatment initiation followed by a long-term survival benefit was observed with pembrolizumab monotherapy compared to chemotherapy (see section 5.1). No specific factor(s) associated with early deaths could be identified. Physicians should consider the delayed onset of pembrolizumab effect before initiating treatment in patients with urothelial carcinoma who are considered eligible for carboplatin-based combination chemotherapy. KEYNOTE-052 also included patients eligible for mono-chemotherapy, for whom no randomised data are available. In addition, no safety and efficacy data are available in frailer patients (e.g., ECOG performance status 3) considered not eligible for chemotherapy. In the absence of these data, pembrolizumab should be used with caution in this population after careful consideration of the potential risk-benefit on an individual basis.

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

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

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

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

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

Use of pembrolizumab for treatment of patients with advanced or recurrent MSI-H or dMMR endometrial carcinoma
A direct comparison of pembrolizumab when used in combination with lenvatinib to pembrolizumab monotherapy is not available. Physicians should consider the benefit/risk balance of the available treatment options (pembrolizumab monotherapy or pembrolizumab in combination with lenvatinib) before initiating treatment in patients with advanced or recurrent MSI-H or dMMR endometrial carcinoma.

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

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

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

Use of pembrolizumab for first-line treatment of patients with BTC
Cholangitis and biliary tract infections are not uncommon in patients with BTC. Cholangitis events were reported in KEYNOTE-966 in both treatment groups (11.2% [n=59] of participants in the pembrolizumab plus chemotherapy arm and 10.3% [n=55] of participants in the placebo plus chemotherapy arm). Patients with biliary stents and drains (n=74) were at increased risk of cholangitis and biliary tract infections in KEYNOTE-966 (39.4% [n=13] of participants in the pembrolizumab plus chemotherapy arm vs. 29.3% [n=12] of participants in the placebo plus chemotherapy arm). Patients with BTC (especially those with biliary stents) should be closely monitored for development of cholangitis or biliary tract infections before initiation of treatment and, regularly, thereafter.

Patients excluded from clinical studies
Patients with the following conditions were excluded from clinical studies: active CNS metastases; ECOG PS ≥ 2 (except for urothelial carcinoma and RCC); HIV infection, hepatitis B or hepatitis C infection (except for BTC); active systemic autoimmune disease; interstitial lung disease; prior pneumonitis requiring systemic corticosteroid therapy; a history of severe hypersensitivity to another monoclonal antibody; receiving immunosuppressive therapy and a history of severe immune-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) for greater than 12 weeks.

Patients with active infections were excluded from clinical studies and were required to have their infection treated prior to receiving pembrolizumab. Patients with active infections occurring during treatment with pembrolizumab were managed with appropriate medical therapy. Patients with clinically significant renal (creatinine > 1.5 x ULN) or hepatic (bilirubin > 1.5 x ULN, ALT, AST > 2.5 x ULN in the absence of liver metastases) abnormalities at baseline were excluded from clinical studies, therefore information is limited in patients with severe renal and moderate to severe hepatic impairment.

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

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

Excipients with known effect
This medicinal product contains 0.2 mg of polysorbate 80 in each mL of concentrate. Polysorbates may cause allergic reactions.

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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

4.6 Fertility, pregnancy and lactation

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

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

Breast-feeding
It is unknown whether pembrolizumab is secreted in human milk. Since it is known that antibodies can be secreted in human milk, a risk to the newborns/infants cannot be excluded. A decision should be

made whether to discontinue breast-feeding or to discontinue pembrolizumab, taking into account the benefit of breast-feeding for the child and the benefit of pembrolizumab therapy for the woman.

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

4.7 Effects on ability to drive and use machines

Pembrolizumab has a minor influence on the ability to drive and use machines. In some patients, dizziness and fatigue have been reported following administration of pembrolizumab (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile
Pembrolizumab is most commonly associated with immune-mediated adverse reactions. Most of these, including severe reactions, resolved following initiation of appropriate medical therapy or withdrawal of pembrolizumab (see "Description of selected adverse reactions" below). The frequencies included below and in Table 2 are based on all reported adverse drug reactions, regardless of the investigator assessment of causality.

Pembrolizumab in monotherapy (see section 4.2)
The safety of pembrolizumab 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 bw 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 pembrolizumab 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-mediated 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 pembrolizumab 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.

Pembrolizumab in combination with chemotherapy, radiation therapy (RT) or chemoradiotherapy (CRT) (see section 4.2)
When pembrolizumab is administered in combination, refer to the SmPC for the respective combination therapy components prior to initiation of treatment.

The safety of pembrolizumab in combination with chemotherapy, RT or CRT has been evaluated in 7 015 patients across tumour types receiving 200 mg, 2 mg/kg bw or 10 mg/kg bw pembrolizumab every 3 weeks or 400 mg pembrolizumab every 6 weeks, in clinical studies. In this patient population, the most frequent adverse reactions were anaemia (51%), nausea (50%), fatigue (36%), diarrhoea (35%), constipation (32%), vomiting (27%), and decreased appetite (26%). Incidences of Grades 3-5 adverse reactions in patients with NSCLC were 69% for pembrolizumab combination therapy and 61% for chemotherapy alone, in patients with HNSCC were 80% for pembrolizumab combination therapy (chemotherapy or RT with or without chemotherapy), and 79% for chemotherapy plus cetuximab or RT with or without chemotherapy, in patients with oesophageal carcinoma were 86% for pembrolizumab combination therapy and 83% for chemotherapy alone, in patients with TNBC were 80% for pembrolizumab combination therapy and 77% for chemotherapy alone, in patients with cervical cancer were 77% for pembrolizumab 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 pembrolizumab combination therapy (chemotherapy with or without trastuzumab) and 68% for chemotherapy with or without trastuzumab, in patients with biliary tract carcinoma were 85% for pembrolizumab combination therapy and 84% for chemotherapy alone, in patients with EC were 59% for pembrolizumab combination therapy and 46% for chemotherapy alone, in patients with malignant pleural

mesothelioma were 44% for pembrolizumab combination therapy and 30% for chemotherapy alone and in patients with ovarian cancer were 83% for pembrolizumab combination therapy (chemotherapy with or without bevacizumab) and 71% for chemotherapy with or without bevacizumab.

Pembrolizumab in combination with tyrosine kinase inhibitor (TKI) (see section 4.2)
When pembrolizumab is administered in combination with axitinib or lenvatinib, refer to the SmPC for axitinib or lenvatinib prior to initiation of treatment. For additional lenvatinib safety information related to advanced RCC see the SmPC for Kisplyx and for advanced EC see the SmPC for Lenvima. For additional axitinib safety information for elevated liver enzymes see also section 4.4.

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

Tabulated summary of adverse reactions
Adverse reactions observed in clinical studies of pembrolizumab as monotherapy or in combination with chemotherapy, RT or CRT or other anti-tumour medicines or reported from post-marketing use of pembrolizumab are listed in Table 2. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000); 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 SmPC for the respective combination therapy components.

Table 2: Adverse reactions in patients treated with pembrolizumab†

MedDRA SOC and frequency category	Monotherapy	In combination with chemotherapy, radiation therapy 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

MedDRA SOC and frequency category	Monotherapy	In combination with chemotherapy, radiation therapy or chemoradiotherapy	In combination with axitinib or lenvatinib
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	headache, dysgeusia
Common	dizziness, neuropathy peripheral, lethargy, dysgeusia	dizziness, dysgeusia	dizziness, neuropathy peripheral, lethargy
Uncommon	myasthenic syndrome*¶, epilepsy	encephalitis*, lethargy	myasthenic syndrome*¶, encephalitis*
Rare	Guillain-Barré syndrome*, encephalitis*, myelitis*, optic neuritis, meningitis (aseptic)*	myasthenic syndrome*¶, Guillain-Barré syndrome*, myelitis, optic neuritis, epilepsy, meningitis (aseptic)	optic neuritis
Eye disorders			
Common	dry eye	dry eye	dry eye
Uncommon	uveitis*	uveitis*	uveitis*

MedDRA SOC and frequency category	Monotherapy	In combination with chemotherapy, radiation therapy or chemoradiotherapy	In combination with axitinib or lenvatinib
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	pancreatic exocrine insufficiency, small intestinal perforation, coeliac disease	pancreatic exocrine insufficiency, small intestinal perforation, coeliac disease	small intestinal perforation
Not known			pancreatic exocrine 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, alopecia, dermatitis acneiform	severe skin reactions*, dermatitis, erythema, dry skin, dermatitis acneiform, eczema	severe skin reactions*, dermatitis, dry skin, erythema, dermatitis acneiform, alopecia

MedDRA SOC and frequency category	Monotherapy	In combination with chemotherapy, radiation therapy or chemoradiotherapy	In combination with axitinib or lenvatinib
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	arthralgia, musculoskeletal pain*	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	lipase increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood creatinine increased
Common	alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, hypercalcaemia, blood bilirubin increased, blood creatinine increased	blood bilirubin increased, blood alkaline phosphatase increased, blood creatinine increased, hypercalcaemia	amylase increased, blood bilirubin increased, blood alkaline phosphatase increased, hypercalcaemia
Uncommon	amylase increased	amylase increased	

†Adverse reaction frequencies presented in Table 2 may not be fully attributable to pembrolizumab alone but may contain contributions from the underlying disease or from other medicinal products used in a combination.
‡Based upon a standard query including bradyarrhythmias and tachyarrhythmias.
¶Myocarditis, myositis, myasthenia gravis can occur simultaneously (as myocarditis-myositis-myasthenia gravis overlap syndrome).
*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 reaction (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, immune-mediated hypothyroidism and autoimmune hypothyroidism)
- adrenal insufficiency (Addison's disease, adrenocortical insufficiency acute, secondary adrenocortical insufficiency and primary adrenal 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 noninfective)
- uveitis (chorioretinitis, iritis and iridocyclitis)
- myocarditis (autoimmune myocarditis and immune-mediated 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, 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 papular 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, 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, lip oedema, face oedema, localised oedema and periorbital oedema)

Pembrolizumab in combination with enfortumab vedotin (see section 4.2)
When pembrolizumab is administered in combination with enfortumab vedotin, refer to the SmPC for enfortumab vedotin prior to initiation of treatment.

The safety of pembrolizumab in combination with enfortumab vedotin has been evaluated among 564 patients with unresectable or metastatic urothelial carcinoma receiving 200 mg pembrolizumab on Day 1 and enfortumab vedotin 1.25 mg/kg on Days 1 and 8 of each 21-day cycle.
Overall, the incidence of adverse reactions for pembrolizumab in combination with enfortumab vedotin was observed to be higher than for pembrolizumab monotherapy reflecting the contribution of enfortumab vedotin and the longer duration of treatment of the combination therapy.
Adverse reactions were generally similar to those observed in patients receiving pembrolizumab or enfortumab vedotin as monotherapy. The incidence of rash maculo-papular was 36% all Grades (10% Grades 3-4), which is higher than observed in pembrolizumab monotherapy.

Generally, adverse event frequencies were higher in patients ≥ 65 years of age compared to < 65 years of age, particularly for serious adverse events (56.3% and 35.3%, respectively) and ≥ Grade 3 events (80.3% and 64.2%, respectively), similar to observations with the chemotherapy comparator.

The safety of pembrolizumab in combination with enfortumab vedotin has been evaluated among 570 patients with MIBC receiving 200 mg pembrolizumab on Day 1 and enfortumab vedotin 1.25 mg/kg on Days 1 and 8 of each 21-day cycle as neoadjuvant treatment and continued after radical cystectomy as adjuvant treatment. Overall, the incidence of adverse reactions for pembrolizumab in combination with enfortumab vedotin was observed to be higher than for pembrolizumab monotherapy reflecting the contribution of enfortumab vedotin. Adverse reactions were generally similar to those occurring in patients with unresectable or metastatic urothelial carcinoma treated with pembrolizumab in combination with enfortumab vedotin.

Description of selected adverse reactions

Data for the following immune-mediated adverse reactions are based on patients who received pembrolizumab 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)

Immune-mediated 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 pembrolizumab. 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 pembrolizumab in 131 (1.7%) patients. Pneumonitis resolved in 196 patients, 6 with sequelae.

In patients with NSCLC, pneumonitis occurred in 230 (6.1%), including Grade 2, 3, 4 or 5 cases in 103 (2.7%), 63 (1.7%), 17 (0.4%) and 10 (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.

Immune-mediated 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 pembrolizumab. The median time to onset of colitis was 4.3 months (range: 2 days to 24.3 months). The median duration was 1.1 month (range: 1 day to 45.2 months). Colitis led to discontinuation of pembrolizumab in 48 (0.6%) patients. Colitis resolved in 132 patients, 2 with sequelae. In patients with CRC treated with pembrolizumab as monotherapy (n=153), the incidence of colitis was 6.5% (all Grades) with 2.0% Grade 3 and 1.3% Grade 4.

Immune-mediated 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 pembrolizumab. 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 29.0+ months). Hepatitis led to discontinuation of pembrolizumab in 37 (0.5%) patients. Hepatitis resolved in 60 patients.

Immune-mediated 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 pembrolizumab as monotherapy. The median time to onset of nephritis was 4.2 months (range: 12 days to 21.4 months). The median duration was 3.3 months (range: 6 days to 28.2+ months). Nephritis led to discontinuation of pembrolizumab in 17 (0.2%) patients. Nephritis resolved in 25 patients, 5 with sequelae. In patients with non-squamous NSCLC

treated with pembrolizumab in combination with pemetrexed and platinum chemotherapy (n=488), the incidence of nephritis was 1.4% (all Grades) with 0.8% Grade 3 and 0.4% Grade 4.

Immune-mediated endocrinopathies
Adrenal insufficiency occurred in 74 (1.0%) patients, including Grade 2, 3 or 4 cases in 34 (0.4%), 31 (0.4%) and 4 (0.1%) patients, respectively, receiving pembrolizumab. The median time to onset of adrenal insufficiency was 5.4 months (range: 1 day to 23.7 months). The median duration was not reached (range: 3 days to 40.1+ months). Adrenal insufficiency led to discontinuation of pembrolizumab 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 pembrolizumab. The median time to onset of hypophysitis was 5.9 months (range: 1 day to 17.7 months). The median duration was 3.6 months (range: 3 days to 48.1+ months). Hypophysitis led to discontinuation of pembrolizumab 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 pembrolizumab. 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 pembrolizumab in 4 (0.1%) patients. Hyperthyroidism resolved in 326 (82.7%) patients, 11 with sequelae. In patients with melanoma, NSCLC and RCC treated with pembrolizumab 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 pembrolizumab. The median time to onset of hypothyroidism was 3.4 months (range: 1 day to 25.9 months). The median duration was not reached (range: 2 days to 63.0+ months). Hypothyroidism led to discontinuation of pembrolizumab 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 recurrent or metastatic HNSCC treated with pembrolizumab as monotherapy (n=909), the incidence of hypothyroidism was 16.1% (all Grades) with 0.3% Grade 3. In patients with recurrent or metastatic HNSCC treated with pembrolizumab in combination with platinum and 5-FU chemotherapy (n=276), the incidence of hypothyroidism was 15.2%, all of which were Grade 1 or 2. In patients with resectable locally advanced HNSCC treated with pembrolizumab as neoadjuvant treatment and in combination with radiation therapy with or without concomitant cisplatin for adjuvant treatment (n=361), the incidence of hypothyroidism was 24.7%, all of which were Grade 1 or 2. In patients treated with pembrolizumab in combination with axitinib or lenvatinib (n=1 456), the incidence of hypothyroidism was 46.2% (all Grades) with 0.8% Grade 3 or 4. In patients with melanoma, NSCLC and RCC treated with pembrolizumab monotherapy in the adjuvant setting (n=2 060), the incidence of hypothyroidism was 18.5%, the majority of which were Grade 1 or 2.

Immune-mediated 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 pembrolizumab. 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 pembrolizumab in 18 (0.2%) patients. Severe skin reactions resolved in 95 patients, 2 with sequelae.

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

Complications of allogeneic HSCT in cHL
Of 14 patients in KEYNOTE-013 who proceeded to allogeneic HSCT after treatment with pembrolizumab, 6 patients reported acute GVHD and 1 patient reported chronic GVHD, none of

which were fatal. Two patients experienced hepatic VOD, one of which was fatal. One patient experienced engraftment syndrome post-transplant.

Of 32 patients in KEYNOTE-087 who proceeded to allogeneic HSCT after treatment with pembrolizumab, 16 patients reported acute GVHD and 7 patients reported chronic GVHD, two of which were fatal. No patients experienced hepatic VOD. No patients experienced engraftment syndrome post-transplant.

Of 14 patients in KEYNOTE-204 who proceeded to allogeneic HSCT after treatment with pembrolizumab, 8 patients reported acute GVHD and 3 patients reported chronic GVHD, none of which were fatal. No patients experienced hepatic VOD. One patient experienced engraftment syndrome post-transplant.

Elevated liver enzymes when pembrolizumab is combined with axitinib in RCC
In a clinical study of previously untreated patients with RCC receiving pembrolizumab in combination with axitinib, a higher than expected incidence of Grades 3 and 4 ALT increased (20%) and AST increased (13%) were observed. The median time to onset of ALT increased was 2.3 months (range: 7 days to 19.8 months). In patients with ALT ≥ 3 times ULN (Grades 2-4, n=116), ALT resolved to Grades 0-1 in 94%. Fifty-nine percent of the patients with increased ALT received systemic corticosteroids. Of the patients who recovered, 92 (84%) were rechallenged with either pembrolizumab (3%) or axitinib (31%) monotherapy or with both (50%). Of these patients, 55% had no recurrence of ALT > 3 times ULN, and of those patients with recurrence of ALT > 3 times ULN, all recovered. There were no Grade 5 hepatic events.

Laboratory abnormalities
In patients treated with pembrolizumab monotherapy, the proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 9.9% 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 pembrolizumab in combination with chemotherapy, RT or CRT, the proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 36.4% for neutrophils decreased, 31.7% for lymphocytes decreased, 23.7% for leukocytes decreased, 20.2% for haemoglobin decreased, 11.4% for platelets decreased, 9.5% for sodium decreased, 7.8% for potassium decreased, 7.2% for phosphate decreased, 5.5% for glucose increased, 5.3% for ALT increased, 4.7% for AST increased, 3.4% for calcium decreased, 3.1% for creatinine increased, 3.0% for bilirubin increased, 3.0% for potassium increased, 2.4% for albumin decreased, 2.3% for alkaline phosphatase increased, 1.6% for calcium increased, 0.9% for glucose decreased, 0.4% for sodium increased and 0.2% for haemoglobin increased.

In patients treated with pembrolizumab in combination with axitinib or lenvatinib, the proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 23.0% for lipase increased (not measured in patients treated with pembrolizumab and axitinib), 12.3% 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.

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

Paediatric population
The safety of pembrolizumab as monotherapy has been evaluated in 161 paediatric patients aged 9 months to 17 years with advanced melanoma, lymphoma, or PD-L1 positive advanced, relapsed, or refractory solid tumours at 2 mg/kg 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 pembrolizumab. The most common adverse reactions (reported in at least 20% of paediatric patients) were pyrexia (33%), vomiting (30%), headache (26%), abdominal pain (22%), anaemia (21%), cough (21%) and constipation (20%). The majority of adverse reactions reported for monotherapy were of Grades 1 or 2 severity. Seventy-six (47.2%) patients had 1 or more Grades 3 to 5 adverse reactions of which 5 (3.1%) patients had 1 or more adverse reactions that resulted in death. The frequencies are based on all reported adverse drug reactions, regardless of the investigator assessment of causality. Long-term safety data of pembrolizumab in adolescents with Stage IIB, IIC and III melanoma treated in the adjuvant setting are currently unavailable.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance. Website: www.hpra.ie.

4.9 Overdose

There is no information on overdose with pembrolizumab.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, PD-1/PDL-1 (Programmed cell death protein 1/death ligand 1) inhibitors. ATC code: L01FF02

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

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

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

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

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

The primary efficacy outcome measures were progression-free survival (PFS; as assessed by Integrated Radiology and Oncology Assessment [IRO] review using Response Evaluation Criteria in Solid Tumours [RECIST], version 1.1) and overall survival (OS). Secondary efficacy outcome measures were objective response rate (ORR) and response duration. Table 3 summarises key efficacy measures in patients naïve to treatment with ipilimumab at the final analysis performed after a minimum of 21 months of follow-up. Kaplan-Meier curves for OS and PFS based on the final analysis are shown in Figures 1 and 2.

Table 3: Efficacy results in KEYNOTE-006

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

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

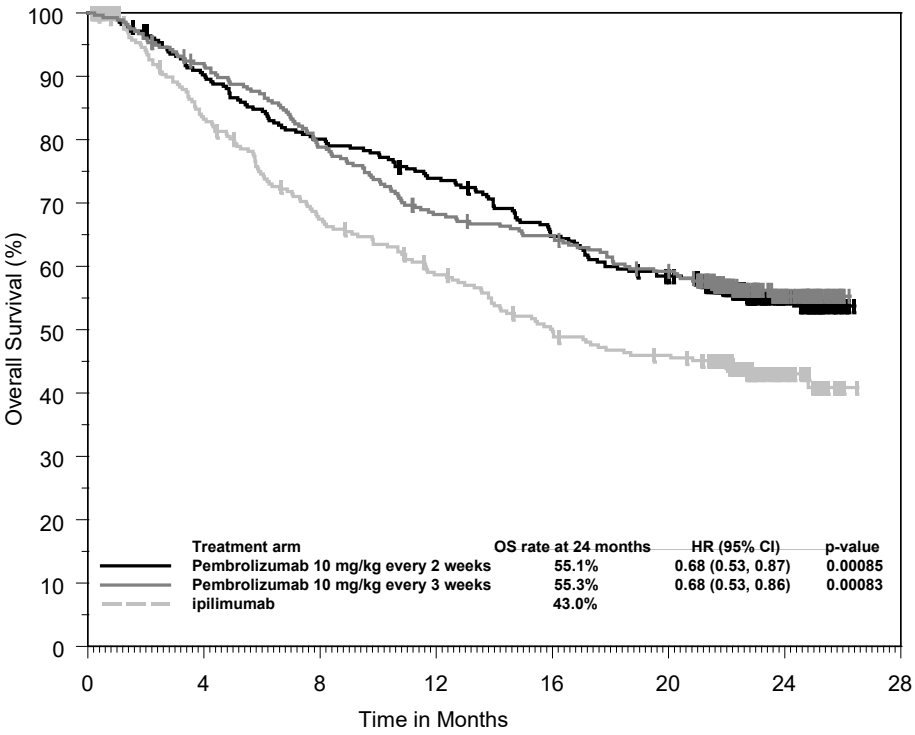
† Based on stratified log-rank test

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

§ Based on Kaplan-Meier estimation

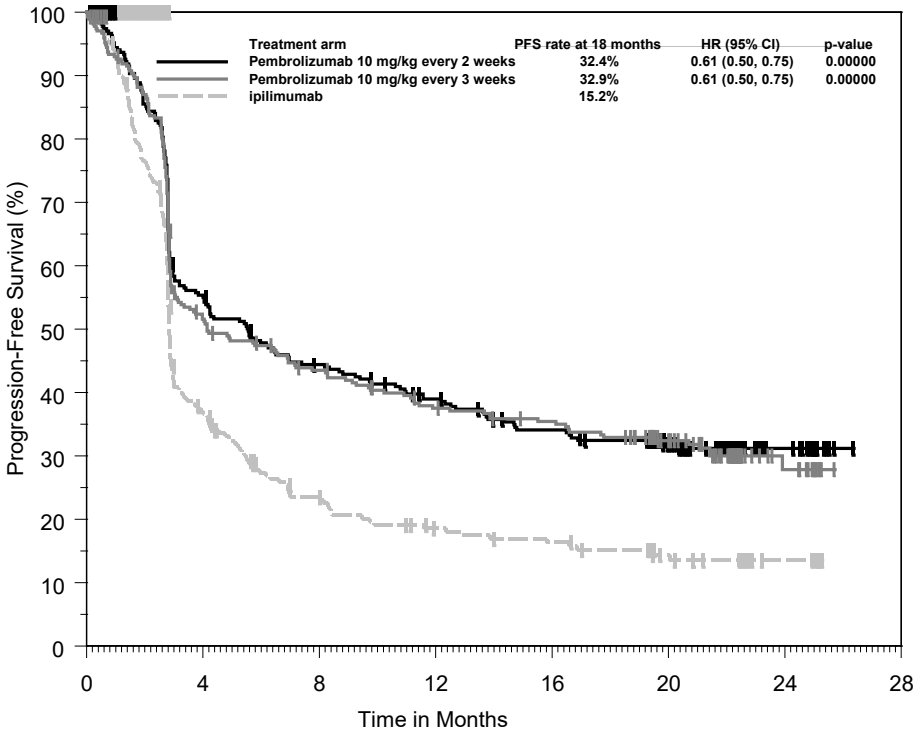
NA = not available

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



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

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



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

KEYNOTE-002: Controlled study in melanoma patients previously treated with ipilimumab
The safety and efficacy of pembrolizumab were investigated in KEYNOTE-002, a multicentre, double-blind, controlled study for the treatment of advanced melanoma in patients previously treated with ipilimumab and if BRAF V600 mutation-positive, with a BRAF or MEK inhibitor. Patients were randomised (1:1:1) to receive pembrolizumab at a dose of 2 (n=180) or 10 mg/kg bw (n=181) every 3 weeks or chemotherapy (n=179; including dacarbazine, temozolomide, carboplatin, paclitaxel, or carboplatin+paclitaxel). The study excluded patients with autoimmune disease or those receiving immunosuppression; further exclusion criteria were a history of severe or life-threatening immune-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.

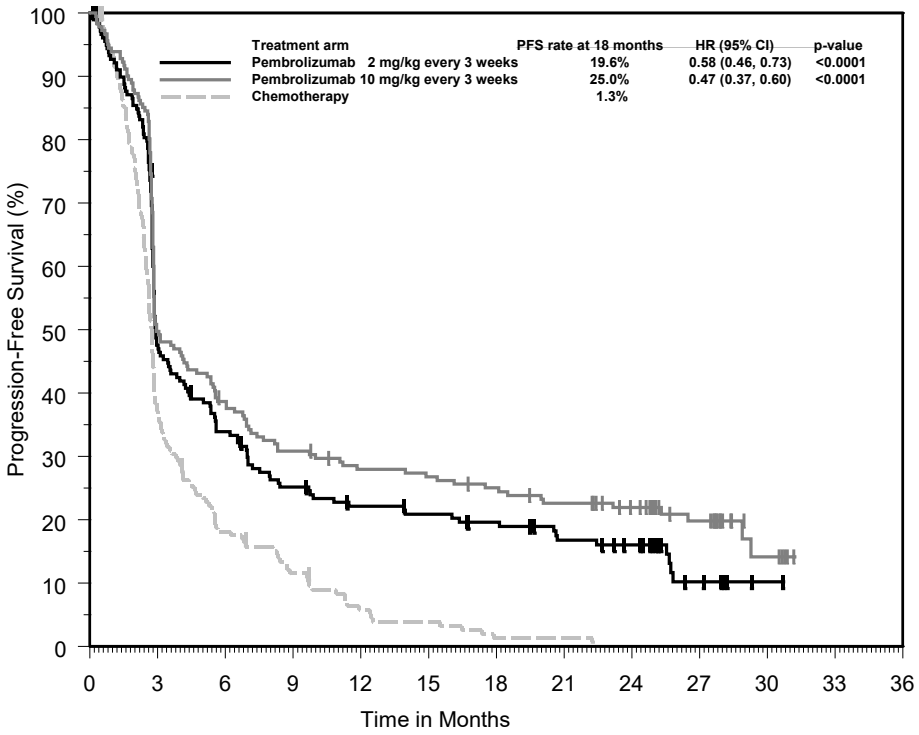
The primary efficacy outcome measures were PFS as assessed by IRO using RECIST version 1.1 and OS. Secondary efficacy outcome measures were ORR and response duration. Table 4 summarises key efficacy measures at the final analysis in patients previously treated with ipilimumab, and the Kaplan-Meier curve 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)



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

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

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

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

The primary efficacy outcome measure was ORR as assessed by independent review using RECIST 1.1. Secondary efficacy outcome measures were disease control rate (DCR; including complete response, partial response and stable disease), response duration, PFS and OS. Tumour

response was assessed at 12 week intervals. Table 5 summarises key efficacy measures in patients previously treated or naïve to treatment with ipilimumab, receiving pembrolizumab at a dose of 2 mg/kg bw based on a minimum follow-up time of 30 months for all patients.

Table 5: Efficacy results in KEYNOTE-001

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

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

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

Sub-population analyses

BRAF mutation status in melanoma

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

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

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

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

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

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

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

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

PD-L1 status in melanoma

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

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

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

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

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

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

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

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

Ocular melanoma

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

KEYNOTE-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 analysis. The study initially demonstrated

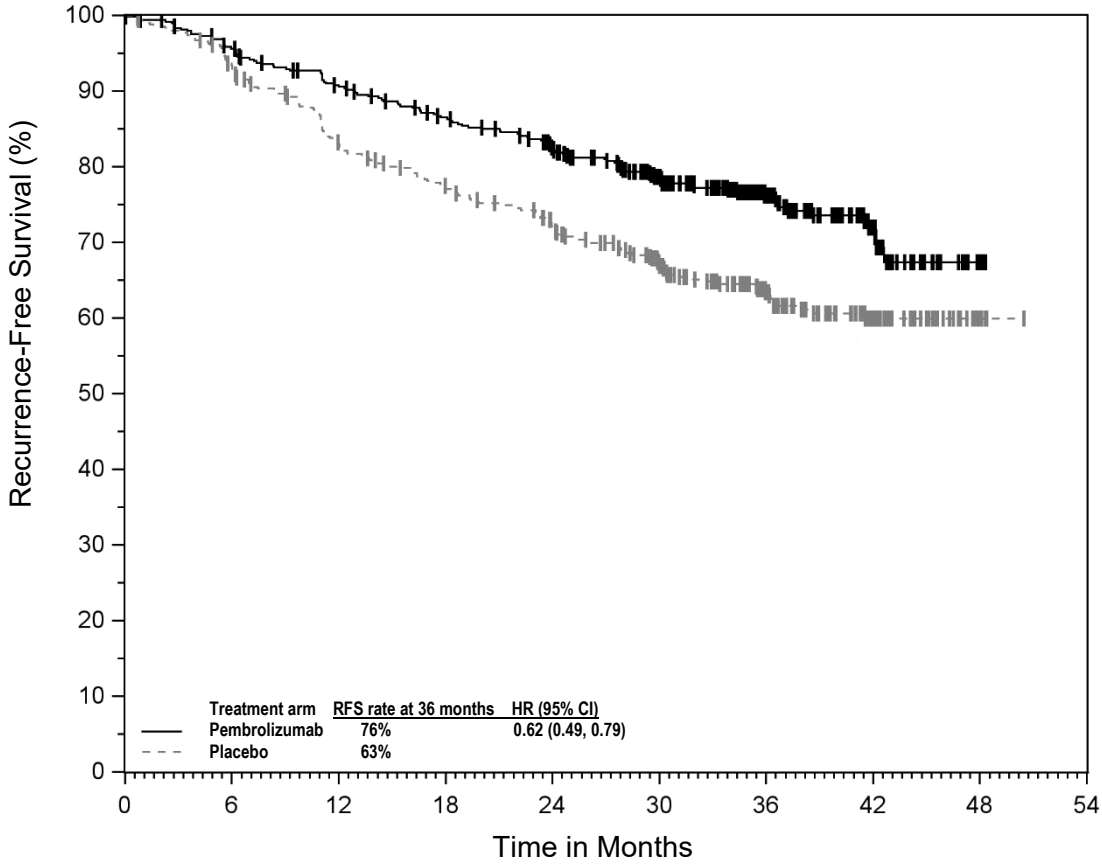
a statistically significant improvement in RFS (HR 0.65; 95% CI 0.46, 0.92; p-Value = 0.00658) for patients randomised to the pembrolizumab arm compared with placebo at its pre-specified interim analysis. Results reported from the pre-specified final analysis for RFS at a median follow-up of 20.5 months 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.

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

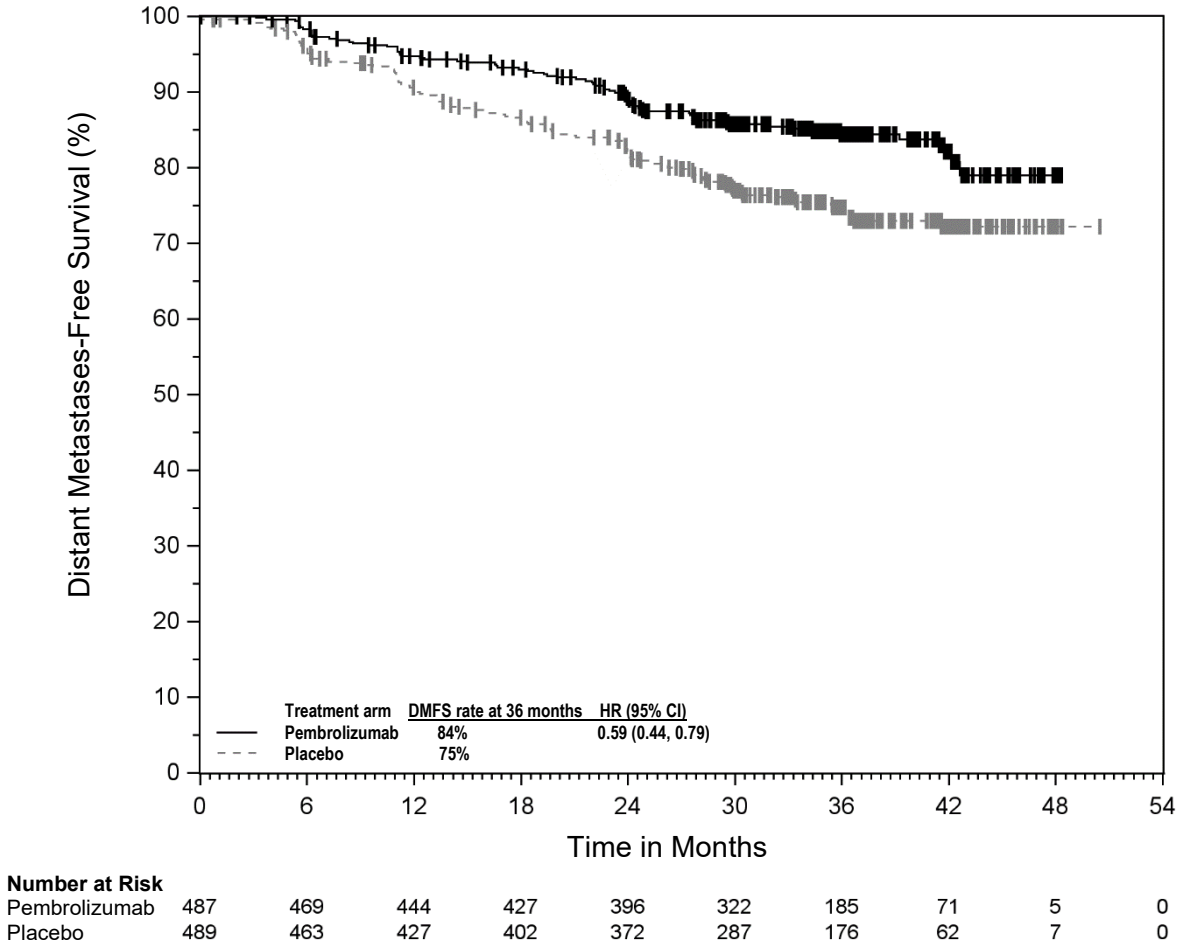
Figure 4: Kaplan-Meier curve for recurrence-free survival by treatment arm in KEYNOTE-716 (intent to treat population)



Number at Risk

Pembrolizumab	487	457	426	400	371	300	173	62	4	0
Placebo	489	452	395	363	331	252	149	51	7	0

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 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 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 occurred first. The secondary outcome measures were 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)

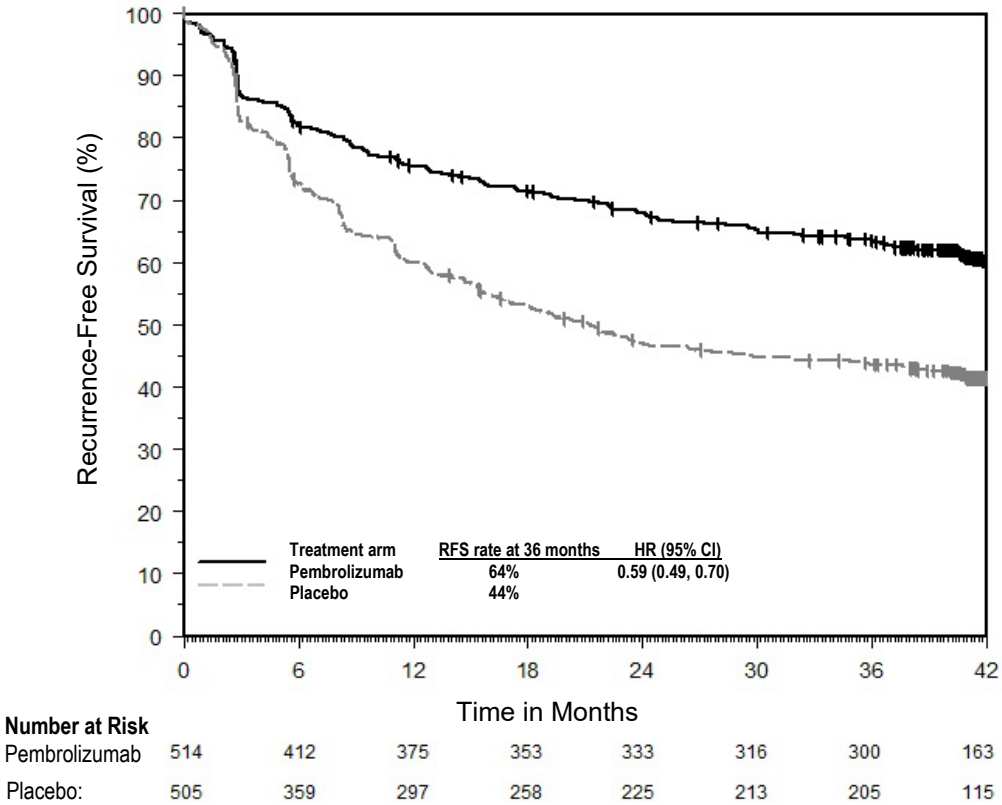
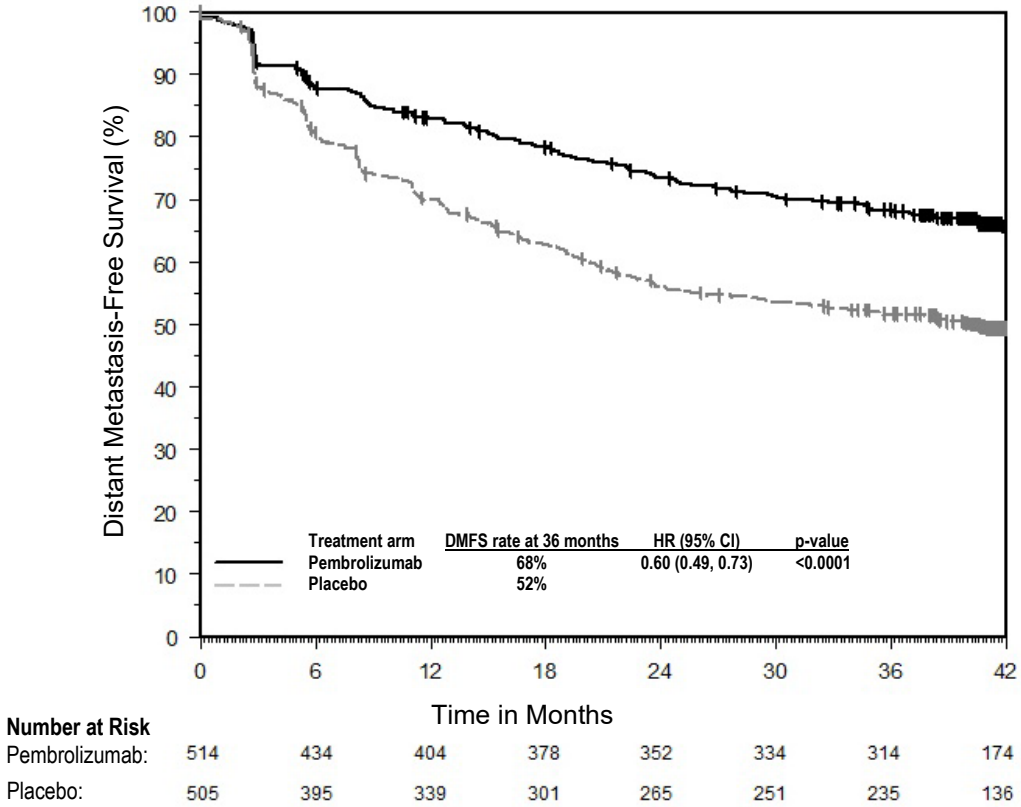


Figure 7: Kaplan-Meier curve for distant metastasis-free survival by treatment arm in KEYNOTE-054 (intent to treat population)



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.

Non-small cell lung carcinoma
KEYNOTE-671: Controlled study for the neoadjuvant and adjuvant treatment of patients with resectable non-small cell lung carcinoma (NSCLC)
The efficacy of pembrolizumab in combination with platinum-containing chemotherapy, given as neoadjuvant treatment and continued as monotherapy as adjuvant treatment was investigated in KEYNOTE-671, a multicentre, randomised, double-blind, placebo-controlled study. Key eligibility criteria were previously untreated and resectable patients with NSCLC who are at high risk (Stage II, IIIA, or IIIB (N2) by AJCC 8th edition) of recurrence, regardless of tumour PD-L1 expression. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx assay. Testing for genomic tumour aberrations or oncogenic drivers was not mandatory for enrolment.

The following selection criteria define patients with high risk of recurrence who are included in the therapeutic indication and are reflective of the patient population with Stage II – IIIB (N2) according to the 8th edition staging system: tumour size > 4 cm; or tumours of any size that are either accompanied by N1 or N2 status; or tumours that invade thoracic structures (directly invade the parietal pleura, chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina); or tumours that involve a mainstem bronchus with tumour > 4 cm; or tumours > 4 cm that cause obstructive atelectasis that extends to the hilum; or tumours with separate nodule(s) in the same lobe or different ipsilateral lobe as the primary lung cancer.

If indicated, patients received adjuvant radiation therapy prior to adjuvant pembrolizumab or placebo. 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% 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. Four percent of patients had EGFR mutations and in 66% EGFR mutation status was unknown. Three percent of patients had ALK translocations and in 68% ALK translocation status was unknown.

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 study demonstrated statistically significant improvements in OS, EFS, pCR and mPR 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. At a pre-specified interim analysis (median follow-up time of 21.4 months (range: 0.4 to 50.6 months)) the EFS HR was 0.58 (95% CI: 0.46, 0.72; $p < 0.0001$) 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. At the time of this analysis, OS results were not mature.

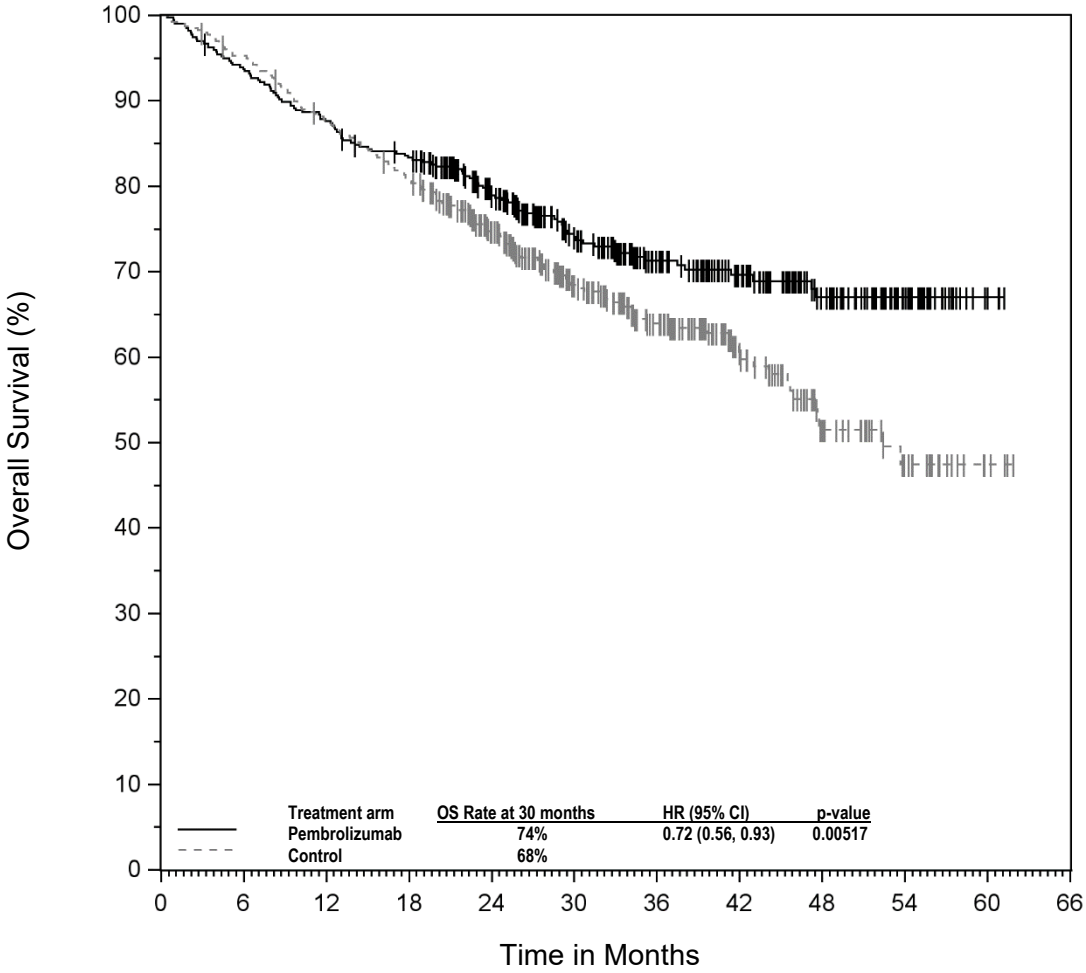
Table 12 summarises key efficacy measures at a pre-specified interim analysis at a median follow-up time of 29.8 months (range: 0.4 to 62.0 months). The Kaplan-Meier curves for OS and EFS are shown in Figures 8 and 9.

Table 12: 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	174 (44%)	248 (62%)
Median in months* (95% CI)	47.2 (32.9, NR)	18.3 (14.8, 22.1)
Hazard ratio† (95% CI)	0.59 (0.48, 0.72)	

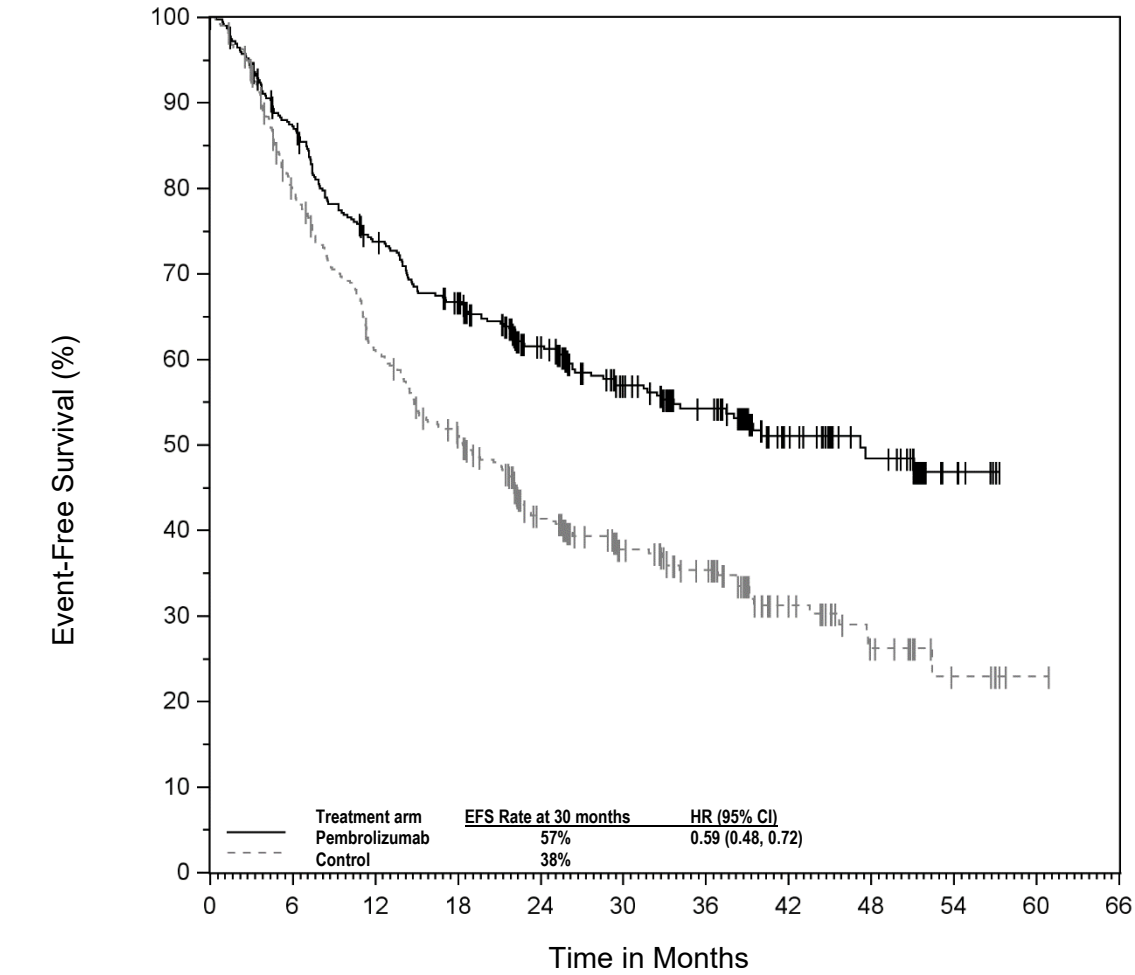
* Based on Kaplan-Meier estimates
† Based on Cox regression model with treatment as a covariate stratified by stage, tumour PD-L1 expression, histology, and geographic region
‡ Based on stratified log-rank test
NR = not reached

Figure 8: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-671 (intent to treat population)



Number at Risk												
Pembrolizumab	397	371	347	327	277	205	148	108	69	32	4	0
Control	400	379	347	319	256	176	125	77	39	20	4	0

Figure 9: Kaplan-Meier curve for event-free survival by treatment arm in KEYNOTE-671 (intent to treat population)



Number at Risk												
Pembrolizumab	397	339	282	250	196	142	102	62	37	10	0	0
Control	400	308	232	189	128	87	66	34	18	6	1	0

A post-hoc exploratory subgroup analysis was performed in KEYNOTE-671 in patients who had PD-L1 TPS ≥ 50% (pembrolizumab arm [n=132; 33%] vs. placebo arm [n=134; 34%]); TPS = 1 - 49% (pembrolizumab arm [n=127; 32%] vs. placebo arm [n=115; 29%]) and TPS < 1% (pembrolizumab arm [n=138; 35%] vs. placebo arm [n=151; 38%]). The EFS HR was, 0.48 (95% CI: 0.33, 0.71) in patients with a TPS ≥ 50%, 0.52 (95% CI: 0.36, 0.73) in patients with a TPS = 1 - 49% and 0.75 (95% CI: 0.56, 1.01) in patients with a TPS < 1%. The OS HR was 0.55 (95% CI: 0.33, 0.92) in patients with a TPS ≥ 50%, 0.69 (95% CI: 0.44, 1.07) in patients with a TPS = 1 - 49% and 0.91 (95% CI: 0.63, 1.32) in patients with a TPS < 1%.

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 study in patients with NSCLC who are at high risk (stage IB [T2a ≥ 4 cm], II or IIIA by AJCC 7th edition) of recurrence following complete resection, 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. Testing for genomic tumour aberrations/oncogenic drivers was not mandatory for enrolment.

The following selection criteria define patients with high risk of recurrence who are included in the therapeutic indication and are reflective of the patient population with stage IB [T2a ≥ 4 cm], II or IIIA according to the 7th edition staging system: Tumour size ≥ 4 cm; or tumours of any size that are either accompanied by N1 or N2 status; or tumours that are invasive of thoracic structures (directly invade

the parietal pleura, chest wall, diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina); or tumours that involve the main bronchus < 2 cm distal to the carina but without involvement of the carina; or tumours that are associated with atelectasis or obstructive pneumonitis of the entire lung; or tumours with separate nodule(s) in the same lobe or different ipsilateral lobe as the primary. The study did not include patients who had N2 status with tumours also invading the mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina, or with separate tumour nodule(s) in a different ipsilateral lobe.

Patients may or may not have received adjuvant chemotherapy as recommended by their physician. 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 (n=590) or placebo (n=587) intravenously every 3 weeks.

Treatment continued until RECIST 1.1-defined disease recurrence as determined by the investigator, unacceptable toxicity, or approximately 1 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.

Of 1 177 patients randomised, 1 010 (86%) received adjuvant platinum-based chemotherapy following complete resection. Among these 1 010 patients in KEYNOTE-091, baseline characteristics were: median age of 64 years (range: 35 to 84), 49% age 65 or older; 68% male; and 77% White, 18% Asian, 86% current or former smokers. Sixty-one percent and 39% had ECOG performance of 0 or 1, respectively. Twelve percent had stage IB (T2a ≥ 4 cm), 57% had stage II, and 31% had stage IIIA disease. Thirty-nine percent had tumour PD-L1 expression TPS < 1% [negative], 33% had TPS 1-49%, 28% had TPS ≥ 50%. Seven percent had known EGFR mutations, thirty-eight percent without EGFR mutations and in fifty-six percent EGFR mutation status was unknown. Fifty-two percent were from Western Europe, 20% from Eastern Europe, 17% from Asia, and 11% from Rest of World.

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%.

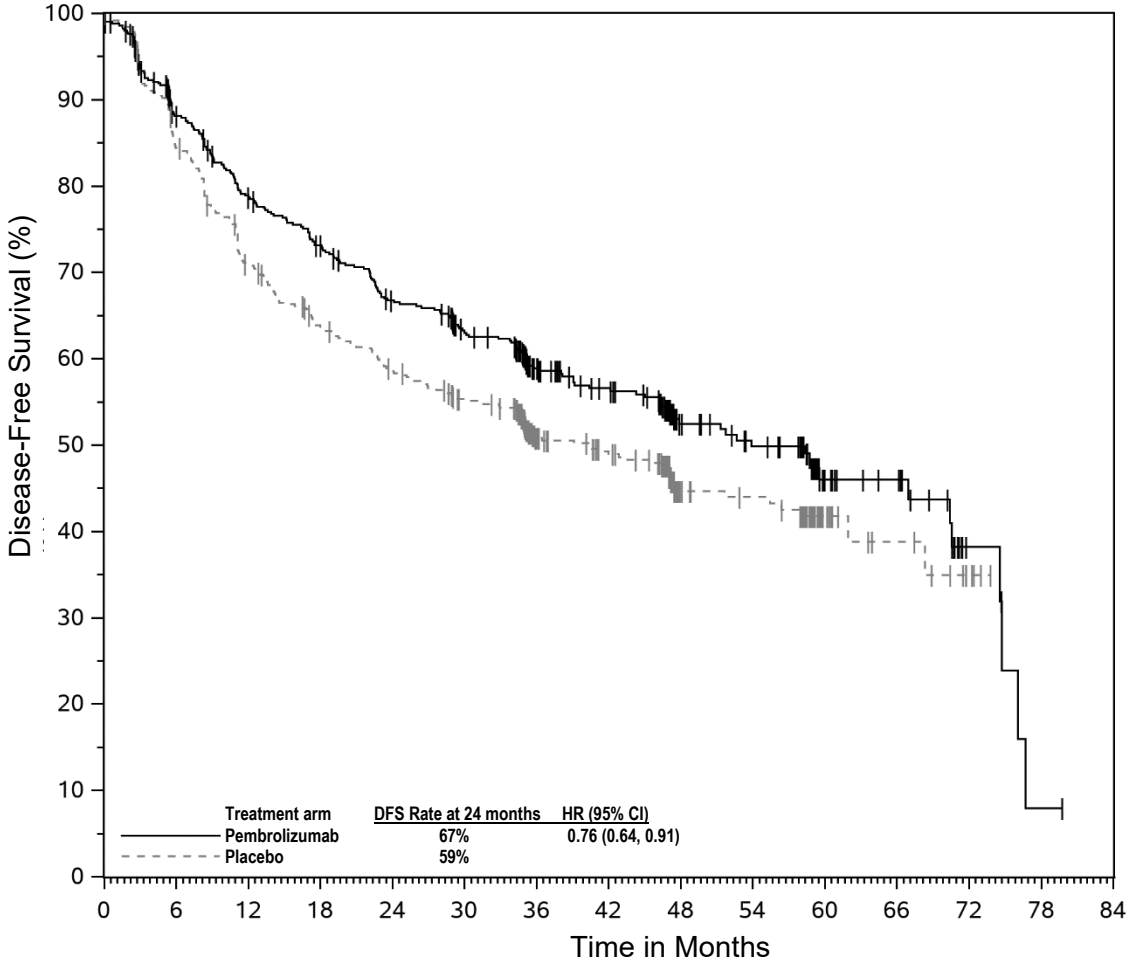
The study demonstrated a statistically significant improvement in DFS in the overall population (HR = 0.76 [95% CI: 0.63, 0.91; p = 0.0014]) at a pre-specified interim analysis with a median follow-up time of 32.4 months (range: 0.6 to 68 months) for patients randomised to the pembrolizumab arm compared to patients randomised to the placebo arm. Table 13 and Figure 10 summarise efficacy results in patients who received adjuvant chemotherapy at the final analysis for DFS performed at a median follow-up time of 46.7 months (range: 0.6 to 84.2). At the time of this analysis, OS results were not mature with only 58% of pre-specified OS events in the overall population. An exploratory analysis of OS suggested a trend in favour of pembrolizumab compared to placebo with a HR of 0.79 (95% CI: 0.62, 1.01) in patients who received adjuvant chemotherapy.

Table 13: Efficacy results in KEYNOTE-091 for patients who received adjuvant chemotherapy

Endpoint	Pembrolizumab 200 mg every 3 weeks n=506	Placebo n=504
DFS		
Number (%) of patients with event	225 (44%)	262 (52%)
Hazard ratio* (95% CI)	0.76 (0.64, 0.91)	
Median in months (95% CI)	53.8 (46.2, 70.4)	40.5 (32.9, 47.4)

* Based on the multivariate Cox regression model

Figure 10: Kaplan-Meier curve for disease-free survival by treatment arm in KEYNOTE-091 (for patients who received adjuvant chemotherapy)



Number at Risk

Pembrolizumab	506	422	373	344	309	281	190	166	85	74	31	23	6	1	0
Placebo	504	422	351	309	284	258	169	151	67	61	19	11	4	0	0

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. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx assay. 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 14 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 14: 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

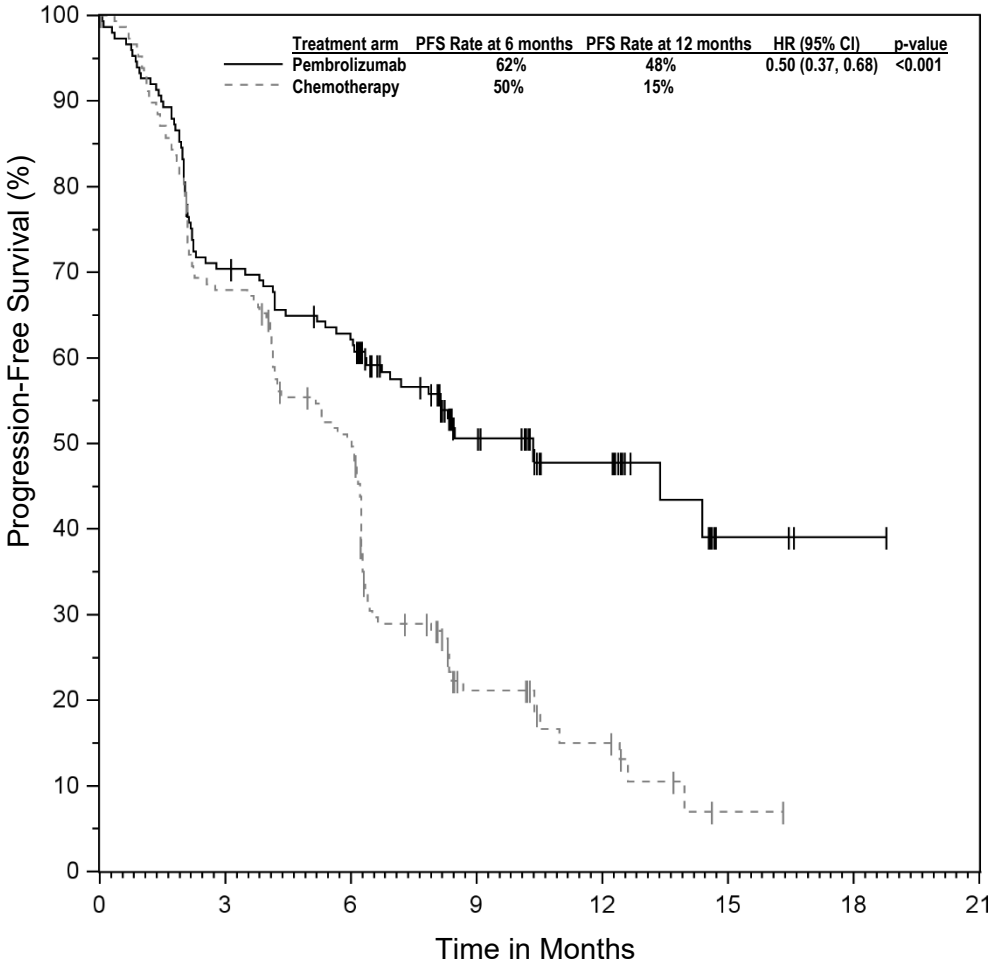
‡ Based on patients with a best objective response as confirmed complete or partial response

§ 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

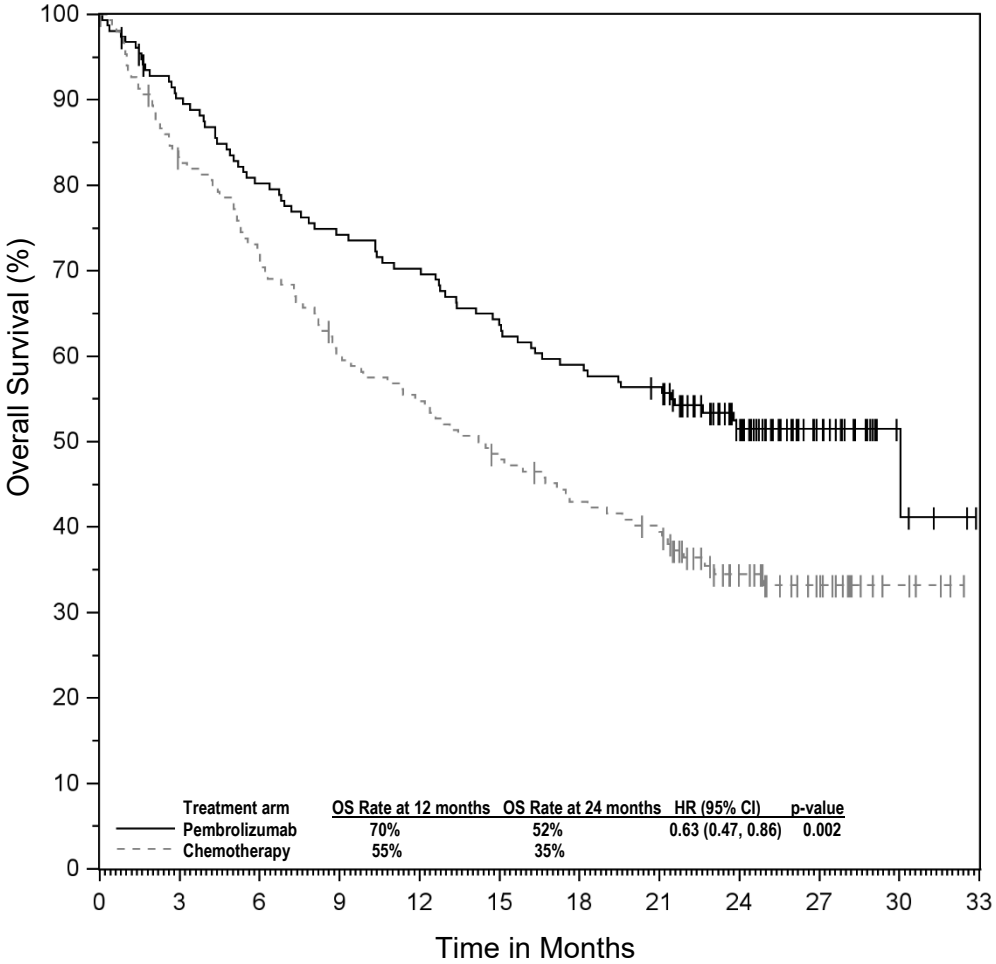
NA = not available

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



Number at Risk								
Pembrolizumab	154	104	89	44	22	3	1	0
Chemotherapy	151	99	70	18	9	1	0	0

Figure 12: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-024 (intent to treat population)



Number at Risk												
Pembrolizumab	154	136	121	112	106	96	89	83	52	22	5	0
Chemotherapy	151	123	107	88	80	70	61	55	31	16	5	0

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. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx assay. 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%. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx assay. 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 15 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 13.

Table 15: Efficacy results (PD-L1 TPS ≥ 50%) in KEYNOTE-042

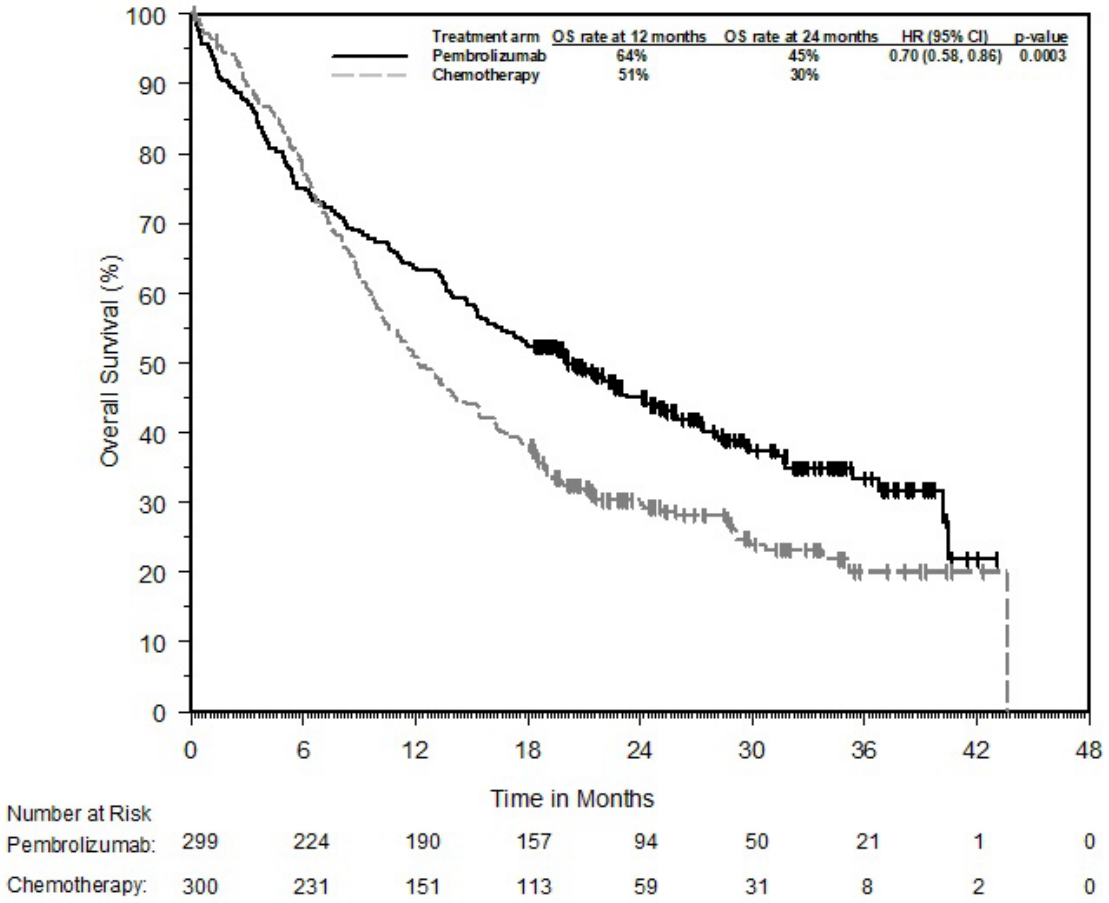
Endpoint	**Pembrolizumab 200 mg every 3 weeks n=299**	**Chemotherapy n=300**
OS		
Number (%) of patients with event	180 (60%)	220 (73%)
Hazard ratio* (95% CI)	0.70 (0.58, 0.86)	
p-Value†	0.0003	
Median in months (95% CI)	20.0 (15.9, 24.2)	12.2 (10.4, 14.6)
PFS		
Number (%) of patients with event	238 (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 13: 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 16 summarises key efficacy measures and Figures 14 and 15 show the Kaplan-Meier curves for OS and PFS based on the final analysis with a median follow-up of 18.8 months.

Table 16: Efficacy results in KEYNOTE-189

Endpoint	**Pembrolizumab + Pemetrexed + Platinum Chemotherapy n=410**	**Placebo + Pemetrexed + Platinum Chemotherapy n=206**
OS*		
Number (%) of patients with event	258 (63%)	163 (79%)
Hazard ratio† (95% CI)	0.56 (0.46, 0.69)	
p-Value‡	< 0.00001	
Median in months (95% CI)	22.0 (19.5, 24.5)	10.6 (8.7, 13.6)
PFS		
Number (%) of patients with event	337 (82%)	197 (96%)
Hazard ratio† (95% CI)	0.49 (0.41, 0.59)	
p-Value‡	< 0.00001	
Median in months (95% CI)	9.0 (8.1, 10.4)	4.9 (4.7, 5.5)
Objective response rate		
ORR§ % (95% CI)	48% (43, 53)	20% (15, 26)
Complete response	1.2%	0.5%
Partial response	47%	19%
p-Value¶	< 0.0001	
Response duration		
Median in months (range)	12.5 (1.1+, 34.9+)	7.1 (2.4, 27.8+)
% with duration ≥ 12 months#	53%	27%

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

† Based on the stratified Cox proportional hazard model

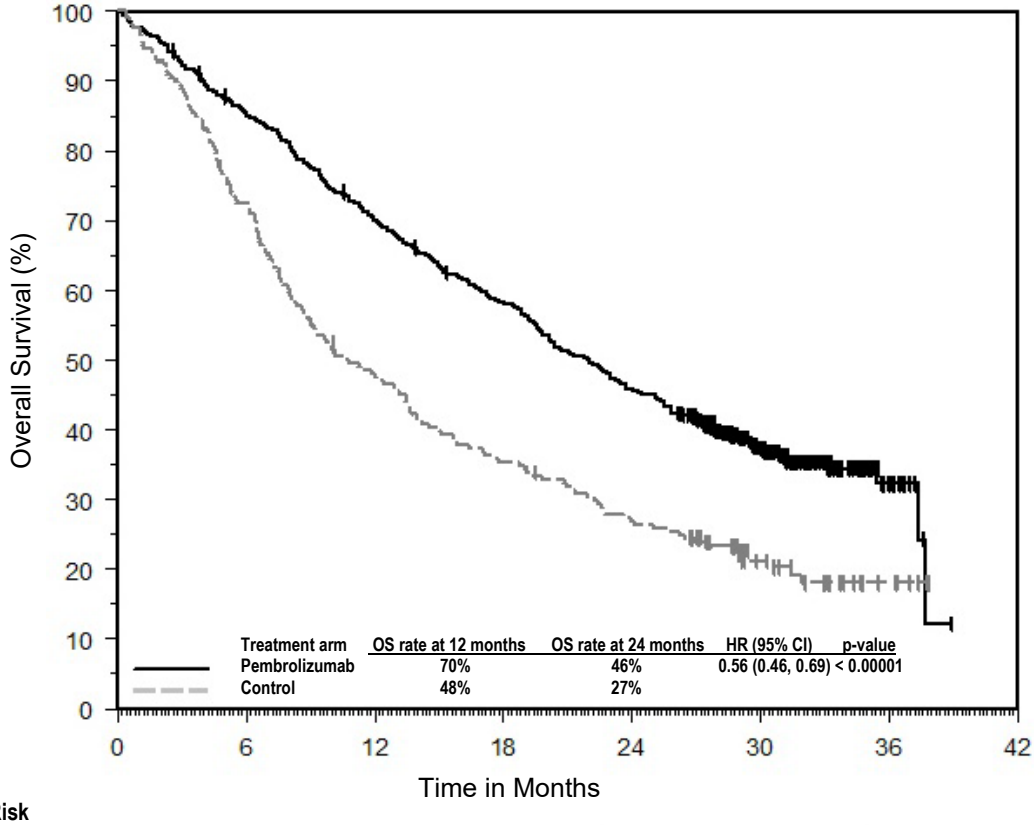
‡ Based on stratified log-rank test

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

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

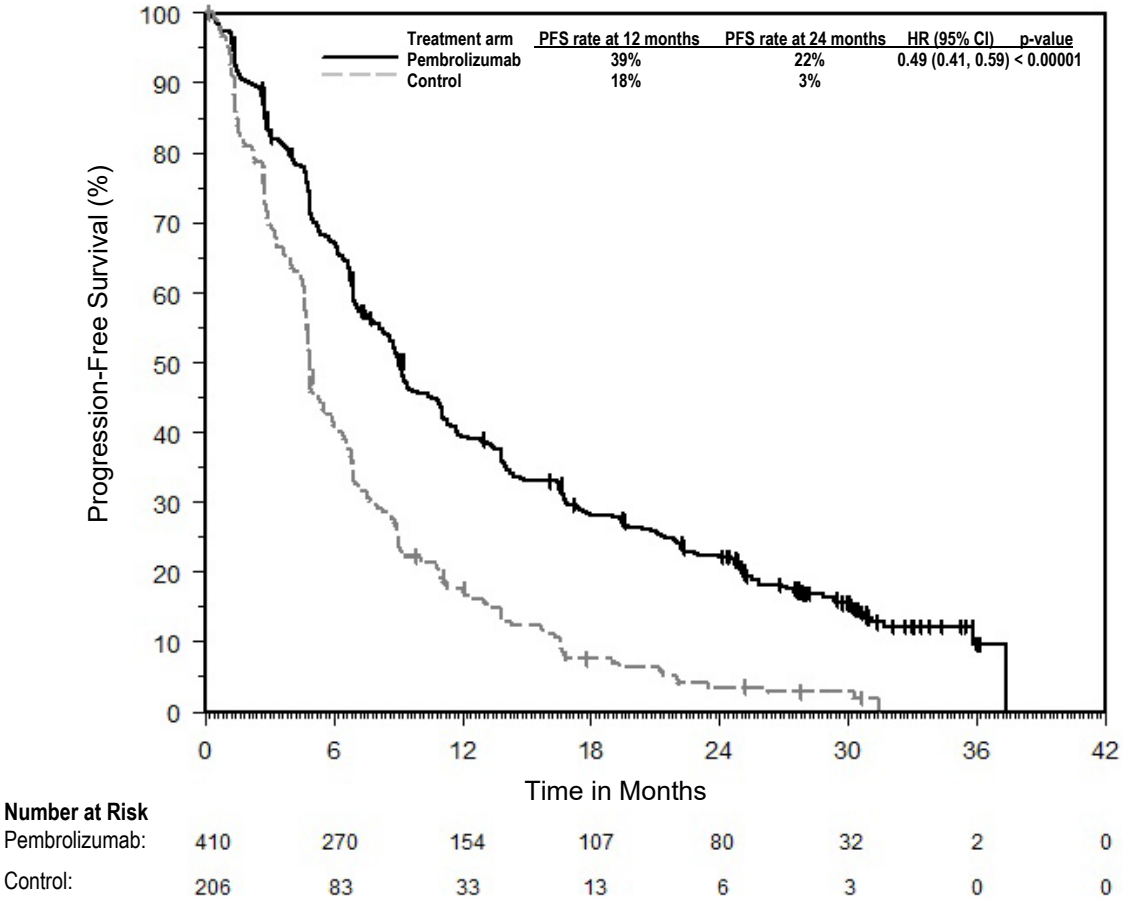
\# Based on Kaplan-Meier estimation

Figure 14: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-189 (intent to treat population)



Number at Risk								
Pembrolizumab:	410	347	283	234	184	86	12	0
Control:	206	149	98	72	55	25	5	0

Figure 15: 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 17).

Table 17: Efficacy results by PD-L1 expression in KEYNOTE-189*

Endpoint	Pembrolizumab combination therapy	Chemotherapy	Pembrolizumab combination therapy	Chemotherapy	Pembrolizumab combination therapy	Chemotherapy
	TPS < 1%		**TPS 1 to 49%**		**TPS ≥ 50%**	
OS Hazard ratio† (95% CI)	0.51 (0.36, 0.71)		0.66 (0.46, 0.96)		0.59 (0.40, 0.86)	
PFS Hazard ratio† (95% CI)	0.67 (0.49, 0.93)		0.53 (0.38, 0.74)		0.35 (0.25, 0.49)	
ORR %	33%	14%	50%	21%	62%	26%

* Based on final analysis

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

At final analysis, a total of 57 NSCLC patients aged ≥ 75 years were enrolled in study KEYNOTE-189 (35 in the pembrolizumab combination and 22 in the control). A HR=1.54 [95% CI 0.76, 3.14] in OS and HR=1.12 [95% CI 0.56, 2.22] in PFS for pembrolizumab combination vs. chemotherapy was reported within this study subgroup. Data about efficacy of pembrolizumab in combination with platinum chemotherapy are limited in this patient population.

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

The efficacy of pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel was investigated in Study KEYNOTE-407, a randomised, double-blind, multicentre, placebo-controlled study. The key eligibility criteria for this study were metastatic squamous NSCLC, regardless of tumour PD-L1 expression status, and no prior systemic treatment for metastatic disease. Patients with autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Randomisation was stratified by tumour PD-L1 expression (TPS < 1% [negative] vs. TPS ≥ 1%), investigator's choice of paclitaxel or nab-paclitaxel, and geographic region (East Asia vs. non-East Asia). Patients were randomised (1:1) to one of the following treatment arms via intravenous infusion:

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

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

Patients in the placebo arm were offered pembrolizumab as a single agent at the time of disease progression.

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

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

The primary efficacy outcome measures were OS and PFS (as assessed by BICR using RECIST 1.1). Secondary efficacy outcome measures were ORR and response duration, as assessed by BICR using RECIST 1.1. Table 18 summarises key efficacy measures and Figures 16 and 17 show the Kaplan-Meier curves for OS and PFS based on the final analysis with a median follow-up of 14.3 months.

Table 18: Efficacy results in KEYNOTE-407

Endpoint	Pembrolizumab Carboplatin Paclitaxel/Nab-paclitaxel n=278	Placebo Carboplatin Paclitaxel/Nab-paclitaxel n=281
OS*		
Number (%) of patients with event	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 patients with event	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 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

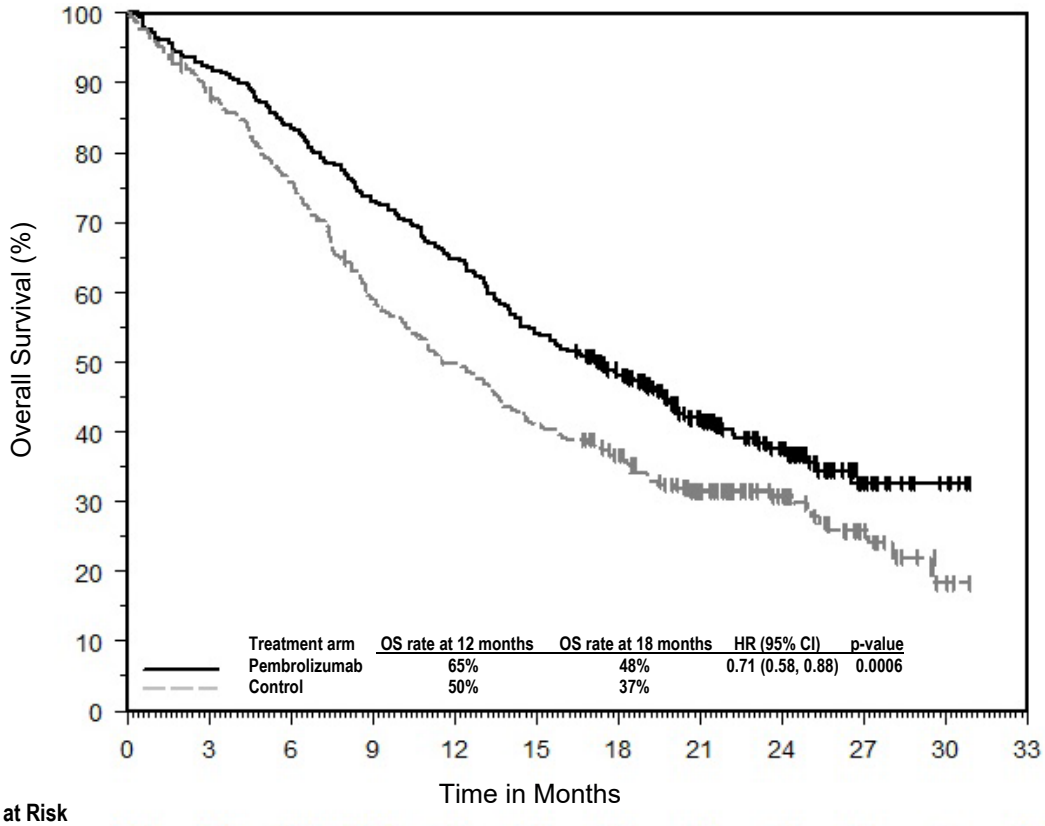
† Based on the stratified Cox proportional hazard model

‡ Based on stratified log-rank test

§ Based on method by Miettinen and Nurminen

¶ Based on Kaplan-Meier estimation

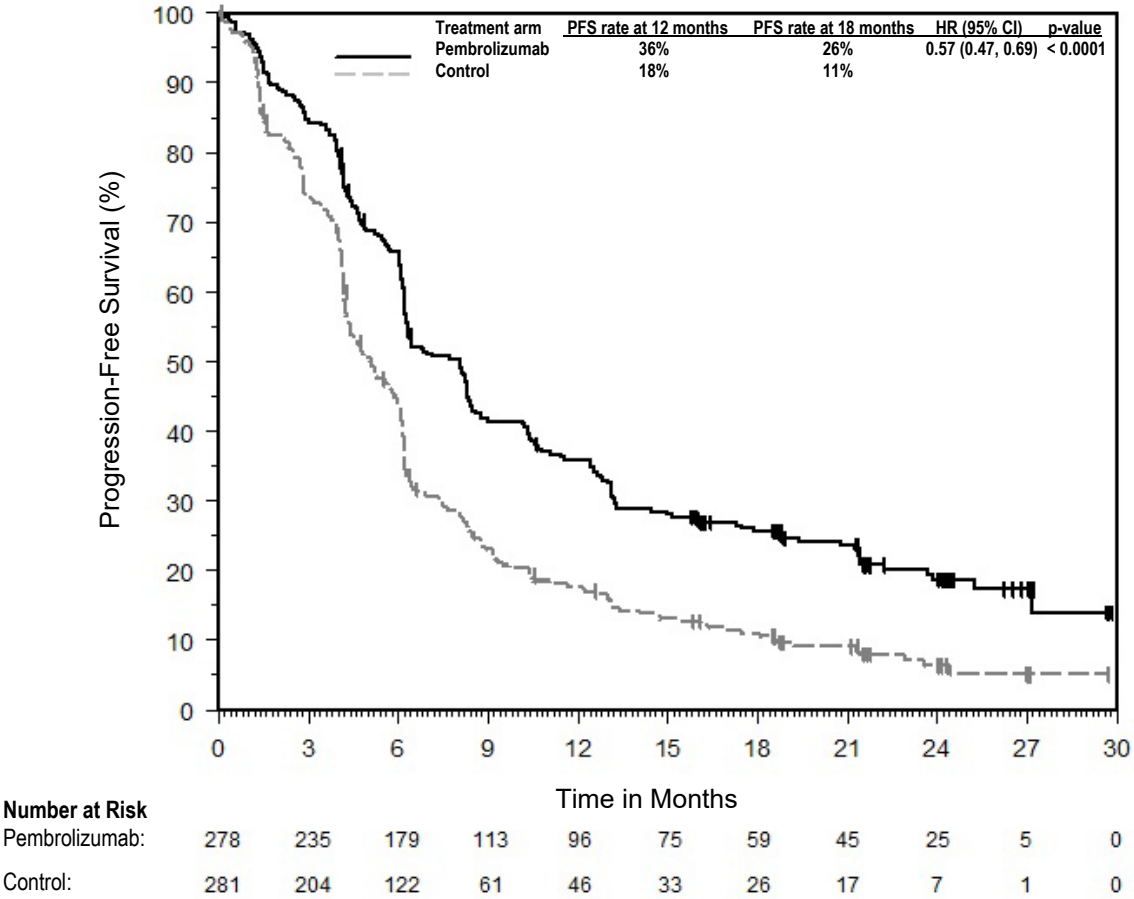
Figure 16: Kaplan-Meier Curve for Overall Survival in KEYNOTE-407



Number at Risk

Pembrolizumab:	278	256	232	203	180	150	119	80	46	14	4	0
Control:	281	245	210	163	137	113	91	61	36	16	3	0

Figure 17: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-407



An analysis was performed in KEYNOTE-407 in patients who had PD-L1 TPS < 1% [pembrolizumab plus chemotherapy arm: n=95 (34%) vs. placebo plus chemotherapy arm: n=99 (35%)], TPS 1% to 49% [pembrolizumab plus chemotherapy arm: n=103 (37%) vs. placebo plus chemotherapy arm: n=104 (37%)] or TPS ≥ 50% [pembrolizumab plus chemotherapy arm: n=73 (26%) vs. placebo plus chemotherapy arm: n=73 (26%)] (see Table 19).

Table 19: 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). A HR=0.81 [95% CI 0.43, 1.55] in OS, a 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. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx assay. 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 20 summarises key efficacy measures for the entire population (TPS ≥ 1%) and for the-patients with TPS ≥ 50%, and Figure 18 shows the Kaplan-Meier curve for OS (TPS ≥ 1%), based on a final analysis with median follow-up of 42.6 months.

Table 20: 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

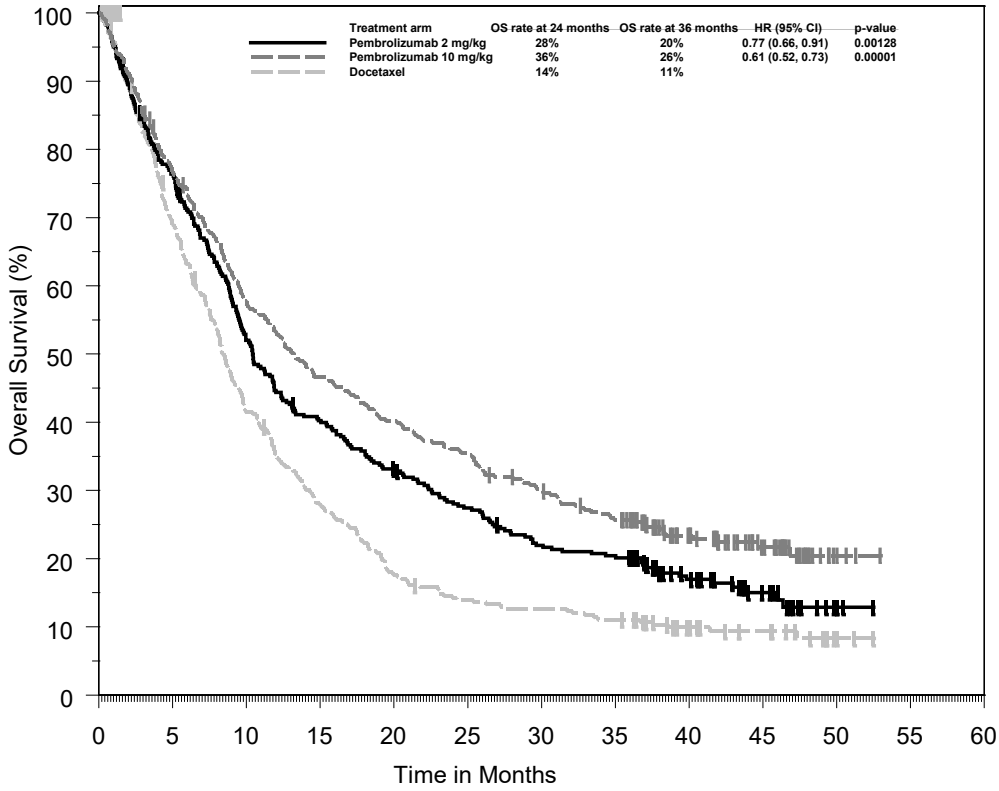
† Based on stratified log-rank test

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



Number at Risk													
Pembrolizumab 2 mg/kg:	344	261	177	136	111	91	72	67	36	17	2	0	0
Pembrolizumab 10 mg/kg:	346	262	197	159	137	120	99	84	50	28	3	0	0
Docetaxel:	343	226	135	90	57	44	40	35	20	13	2	0	0

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

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

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

Malignant pleural mesothelioma
KEYNOTE-483: Controlled study of combination therapy in patients with untreated unresectable advanced or metastatic malignant pleural mesothelioma (MPM)
The efficacy of pembrolizumab in combination with pemetrexed and platinum chemotherapy was investigated in KEYNOTE-483, a multicentre, randomised, open-label, active-controlled study. Key eligibility criteria were unresectable advanced or metastatic MPM with no prior systemic therapy for advanced/metastatic disease. Patients were enrolled regardless of tumour PD-L1 expression. Patients with autoimmune disease that required systemic therapy within 3 years of treatment or a medical condition that required immunosuppression were ineligible. Randomisation was stratified by histological subtype (epithelioid vs. non-epithelioid). Patients were randomised (1:1) to one of the following treatment arms; all study medications were administered via intravenous infusion:

- Pembrolizumab 200 mg with pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 or carboplatin AUC 5-6 mg/mL/min on Day 1 of each 21-day cycle for up to 6 cycles,

followed by pembrolizumab 200 mg every 3 weeks (n=222). Pembrolizumab was administered prior to chemotherapy on Day 1.

- Pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 or carboplatin AUC 5-6 mg/mL/min on Day 1 of each 21-day cycle for up to 6 cycles (n=218).

Treatment with pembrolizumab continued until disease progression as determined by the investigator according to modified RECIST 1.1 for mesothelioma (mRECIST), unacceptable toxicity, or a maximum of 24 months. Assessment of tumour status was performed every 6 weeks for 18 weeks, followed by every 12 weeks thereafter.

Among the 95 patients with non-epithelioid histology in KEYNOTE-483, baseline characteristics were: median age of 71 years (range: 48-85 years of age) with 76% age 65 or older; 83% male; 85% White, 15% not reported or unknown; 1% Hispanic or Latino and 44% and 56% ECOG performance status of 0 or 1, respectively.

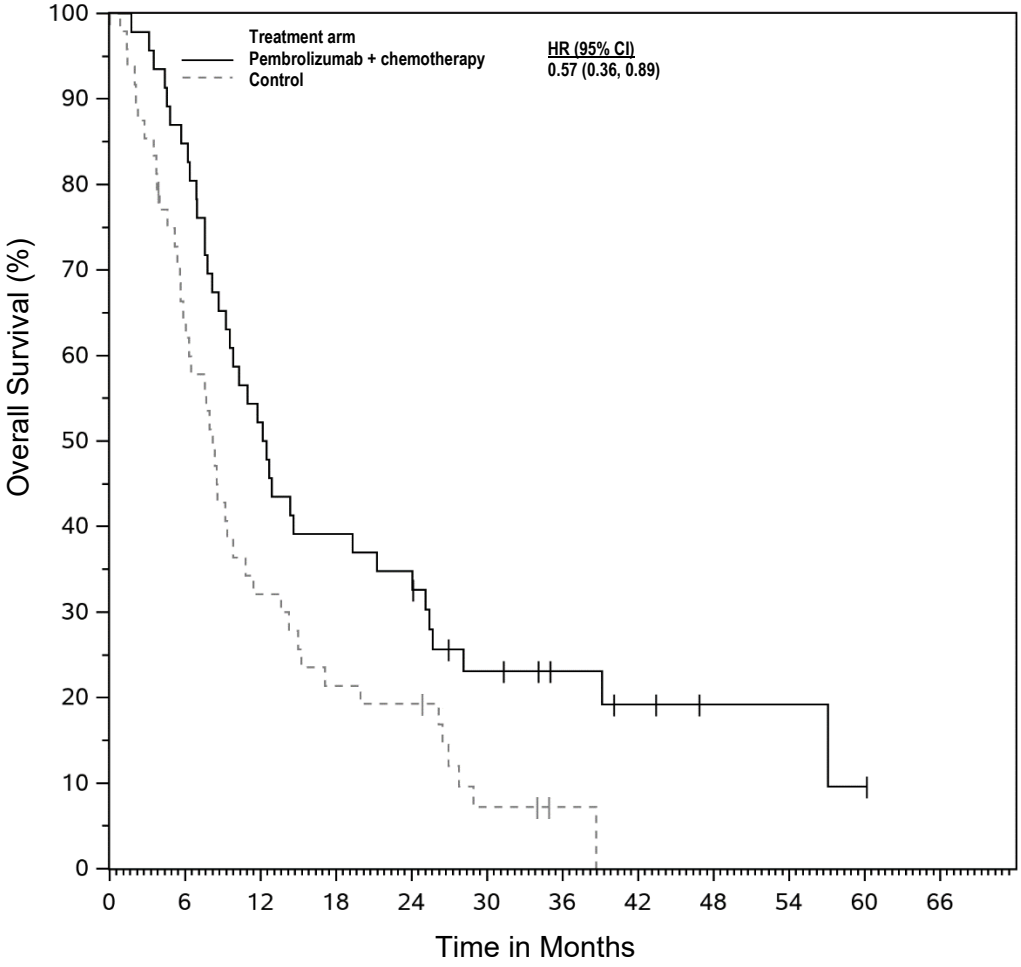
The primary efficacy outcome measure was OS. Additional efficacy outcome measures were PFS, ORR, and DoR, as assessed by BICR using mRECIST. The study demonstrated statistically significant improvement in the overall population in OS [HR 0.79; 95% CI 0.64, 0.98; p-Value 0.0162] and PFS [HR 0.80; 95% CI 0.65, 0.99; p-Value 0.0194] at the final analysis and ORR [52% (95% CI 45, 59) vs. 29% (95% CI 23, 35); p-Value < 0.00001] at the interim analysis in patients randomised to pembrolizumab in combination with chemotherapy compared with patients randomised to chemotherapy alone. Table 21 summarises key efficacy measures and Figures 19 and 20 show the Kaplan-Meier curves for OS and PFS based on the final analysis with a median follow-up time of 9.8 months (range: 0.9 to 60.3 months) in the patients with non-epithelioid malignant pleural mesothelioma.

Table 21: Efficacy results in KEYNOTE-483 for patients with non-epithelioid malignant pleural mesothelioma

Endpoint	Pembrolizumab 200 mg every 3 weeks + Pemetrexed + Platinum Chemotherapy (n=46)	Pemetrexed + Platinum Chemotherapy (n=49)
OS		
Number (%) of patients with event	37 (80%)	44 (90%)
Hazard ratio* (95% CI)	0.57 (0.36, 0.89)	
Median in months† (95% CI)	12.3 (8.7, 21.2)	8.2 (5.8, 9.8)
PFS		
Number (%) of patients with event	36 (78%)	38 (78%)
Hazard ratio* (95% CI)	0.47 (0.29, 0.77)	
Median in months† (95% CI)	7.1 (4.5, 9.8)	4.5 (4.0, 6.4)
Objective response rate		
ORR % (95% CI)‡	41% (27, 57)	6% (1, 17)
Response duration†		
Median in months (range)	11.1 (1.3+, 38.9+)	4.0 (2.4+, 5.2)

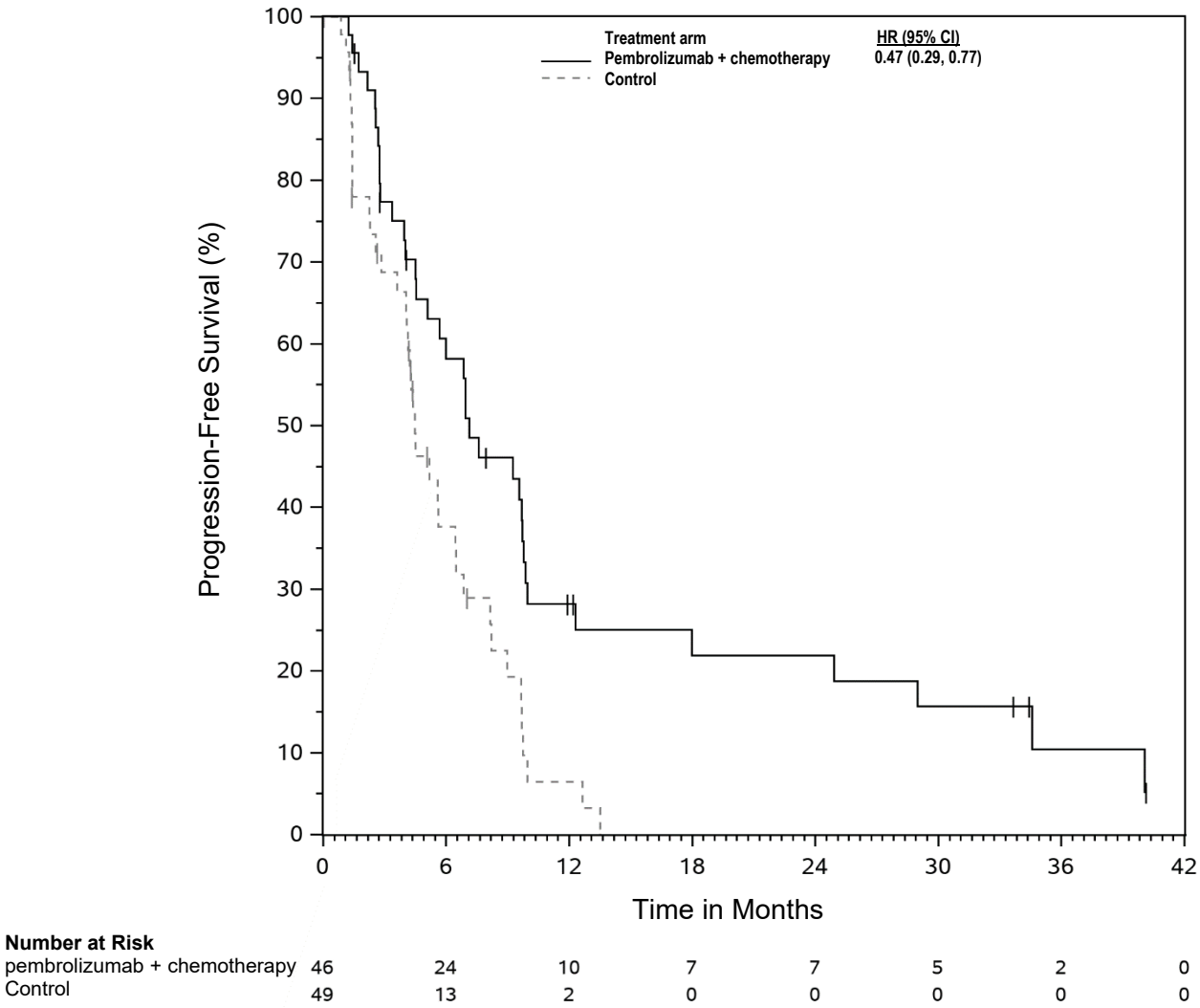
* Based on Cox regression model with Efron's method of tie handling with treatment as a covariate
† From product-limit (Kaplan-Meier) method for censored data
‡ Based on the exact method for binomial data

Figure 19: Kaplan-Meier curve for overall survival in patients with non-epithelioid MPM in KEYNOTE-483



Number at Risk												
pembrolizumab + chemotherapy	46	39	24	18	16	9	6	4	2	2	1	0
Control	49	30	15	10	9	3	1	0	0	0	0	0

Figure 20: Kaplan-Meier curve for progression-free survival in patients with non-epithelioid MPM in KEYNOTE-483



Classical Hodgkin lymphoma

KEYNOTE-204: Controlled study in patients with relapsed or refractory classical Hodgkin lymphoma (cHL)

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

- Pembrolizumab 200 mg intravenously every 3 weeks.
- Brentuximab vedotin (BV) 1.8 mg/kg bw intravenously every 3 weeks.

Patients received pembrolizumab 200 mg intravenously every 3 weeks until unacceptable toxicity or documented disease progression, or a maximum of 35 cycles. Limited data are currently available on response duration following pembrolizumab discontinuation at cycle 35. Response was assessed every 12 weeks, with the first planned post-baseline assessment at Week 12.

Among the 304 patients in KEYNOTE-204, there is a subpopulation consisting of 112 patients who failed a transplant before enrolling and 137 who failed 2 or more prior therapies and were ineligible for ASCT at the time of enrolment. The baseline characteristics of these 249 patients were: median age 34 years (11% age 65 or older); 56% male; 80% White and 7% Asian and 58% and 41% with an ECOG performance status 0 and 1, respectively. Approximately 30% were refractory to frontline chemotherapy and ~ 45% had received prior ASCT. Nodular sclerosis was the more represented cHL histological subtype (~ 81%) and bulky disease, B symptoms and bone marrow involvement were present in approximately 21%, 28% and 4% of patients, respectively.

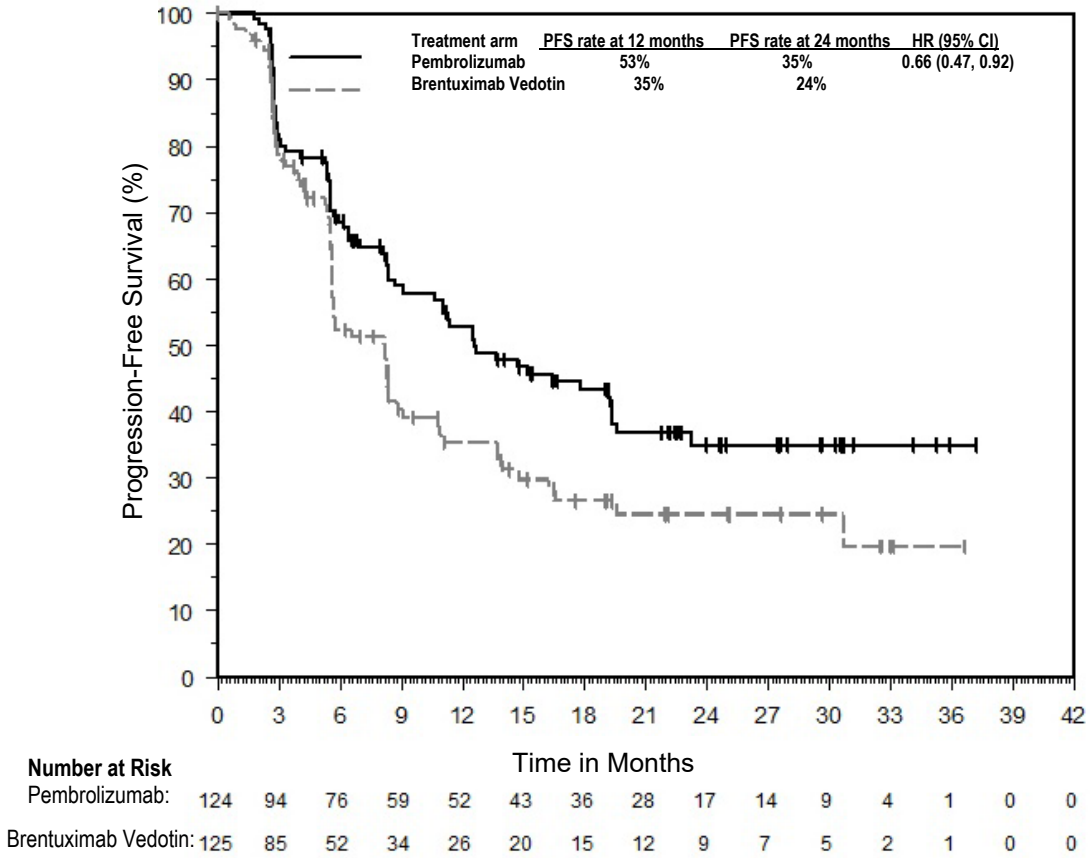
The primary efficacy outcome was PFS and the secondary efficacy outcome measure was ORR, both assessed by BICR according to the 2007 revised International Working Group (IWG) criteria. The additional primary efficacy outcome measure, OS, was not formally assessed at the time of the analysis. In the ITT population, the median follow-up time for 151 patients treated with pembrolizumab was 24.9 months (range: 1.8 to 42.0 months). The initial analysis resulted in a HR for PFS of 0.65 (95% CI: 0.48, 0.88) with a one-sided p value of 0.0027. The ORR was 66% for pembrolizumab compared to 54% for standard treatment with a p-Value of 0.0225. Table 22 summarises the efficacy results in the subpopulation. Efficacy results in this subpopulation were consistent with the ITT population. The Kaplan-Meier curve for PFS for this subpopulation is shown in Figure 21.

Table 22: Efficacy results in cHL patients who failed a transplant before enrolling or who failed 2 or more prior therapies and were ineligible for ASCT in KEYNOTE-204

Endpoint	**Pembrolizumab** **200 mg every 3 weeks n=124**	**Brentuximab vedotin 1.8 mg/kg bw every 3 weeks n=125**
PFS		
Number (%) of patients with event	68 (55%)	75 (60%)
Hazard ratio* (95% CI)	0.66 (0.47, 0.92)	
Median in months (95% CI)	12.6 (8.7, 19.4)	8.2 (5.6, 8.8)
Objective response rate		
ORR‡ % (95% CI)	65% (56.3, 73.6)	54% (45.3, 63.3)
Complete response	27%	22%
Partial response	39%	33%
Stable disease	12%	23%
Response duration		
Median in months (range)	20.5 (0.0+, 33.2+)	11.2 (0.0+, 33.9+)
Number (%¶) of patients with duration ≥ 6 months	53 (80.8%)	28 (61.2%)
Number (%¶) of patients with duration ≥ 12 months	37 (61.7%)	17 (49.0%)

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

Figure 21: Kaplan-Meier curve for progression-free survival by treatment arm in cHL patients who failed a transplant before enrolling or who failed 2 or more prior therapies and were ineligible for ASCT in KEYNOTE-204



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

Among KEYNOTE-087 patients, the baseline characteristics were median age 35 years (9% age 65 or older); 54% male; 88% White; and 49% and 51% had an ECOG performance status 0 and 1, respectively. The median number of prior lines of therapy administered for the treatment of cHL was 4 (range: 1 to 12). Eighty-one percent were refractory to at least one prior therapy, including 34% who were refractory to first-line therapy. Sixty-one percent of patients had received ASCT, 38% were transplant ineligible; 17% had no prior brentuximab vedotin use; and 37% of patients had prior radiation therapy. Disease subtypes were 81% nodular sclerosis, 11% mixed cellularity, 4% lymphocyte-rich and 2% lymphocyte-depleted.

Among KEYNOTE-013 patients, the baseline characteristics were median age 32 years (7% age 65 or older), 58% male, 94% White; and 45% and 55% had an ECOG performance status 0 and 1, respectively. The median number of prior lines of therapy administered for the treatment of cHL was 5

(range: 2 to 15). Eighty-four percent were refractory to at least one prior therapy, including 35% who were refractory to first-line therapy. Seventy-four percent of patients had received ASCT, 26% were transplant ineligible, and 45% of patients had prior radiation therapy. Disease subtypes were 97% nodular sclerosis and 3% mixed cellularity.

The primary efficacy outcome measures (ORR and CRR) were assessed by BICR according to the IWG 2007 criteria. Secondary efficacy outcome measures were duration of response, PFS and OS. Response was assessed in KEYNOTE-087 and KEYNOTE-013 every 12 and 8 weeks, respectively, with the first planned post-baseline assessment at Week 12. Main efficacy results are summarised in Table 23.

Table 23: Efficacy results in KEYNOTE-087 and KEYNOTE-013

	KEYNOTE-087*	**KEYNOTE-013†**
Endpoint	**Pembrolizumab 200 mg every 3 weeks n=210**	**Pembrolizumab 10 mg/kg bw every 2 weeks n=31**
Objective response rate‡		
ORR % (95% CI)	71% (64.8, 77.4)	58% (39.1, 75.5)
Complete remission	28%	19%
Partial remission	44%	39%
Response duration‡		
Median in months (range)	16.6 (0.0+, 62.1+)§	Not reached (0.0+, 45.6+)¶
% with duration ≥ 12-months	59%#	70%Þ
% with duration ≥ 24-months	45%ß	---
% with duration ≥ 60-months	25%à	---
Time to response		
Median in months (range)	2.8 (2.1, 16.5)§	2.8 (2.4, 8.6)¶
OS		
Number (%) of patients with event	59 (28%)	6 (19%)
12-month OS rate	96%	87%
24-month OS rate	91%	87%
60-month OS rate	71%	---

* Median follow-up time of 62.9 months
† Median follow-up time of 52.8 months
‡ Assessed by BICR according to the IWG 2007 criteria by PET CT scans
§ Based on patients (n=150) with a response by independent review
¶ Based on patients (n=18) with a response by independent review
\# Based on Kaplan-Meier estimation; includes 62 patients with responses of 12 months or longer
Þ Based on Kaplan-Meier estimation; includes 7 patients with responses of 12 months or longer
ß Based on Kaplan-Meier estimation; includes 37 patients with responses of 24 months or longer
à Based on Kaplan-Meier estimation; includes 4 patients with responses of 60 months or longer

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

Urothelial carcinoma
KEYNOTE-B15: Controlled study of combination with enfortumab vedotin for the neoadjuvant and adjuvant treatment of patients with MIBC who are eligible for cisplatin-containing chemotherapy
The efficacy of pembrolizumab in combination with enfortumab vedotin as neoadjuvant treatment and continued after radical cystectomy as adjuvant treatment was investigated in KEYNOTE-B15, an open-label, randomised, multicentre, active-controlled study in patients with MIBC. Key eligibility criteria were previously untreated Stage cT2-T4aN0M0 or cT1-T4aN1M0 MIBC in patients who were cisplatin-eligible and were eligible for radical cystectomy (RC) and pelvic lymph node dissection (PLND), regardless of PD-L1 status. 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 tumour stage (T2N0 vs. T3/T4aN0 vs. T1-T4aN1), PD-L1 combined positive score (CPS ≥ 10 vs. CPS < 10), and geographic region (United States vs. European Union vs. Most of the World). Patients were randomised (1:1) to one of the following treatment arms; all study medications were administered via intravenous infusion.

- Pembrolizumab in combination with enfortumab vedotin (n=405): neoadjuvant pembrolizumab 200 mg over 30 minutes on Day 1 and enfortumab vedotin 1.25 mg/kg on Days 1 and 8 of each 21-day cycle for 4 cycles. Following RC and PLND, adjuvant pembrolizumab 200 mg over 30 minutes on Day 1 of each 21-day cycle for 13 cycles and adjuvant enfortumab vedotin 1.25 mg/kg on Days 1 and 8 of each 21-day cycle for 5 cycles.
- Gemcitabine and cisplatin (n=403): neoadjuvant gemcitabine 1 000 mg/m^2 on Days 1 and 8 and cisplatin 70 mg/m^2 on Day 1 of each 21-day cycle for 4 cycles. Following RC and PLND, followed by observation.

Treatment continued until completion of study medications, disease progression that precluded RC and PLND, not undergoing or refusal of RC and PLND, disease recurrence in the adjuvant phase, or unacceptable toxicity. Assessment of tumour status was performed at baseline, within 5 weeks prior to RC and PLND, and at 6 weeks post-radical cystectomy. Following RC and PLND, assessment of tumour status was performed every 12 weeks up to 2 years, and every 24 weeks thereafter.

The study population characteristics were: median age of 66 years; 81% male; and 80% White; 57% were CPS ≥ 10 and 43% were CPS < 10; 78% had ECOG PS of 0 and 22% had ECOG PS of 1; 19% were T2N0, 73% T3/T4aN0, and 8% T1-T4aN1. Eighty-nine percent of patients had urothelial carcinoma histology; 4.8% had urothelial carcinoma with squamous differentiation, 2.6% had urothelial carcinoma with glandular differentiation, and 3.1% had urothelial carcinoma with other histologic variants.

A total of 351 (87%) patients in the pembrolizumab in combination with enfortumab vedotin arm and 361 (90%) patients in the gemcitabine and cisplatin based chemotherapy arm underwent radical cystectomy.

The primary efficacy outcome measure was EFS as assessed by BICR. Additional efficacy outcome measures were pCR rate as assessed by BICR and OS.

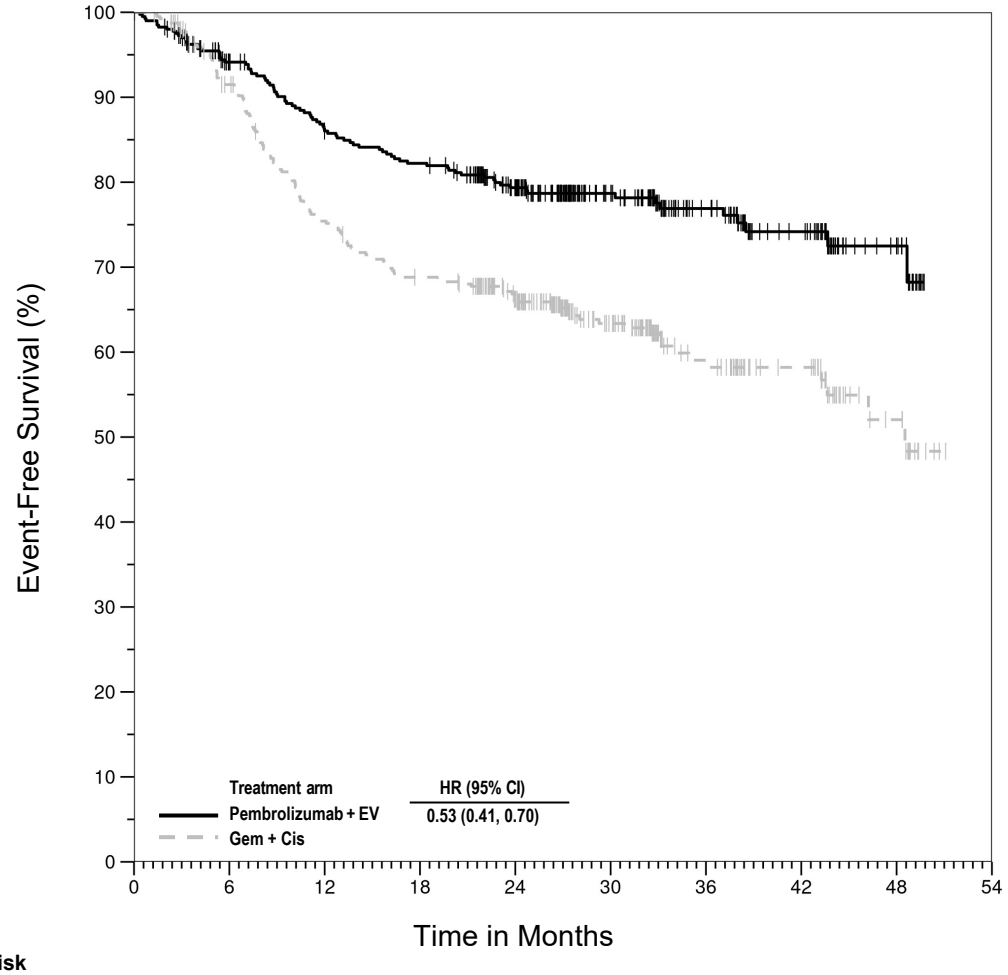
The study demonstrated a statistically significant improvement in EFS, OS, and pCR in patients treated with neoadjuvant and adjuvant pembrolizumab in combination with enfortumab vedotin compared with patients treated with neoadjuvant chemotherapy. The median follow-up time for patients randomised to treatment with pembrolizumab in combination with enfortumab vedotin was 31.3 months (range: 0.5-53.6 months). Table 24 summarises key efficacy measures. Figures 22 and 23 show the Kaplan-Meier curves for EFS and OS.

Table 24: Efficacy results in KEYNOTE-B15

Endpoint	Pembrolizumab 200 mg every 3 weeks in combination with enfortumab vedotin n=405	Gemcitabine with cisplatin chemotherapy n=403
EFS		
Number of patients with event (%)	87 (21%)	146 (36%)
Median in months* (95% CI)	NR (NR, NR)	48.5 (43.3, NR)
Hazard ratio† (95% CI)	0.53 (0.41, 0.70)	
p-Value‡	< 0.0001	
OS		
Number of patients with event (%)	69 (17%)	99 (25%)
Median in months* (95% CI)	NR (NR, NR)	NR (NR, NR)
Hazard ratio† (95% CI)	0.65 (0.48, 0.89)	
p-Value‡	0.0029	
pCR		
Number of patients with pCR	226	131
pCR Rate (%), (95% CI)	55.8 (50.8, 60.7)	32.5 (28.0, 37.3)
Treatment difference estimate (%), (95% CI)§	23.4 (16.7, 29.8)	
p-Value	< 0.0001	

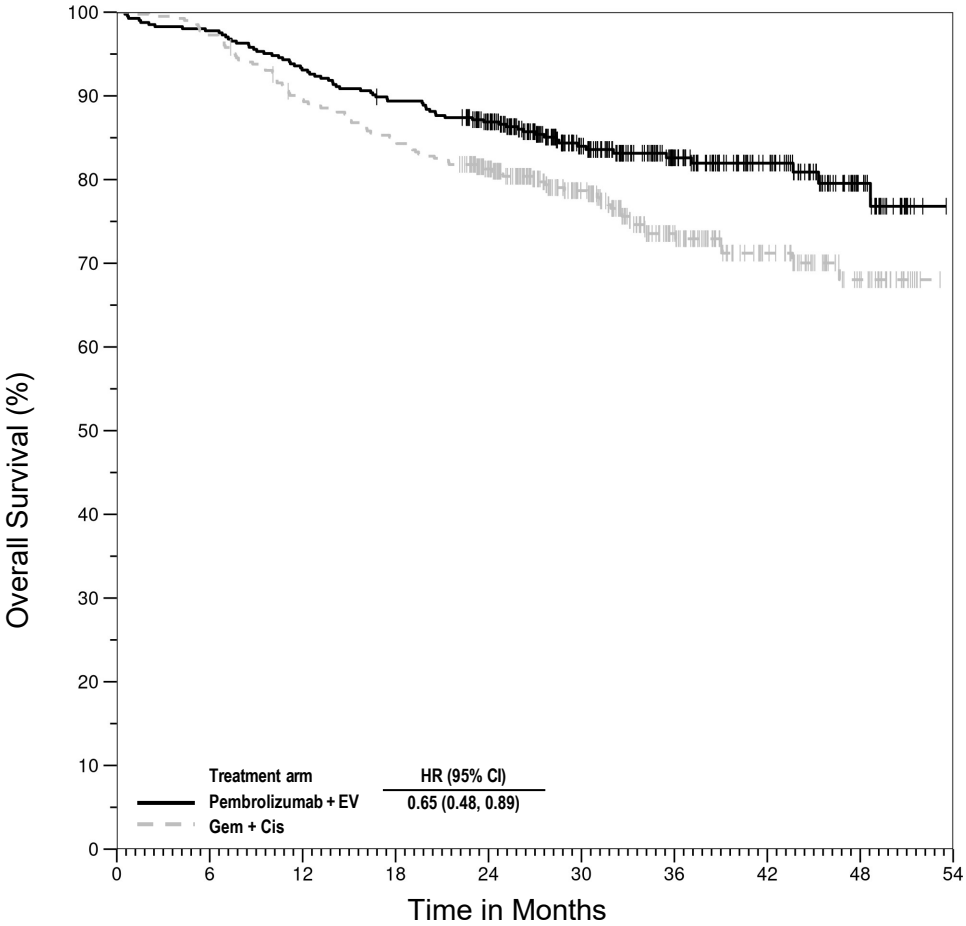
* Based on Kaplan-Meier estimates
† Based on stratified Cox regression model with Efron's method of tie handling with treatment as a covariate
‡ Based on stratified log-rank test
§ Based on stratified Miettinen and Nurminen method
NR = not reached

Figure 22: Kaplan-Meier curve for event-free survival by treatment arm in KEYNOTE-B15



Number at Risk										
Pembrolizumab + EV	405	351	317	303	257	154	100	63	23	0
Gem + Cis	403	350	286	259	216	131	70	45	16	0

Figure 23: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-B15



Number at Risk										
Pembrolizumab + EV	405	396	377	361	325	215	142	90	34	0
Gem + Cis	403	392	358	338	295	201	119	67	29	0

KEYNOTE-905: Controlled study of combination with enfortumab vedotin for neoadjuvant and adjuvant treatment of patients with MIBC who are ineligible for cisplatin-containing chemotherapy
The efficacy of pembrolizumab in combination with enfortumab vedotin as neoadjuvant treatment and continued after radical cystectomy as adjuvant treatment was investigated in KEYNOTE-905, an open-label, randomised, multicentre, active-controlled study in patients with MIBC. Key eligibility criteria were previously untreated cT2-T4aN0M0 or cT1-T4aN1M0 MIBC in patients who were ineligible for or declined cisplatin-based chemotherapy and were eligible for radical cystectomy (RC) and pelvic lymph node dissection (PLND), regardless of PD-L1 status. Patients with active autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Patients were randomised 1:1:1 to receive neoadjuvant and adjuvant pembrolizumab in combination with enfortumab vedotin, neoadjuvant and adjuvant pembrolizumab monotherapy, or RC and PLND alone. Randomisation was stratified by tumour stage (T2N0 vs. T3/T4aN0 vs. T1-T4aN1), cisplatin eligibility (cisplatin-ineligible vs. cisplatin-eligible but declined), and geographic region (United States vs. European Union vs. Rest of the World). The study population characteristics and evaluation of efficacy were based on the following treatment arms; all study medications were administered via intravenous infusion.

1. Pembrolizumab in combination with enfortumab vedotin (n=170): neoadjuvant pembrolizumab 200 mg over 30 minutes on Day 1 and enfortumab vedotin 1.25 mg/kg on Days 1 and 8 of each 21-day cycle for 3 cycles. Following RC and PLND, adjuvant pembrolizumab 200 mg over 30 minutes on Day 1 of each 21-day cycle for 14 cycles and adjuvant enfortumab vedotin 1.25 mg/kg on Days 1 and 8 of each 21-day cycle for 6 cycles.
2. RC and PLND alone (n=174).

Treatment continued until completion of study medications, disease progression that precluded RC and PLND, not undergoing or refusal of RC and PLND, disease recurrence in the adjuvant phase, or unacceptable toxicity. Assessment of tumour status was performed at baseline, within 5 weeks prior to RC and PLND, and at 6 weeks post-radical cystectomy. Following RC and PLND, assessment of tumour status was performed every 12 weeks up to 2 years, and every 24 weeks thereafter.

The study population characteristics were: median age of 73 years; 78% male; and 78% White; 47% were CPS ≥ 10 and 51% were CPS < 10; 86% had ECOG PS of 0-1 and 14% had ECOG PS of 2; 18% were T2N0, 77% T3/T4aN0, and 5% T1-T4aN1. Forty-one percent of patients had baseline creatinine clearance of ≥ 60 mL/min, 59% had < 60 mL/min but ≥ 30 mL/min, and 0.3% had < 30 mL/min, respectively. Ninety-one percent of patients had urothelial carcinoma histology; 4% had urothelial carcinoma with squamous differentiation, 3% had urothelial carcinoma with glandular differentiation, and 2% had urothelial carcinoma with other variant histology.

A total of 149 (88%) patients in the pembrolizumab in combination with enfortumab vedotin arm and 156 (90%) patients in the RC and PLND alone arm underwent radical cystectomy.

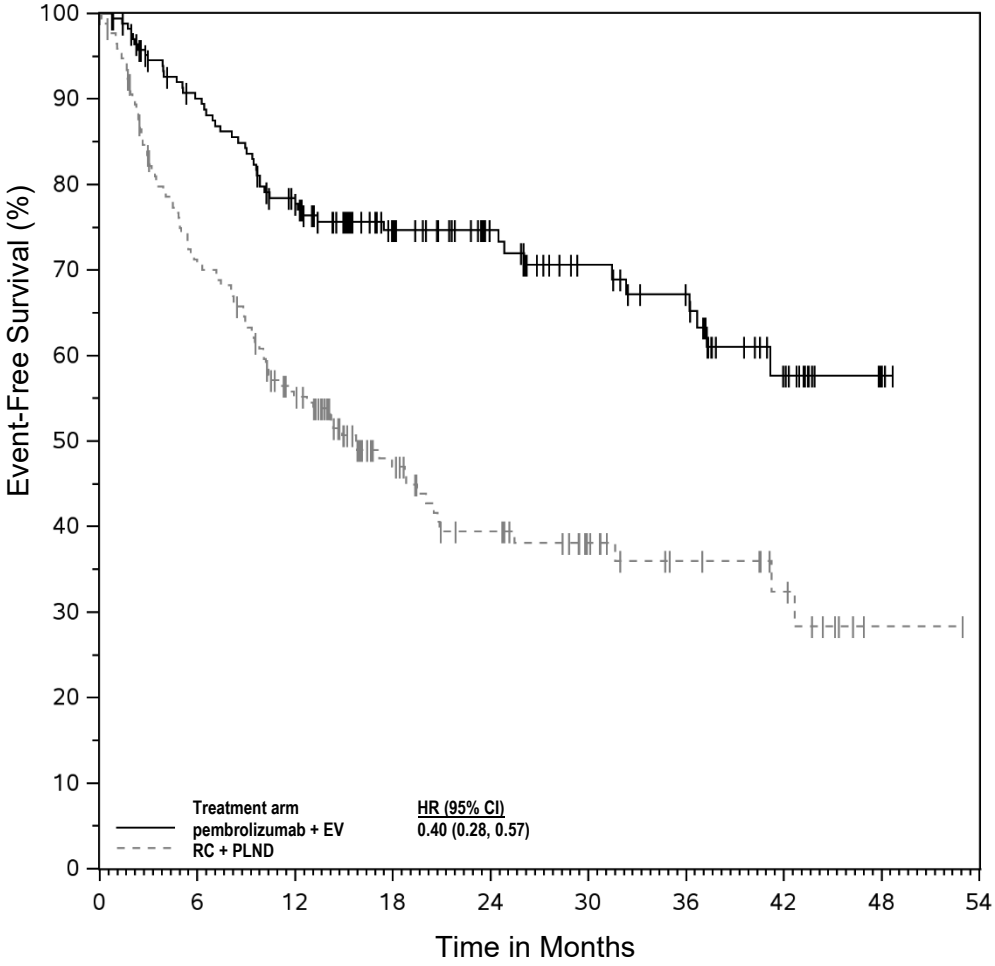
The primary efficacy outcome measure was EFS as assessed by BICR. Additional efficacy outcome measures were pCR rate as assessed by BICR and OS. The study demonstrated a statistically significant improvement in EFS, OS, and pCR in patients treated with neoadjuvant and adjuvant pembrolizumab in combination with enfortumab vedotin compared with RC and PLND alone. The median follow-up time for patients randomised to treatment with pembrolizumab in combination with enfortumab vedotin was 20.4 months (range: 1.4-52.6 months). Table 25 summarises key efficacy measures. Figures 24 and 25 show the Kaplan-Meier curves for EFS and OS.

Table 25: Efficacy results in KEYNOTE-905

Endpoint	Pembrolizumab 200 mg every 3 weeks in combination with enfortumab vedotin n=170	RC and PLND alone n=174
EFS		
Number of patients with event (%)	48 (28%)	95 (55%)
Median in months* (95% CI)	NR (37.3, NR)	15.7 (10.3, 20.5)
Hazard ratio† (95% CI)	0.40 (0.28, 0.57)	
p-Value‡	< 0.0001	
OS		
Number of patients with event (%)	38 (22%)	68 (39%)
Median in months* (95% CI)	NR (NR, NR)	41.7 (31.8, NR)
Hazard ratio† (95% CI)	0.50 (0.33, 0.74)	
p-Value‡	0.0002	
pCR		
Number of patients with pCR	97	15
pCR Rate (%), (95% CI)	57.1 (49.3, 64.6)	8.6 (4.9, 13.8)
Treatment difference estimate (%), (95% CI)§	48.3 (39.5, 56.5)	
p-Value	< 0.0001	

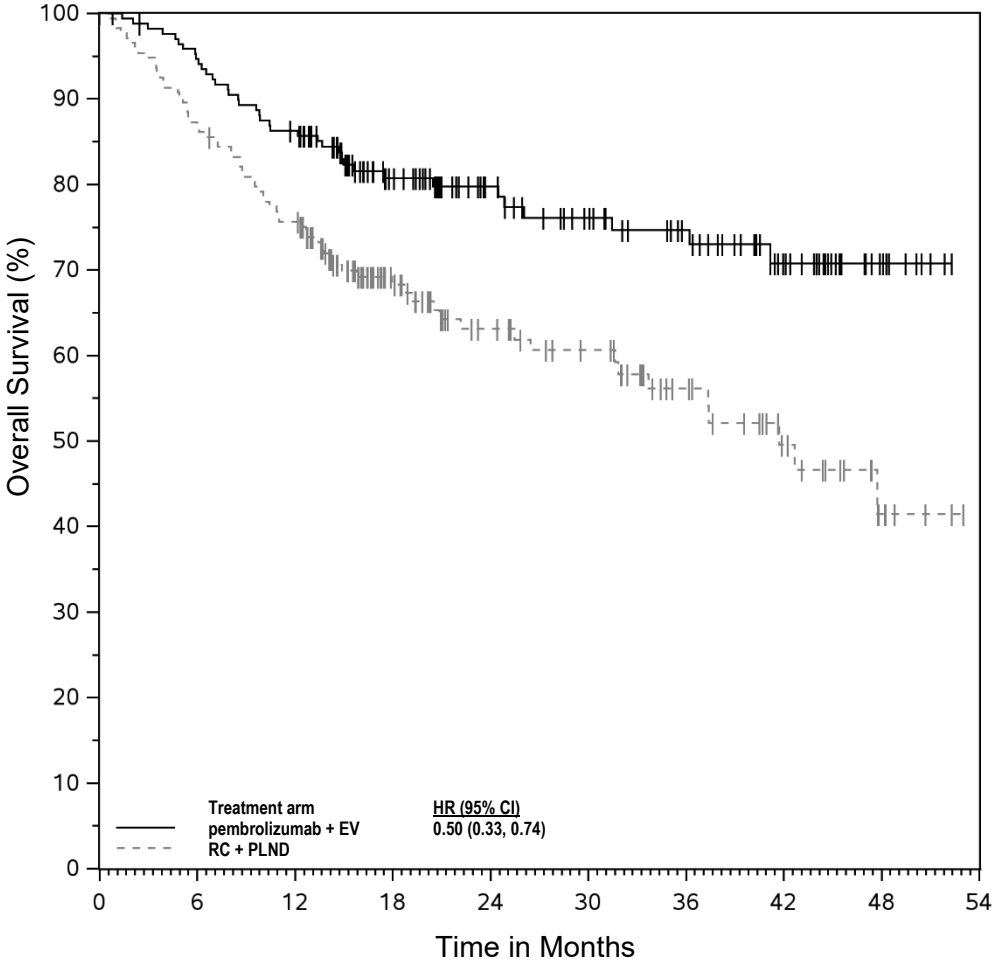
* Based on Kaplan-Meier estimates
† Based on stratified Cox regression model with Efron's method of tie handling with treatment as a covariate
‡ Based on stratified log-rank test
§ Based on stratified Miettinen and Nurminen method
NR = not reached

Figure 24: Kaplan-Meier curve for event-free survival by treatment arm in KEYNOTE-905



Number at Risk										
pembrolizumab + EV	170	140	116	73	56	42	35	16	3	0
RC + PLND	174	116	84	48	33	22	14	9	1	0

Figure 25: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-905



Number at Risk										
pembrolizumab + EV	170	159	144	94	68	56	45	28	10	0
RC + PLND	174	150	130	75	54	45	30	18	6	0

KEYNOTE-A39: Controlled study of combination therapy with enfortumab vedotin for the first-line treatment of unresectable or metastatic urothelial carcinoma

The efficacy of pembrolizumab in combination with enfortumab vedotin was investigated in KEYNOTE-A39, an open-label, multicentre, randomised, active-controlled study, that enrolled 886 patients with unresectable or metastatic urothelial carcinoma. The study excluded patients with autoimmune disease or a medical condition that required immunosuppression, active CNS metastases, ongoing sensory or motor neuropathy ≥ Grade 2, or uncontrolled diabetes defined as haemoglobin A1C (HbA1c) ≥ 8% or HbA1c ≥ 7% with associated diabetes symptoms, pneumonitis, or other forms of interstitial lung disease. Patients who received neoadjuvant chemotherapy or patients who received adjuvant chemotherapy following cystectomy were included in the study if recurrence was > 12 months from completion of therapy. Patients were considered cisplatin-ineligible if they had at least one of the following criteria: glomerular filtration rate 30-59 mL/min, ECOG PS ≥ 2, Grade ≥ 2 hearing loss, or NYHA Class III heart failure. Patients randomised to the gemcitabine and platinum-based chemotherapy arm were permitted to receive maintenance immunotherapy. Randomisation was stratified by cisplatin eligibility (eligible or ineligible), PD-L1 expression (CPS ≥ 10 or CPS < 10 determined using the PD-L1 IHC 22C3 pharmDx assay), and liver metastases (present or absent). Patients were randomised (1:1) to one of the following treatment arms; all study medications were administered via intravenous infusion;

- Pembrolizumab 200 mg over 30 minutes on Day 1 and enfortumab vedotin 1.25 mg/kg on Days 1 and 8 of each 21-day cycle.

- Gemcitabine 1 000 mg/m^2 on Days 1 and 8 and investigator's choice of cisplatin 70 mg/m^2 or carboplatin (AUC 4.5 or 5 mg/mL/min according to local guidelines) on Day 1 of each 21-day cycle.

Treatment with pembrolizumab and enfortumab vedotin continued until RECIST v1.1-defined progression of disease, unacceptable toxicity, or for pembrolizumab a maximum of 35 cycles (up to approximately 2 years). Assessment of tumour status was performed every 9 weeks for 18 months, and then every 12 weeks thereafter.

Among 886 patients with urothelial carcinoma, baseline characteristics were: median age of 69 years; 77% male; and 67% White. Ninety-five percent had M1 disease, and 5% had M0 disease. Seventy-three percent had a primary tumour in the lower tract, and 27% in the upper tract. Fifty-four percent was cisplatin-eligible, 58% had PD-L1 CPS ≥ 10, and 72% had visceral metastases, including 22% with liver metastases. Twenty percent had normal renal function, and 37%, 41% and 2% were characterised with mild, moderate, or severe renal impairment, respectively. Ninety-seven percent had ECOG PS of 0-1 and 3% had ECOG PS of 2. Eighty-five percent had transitional cell carcinoma (TCC) histology, 2% had TCC with other histology and 6% had TCC with squamous differentiation. Thirty-two percent of patients in the gemcitabine and platinum-based chemotherapy arm received maintenance immunotherapy.

The primary efficacy outcome measures were PFS as assessed by BICR according to RECIST v1.1 and OS. Secondary outcome measures were ORR and DoR as assessed by BICR according to RECIST v1.1 and time to pain progression (TTPP).

The study demonstrated a statistically significant improvement in OS, PFS and ORR in patients randomised to pembrolizumab in combination with enfortumab vedotin compared with patients randomised to gemcitabine and platinum-based chemotherapy.

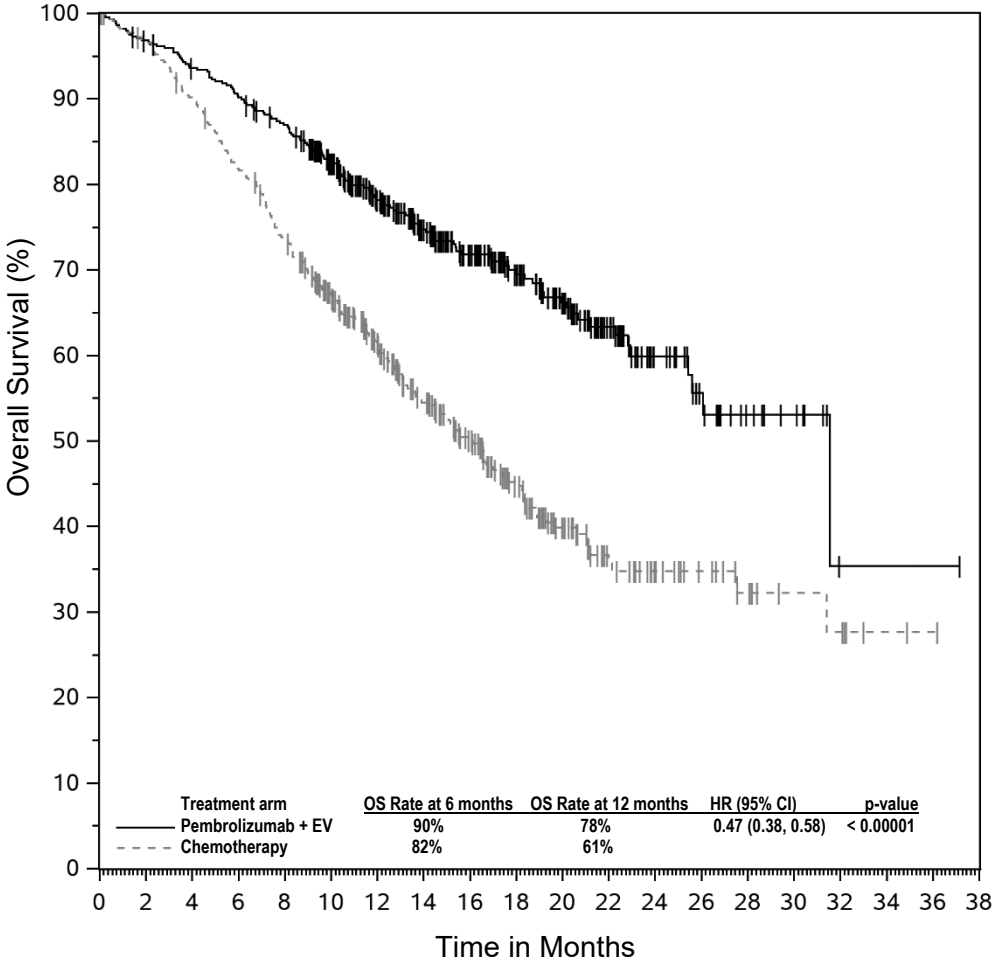
The median follow-up time for 442 patients treated with pembrolizumab and enfortumab vedotin was 17.3 months (range: 0.3 to 37.2 months). Key efficacy results are summarised in Table 26 and Figures 26 and 27.

Table 26: Efficacy results in KEYNOTE-A39

Endpoint	Pembrolizumab 200 mg every 3 weeks in combination with Enfortumab vedotin n=442	Gemcitabine + Platinum chemotherapy with or without maintenance immunotherapy n=444
OS		
Number (%) of patients with event	133 (30%)	226 (51%)
Median in months (95% CI)	31.5 (25.4, NR)	16.1 (13.9, 18.3)
Hazard ratio* (95% CI)	0.47 (0.38, 0.58)	
p-Value†	< 0.00001	
PFS		
Number (%) of patients with event	223 (50%)	307 (69%)
Median in months (95% CI)	12.5 (10.4, 16.6)	6.3 (6.2, 6.5)
Hazard ratio* (95% CI)	0.45 (0.38, 0.54)	
p-Value†	< 0.00001	
Objective response rate‡		
ORR§ % (95% CI)	68% (63.1, 72.1)	44% (39.7, 49.2)
p-Value¶	< 0.00001	
Response duration		
Median in months (range)	NR (2.0+, 28.3+)	7.0 (1.5+, 30.9+)

* Based on the stratified Cox proportional hazard regression model
† Two-sided p-Value based on stratified log-rank test
‡ Includes only patients with measurable disease at baseline
§ Based on patients with a best overall response as confirmed complete or partial response
¶ Two-sided p-Value based on Cochran-Mantel-Haenszel test stratified by PD-L1 expression, cisplatin eligibility and liver metastases
NR = not reached

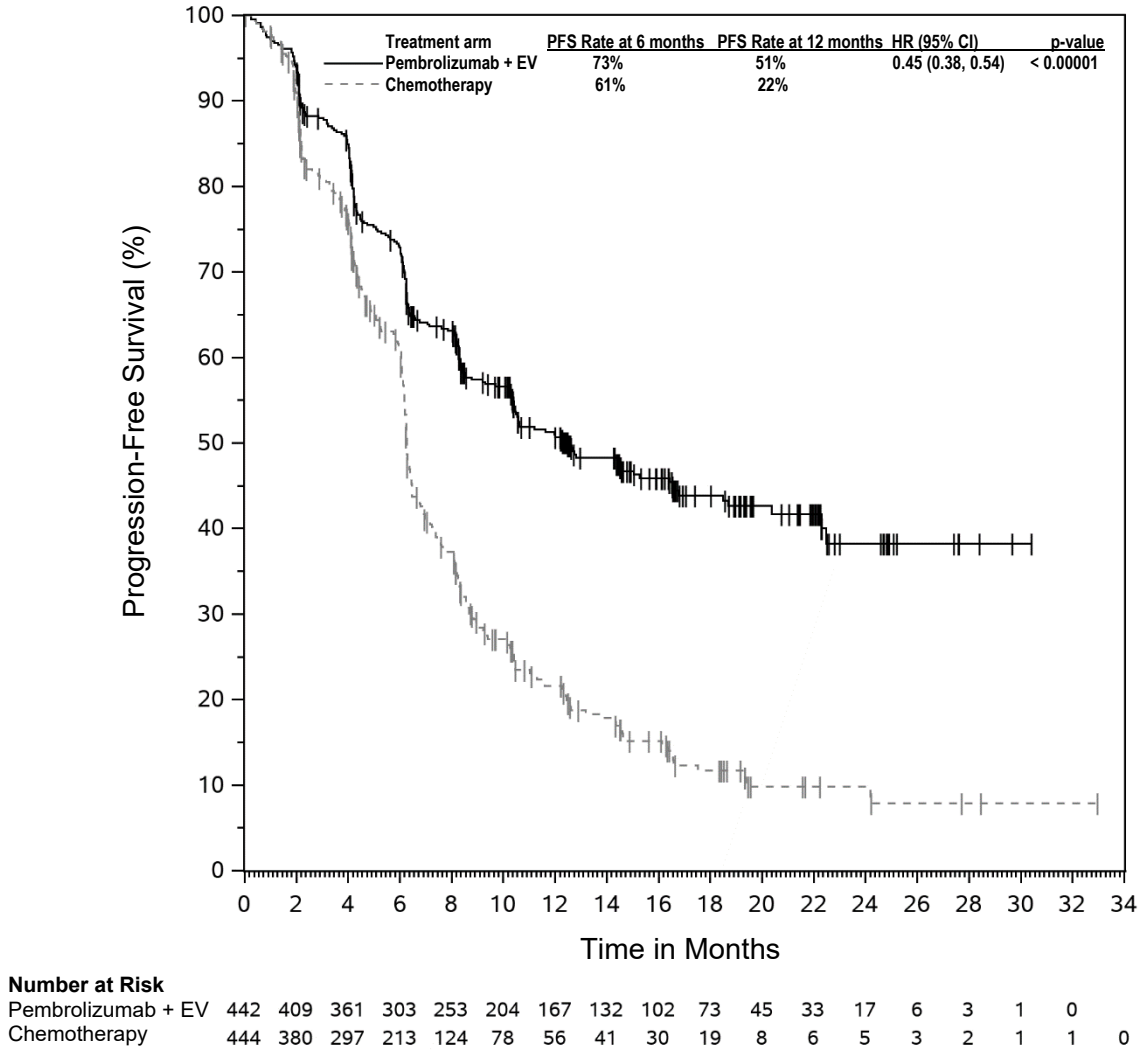
Figure 26: Kaplan-Meier curve for overall survival in KEYNOTE-A39



Number at Risk

Pembrolizumab + EV	442	426	409	394	376	331	270	222	182	141	108	67	36	22	12	8	1	1	1	0
Chemotherapy	444	423	393	356	317	263	209	164	125	90	60	37	25	18	12	7	6	2	1	0

Figure 27: Kaplan-Meier curve for progression-free survival in KEYNOTE-A39



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.

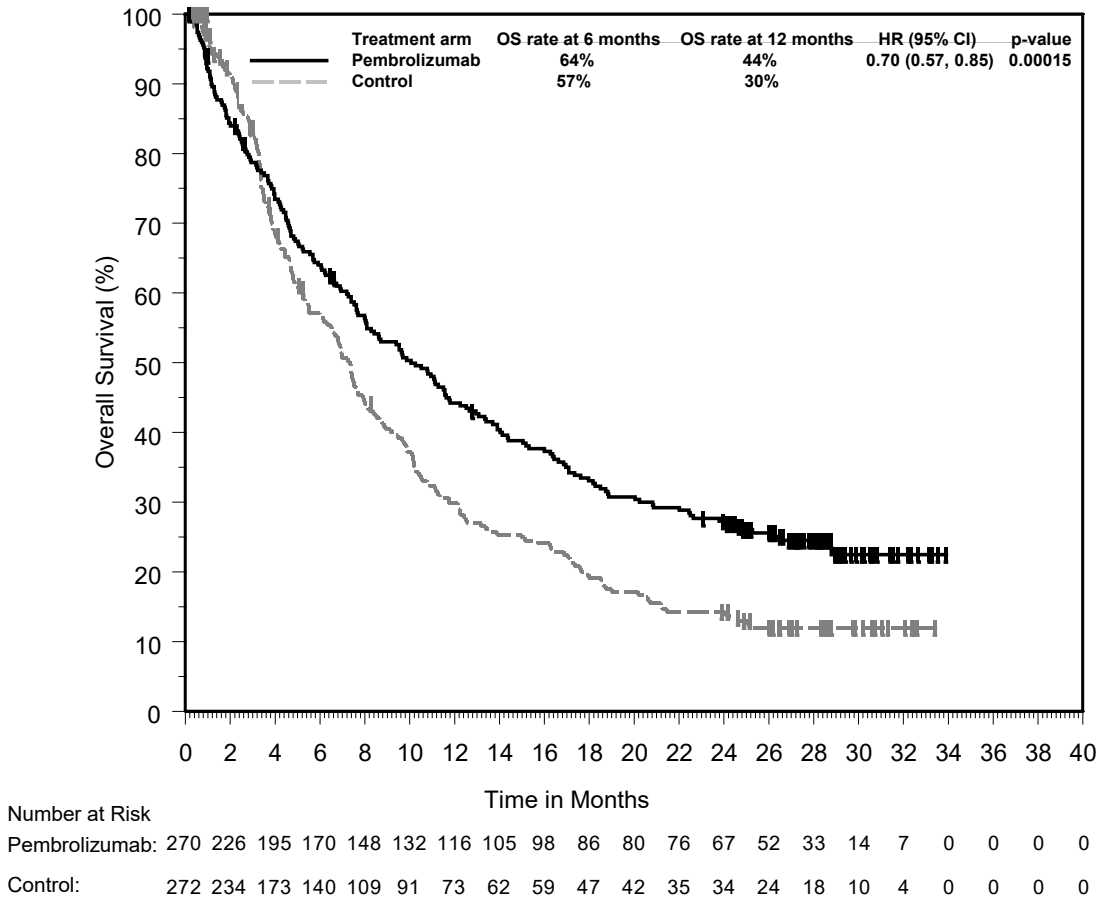
The primary efficacy outcomes were OS and PFS as assessed by BICR using RECIST v1.1. Secondary outcome measures were ORR (as assessed by BICR using RECIST v1.1) and duration of response. Table 27 summarises the key efficacy measures for the ITT population at the final analysis. The Kaplan-Meier curve based on the final analysis for OS is shown in Figure 28. 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 27: Response to pembrolizumab 200 mg every 3 weeks in patients with urothelial carcinoma previously treated with chemotherapy in KEYNOTE-045

Endpoint	**Pembrolizumab 200 mg every 3 weeks n=270**	**Chemotherapy n=272**
OS		
Number (%) of patients with event	200 (74%)	219 (81%)
Hazard ratio* (95% CI)	0.70 (0.57, 0.85)	
p-Value†	< 0.001	
Median in months (95% CI)	10.1 (8.0, 12.3)	7.3 (6.1, 8.1)
PFS‡		
Number (%) of patients with event	233 (86%)	237 (87%)
Hazard ratio* (95% CI)	0.96 (0.79, 1.16)	
p-Value†	0.313	
Median in months (95% CI)	2.1 (2.0, 2.2)	3.3 (2.4, 3.6)
Objective response rate‡		
ORR % (95% CI)	21% (16, 27)	11% (8, 15)
p-Value§	< 0.001	
Complete response	9%	3%
Partial response	12%	8%
Stable disease	17%	34%
Response duration‡,¶		
Median in months (range)	Not reached (1.6+, 30.0+)	4.4 (1.4+, 29.9+)
Number (%#) of patients with duration ≥ 6 months	46 (84%)	8 (47%)
Number (%#) of patients with duration ≥ 12 months	35 (68%)	5 (35%)

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

Figure 28: 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 28).

Table 28: 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 29 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 29: 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%) (see Table 30). PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx assay.

Table 30: ORR and OS by PD-L1 expression

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

* BICR using RECIST 1.1

KEYNOTE-361 is a Phase III, randomised, controlled, open-label clinical study of pembrolizumab with or without platinum-based combination chemotherapy (i.e., either cisplatin or carboplatin with gemcitabine) versus chemotherapy as first-line treatment in subjects with advanced or metastatic urothelial carcinoma. Results of KEYNOTE-361 for pembrolizumab in combination with chemotherapy did not show statistically significant improvement in PFS as assessed by BICR using RECIST 1.1 (HR 0.78; 95% CI: 0.65, 0.93; p=0.0033), and OS (HR 0.86; 95% CI: 0.72, 1.02; p=0.0407) versus chemotherapy alone. Per the pre-specified hierarchical testing order no formal tests for statistical significance of pembrolizumab versus chemotherapy could be performed. The key efficacy results of pembrolizumab monotherapy in patients for whom carboplatin rather than cisplatin was selected by the investigator as the better choice of chemotherapy were consistent with KEYNOTE-052 results. Efficacy results in patients whose tumours express PD-L1 with CPS ≥ 10 were similar to the overall population for whom carboplatin was selected as the choice of chemotherapy. See Table 31 and Figures 29 and 30.

Table 31: Response to pembrolizumab 200 mg every 3 weeks or chemotherapy in patients with previously untreated urothelial carcinoma for whom carboplatin rather than cisplatin was selected by the investigator as the better choice of chemotherapy in KEYNOTE-361

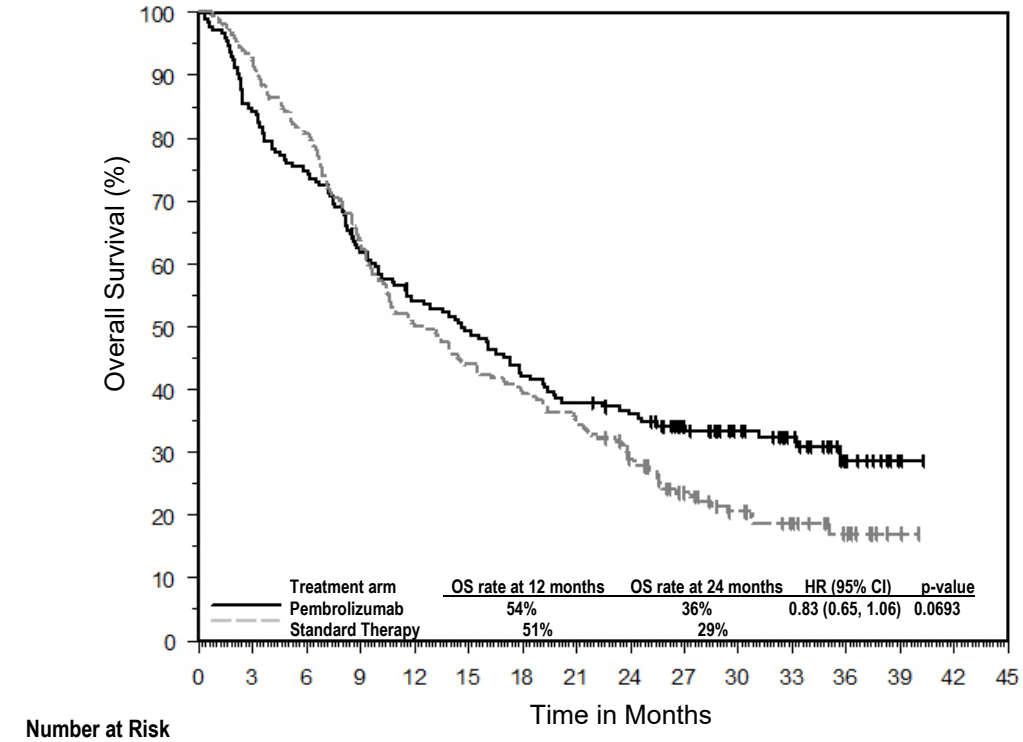
Endpoint	**Pembrolizumab n=170**	**Chemotherapy n=196**	**Pembrolizumab CPS ≥ 10 n=84**	**Chemotherapy CPS ≥ 10 n=89**
Objective response rate*				
ORR % (95% CI)	28% (21.1, 35.0)	42% (34.8, 49.1)	30% (20.3, 40.7)	46% (35.4, 57.0)
Complete response	10%	11%	12%	18%
Partial response	18%	31%	18%	28%
Response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

* Assessed by BICR using RECIST 1.1

† Based on Kaplan-Meier estimation

NR = not reached

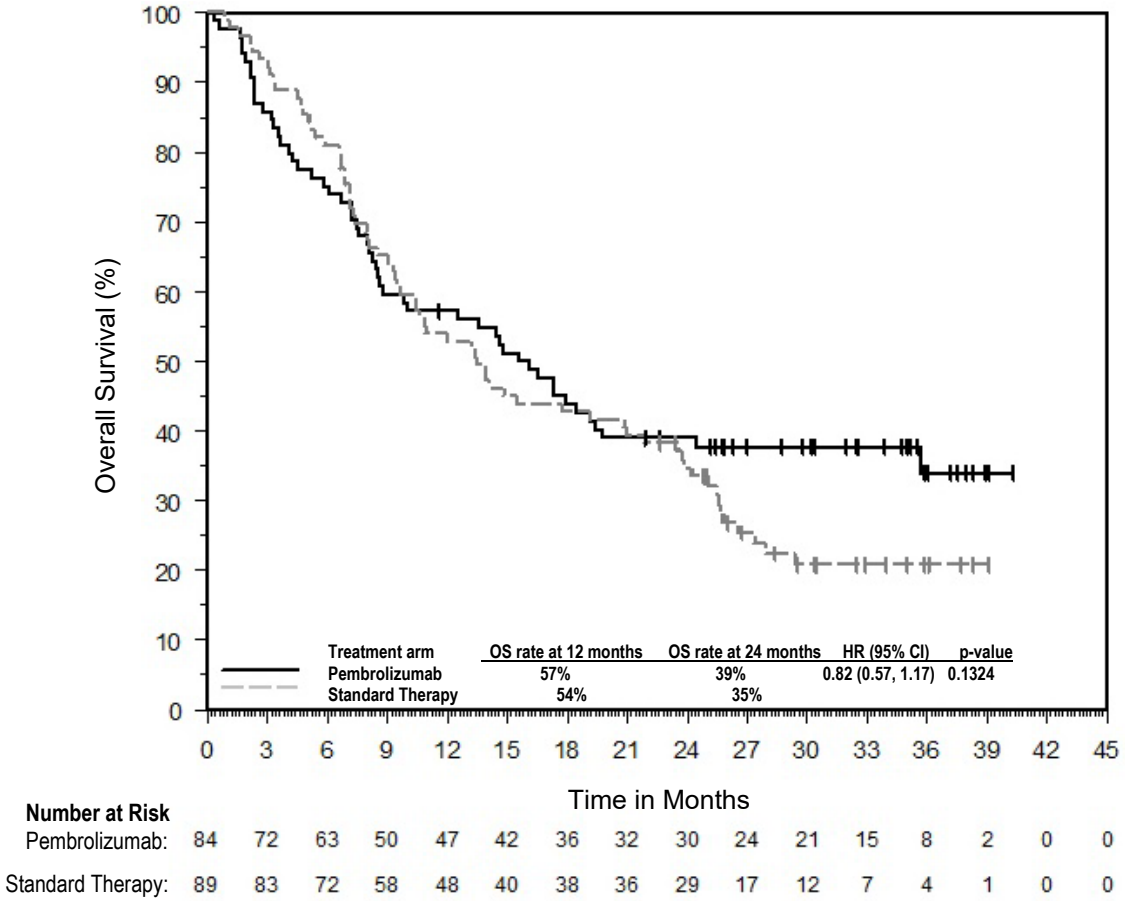
Figure 29: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-361 (intent to treat population, choice of carboplatin)



Number at Risk

Pembrolizumab:	170	143	127	104	90	82	70	63	58	45	34	24	11	2	0	0
Standard Therapy:	196	182	158	125	99	86	78	68	51	34	24	16	9	2	0	0

Figure 30: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-361 (patients with PD-L1 expression CPS ≥ 10, intent to treat population, choice of carboplatin)



Head and Neck Squamous Cell Carcinoma

KEYNOTE-689: Controlled study for the neoadjuvant and adjuvant treatment of patients with resectable locally advanced HNSCC

The efficacy of pembrolizumab was investigated in KEYNOTE-689, a randomised, multicentre, open-label, active-controlled study conducted in 714 patients with resectable locally advanced (Stage III-IVA) HNSCC. Patients with active autoimmune disease that required systemic therapy within two years of treatment or a medical condition that required immunosuppression were ineligible. Randomisation was stratified by primary tumour site (oropharynx/oral cavity vs. larynx vs. hypopharynx), tumour stage by AJCC 8th edition (III vs. IVA) and PD-L1 status (TPS ≥ 50% vs. TPS < 50%).

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

- Treatment arm A: Neoadjuvant pembrolizumab 200 mg for 2 cycles prior to surgical resection. Within 6 weeks following surgery, pembrolizumab 200 mg for 3 cycles in combination with either radiation + 3 cycles of concomitant cisplatin 100 mg/m^2 every 3 weeks for patients with high-risk pathological features after surgery or radiation alone for patients without high-risk pathological features after surgery. This was followed by pembrolizumab 200 mg every 3 weeks for up to 12 cycles.
- Treatment arm B: No neoadjuvant treatment prior to surgery. Within 6 weeks following surgery, either radiation + 3 cycles of concomitant cisplatin 100 mg/m^2 every 3 weeks for patients with high-risk pathological features after surgery or radiation alone for patients without high-risk pathological features after surgery.

High-risk pathologic features are defined by evidence of positive margins or extranodal extension following surgical resection.

Treatment with pembrolizumab continued until RECIST v1.1-defined progression of disease as assessed by BICR, 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 prior to surgery at Week 6 in the neoadjuvant phase. Following the start of the adjuvant phase, assessment of tumour status was performed 12 weeks after end of RT ± cisplatin treatment and then every 3 months until the end of Year 3; then every 6 months thereafter up to the end of Year 5. In arm A, 89% of the patients had surgery compared to 88% in arm B. In arm A, 29% of patients received cisplatin plus radiation and 46% received radiation alone. In arm B, 40% of patients received cisplatin plus radiation and 39% received radiation alone.

Among the 714 patients in KEYNOTE-689, 682 (96%) had tumours that expressed PD-L1 with a CPS ≥ 1. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx assay. The baseline characteristics of these 682 patients were: median age of 60 years (range: 22 to 87), 33% age 65 or older; 79% male; 78% White, 13% Asian and 2.5% Black; 43% had ECOG PS of 1, and 79% were former/current smokers. Four percent of patients' tumours were HPV-positive, and 26% had Stage III disease, 74% had Stage IVA disease.

The primary efficacy outcome measure was EFS by BICR 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 disease progression or recurrence, or death due to any cause. Secondary primary malignancy was not considered an event. Additional efficacy outcome measures were mPR as assessed by BIPR, OS, and pCR as assessed by BIPR.

The study demonstrated a statistically significant improvement in EFS (HR 0.73; 95% CI: 0.58, 0.92; p-Value 0.00411) in patients randomised to pembrolizumab in combination with radiation with or without concomitant cisplatin compared to those randomised to radiation with or without concomitant cisplatin at the first pre-specified interim analysis in the overall population. OS at interim analysis was not formally tested. Table 32 summarises key efficacy results for the pre-specified subgroup of patients whose tumours expressed PD-L1 with a CPS ≥ 1 at a median follow-up time of 27.0 months (range: 0.5 to 66.5 months). Figures 31 and 32 show the Kaplan-Meier curves for EFS and OS.

Table 32: Efficacy results in KEYNOTE-689 for patients with PD-L1 expression (CPS ≥ 1)

Endpoint	Pembrolizumab 200 mg every 3 weeks with RT with or without cisplatin n=347	RT with or without cisplatin n=335
EFS		
Number (%) of patients with event	128 (37%)	156 (47%)
Median in months* (95% CI)	59.7 (37.9, NR)	29.6 (19.5, 41.9)
Hazard ratio† (95% CI)	0.70 (0.55, 0.89)	
p-Value‡	0.00140	
OS		
Number (%) of patients with event	106 (31%)	128 (38%)
Median in months* (95% CI)	NR (NR, NR)	61.8 (49.2, NR)
Hazard ratio† (95% CI)	0.72 (0.56, 0.94)	

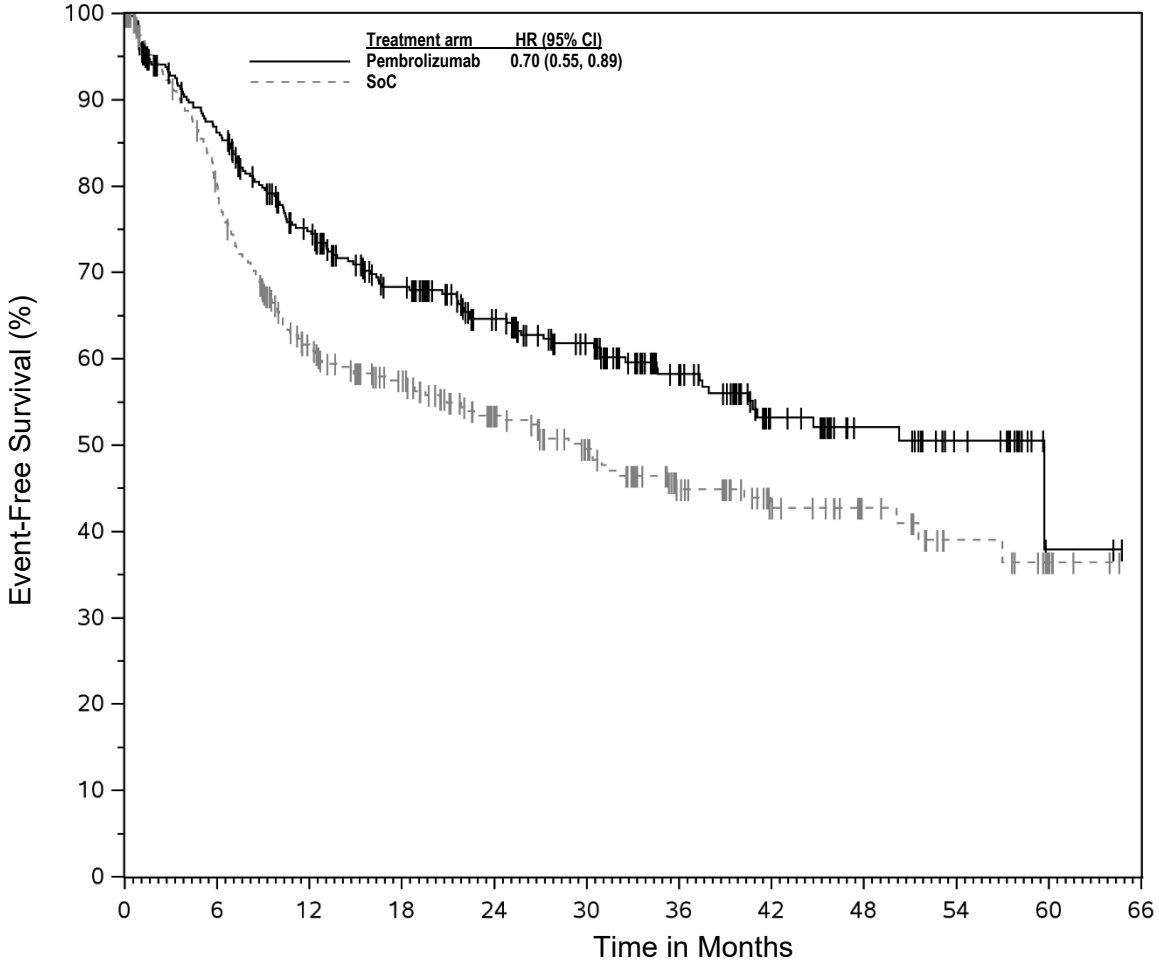
* From product-limit (Kaplan-Meier) method for censored data

† Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by primary tumour site and tumour stage

‡ One-sided p-Value based on log-rank test stratified by primary tumour site and tumour stage: Compared to a one-sided p-Value boundary of 0.0124

NR = not reached

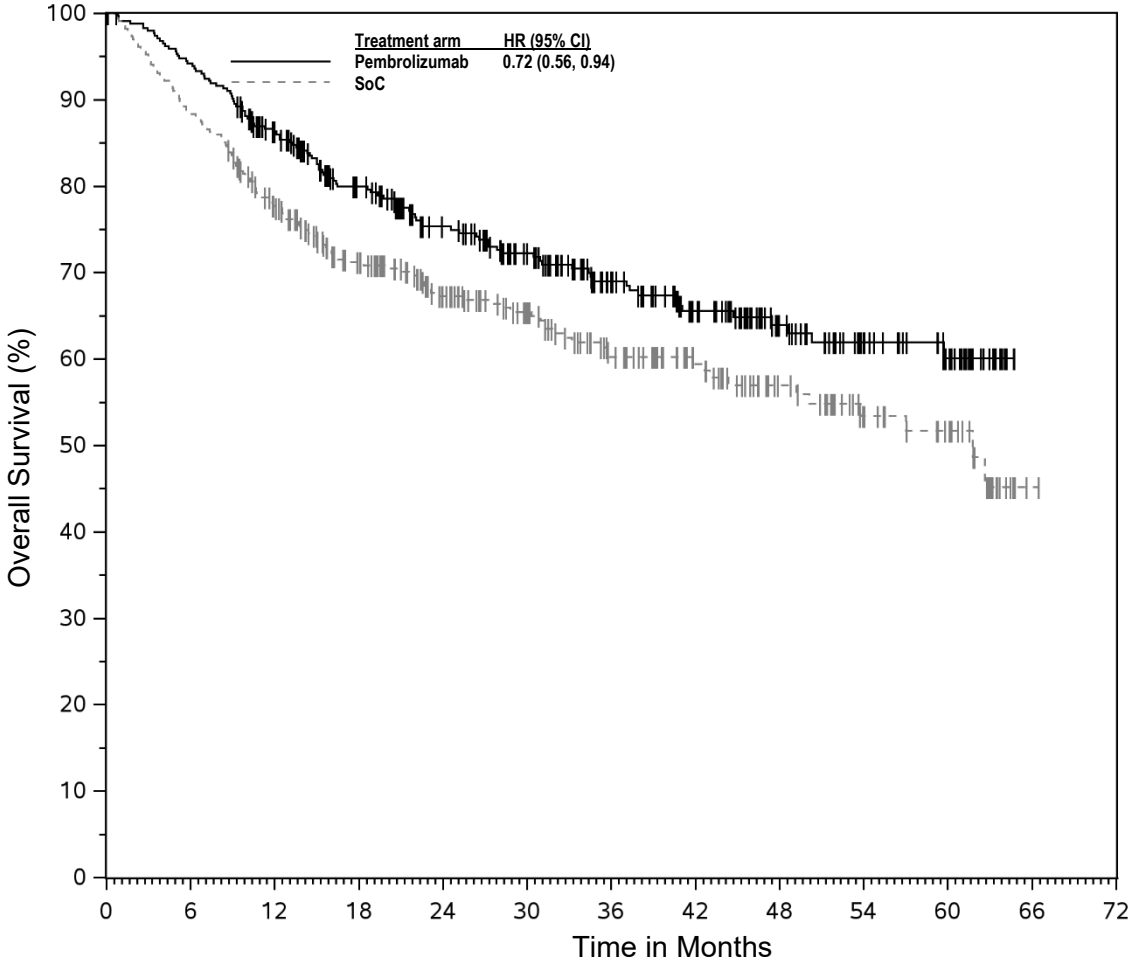
Figure 31: Kaplan-Meier curve for event-free survival by treatment arm in KEYNOTE-689 for patients with PD-L1 expression (CPS ≥ 1)



Number at Risk

Pembrolizumab	347	274	220	181	147	122	83	51	33	21	2	0
SoC	335	245	170	140	104	82	56	36	25	15	7	0

Figure 32: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-689 for patients with PD-L1 expression (CPS ≥ 1)



KEYNOTE-048: Controlled study of monotherapy and combination therapy in HNSCC patients naïve to treatment in the recurrent or metastatic setting

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

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

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

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

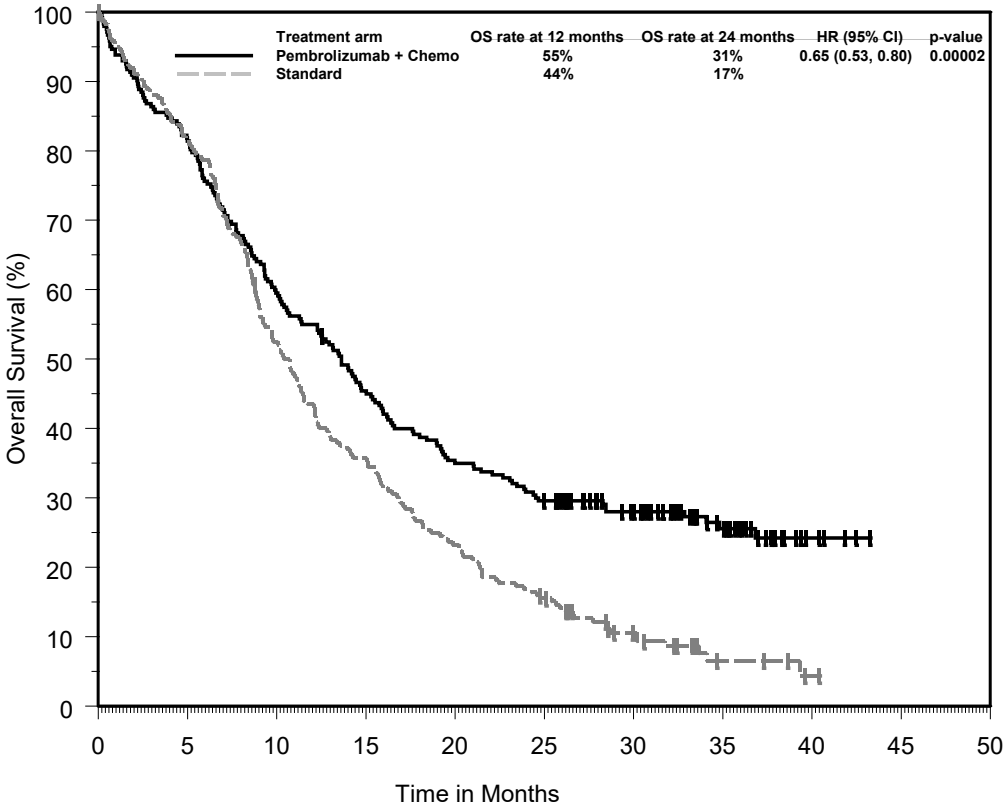
The primary efficacy outcome measures were OS and PFS (assessed by BICR according to RECIST 1.1). The study demonstrated a statistically significant improvement in OS for all patients randomised to pembrolizumab in combination with chemotherapy compared to standard treatment (HR 0.72; 95% CI 0.60-0.87) and in patients whose tumours expressed PD-L1 CPS ≥ 1 randomised to pembrolizumab monotherapy compared to standard treatment. Tables 33 and 34 summarise key efficacy results for pembrolizumab in patients whose tumours expressed PD-L1 with a CPS ≥ 1 in KEYNOTE-048 at the final analysis performed at a median follow-up of 13 months for pembrolizumab in combination with chemotherapy and at a median follow-up of 11.5 months for pembrolizumab monotherapy. Kaplan-Meier curves for OS based on the final analysis are shown in Figures 33 and 34.

Table 33: Efficacy results for pembrolizumab plus chemotherapy in KEYNOTE-048 with PD-L1 expression (CPS ≥ 1)

Endpoint	Pembrolizumab + Platinum Chemotherapy + 5-FU n=242	Standard Treatment* n=235
OS		
Number (%) of patients with event	177 (73%)	213 (91%)
Median in months (95% CI)	13.6 (10.7, 15.5)	10.4 (9.1, 11.7)
Hazard ratio† (95% CI)	0.65 (0.53, 0.80)	
p-Value‡	0.00002	
PFS		
Number (%) of patients with event	212 (88%)	221 (94%)
Median in months (95% CI)	5.1 (4.7, 6.2)	5.0 (4.8, 6.0)
Hazard ratio† (95% CI)	0.84 (0.69, 1.02)	
p-Value‡	0.03697	
Objective response rate		
ORR§ % (95% CI)	36% (30.3, 42.8)	36% (29.6, 42.2)
Complete response	7%	3%
Partial response	30%	33%
p-Value¶	0.4586	
Response duration		
Median in months (range)	6.7 (1.6+, 39.0+)	4.3 (1.2+, 31.5+)
% with duration ≥ 6 months	54%	34%

* Cetuximab, platinum, and 5-FU
† Based on the stratified Cox proportional hazard model
‡ Based on stratified log-rank test
§ Response: Best objective response as confirmed complete response or partial response
¶ Based on Miettinen and Nurminen method stratified by ECOG (0 vs. 1), HPV status (positive vs. negative) and PD-L1 status (strongly positive vs. not strongly positive)

Figure 33: Kaplan-Meier curve for overall survival for pembrolizumab plus chemotherapy in KEYNOTE-048 with PD-L1 expression (CPS ≥ 1)



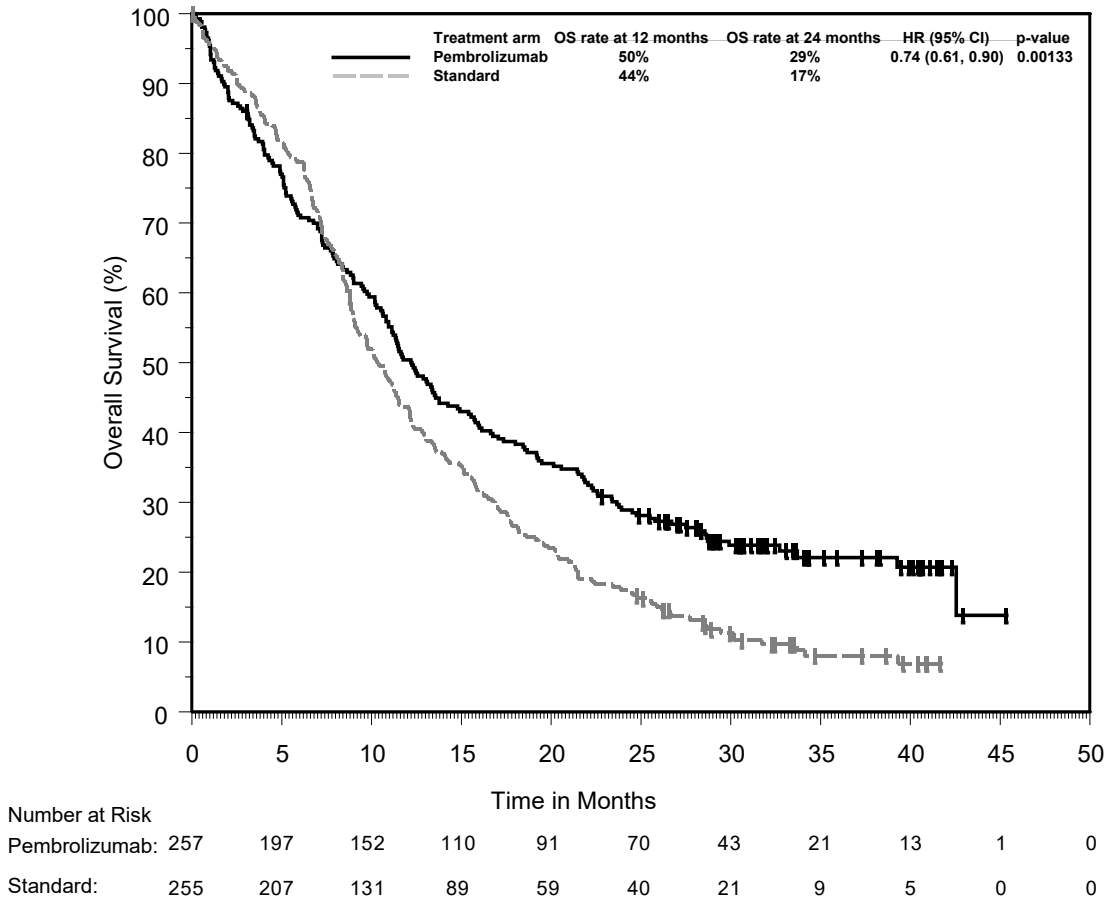
Number at Risk											
Pembrolizumab + Chemo:	242	197	144	109	84	70	52	29	5	0	0
Standard:	235	191	122	83	54	35	17	5	1	0	0

Table 34: Efficacy results for pembrolizumab as monotherapy in KEYNOTE-048 with PD-L1 expression (CPS ≥ 1)

Endpoint	Pembrolizumab n=257	Standard Treatment* n=255
OS		
Number (%) of patients with event	197 (77%)	229 (90%)
Median in months (95% CI)	12.3 (10.8, 14.3)	10.3 (9.0, 11.5)
Hazard ratio† (95% CI)	0.74 (0.61, 0.90)	
p-Value‡	0.00133	
PFS		
Number (%) of patients with event	228 (89%)	237 (93%)
Median in months (95% CI)	3.2 (2.2, 3.4)	5.0 (4.8, 6.0)
Hazard ratio† (95% CI)	1.13 (0.94, 1.36)	
p-Value‡	0.89580	
Objective response rate		
ORR§ % (95% CI)	19.1% (14.5, 24.4)	35% (29.1, 41.1)
Complete response	5%	3%
Partial response	14%	32%
p-Value¶	1.0000	
Response duration		
Median in months (range)	23.4 (1.5+, 43.0+)	4.5 (1.2+, 38.7+)
% with duration ≥ 6 months	81%	36%

* Cetuximab, platinum, and 5-FU
† Based on the stratified Cox proportional hazard model
‡ Based on stratified log-rank test
§ Response: Best objective response as confirmed complete response or partial response
¶ Based on Miettinen and Nurminen method stratified by ECOG (0 vs. 1), HPV status (positive vs. negative) and PD-L1 status (strongly positive vs. not strongly positive)

Figure 34: Kaplan-Meier curve for overall survival for pembrolizumab as monotherapy in KEYNOTE-048 with PD-L1 expression (CPS ≥ 1)



An analysis was performed in KEYNOTE-048 in patients whose tumours expressed PD-L1 CPS ≥ 20 [pembrolizumab plus chemotherapy: n=126 (49%) vs. standard treatment: n=110 (43%) and pembrolizumab monotherapy: n=133 (52%) vs. standard treatment: n=122 (48%)] (see Table 35).

Table 35: Efficacy results for pembrolizumab plus chemotherapy and pembrolizumab as monotherapy by PD-L1 expression in KEYNOTE-048 (CPS ≥ 20)

Endpoint	Pembrolizumab + Platinum Chemotherapy + 5-FU n=126	Standard Treatment* n=110	Pembrolizumab Monotherapy n=133	Standard Treatment* n=122
OS				
Number (%) of patients with event	84 (66.7%)	98 (89.1%)	94 (70.7%)	108 (88.5%)
Median in months (95% CI)	14.7 (10.3, 19.3)	11.0 (9.2, 13.0)	14.8 (11.5, 20.6)	10.7 (8.8, 12.8)
Hazard ratio† (95% CI)	0.60 (0.45, 0.82)		0.58 (0.44, 0.78)	
p-Value‡	0.00044		0.00010	
OS rate at 6 months (95% CI)	74.6 (66.0, 81.3)	80.0 (71.2, 86.3)	74.4 (66.1, 81.0)	79.5 (71.2, 85.7)
OS rate at 12 months (95% CI)	57.1 (48.0, 65.2)	46.1 (36.6, 55.1)	56.4 (47.5, 64.3)	44.9 (35.9, 53.4)
OS rate at 24 months (95% CI)	35.4 (27.2, 43.8)	19.4 (12.6, 27.3)	35.3 (27.3, 43.4)	19.1 (12.7, 26.6)

Endpoint	Pembrolizumab + Platinum Chemotherapy + 5-FU n=126	Standard Treatment* n=110	Pembrolizumab Monotherapy n=133	Standard Treatment* n=122
PFS				
Number (%) of patients with event	106 (84.1%)	104 (94.5%)	115 (86.5%)	114 (93.4%)
Median in months (95% CI)	5.8 (4.7, 7.6)	5.3 (4.9, 6.3)	3.4 (3.2, 3.8)	5.3 (4.8, 6.3)
Hazard ratio† (95% CI)	0.76 (0.58, 1.01)		0.99 (0.76, 1.29)	
p-Value‡	0.02951		0.46791	
PFS rate at 6 months (95% CI)	49.4 (40.3, 57.9)	47.2 (37.5, 56.2)	33.0 (25.2, 41.0)	46.6 (37.5, 55.2)
PFS rate at 12 months (95% CI)	23.9 (16.7, 31.7)	14.0 (8.2, 21.3)	23.5 (16.6, 31.1)	15.1 (9.3, 22.2)
PFS rate at 24 months (95% CI)	14.6 (8.9, 21.5)	5.0 (1.9, 10.5)	16.8 (10.9, 23.8)	6.1 (2.7, 11.6)
Objective response rate				
ORR§ % (95% CI)	42.9 (34.1, 52.0)	38.2 (29.1, 47.9)	23.3 (16.4, 31.4)	36.1 (27.6, 45.3)
Response duration				
Number of responders	54	42	31	44
Median in months (range)	7.1 (2.1+, 39.0+)	4.2 (1.2+, 31.5+)	22.6 (2.7+, 43.0+)	4.2 (1.2+, 31.5+)

* Cetuximab, platinum, and 5-FU
† Based on the stratified Cox proportional hazard model
‡ Based on stratified log-rank test
§ Response: Best objective response as confirmed complete response or partial response

An exploratory subgroup analysis was performed in KEYNOTE-048 in patients whose tumours expressed PD-L1 CPS ≥ 1 to < 20 [pembrolizumab plus chemotherapy: n=116 (45%) vs. standard treatment: n=125 (49%) and pembrolizumab monotherapy: n=124 (48%) vs. standard treatment: n=133 (52%)] (see Table 36).

Table 36: Efficacy results for pembrolizumab plus chemotherapy and pembrolizumab as monotherapy by PD-L1 expression in KEYNOTE-048 (CPS ≥ 1 to < 20)

Endpoint	Pembrolizumab + Platinum Chemotherapy + 5-FU n=116	Standard Treatment* n=125	Pembrolizumab Monotherapy n=124	Standard Treatment* n=133
OS				
Number (%) of patients with event	93 (80.2%)	115 (92.0%)	103 (83.1%)	121 (91.0%)
Median in months (95% CI)	12.7 (9.4, 15.3)	9.9 (8.6, 11.5)	10.8 (9.0, 12.6)	10.1 (8.7, 12.1)
Hazard ratio† (95% CI)	0.71 (0.54, 0.94)		0.86 (0.66, 1.12)	
OS rate at 6 months (95% CI)	76.7 (67.9, 83.4)	77.4 (69.0, 83.8)	67.6 (58.6, 75.1)	78.0 (70.0, 84.2)
OS rate at 12 months (95% CI)	52.6 (43.1, 61.2)	41.1 (32.4, 49.6)	44.0 (35.1, 52.5)	42.4 (33.9, 50.7)
OS rate at 24 months (95% CI)	25.9 (18.3, 34.1)	14.5 (9.0, 21.3)	22.0 (15.1, 29.6)	15.9 (10.3, 22.6)
PFS				
Number (%) of patients with event	106 (91.4%)	117 (93.6%)	113 (91.1%)	123 (92.5%)
Median in months (95% CI)	4.9 (4.2, 5.3)	4.9 (3.7, 6.0)	2.2 (2.1, 2.9)	4.9 (3.8, 6.0)
Hazard ratio† (95% CI)	0.93 (0.71, 1.21)		1.25 (0.96, 1.61)	
PFS rate at 6 months (95% CI)	40.1 (31.0, 49.0)	40.0 (31.2, 48.5)	24.2 (17.1, 32.0)	41.4 (32.8, 49.7)
PFS rate at 12 months (95% CI)	15.1 (9.1, 22.4)	11.3 (6.4, 17.7)	17.5 (11.4, 24.7)	12.1 (7.2, 18.5)
PFS rate at 24 months (95% CI)	8.5 (4.2, 14.7)	5.0 (1.9, 10.1)	8.3 (4.3, 14.1)	6.3 (2.9, 11.5)
Objective response rate				
ORR‡ % (95% CI)	29.3 (21.2, 38.5)	33.6 (25.4, 42.6)	14.5 (8.8, 22.0)	33.8 (25.9,42.5)
Response duration				
Number of responders	34	42	18	45
Median in months (range)	5.6 (1.6+, 25.6+)	4.6 (1.4+, 31.4+)	NR (1.5+, 38.9+)	5.0 (1.4+, 38.7+)

* Cetuximab, platinum, and 5-FU
† Based on the stratified Cox proportional hazard model
‡ Response: Best objective response as confirmed complete response or partial response
NR = not reached

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

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

that required immunosuppression, or who were previously treated with 3 or more systemic regimens for recurrent and/or metastatic HNSCC. Assessment of tumour status was performed at 9 weeks, then every 6 weeks through Week 52, followed by every 9 weeks through 24 months.

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

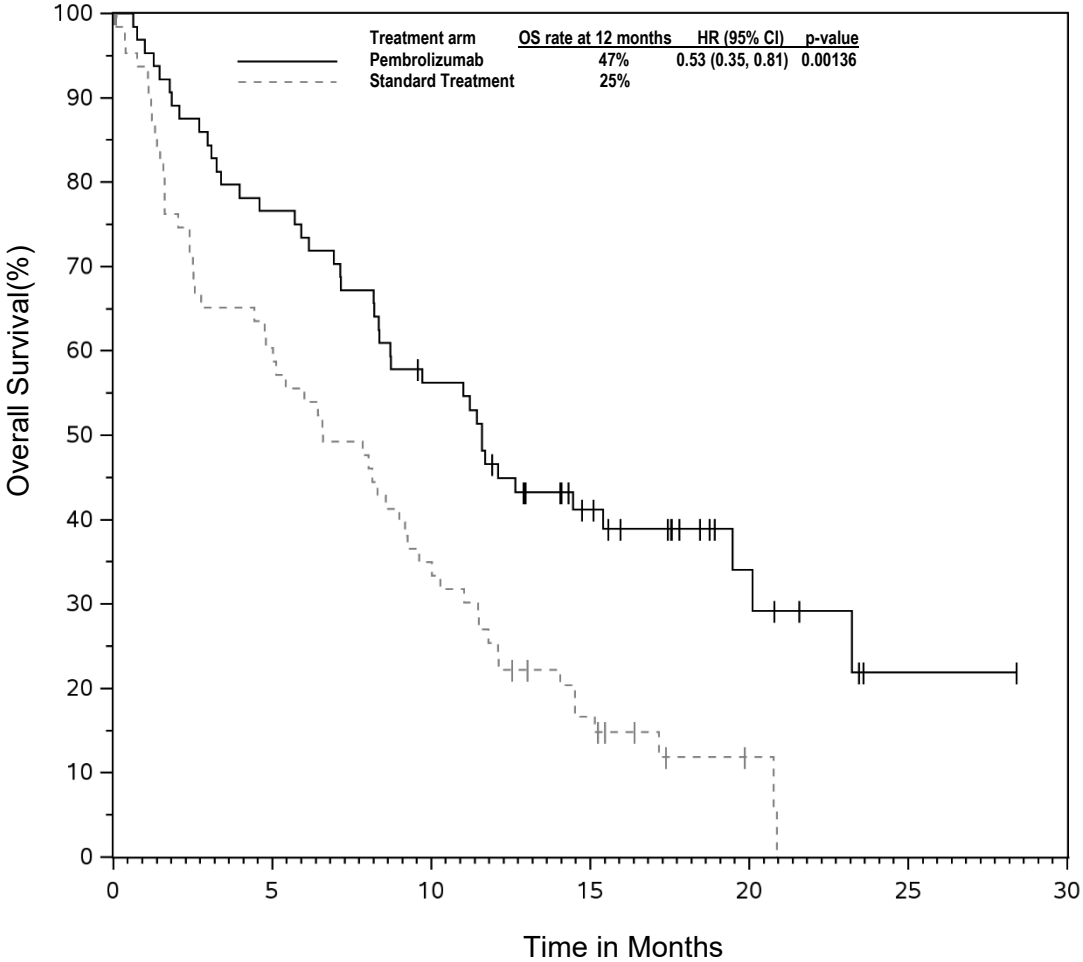
The primary efficacy outcome was OS in the ITT population. The initial analysis resulted in a HR for OS of 0.82 (95% CI: 0.67, 1.01) with a one-sided p-Value of 0.0316. The median OS was 8.4 months for pembrolizumab compared to 7.1 months for standard treatment. Table 37 summarises the key efficacy measures for the TPS ≥ 50% population. The Kaplan-Meier curve for OS for the TPS ≥ 50% population is shown in Figure 35.

Table 37: Efficacy of pembrolizumab 200 mg every 3 weeks in HNSCC patients with TPS ≥ 50% who were previously treated with platinum chemotherapy in KEYNOTE-040

Endpoint	**Pembrolizumab 200 mg every 3 weeks n=64**	**Standard Treatment[*] n=65**
OS		
Number (%) of patients with event	41 (64%)	56 (86%)
Hazard ratio[†] (95% CI)	0.53 (0.35, 0.81)	
p-Value[‡]	0.001	
Median in months (95% CI)	11.6 (8.3, 19.5)	6.6 (4.8, 9.2)
PFS[§]		
Number (%) of patients with event	52 (81%)	58 (89%)
Hazard ratio[†] (95% CI)	0.58 (0.39, 0.86)	
p-Value[‡]	0.003	
Median in months (95% CI)	3.5 (2.1, 6.3)	2.1 (2.0, 2.4)
Rate (%) at 6 months (95% CI)	40.1 (28.1, 51.9)	17.1 (8.8, 27.7)
Objective response rate[§]		
ORR % (95% CI)	26.6 (16.3, 39.1)	9.2 (3.5, 19.0)
p-Value[¶]	0.0009	
Complete response	5%	2%
Partial response	22%	8%
Stable disease	23%	23%
Response duration[§,#]		
Median in months (range)	Not reached (2.7, 13.8+)	6.9 (4.2, 18.8)
Number (%[Þ]) of patients with duration ≥ 6 months	9 (66%)	2 (50%)

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

Figure 35: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-040 patients with PD-L1 expression (TPS ≥ 50%)



Number at Risk							
Pembrolizumab	64	49	35	19	7	1	0
Standard Treatment	65	38	22	9	2	0	0

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.

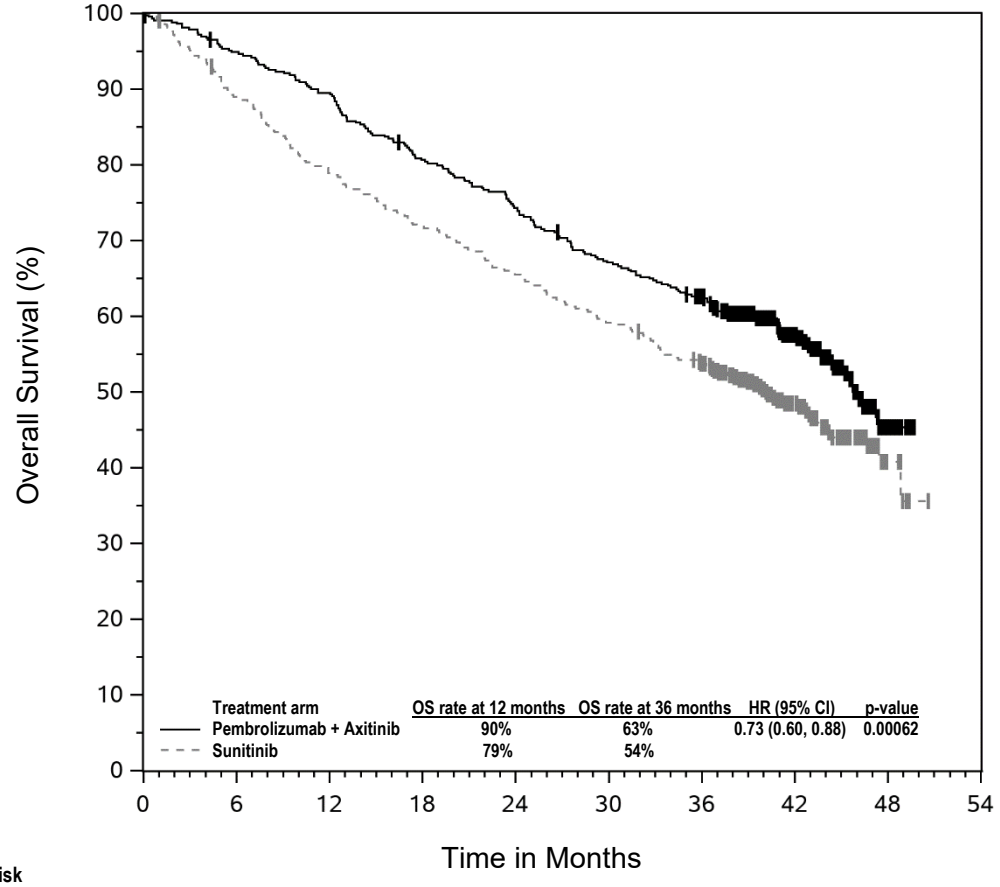
The primary efficacy outcome measures were OS and PFS (as assessed by BICR using RECIST 1.1). Secondary efficacy outcome measures were ORR and response duration, as assessed by BICR using RECIST 1.1. The study demonstrated a statistically significant improvement in OS (HR 0.53; 95% CI 0.38, 0.74; p-Value = 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 38 summarises key efficacy measures and Figures 36 and 37 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 38: Efficacy results in KEYNOTE-426

Endpoint	Pembrolizumab Axitinib n=432	Sunitinib n=429
OS		
Number (%) of patients with event	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 event	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)	23.6 (1.4+, 43.4+)	15.3 (2.3, 42.8+)
Number (%#) of patients with duration ≥ 30 months	87 (45%)	29 (32%)

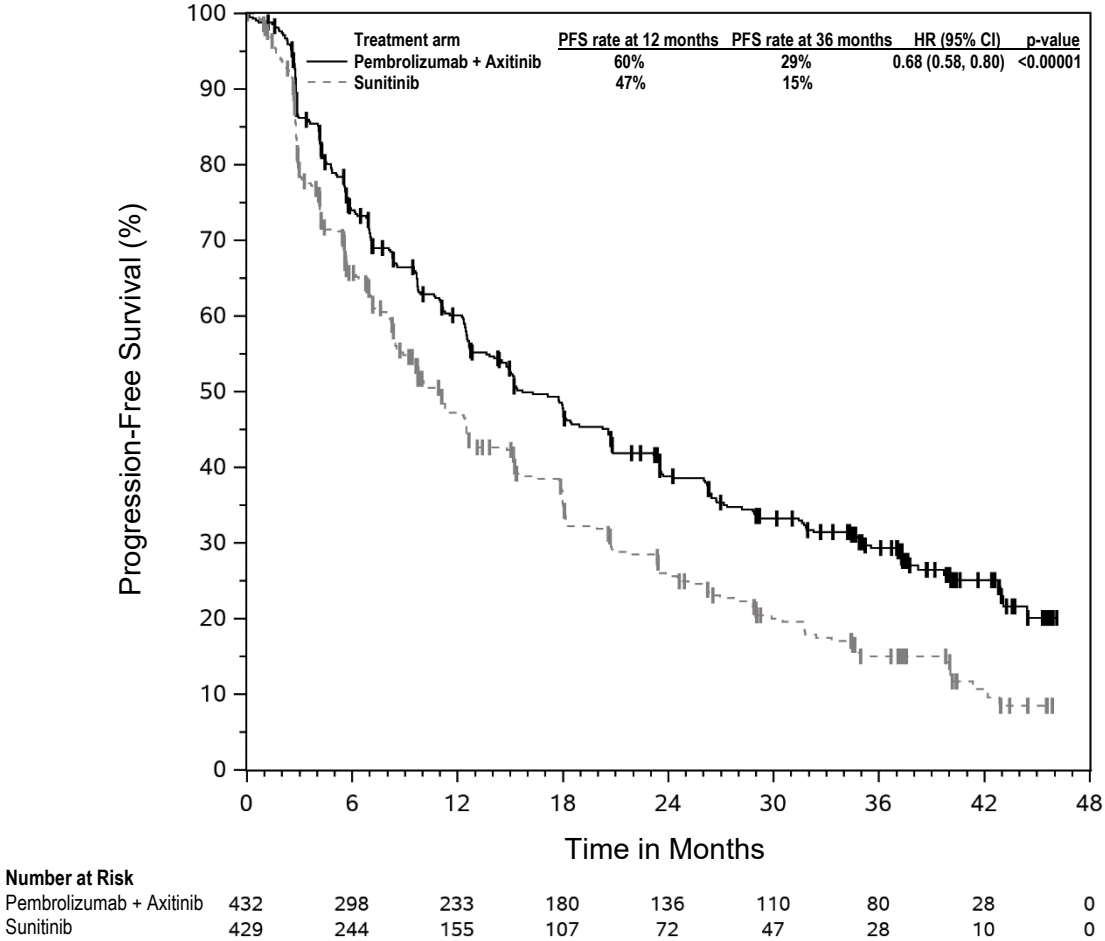
* Based on the stratified Cox proportional hazard model
† Nominal p-Value based on stratified log-rank test
‡ Assessed by BICR using RECIST 1.1
§ Based on patients with a best objective response as confirmed complete or partial response
¶ Nominal p-Value based on Miettinen and Nurminen method stratified by IMDC risk group and geographic region. At the pre-specified interim analysis of ORR (median follow-up time of 12.8 months), statistically significant superiority was achieved for ORR comparing pembrolizumab plus axitinib with sunitinib p-Value < 0.0001
\# Based on Kaplan-Meier estimation
NA = not available

Figure 36: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-426 (intent to treat population)



Number at Risk										
Pembrolizumab + Axitinib	432	407	384	345	318	286	259	141	16	0
Sunitinib	429	379	336	306	279	252	224	110	12	0

Figure 37: 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%)] and 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.

Table 39 summarises the efficacy measures by IMDC risk category based on the final OS analysis at a median follow-up of 37.7 months.

Table 39: 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)

Endpoint*	Pembrolizumab + Axitinib n=432	Sunitinib n=429	Pembrolizumab + Axitinib vs. Sunitinib
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 Center (MSKCC) prognostic groups (favourable versus intermediate versus poor).
Patients were randomised (1:1:1) to one of the following treatment arms:

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

Treatment continued until unacceptable toxicity or disease progression as determined by the investigator and confirmed by BICR using RECIST 1.1. Administration of pembrolizumab with lenvatinib was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered by the investigator to be deriving clinical benefit. Pembrolizumab was continued for a maximum of 24 months; however, treatment with lenvatinib could be continued beyond 24 months. 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 a 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 40 and Figures 38 and 39. 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 41.

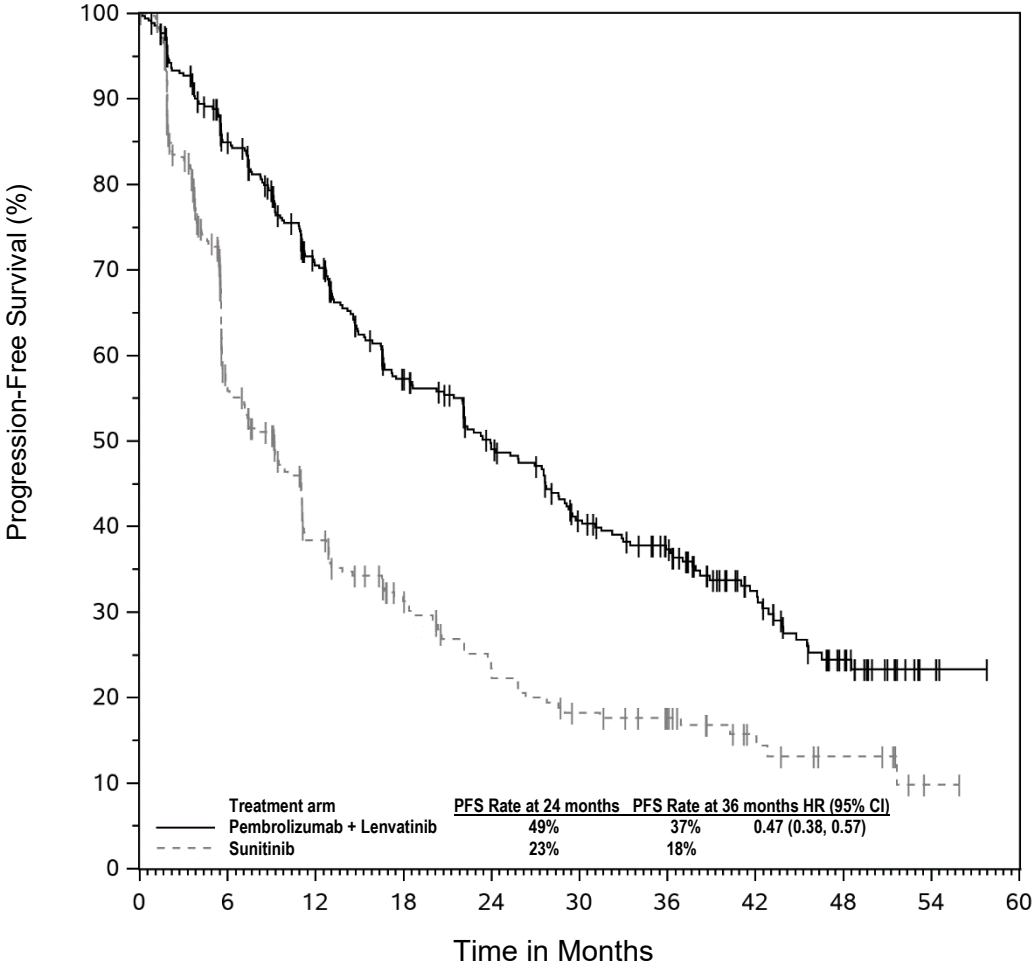
Table 40: Efficacy results in KEYNOTE-581 (CLEAR)

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)	53.7 (48.7, 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%	5%
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

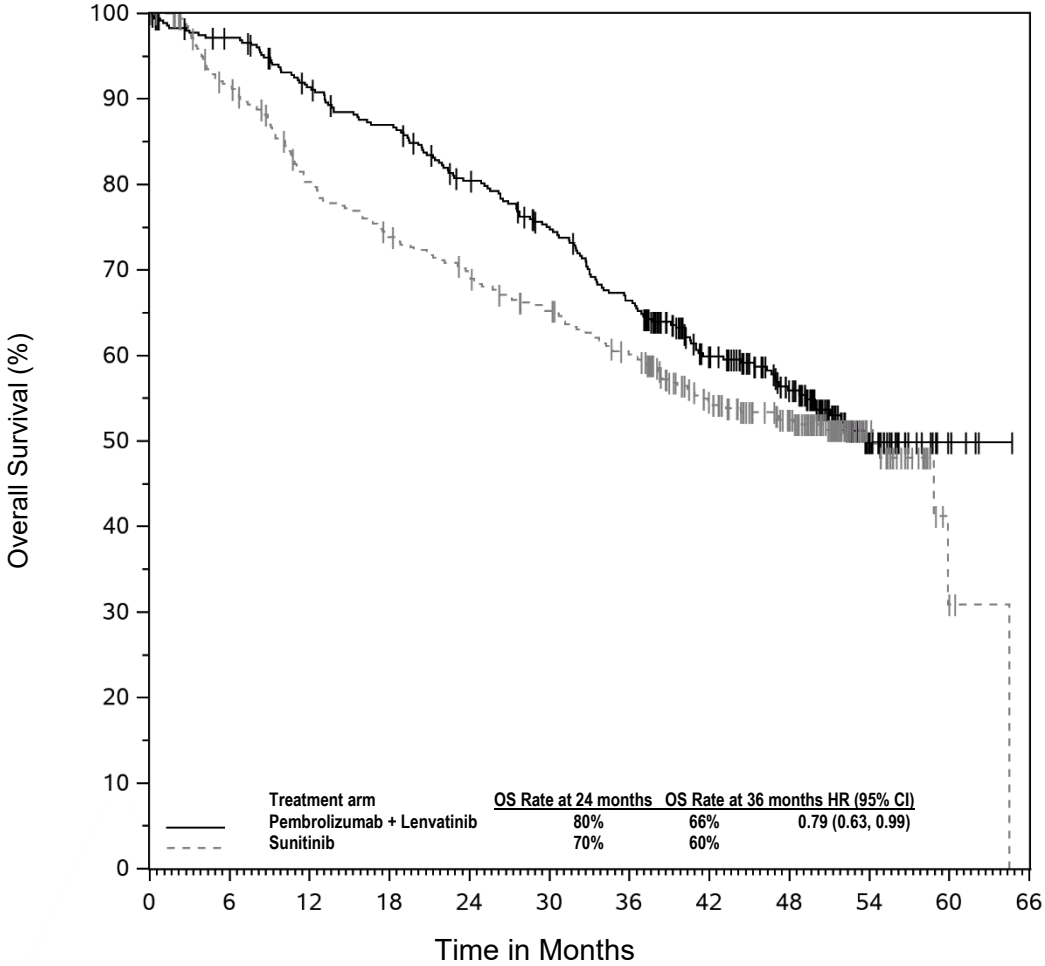
The final OS analysis was not adjusted to account for subsequent therapies, with 195/357 (54.6%) patients in the sunitinib arm and 56/355 (15.8%) patients in the pembrolizumab plus lenvatinib arm receiving subsequent anti-PD-1/PD-L1 therapy.

Figure 38: Kaplan-Meier curve for progression-free survival by treatment arm in KEYNOTE-581 (CLEAR)



Number at Risk											
Pembrolizumab + Lenvatinib	355	276	213	161	128	99	81	49	25	4	0
Sunitinib	357	145	85	59	41	30	23	12	7	1	0

Figure 39: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-581 (CLEAR)



Number at Risk												
Pembrolizumab + Lenvatinib	355	338	313	296	269	245	216	158	117	34	5	0
Sunitinib	357	308	264	242	226	208	188	145	108	33	3	0

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

Subgroup analyses were performed by MSKCC prognostic group.
Table 41 summarises the efficacy measures by MSKCC prognostic group based on the final OS analysis at a median follow-up of 49.4 months.

Table 41: 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 BICR*					**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-B61: Open-label single arm Phase II study
Additional data are available from the open-label single arm Phase II study KEYNOTE-B61 of pembrolizumab (400 mg every 6 weeks) in combination with lenvatinib (20 mg OD) for the first-line treatment of patients with advanced or metastatic RCC with non-clear cell histology (n=158), including 59% papillary, 18% chromophobe, 4% translocation, 1% medullary, 13% unclassified, and 6% other. The ORR was 50.6% (95% CI: 42.6, 58.7) and the median duration of response was 19.5 months (95% CI: 15.3, NR).

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 DFS and OS 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

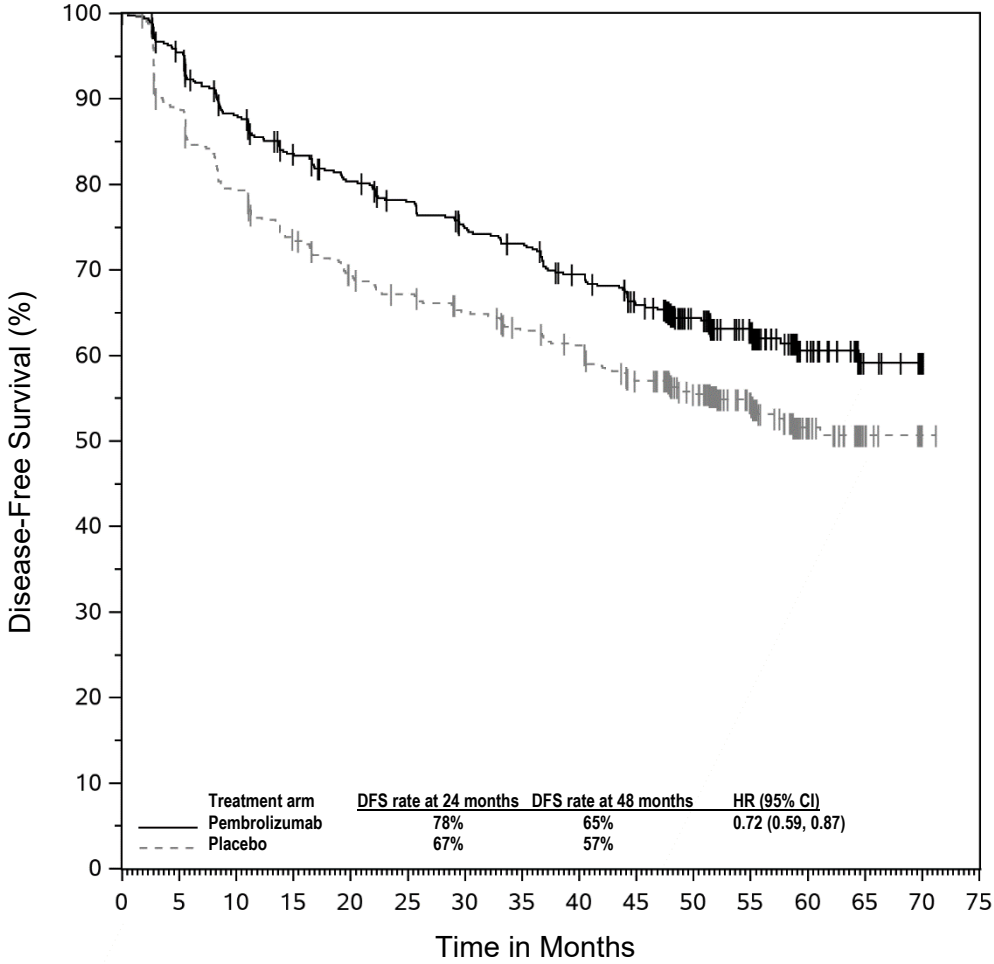
was 0.68 (95% CI 0.53, 0.87; p-Value = 0.0010). Efficacy results with a median follow-up time of 55.8 months are summarised in Table 42 and Figures 40 and 41.

Table 42: 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)
Hazard ratio* (95% CI)	0.62 (0.44, 0.87)	
p-Value†	0.0024	

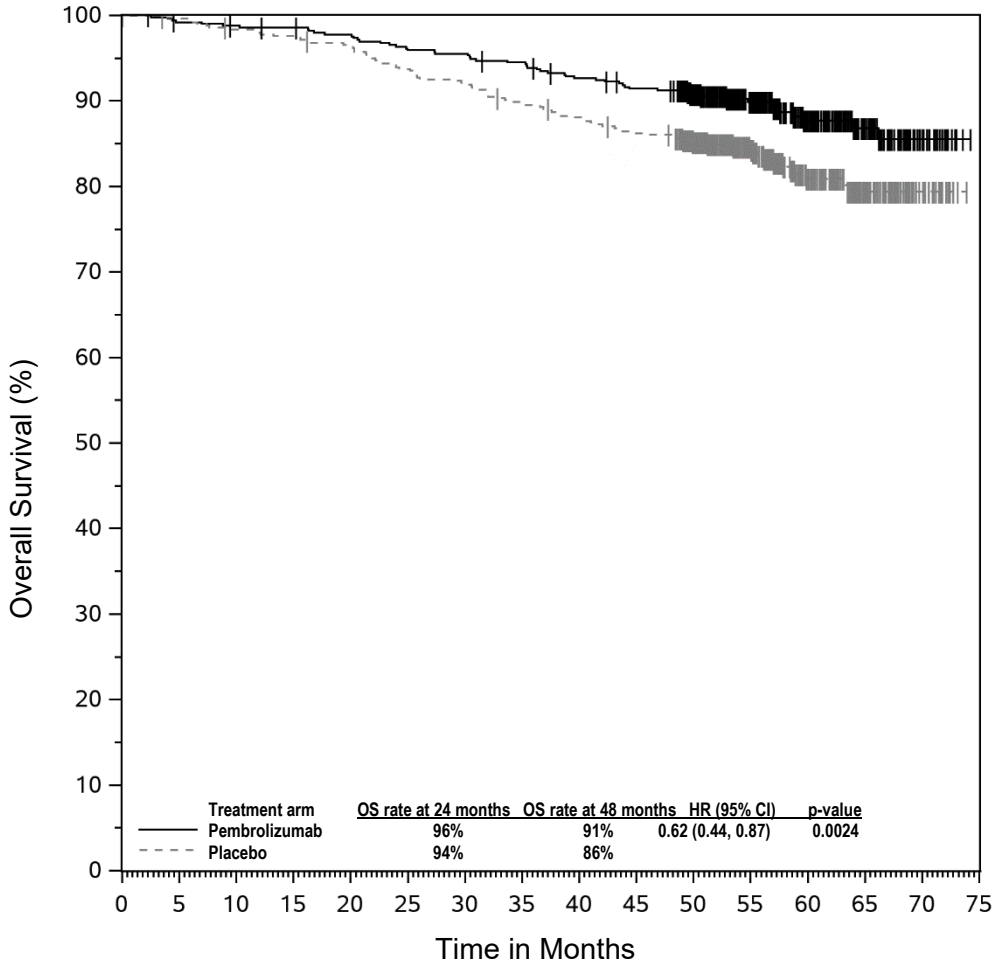
* Based on the stratified Cox proportional hazard model
† One-sided p-Value based on stratified log-rank test
NR = not reached

Figure 40: Kaplan-Meier curve for disease-free survival by treatment arm in KEYNOTE-564 (intent to treat population)



Number at Risk																
Pembrolizumab	496	458	416	388	370	355	337	327	307	284	221	160	65	19	5	0
Placebo	498	438	390	357	333	320	307	292	282	254	210	139	62	16	2	0

Figure 41: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-564 (intent to treat population)



Number at Risk																
Pembrolizumab	496	489	486	484	479	470	468	462	451	443	397	270	168	81	22	0
Placebo	498	494	487	483	476	463	455	441	433	423	382	248	155	79	22	0

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.

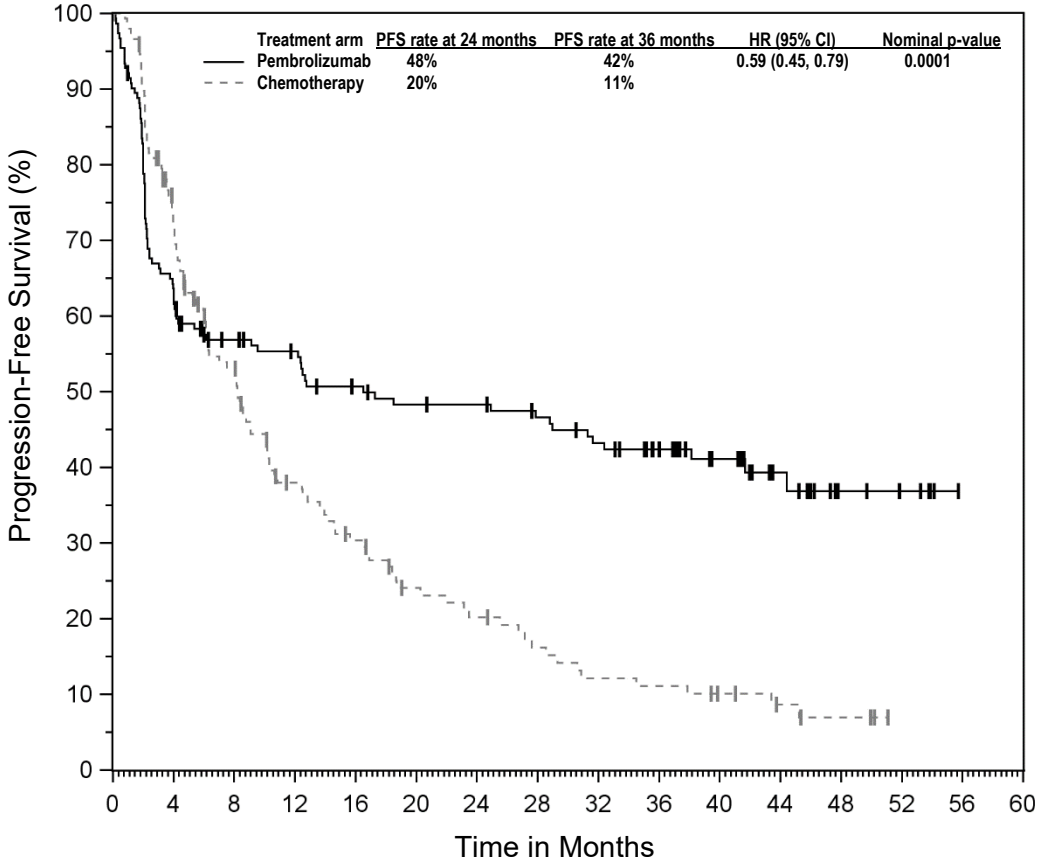
The primary efficacy outcome measures were PFS assessed by BICR according to RECIST v1.1 and OS. Secondary outcome measures were ORR and response duration. The study demonstrated a statistically significant improvement in PFS (HR 0.60; 95% CI 0.45, 0.80; p-Value 0.0002) for patients randomised to the 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 43 summarises the key efficacy measures and Figures 42 and 43 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 43: 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+)
% 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
§ Not statistically significant after adjustment for multiplicity
¶ Based on Kaplan-Meier estimation
NR = not reached

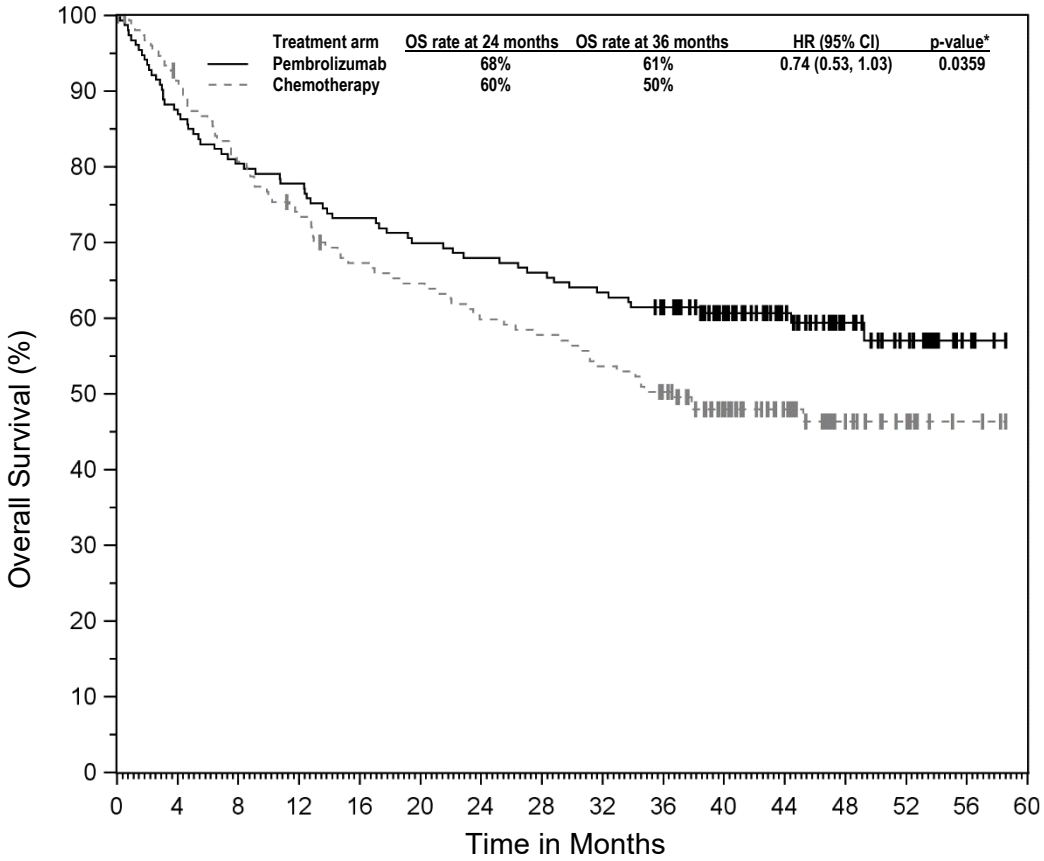
Figure 42: Kaplan-Meier curve for progression-free survival by treatment arm in KEYNOTE-177 (intent to treat population)



Number at Risk

Pembrolizumab	153	96	77	72	64	60	59	55	50	42	28	16	7	5	0	0
Chemotherapy	154	101	69	45	35	25	21	16	12	11	8	5	3	0	0	0

Figure 43: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-177 (intent to treat population)



* Not statistically significant after adjustment for multiplicity

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

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

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

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

The primary efficacy outcome measure was ORR as assessed by BICR using RECIST 1.1. Secondary efficacy outcome measures included response duration, PFS, and OS. The median follow-up time in months was 37.3 (range: 0.1 to 65.2). Efficacy results are summarised in Table 44.

Table 44: Efficacy results in KEYNOTE-164

Endpoint	n=124
Objective response rate*	
ORR % (95% CI)	34% (25.6, 42.9)
Complete response	10%
Partial response	24%
Response duration*	
Median in months (range)	NR (4.4, 58.5+)
% with duration ≥ 36 months#	92%

* Based on patients with a best objective response as confirmed complete or partial response
\# Based on Kaplan-Meier estimation
\+ Denotes there is no progressive disease by the time of last disease assessment
NR = not reached

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

Non-colorectal cancers
KEYNOTE-158: Open-label study in patients with unresectable or metastatic MSI-H or dMMR endometrial, gastric, small intestine, or biliary cancer who have received prior therapy
The efficacy of pembrolizumab was investigated in 377 patients with unresectable or metastatic MSI-H or dMMR non-CRC solid tumours enrolled in a multicentre, non-randomised, open-label Phase II study (KEYNOTE-158), including patients with endometrial, gastric, small intestine, or biliary cancer. MSI or MMR tumour status was determined prospectively using PCR or IHC, respectively.

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

Among the 83 patients with endometrial cancer, the baseline characteristics were: median age of 64 years (range: 42 to 86), 46% age 65 or older; 84% White, 6% Asian, and 4% Black; and ECOG PS 0 (46%) and 1 (54%). Ninety-eight percent of the patients had M1 disease and 2% had M0 disease. Forty-seven percent of patients received 2 or more prior lines of therapy.

Among the 67 patients with gastric cancer, the baseline characteristics were: median age 68 years (range: 41 to 89); 61% age 65 or older; 64% male, 61% White, 25% Asian; and ECOG PS 0 (43%) and 1 (57%). All patients had M1 disease. Forty-five percent of patients received 2 or more prior lines of therapy.

Among the 33 patients with small intestinal cancer, the baseline characteristics were: median age 60 years (range: 21 to 78); 39% age 65 or older; 58% male, 85% White, 9% Asian; and ECOG PS 0 (52%) and 1 (48%). Ninety-seven percent of patients had M1 disease and 3% M0 disease. Thirty-three percent of patients received 2 or more prior lines of therapy. All patients had a tumour histology of adenocarcinoma.

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

The primary efficacy outcome measure was ORR as assessed by BICR using RECIST 1.1. Secondary efficacy outcome measures included response duration, PFS, and OS. The median follow-up time in

months was 53.5 (range: 1.5 to 99.4) for endometrial, 12.9 (range: 1.0 to 102.6) for gastric, 39.4 (range: 4.2 to 103.0) for small intestine, and 19.4 (range: 1.1 to 97.1) for biliary cancer. Efficacy results are summarised in Table 45.

Table 45: Efficacy results in KEYNOTE-158

Endpoint	Endometrial n=83	Gastric¶ n=65	Small Intestine¶ n=32	Biliary n=22
Objective response rate*				
ORR % (95% CI)	52% (40.6, 62.9)	40% (28.0, 52.9)	63% (43.7, 78.9)	45% (24.4, 67.8)
Complete response	18%	18%	19%	14%
Partial response	34%	22%	44%	32%
Response duration*				
Median in months (range)	NR (2.9, 91.9+)	NR (1.9+, 96.1+)	NR (3.7+, 91.4+)	NR (6.2, 92.1+)
% with duration ≥ 12 months#	86%	88%	87%	90%
% with duration ≥ 60 months#	64%	72%	72%	50%

* Based on patients with a best objective response as confirmed complete or partial response
\# Based on Kaplan-Meier estimation
\+ Denotes there is no progressive disease by the time of last disease assessment
NR = not reached
¶ Efficacy analysis population consists of participants in the All Participants as Treated (APaT) population, who were enrolled at least 26 weeks prior to the cutoff date

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

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

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

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

Among the 749 patients in KEYNOTE-590, 383 (51%) had tumours that expressed PD-L1 with a CPS ≥ 10. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx assay. The baseline characteristics of these 383 patients were: median age of 63 years (range: 28 to 89), 41% age 65 or older; 82% male; 34% White and 56% Asian; 43% and 57% had an ECOG performance status of 0

and 1, respectively. Ninety-three percent had M1 disease. Seventy-five percent had a tumour histology of squamous cell carcinoma, and 25% had adenocarcinoma.

The primary efficacy outcome measures were OS and PFS as assessed by the investigator according to RECIST 1.1 in squamous cell histology, CPS ≥ 10, and in all patients. The study demonstrated a statistically significant improvement in OS and PFS for all pre-specified study populations. In all patients randomised to pembrolizumab in combination with chemotherapy, compared to chemotherapy the OS HR was 0.73 (95% CI 0.62-0.86) and the PFS HR was 0.65 (95% CI 0.55-0.76). Secondary efficacy outcome measures were ORR and duration of response, according to RECIST 1.1 as assessed by the investigator. Table 46 summarises key efficacy measures from the pre-specified analysis in patients whose tumours expressed PD-L1 with a CPS ≥ 10 in KEYNOTE-590 performed at a median follow-up time of 13.5 months (range: 0.5 to 32.7 months). The Kaplan-Meier curve for OS and PFS are shown in Figures 44 and 45.

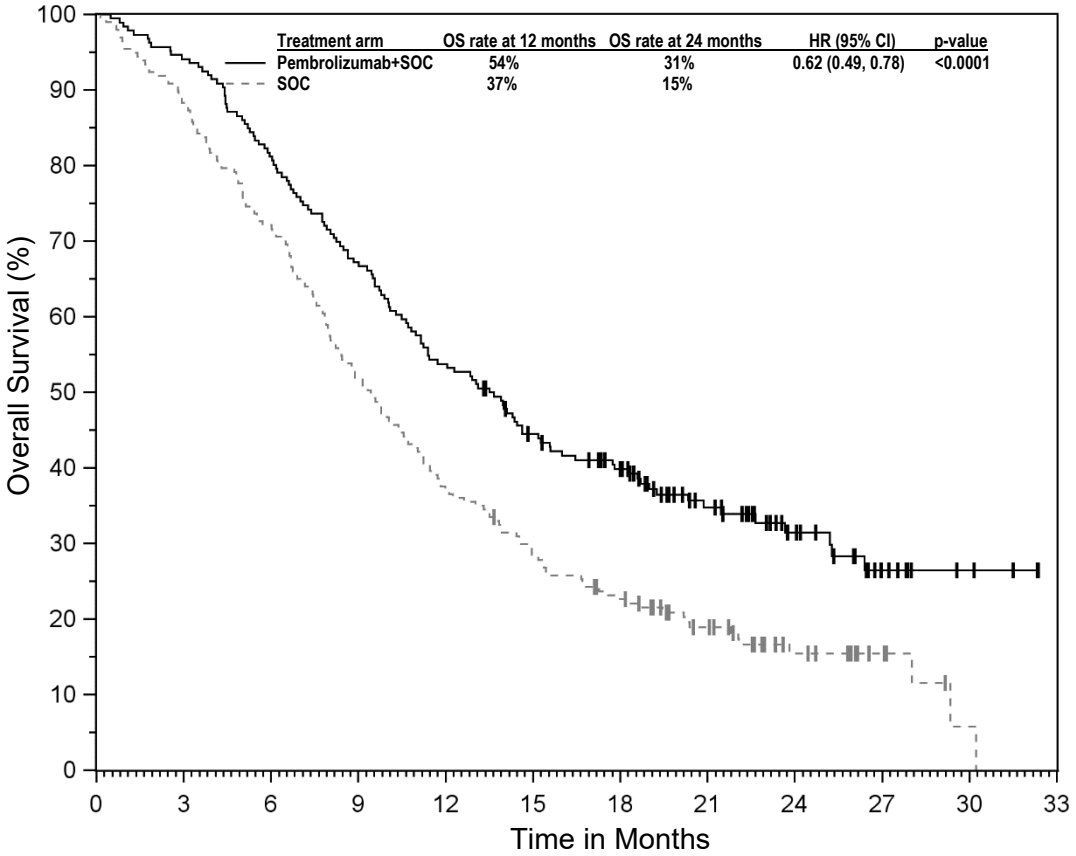
Table 46: Efficacy results for pembrolizumab plus chemotherapy in KEYNOTE-590 with PD-L1 expression (CPS ≥ 10)

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

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

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

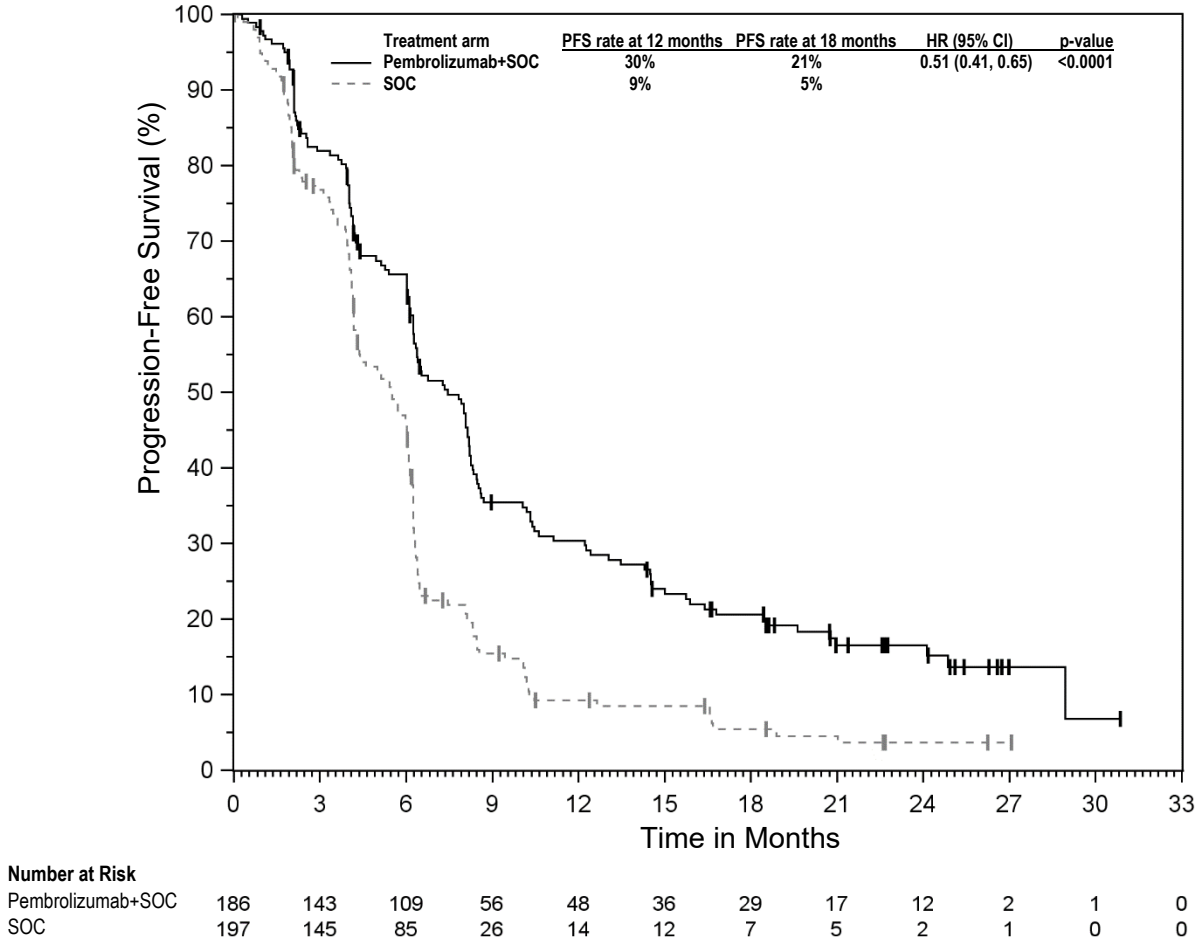
Figure 44: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-590 with PD-L1 expression (CPS ≥ 10)



Number at Risk

Pembrolizumab+SOC	186	175	151	125	100	79	66	40	23	10	4	0
SOC	197	174	142	102	73	55	42	28	13	6	1	0

Figure 45: Kaplan-Meier curve for progression-free survival by treatment arm in KEYNOTE-590 with PD-L1 expression (CPS ≥ 10)



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 regimen
- 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 pCR rate and 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. A secondary efficacy outcome measure was OS.

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 interim analysis (median follow-up time for all patients of 37.8 months (range: 2.7-48.0 months), HR=0.63 (95% CI: 0.48, 0.82; p-Value 0.00031)). At a median follow-up time for all patients of 73.1 months (range: 2.7-83.9 months), the study also demonstrated a statistically significant improvement in OS.

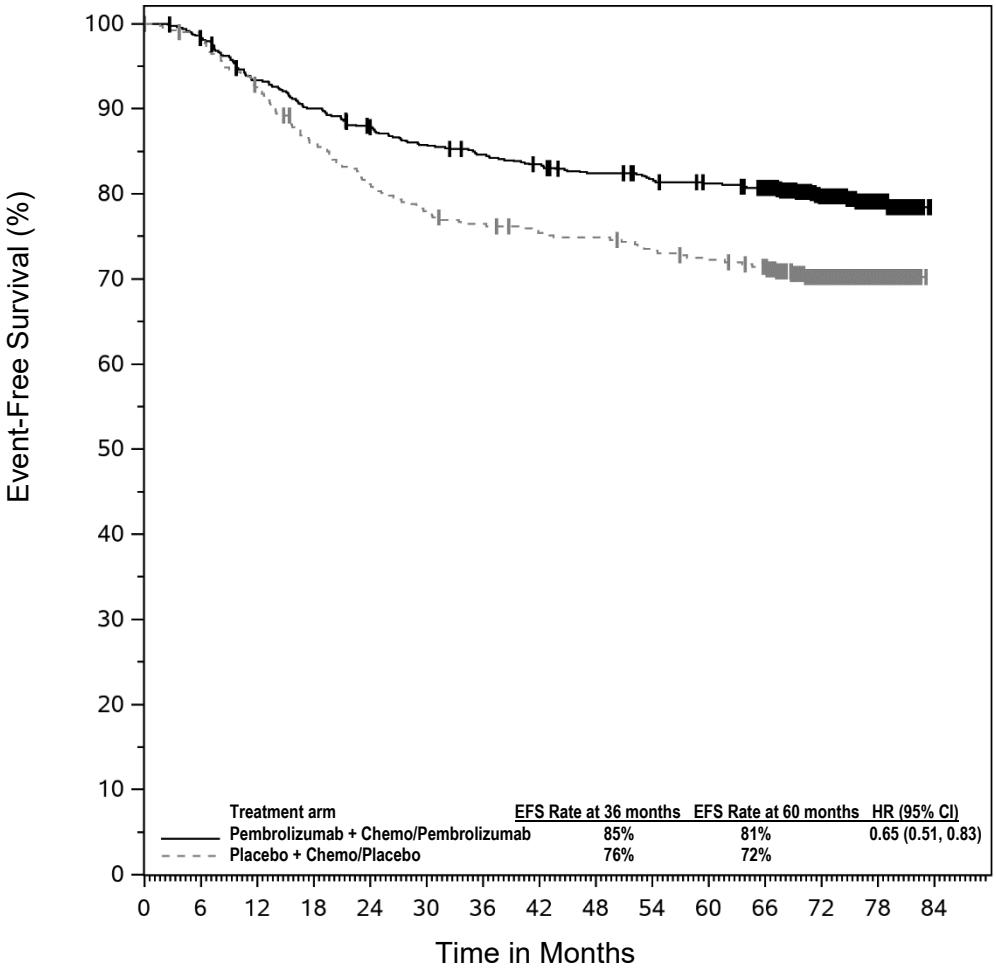
Results reported from the pre-specified pCR final analysis (n=1 002) and key efficacy measures from the EFS and OS pre-specified interim analysis at median follow-up time for all patients of 73.1 months (range: 2.7-83.9 months) are summarised in Table 47. The Kaplan-Meier curves for EFS and OS are shown in Figures 46 and 47.

Table 47: 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	159 (20.3%)	114 (29.2%)
Hazard ratio (95% CI)¶	0.65 (0.51, 0.83)	
OSÞ	**n=784**	**n=390**
Number (%) of patients with event	115 (14.7%)	85 (21.8%)
Hazard ratio (95% CI)¶	0.66 (0.50, 0.87)	
p-Value#	0.00150	

* 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 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
Þ Based on a pre-specified OS interim analysis (compared to a significance level of 0.00503)
\# One-sided p-Value based on log-rank test stratified by nodal status, tumour size, and choice of carboplatin

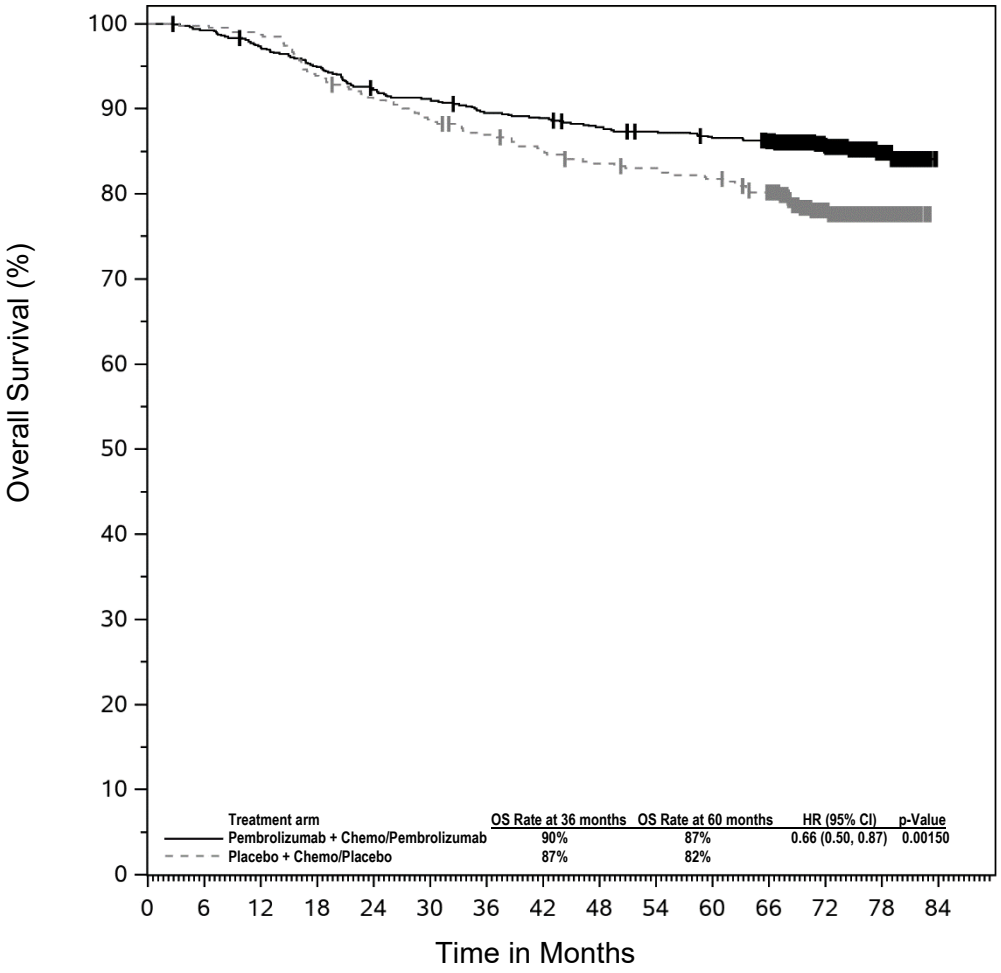
Figure 46: Kaplan-Meier curve for event-free survival by treatment arm in KEYNOTE-522 (intent to treat population)



Number at Risk

Pembrolizumab + Chemo/Pembrolizumab	784	769	728	702	681	665	654	644	633	625	618	602	409	164	0
Placebo + Chemo/Placebo	390	382	358	330	312	300	293	287	285	278	273	264	178	76	0

Figure 47: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-522 (intent to treat population)



Number at Risk

Pembrolizumab + Chemo/Pembrolizumab	784	777	760	742	720	712	698	693	683	677	670	656	448	176	0
Placebo + Chemo/Placebo	390	389	385	366	354	345	336	328	321	318	313	300	199	82	0

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. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx assay. 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 48 summarises key efficacy measures and Figures 48 and 49 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 48: Efficacy results in KEYNOTE-355 patients with CPS ≥ 10

Endpoint	Pembrolizumab with chemotherapy* n=220	Placebo with chemotherapy* n=103
PFS†		
Number (%) of patients with event	144 (65%)	81 (79%)
Hazard ratio‡ (95% CI)	0.66 (0.50, 0.88)	
p-Value§	0.0018	
Median in months (95% CI)	9.7 (7.6, 11.3)	5.6 (5.3, 7.5)
OS		
Number (%) of patients with event	155 (70%)	84 (82%)
Hazard ratio‡ (95% CI)	0.73 (0.55, 0.95)	
p-Value¶	0.0093	
Median in months (95% CI)	23.0 (19.0, 26.3)	16.1 (12.6, 18.8)
Objective response rate†		
ORR % (95% CI)	53% (46, 59)	41% (31, 51)
Complete response	17%	14%
Partial response	35%	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)

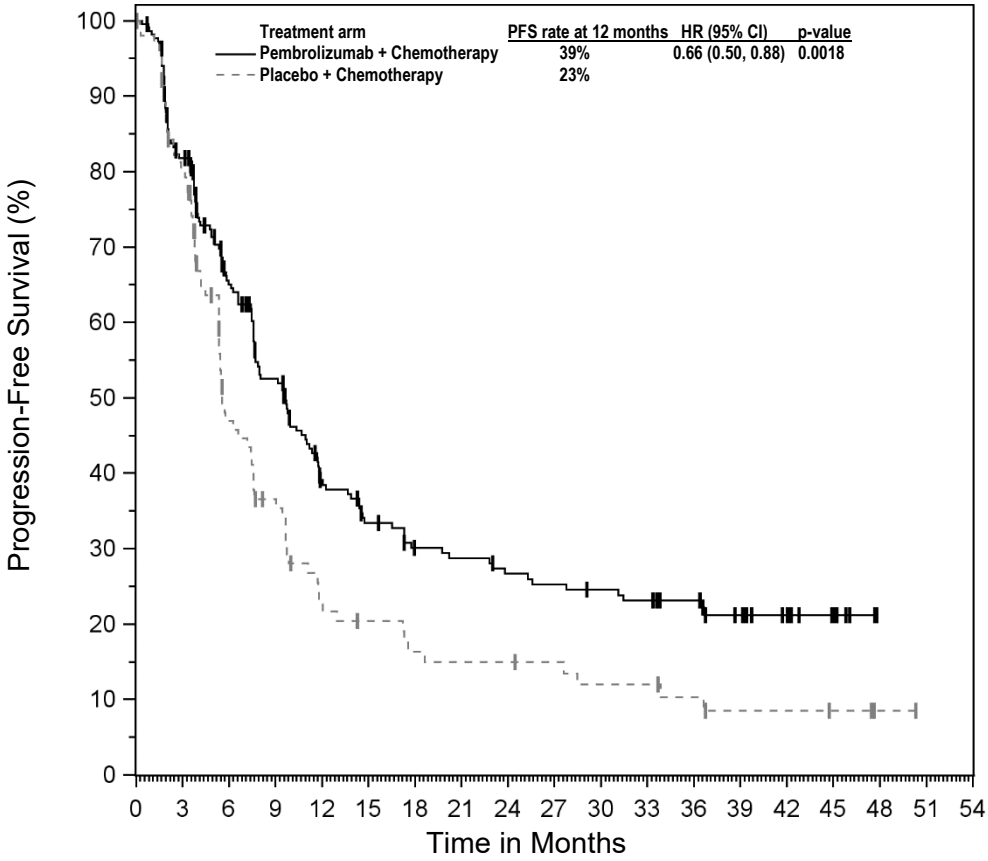
§ Nominal p-Value based on log-rank test stratified by chemotherapy on study (taxane vs. gemcitabine and carboplatin) and prior treatment with same class of chemotherapy in the neoadjuvant setting (yes vs. no). At the pre-specified interim analysis of PFS (median follow-up time of 19.2 months), statistically 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

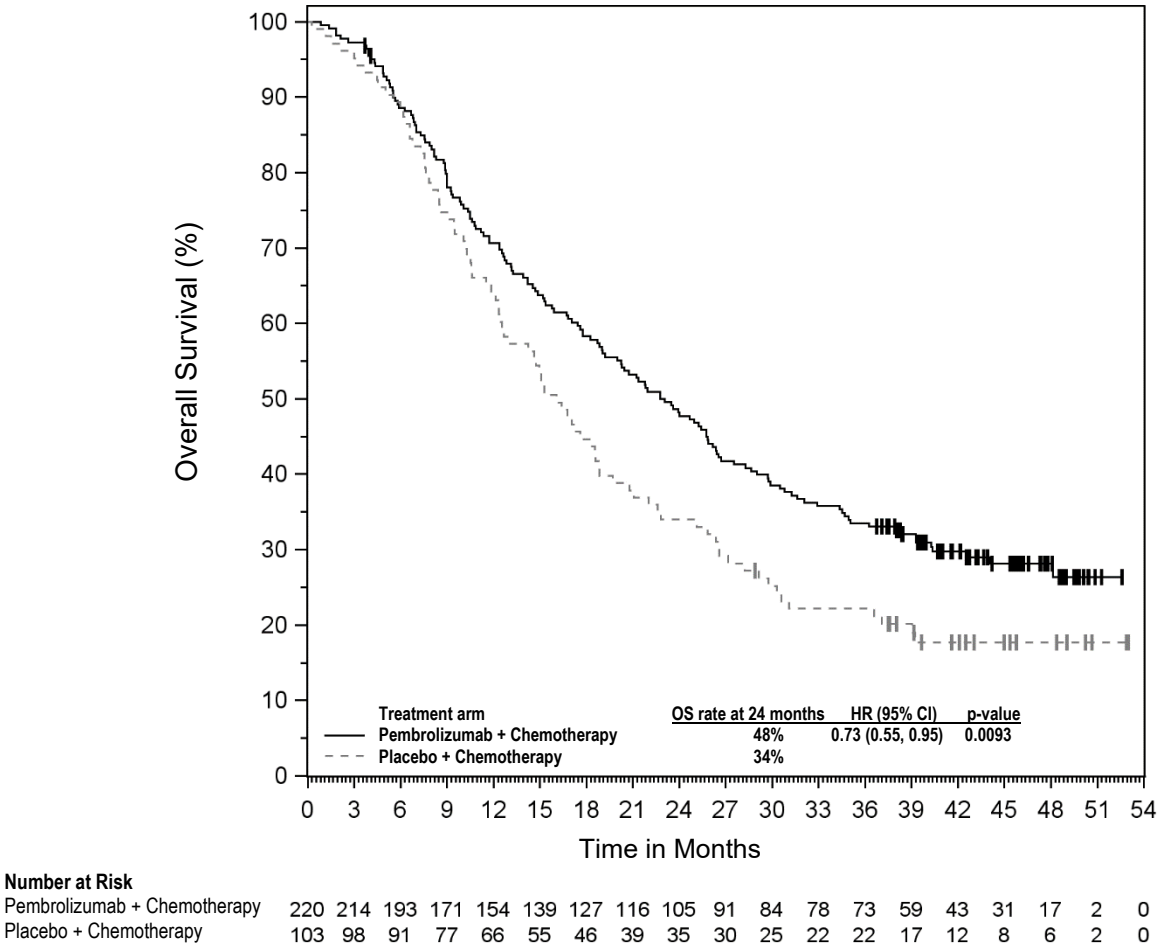
Figure 48: Kaplan-Meier curve for progression-free survival by treatment arm in KEYNOTE-355 patients with PD-L1 expression (CPS ≥ 10)



Number at Risk

Pembrolizumab + Chemotherapy	220	173	122	95	63	52	44	42	38	36	34	32	27	19	13	6	0	0	0
Placebo + Chemotherapy	103	80	41	30	18	15	12	11	11	10	8	8	6	4	4	3	1	0	0

Figure 49: 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 study of combination therapy for treatment of patients with primary advanced or recurrent EC

The efficacy of pembrolizumab in combination with paclitaxel and carboplatin was investigated in KEYNOTE-868 (NRG-GY018), a randomised, multicentre, double-blind, placebo-controlled study in 810 patients with advanced or recurrent endometrial carcinoma including those 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, and 14% grade 3), adenocarcinoma Not Otherwise Specified (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, and 16% grade 3), serous (26%), adenocarcinoma NOS (10%), clear cell carcinoma (7%), and other (5% including mixed epithelial and dedifferentiated/undifferentiated).

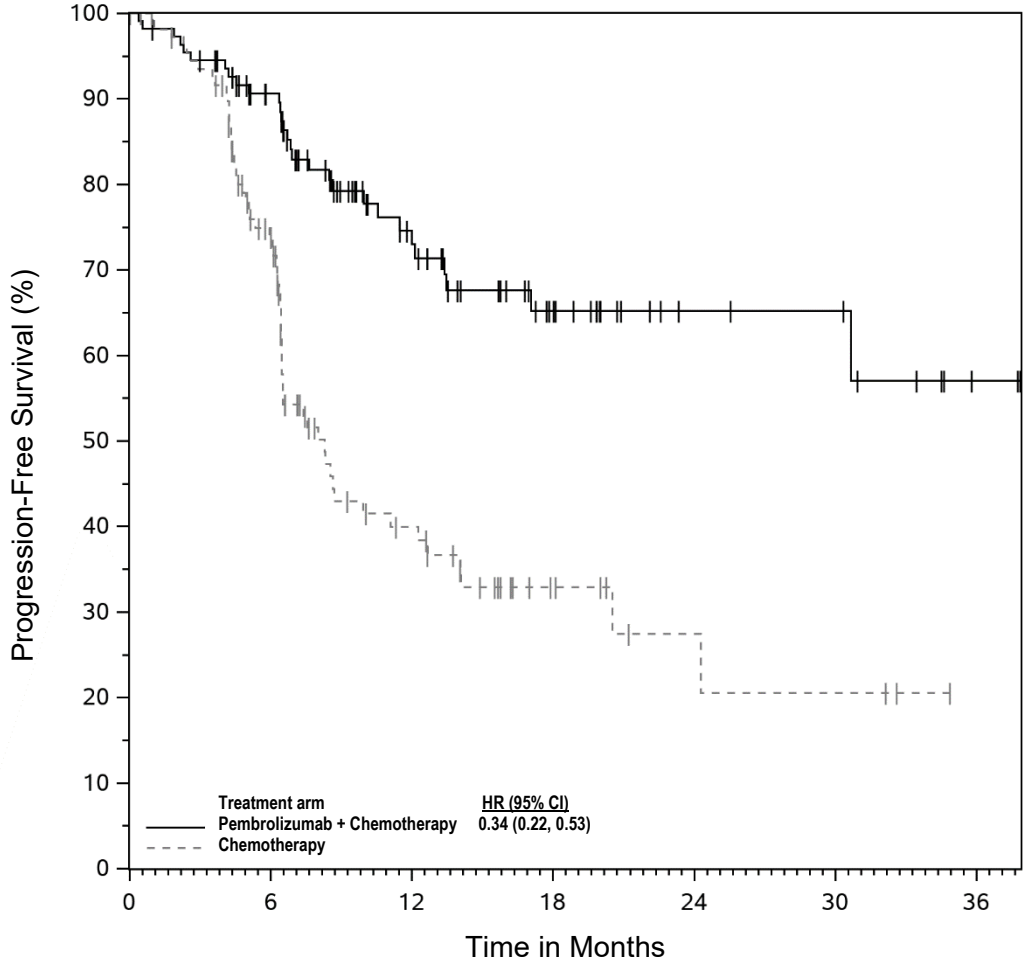
The primary efficacy outcome measure was PFS as assessed by the investigator according to RECIST 1.1 in the dMMR and pMMR populations. Secondary efficacy outcome measures included OS, ORR and response duration in the dMMR and pMMR populations. The study demonstrated statistically significant improvements 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 results were not mature. Efficacy results by MMR status are summarised in Table 49. The Kaplan-Meier curves for PFS by MMR status are shown in Figures 50 and 51, respectively.

Table 49: Efficacy results in KEYNOTE-868 (NRG-GY018)

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)	
Objective response rate				
Number of participants with measurable disease at baseline	n=95	n=95	n=220	n=235
ORR¶ % (95% CI)	78% (68, 86)	69% (59, 79)	61% (55, 68)	51% (45, 58)
Response duration				
Median in months (range)	NR (0.0+, 33.0+)	4.4 (0.0+, 32.8+)	7.1 (0.0+, 32.8+)	6.4 (0.0+, 20.1+)

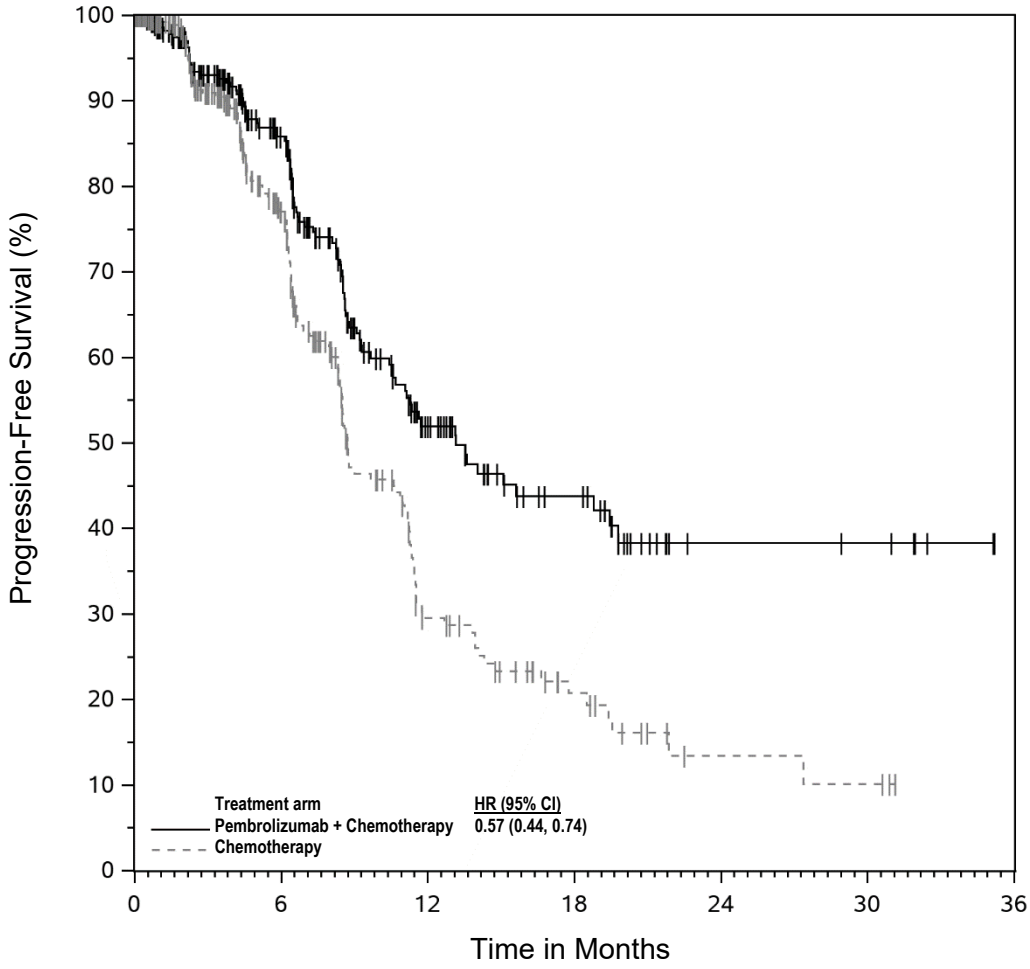
* Chemotherapy (paclitaxel and carboplatin)
† Based on the stratified Cox proportional hazard model
‡ One-sided p-value based on stratified log-rank test (compared to an alpha boundary of 0.00207 for dMMR and 0.00116 for pMMR)
¶ Response: Best objective response as confirmed complete response or partial response
NR = not reached

Figure 50: Kaplan-Meier curve for progression-free survival in KEYNOTE-868 (NRG-GY018) in dMMR population



Number at Risk							
Pembrolizumab + Chemotherapy	110	85	45	24	10	9	2
Chemotherapy	112	69	25	9	4	3	0

Figure 51: Kaplan-Meier curve for progression-free survival in KEYNOTE-868 (NRG-GY018) in pMMR population



Number at Risk							
Pembrolizumab + Chemotherapy	294	162	57	29	7	6	0
Chemotherapy	294	144	36	15	4	3	0

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. At the pre-specified interim analysis, with a median follow-up time of 11.4 months (range: 0.3 to 26.9 months), the study demonstrated a statistically significant improvement in OS and PFS. The pre-specified final OS analysis with approximately 16 months of additional follow-up duration from the interim analysis (overall median follow-up time of 14.7 months [range: 0.3 to 43.0 months]) was performed without multiplicity adjustment. Efficacy results by MMR subgroups were consistent with overall study results. PFS, ORR and response duration results at the interim analysis and OS results at final analysis are summarised in Table 50. Kaplan-Meier curves for final OS and interim PFS analyses are shown in Figures 52 and 53, respectively.

Table 50: Efficacy results in KEYNOTE-775

Endpoint	Pembrolizumab 200 mg every 3 weeks Lenvatinib n=411	Chemotherapy* n=416
OS		
Number (%) of patients with event	276 (67%)	329 (79%)
Median in months (95% CI)	18.7 (15.6, 21.3)	11.9 (10.7, 13.3)
Hazard ratio† (95% CI)	0.65 (0.55, 0.77)	
p-Value[Þ]	< 0.0001	
PFS[ß]		
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[ß]		
ORR§ % (95% CI)	32% (27, 37)	15% (11, 18)
Complete response	7%	3%
Partial response	25%	12%
p-Value¶	< 0.0001	
Response duration[ß]		
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

Þ One-sided nominal p-Value for final analysis based on stratified log-rank test. At the pre-specified interim analysis of OS with a median follow-up time of 11.4 months (range: 0.3 to 26.9 months), statistically significant superiority was achieved for OS comparing the combination of pembrolizumab and lenvatinib with chemotherapy (HR: 0.62 [95% CI: 0.51, 0.75] p-Value < 0.0001)

ß At pre-specified interim analysis

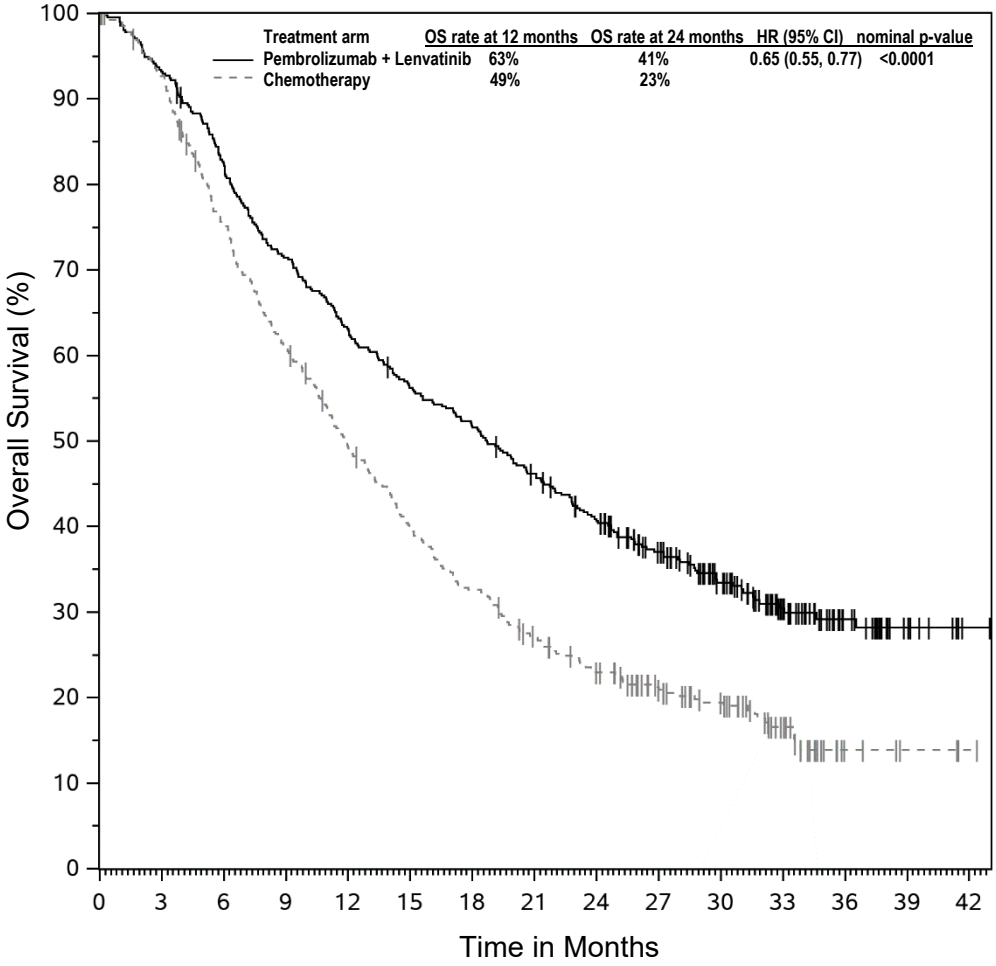
‡ One-sided p-Value based on stratified log-rank test

§ 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

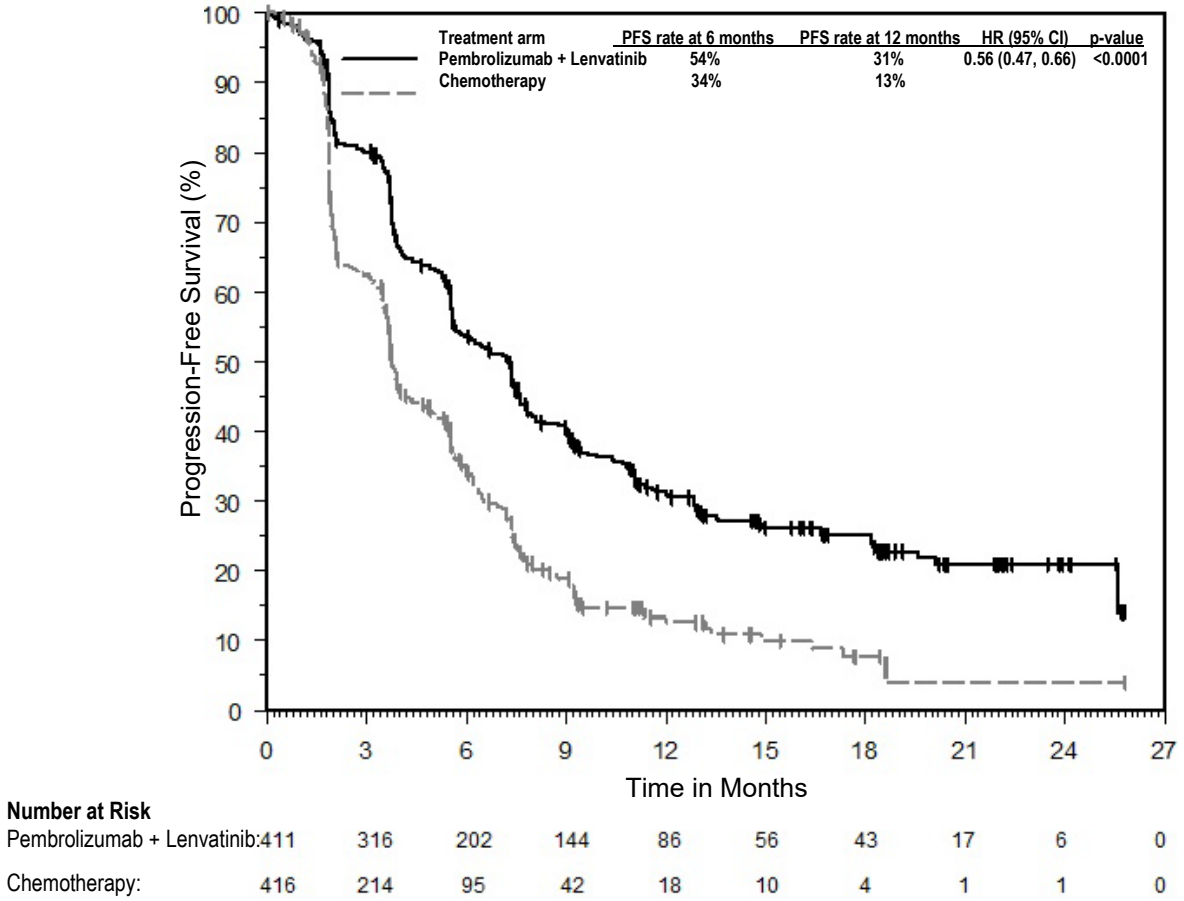
Figure 52: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-775 (intent to treat population)



Number at Risk

Pembrolizumab + Lenvatinib	411	383	337	292	258	229	211	186	160	125	91	58	30	10	2
Chemotherapy	416	378	305	246	196	158	129	104	84	64	49	28	6	3	1

Figure 53: Kaplan-Meier curve for progression free-survival by treatment arm in KEYNOTE-775 (intent to treat population)



Cervical cancer

KEYNOTE-A18: Controlled study of combination therapy with CRT in patients with 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 study that enrolled 1 060 patients with locally advanced cervical cancer who had not previously received any definitive surgery, radiation, or systemic therapy for cervical cancer. There were 601 patients with FIGO (International Federation of Gynaecology and Obstetrics) 2014 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 and 459 patients with 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. 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 the 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 the investigator or unacceptable toxicity. Assessment of tumour status was performed every 12 weeks for the first two years, every 24 weeks in Year 3, and then annually.

Among the 601 patients with FIGO 2014 Stage III - IVA disease enrolled in KEYNOTE-A18, the baseline characteristics were: median age of 51 years (range: 22 to 87), 16% age 65 or older; 36% White, 1% Black, 34% Asian, 38% Hispanic or Latino; 68% ECOG performance status of 0 and 32% ECOG performance status of 1; 93% with CPS ≥ 1; 71% had positive pelvic and/or positive para-aortic lymph node(s), 29% had neither positive pelvic nor para-aortic lymph node, 86% IMRT or VMAT EBRT, 90% ≥ 70 Gy (EQD2). Eighty-four percent had squamous cell carcinoma and 16% had non-squamous histology.

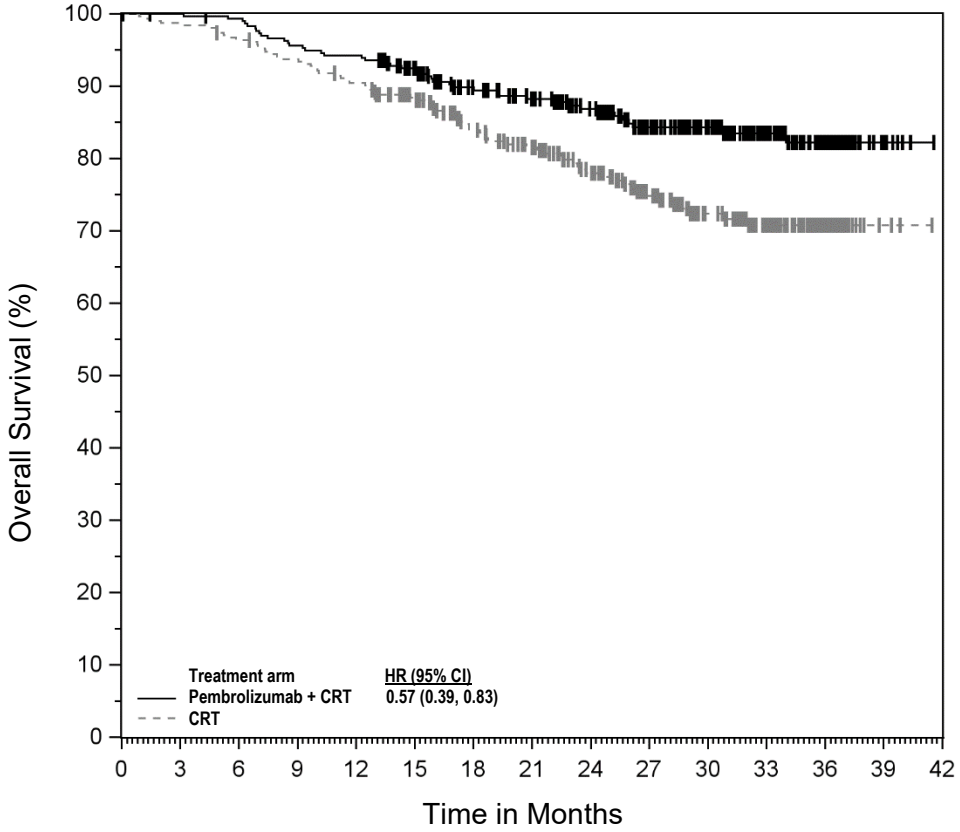
The primary efficacy outcomes were PFS (as assessed by investigator according to RECIST v1.1 or histopathologic confirmation) and OS. The study demonstrated statistically significant improvements in PFS [0.70 (95% CI 0.55, 0.89; p-Value 0.0020)] from the first pre-specified interim analysis and OS [0.67 (95% CI 0.50, 0.90; p-Value 0.0040)] from the second pre-specified interim analysis in the overall population for patients randomised to pembrolizumab with CRT compared to placebo with CRT. Table 51 summarises key efficacy measures from the second pre-specified interim analysis in patients with FIGO 2014 Stage III - IVA disease with median follow-up time of 26.6 months (range: 0.9 to 41.7 months). The Kaplan-Meier curves in patients with FIGO 2014 Stage III - IVA disease for OS and PFS based on this analysis are shown in Figures 54 and 55, respectively.

Table 51: Efficacy results in KEYNOTE-A18 for patients with FIGO 2014 Stage III - IVA cervical cancer

Endpoint	**Pembrolizumab 200 mg every 3 weeks and 400 mg every 6 weeks with CRT n=296**	**Placebo with CRT n=305**
OS		
Number (%) of patients with event	43 (15%)	73 (24%)
Median in months (95% CI)	NR (NR, NR)	NR (NR, NR)
Hazard ratio* (95% CI)	0.57 (0.39, 0.83)	
PFS by investigator		
Number (%) of patients with event	79 (27%)	125 (41%)
Median in months (95% CI)	NR (NR, NR)	NR (26.3, NR)
Hazard ratio* (95% CI)	0.57 (0.43, 0.76)	

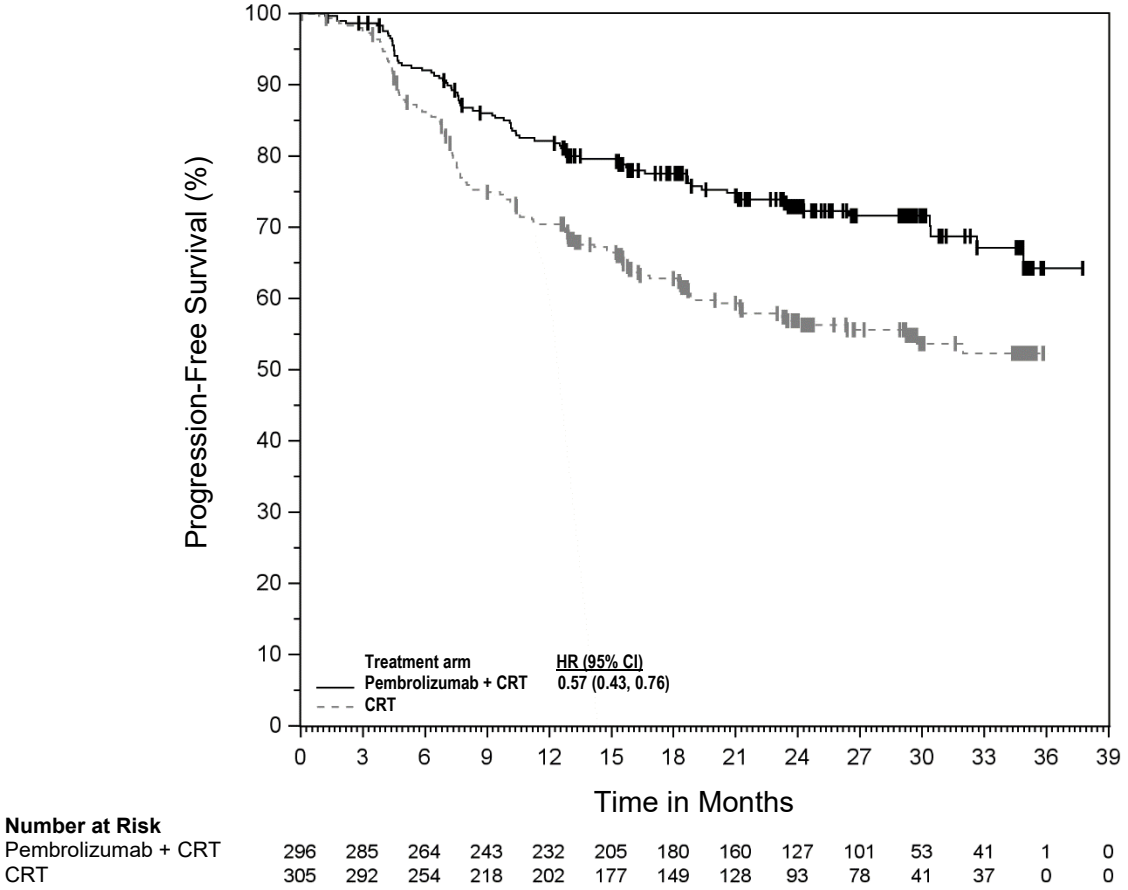
* Based on the unstratified Cox proportional hazard model
CRT = Chemoradiotherapy
NR = not reached

Figure 54: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-A18 for patients with FIGO 2014 Stage III - IVA cervical cancer



Number at Risk															
Pembrolizumab + CRT	296	294	291	280	276	254	227	207	184	149	115	77	38	7	0
CRT	305	301	293	284	273	250	216	196	167	134	100	66	28	3	0

Figure 55: Kaplan-Meier curve for progression-free survival by treatment arm in KEYNOTE-A18 for patients with FIGO 2014 Stage III - IVA cervical cancer



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

The efficacy of pembrolizumab in combination with paclitaxel and cisplatin or paclitaxel and carboplatin, with or without bevacizumab, was investigated in KEYNOTE-826, a multicentre, randomised, double-blind, placebo-controlled study that enrolled 617 patients with persistent, recurrent, or first-line metastatic cervical cancer who had not been treated with chemotherapy except when used concurrently as a radio-sensitising agent. Patients were enrolled regardless of tumour PD-L1 expression status. Patients with autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Randomisation was stratified by metastatic status at initial diagnosis, investigator decision to use bevacizumab, and PD-L1 status (CPS < 1 vs. CPS 1 to < 10 vs. CPS ≥ 10). Patients were randomised (1:1) to one of the two treatment groups:

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

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

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

All study medications were administered as an intravenous infusion. All study treatments were administered on Day 1 of each 3-week treatment cycle. Cisplatin could be administered on Day 2 of each 3-week treatment cycle. The option to use bevacizumab was by investigator choice prior to randomisation. Treatment with pembrolizumab continued until RECIST v1.1-defined progression of disease, unacceptable toxicity, or a maximum of 24 months. Administration of pembrolizumab was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Assessment of tumour status was performed at Week 9 and then every 9 weeks for the first year, followed by every 12 weeks thereafter.

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

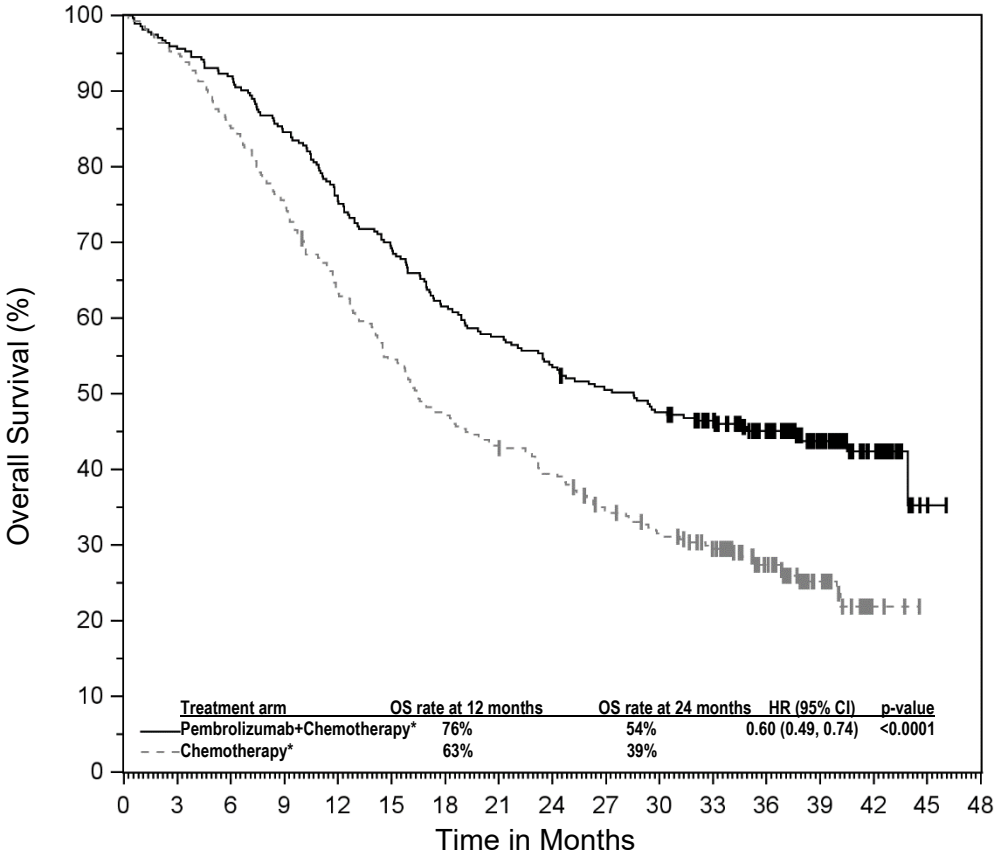
The primary efficacy outcome measures were OS and PFS as assessed by investigator according to RECIST v1.1. Secondary efficacy outcome measures were ORR and duration of response, according to RECIST v1.1, as assessed by investigator. At a pre-specified interim analysis, the study demonstrated statistically significant improvements in OS (HR 0.64; 95% CI 0.50, 0.81; p-Value = 0.0001) and PFS (HR 0.62; 95% CI 0.50, 0.77; p-Value < 0.0001) for patients whose tumours expressed PD-L1 with a CPS ≥ 1 randomised to pembrolizumab in combination with chemotherapy with or without bevacizumab compared to placebo in combination with chemotherapy with or without bevacizumab. The study also demonstrated statistically significant improvements in OS and PFS in the overall population. Table 52 summarises key efficacy measures for patients whose tumours expressed PD-L1 with a CPS ≥ 1 in KEYNOTE-826 at the final analysis with a median duration of follow-up of 21.3 months. The Kaplan-Meier curves for OS and PFS based on the final analysis are shown in Figures 56 and 57.

Table 52: Efficacy results in KEYNOTE-826 for patients with PD-L1 expression (CPS ≥ 1)

Endpoint	Pembrolizumab 200 mg every 3 weeks plus Chemotherapy* with or without bevacizumab n=273	Placebo plus Chemotherapy* with or without bevacizumab n=275
OS		
Number (%) of patients with event	153 (56%)	201 (73%)
Median in months (95% CI)	28.6 (22.1, 38.0)	16.5 (14.5, 20.0)
Hazard ratio† (95% CI)	0.60 (0.49, 0.74)	
p-Value‡	< 0.0001	
PFS		
Number (%) of patients with event	171 (63%)	220 (80%)
Median in months (95% CI)	10.5 (9.7, 12.3)	8.2 (6.3, 8.5)
Hazard ratio† (95% CI)	0.58 (0.47, 0.71)	
p-Value‡	< 0.0001	
Objective response rate		
ORR¶ % (95% CI)	69% (63, 74)	51% (45, 57)
Complete response	26%	15%
Partial response	43%	36%
Response duration		
Median in months (range)	19.2 (1.3+, 40.9+)	10.4 (1.5+, 40.7+)
% with duration ≥ 12 months#	56	45
% with duration ≥ 24 months#	48	30

* Chemotherapy (paclitaxel and cisplatin or paclitaxel and carboplatin)
† Based on the stratified Cox proportional hazard model
‡ Nominal p-Value based on stratified log-rank test
¶ Response: Best objective response as confirmed complete response or partial response
\# Based on Kaplan-Meier estimation

Figure 56: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-826 patients with PD-L1 expression (CPS ≥ 1)

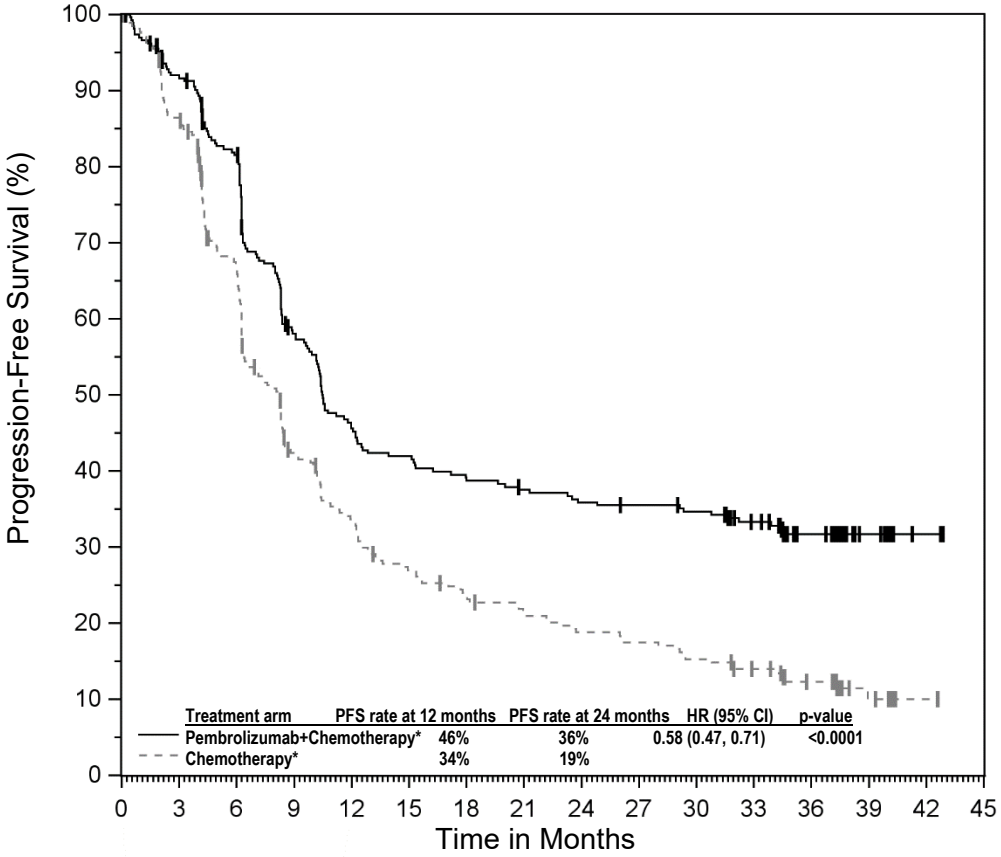


Number at Risk

Pembrolizumab+Chemotherapy*	273	261	251	231	206	189	168	157	146	136	128	116	90	52	22	2	0
Chemotherapy*	275	261	235	207	173	149	129	117	107	91	81	68	45	24	3	0	0

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

Figure 57: Kaplan-Meier curve for progression free survival by treatment arm in KEYNOTE-826 patients with PD-L1 expression (CPS ≥ 1)



Number at Risk

Pembrolizumab+Chemotherapy*	273	238	208	144	113	104	97	92	88	86	83	70	46	25	6	0
Chemotherapy*	275	229	170	103	81	64	55	49	43	40	35	28	18	7	2	0

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

Gastric or gastro-oesophageal junction (GEJ) adenocarcinoma

KEYNOTE-811: Controlled study of combination therapy in locally advanced unresectable or metastatic HER2-positive gastric or gastro-oesophageal junction adenocarcinoma patients naïve to treatment

The efficacy of pembrolizumab in combination with trastuzumab plus fluoropyrimidine and platinum-containing chemotherapy was investigated in KEYNOTE-811, a multicentre, randomised, double-blind, placebo-controlled study that enrolled 698 patients with HER2-positive advanced gastric or 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 treatment 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. 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 assay. The baseline characteristics of the 594 patients with tumour PD-L1 expression CPS ≥ 1 included: 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 second interim analysis in the overall population, the study demonstrated a statistically significant improvement in PFS (HR 0.72; 95% CI 0.60, 0.87; p-Value 0.0002) for patients randomised to the pembrolizumab arm in combination with trastuzumab and chemotherapy compared with placebo in combination with trastuzumab and chemotherapy. At this interim analysis, there was no statistically significant difference with respect to OS. The median follow-up time was 15.4 months (range: 0.3 to 41.6 months). 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 ORR (74.4% vs. 51.9%, representing a 22.7% difference in ORR, [95%CI: 11.2, 33.7]; p-Value 0.00006).

Table 53 summarises key efficacy results at the second interim analysis for the pre-specified subgroup of patients whose tumours expressed PD-L1 with a CPS ≥ 1 and Figures 58 and 59 show the Kaplan-Meier curves for PFS and OS.

Table 53: Efficacy results for KEYNOTE-811 for patients with PD-L1 expression (CPS ≥ 1)

Endpoint	Pembrolizumab Trastuzumab and Chemotherapy n=298	Placebo Trastuzumab and 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 (62%)
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	14%	10%
Partial response	59%	49%
p-Value#	0.00008	
Response duration		
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 unstratified Cox proportional hazard model

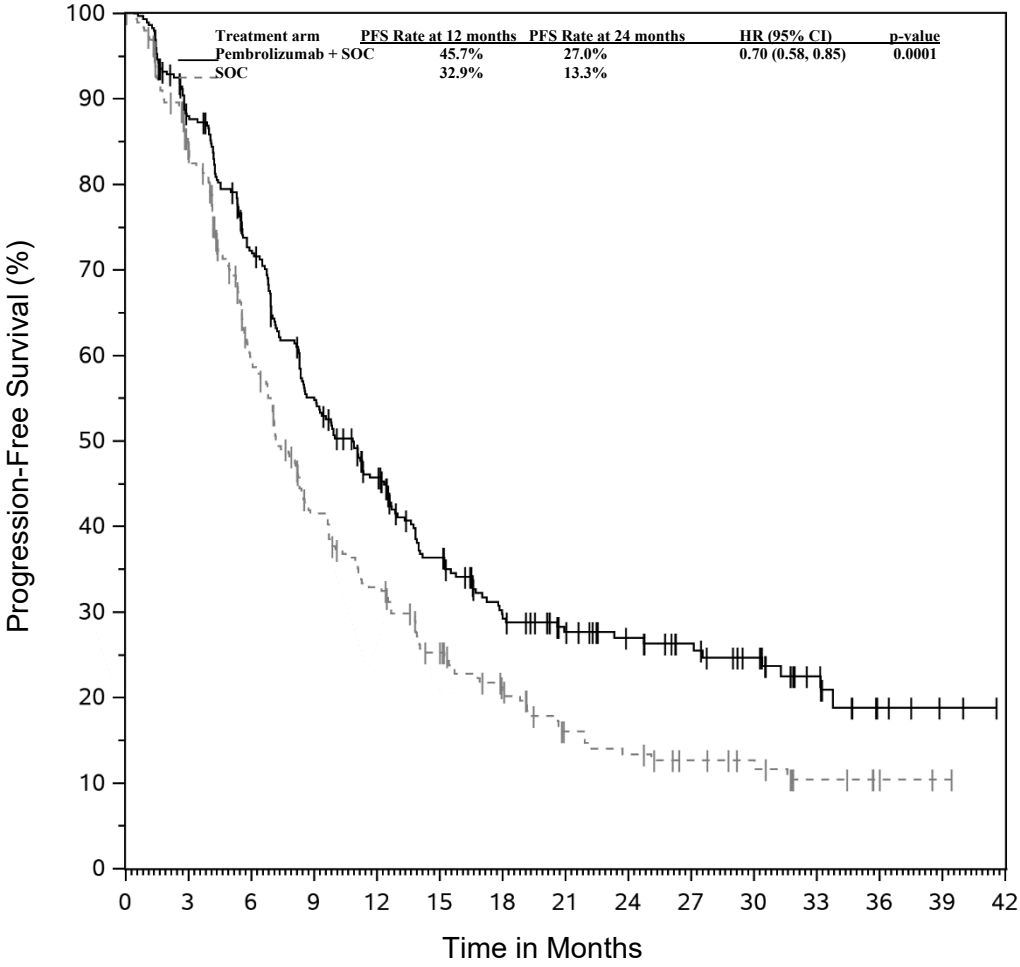
† Nominal p-value based on unstratified log-rank test; no formal test was performed in patients with PD-L1 expression (CPS ≥ 1)

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

\# Nominal p-value based on unstratified Miettinen and Nurminen method; no formal test was performed in patients with PD-L1 expression (CPS ≥ 1)

¶ Based on Kaplan-Meier estimation

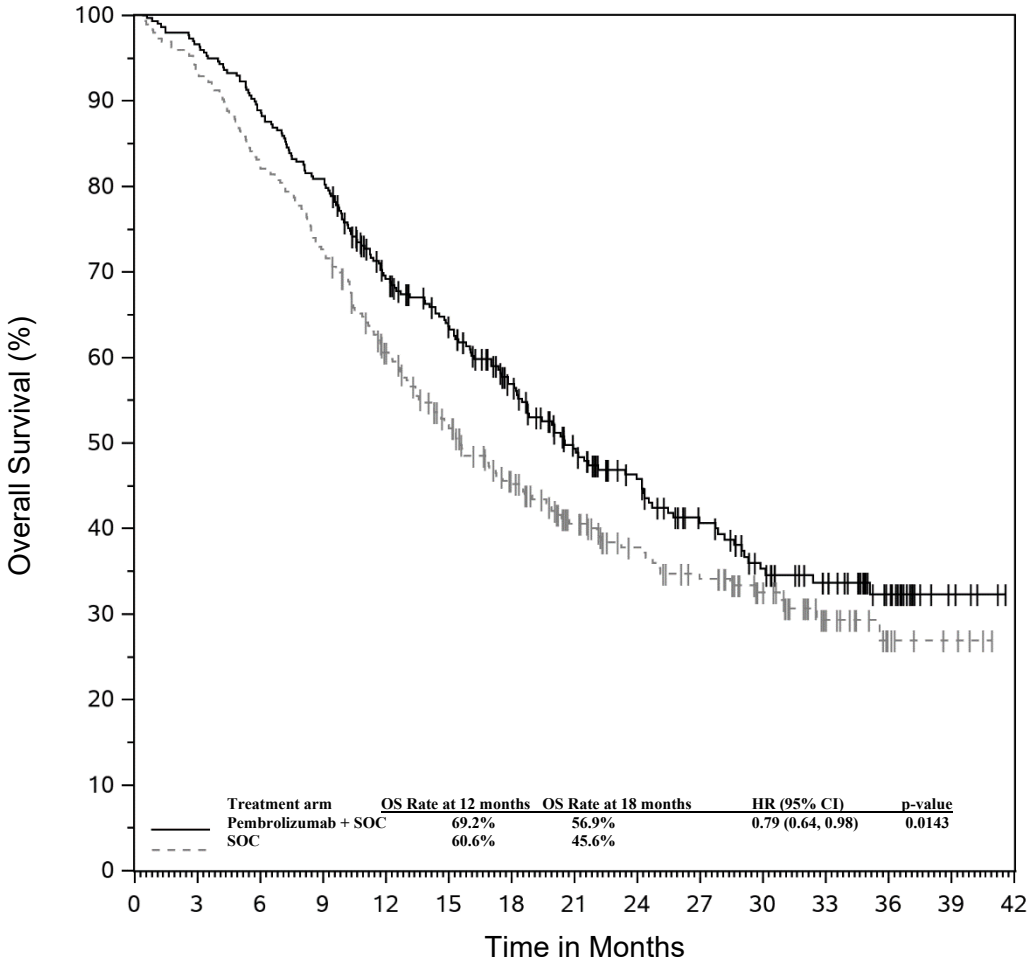
Figure 58: Kaplan-Meier curve for progression free survival by treatment arm in KEYNOTE-811 patients with PD-L1 expression (CPS ≥ 1)



Number at Risk

Pembrolizumab + SOC	298	250	200	150	116	84	61	48	40	33	26	14	5	2	0
SOC	296	231	150	98	76	54	38	24	20	15	12	6	3	1	0

Figure 59: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-811 patients with PD-L1 expression (CPS ≥ 1)



Number at Risk															
Pembrolizumab + SOC	298	288	265	241	194	169	134	103	83	64	49	37	20	5	0
SOC	296	277	244	215	169	136	106	79	62	52	38	19	8	4	0

KEYNOTE-859: Controlled study of combination therapy in locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction adenocarcinoma 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 study that enrolled 1 579 patients with HER2-negative advanced gastric or GEJ adenocarcinoma regardless of PD-L1 expression status, who had not previously received systemic therapy for metastatic disease. Prior neoadjuvant and/or adjuvant therapy was allowed if it was completed at least 6 months prior to randomisation. Patients with an autoimmune disease that required systemic therapy within 2 years of treatment, a medical condition that required immunosuppression, or patients who had received prior treatment with immune checkpoint inhibitors 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 treatment 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. Duration

of cisplatin or oxaliplatin treatment could be capped at 6 cycles as per local country guidelines. 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. Duration of cisplatin or oxaliplatin treatment could be capped at 6 cycles as per local country guidelines. 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. Assessment of tumour status was performed every 6 weeks.

Among the 1 579 patients in KEYNOTE-859, 1 235 (78%) had tumours that expressed PD-L1 with a CPS ≥ 1. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx assay. The baseline characteristics of the 1 235 patients with tumour PD-L1 expression CPS ≥ 1 included: median age of 62 years (range: 24 to 86), 40% age 65 or older; 70.4% male; 55.5% White; 33.1% Asian; 36.5% ECOG PS of 0 and 63.5% ECOG PS of 1. Ninety-six percent of patients had metastatic disease (stage IV) and 4% had locally advanced unresectable disease. Five percent (n=66) had tumours that were MSI-H. Eighty-six percent of patients received CAPOX.

The primary efficacy outcome measure was OS. Additional secondary efficacy outcome measures included PFS, ORR, and DOR as assessed by BICR using RECIST 1.1.

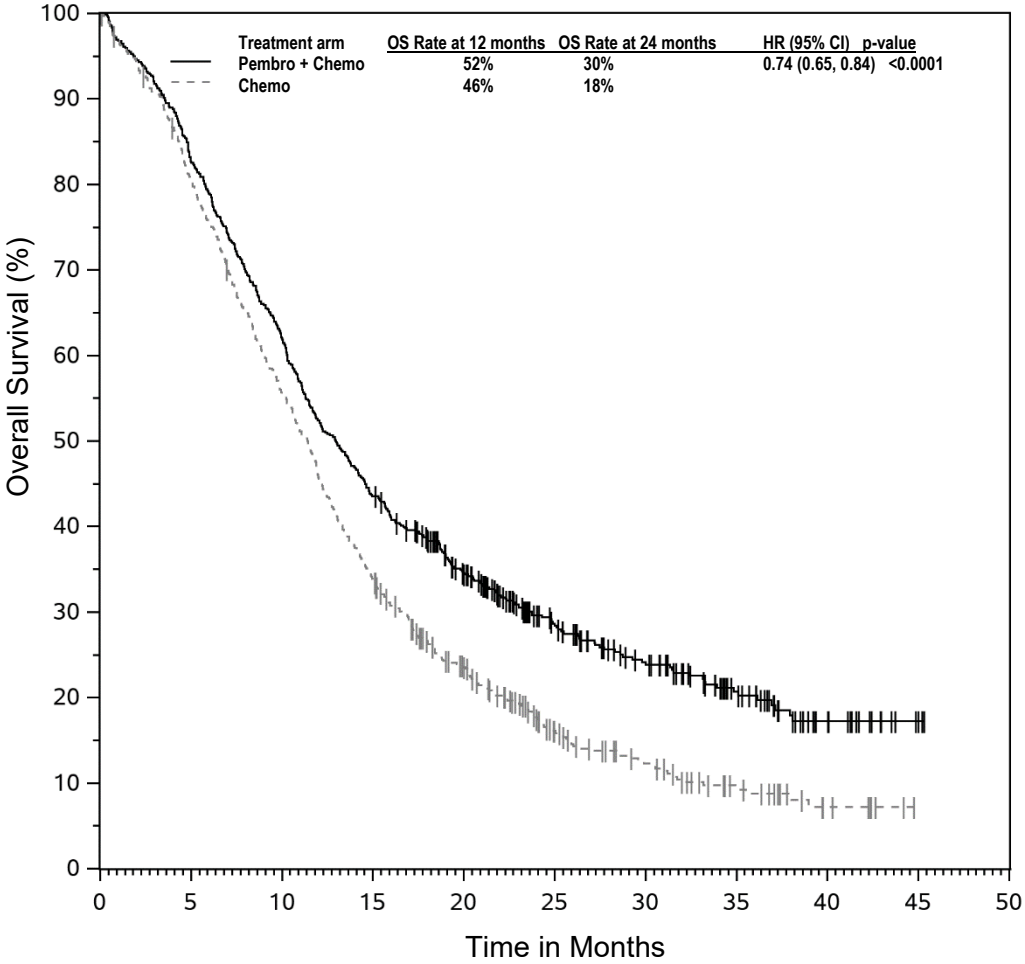
The study demonstrated a statistically significant improvement in OS (HR 0.78; 95% CI 0.70, 0.87; p-Value < 0.0001), PFS (HR 0.76; 95% CI 0.67, 0.85; p-Value < 0.0001) and ORR (51% [95% CI 47.7, 54.8] vs. 42% [95% CI 38.5, 45.5]; p-Value 0.00009) in patients randomised to pembrolizumab in combination with chemotherapy compared with placebo in combination with chemotherapy in the overall population. The median follow-up time was 12 months (range: 0.1 to 45.9 months). Table 54 summarises key efficacy results for the pre-specified subgroup of patients whose tumours expressed PD-L1 with a CPS ≥ 1 and Figures 60 and 61 show the Kaplan-Meier curves for OS and PFS.

Table 54: Efficacy results in KEYNOTE-859 for patients with PD-L1 expression (CPS ≥ 1)

Endpoint	Pembrolizumab Fluoropyrimidine and Platinum Chemotherapy n=618	Placebo Fluoropyrimidine and Platinum Chemotherapy n=617
OS		
Number (%) of patients with event	464 (75%)	526 (85%)
Median in months* (95% CI)	13.0 (11.6, 14.2)	11.4 (10.5, 12.0)
Hazard ratio† (95% CI)	0.74 (0.65, 0.84)	
p-Value‡	< 0.0001	
PFS		
Number (%) of patients with event	443 (72%)	483 (78%)
Median in months* (95% CI)	6.9 (6.0, 7.2)	5.6 (5.4, 5.7)
Hazard ratio† (95% CI)	0.72 (0.63, 0.82)	
p-Value‡	< 0.0001	
Objective response rate		
ORR§ (95% CI)	52% (48.1, 56.1)	43% (38.7, 46.6)
Complete response	10%	6%
Partial response	42%	37%
p-Value¶	0.00041	
Response duration		
Median in months* (range)	8.3 (1.2+, 41.5+)	5.6 (1.3+, 34.2+)
% with duration ≥ 12 months*	41%	26%

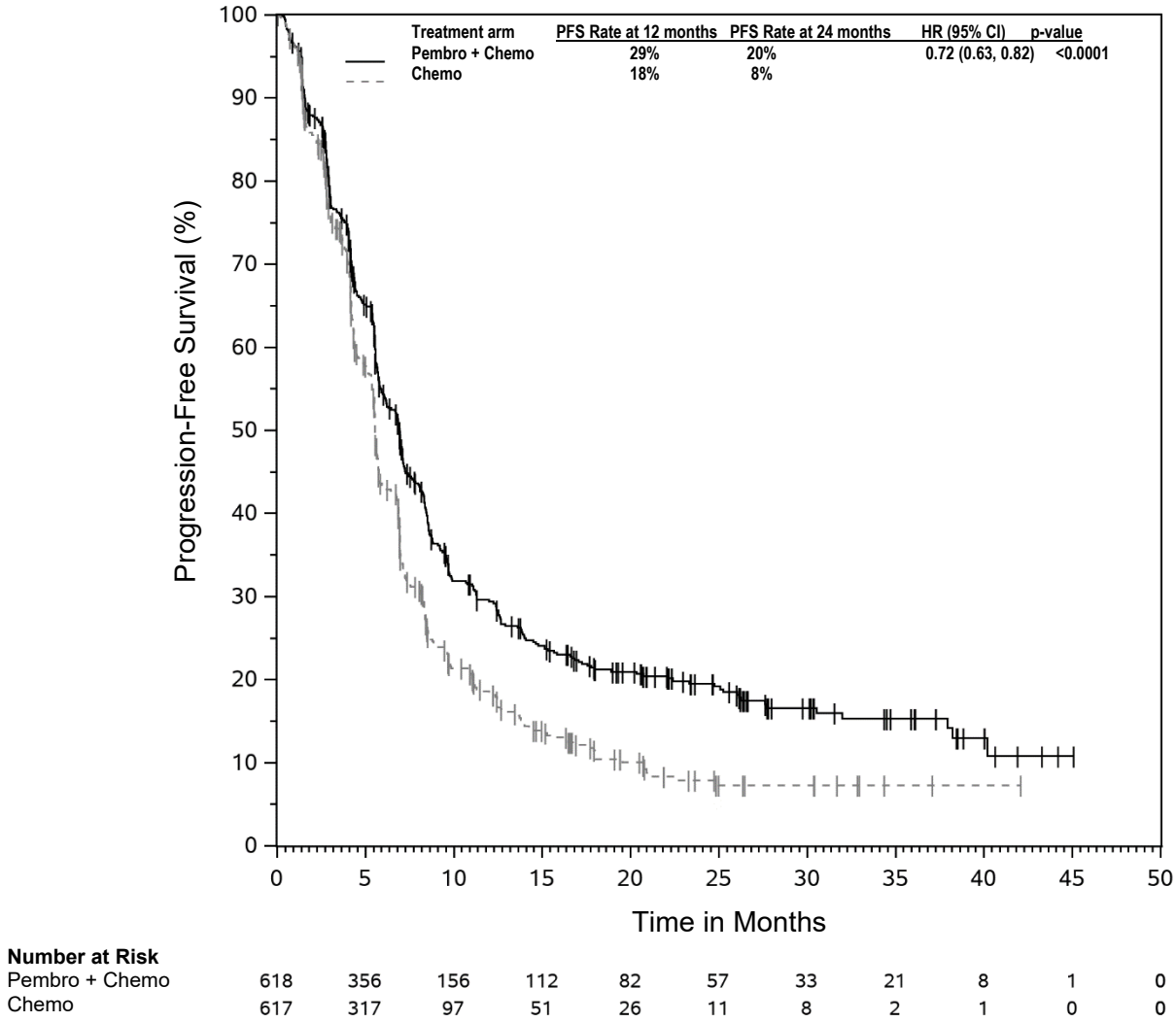
* Based on Kaplan-Meier estimation
† Based on the stratified Cox proportional hazard model
‡ One sided p-Value based on stratified log-rank test
§ Response: Best objective response as confirmed complete response or partial response
¶ One sided p-Value based on stratified Miettinen and Nurminen method

Figure 60: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-859 patients with PD-L1 expression (CPS ≥ 1)



Number at Risk											
Pembro + Chemo	618	511	383	269	192	121	81	46	17	3	0
Chemo	617	493	339	206	126	66	41	20	7	0	0

Figure 61: Kaplan-Meier curve for progression-free survival by treatment arm in KEYNOTE-859 patients with PD-L1 expression (CPS ≥ 1)



An analysis was performed in KEYNOTE-859 in patients whose tumours expressed PD-L1 with a CPS ≥ 1 to < 10 or CPS ≥ 10 in both arms (see Table 55).

Table 55: Efficacy results by PD-L1 expression in KEYNOTE-859

Endpoint	Pembrolizumab combination therapy n=337	Chemotherapy n=345	Pembrolizumab combination therapy n=279	Chemotherapy n=272
	CPS ≥ 1 to < 10		CPS ≥ 10	
OS HR (95% CI)	0.83 (0.70, 0.98)*		0.65 (0.53, 0.79)†	
PFS HR (95% CI)	0.83 (0.70, 0.99)*		0.62 (0.51, 0.76)†	
ORR§ (95% CI)	45% (39.7, 50.6)	42% (37.0, 47.7)	61% (54.6, 66.3)	43% (37.1, 49.1)

* Hazard ratio (pembrolizumab combination therapy compared to chemotherapy) based on unstratified Cox proportional hazard model

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

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

Biliary tract carcinoma
KEYNOTE-966: Controlled study of combination therapy in patients with locally advanced unresectable or metastatic BTC
The efficacy of pembrolizumab in combination with gemcitabine and cisplatin was investigated in KEYNOTE-966, a multicentre, randomised, double-blind, placebo-controlled study 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 were enrolled regardless of tumour PD-L1 expression. Patients must have had acceptable serum bilirubin levels (≤ 1.5 x ULN or direct bilirubin ≤ ULN for participants with total bilirubin levels > 1.5 × ULN) and any clinically significant biliary obstruction had to be resolved before randomisation. 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 geographic region (Asia vs. non-Asia), locally advanced versus 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. 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 using RECIST 1.1. The study demonstrated a statistically significant improvement in OS at final analysis for patients randomised to pembrolizumab in combination with chemotherapy compared to placebo in combination with chemotherapy. Table 56 summarises key efficacy measures and Figures 62 and 63 show the Kaplan-Meier curves for PFS and OS based on the final analysis with a median follow-up time of 11.6 months (range: 0.2 to 37.5 months).

Table 56: Efficacy results 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	428 (80%)	448 (84%)
Median in months (95% CI)	6.5 (5.7, 6.9)	5.6 (4.9, 6.5)
Hazard ratio* (95% CI)	0.87 (0.76, 0.99)	
p-Value‡	0.0171	
Objective response rate		
ORR% (95% CI)	29.3% (25.4, 33.3)	28.4% (24.6, 32.4)
Complete response	2.6%	1.7%
Partial response	26.6%	26.7%
p-Value$^{\alpha}$	0.3610	
Response duration§, ¶		
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%

* Based on the stratified Cox proportional hazard model

† One-sided p-Value based on a stratified log-rank test. The OS result met the pre-specified one-sided significance level of 0.0200

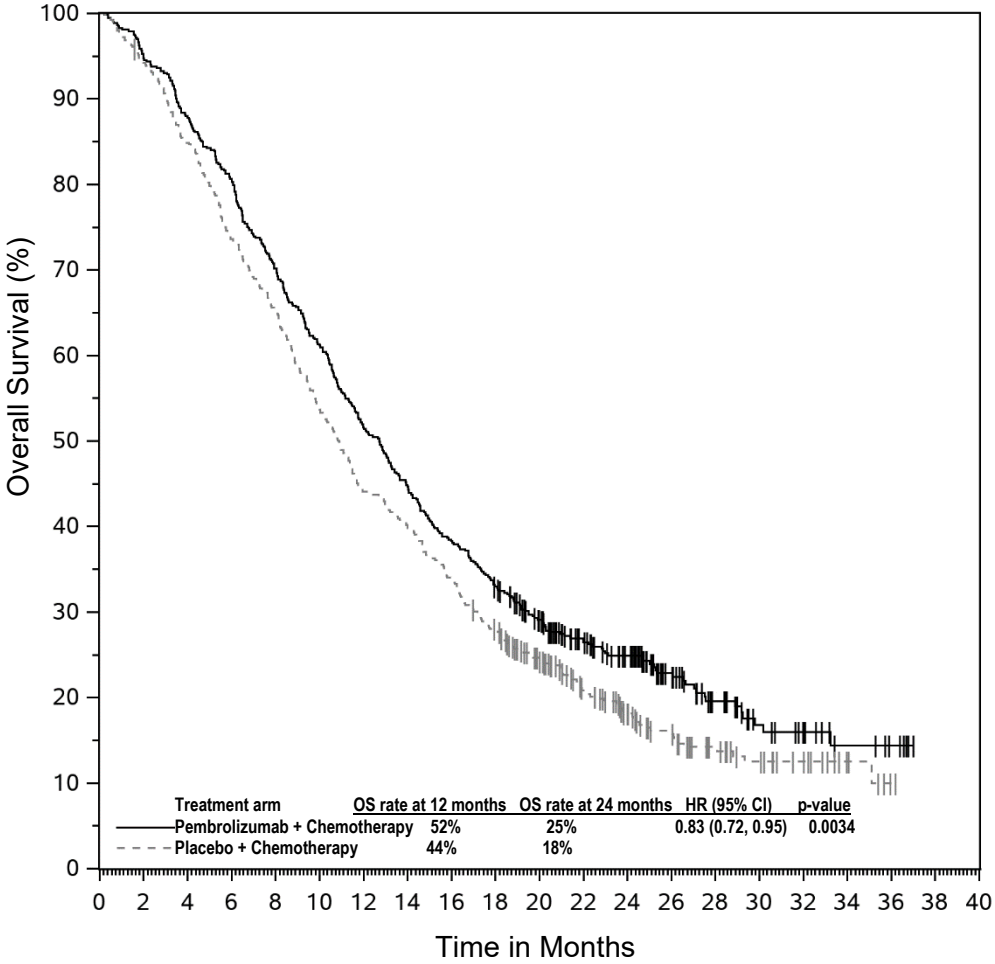
‡ One-sided p-Value based on stratified log-rank test. The PFS result did not meet the pre-specified one-sided significance level of 0.0125

$^{\alpha}$ One-sided p-Value based on the stratified Miettinen and Nurminen method. The ORR result did not meet the pre-specified one-sided significance level of 0.0125

§ Based on patients with objective response that is confirmed complete response or partial response

¶ Based on Kaplan-Meier estimate

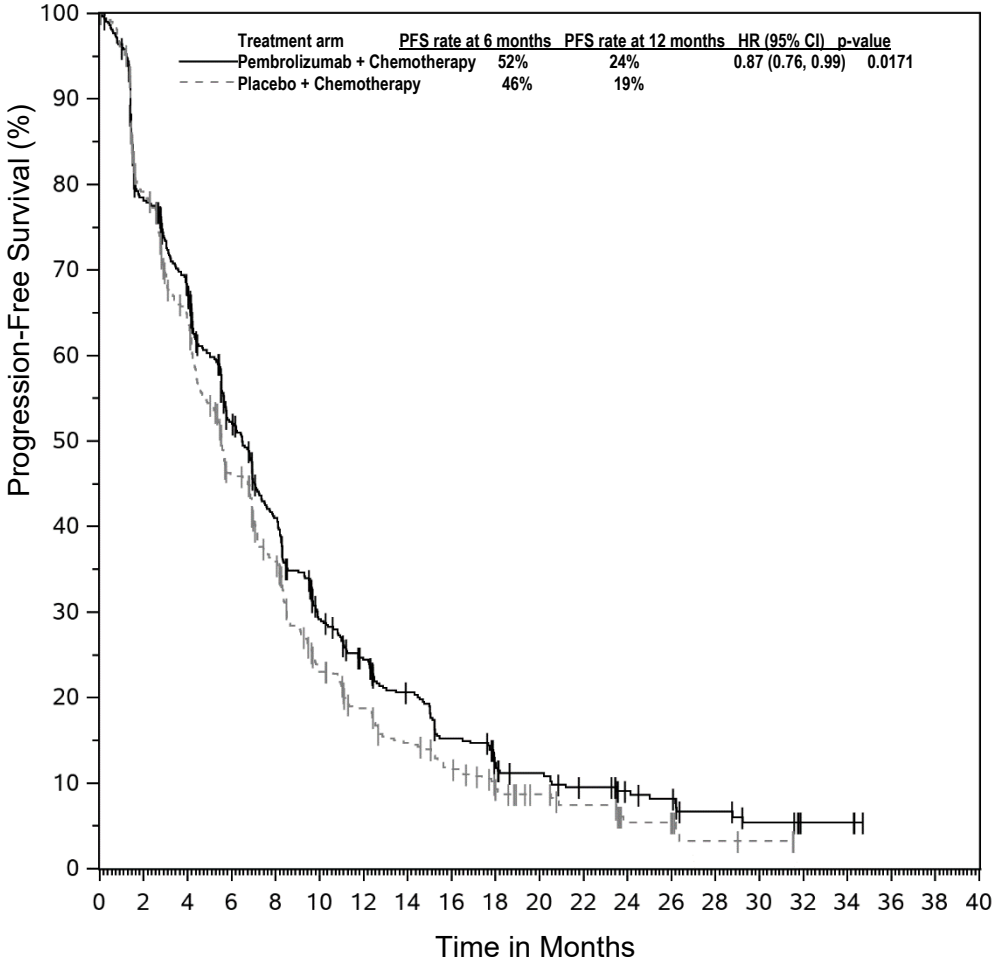
Figure 62: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-966 (intent to treat population)



Number at Risk

Pembrolizumab + Chemotherapy	533	505	469	430	374	326	275	238	204	175	142	108	88	56	35	21	16	8	5	0	0
Placebo + Chemotherapy	536	504	454	394	349	287	236	213	181	148	115	81	59	43	28	20	14	7	1	0	0

Figure 63: Kaplan-Meier curve for progression-free survival by treatment arm in KEYNOTE-966 (intent to treat population)



Ovarian Cancer

KEYNOTE-B96: Controlled study of combination therapy in platinum-resistant ovarian carcinoma patients

The efficacy of pembrolizumab in combination with paclitaxel, with or without bevacizumab, was investigated in KEYNOTE-B96, a multicentre, randomised, double-blind, placebo-controlled study that enrolled 643 patients with histologically-confirmed epithelial ovarian, fallopian tube, or primary peritoneal carcinoma with one or two prior systemic treatment regimens. Prior therapy must have included at least one platinum-based therapy with radiographic evidence of disease progression within 6 months after the last dose. Prior therapy with an anti-PD-1/PD-L1 inhibitor, PARP inhibitor, or bevacizumab was permitted. Patients with autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression and patients with primary platinum-refractory disease were ineligible.

Randomisation was stratified by investigator decision to use bevacizumab, geographic region, 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:

- Pembrolizumab 400 mg every 6 weeks plus paclitaxel 80 mg/m^2 with or without bevacizumab 10 mg/kg.
- Placebo every 6 weeks plus paclitaxel 80 mg/m^2 with or without bevacizumab 10 mg/kg.

All study medications were administered as an intravenous infusion. Pembrolizumab 400 mg or placebo were administered on Day 1 of each six-week treatment cycle and paclitaxel 80 mg/m^2 was

administered on Days 1, 8, and 15 of each three-week treatment cycle. The option to use bevacizumab was by investigator choice prior to randomisation. Bevacizumab 10 mg/kg was administered on Day 1 of a two-week treatment cycle. Treatment with pembrolizumab continued until RECIST v1.1-defined progression of disease, unacceptable toxicity, or a maximum of 24 months. Assessment of tumour status was performed at Week 9 and then every 9 weeks for the first year, followed by every 12 weeks thereafter.

Among the 643 patients in KEYNOTE-B96, 466 (72%) had tumours that expressed PD-L1 with a CPS ≥ 1. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx assay. The study population characteristics of these 466 patients were: median age of 62 years (range: 37 to 85), 38% age 65 or older; 67% White, 20% Asian, and 2% Black; 13% Hispanic or Latino; 55% and 44% ECOG performance status of 0 or 1, respectively; 73% received bevacizumab as study treatment; 64% received two prior lines of therapy and 36% of patients had one prior line, the percentage of patients who received prior systemic therapy includes: 46% with bevacizumab, 39% with a PARP inhibitor, or 3% with an anti-PD-1/PD-L1 inhibitor. Eighty-nine percent had high-grade serous histology.

The primary efficacy outcome measure was PFS as assessed by investigator according to RECIST v1.1. The secondary efficacy outcome measure was OS. At the first pre-specified interim analysis, the study demonstrated statistically significant improvement in PFS for patients randomised to pembrolizumab in combination with paclitaxel with or without bevacizumab compared to placebo in combination with paclitaxel with or without bevacizumab in the overall population (HR = 0.70 [95% CI: 0.58, 0.84; p-Value < 0.0001]; median follow-up time of 11.8 months [range: 0.1 to 27.0 months]) and in patients whose tumours expressed PD-L1 CPS ≥ 1. The study demonstrated statistically significant improvement in OS for patients randomised to pembrolizumab in combination with chemotherapy with or without bevacizumab compared to placebo in combination with chemotherapy with or without bevacizumab whose tumours expressed PD-L1 CPS ≥ 1 at the second pre-specified interim analysis and in the overall population (HR = 0.82 [95% CI: 0.69, 0.97; p-Value 0.0115]) at the final analysis with median follow-up time of 15.6 months (range: 0.1 to 44.1 months).

Table 57 summarises the efficacy results in patients whose tumours expressed PD-L1 with a CPS ≥ 1 and the Figures 64 and 65 show the Kaplan-Meier curves for PFS and OS.

Table 57: Efficacy results in KEYNOTE-B96 for patients with PD-L1 expression (CPS ≥ 1)

Endpoint	Pembrolizumab 400 mg every 6 weeks plus paclitaxel with or without bevacizumab n=234	Placebo plus paclitaxel with or without bevacizumab n=232
PFS*		
Number (%) of patients with event	162 (69%)	180 (78%)
Median in months (95% CI)	8.3 (7.0, 9.4)	7.2 (6.2, 8.1)
Hazard ratio† (95% CI)	0.72 (0.58, 0.89)	
p-Value‡	0.0014	
OS§		
Number (%) of patients with event	157 (67%)	175 (75%)
Median in months (95% CI)	18.2 (15.3, 21.0)	14.0 (12.5, 16.1)
Hazard ratio† (95% CI)	0.76 (0.61, 0.94)	
p-Value¶	0.0053	

* Based on the first pre-specified interim analysis with a median follow-up time of 12.0 months (range: 0.5 to 27.0 months)

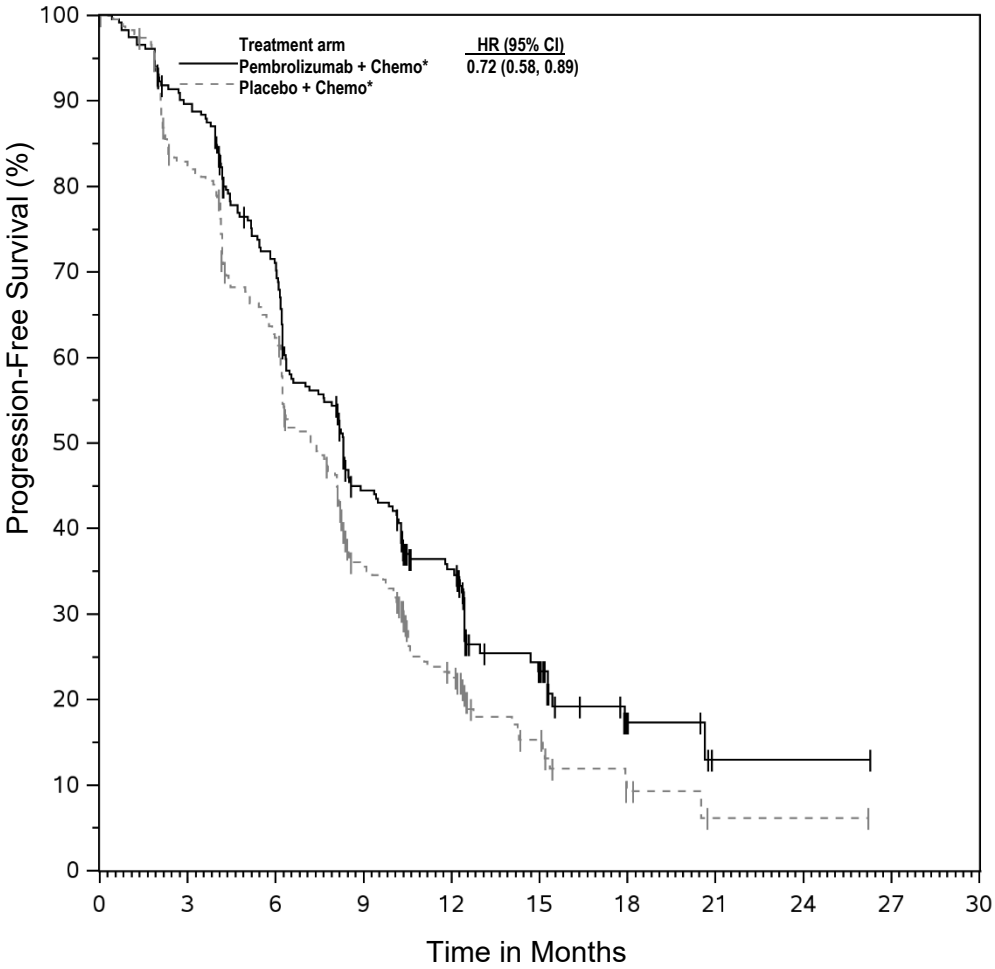
† Based on the stratified Cox regression model

‡ One-sided p-Value based on stratified log-rank test (compared to an alpha boundary of 0.0116)

§ Based on the second pre-specified interim analysis with a median follow-up time of 15.8 months (range: 0.5 to 38.0 months)

¶ One-sided p-Value based on stratified log-rank test (compared to an alpha boundary of 0.0083)

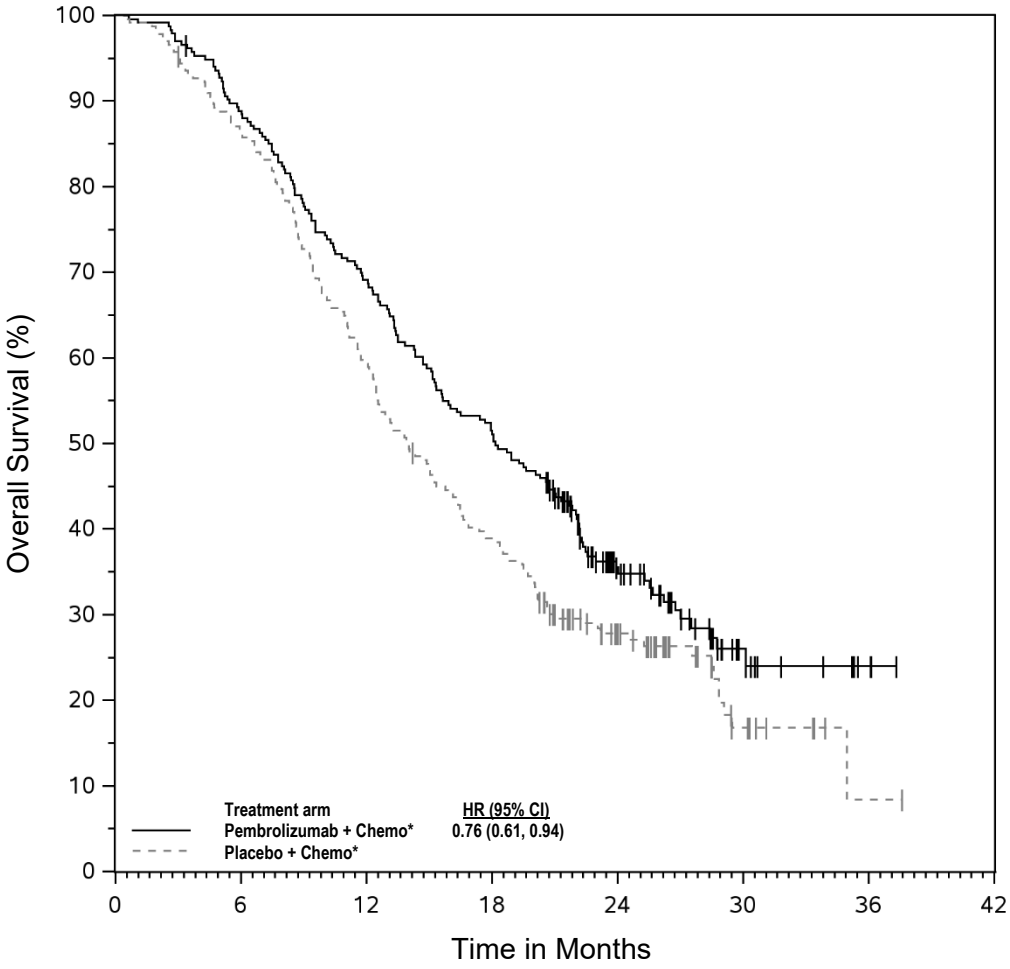
Figure 64: Kaplan-Meier curve for progression-free survival by treatment arm in KEYNOTE-B96 for patients with PD-L1 expression (CPS ≥ 1)



Number at Risk											
Pembrolizumab + Chemo*	234	206	158	92	56	21	6	1	1	0	0
Placebo + Chemo*	232	186	138	69	36	16	5	1	1	0	0

*Chemotherapy (paclitaxel) with or without bevacizumab

Figure 65: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-B96 for patients with PD-L1 expression (CPS ≥ 1)



Number at Risk								
Pembrolizumab + Chemo*	234	207	161	120	49	13	3	0
Placebo + Chemo*	232	200	137	89	41	10	1	0

*Chemotherapy (paclitaxel) with or without bevacizumab

Elderly population

No overall differences in safety were observed in patients ≥ 75 years of age compared to younger patients receiving pembrolizumab monotherapy. Based on limited safety data from patients ≥ 75 years of age, when administrated in combination with chemotherapy, pembrolizumab showed less tolerability in patients ≥ 75 years of age compared to younger patients. For efficacy data in patients ≥ 75 years of age please refer to the relevant section of each indication.

Paediatric population

In KEYNOTE-051, 161 paediatric patients (62 children aged 9 months to less than 12 years and 99 adolescents aged 12 years to 17 years) with advanced melanoma or PD-L1 positive advanced, relapsed, or refractory solid tumours or lymphoma were administered pembrolizumab 2 mg/kg 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 64% 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. Data from clinical studies in adolescent melanoma patients is very limited and extrapolation from adult data has been used to establish efficacy. Among the 5 adolescent participants with advanced melanoma treated in KEYNOTE-051, no patient had a complete or a partial response, and 1 patient had stable disease.

The European Medicines Agency has deferred the obligation to submit the results of studies with pembrolizumab in one or more subsets of the paediatric population in treatment of Hodgkin lymphoma (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics of pembrolizumab was studied in 2 993 patients with metastatic or unresectable melanoma, NSCLC, or carcinoma who received doses in the range: of 1 to 10 mg/kg bw every 2 weeks, 2 to 10 mg/kg bw every 3 weeks, or 200 mg every 3 weeks.

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

Distribution
Consistent with a limited extravascular distribution, the volume of distribution of pembrolizumab at steady-state is small (~6.0 L; CV: 20%). As expected for an antibody, pembrolizumab does not bind to plasma proteins in a specific manner.

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

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

Linearity/non-linearity
Exposure to pembrolizumab as expressed by peak concentration (C_{max}) or area under the plasma concentration time curve (AUC) increased dose proportionally within the dose range for efficacy. Steady-state concentrations of pembrolizumab were reached by 16 weeks of repeated dosing with an every 3 week regimen and the systemic accumulation was 2.1-fold. The median trough concentrations (C_{trough}) at steady-state were approximately 22 mcg/mL at a dose of 2 mg/kg bw every 3 weeks and 29 mcg/mL at a dose of 200 mg every 3 weeks. The median area under the concentration time curve at steady-state over 3 weeks ($AUC_{0\text{-}3weeks}$) was 794 mcg•day/mL at a dose of 2 mg/kg bw every 3 weeks and 1 053 mcg•day/mL at a dose of 200 mg every 3 weeks.

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

Special populations
The effects of various covariates on the pharmacokinetics of pembrolizumab were assessed in population pharmacokinetic analyses. The following factors had no clinically important effect on the clearance of pembrolizumab: age (range: 15-94 years), sex, 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 analyses in patients with mild or moderate renal impairment compared to patients with normal renal function. No clinically important differences in the clearance of pembrolizumab were found between patients with mild or moderate renal impairment and patients with normal renal function. Pembrolizumab has not been studied in patients with severe renal impairment (see section 4.2).

Hepatic impairment
The effect of hepatic impairment on the clearance of pembrolizumab was evaluated by population pharmacokinetic analyses in patients with mild and moderate hepatic impairment (as defined using the US National Cancer Institute criteria of hepatic dysfunction) compared to patients with normal hepatic function. No clinically important differences in the clearance of pembrolizumab were found between patients with mild or moderate hepatic impairment and normal hepatic function. Pembrolizumab has not been studied in patients with severe hepatic impairment (see section 4.2).

5.3 Preclinical safety data

The safety of pembrolizumab was evaluated in a 1-month and a 6-month repeat-dose toxicity study in Cynomolgus monkeys administered intravenous doses of 6, 40 or 200 mg/kg bw once a week in the 1-month study and once every two weeks in the 6-month study, followed by a 4-month treatment-free period. No findings of toxicological significance were observed and the no observed adverse effect level (NOAEL) in both studies was ≥ 200 mg/kg bw, which produced exposure multiples of 19 and 94 times the exposure in humans at doses of 10 and 2 mg/kg bw, respectively. The exposure multiple between the NOAEL and a human dose of 200 mg was 74.

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-histidine
L-histidine hydrochloride monohydrate
Sucrose
Polysorbate 80 (E433)
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial
2 years

After preparation of infusion
Chemical and physical in-use stability has been demonstrated for up to 42 days at 2 °C to 8 °C or at 23 °C to 27 °C.
From a microbiological point of view, the product, once diluted, should be used immediately. The diluted solution must not be frozen. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 7 days at 2 °C to 8 °C, or 12 hours at room temperature, unless dilution has taken place in controlled and validated aseptic conditions. If refrigerated, the vials and/or intravenous bags must be allowed to come to room temperature prior to use.

6.4 Special precautions for storage

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

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

6.5 Nature and contents of container

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

Pack sizes: one or two vials per carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Preparation and administration of the infusion

- Do not shake the vial.
- Equilibrate the vial to room temperature (at or below 25 °C).
- Prior to dilution, the vial of liquid can be out of refrigeration (temperatures at or below 25 °C) for up to 24 hours.
- Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration. The concentrate is a clear to slightly opalescent, colourless to slightly yellow solution. Discard the vial if visible particles are observed.
- Withdraw the required volume up to 4 mL (100 mg) of concentrate and transfer into an intravenous bag containing sodium chloride 9 mg/mL (0.9%) or glucose 50 mg/mL (5%) to prepare a diluted solution with a final concentration ranging from 1 to 10 mg/mL. Each vial contains an excess fill of 0.25 mL (total content per vial 4.25 mL) to ensure the recovery of 4 mL of concentrate. Mix diluted solution by gentle inversion.
- If refrigerated, the vials and/or intravenous bags must be allowed to come to room temperature prior to use. Translucent to white proteinaceous particles may be seen in diluted solution. Administer the infusion solution intravenously over 30 minutes using a sterile, non-pyrogenic, low-protein binding 0.2 to 5 µm in-line or add-on filter.

- Do not co-administer other medicinal products through the same infusion line.
- KEYTRUDA is for single use only. Discard any unused portion left in the vial.

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

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

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EU/1/15/1024/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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

10. DATE OF REVISION OF THE TEXT

16 October 2026

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