▼This medicinal product is subject to additional monitoring in Australia due to provisional approval of an extension of indication. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – KEYTRUDA® (pembrolizumab (rch))

1 NAME OF THE MEDICINE

pembrolizumab (rch)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

KEYTRUDA® 50 mg powder for injection
One vial contains 50 mg of pembrolizumab.
After reconstitution, 1 mL of solution contains 25 mg of pembrolizumab.

KEYTRUDA® 100 mg/4 mL concentrated injection
One vial contains 100 mg of pembrolizumab in 4 mL of solution.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

KEYTRUDA® 50 mg powder for injection
KEYTRUDA 50 mg powder for injection is a sterile, preservative-free, white to off-white lyophilised powder.
Not for direct infusion or injection (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

KEYTRUDA® 100 mg/4 mL concentrated injection
KEYTRUDA 100 mg/4 mL concentrated injection is a sterile, preservative-free, clear to slightly opalescent, colourless to slightly yellow solution.
Not for direct infusion or injection (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Melanoma
KEYTRUDA® (pembrolizumab) is indicated as monotherapy for the treatment of unresectable or metastatic melanoma in adults.

KEYTRUDA® (pembrolizumab) is indicated as monotherapy for the adjuvant treatment of patients with melanoma with lymph node involvement who have undergone complete resection.

Non-small cell lung cancer (NSCLC)

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

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

KEYTRUDA® (pembrolizumab) is indicated as monotherapy for the first-line treatment of patients with NSCLC expressing PD-L1 [tumour proportion score (TPS) ≥1%] as determined by a validated test, with no EGFR or ALK genomic tumour aberrations, and is

- stage III where patients are not candidates for surgical resection or definitive chemoradiation, or
- metastatic.

KEYTRUDA® (pembrolizumab) is indicated as monotherapy for the treatment of patients with advanced NSCLC whose tumours express PD-L1 with a ≥1% TPS as determined by a validated test and who have received platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have received prior therapy for these aberrations prior to receiving KEYTRUDA.

Head and Neck Squamous Cell Cancer (HNSCC)

KEYTRUDA® (pembrolizumab), as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, is indicated for the first-line treatment of patients with metastatic or unresectable recurrent HNSCC, and whose tumours express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by a validated test.

KEYTRUDA® (pembrolizumab) is indicated as monotherapy for the treatment of patients with metastatic or unresectable recurrent HNSCC with disease progression on or after platinum-containing chemotherapy and whose tumours express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by a validated test.

Classical Hodgkin Lymphoma (cHL)

KEYTRUDA® (pembrolizumab) is indicated as monotherapy for the treatment of adult and paediatric patients with relapsed or refractory classical Hodgkin Lymphoma (cHL):

1. following autologous stem cell transplant (ASCT) or
2. following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option.

The approval of this indication in paediatric patients is on the basis of objective response rate from patients aged 11 years and older from single arm trial data and extrapolation from adult data (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials).

Primary mediastinal B-Cell Lymphoma (PMBCL)

KEYTRUDA® (pembrolizumab) is indicated for the treatment of adult and paediatric patients with refractory primary mediastinal B-cell lymphoma (PMBCL), or who have relapsed after 2 or more prior lines of therapy. The approval of this indication is on the basis of objective response rate (ORR) and duration of response from non-randomised studies. See Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials.

Urothelial carcinoma

KEYTRUDA® (pembrolizumab) is indicated as monotherapy for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing therapy and whose tumours express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by a validated test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status. This indication is approved based on overall response rate and duration of response in a single-arm study. Improvements in overall survival, progression-free survival, or health-related quality of life have not been established.

KEYTRUDA® (pembrolizumab) is indicated as monotherapy for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have received platinum-containing chemotherapy.

KEYTRUDA® (pembrolizumab) is indicated for the treatment of patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in-situ (CIS) with or without papillary tumours who are ineligible for or have elected not to undergo cystectomy. This indication was approved via the **provisional approval** pathway based on complete response rate and duration of response. Continued approval of this indication depends on verification and description of benefit in confirmatory trials.

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

Colorectal (previously untreated)

KEYTRUDA® (pembrolizumab) is indicated for the first-line treatment of patients with unresectable or metastatic colorectal cancer (CRC) that is MSI-H or dMMR as determined by a validated test.

Colorectal (previously treated)

KEYTRUDA® (pembrolizumab) is indicated in adult and paediatric patients for the treatment of unresectable or metastatic CRC that is MSI-H or dMMR as determined by a validated test, and that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. This indication was approved via the **provisional approval** pathway, based on objective response rate and response duration in a single-arm trial. Continued approval for this indication depends on verification and description of clinical benefit in the confirmatory trials.

Non-colorectal

KEYTRUDA® (pembrolizumab) is indicated in adult and paediatric patients for the treatment of unresectable or metastatic solid tumours that are MSI-H or dMMR as determined by a validated test, that have progressed following prior treatment and when there are no satisfactory alternative treatment options. This indication was approved via the **provisional approval** pathway, based on the pooling of data on objective response rate and response duration across multiple different tissue types in a single-arm trial. Sample sizes for individual

tissue types were too small to provide data on clinical utility of the MSI-H/dMMR tests for each of the tissue types, individually. The assumption that MSI-H/dMMR-status is predictive of the treatment effect of KEYTRUDA for every tissue type has not been verified. Continued approval for this indication depends on verification and description of clinical benefit in the confirmatory trials.

The safety and effectiveness of KEYTRUDA in paediatric patients with MSI-H/dMMR central nervous system cancers have not been established.

Endometrial carcinoma

KEYTRUDA® (pembrolizumab), in combination with lenvatinib, is indicated for the treatment of patients with advanced endometrial carcinoma that is not MSI-H or dMMR as determined by a validated test, who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation. This indication was approved via the **provisional approval** pathway, based on objective response rate and duration of response in a single-arm trial. Full registration for this indication depends on verification and description of clinical benefit in confirmatory trials.

Renal Cell Carcinoma (RCC)

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

Cutaneous Squamous Cell Carcinoma

KEYTRUDA® (pembrolizumab) is indicated as monotherapy for the treatment of adult patients with recurrent or metastatic cutaneous squamous cell carcinoma (cSCC) that is not curable by surgery or radiation. This indication was approved via the **provisional approval** pathway based on objective response rate and duration of response from a single-arm study. Improvements in overall survival, progression-free survival, or health-related quality of life have not been established. Full registration for this indication depends on submission of further clinical data to confirm the clinical benefit of the medicine.

Oesophageal Cancer

KEYTRUDA® (pembrolizumab), in combination with platinum and fluoropyrimidine based chemotherapy, is indicated for the first-line treatment of patients with locally advanced or metastatic carcinoma of the oesophagus or HER2 negative gastroesophageal junction adenocarcinoma (tumour centre 1 to 5 centimetres above the gastroesophageal junction) that is not amenable to surgical resection or definitive chemoradiation.

Tumour Mutational Burden-High (TMB-H) cancer

KEYTRUDA® (pembrolizumab) is indicated for the treatment of adult and paediatric patients with unresectable or metastatic tumour mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumours, as determined by a validated test, that have progressed following prior treatment and who have no satisfactory alternative treatment options. This indication was approved via the **provisional approval** pathway, based on the pooling of data on objective response rate and response duration across multiple different tissue types in a single-arm trial. The assumption that TMB-H status is predictive of the

treatment effect of KEYTRUDA for every tissue type has not been verified. Full registration for this indication depends on verification and description of clinical benefit in confirmatory trials.

4.2 DOSE AND METHOD OF ADMINISTRATION

Treatment must be initiated and supervised by specialised healthcare professionals experienced in the treatment of cancer.

Patient Selection

The safe and effective use of KEYTRUDA depends on selection of patients using in vitro diagnostic testing for the following indications:

- Stage III NSCLC in patients who are not candidates for surgical resection or definitive chemoradiation
- Metastatic NSCLC
- Previously untreated locally advanced or metastatic urothelial carcinoma, in patients who are cisplatin ineligible
- HNSCC
- MSI-H or dMMR cancers, including CRC
- TMB-H cancers

Before such treatment is commenced, the relevant biomarker (tumour PD-L1 expression, MSI-H/dMMR status, or TMB-H status) must be confirmed using a validated test (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials).

Because the effect of prior chemotherapy on test results for tumour mutation burden (TMB-H), MSI-H, or dMMR in patients with high grade gliomas is unclear, it is recommended to test for these markers in the primary tumour specimens obtained prior to initiation of temozolomide chemotherapy in patients with high grade gliomas.

Recommended Dosing

KEYTRUDA is administered as an intravenous infusion over 30 minutes.

The recommended dose of KEYTRUDA in adults is:

- 200 mg every 3 weeks or 400 mg every 6 weeks for melanoma or NSCLC as monotherapy
- 200 mg every 3 weeks in combination therapy for NSCLC, HNSCC, endometrial carcinoma, RCC, or oesophageal carcinoma, or as monotherapy for HNSCC, cHL, PMBCL, urothelial carcinoma, MSI-H/dMMR cancers (including CRC), cSCC or TMB-H cancers.

The recommended dose of KEYTRUDA in paediatric patients is 2 mg/kg (up to a maximum of 200 mg) every 3 weeks for relapsed or refractory cHL, PMBCL, MSI-H/dMMR cancers, or TMB-H cancers.

KEYTRUDA was originally developed using an every-three-weeks monotherapy dosing regimen (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials). Subsequent approval of the every-six-weeks monotherapy dosing regimen was based on pharmacokinetic and exposure-response modelling and simulations, which are supported by observed

pharmacokinetic data. Clinical endpoint data (such as PFS or OS) from randomised controlled trials of every-three-weeks versus every-six-weeks dosing of KEYTRUDA is not available.

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

For RCC patients treated with KEYTRUDA in combination with axitinib, see the Product Information regarding dosing of axitinib. When used in combination with KEYTRUDA, dose escalation of axitinib above the initial 5 mg dose may be considered at intervals of six weeks or longer (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials).

Patients should be treated with KEYTRUDA until disease progression or unacceptable toxicity. Patients with urothelial carcinoma (locally advanced or metastatic), NSCLC, HNSCC, PMBCL, MSI-H/dMMR cancers, cSCC or TMB-H cancers without disease progression can be treated for up to 24 months, or the equivalent number of treatment cycles [see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials]. Atypical responses (i.e., an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed. Clinically stable patients with initial evidence of disease progression can, under some circumstances remain on treatment until disease progression is confirmed (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials for a description of the circumstances where such continued treatment was allowed in the pivotal studies).

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

For the treatment of high-risk BCG-unresponsive NMIBC, KEYTRUDA should be administered until persistent or recurrent high-risk NMIBC, disease progression, unacceptable toxicity, or up to 24 months.

For the treatment of endometrial carcinoma that is not MSI-H or dMMR, KEYTRUDA should be administered as above in combination with lenvatinib 20 mg orally once daily until disease progression, unacceptable toxicity, or for KEYTRUDA, up to 24 months in patients without disease progression. Refer to the lenvatinib Product Information for recommended dosing information.

Dose Modifications

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

Table 1: Recommended Dose Modifications [see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE]

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

Immune-mediated colitis	Moderate or severe (Grades 2 or 3)	Withhold until adverse reactions recover to Grades 0-1*
	Life-threatening (Grade 4) or recurrent severe (Grade 3)	Permanently discontinue
Immune-mediated nephritis	Moderate (Grade 2)	Withhold until adverse reactions recover to Grades 0-1*
	Severe or life-threatening (Grades 3 or 4)	Permanently discontinue
Immune-mediated endocrinopathies	Severe or life-threatening (Grades 3 or 4)	Withhold until adverse reactions recover to Grades 0-1* For patients with severe (Grade 3) or life-threatening (Grade 4) endocrinopathy that improves to Grade 2 or lower and is controlled with hormone replacement, continuation of KEYTRUDA may be considered.
Immune-mediated hepatitis For liver enzyme elevations in RCC patients treated with combination therapy, see dosing guidelines following this table.	Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 to 5 times upper limit of normal (ULN) or total bilirubin >1.5 to 3 times ULN	Withhold until adverse reactions recover to Grades 0-1*
	AST or ALT >5 times ULN or total bilirubin >3 times ULN	Permanently discontinue
	For patients with liver metastases who begin treatment with moderate (Grade 2) elevation of AST or ALT, if AST or ALT increases ≥50% relative to baseline and lasts ≥1 week	Permanently discontinue
Immune-mediated skin reactions or Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Severe skin reactions (Grade 3) or suspected SJS or TEN	Withhold until adverse reactions recover to Grades 0-1*
	Severe skin reactions (Grade 4) or confirmed SJS or TEN	Permanently discontinue
Other immune-mediated adverse reactions	Based on severity and type of reaction (Grade 2 or Grade 3)	Withhold until adverse reactions recover to Grades 0-1*
	Severe or life-threatening (Grades 3 or 4) myocarditis, encephalitis, or Guillain-Barré syndrome	Permanently discontinue

	Life-threatening (Grade 4) or recurrent severe (Grade 3)	Permanently discontinue
Infusion-related reactions	Severe or life-threatening (Grades 3 or 4)	Permanently discontinue

Note: toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI CTCAE v.4)
* If corticosteroid dosing cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks or a treatment-related toxicity does not resolve to Grades 0-1 within 12 weeks after last dose of KEYTRUDA, then KEYTRUDA should be permanently discontinued.

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

When administering KEYTRUDA in combination with lenvatinib for the treatment of endometrial carcinoma, interrupt one or both as appropriate. No dose reductions are recommended for KEYTRUDA. Withhold, dose reduce, or discontinue lenvatinib in accordance with the instructions in the lenvatinib Product Information.

In patients with RCC being treated with KEYTRUDA in combination with axitinib:

- If ALT or AST ≥3 times ULN but <10 times ULN without concurrent total bilirubin ≥2 times ULN, withhold both KEYTRUDA and axitinib until these adverse reactions recover to Grades 0-1. Consider corticosteroid therapy. Consider rechallenge with a single drug or sequential rechallenge with both drugs after recovery. If rechallenging with axitinib, consider dose reduction as per the axitinib Product Information.
- If ALT or AST ≥10 times ULN or >3 times ULN with concurrent total bilirubin ≥2 times ULN, permanently discontinue both KEYTRUDA and axitinib and consider corticosteroid therapy.

Preparation and Administration

Preparation of KEYTRUDA 50 mg powder for injection

- Prior to reconstitution, the vial of lyophilised powder can be out of refrigeration (temperatures at or below 25°C) for up to 24 hours.
- Aseptically add 2.3 mL of sterile water for injection to yield a 25 mg/mL (pH 5.2-5.8) solution of KEYTRUDA.
- To avoid foaming, deliver the water along the walls of the vial and not directly on the lyophilised powder.
- Slowly swirl the vial to allow reconstitution of the lyophilised powder. Allow up to 5 minutes for the bubbles to clear. Do not shake the vials.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Reconstituted KEYTRUDA is a clear to slightly opalescent, colourless to slightly yellow solution. Discard the vial if visible particles are observed.
- Withdraw the required volume up to 2 mL (50 mg) of KEYTRUDA and transfer into an intravenous bag containing 0.9% sodium chloride or 5% glucose (dextrose) to prepare a diluted solution with a final concentration ranging from 1 to 10 mg/mL. Mix diluted solution by gentle inversion (see Administration).

Preparation of KEYTRUDA 100 mg/4 mL concentrated injection

- Protect from light. Do not freeze. Do not shake.
- Equilibrate the vial of KEYTRUDA to room temperature.
- Prior to dilution, the vial of liquid can be out of refrigeration (temperatures at or below 25°C) for up to 24 hours.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. KEYTRUDA is a clear to slightly opalescent, colourless to slightly yellow solution. Discard the vial if visible particles are observed.
- Withdraw the required volume up to 4 mL (100 mg) of KEYTRUDA and transfer into an intravenous bag containing 0.9% sodium chloride or 5% glucose (dextrose) to prepare a diluted solution with a final concentration ranging from 1 to 10 mg/mL. Mix diluted solution by gentle inversion (see Administration).

Administration

- Do not freeze the infusion solution.
- The product does not contain preservative. The reconstituted and/or diluted product should be used immediately. If not used immediately, reconstituted and diluted solutions of KEYTRUDA may be stored at room temperature for a cumulative time of up to 6 hours. Reconstituted and diluted solutions of KEYTRUDA may also be stored under refrigeration at 2°C to 8°C; however, the total time from reconstitution or dilution of KEYTRUDA to completion of infusion should not exceed 96 hours. If refrigerated, allow the vials and/or IV bags to come to room temperature prior to use.
- Translucent to white proteinaceous particles may be seen in the diluted solution, and are not of concern, as particles will be removed by the filter during administration. Administer infusion solution intravenously over 30 minutes using a sterile, non-pyrogenic, low-protein binding 0.2 to 5 µm in-line or add-on filter.
- Do not co-administer other drugs through the same infusion line.
- Product is for single use in one patient only, Discard any residue.

Paediatric Patients

In relapsed or refractory cHL, PMBCL, MSI-H/dMMR cancers, and TMB-H cancers, the recommended dose of KEYTRUDA in paediatric patients is 2 mg/kg (up to a maximum of 200 mg), administered as an intravenous infusion over 30 minutes every 3 weeks [see Section 4.1 THERAPEUTIC INDICATIONS and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE].

Geriatric Patients

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

For combination therapy with pembrolizumab and axitinib in patients with advanced RCC, limited safety data is available regarding patients ≥75 years of age.

Renal Insufficiency

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 Section 5.2 PHARMACOKINETIC PROPERTIES, Special populations].

Hepatic Insufficiency

No dose adjustment is needed for patients with mild hepatic impairment. KEYTRUDA has not been studied in patients with moderate or severe hepatic impairment [See Section 5.2 PHARMACOKINETIC PROPERTIES, Special populations].

4.3 CONTRAINDICATIONS

None.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 KEYTRUDA. In clinical trials, most immune-mediated adverse reactions occurred during treatment, were reversible and managed with interruptions of KEYTRUDA, administration of corticosteroids and/or supportive care. Immune-related adverse reactions have occurred after discontinuation of treatment with KEYTRUDA. Immune-mediated adverse reactions affecting more than one body system can occur simultaneously.

For suspected immune-mediated adverse reactions, ensure adequate evaluation to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, withhold KEYTRUDA and consider administration of corticosteroids. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Based on limited data from clinical studies in patients whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered. Restart KEYTRUDA if the adverse reaction remains at Grade 1 or less following corticosteroid taper. If another episode of a severe adverse reaction occurs, permanently discontinue KEYTRUDA [See Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)].

Immune-mediated pneumonitis

Pneumonitis (including fatal cases) has been reported in patients receiving KEYTRUDA [See Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)].

Monitor patients for signs and symptoms of pneumonitis. If pneumonitis is suspected, evaluate with radiographic imaging and exclude other causes. Administer corticosteroids for Grade 2 or greater events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper), withhold KEYTRUDA for moderate (Grade 2) pneumonitis, and permanently discontinue KEYTRUDA for severe (Grade 3), life-threatening (Grade 4) or recurrent moderate (Grade 2) pneumonitis [See Section 4.2 DOSE AND METHOD OF ADMINISTRATION, Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) and Immune-mediated Adverse Reactions

above].

Immune-mediated colitis

Colitis has been reported in patients receiving KEYTRUDA [See Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)].

Monitor patients for signs and symptoms of colitis and exclude other causes. Administer corticosteroids for Grade 2 or greater events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper), withhold KEYTRUDA for moderate (Grade 2) or severe (Grade 3) colitis, and permanently discontinue KEYTRUDA for life-threatening (Grade 4) colitis [See Section 4.2 DOSE AND METHOD OF ADMINISTRATION, Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) and Immune-mediated Adverse Reactions above]. The potential risk of gastrointestinal perforation should be taken into consideration.

Immune-mediated hepatitis (KEYTRUDA) and hepatotoxicity (KEYTRUDA in Combination with Axitinib)

Immune-mediated hepatitis

Hepatitis has been reported in patients receiving KEYTRUDA [See Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)].

Monitor patients for changes in liver function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and symptoms of hepatitis and exclude other causes. Administer corticosteroids (initial dose of 0.5-1 mg/kg/day [for Grade 2 events] and 1-2 mg/kg/day [for Grade 3 or greater events] prednisone or equivalent followed by a taper) and, based on severity of liver enzyme elevations, withhold or discontinue KEYTRUDA [See Section 4.2 DOSE AND METHOD OF ADMINISTRATION, Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) and Immune-mediated Adverse Reactions above].

Hepatotoxicity in Combination with Axitinib

KEYTRUDA in combination with axitinib can cause hepatic toxicity with higher than expected frequencies of Grades 3 and 4 ALT and AST elevations compared to KEYTRUDA alone. Monitor liver enzymes before initiation of and periodically throughout treatment. Consider more frequent monitoring of liver enzymes as compared to when the drugs are administered as single agents. For elevated liver enzymes, interrupt KEYTRUDA and axitinib and consider administering corticosteroids as needed [See Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS].

With the combination of KEYTRUDA and axitinib, Grades 3 and 4 increased ALT (20%) and increased AST (13%) were seen. The median time to onset of increased ALT was 2.3 months (range: 7 days to 19.8 months). Fifty-nine percent of the patients with increased ALT received systemic corticosteroids. In patients with ALT ≥3 times ULN (Grades 2-4, n=116), ALT resolved to Grades 0-1 in 94%. Among the 92 patients who were rechallenged with either KEYTRUDA (3%) or axitinib (31%) administered as a single agent or with both (50%), 55% had no recurrence of ALT >3 times ULN. There were no Grade 5 hepatic events.

Immune-mediated nephritis

Nephritis has been reported in patients receiving KEYTRUDA. Nephritis appears to be more common when pembrolizumab is used in combination with pemetrexed and platinum chemotherapy than when pembrolizumab is used alone [See Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)].
Monitor patients for changes in renal function and exclude other causes. Administer corticosteroids for Grade 2 or greater events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper), withhold KEYTRUDA for moderate (Grade 2), and permanently discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) nephritis. [See Section 4.2 DOSE AND METHOD OF ADMINISTRATION, Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) and Immune-mediated Adverse Reactions above].

Immune-mediated endocrinopathies

Adrenal insufficiency (primary and secondary) has been reported in patients receiving KEYTRUDA. Hypophysitis has also been reported in patients receiving KEYTRUDA. [See Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)].
Monitor patients for signs and symptoms of adrenal insufficiency and hypophysitis (including hypopituitarism) and exclude other causes. Administer corticosteroids to treat adrenal insufficiency and other hormone replacement as clinically indicated, withhold KEYTRUDA for moderate (Grade 2), withhold or discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency or hypophysitis. [See Section 4.2 DOSE AND METHOD OF ADMINISTRATION, Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) and Immune-mediated Adverse Reactions above].

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

Thyroid disorders, including hyperthyroidism, hypothyroidism and thyroiditis, have been reported in patients receiving KEYTRUDA and can occur at any time during treatment, therefore monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and clinical signs and symptoms of thyroid disorders. Hypothyroidism may be managed with replacement therapy without treatment interruption and without corticosteroids. Hyperthyroidism may be managed symptomatically. Withhold or discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) hyperthyroidism [See Section 4.2 DOSE AND METHOD OF ADMINISTRATION, Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) and Immune-mediated Adverse Reactions above].

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

Severe skin reactions

Immune-mediated severe skin reactions have been reported in patients treated with KEYTRUDA. Monitor patients for suspected severe skin reactions and exclude other causes.

Based on the severity of the adverse reaction, withhold or permanently discontinue KEYTRUDA and administer corticosteroids [See Section 4.2 DOSE AND METHOD OF ADMINISTRATION].

Cases of Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and bullous pemphigoid, have been reported in patients treated with KEYTRUDA. Some cases of SJS and TEN have had a fatal outcome. For signs or symptoms of SJS or TEN, withhold KEYTRUDA and refer the patient for specialized care for assessment and treatment. If SJS or TEN is confirmed, permanently discontinue KEYTRUDA. [See Section 4.2 DOSE AND METHOD OF ADMINISTRATION].

Other immune-mediated adverse reactions

The following additional clinically significant, immune-mediated adverse reactions were reported in less than 1% of patients treated with KEYTRUDA in KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, and KEYNOTE-010: uveitis, myositis, Guillain-Barre syndrome, pancreatitis, encephalitis, sarcoidosis, myasthenic syndrome/myasthenia gravis (including exacerbation), myelitis, and vasculitis. The following were reported in other clinical studies with KEYTRUDA or in post-marketing use: myocarditis, pericarditis and pericardial effusion, peripheral neuropathy and sclerosing cholangitis.

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

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

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

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

Infusion-related reactions

Severe infusion reactions, including hypersensitivity and anaphylaxis, have been reported in 6 (0.2%) of 2799 patients receiving KEYTRUDA in KEYNOTE-001, KEYNOTE-002, KEYNOTE-006 and KEYNOTE-010. For severe infusion reactions, stop infusion and permanently discontinue KEYTRUDA [See Section 4.2 DOSE AND METHOD OF ADMINISTRATION]. Patients with mild or moderate infusion reaction may continue to receive KEYTRUDA with close monitoring; premedication with antipyretic and antihistamine may be considered.

Patients excluded from clinical trials

Patients with the following conditions were excluded from clinical trials: active CNS metastases; ECOG PS ≥ 2 (except for urothelial carcinoma and RCC); HIV, hepatitis B or

hepatitis C infection; active systemic autoimmune disease; interstitial lung disease; prior pneumonitis requiring systemic corticosteroid therapy; a history of severe hypersensitivity to another monoclonal antibody; receiving immunosuppressive therapy and a history of severe immune-related adverse reactions from treatment with ipilimumab, defined as any Grade 4 toxicity or Grade 3 toxicity requiring corticosteroid treatment (> 10 mg/day prednisone or equivalent) for greater than 12 weeks. Patients with active infections were excluded from clinical trials 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 trials, therefore information is limited in patients with severe renal and moderate to severe hepatic impairment.

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

Patient Alert Card

The prescriber must discuss the risks of KEYTRUDA therapy with the patient. The patient should be provided with the Patient Alert Card.

Effects on Fertility

Fertility studies have not been conducted with pembrolizumab. There were no notable effects on male and female reproductive organs observed in general repeat-dose toxicity studies conducted with pembrolizumab in Cynomolgus monkeys, involving IV administration at doses up to 200 mg/kg once a week for 1 month or once every two weeks for 6 months. No findings of toxicological significance were observed and the no observed adverse effect level (NOAEL) in both studies was ≥200 mg/kg, which produced exposure multiples of 19 and 94 times the exposure in humans at doses of 10 and 2 mg/kg, respectively. The exposure multiple between the NOAEL and a human dose of 200 mg was 74.

Use in Pregnancy

Category D. There are no data on the use of pembrolizumab in pregnant women. Animal reproduction studies have not been conducted with pembrolizumab; however, blockade of the PD-1 pathway has been shown in mouse models of pregnancy to disrupt tolerance to the foetus and to result in an increase in foetal loss. These results indicate a potential risk, based on its mechanism of action, that administration of KEYTRUDA during pregnancy could cause foetal harm, including increased rates of abortion or stillbirth. Human IgG4 (immunoglobulin) is known to cross the placental barrier and pembrolizumab is an IgG4; therefore, pembrolizumab has the potential to be transmitted from the mother to the developing foetus. KEYTRUDA is not recommended during pregnancy unless the clinical benefit outweighs the potential risk to the foetus. Women of childbearing potential should use effective contraception during treatment with KEYTRUDA and for at least 4 months following the last dose of KEYTRUDA.

Use in Lactation

It is unknown whether KEYTRUDA is secreted in human milk. Because many drugs are secreted in human milk, a decision should be made whether to discontinue breast-feeding or to discontinue KEYTRUDA, taking into account the benefit of breast-feeding for the child and

the benefit of KEYTRUDA therapy for the woman.

Paediatric Use

There is limited experience with KEYTRUDA in paediatric patients. In KEYNOTE-051, 161 paediatric patients (62 children ages 6 months to less than 12 years and 99 adolescents ages 12 years to 17 years) with advanced melanoma, lymphoma, or PD-L1 positive advanced, relapsed, or refractory solid tumours were administered KEYTRUDA 2 mg/kg every 3 weeks. The cHL population (n=22) included patients 11 to 17 years of age. Patients received KEYTRUDA for a median of 4 doses (range 1-35 doses), with 138 patients (86%) receiving KEYTRUDA for 2 doses or more. The concentrations of pembrolizumab in paediatric patients were comparable to those observed in adult patients at the same dose regimen of 2 mg/kg every 3 weeks.

The safety profile in these paediatric patients was 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. No new immune-mediated AEs causally associated with pembrolizumab are identified in this population.

Efficacy for paediatric patients with relapsed or refractory cHL, PMBCL, or MSI-H/dMMR cancers, or TMB-H cancers, is extrapolated from the results in the respective adult population [see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials]. Efficacy has not been established in other paediatric malignancies.

Use in the elderly

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

Effect on Laboratory Tests

Thyroid and liver (hepatic transaminase and bilirubin levels) function tests should be performed at the start of treatment, periodically during treatment and as indicated based on clinical evaluation [see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and Section 4.2 DOSE AND METHOD OF ADMINISTRATION].

Complications of allogeneic Haematopoietic Stem Cell Transplant (HSCT)

Allogeneic HSCT after treatment with KEYTRUDA in classical Hodgkin Lymphoma

Immune-mediated complications, including fatal events, occurred in patients who underwent allogeneic hematopoietic stem cell transplantation (HSCT) after being treated with KEYTRUDA.

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.

Cases of fatal hyperacute GVHD after allogeneic HSCT have also been reported in patients with lymphoma who received a PD-1 receptor blocking antibody before transplantation. These complications may occur despite intervening therapy between PD-1 blockade and allogeneic HSCT. Follow patients closely for early evidence of transplant-related complications such as hyperacute GVHD, severe (Grade 3 to 4) acute GVHD, steroid-requiring febrile syndrome, hepatic VOD, and other immune mediated adverse reactions, and intervene promptly.

Allogeneic HSCT prior to treatment with KEYTRUDA

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

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 cancer, a higher number of deaths within 2 months was observed in pembrolizumab compared to chemotherapy (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials). Factors associated with early deaths were fast progressive disease on prior platinum therapy and liver metastases.

Use of pembrolizumab in urothelial cancer for patients who are considered cisplatin ineligible

The baseline and prognostic disease characteristics of the study population of KEYNOTE-052 included a proportion of patients eligible for a carboplatin-based combination or mono-chemotherapy for whom the benefit has not yet been assessed in a comparative study. 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 in combination with chemotherapy 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 DOSE AND METHOD OF ADMINISTRATION and 4.8 ADVERSE EFFECTS). A direct comparison of the safety of pembrolizumab when used in combination with pemetrexed and platinum chemotherapy to pembrolizumab monotherapy is not available.

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

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

The use of systemic corticosteroids or immunosuppressants before starting KEYTRUDA should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of KEYTRUDA. However, systemic corticosteroids or other immunosuppressants can be used after starting KEYTRUDA to treat immune-mediated adverse reactions [See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE]. Corticosteroids can also be used as premedication, when KEYTRUDA is used in combination with chemotherapy, as antiemetic prophylaxis and/or to alleviate chemotherapy-related adverse reactions.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Effects on Fertility.

Use in pregnancy

Category D (See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Use in Pregnancy).

Use in lactation

See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Use in Lactation.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

KEYTRUDA may have an influence on the ability to drive and use machines. Fatigue has been reported following administration of KEYTRUDA [see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)].

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical trials experience

The safety of KEYTRUDA was evaluated in 2799 patients with unresectable or metastatic melanoma or metastatic NSCLC in controlled and uncontrolled studies. The median treatment duration was 4.2 months (range 1 day to 30.4 months) including 1153 patients treated for greater than or equal to six months and 600 patients treated for greater than or equal to one year.

KEYTRUDA was discontinued for treatment-related adverse reactions in 5% of patients. Treatment-related serious adverse events (SAEs) reported up to 90 days after the last dose occurred in 10% of patients receiving KEYTRUDA. Of these treatment-related SAEs, the most common were: pneumonitis, colitis, diarrhoea, and pyrexia. The most common treatment-related adverse reactions (reported in >10% of patients) were: fatigue, pruritus, rash, diarrhoea, and nausea. The safety profile was generally similar for patients with melanoma and NSCLC.

Immune-mediated adverse reactions [see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE]

Immune-mediated adverse reactions are presented based on 2799 patients with melanoma and NSCLC. The safety profile was generally similar for patients with melanoma and NSCLC. Table 2 presents the incidence of immune-mediated adverse reactions by Grade that occurred in patients receiving KEYTRUDA.

Table 2: Immune-Mediated Adverse Reactions

	KEYTRUDA 2 mg/kg every 3 weeks or 10 mg/kg every 2 or 3 weeks n=2799				
Adverse Reaction	**All Grades (%)**	**Grade 2 (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**Grade 5 (%)**
Hypothyroidism*	8.5	6.2	0.1	0	0
Hyperthyroidism	3.4	0.8	0.1	0	0
Pneumonitis†	3.4	1.3	0.9	0.3	0.1
Colitis	1.7	0.4	1.1	<0.1	0
Adrenal Insufficiency	0.8	0.3	0.3	<0.1	0
Hepatitis	0.7	0.1	0.4	<0.1	0
Hypophysitis	0.6	0.2	0.3	<0.1	0
Nephritis	0.3	0.1	0.1	<0.1	0
Type 1 Diabetes Mellitus	0.2	<0.1	0.1	0.1	0

* In individual studies of patients with HNSCC treated with KEYTRUDA as monotherapy (n=909) the incidence of hypothyroidism was 16.1% (all Grades) with 0.3% Grade 3. In patients with HNSCC treated with KEYTRUDA in combination with platinum and 5-FU chemotherapy (n=276) the incidence of hypothyroidism was 15.2%, all of which were Grade 1 or 2. In patients with cHL (n=389) the incidence of hypothyroidism was 17%, all of which were Grade 1 or 2.

† In individual studies of patients with NSCLC treated with KEYTRUDA as monotherapy (total n=2022), the incidence of pneumonitis (all Grades) ranged from 3.8% to 8.3%. In cHL patients treated with KEYTRUDA as monotherapy, 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.

Incidences of pneumonitis in individual studies in patients with melanoma or non-small cell lung cancer treated with KEYTRUDA as monotherapy ranged from 1.6% to 5.8%.

***Endocrinopathies*:** The median time to onset of adrenal insufficiency was 5.3 months (range 26 days to 16.6 months). The median duration was not reached (range 4 days to 1.9+ years). Adrenal insufficiency led to discontinuation of KEYTRUDA in 1 (<0.1%) patient. Adrenal insufficiency resolved in 5 patients. The median time to onset of hypophysitis was 3.7 months (range 1 day to 11.9 months). The median duration was 4.7 months (range 8+ days to 12.7+ months). Hypophysitis led to discontinuation of KEYTRUDA in 4 (0.1%) patients. Hypophysitis resolved in 7 patients. The median time to onset of hyperthyroidism was 1.4 months (range 1 day to 21.9 months). The median duration was 2.1 months (range 3 days to 15.0+ months). Hyperthyroidism led to discontinuation of KEYTRUDA in 2 (<0.1%) patients. Hyperthyroidism resolved in 71 patients. The median time to onset of hypothyroidism was 3.5 months (range 1 day to 18.9 months). The median duration was not reached (range 2 days to 27.7+ months). One (<0.1%) patient discontinued KEYTRUDA due to hypothyroidism.
***Pneumonitis*:** The median time to onset of pneumonitis was 3.3 months (range 2 days to 19.3 months). The median duration was 1.5 months (range 1 day to 17.2+ months). Pneumonitis led to discontinuation of KEYTRUDA in 36 (1.3%) patients. Pneumonitis resolved in 55 patients.
***Colitis*:** The median time to onset of colitis was 3.5 months (range 10 days to 16.2 months). The median duration was 1.3 months (range 1 day to 8.7+ months). Colitis led to discontinuation of KEYTRUDA in 15 (0.5%) patients. Colitis resolved in 41 patients.
***Hepatitis*:** The median time to onset of hepatitis was 1.3 months (range 8 days to 21.4 months). The median duration was 1.8 months (range 8 days to 20.9+ months). Hepatitis led to discontinuation of KEYTRUDA in 6 (0.2%) patients. Hepatitis resolved in 15 patients.
***Nephritis*:** The median time to onset of nephritis was 5.1 months (range 12 days to 12.8 months). The median duration was 3.3 months (range 12 days to 8.9+ months). Nephritis led to discontinuation of KEYTRUDA in 3 (0.1%) patients. Nephritis resolved in 5 patients. In patients with non-squamous NSCLC treated with pembrolizumab in combination with pemetrexed and platinum chemotherapy (n=405), the incidence of nephritis was 1.7% (all Grades) with 1.0% Grade 3 and 0.5% Grade 4.

Other adverse events

Melanoma

Table 3 summarises the adverse events that occurred in at least 10% of patients with melanoma treated with KEYTRUDA in KEYNOTE-006. The most common adverse events (reported in at least 15% of patients) were arthralgia and cough.

Table 3: Adverse Events Occurring in ≥10% of Patients treated with KEYTRUDA and at a Higher Incidence than in the Ipilimumab Arm (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grade 3]) (KEYNOTE-006)

	KEYTRUDA 10 mg/kg every 2 or 3 weeks n=555		Ipilimumab 3 mg/kg every 3 weeks n=256	
Adverse Events	**All Grades (%)**	**Grade 3* (%)**	**All Grades (%)**	**Grade 3* (%)**
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	18	0	10	1
Back pain	12	1	7	1
Respiratory, Thoracic and Mediastinal Disorders				
Cough	17	0	7	0
Skin And Subcutaneous Tissue Disorders				
Vitiligo	11	0	2	0

* Of these ≥10% adverse events, none was reported as Grade 4.

Table 4: Laboratory Abnormalities Worsened from Baseline in ≥20% of Patients with Unresectable or Metastatic Melanoma and at a Higher Incidence than in the Ipilimumab Arm (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-4]) (KEYNOTE-006)

	KEYTRUDA 10 mg/kg every 2 or 3 weeks n=555		Ipilimumab n=256	
Laboratory Test	**All Grades %**	**Grades 3-4 %**	**All Grades %**	**Grades 3-4 %**
Haematology				
Lymphopenia	45	5	36	5
Chemistry				
Hypertriglyceridemia	40	2	33	1

Table 5 summarises the adverse events that occurred in at least 10% of patients treated with KEYTRUDA in KEYNOTE-002. The most common adverse event (reported in at least 20% of patients) was pruritus.

Table 5: Adverse Events Occurring in ≥10% of Patients Treated with KEYTRUDA and at a Higher Incidence than in the Chemotherapy Arm (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-4]) (KEYNOTE-002)

	KEYTRUDA 2 mg/kg every 3 weeks n=178		Chemotherapy n=171	
Adverse Event	**All Grades (%)**	**Grade 3-4* (%)**	**All Grades (%)**	**Grade 3-4* (%)**
Gastrointestinal Disorders				
Abdominal pain	13	2	8	1
Skin and Subcutaneous Tissue Disorders				
Pruritus	25	0	8	0
Rash	13	0	8	0
Metabolism and Nutrition Disorders				
Hyponatremia	11	3	5	1
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	15	1	10	1

* Of these ≥10% adverse events, none was reported as Grade 4 in patients receiving KEYTRUDA at 2 mg/kg. Hyponatremia was reported as Grade 4 in one patient receiving chemotherapy.

Table 6: Laboratory Abnormalities Worsened from Baseline in ≥20% of Patients with Unresectable or Metastatic Melanoma and at a Higher Incidence than in the Chemotherapy Arm (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-4]) (KEYNOTE-002)

	KEYTRUDA 2 mg/kg every 3 weeks n=178		Chemotherapy n=171	
Laboratory Test	**All Grades %**	**Grades 3-4 %**	**All Grades %**	**Grades 3-4 %**
Chemistry				
Hyperglycaemia	63	9	56	6
Hyponatremia	45	8	29	5
Hypoalbuminemia	43	4	39	1
Increased Aspartate Aminotransferase	26	2	17	1
Increased Alkaline Phosphatase	35	4	28	2
Haematology				
Anaemia	69	12	76	8

Overall, the safety profile was similar across all doses and between patients previously treated with ipilimumab and patients naïve to treatment with ipilimumab.

Resected Melanoma

Among the 509 patients with resected melanoma treated with adjuvant pembrolizumab in KEYNOTE-054 (mean duration of treatment 9 months), adverse events that were reported in at least 5% of patients, and at least 5% more frequently with pembrolizumab than placebo, were hypothyroidism (14.7% vs 2.8%), hyperthyroidism (10.4% vs 1.2%) and pruritus (19.4% vs. 11.6%).

The overall safety profile of pembrolizumab for the adjuvant treatment of melanoma was generally similar to that described for unresectable or metastatic melanoma and NSCLC, with immune-related adverse reactions the predominant significant toxicity. Discontinuation due to adverse events was 14% with adjuvant pembrolizumab treatment, most commonly due to pneumonitis, colitis, and diarrhoea. Compared to placebo, pembrolizumab was associated with increases in grade 3-5 adverse events (31.0% vs. 19.1%) and serious adverse events (25.1% vs. 16.3%). A fatal event of immune-mediated myositis occurred in the pembrolizumab arm.

Non-Small Cell Lung Carcinoma (NSCLC)

Combination Therapy

Table 7 summarises the adverse events that occurred in at least 20% of patients treated with KEYTRUDA, pemetrexed, and platinum chemotherapy in KEYNOTE-189. Adverse events occurring in previously untreated patients with NSCLC receiving KEYTRUDA in combination with carboplatin and either paclitaxel or nab-paclitaxel in KEYNOTE-407 were generally similar to those occurring in patients in KEYNOTE-189 with the exception of alopecia (46%) and arthralgia (21%).

Table 7: Adverse events occurring in ≥20% of patients receiving KEYTRUDA with pemetrexed and platinum chemotherapy and at a higher incidence than in patients receiving placebo with pemetrexed and platinum chemotherapy (between-arm difference of ≥5% [All Grades] or ≥2% [Grades 3-4]) (KEYNOTE-189)

	KEYTRUDA + Pemetrexed + Platinum Chemotherapy n=405		**Placebo + Pemetrexed + Platinum Chemotherapy n=202**	
Adverse Events	**All Grades* (%)**	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
General Disorders and Administration Site Conditions				
Fatigue	41	6	38	2.5
Asthenia	20	6	24	3.5
Gastrointestinal Disorders				
Diarrhoea	31	5	21	3.0
Blood and Lymphatic System Disorders				
Neutropenia	27	16	24	12
Skin and Subcutaneous Tissue Disorders				
Rash	20	1.7	11	1.5

* Graded per NCI CTCAE v4.03

Monotherapy

Table 8 summarises the adverse events that occurred in at least 10% of previously untreated patients with NSCLC receiving KEYTRUDA in KEYNOTE-042. The most common adverse events (reported in at least 15% of patients) were dyspnoea and cough. Adverse events occurring in previously untreated patients with NSCLC receiving KEYTRUDA in KEYNOTE-024 and previously treated patients in KEYNOTE-010 were generally similar to those occurring in patients in KEYNOTE-042.

Table 8: Adverse Events Occurring in ≥10% of NSCLC Patients Treated with KEYTRUDA and at a Higher Incidence than in the Chemotherapy Arm (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-5]) (KEYNOTE-042)

	KEYTRUDA 200 mg every 3 weeks n=636		Chemotherapy n=615	
Adverse Event	**All Grades* (%)**	**Grades 3-5 (%)**	**All Grades (%)**	**Grades 3-5 (%)**
Respiratory, Thoracic and Mediastinal Disorders				
Dyspnoea	17	2.0	11	0.8
Cough	16	0.2	11	0.3
Endocrine Disorders				
Hypothyroidism	12	0.2	1.5	0

* Graded per NCI CTCAE v4.03

Head and Neck Cancer

First-line treatment of metastatic or unresectable, recurrent HNSCC

The safety of KEYTRUDA, as a single agent and in combination with platinum (cisplatin or carboplatin) and 5-FU chemotherapy, was investigated in KEYNOTE-048, a multicentre, open-label, randomised (1:1:1), active-controlled trial in patients with previously untreated, recurrent or metastatic HNSCC *[see Clinical Studies (14.4)]*. Patients with autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. A total of 576 patients received KEYTRUDA 200 mg every 3 weeks either as a single agent (n=300) or in combination with platinum and 5-FU (n=276) every 3 weeks for 6 cycles followed by KEYTRUDA, compared to 287 patients who received cetuximab weekly in combination with platinum and 5-FU every 3 weeks for 6 cycles followed by cetuximab.

The median duration of exposure to KEYTRUDA was 3.5 months (range: 1 day to 24.2 months) in the KEYTRUDA single agent arm and was 5.8 months (range: 3 days to 24.2 months) in the combination arm. Seventeen percent of patients in the KEYTRUDA single agent arm and 18% of patients in the combination arm were exposed to KEYTRUDA for ≥12 months. Fifty-seven percent of patients receiving KEYTRUDA in combination with chemotherapy started treatment with carboplatin.

KEYTRUDA was discontinued for adverse reactions in 12% of patients in the KEYTRUDA single agent arm. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA were sepsis (1.7%) and pneumonia (1.3%). Adverse reactions leading to the interruption of KEYTRUDA occurred in 31% of patients; the most common adverse reactions leading to interruption of KEYTRUDA (≥2%) were pneumonia (2.3%), pneumonitis (2.3%), and hyponatremia (2%).

KEYTRUDA was discontinued for adverse reactions in 16% of patients in the combination arm. The most common adverse reactions resulting in permanent discontinuation of KEYTRUDA were pneumonia (2.5%), pneumonitis (1.8%), and septic shock (1.4%). Adverse reactions leading to the interruption of KEYTRUDA occurred in 45% of patients; the most common adverse reactions leading to interruption of KEYTRUDA (≥2%) were neutropenia (14%), thrombocytopenia (10%), anaemia (6%), pneumonia (4.7%), and febrile neutropenia (2.9%).

Tables 9 and 10 summarise adverse reactions and laboratory abnormalities, respectively, in

patients on KEYTRUDA in KEYNOTE-048.

Table 9: Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE 048

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks n=300		KEYTRUDA 200 mg every 3 weeks *Platinum 5-FU* n=276		Cetuximab Platinum 5-FU n=287	
	All Grades* (%)	Grades 3-4 (%)	All Grades* (%)	Grades 3-4 (%)	All Grades* (%)	Grades 3-4 (%)
General						
Fatigue[†]	33	4	49	11	48	8
Pyrexia	13	0.7	16	0.7	12	0
Mucosal inflammation	4.3	1.3	31	10	28	5
Gastrointestinal						
Constipation	20	0.3	37	0	33	1.4
Nausea	17	0	51	6	51	6
Diarrhoea[‡]	16	0.7	29	3.3	35	3.1
Vomiting	11	0.3	32	3.6	28	2.8
Dysphagia	8	2.3	12	2.9	10	2.1
Stomatitis	3	0	26	8	28	3.5
Skin						
Rash[§]	20	2.3	17	0.7	70	8
Pruritus	11	0	8	0	10	0.3
Respiratory, Thoracic and Mediastinal						
Cough[¶]	18	0.3	22	0	15	0
Dyspnoea[#]	14	2.0	10	1.8	8	1.0
Endocrine						
Hypothyroidism	18	0	15	0	6	0
Metabolism and Nutrition						
Decreased appetite	15	1.0	29	4.7	30	3.5
Weight loss	15	2	16	2.9	21	1.4
Infections						
Pneumonia[Þ]	12	7	19	11	13	6
Nervous System						
Headache	12	0.3	11	0.7	8	0.3
Dizziness	5	0.3	10	0.4	13	0.3
Peripheral sensory neuropathy[ß]	1	0	14	1.1	7	1
Musculoskeletal						
Myalgia[à]	12	1.0	13	0.4	11	0.3
Neck pain	6	0.7	10	1.1	7	0.7
Psychiatric						
Insomnia	7	0.7	10	0	8	0

* Graded per NCI CTCAE v4.0

† Includes fatigue, asthenia

‡ Includes diarrhoea, colitis, hemorrhagic diarrhoea, microscopic colitis
§ Includes dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis bullous, dermatitis contact, dermatitis exfoliative, drug eruption, erythema, erythema multiforme, rash, erythematous rash, generalized rash, macular rash, maculo-papular rash, pruritic rash, seborrheic dermatitis
¶ Includes cough, productive cough
# Includes dyspnoea, exertional dyspnoea
Þ Includes pneumonia, atypical pneumonia, bacterial pneumonia, staphylococcal pneumonia, aspiration pneumonia, lower respiratory tract infection, lung infection, lung infection pseudomonal
β Includes peripheral sensory neuropathy, peripheral neuropathy, hypoesthesia, dysesthesia
à Includes back pain, musculoskeletal chest pain, musculoskeletal pain, myalgia

Table 10: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients Receiving KEYTRUDA in KEYNOTE-048

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks		KEYTRUDA 200 mg every 3 weeks Platinum 5-FU		Cetuximab Platinum 5-FU	
	All Grades† (%)	Grades 3-4 (%)	All Grades† (%)	Grades 3-4 (%)	All Grades† (%)	Grades 3-4 (%)
Haematology						
Lymphopenia	54	25	69	35	74	45
Anaemia	52	7	89	28	78	19
Thrombocytopenia	12	3.8	73	18	76	18
Neutropenia	7	1.4	67	35	71	42
Chemistry						
Hyperglycemia	47	3.8	55	6	66	4.7
Hyponatremia	46	17	56	20	59	20
Hypoalbuminemia	44	3.2	47	4.0	49	1.1
Increased AST	28	3.1	24	2.0	37	3.6
Increased ALT	25	2.1	22	1.6	38	1.8
Increased alkaline phosphatase	25	2.1	27	1.2	33	1.1
Hypercalcemia	22	4.6	16	4.3	13	2.6
Hypocalcemia	22	1.1	32	4	58	7
Hyperkalemia	21	2.8	27	4.3	29	4.3
Hypophosphatemia	20	5	35	12	48	19
Hypokalemia	19	5	34	12	47	15
Increased creatinine	18	1.1	36	2.3	27	2.2
Hypomagnesemia	16	0.4	42	1.7	76	6

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA/chemotherapy (range: 235 to 266 patients), KEYTRUDA (range: 241 to 288 patients), cetuximab/chemotherapy (range: 249 to 282 patients).
† Graded per NCI CTCAE v4.0

Classical Hodgkin Lymphoma

KEYNOTE-204

The safety of KEYTRUDA for the treatment of patients with cHL was investigated in KEYNOTE-204, an open-label, randomised, active-controlled trial in which 300 patients received KEYTRUDA 200 mg or brentuximab vedotin (BV) 1.8 mg/kg every 3 weeks (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials).

The median duration of exposure to KEYTRUDA was 10.0 months (range: 1 day to 26.7 months). KEYTRUDA was discontinued due to adverse reactions in 14% of patients and treatment was interrupted due to adverse reactions in 30%. Thirty-eight percent of patients had an adverse reaction requiring systemic corticosteroid therapy. Serious adverse reactions occurred in 30% of patients receiving KEYTRUDA. The most frequent serious adverse reactions (≥1%) included pneumonia, pneumonitis, interstitial lung disease, pyrexia, myocarditis, acute kidney injury, and febrile neutropenia. Three patients died from causes other than disease progression; one from pneumonia, one from hypovolemic shock, and one due to unknown cause. Tables 11 and 16 summarise adverse reactions and laboratory abnormalities, respectively, in patients in KEYNOTE-204.

Table 11: Adverse Reactions (≥10%) in Patients with cHL who Received KEYTRUDA in KEYNOTE-204

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks N=148		Brentuximab Vedotin 1.8 mg/kg every 3 weeks N=152	
	All Grades* (%)	Grade 3-4 (%)	All Grades* (%)	Grade 3-4† (%)
Infections				
Upper respiratory tract infection‡	41	1.4	24	0
Urinary tract infection	11	0	3	0.7
Musculoskeletal and Connective Tissue				
Musculoskeletal pain§	32	0	29	1.3
Gastrointestinal				
Diarrhoea¶	22	2.7	17	1.3
Nausea	14	0	24	0.7
Vomiting	14	1.4	20	0
Abdominal pain#	11	0.7	13	1.3
General				
Pyrexia	20	0.7	13	0.7
Fatigueᵖ	20	0	22	0.7
Skin and Subcutaneous Tissue				
Rashβ	20	0	19	0.7
Pruritus	18	0	12	0
Respiratory, Thoracic and Mediastinal				
Coughà	20	0.7	14	0.7
Pneumonitisè	11	5	3	1.3
Dyspnoeað	11	0.7	7	0.7
Endocrine				
Hypothyroidism	19	0	3	0
Nervous System				
Peripheral neuropathyø	11	0.7	43	7
Headacheý	11	0	11	0

* Graded per NCI CTCAE v4.0
† Adverse reactions in BV arm were Grade 3 only.
‡ Includes acute sinusitis, nasopharyngitis, pharyngitis, pharyngotonsillitis, rhinitis, sinusitis, sinusitis bacterial, tonsillitis, upper respiratory tract infection, viral upper respiratory tract infection
§ Includes arthralgia, back pain, bone pain, musculoskeletal discomfort, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, pain in extremity
¶ Includes diarrhoea, gastroenteritis, colitis, enterocolitis
# Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper
Þ Includes fatigue, asthenia
β Includes dermatitis acneiform, dermatitis atopic, dermatitis allergic, dermatitis contact, dermatitis exfoliative, dermatitis psoriasiform, eczema, rash, rash erythematous, rash follicular, rash maculo-papular, rash papular, rash pruritic, toxic skin eruption
à Includes cough, productive cough
è Includes pneumonitis, interstitial lung disease
ð Includes dyspnoea, dyspnoea exertional, wheezing
ø Includes dysaesthesia, hypoaesthesia, neuropathy peripheral, paraesthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, polyneuropathy
ý Includes headache, migraine, tension headache

Clinically relevant adverse reactions in <10% of patients who received KEYTRUDA included herpes virus infection (9%), pneumonia (8%), oropharyngeal pain (8%), hyperthyroidism (5%), hypersensitivity (4.1%), infusion reactions (3.4%), altered mental state (2.7%), and in 1.4% each, uveitis, myocarditis, thyroiditis, febrile neutropenia, sepsis, and tumour flare.

Table 12: Laboratory Abnormalities (≥15%) That Worsened from Baseline in Patients with cHL in KEYNOTE 204

Laboratory Abnormality*	KEYTRUDA 200 mg every 3 weeks		Brentuximab Vedotin 1.8 mg/kg every 3 weeks	
	All Grades† (%)	Grades 3-4 (%)	All Grades† (%)	Grades 3-4 (%)
Chemistry				
Hyperglycemia	46	4.1	36	2.0
Increased AST	39	5	41	3.9
Increased ALT	34	6	45	5
Hypophosphatemia	31	5	18	2.7
Increased creatinine	28	3.4	14	2.6
Hypomagnesemia	25	0	12	0
Hyponatremia	24	4.1	20	3.3
Hypocalcemia	22	2.0	16	0
Increased alkaline phosphatase	21	2.1	22	2.6
Hyperbilirubinemia	16	2.0	9	1.3
Hypoalbuminemia	16	0.7	19	0.7
Hyperkalemia	15	1.4	8	0
Haematology				
Lymphopenia	35	9	32	13
Thrombocytopenia	34	10	26	5
Neutropenia	28	8	43	17
Anaemia	24	5	33	8

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (range: 143 to 148 patients) and BV (range: 146 to 152 patients); hypomagnesemia: KEYTRUDA n=53 and BV n=50.
† Graded per NCI CTCAE v4.0

KEYNOTE-087

Among the 210 patients with cHL who received KEYTRUDA in KEYNOTE-087 (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials), the median duration of exposure to KEYTRUDA was 8.4 months (range: 1 day to 15.2 months). Serious adverse reactions occurred in 16% of patients who received KEYTRUDA. Serious adverse reactions that occurred in ≥1% of patients included pneumonia, pneumonitis, pyrexia, dyspnoea, graft versus host disease (GVHD) and herpes zoster. Two patients died from causes other than disease progression; one from GVHD after subsequent allogeneic HSCT and one from septic shock.

Permanent discontinuation of KEYTRUDA due to an adverse reaction occurred in 5% of patients and dosage interruption due to an adverse reaction occurred in 26%. Fifteen percent of patients had an adverse reaction requiring systemic corticosteroid therapy. Tables 13 and 14 summarise adverse reactions and laboratory abnormalities, respectively, in KEYNOTE-087.

Table 13: Adverse Reactions (≥10%) in Patients with cHL who Received KEYTRUDA in KEYNOTE-087

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks N=210	
	All Grades* (%)	Grade 3 (%)
General		
Fatigue†	26	1.0
Pyrexia	24	1.0
Respiratory, Thoracic and Mediastinal		
Cough‡	24	0.5
Dyspnoea§	11	1.0
Musculoskeletal and Connective Tissue		
Musculoskeletal pain¶	21	1.0
Arthralgia	10	0.5
Gastrointestinal		
Diarrhoea#	20	1.4
Vomiting	15	0
Nausea	13	0
Skin and Subcutaneous Tissue		
Rash Þ	20	0.5
Pruritus	11	0
Endocrine		
Hypothyroidism	14	0.5
Infections		
Upper respiratory tract infection	13	0
Nervous System		
Headache	11	0.5
Peripheral neuropathyβ	10	0

* Graded per NCI CTCAE v4.0
† Includes fatigue, asthenia
‡ Includes cough, productive cough
§ Includes dyspnoea, dyspnoea exertional, wheezing
¶ Includes back pain, myalgia, bone pain, musculoskeletal pain, pain in extremity, musculoskeletal chest pain, musculoskeletal discomfort, neck pain
# Includes diarrhoea, gastroenteritis, colitis, enterocolitis
Þ Includes rash, rash maculo-papular, drug eruption, eczema, eczema asteatotic, dermatitis, dermatitis acneiform, dermatitis contact, rash erythematous, rash macular, rash papular, rash pruritic, seborrhoeic dermatitis, dermatitis psoriasiform
β Includes neuropathy peripheral, peripheral sensory neuropathy, hypoesthesia, paresthesia, dysesthesia, polyneuropathy

Clinically relevant adverse reactions in <10% of patients who received KEYTRUDA included infusion reactions (9%), hyperthyroidism (3%), pneumonitis (3%), uveitis and myositis (1% each), and myelitis and myocarditis (0.5% each).

Table 14: Select Laboratory Abnormalities (≥15%) That Worsened from Baseline in Patients with cHL who Received KEYTRUDA in KEYNOTE-087

Laboratory Abnormality*	KEYTRUDA 200 mg every 3 weeks	
	All Grades† (%)	Grades 3-4 (%)
Chemistry		
Hypertransaminasemia‡	34	2
Increased alkaline phosphatase	17	0
Increased creatinine	15	0.5
Haematology		
Anaemia	30	6
Thrombocytopenia	27	4
Neutropenia	24	7

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (range: 208 to 209 patients)
† Graded per NCI CTCAE v4.0
‡ Includes elevation of AST or ALT

Hyperbilirubinemia occurred in less than 15% of patients on KEYNOTE-087 (10% all Grades, 2.4% Grade 3-4).

Primary Mediastinal B-Cell Lymphoma

In patients with PMBCL, a higher incidence of pyrexia (28%) possibly due to B-symptoms, and neutropenia (26%) have been noted. The incidence of grade 3 or 4 neutropenia was 17%, and febrile neutropenia was 2%. A causal relationship with KEYTRUDA has not been established, and the neutropenia may have been due to prior myelotoxic therapy. Other adverse events were generally similar to those occurring in patients with melanoma or NSCLC.

Urothelial Carcinoma

Cisplatin Ineligible Patients with Urothelial Carcinoma
The safety of KEYTRUDA was investigated in Study KEYNOTE-052, a single-arm trial that enrolled 370 patients with locally advanced or metastatic urothelial carcinoma who were not eligible for cisplatin-containing chemotherapy. Patients with autoimmune disease or medical conditions that required systemic corticosteroids or other immunosuppressive medications were ineligible. Patients received KEYTRUDA 200 mg every 3 weeks until unacceptable toxicity or either radiographic or clinical disease progression. The median duration of exposure to KEYTRUDA was 2.8 months (range: 1 day to 15.8 months).

The most common adverse reactions (reported in at least 20% of patients) were fatigue, musculoskeletal pain, decreased appetite, constipation, rash and diarrhoea. KEYTRUDA was discontinued due to adverse reactions in 11% of patients. Eighteen patients (5%) died from causes other than disease progression. Five patients (1.4%) who were treated with KEYTRUDA experienced sepsis which led to death, and three patients (0.8%) experienced pneumonia which led to death. Adverse reactions leading to interruption of KEYTRUDA occurred in 22% of patients; the most common (≥1%) were liver enzyme increase, diarrhoea, urinary tract infection, acute kidney injury, fatigue, joint pain, and pneumonia. Serious adverse reactions occurred in 42% of patients. The most frequent serious adverse reactions (≥2%) were urinary tract infection, hematuria, acute kidney injury, pneumonia, and urosepsis.

Immune-related adverse reactions that required systemic glucocorticoids occurred in 8% of patients, use of hormonal supplementation due to an immune-related adverse reaction occurred in 8% of patients, and 5% of patients required at least one steroid dose ≥40 mg oral prednisone equivalent.

Table 15 summarises the incidence of adverse reactions occurring in at least 10% of patients receiving KEYTRUDA.

Table 15: Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-052

	KEYTRUDA 200mg every 3 weeks N=370	
Adverse Reaction	**All Grades[*] (%)**	**Grades 3 – 4 (%)**
All Adverse Reactions	96	49
Blood and Lymphatic System Disorders		
Anaemia	17	7
Gastrointestinal Disorders		
Constipation	21	1.1
Diarrhoea[†]	20	2.4
Nausea	18	1.1
Abdominal pain[‡]	18	2.7
Elevated LFTs[§]	13	3.5
Vomiting	12	0
General Disorders and Administration Site Conditions		
Fatigue[¶]	38	6
Pyrexia	11	0.5
Weight decreased	10	0
Infections and Infestations		
Urinary tract infection	19	9
Metabolism and Nutrition Disorders		
Decreased appetite	22	1.6
Hyponatremia	10	4.1
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[#]	24	4.9
Arthralgia	10	1.1
Renal and Urinary Disorders		
Blood creatinine increased	11	1.1
Hematuria	13	3.0
Respiratory, Thoracic, and Mediastinal Disorders		
Cough	14	0
Dyspnoea	11	0.5
Skin and Subcutaneous Tissue Disorders		
Rash[Þ]	21	0.5
Pruritis	19	0.3
Oedema peripheral	14	1.1

[*] Graded per NCI CTCAE v4.0
[†] Includes diarrhoea, colitis, enterocolitis, gastroenteritis, frequent bowel movements
[‡] Includes abdominal pain, pelvic pain, flank pain, abdominal pain lower, tumour pain, bladder pain, hepatic pain, suprapubic pain, abdominal discomfort, abdominal pain upper
[§] Includes autoimmune hepatitis, hepatitis, hepatitis toxic, liver injury, transaminases increased, hyperbilirubinemia, blood bilirubin increased, alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzymes increased, liver function tests increased
[¶] Includes fatigue, asthenia
[#] Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, pain in extremity, spinal pain
[Þ] Includes dermatitis, dermatitis bullous, eczema, erythema, rash, rash macular, rash maculo-papular, rash pruritic, rash pustular, skin reaction, dermatitis acneform, seborrheic dermatitis, palmar-plantar erythrodysesthesia syndrome, rash generalized

Previously Treated Urothelial Carcinoma
The safety of KEYTRUDA for the treatment of patients with locally advanced or metastatic urothelial carcinoma with disease progression following platinum-containing chemotherapy was investigated in Study KEYNOTE-045. KEYNOTE-045 was a multicentre, open-label, randomised (1:1), active-controlled trial in which 266 patients received KEYTRUDA 200 mg every 3 weeks or investigator's choice of chemotherapy (n=255), consisting of paclitaxel (n=84), docetaxel (n=84) or vinflunine (n=87) [see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials]. Patients with autoimmune disease or a medical condition that required systemic corticosteroids or other immunosuppressive medications were ineligible. The median duration of exposure was 3.5 months (range: 1 day to 20 months) in patients who received KEYTRUDA and 1.5 months (range: 1 day to 14 months) in patients who received chemotherapy.

KEYTRUDA was discontinued due to adverse reactions in 8% of patients. The most common adverse reaction resulting in permanent discontinuation of KEYTRUDA was pneumonitis (1.9%). Adverse reactions leading to interruption of KEYTRUDA occurred in 20% of patients; the most common (≥1%) were urinary tract infection (1.5%), diarrhoea (1.5%), and colitis (1.1%). The most common adverse reactions (occurring in at least 20% of patients who received KEYTRUDA) were fatigue, musculoskeletal pain, pruritus, decreased appetite, nausea and rash. Serious adverse reactions occurred in 39% of KEYTRUDA-treated patients. The most frequent serious adverse reactions (≥2%) in KEYTRUDA-treated patients were urinary tract infection, pneumonia, anaemia, and pneumonitis.

Table 16 summarises the incidence of adverse reactions occurring in at least 10% of patients receiving KEYTRUDA. Table 17 summarises the incidence of laboratory abnormalities that occurred in at least 20% of patients receiving KEYTRUDA.

Table 16: Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-045

	KEYTRUDA 200 mg every 3 weeks N=266		Chemotherapy* N=255	
Adverse Reaction	**All Grades† (%)**	**Grades 3 – 4 (%)**	**All Grades† (%)**	**Grades 3 – 4 (%)**
Gastrointestinal Disorders				
Nausea	21	1.1	29	1.6
Constipation	19	1.1	32	3.1
Diarrhoea‡	18	2.3	19	1.6
Vomiting	15	0.4	13	0.4
Abdominal pain	13	1.1	13	2.7
General Disorders and Administration Site Conditions				
Fatigue§	38	4.5	56	11
Pyrexia	14	0.8	13	1.2
Infections and Infestations				
Urinary tract infection	15	4.9	14	4.3
Metabolism and Nutrition Disorders				
Decreased appetite	21	3.8	21	1.2
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal pain¶	32	3.0	27	2.0
Renal and Urinary Disorders				
Hematuria#	12	2.3	8	1.6
Respiratory, Thoracic and Mediastinal Disorders				
Coughᵖ	15	0.4	9	0
Dyspnoeaß	14	1.9	12	1.2
Skin and Subcutaneous Tissue Disorders				
Pruritus	23	0	6	0.4
Rashà	20	0.4	13	0.4

* Chemotherapy: paclitaxel, docetaxel, or vinflunine
† Graded per NCI CTCAE v4.0
‡ Includes diarrhoea, gastroenteritis, colitis, enterocolitis
§ Includes asthenia, fatigue, malaise lethargy
¶ Includes back pain, myalgia, bone pain, musculoskeletal pain, pain in extremity, musculoskeletal chest pain, musculoskeletal discomfort, neck pain
# Includes blood urine present, hematuria, chromaturia
ᵖ Includes cough, productive cough
ß Includes dyspnoea, dyspnoea exertional, wheezing
à Includes rash maculo-papular, rash genital rash, rash erythematous, rash papular, rash pruritic, rash pustular, erythema, drug eruption, eczema, eczema asteatotic, dermatitis contact, dermatitis acneiform, dermatitis, seborrhoeic keratosis, lichenoid keratosis

Table 17: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Urothelial Carcinoma Patients Receiving KEYTRUDA in KEYNOTE-045

	KEYTRUDA 200 mg every 3 weeks		Chemotherapy	
Laboratory Test*	**All Grades† (%)**	**Grades 3 – 4 (%)**	**All Grades† (%)**	**Grades 3 – 4 (%)**
Chemistry				
Glucose increased	52	8	60	7
Hemoglobin decreased	52	13	68	18
Lymphocytes decreased	45	15	53	25
Albumin decreased	43	1.7	50	3.8
Sodium decreased	37	9	47	13
Alkaline phosphatase increased	37	7	33	4.9
Creatinine increased	35	4.4	28	2.9
Phosphate decreased	29	8	34	14
Aspartate aminotransferase increased	28	4.1	20	2.5
Potassium increased	28	0.8	27	6
Calcium decreased	26	1.6	34	2.1

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (range: 240 to 248 patients) and chemotherapy (range: 238 to 244 patients); phosphate decreased: KEYTRUDA n=232 and chemotherapy n=222.
† Graded per NCI CTCAE v4.0

BCG-unresponsive High-risk NMIBC
The safety of KEYTRUDA was investigated in KEYNOTE 057, a multicentre, open-label, single-arm trial that enrolled 148 patients with high-risk non-muscle invasive bladder cancer (NMIBC), 96 of whom had BCG-unresponsive carcinoma in situ (CIS) with or without papillary tumours. Patients received KEYTRUDA 200 mg every 3 weeks until unacceptable toxicity, persistent or recurrent high-risk NMIBC or progressive disease, or up to 24 months of therapy without disease progression.

The median duration of exposure to KEYTRUDA was 4.3 months (range: 1 day to 25.6 months).

KEYTRUDA was discontinued due to adverse reactions in 10% of patients. The most common adverse (>1%) reaction resulting in permanent discontinuation of KEYTRUDA was pneumonitis (1.4%). Adverse reactions leading to interruption of KEYTRUDA occurred in 24% of patients; the most common (≥2%) were diarrhoea (2%) and urinary tract infection (2%). Serious adverse reactions occurred in 27% of KEYTRUDA-treated patients. The most frequent serious adverse reactions (≥2%) in KEYTRUDA-treated patients were pneumonia (3%), colitis (2%), pulmonary embolism (2%), and urinary tract infection (2%). Tables 18 and 19 summarise adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-057.

Table 18: Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-057

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks N=148	
	All Grades* (%)	Grades 3–4 (%)
General		
Fatigue†	29	0.7
Peripheral oedema‡	11	0
Gastrointestinal		
Diarrhoea§	24	2.0
Nausea	13	0
Constipation	12	0
Skin and Subcutaneous Tissue		
Rash¶	24	0.7
Pruritus	20	0.7
Musculoskeletal and Connective Tissue		
Musculoskeletal pain#	20	0
Arthralgia	14	1.4
Renal and Urinary		
Haematuria	19	1.4
Respiratory, Thoracic, and Mediastinal		
Coughᵖ	19	0
Infections		
Urinary tract infection	12	2.0
Nasopharyngitis	10	0
Endocrine		
Hypothyroidism	11	0

* Graded per NCI CTCAE v4.03
† Includes asthenia, fatigue, malaise
‡ Includes oedema peripheral, peripheral swelling
§ Includes diarrhoea, gastroenteritis, colitis
¶ Includes rash maculo-papular, rash, rash erythematous, rash pruritic, rash pustular, erythema, eczema, eczema asteatotic, lichenoid keratosis, urticaria, dermatitis
# Includes back pain, myalgia, musculoskeletal pain, pain in extremity, musculoskeletal chest pain, neck pain
ᵖ Includes cough, productive cough

Table 19: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of BCG-unresponsive NMIBC Patients Receiving KEYTRUDA in KEYNOTE-057

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks	
	All Grades† (%)	Grades 3-4 (%)
Chemistry		
Hyperglycemia	61	8
Increased ALT	25	3.4
Hyponatremia	26	7
Hypophosphatemia	24	6
Hypoalbuminemia	25	2.1
Hyperkalemia	23	1.4
Hypocalcemia	22	0.7
Increased AST	21	3.4
Increased creatinine	21	0.7
Haematology		
Anaemia	35	1.4
Lymphopenia	30	1.6

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (range: 124 to 147 patients)

† Graded per NCI CTCAE v4.03

MSI-H/dMMR cancer

Adverse events occurring in patients with MSI-H/dMMR cancer, including previously untreated CRC, were generally similar to those occurring in patients with melanoma or NSCLC.

Endometrial Carcinoma

The safety of KEYTRUDA in combination with lenvatinib (20 mg orally once daily) was investigated in KEYNOTE-146, a single-arm, multicentre, open-label trial in 94 patients with endometrial carcinoma whose tumours had progressed following one line of systemic therapy and were not MSI-H or dMMR. The median duration of study treatment was 7 months (range: 0.03 to 37.8 months). The median duration of exposure to KEYTRUDA was 6 months (range: 0.03 to 23.8 months). KEYTRUDA was continued for a maximum of 24 months; however, treatment with lenvatinib could be continued beyond 24 months.

Fatal adverse reactions occurred in 3% of patients receiving KEYTRUDA and lenvatinib, including gastrointestinal perforation, reversible posterior leukoencephalopathy syndrome (RPLS) with intraventricular haemorrhage, and intracranial haemorrhage.

Serious adverse reactions occurred in 52% of patients receiving KEYTRUDA and lenvatinib. Serious adverse reactions in ≥3% of patients were hypertension (9%), abdominal pain (6%), musculoskeletal pain (5%), haemorrhage (4%), fatigue (4%), nausea (4%), confusional state (4%), pleural effusion (4%), adrenal insufficiency (3%), colitis (3%), dyspnoea (3%), and pyrexia (3%).

KEYTRUDA was discontinued for adverse reactions (Grade 1-4) in 19% of patients, regardless of action taken with lenvatinib. The most common adverse reactions (≥ 2%) leading to discontinuation of KEYTRUDA were adrenal insufficiency (2%), colitis (2%), pancreatitis (2%), and muscular weakness (2%).

Adverse reactions leading to interruption of KEYTRUDA occurred in 49% of patients; the most common adverse reactions leading to interruption of KEYTRUDA (≥2%) were: fatigue (14%), diarrhoea (6%), decreased appetite (6%), rash (5%), renal impairment (4%), vomiting (4%), increased lipase (4%), weight loss (4%), nausea (3%), increased blood alkaline phosphatase (3%), skin ulcer (3%), adrenal insufficiency (2%), increased amylase (2%), hypocalcaemia (2%), hypomagnesemia (2%), hyponatremia (2%), peripheral oedema (2%), musculoskeletal pain (2%), pancreatitis (2%), and syncope (2%).

Tables 20 and 21 summarise adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in combination with lenvatinib.

Table 20: Adverse reactions occurring in ≥20% of patients with endometrial carcinoma in KEYNOTE-146

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks with lenvatinib N=94	
	All Grades (%)	Grades 3-4 (%)
General		
Fatigue*	65	17
Musculoskeletal and Connective Tissue		
Musculoskeletal pain†	65	3
Vascular		
Hypertension‡	65	38
Haemorrhagic events§	28	4
Gastrointestinal		
Diarrhoea¶	64	4
Nausea	48	5
Stomatitis#	43	0
Vomiting	39	0
Abdominal painÞ	33	6
Constipation	32	0
Metabolism		
Decreased appetiteß	52	0
Hypomagnesemia	27	3
Endocrine		
Hypothyroidismà	51	1
Investigations		
Weight loss	36	3
Nervous System		
Headache	33	1
Infections		
Urinary tract infectionè	31	4
Respiratory, Thoracic and Mediastinal		
Dysphonia	29	0
Dyspnoeað	24	2
Cough	21	0
Skin and Subcutaneous Tissue		
Palmar-plantar erythrodysesthesia syndrome	26	3
Rashø	21	3

* Includes asthenia, fatigue, and malaise

† Includes arthralgia, arthritis, back pain, breast pain, musculoskeletal chest pain, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, non-cardiac chest pain, pain in extremity
‡ Includes essential hypertension, hypertension, and hypertensive encephalopathy
§ Includes catheter site bruise, contusion, epistaxis, gastrointestinal haemorrhage, haematemesis, haematuria, haemorrhage intracranial, injection site haemorrhage, intraventricular haemorrhage, large intestinal haemorrhage, metrorrhagia, mouth haemorrhage, uterine haemorrhage, and vaginal haemorrhage
¶ Includes diarrhoea, gastroenteritis, gastrointestinal viral infection, and viral diarrhoea
# Includes glossitis, mouth ulceration, oral discomfort, oral mucosal blistering, oropharyngeal pain, and stomatitis
Þ Includes abdominal discomfort, abdominal pain, lower abdominal pain, and upper abdominal pain
ß Includes decreased appetite and early satiety
à Includes increased blood thyroid stimulating hormone and hypothyroidism
è Includes cystitis and urinary tract infection
ð Includes dyspnoea and exertional dyspnoea
ø Includes rash, rash generalized, rash macular, and rash maculo-papular

Table 21: Laboratory abnormalities worsened from baseline occurring in ≥20% (All Grades) or ≥3% (Grades 3-4) of patients with endometrial carcinoma in KEYNOTE-146

Laboratory Test*	**KEYTRUDA 200 mg every 3 weeks with lenvatinib**	
	All Grades %†	**Grade 3-4 %†**
Chemistry		
Increased creatinine	80	7
Hypertriglyceridemia	58	4
Hyperglycaemia	53	1
Hypercholesteremia	49	6
Hypoalbuminemia	48	0
Hypomagnesemia	47	2
Increased aspartate aminotransferase	43	4
Hyponatremia	42	13
Increased lipase	42	18
Increased alanine aminotransferase	35	3
Increased alkaline phosphatase	32	1
Hypokalaemia	27	5
Increased amylase	19	6
Hypocalcaemia	14	3
Hypermagnesemia	4	3
Haematology		
Thrombocytopenia	48	0
Leukopenia	38	2
Lymphopenia	36	7
Anaemia	35	1
Increased INR	21	3
Neutropenia	12	3

* With at least 1 grade increase from baseline
† Laboratory abnormality percentage is based on the number of patients who had both baseline and at least one post-baseline laboratory measurement for each parameter (range: 71 to 92 patients).

Renal Cell Carcinoma

The most common adverse reactions that occurred in at least 20% of previously untreated patients with RCC receiving KEYTRUDA and axitinib in KEYNOTE-426 were diarrhoea, fatigue/ asthenia, hypertension, hypothyroidism, decreased appetite, hepatotoxicity, palmar-plantar erythrodysesthesia, nausea, stomatitis/mucosal inflammation, dysphonia, rash, cough, and constipation. Incidences of Grades 3-5 adverse reactions were 76% for KEYTRUDA combination therapy and 71% for sunitinib alone.

Table 22: Adverse Reactions Occurring in ≥20% of Patients Receiving KEYTRUDA with Axitinib in KEYNOTE-426

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks and Axitinib n=429		Sunitinib n=425	
	All Grades* (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Gastrointestinal				
Diarrhoea†	56	11	45	5
Nausea	28	0.9	32	0.9
Constipation	21	0	15	0.2
General				
Fatigue/Asthenia	52	5	51	10
Vascular				
Hypertension‡	48	24	48	20
Hepatobiliary				
Hepatotoxicity§	39	20	25	4.9
Endocrine				
Hypothyroidism	35	0.2	32	0.2
Metabolism and Nutrition				
Decreased appetite	30	2.8	29	0.7
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysesthesia syndrome	28	5	40	3.8
Stomatitis/Mucosal inflammation	27	1.6	41	4
Rash¶	25	1.4	21	0.7
Respiratory, Thoracic and Mediastinal				
Dysphonia	25	0.2	3.3	0
Cough	21	0.2	14	0.5

* Graded per NCI CTCAE v4.03

† Includes diarrhoea, colitis, enterocolitis, gastroenteritis, enteritis, enterocolitis haemorrhagic

‡ Includes hypertension, blood pressure increased, hypertensive crisis, labile hypertension

§ Includes ALT increased, AST increased, autoimmune hepatitis, blood bilirubin increased, drug- induced liver injury, hepatic enzyme increased, hepatic function abnormal, hepatitis, hepatitis fulminant, hepatocellular injury, hepatotoxicity, hyperbilirubinemia, immune-mediated hepatitis, liver function test increased, liver injury, transaminases increased

¶ Includes rash, butterfly rash, dermatitis, dermatitis acneiform, dermatitis atopic, dermatitis bullous, dermatitis contact, exfoliative rash, genital rash, rash erythematous, rash generalised, rash macular, rash maculopapular, rash papular, rash pruritic, seborrhoeic dermatitis, skin discolouration, skin exfoliation, perineal rash

Table 23: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients Receiving KEYTRUDA with Axitinib in KEYNOTE-426

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks and Axitinib		Sunitinib	
	All Grades† %	Grades 3-4 %	All Grades %	Grades 3-4 %
Chemistry				
Hyperglycaemia	62	9	54	3.2
Increased ALT	60	20	44	5
Increased AST	57	13	56	5
Increased creatinine	43	4.3	40	2.4
Hyponatremia	35	8	29	8
Hyperkalaemia	34	6	22	1.7
Hypoalbuminemia	32	0.5	34	1.7
Hypercalcemia	27	0.7	15	1.9
Hypophosphatemia	26	6	49	17
Increased alkaline phosphatase	26	1.7	30	2.7
Hypocalcaemia‡	22	0.2	29	0.7
Blood bilirubin increased	22	2.1	21	1.9
Activated partial thromboplastin time prolonged§	22	1.2	14	0
Haematology				
Lymphopenia	33	11	46	8
Anaemia	29	2.1	65	8
Thrombocytopenia	27	1.4	78	14

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA/axitinib (range: 342 to 425 patients) and sunitinib (range: 345 to 422 patients).
† Graded per NCI CTCAE v4.03
‡ Corrected for albumin
§ Two patients with a Grade 3 elevated activated partial thromboplastin time prolonged (aPTT) were also reported as having an adverse reaction of hepatotoxicity.

Cutaneous Squamous Cell Carcinoma

Adverse events occurring in patients with cSCC were generally similar to those occurring in patients with melanoma or NSCLC.

Oesophageal Cancer

In patients with oesophageal cancer, adverse reactions occurring in at least 20% of patients and at a higher incidence (≥2%) of Grades 3-5 severity for KEYTRUDA in combination with chemotherapy (cisplatin and 5-FU) compared to placebo and chemotherapy (cisplatin and 5-FU) were: vomiting (7% vs. 5%), stomatitis (6% vs. 3.8%), neutrophil count decreased (24.1% vs 17.3%), and white blood cell count decreased (9.2% vs. 4.9%).

TMB-H cancer

The safety of KEYTRUDA was investigated in 105 adult patients with TMB-H cancer enrolled in KEYNOTE-158 (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials).

The median duration of exposure to KEYTRUDA was 4.9 months (range: 0.03 to 35.2 months). Adverse reactions occurring in patients with TMB-H cancer were similar to those occurring in patients with other solid tumours who received KEYTRUDA as a single agent.

Post-marketing Experience

The following adverse reactions have been identified during post-approval use of KEYTRUDA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and lymphatic disorders: autoimmune haemolytic anaemia
Eye disorders: Vogt-Koyanagi-Harada syndrome
Immune system disorders: haemophagocytic lymphohistiocytosis
Musculoskeletal and connective tissue disorders: arthritis, Sjögren's syndrome

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is no information on overdosage with KEYTRUDA. The maximum tolerated dose of KEYTRUDA has not been determined. In clinical trials, patients received up to 10 mg/kg with a similar safety profile to that seen in patients receiving 2 mg/kg.

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

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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

Mechanism of action

PD-1 is an immune-checkpoint receptor that limits the activity of T lymphocytes in peripheral tissues. The PD-1 pathway is an immune control checkpoint that may be engaged by tumour cells to inhibit active T-cell immune surveillance. KEYTRUDA is a high affinity antibody against PD-1, which exerts ligand blockade of the PD-1 pathway, including PD-L1 and PD-L2, on antigen presenting or tumour cells. By inhibiting the PD-1 receptor from binding to its ligands, KEYTRUDA reactivates tumour-specific cytotoxic T lymphocytes in the tumour microenvironment and reactivates anti-tumour immunity.

Based on the modelling of dose/exposure relationships for efficacy and safety for pembrolizumab, there are no clinically significant differences in efficacy and safety between the doses of 200 mg or 2 mg/kg every 3 weeks or 400 mg every 6 weeks.

In peripheral blood of patients who received KEYTRUDA 2 mg/kg every 3 weeks or 10 mg/kg every 2 weeks or 3 weeks, an increased percentage of activated (i.e., HLA-DR+) CD4+ and CD8+ T-cells was observed after treatment at all doses and schedules without an increase in the circulating T-lymphocyte number.

Clinical Trials

Melanoma

KEYNOTE-006: Controlled trial in melanoma patients naïve to treatment with ipilimumab
The safety and efficacy of KEYTRUDA were investigated in KEYNOTE-006, a multicentre, controlled, Phase III study for the treatment of unresectable or metastatic melanoma in patients who were naïve to ipilimumab and who received no or one prior systemic therapy. Patients were randomised (1:1:1) to receive KEYTRUDA at a dose of 10 mg/kg every 2 (n=279) or 3 weeks (n=277) or ipilimumab (n=278). Randomisation was stratified by line of therapy, ECOG performance status, and PD-L1 expression status. The study excluded patients with autoimmune disease or those receiving immunosuppression; previous severe hypersensitivity to other monoclonal antibodies; and HIV, hepatitis B or hepatitis C infection. Patients with BRAF V600E mutant melanoma were not required to have received prior BRAF inhibitor therapy.

Patients were treated with KEYTRUDA 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 in KEYNOTE-006, 60% were male, 44% were ≥65 years (median age was 62 years [range 18-89]) and 98% were white. Sixty-six percent had no prior systemic therapies and thus received study therapy as first-line treatment whereas 34% had one prior therapy and thus received study therapy as second-line treatment. Thirty-one percent had an ECOG PS of 1 and 69% had an ECOG PS of 0. Eighty percent of patients were PD-L1 positive (PD-L1 membrane expression in ≥1% of tumour and associated immune cells as assessed prospectively by an immunohistochemistry assay with the 22C3 anti-PD-L1 antibody) and 18% were PD-L1 negative. Sixty-five percent of patients had M1c stage, 32% had elevated LDH and 9% had brain metastases. BRAF mutations were reported in 302 (36%) patients. Among patients with BRAF mutant tumours, 139 (46%) were previously treated with a BRAF inhibitor. Baseline characteristics were well-balanced across treatment arms.

The primary efficacy outcome measures were overall survival (OS) and progression free survival (PFS; as assessed by Integrated Radiology and Oncology Assessment [IRO] review using Response Evaluation Criteria in Solid Tumours [RECIST 1.1]). Secondary efficacy outcome measures were overall response rate (ORR) and response duration. Table 24 summarises key efficacy measures.

Table 24: Response to KEYTRUDA 10 mg/kg every 2 or 3 weeks in patients with ipilimumab-naïve advanced melanoma in KEYNOTE-006

Endpoint	KEYTRUDA 10 mg/kg every 3 weeks n=277	KEYTRUDA 10 mg/kg every 2 weeks n=279	Ipilimumab n=278
OS*			
Number (%) of patients with event	92 (33%)	85 (30%)	112 (40%)
Hazard ratio† (95% CI)	0.69 (0.52, 0.90)	0.63 (0.47, 0.83)	---
p-Value‡	0.00358	0.00052	---
Median in months (95% CI)	Not reached (NA, NA)	Not reached (NA, NA)	Not reached (13, NA)
PFS§ by IRO¶			
Number (%) of patients with event	157 (57%)	157 (56%)	188 (68%)
Hazard ratio† (95% CI)	0.58 (0.47, 0.72)	0.58 (0.46, 0.72)	---
p-Value‡	<0.00001	<0.00001	---
Median in months (95% CI)	4.1 (2.9, 6.9)	5.5 (3.4, 6.9)	2.8 (2.8, 2.9)
Best Overall Response§ by IRO¶			
ORR % (95% CI)	33% (27, 39)	34% (28, 40)	12% (8, 16)
Complete response %	6%	5%	1%
Partial response %	27%	29%	10%
Response duration by IRO¶			
Median in months (range)	Not reached (2.0+, 22.8+)	Not reached (1.8+, 22.8)	Not reached (1.1+, 23.8+)
% ongoing at 12 monthsÞ	79%	75%	79%

* Based on second interim analysis
† Hazard ratio (KEYTRUDA compared to ipilimumab) based on the stratified Cox proportional hazard model
‡ Based on stratified log-rank test
§ Based on first interim analysis
¶ IRO = Independent radiology plus oncologist review using RECIST 1.1
# Based on patients with a best overall response as confirmed complete or partial response from the final analysis
Þ Based on Kaplan-Meier estimates
NA = not available

The final analysis was performed after all patients had at least 21 months of follow-up. The final OS analysis was performed after 383 patient events (119 for KEYTRUDA 10 mg/kg every 3 weeks, 122 for KEYTRUDA 10 mg/kg every 2 weeks and 142 for ipilimumab). The OS HRs vs. ipilimumab were 0.68 (95% CI: 0.53, 0.86; p<0.001) for patients treated with KEYTRUDA 10 mg/kg every 3 weeks and 0.68 (95% CI: 0.53, 0.87; p<0.001) for patients treated with KEYTRUDA 10 mg/kg every 2 weeks. The OS rate at 18 months and 24 months were 62% and 55% respectively for KEYTRUDA 10 mg/kg every 3 weeks, 60% and 55% respectively for KEYTRUDA 10 mg/kg every 2 weeks, and 47% and 43% respectively for ipilimumab. At the final analysis, a long-term PFS analysis was performed based on 566 patient events (183 for KEYTRUDA 10 mg/kg every 3 weeks, 181 for KEYTRUDA 10 mg/kg every 2 weeks and 202 for ipilimumab). The PFS HRs vs. ipilimumab were 0.61 (95% CI: 0.50, 0.75) for patients treated with KEYTRUDA 10 mg/kg every 3 weeks and 0.61 (95% CI: 0.50, 0.75) for patients treated with KEYTRUDA 10 mg/kg every 2 weeks. (See Figures 1 and 2). The percentage of responders with an ongoing response at 18 months was 68% for KEYTRUDA 10 mg/kg every 3 weeks, 71% for KEYTRUDA 10 mg/kg every 2 weeks and 70% for ipilimumab.

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

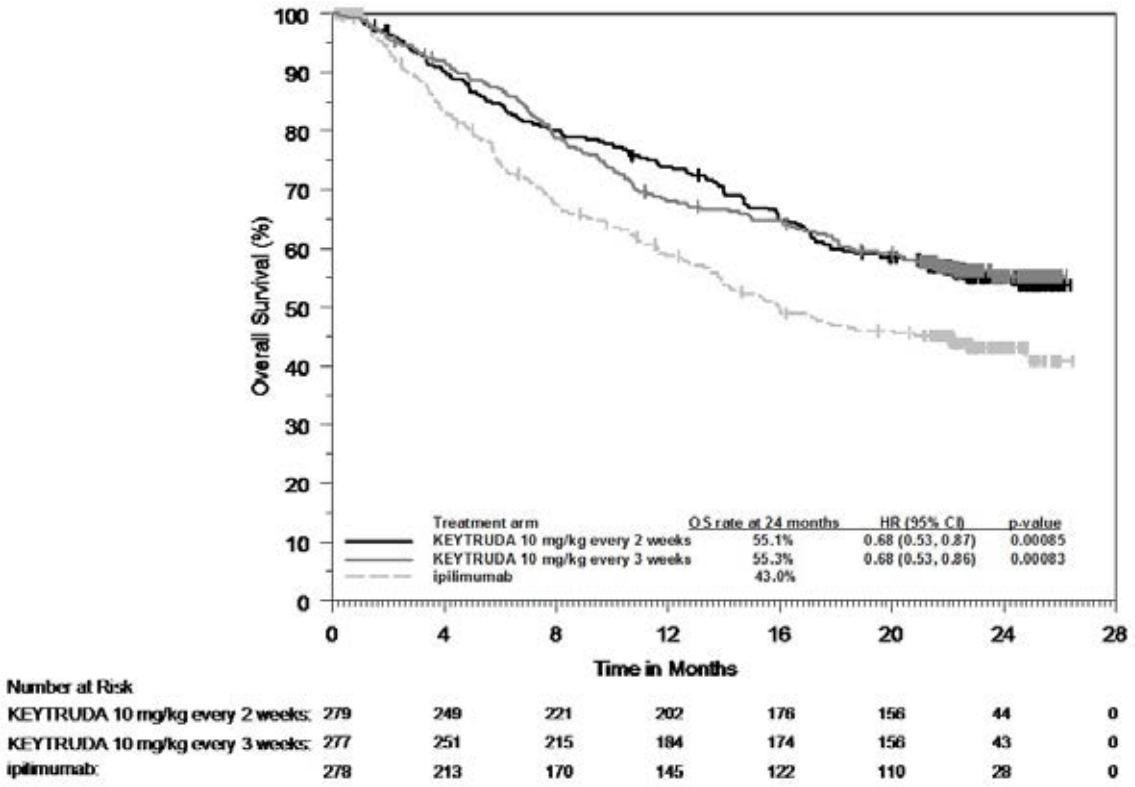
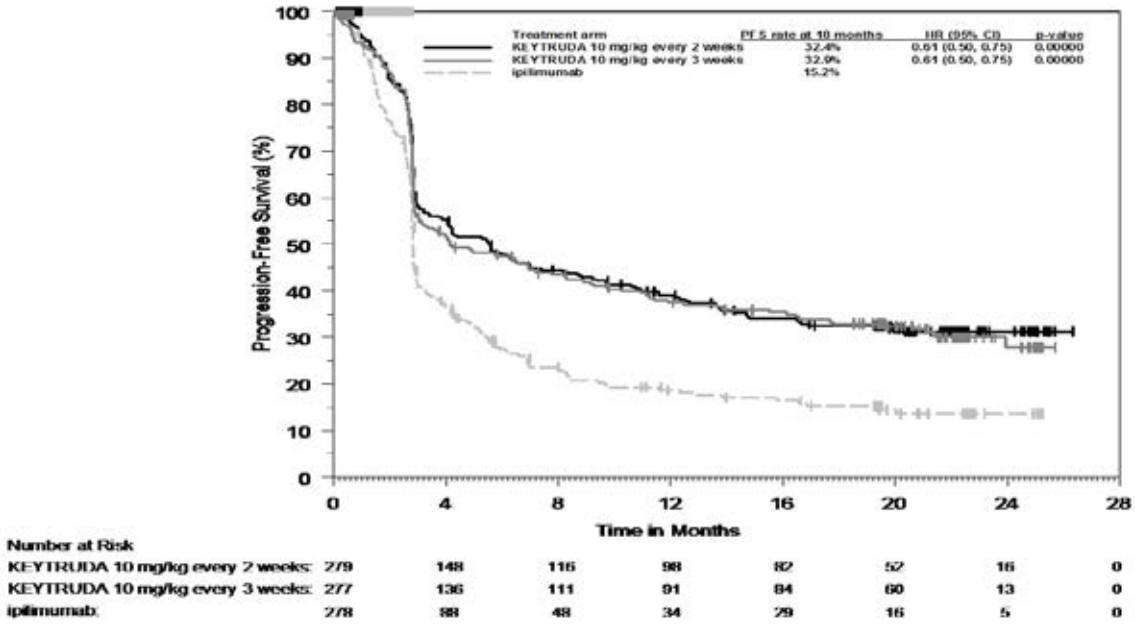


Figure 2: Kaplan-Meier curve for progression-free survival (based on IRO) by treatment arm in KEYNOTE-006 (intent to treat population)



Sub-population analysis by BRAF mutation status
A subgroup analysis was performed as part of the final analysis of KEYNOTE-006 in patients who were BRAF wild type, BRAF mutant without prior BRAF treatment and BRAF mutant with prior BRAF treatment. The PFS hazard ratios (HRs) (pooled KEYTRUDA [10 mg/kg every 2 or 3 weeks] vs. ipilimumab) were 0.61 (95% CI: 0.49, 0.76) for BRAF wild type, 0.52 (95% CI: 0.35, 0.78) for BRAF mutant without prior BRAF treatment, and 0.76 (95% CI: 0.51, 1.14) for BRAF mutant with prior BRAF treatment. The OS HRs for pooled KEYTRUDA vs. ipilimumab were 0.68 (95% CI: 0.52, 0.88) for BRAF wild type, 0.70 (95% CI: 0.40, 1.22) for BRAF mutant without prior BRAF treatment, and 0.66 (95% CI: 0.41, 1.04) for BRAF mutant with prior BRAF treatment. ORR for pooled KEYTRUDA vs. ipilimumab was 38% vs. 14% for BRAF wild type, 41% vs. 15% for BRAF mutant without prior BRAF treatment, and 24% vs. 10% for BRAF mutant with prior BRAF treatment.

Sub-population analysis by PD-L1 status
A subgroup analysis was performed as part of the final analysis of KEYNOTE-006 in patients who were PD-L1 positive vs. PD-L1 negative. The PFS HRs (pooled KEYTRUDA [10 mg/kg every 2 or 3 weeks] vs. ipilimumab) were 0.53 (95% CI: 0.44, 0.65) for PD-L1 positive patients and 0.87 (95% CI: 0.58, 1.30) for PD-L1 negative patients. The OS HRs for pooled KEYTRUDA vs. ipilimumab were 0.63 (95% CI: 0.50, 0.80) for PD-L1 positive patients and 0.76 (95% CI: 0.48, 1.19) for PD-L1 negative patients.

KEYNOTE-002: Controlled trial in melanoma patients previously treated with ipilimumab
The safety and efficacy of KEYTRUDA were investigated in KEYNOTE-002, a multicentre, controlled study for the treatment of unresectable or metastatic melanoma in patients previously treated with ipilimumab and if BRAF V600 mutation-positive, a BRAF or MEK inhibitor. Patients were randomised (1:1:1) to receive KEYTRUDA at a dose of 2 (n=180) or 10 mg/kg (n=181) every 3 weeks or chemotherapy (n=179; including dacarbazine, temozolomide, carboplatin, paclitaxel, or carboplatin+paclitaxel). The study excluded patients with autoimmune disease or those receiving immunosuppression; 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 (greater than 10 mg/day prednisone or equivalent dose) for greater than 12 weeks; previous severe hypersensitivity to other monoclonal antibodies; a history of pneumonitis or interstitial lung disease; HIV, Hepatitis B or Hepatitis C infection.

Patients were treated with KEYTRUDA until disease progression or unacceptable toxicity. Clinically stable patients with initial evidence of disease progression were permitted to remain on treatment until disease progression was confirmed. Assessment of tumour status was performed at 12 weeks, then every 6 weeks through Week 48, followed by every 12 weeks thereafter. Patients on chemotherapy who experienced independently-verified progression of disease after the first scheduled disease assessment were able to crossover and receive 2 mg/kg or 10 mg/kg of KEYTRUDA every 3 weeks in a double-blind fashion.

Of the 540 patients in KEYNOTE-002, 61% were male, 43% were ≥65 years (median age was 62 years [range 15-89]) and 98% were white. Eighty-two percent of patients had M1c stage, 73% had at least two and 32% had three or more prior systemic therapies for advanced melanoma. Forty-five percent had an ECOG PS of 1, 40% had elevated LDH and 23% had a BRAF mutated tumour. Baseline characteristics were well-balanced across treatment arms.

The primary efficacy outcome measures were PFS (as assessed by IRO review using RECIST 1.1) and overall survival (OS). Secondary efficacy outcome measures were PFS as assessed

by Investigator using RECIST 1.1, ORR and response duration. Table 25 summarises key efficacy measures in patients previously treated with ipilimumab. There was no statistically significant difference between KEYTRUDA 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 KEYTRUDA.

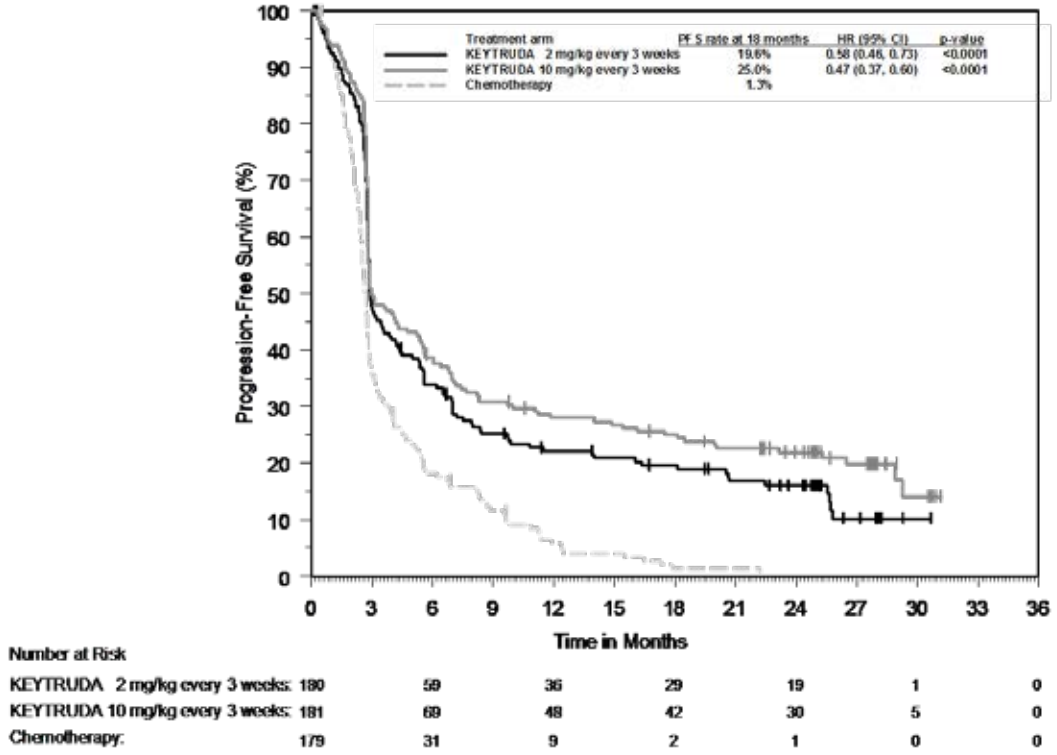
Table 25: Response to KEYTRUDA 2 mg/kg or 10 mg/kg Every 3 Weeks in patients with unresectable or metastatic melanoma in KEYNOTE-002

Endpoint	KEYTRUDA 2 mg/kg every 3 weeks n=180	KEYTRUDA 10 mg/kg every 3 weeks n=181	Chemotherapy n=179
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‡	0.117	0.011è	---
Median in months (95% CI)	13.4 (11.0, 16.4)	14.7 (11.3, 19.5)	11.0 (8.9, 13.8)
PFS§ by IRO¶			
Number (%) of patients with event	129 (72%)	126 (70%)	155 (87%)
Hazard ratio† (95% CI)	0.57 (0.45, 0.73)	0.50 (0.39, 0.64)	---
p-Value‡	<0.0001	<0.0001	---
Median in months (95% CI)	2.9 (2.8, 3.8)	2.9 (2.8, 4.7)	2.7 (2.5, 2.8)
Mean in months (95% CI)#	5.4 (4.7, 6.0)	5.8 (5.1, 6.4)	3.6 (3.2, 4.1)
PFS§ by INVÞ			
Number (%) of patients with event	122 (68%)	112 (62%)	157 (88%)
Hazard ratio† (95% CI)	0.49 (0.38, 0.62)	0.41 (0.32, 0.52)	---
p-Value‡	<0.0001	<0.0001	---
Median in months (95% CI)	3.7 (2.9, 5.4)	5.4 (3.8, 6.8)	2.6 (2.4, 2.8)
Mean in months (95% CI) #	5.8 (5.2, 6.4)	6.5 (5.8, 7.1)	3.7 (3.2, 4.1)
Best Overall Response§ by IRO¶			
ORR % (95% CI)	21% (15, 28)	25% (19, 32)	4% (2, 9)
Complete response %	2%	3%	0%
Partial response %	19%	23%	4%
Response durationß by IRO¶			
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 monthsà	73%	79%	Not reachedð

* Based on final analysis
† Hazard ratio (KEYTRUDA compared to chemotherapy) based on the stratified Cox proportional hazard model
‡ Based on stratified log-rank test
§ Based on second interim analysis
¶ IRO = Independent radiology plus oncologist review using RECIST 1.1
# Restricted mean progression free survival time based on follow up of 12 months
Þ INV = Investigator assessment using RECIST 1.1
ß Based on patients with a best overall response as confirmed complete or partial response from the final analysis
à Based on Kaplan-Meier estimates
è Not statistically significant after adjustment for multiplicity
ð The maximum follow-up for ongoing patients in the chemotherapy arm is 11.3 months; patients continue to be followed

At the final analysis, a long-term PFS analysis was performed based on 466 PFS events (150 for KEYTRUDA 2 mg/kg every 3 weeks; 144 for KEYTRUDA 10 mg/kg every 3 weeks and 172 for chemotherapy). The PFS HRs vs. chemotherapy were 0.58 (95% CI: 0.46, 0.73) for patients treated with KEYTRUDA 2 mg/kg every 3 weeks and 0.47 (95% CI: 0.37, 0.60 for patients treated with KEYTRUDA 10 mg/kg every 3 weeks (Figure 3).

Figure 3: Kaplan-Meier curve for progression free survival (based on IRO) by treatment arm in KEYNOTE-002 (intent to treat population)



KEYNOTE-001: Open label study in melanoma patients

The safety and efficacy of KEYTRUDA were also investigated in an uncontrolled, open-label study for the treatment of unresectable or metastatic melanoma. Efficacy was evaluated for 276 patients from two defined cohorts of KEYNOTE-001, one which included patients previously treated with ipilimumab (and if BRAF V600 mutation-positive, a BRAF or MEK inhibitor) and another with included patients naïve to treatment with ipilimumab. Patients were randomised to receive KEYTRUDA at a dose of 2 mg/kg every 3 weeks or 10 mg/kg every 3 weeks. The study excluded patients with autoimmune disease; medical conditions that required immunosuppression; a history of severe immune-mediated adverse reactions with ipilimumab, defined as any Grade 4 toxicity requiring treatment with corticosteroids or Grade 3 toxicity requiring corticosteroid treatment (greater than 10 mg/day prednisone or equivalent dose) for greater than 12 weeks; medical conditions that required systemic corticosteroids or other immunosuppressive medication; a history of pneumonitis or interstitial lung disease; or any active infection requiring therapy, including HIV, HBV or HCV. Patients were treated with KEYTRUDA until disease progression that was symptomatic, was rapidly progressive, required urgent intervention, or occurred with a decline in performance status, at the discretion

of the investigator, based on clinical judgment. Patients were also discontinued if disease progression was confirmed at 4 to 6 weeks with repeat imaging or unacceptable toxicity.

Of the 89 patients receiving 2 mg/kg of KEYTRUDA 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 of patients had M1c stage and 8% of patients had a history of brain metastases. Seventy-eight percent of patients 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.

Of the 51 patients receiving 2 mg/kg of KEYTRUDA 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 of patients had M1c stage and 2% had a history of brain metastases. Forty-five percent had no prior therapies for advanced melanoma. BRAF mutations were reported in 39% of the study population.

The primary efficacy outcome measure was ORR as assessed by independent review using confirmed responses and 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 26 summarises key efficacy measures in patients previously treated or naïve to treatment with ipilimumab, receiving KEYTRUDA based on a minimum follow-up time of 30 months for all patients.

Table 26: Response to KEYTRUDA 2 mg/kg every 3 Weeks in Patients with Unresectable or Metastatic Melanoma in KEYNOTE-001

Endpoint	KEYTRUDA 2 mg/kg every 3 weeks in patients previously treated with ipilimumab n=89	KEYTRUDA 2 mg/kg every 3 weeks in patients naïve to treatment with ipilimumab n=51
Best Overall Response* by IRO†		
ORR %, (95% CI)	26% (17, 36)	35% (22, 50)
Disease Control Rate %‡	48%	49%
Complete response	7%	12%
Partial response	19%	24%
Stable disease	20%	14%
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 = Independent radiology plus oncologist review using RECIST 1.1
‡ Based on best response of stable disease or better
§ Based on patients with a confirmed response by independent review, starting from the date the response was first recorded; n=23 for patients previously treated with ipilimumab; n=18 for patients naïve to treatment with ipilimumab
¶ Based on Kaplan-Meier estimation

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

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

The efficacy of KEYTRUDA was evaluated in KEYNOTE-054, a multicentre, randomised double-blind, placebo-controlled trial in patients with completely resected stage IIIA (> 1 mm lymph node metastasis), IIIB or IIIC melanoma. A total of 1019 patients were randomised (1:1) to receive KEYTRUDA 200 mg every three weeks (n=514) or placebo (n=505), for up to one year until disease recurrence or unacceptable toxicity. Randomisation was stratified by American Joint Committee on Cancer 7th edition (AJCC) stage (IIIA vs. IIIB vs. IIIC 1-3 positive lymph nodes vs. IIIC ≥4 positive lymph nodes) and geographical 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 underwent imaging every 12 weeks after the first dose of KEYTRUDA for the first two years, then every 6 months from year 3 to 5, and then annually.

Among the 1019 patients, the baseline characteristics were: median age of 54 years (25% age 65 or older); 62% male; 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; 84% had melanoma that was PD-L1 positive defined as a tumour proportion score (TPS) ≥1% according to an investigational use only assay.

The primary efficacy outcome measures were investigator-assessed recurrence free survival (RFS) in the whole population and RFS in the subgroup with PD-L1 positive tumours. 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 trial demonstrated a statistically significant improvement in RFS for patients randomised to the KEYTRUDA arm compared with placebo. Efficacy results are summarised in Table 27 and Figure 4.

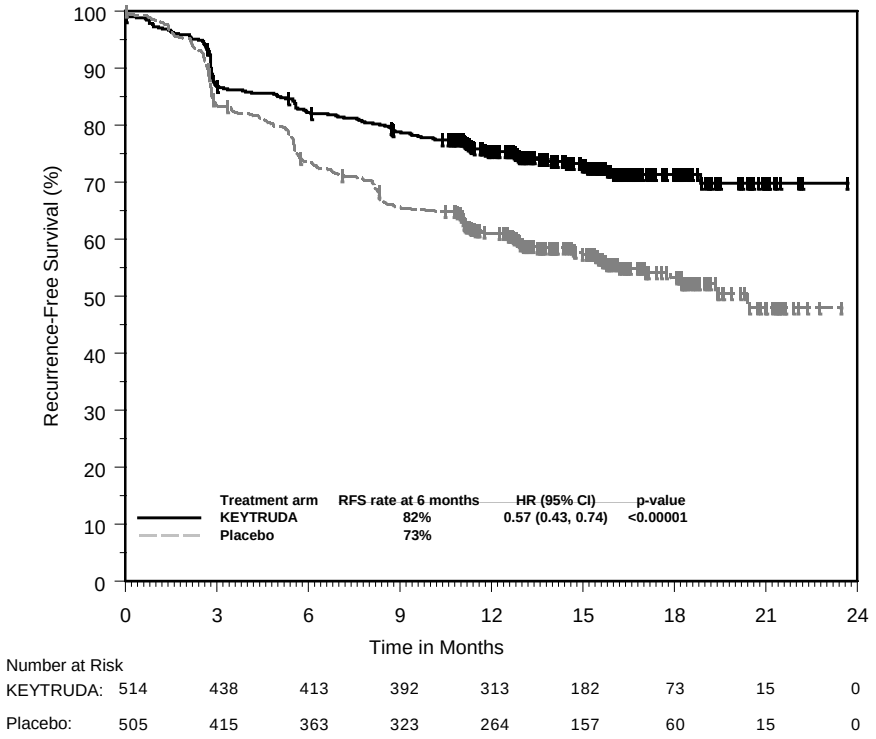
Table 27: Efficacy Results in KEYNOTE-054

Endpoint	**KEYTRUDA 200 mg every 3 weeks n=514**	**Placebo n=505**
RFS at 6 months		
Number (%) of patients with event	135 (26%)	216 (43%)
RFS rate	82%	73%
Median in months (95% CI)	NR	20.4 (16.2, NR)
Hazard ratio (HR)* (98% CI)	0.57 (0.43, 0.74)	
p-value (stratified log-rank)	<0.0001†	
RFS at 12 months		
RFS rate	75%	61%

* Based on the stratified Cox proportional hazard model
† The allocated alpha for this interim analysis was 0.008.
NR = not reached

For patients with PD-L1 positive tumours, the RFS rate at 6 months was 84% in the KEYTRUDA arm and 75% in the placebo arm (HR 0.54 (95% CI: 0.42, 0.69); p<0.0001). Predefined subgroup analyses indicated the RFS benefit with KEYTRUDA compared to placebo was also observed for patients whose tumours were PD-L1 negative (HR 0.47, 95% CI: 0.26, 0.85), BRAF mutation positive (HR 0.49, 95% CI: 0.36, 0.67) and BRAF mutation negative (HR 0.64, 95% CI: 0.47, 0.87).

Figure 4: Kaplan-Meier Curve for Recurrence-Free Survival in KEYNOTE-054 (intent to treat population)



Non-Small Cell Lung Cancer (NSCLC)

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

The efficacy of KEYTRUDA in combination with pemetrexed and platinum chemotherapy was investigated in a multicentre, randomised, active-controlled, double-blind trial, 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:

- KEYTRUDA 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 KEYTRUDA 200 mg and pemetrexed 500 mg/m^2 intravenously every 3 weeks.

- 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.

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

Among the 616 patients in KEYNOTE-189 (410 patients in the KEYTRUDA combination arm and 206 in the placebo plus chemotherapy arm), 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% with PD-L1 TPS <1% (using the PD-L1 IHC 22C3 pharmDx Kit); and 18% with treated or untreated brain metastases at baseline. A total of 67 patients in the placebo plus chemotherapy arm crossed over to receive monotherapy KEYTRUDA at the time of disease progression and 18 additional patients received a checkpoint inhibitor as subsequent therapy.

The primary efficacy outcome measures were OS and PFS (as assessed by BICR using RECIST 1.1). Secondary efficacy outcome measures were ORR and response duration, as assessed by BICR using RECIST 1.1. The median follow-up time was 10.5 months (range: 0.2 – 20.4 months). Table 28 summarises key efficacy measures.

Table 28: Response to KEYTRUDA, pemetrexed, and platinum chemotherapy in patients with non-squamous NSCLC in KEYNOTE-189

Endpoint	KEYTRUDA + Pemetrexed + Platinum Chemotherapy n=410	Placebo + Pemetrexed + Platinum Chemotherapy n=206
OS		
Number (%) of patients with event	127 (31%)	108 (52%)
Hazard ratio* (95% CI)	0.49 (0.38, 0.64)	
p-Value†	<0.00001	
Median in months (95% CI)	Not reached (NA, NA)	11.3 (8.7, 15.1)
PFS		
Number (%) of patients with event	245 (60%)	166 (81%)
Hazard ratio* (95% CI)	0.52 (0.43, 0.64)	
p-Value†	<0.00001	
Median in months (95% CI)	8.8 (7.6, 9.2)	4.9 (4.7, 5.5)
Objective Response Rate		
ORR‡ % (95% CI)	48% (43, 53)	19% (14, 25)
Complete response %	0.5%	0.5%
Partial response %	47%	18%
p-Value§	<0.0001	
Response duration		
Median in months (range)	11.2 (1.1+, 18.0+)	7.8 (2.1+, 16.4+)
% with duration ≥6 months¶	81%	63%
% with duration ≥9 months¶	59%	44%

* Based on the stratified Cox proportional hazard model
† Based on stratified log-rank test
‡ Based on patients with a best overall 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
NA = not available

The final OS analysis was performed at a median duration of follow-up of 18.8 months after 421 patient events (258 for KEYTRUDA combination arm and 163 for the placebo plus chemotherapy arm). Median OS was 22.0 months (95% CI: 19.5, 24.5) for the KEYTRUDA combination arm and 10.6 months (95% CI: 8.7, 13.6) for the placebo plus chemotherapy arm. The OS HR was 0.56 (95% CI: 0.46, 0.69; p<0.00001). At final analysis, a PFS analysis was performed based on 534 patient events (337 for the KEYTRUDA combination arm and 197 for the placebo plus chemotherapy arm). The median PFS was 9.0 months (95% CI: 8.1, 10.4) for the KEYTRUDA combination arm and 4.9 months (95% CI: 4.7, 5.5) for the placebo plus chemotherapy arm. The PFS HR was 0.49 (95% CI: 0.41, 0.59, p<0.00001). See Figures 5 and 6.

The ORR at the final analysis was 48% for the KEYTRUDA combination arm and 20% for the placebo plus chemotherapy arm. The median duration of response was 12.5 months (range 1.1+, 34.9+) for the KEYTRUDA combination arm and 7.1 months (range 2.4, 27.8+) for the

placebo plus chemotherapy arm. The percentage of patients with ongoing responses based on Kaplan-Meier estimation was 53% at 12 months or longer, in patients who received KEYTRUDA combination therapy, vs. 27% in patients who received placebo plus chemotherapy.

Figure 5: Kaplan-Meier Curve for overall survival by treatment arm in KEYNOTE-189 (intent to treat population)

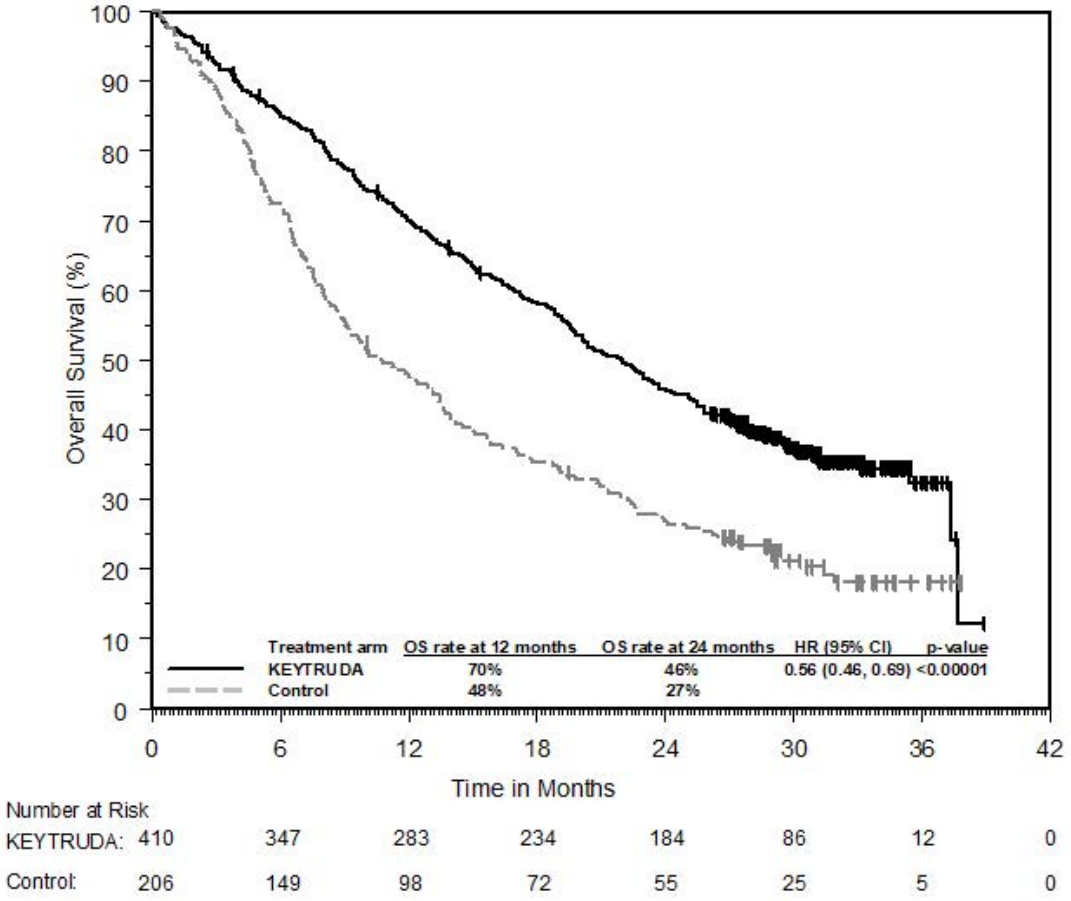
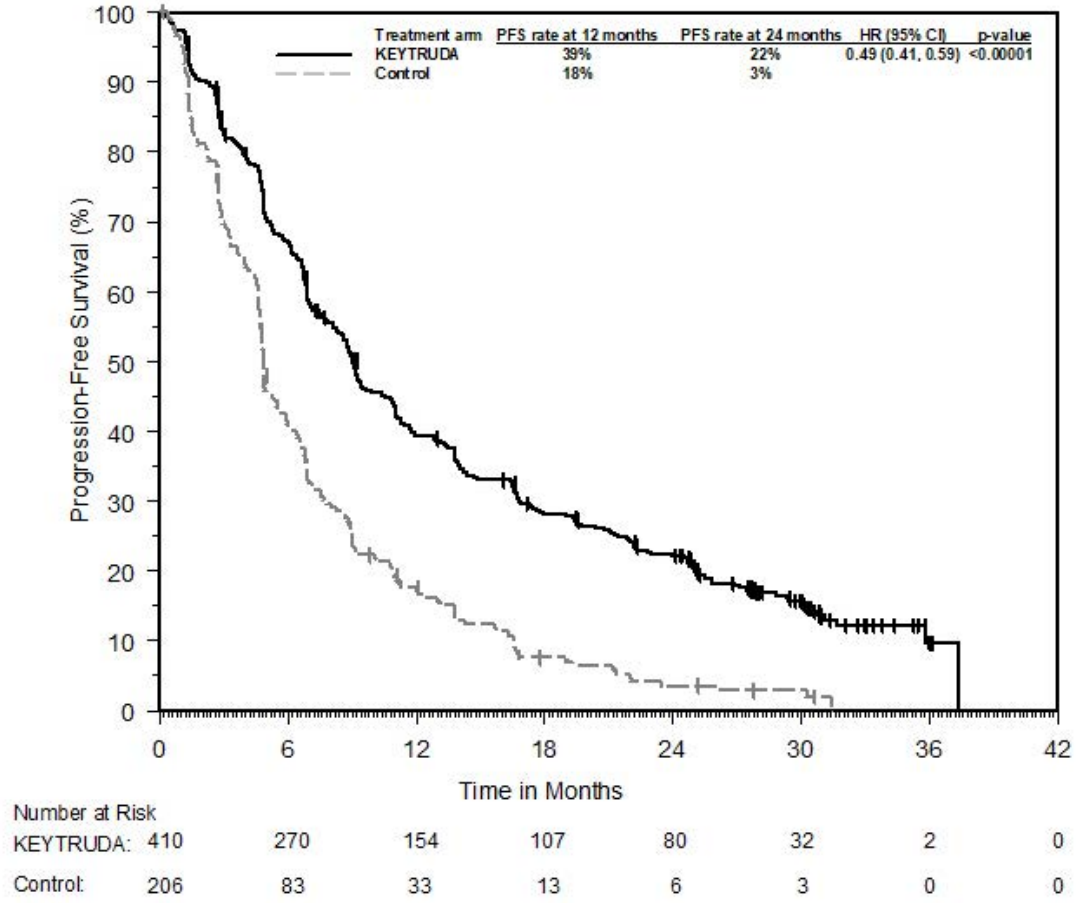


Figure 6: Kaplan-Meier curve for progression-free survival by treatment arm in KEYNOTE-189 (intent to treat population)



Patient-reported outcomes were assessed using the EORTC QLQ-C30 and EORTC QLQ-LC13. Exploratory analyses of patients receiving pembrolizumab combination therapy showed stable EORTC QLQ-C30 Global Health Status/QoL at Week 12 and Week 21 vs declines in patients receiving placebo plus chemotherapy. There was a trend toward a prolonged time to deterioration in the EORTC QLQ-LC13/QLQ-C30 endpoint of cough, dyspnoea or chest pain observed for patients receiving pembrolizumab combination therapy.

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

The efficacy of KEYTRUDA 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; all study medications were administered via intravenous infusion.

- KEYTRUDA 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 KEYTRUDA 200 mg every 3 weeks. KEYTRUDA 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 KEYTRUDA or placebo continued until RECIST 1.1-defined progression of disease as determined by blinded independent central review (BICR), unacceptable toxicity, or a maximum of 24 months. Administration of KEYTRUDA was permitted beyond RECIST-defined disease progression if the patient was clinically stable and deriving clinical benefit as determined by the investigator. Treatment with KEYTRUDA could be reinitiated for subsequent disease progression and administered for up to 1 additional year.

Patients in the placebo arm were offered KEYTRUDA as a monotherapy 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. The major efficacy outcome measures were progression-free survival and objective response rate (ORR) as assessed by BICR using RECIST 1.1 and overall survival. An additional efficacy outcome measure was duration of response as assessed by BICR using RECIST 1.1.

A total of 559 patients were randomised: 278 patients to the KEYTRUDA arm and 281 to the placebo arm. 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 brain metastases at baseline. Thirty-five percent had tumour PD-L1 expression TPS <1% [negative]; 19% were from the East Asian region; and 60% received paclitaxel.

In KEYNOTE-407, there was a statistically significant improvement in OS, PFS and ORR in patients randomised to KEYTRUDA in combination with carboplatin and either paclitaxel or nab-paclitaxel compared with patients randomised to placebo with carboplatin and either paclitaxel or nab-paclitaxel (see Table 29).

Table 29: Efficacy Results in KEYNOTE-407

Endpoint	KEYTRUDA Carboplatin Paclitaxel/Nab-paclitaxel n=278	Placebo Carboplatin Paclitaxel/Nab-paclitaxel n=281
OS		
Number of events (%)	85 (31%)	120 (43%)
Median in months (95% CI)	15.9 (13.2, NA)	11.3 (9.5, 14.8)
Hazard ratio* (95% CI)	0.64 (0.49, 0.85)	
p-Value (stratified log-rank)	0.0008	
PFS		
Number of events (%)	152 (55%)	197 (70%)
Median in months (95% CI)	6.4 (6.2, 8.3)	4.8 (4.2, 5.7)
Hazard ratio* (95% CI)	0.56 (0.45, 0.70)	
p-Value(stratified log-rank)	<0.0001	
Overall Response Rate		
Overall response rate†	58%	38%
(95% CI)	(52, 64)	(33, 44)
Duration of Response		
Median duration of response in months (range)	7.7 (1.1+, 14.7+)	4.8 (1.3+, 15.8+)
% with duration ≥ 6 months‡	62%	40%

* Based on the stratified Cox proportional hazard model

† At the initial interim analysis (n=101 for KEYTRUDA combination therapy, n=102 for placebo), a statistically significant difference was observed; ORR was 58% [95% CI (48, 64)] and 35% [95% CI (26, 45)] for placebo, p=0.0004

‡ Based on Kaplan-Meier estimation

NA = not available

The final OS analysis was performed at a median duration of follow-up of 14.3 months after 365 patient events (168 for KEYTRUDA combination arm and 197 for placebo plus chemotherapy arm). Median OS was 17.1 months (95% CI: 14.4, 19.9) for the KEYTRUDA combination arm and 11.6 months (95% CI: 10.1, 13.7) for the placebo plus chemotherapy arm. The OS HR was 0.71 (95% CI: 0.58, 0.88; p=0.0006). At final analysis, a PFS analysis was performed based on 469 patient events (217 for the KEYTRUDA combination arm and 252 for the placebo plus chemotherapy arm). The median PFS was 8.0 months (95% CI: 6.3, 8.4) for the KEYTRUDA combination arm and 5.1 months (95% CI: 4.3, 6.0) for the placebo plus chemotherapy arm. The PFS HR was 0.57 (95% CI: 0.47, 0.69, p<0.0001). See Figures 7 and 8.

The ORR at the final analysis was 63% for the KEYTRUDA combination arm and 38% for the placebo plus chemotherapy arm. The median duration of response was 8.8 months (range 1.3+, 28.4+) for the KEYTRUDA combination arm and 4.9 months (range 1.3+, 28.3+) for the placebo plus chemotherapy arm. The percentage of patients with ongoing responses based on Kaplan-Meier estimation were 64% and 38% at 6 and 12 months or longer, in patients who received KEYTRUDA combination therapy, vs. 44% and 25% in patients who received placebo plus chemotherapy.

Figure 7: Kaplan-Meier Curve for Overall Survival in KEYNOTE-407

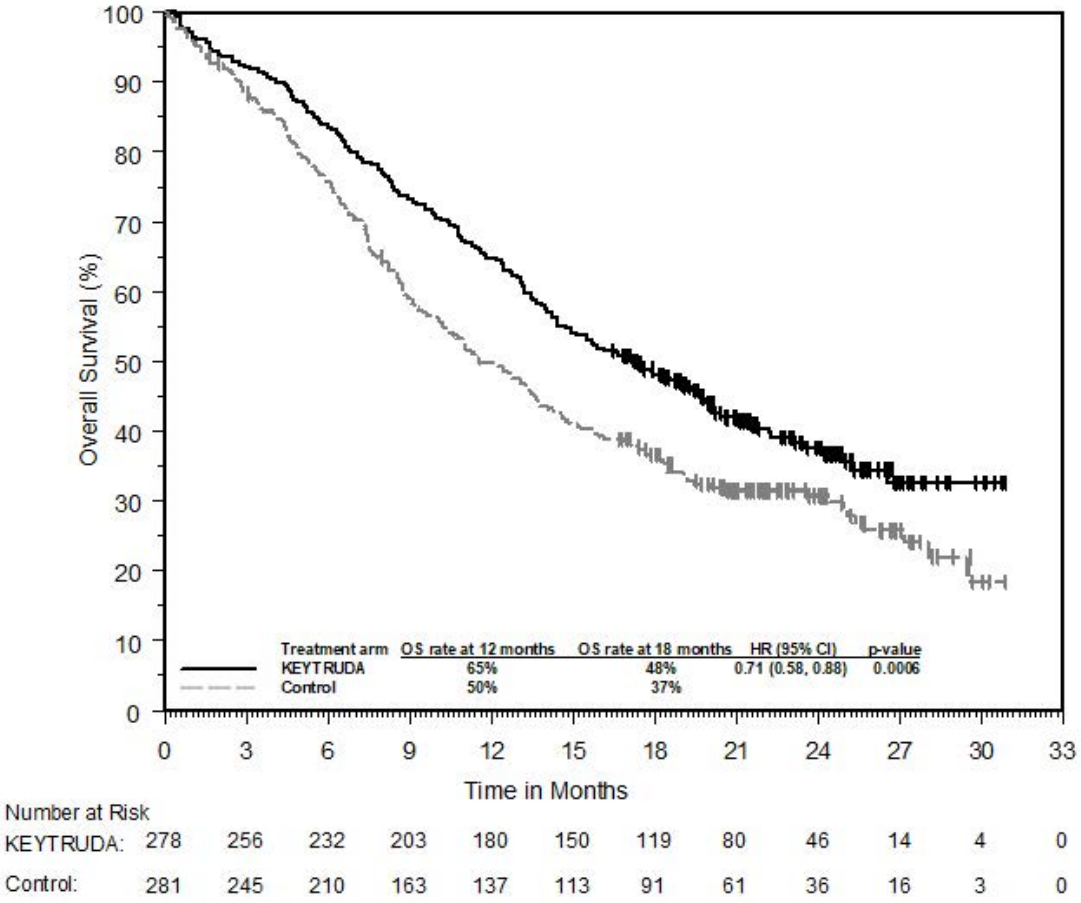
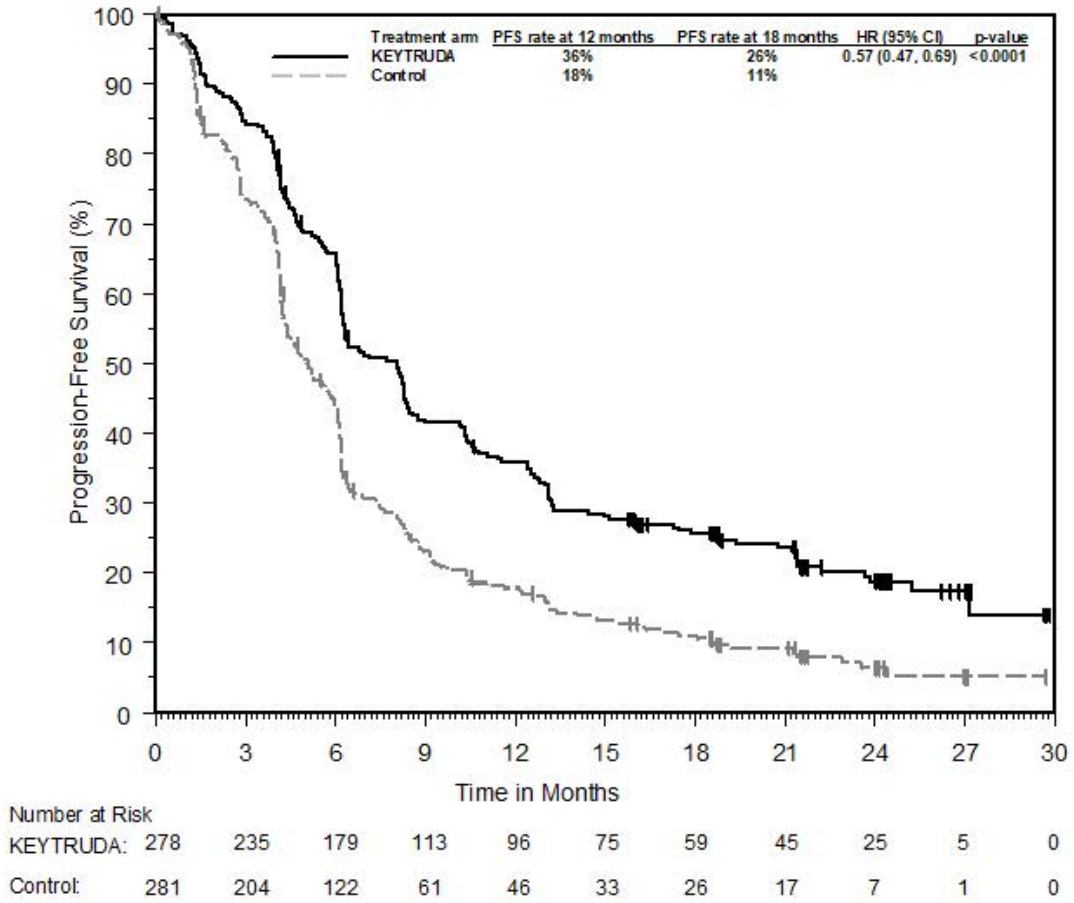


Figure 8: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-407



KEYNOTE-042: Controlled trial of NSCLC patients naïve to treatment
The efficacy of KEYTRUDA was investigated in KEYNOTE-042, a multicentre, randomised, controlled trial conducted in 1274 patients with stage III NSCLC who were not candidates for surgical resection or definitive chemoradiation, or patients with metastatic NSCLC. Only patients whose tumours expressed PD-L1 (TPS ≥ 1%) by an immunohistochemistry assay using the PD-L1 IHC 22C3 pharmDx kit and who had not received prior systemic treatment for metastatic NSCLC were eligible. 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 were ineligible. Patients were randomised (1:1) to receive KEYTRUDA 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). Patients were treated with KEYTRUDA 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. Treatment with KEYTRUDA could be reinitiated for subsequent disease progression and administered for up to 1 additional year. Assessment of tumour status was performed every 9 weeks for the first 45 weeks, and every 12 weeks thereafter.

Among the 1274 patients in KEYNOTE-042, baseline characteristics were: median age 63 years (45% age 65 or older); 71% male; 64% White and 30% Asian: 19% Hispanic or

Latino; and 31% and 69% with an ECOG performance status 0 and 1, respectively. Disease characteristics were squamous (39%) and non-squamous (61%); M0 (13%), M1 (87%); and treated brain metastases (6%). Forty-seven percent of patients had TPS ≥50%, and 53% had TPS 1 to 49%.

The primary efficacy outcome measure was OS. Secondary efficacy outcome measures were PFS and ORR as assessed by blinded independent central review (BICR) using RECIST 1.1. Table 30 summarises key efficacy measures for the subgroup of patients with TPS ≥ 50% and the entire ITT population (TPS ≥ 1%).

Table 30: Efficacy results of All Randomised Patients (PD-L1 TPS ≥1% and TPS ≥50%) in KEYNOTE-042

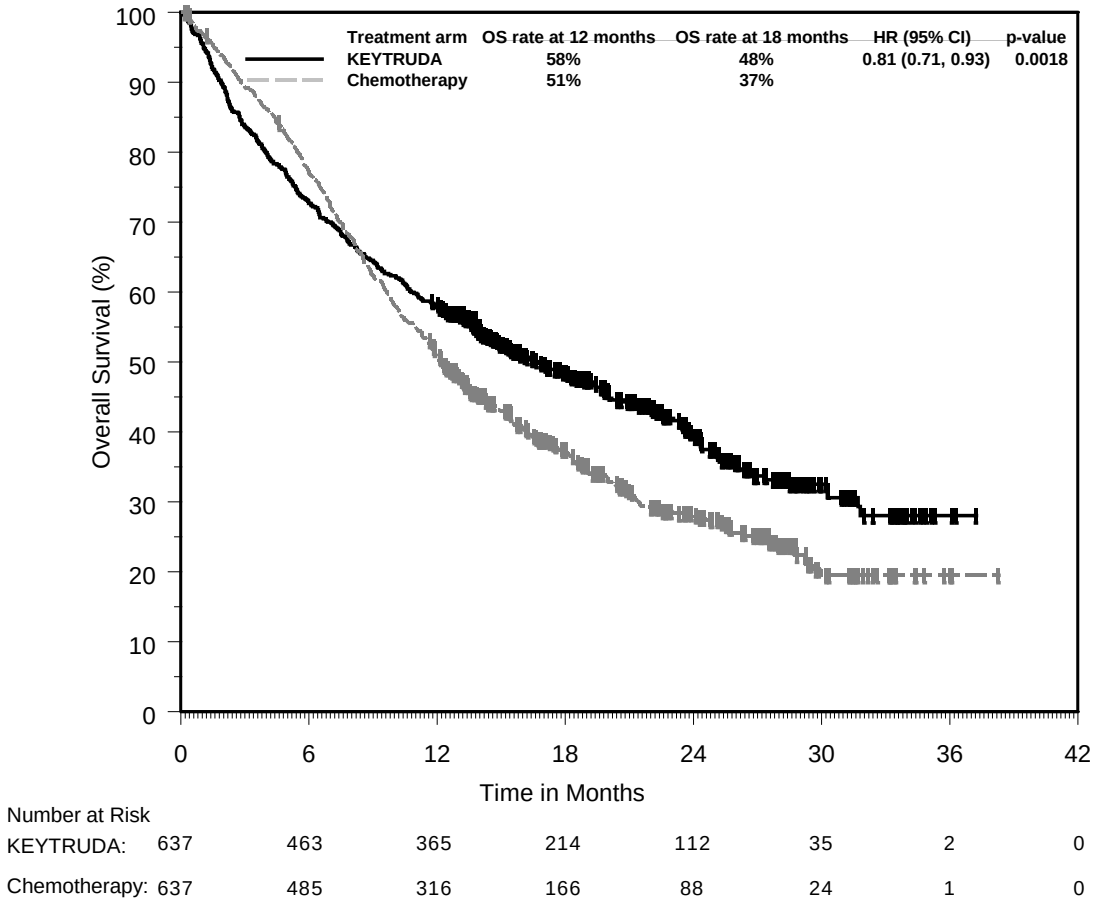
	TPS ≥1%		**TPS ≥50%**	
Endpoint	**KEYTRUDA 200 mg every 3 weeks (n=637)**	**Chemotherapy (n=637)**	**KEYTRUDA 200 mg every 3 weeks (n=299)**	**Chemotherapy (n=300)**
OS				
Number (%) of patients with event	371 (58%)	438 (69%)	157 (53%)	199 (66%)
Hazard ratio* (95% CI)	0.81 (0.71, 0.93)		0.69 (0.56, 0.85)	
p-Value†	0.002		0.0003	
Median in months (95% CI)	16.7 (13.9, 19.7)	12.1 (11.3, 13.3)	20.0 (15.4, 24.9)	12.2 (10.4, 14.2)
PFS‡				
Number (%) of patients with event	507 (80%)	506 (79%)	221 (74%)	233 (78%)
Hazard ratio*,§ (95% CI)	1.07 (0.94, 1.21)		0.82 (0.68, 0.99)	
Median in months (95% CI)	5.4 (4.3, 6.2)	6.5 (6.3, 7.0)	6.9 (5.9, 9.0)	6.4 (6.1, 6.9)
Overall response rate‡				
ORR %§ (95% CI)	27% (24, 31)	27% (23, 30)	39% (34, 45)	32% (27, 38)
Complete response %	1%	1%	1%	0.3%
Partial response %	27%	26%	39%	32%
Response duration‡,¶				
Median in months (range)	20.2 (2.1+, 31.2+)	8.3 (1.8+, 28.1)	22.0 (2.1+, 36.5+)	10.8 (1.8+, 30.4+)
% with duration ≥ 18 months	53%	30%	57%	34%

* Hazard ratio (KEYTRUDA compared to chemotherapy) based on the stratified Cox proportional hazard model
† Based on stratified log-rank test
‡ Assessed by BICR using RECIST 1.1
§ Not evaluated for statistical significance as a result of the sequential testing procedure for the secondary endpoints.
¶ Based on patients with a best overall response as confirmed complete or partial response; based on Kaplan-Meier estimates

The results of all efficacy outcome measures in the subgroup of patients with PD-L1 TPS

≥20% NSCLC were intermediate between the results of those with PD-L1 TPS ≥1% and those with PD-L1 TPS ≥50%. In a pre-specified exploratory subgroup analysis for patients with TPS 1-49% NSCLC, the median OS was 13.4 months (95% CI: 10.7, 18.2) for the pembrolizumab group and 12.1 months (95% CI: 11.0, 14.0) in the chemotherapy group, with an HR of 0.92 (95% CI: 0.77, 1.11).

Figure 9: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-042 (TPS ≥ 1%, Intent-to-Treat Population)



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

The efficacy of KEYTRUDA in previously untreated patients with NSCLC was also investigated in KEYNOTE-024, a multicentre, randomised, controlled trial. The study design was similar to that of KEYNOTE-042, except that only patients with metastatic NSCLC whose tumours expressed PD-L1 with TPS of 50% or greater by an immunohistochemistry assay using the PD-L1 IHC 22C3 pharmDx Kit were eligible. Patients with treated brain metastases were eligible if neurologically returned to baseline prior to enrolment and off corticosteroids. Patients were randomised (1:1) to receive KEYTRUDA 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 on chemotherapy who experienced independently-verified progression of disease were able to crossover and receive KEYTRUDA. Assessment of tumour status was performed every 9 weeks.

Among the 305 patients in KEYNOTE-024, baseline characteristics were: median age 65 years (54% age 65 or older); 61% male; 82% White and 15% Asian; and 35% and 65% with an ECOG performance status 0 and 1, respectively. Subjects with ECOG performance status > 1 and subjects with significant organ dysfunction were ineligible. 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 31 summarises key efficacy measures for the entire ITT population.

Table 31: Efficacy Results in KEYNOTE-024

Endpoint	**KEYTRUDA 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	44 (29%)	64 (42%)
Hazard ratio† (95% CI)	0.60 (0.41, 0.89)	
p-Value‡	0.005	
Median in months (95% CI)	Not reached (NA, NA)	Not reached (9.4, NA)
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%

* Assessed by BICR using RECIST 1.1
† Hazard ratio (KEYTRUDA compared to chemotherapy) based on the stratified Cox proportional hazard model
‡ Based on stratified log-rank test
§ Based on patients with a best overall response as confirmed complete or partial response
¶ Based on Kaplan-Meier estimates
NA = not available

The final OS analysis was performed at a median follow-up of 25 months after 169 patient events (73 for KEYTRUDA and 96 for chemotherapy). Median OS was 30.0 months (95% CI: 18.3, NA) for KEYTRUDA and 14.2 months (95% CI: 9.8, 19.0) for chemotherapy. The OS HR was 0.63 (95% CI: 0.47, 0.86; p=0.002). See Figure 11.

Figure 10: Kaplan-Meier Progression-Free Survival by Treatment Arm in KEYNOTE-024 (Intent to Treat Population)

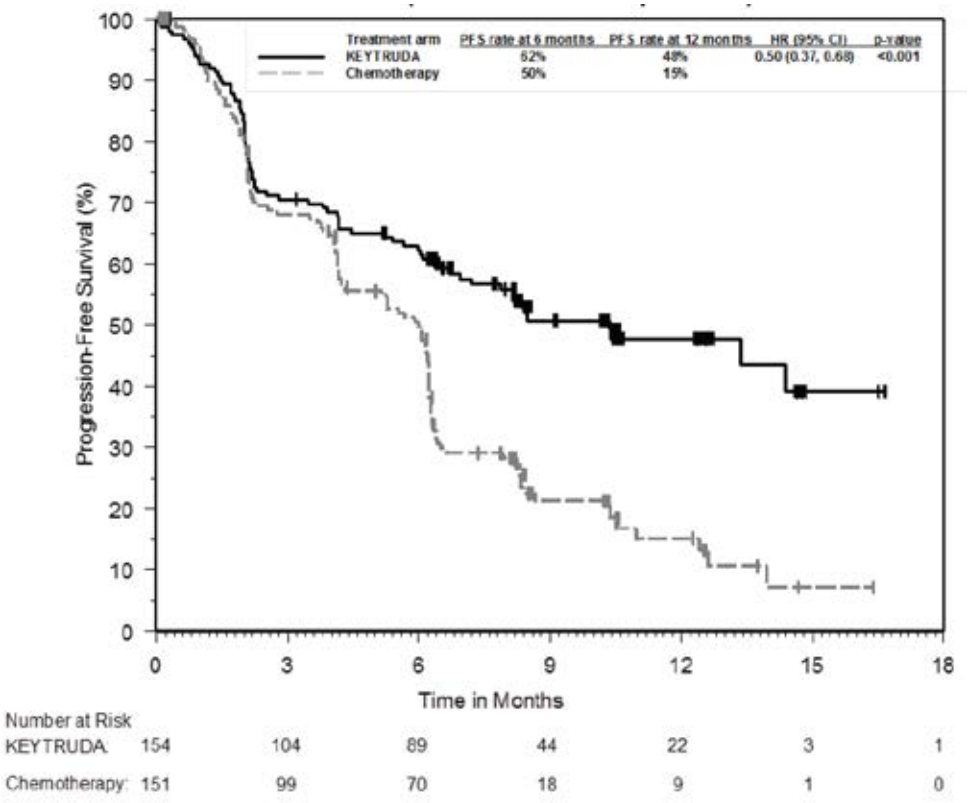
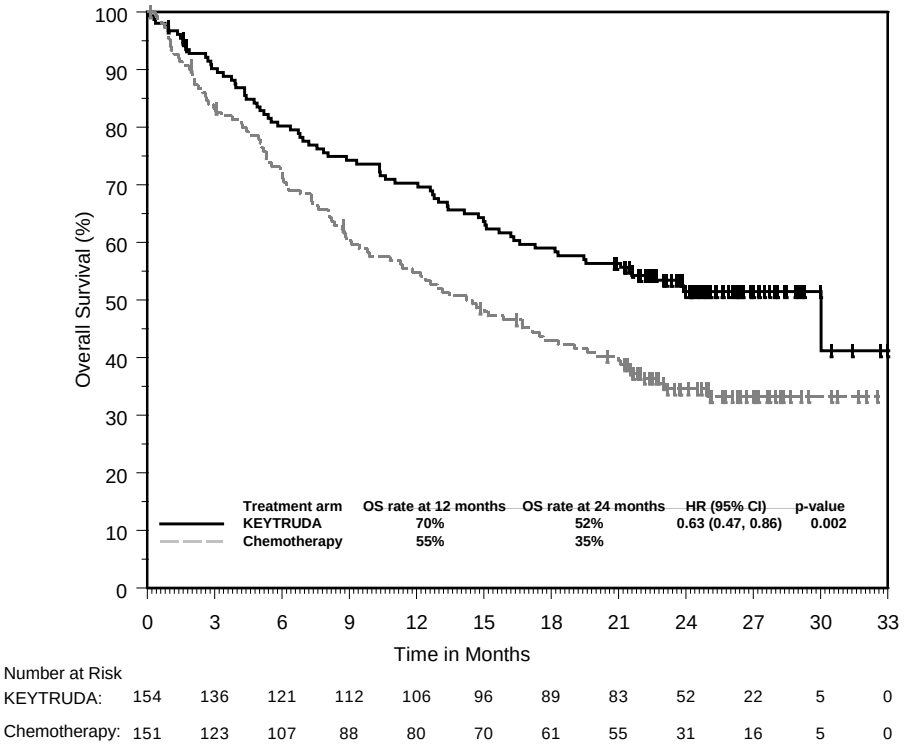


Figure 11: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-024 (Intent to Treat Population)



The improved benefit as assessed by PFS, OS, ORR, and response duration for KEYTRUDA as compared to chemotherapy in the population studied was associated with improvements in health-related quality of life (HRQoL). The change from baseline to Week 15 showed a meaningful improvement in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) C30 global health status/QoL score for patients receiving KEYTRUDA compared to chemotherapy (difference in LS means = 7.82; 95% CI: 2.85, 12.79; two-sided p=0.002). The time to deterioration in the EORTC QLQ-LC13 composite endpoint of cough, dyspnoea, and chest pain was prolonged for patients receiving KEYTRUDA compared to chemotherapy (HR = 0.66; 95% CI: 0.44, 0.97; two-sided p=0.029), where deterioration is defined as a confirmed 10-point or greater score decrease from baseline in any one of these three symptoms.

KEYNOTE-010: Controlled trial of NSCLC patients previously treated with chemotherapy

The efficacy of KEYTRUDA was investigated in KEYNOTE-010, a multicentre, randomised, controlled trial. Key eligibility criteria were advanced NSCLC that had progressed following platinum-containing chemotherapy, and if appropriate, targeted therapy for ALK or EGFR mutations, and PD-L1 expression TPS of 1% or greater by a clinical trial assay version of the PD-L1 IHC 22C3 pharmDx™ kit. Patients with autoimmune disease; a medical condition that required immunosuppression; who had received more than 30 Gy of thoracic radiation within the prior 26 weeks; or with untreated brain metastases were ineligible. Patients with treated brain metastases were eligible if neurologically returned to baseline prior to enrolment and off corticosteroids. Patients were randomised (1:1:1) to receive 2 mg/kg (n=344) or 10 mg/kg (n=346) of KEYTRUDA every 3 weeks or 75 mg/m2 of docetaxel every 3 weeks (n=343). Patients were treated with KEYTRUDA until unacceptable toxicity or disease progression, up to a maximum of 35 treatments (24 months). Assessment of tumour status was performed

every 9 weeks.

Among the 1033 patients in KEYNOTE-010, baseline characteristics were: 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%); M1 (91%); brain metastases (15%); and the incidence of genomic aberrations was EGFR (8%) or ALK (1%). Prior therapy included platinum-doublet regimen (100%); patients received one (69%), or two or more (29%) prior therapies.

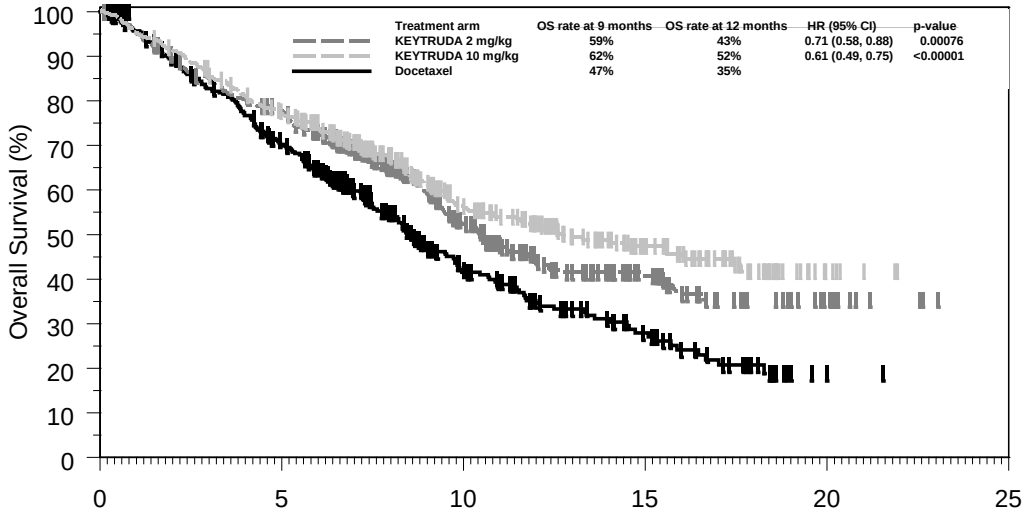
The primary efficacy outcome measures were OS and PFS as assessed by an independent review committee using RECIST 1.1. Secondary efficacy outcome measures were ORR and response duration. Table 32 summarises key efficacy measures for the entire ITT population (TPS ≥1%) and for the subgroup of patients with TPS ≥50%. Kaplan-Meier curves for OS (TPS ≥1% and TPS ≥50%) are shown in Figures 12 and 13.

Table 32: Response to KEYTRUDA 2 or 10 mg/kg Every 3 Weeks in Previously Treated Patients with NSCLC in KEYNOTE-010

Endpoint	KEYTRUDA 2 mg/kg every 3 weeks	KEYTRUDA 10 mg/kg every 3 weeks	Docetaxel 75 mg/m^2 every 3 weeks
TPS ≥1%			
Number of patients	344	346	343
OS			
Number (%) of patients with event	172 (50%)	156 (45%)	193 (56%)
Hazard ratio* (95% CI)	0.71 (0.58, 0.88)	0.61 (0.49, 0.75)	---
p-Value†	<0.001	<0.001	---
Median in months (95% CI)	10.4 (9.4, 11.9)	12.7 (10.0, 17.3)	8.5 (7.5, 9.8)
PFS‡			
Number (%) of patients with event	266 (77%)	255 (74%)	257 (75%)
Hazard ratio* (95% CI)	0.88 (0.73, 1.04)	0.79 (0.66, 0.94)	---
p-Value†	0.068	0.005	---
Median in months (95% CI)	3.9 (3.1, 4.1)	4.0 (2.6, 4.3)	4.0 (3.1, 4.2)
Overall response rate‡			
ORR %§ (95% CI)	18% (14, 23)	18% (15, 23)	9% (7, 13)
Response duration‡,¶,#			
Median in months (range)	Not reached (0.7+, 20.1+)	Not reached (2.1+, 17.8+)	6.2 (1.4+, 8.8+)
% ongoing	73%	72%	34%
TPS ≥50%			
Number of patients	139	151	152
OS			
Number (%) of patients with event	58 (42%)	60 (40%)	86 (57%)
Hazard ratio* (95% CI)	0.54 (0.38, 0.77)	0.50 (0.36, 0.70)	---
p-Value†	<0.001	<0.001	---
Median in months (95% CI)	14.9 (10.4, NA)	17.3 (11.8, NA)	8.2 (6.4, 10.7)
PFS‡			
Number (%) of patients with event	89 (64%)	97 (64%)	118 (78%)
Hazard ratio* (95% CI)	0.58 (0.43, 0.77)	0.59 (0.45, 0.78)	---
p-Value†	<0.001	<0.001	---
Median in months (95% CI)	5.2 (4.0, 6.5)	5.2 (4.1, 8.1)	4.1 (3.6, 4.3)
Overall response rate‡			
ORR %§ (95% CI)	30% (23, 39)	29% (22, 37)	8% (4, 13)
Response duration‡,¶,Þ			
Median in months (range)	Not reached (0.7+, 16.8+)	Not reached (2.1+, 17.8+)	8.1 (2.1+, 8.8+)
% ongoing	76%	75%	33%

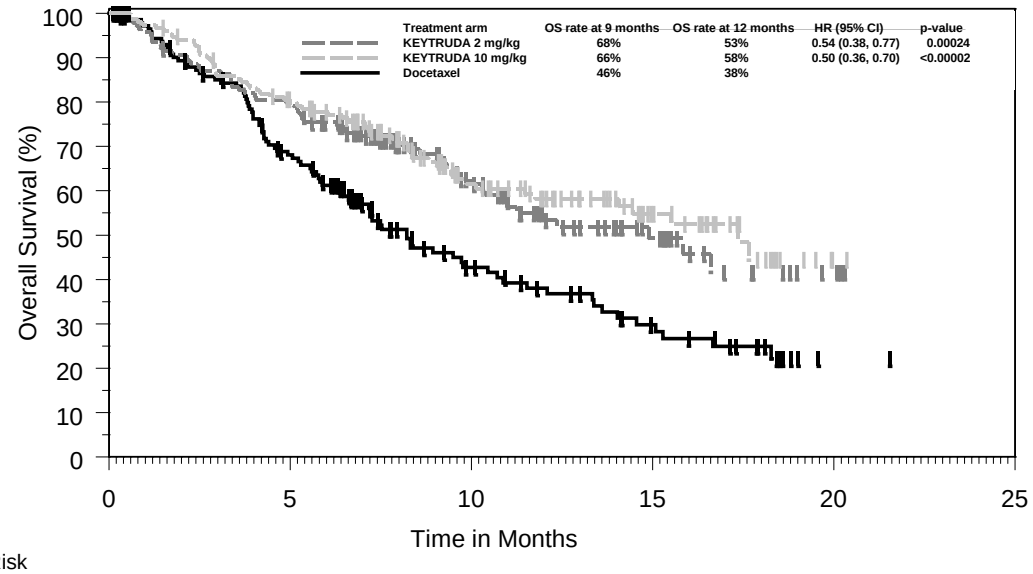
* Hazard ratio (KEYTRUDA compared to docetaxel) based on the stratified Cox proportional hazard model
† Based on stratified log-rank test
‡ Assessed by BICR using RECIST 1.1
§ All responses were partial responses
¶ Based on patients with a best overall response as confirmed complete or partial response
# Includes 30, 31, and 2 patients with ongoing responses of 6 months or longer in the KEYTRUDA 2 mg/kg, KEYTRUDA 10 mg/kg, and docetaxel groups respectively
Þ Includes 22, 24, and 1 patients with ongoing responses of 6 months or longer in the KEYTRUDA 2 mg/kg, KEYTRUDA 10 mg/kg, and docetaxel groups respectively

Figure 12: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-010 (TPS ≥ 1%, Intent to Treat Population)



Number at Risk						
KEYTRUDA 2 mg/kg:	344	259	115	49	12	0
KEYTRUDA 10 mg/kg:	346	255	124	56	6	0
Docetaxel:	343	212	79	33	1	0

Figure 13: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-010 (TPS ≥ 50%, Intent to Treat Population)



Number at Risk						
KEYTRUDA 2 mg/kg:	139	110	51	20	3	0
KEYTRUDA 10 mg/kg:	151	115	60	25	1	0
Docetaxel:	152	90	38	19	1	0

Efficacy results were similar for the 2 mg/kg and 10 mg/kg KEYTRUDA arms. Efficacy results

for OS were consistent regardless of the age of tumour specimen (new versus archival).

Sub-population analysis of patients with 1% ≤ TPS ≤ 49% in KEYNOTE-010
A subgroup analysis of KEYNOTE 010 in patients with TPS 1-49% was performed. The OS HRs for KEYTRUDA vs. docetaxel were 0.79 (95% CI: 0.61,1.04) for patients treated with 2 mg/kg every three weeks and 0.71 (95% CI: 0.53, 0.94) for patients treated with 10 mg/kg every 3 weeks. The median OS was 9.4 months (95% CI: 8.7, 10.5), 10.8 months (95% CI: 8.9, 13.3) and 8.6 months (95% CI: 7.8, 9.9) for patients treated with KEYTRUDA 2 mg/kg every three weeks (n=205), 10 mg/kg every three weeks (n=195) and docetaxel (n=191) respectively. The PFS HRs (KEYTRUDA vs. docetaxel) were 1.07 (95% CI: 0.85, 1.34) for patients treated with 2 mg/kg every three weeks and 0.99 (95% CI: 0.78, 1.25) for patients treated with 10 mg/kg every 3 weeks. The median PFS was 3.1 months (95% CI: 2.1, 3.8), 2.3 months (95% CI: 2.1, 4.0) and 3.9 months (95% CI: 2.5, 4.3) for KEYTRUDA 2 mg/kg every three weeks, 10 mg/kg every three weeks and docetaxel respectively. The ORR was 10% (95% CI: 6, 15), 10% (95% CI: 6, 15) and 10% (95% CI: 7, 16) for KEYTRUDA 2 mg/kg every three weeks, 10 mg/kg every three weeks and docetaxel respectively. Furthermore, the median duration of response was 10.6 months (range: 2.1+, 20.1+), 10.4 months (range: 3.0+, 17.1+) and 6.0 months (range: 1.4+, 7.2) for KEYTRUDA 2 mg/kg every three weeks, 10 mg/kg every three weeks and docetaxel respectively.

Head and Neck Cancer

KEYNOTE-048: Controlled trial of first-line monotherapy or combination therapy in HNSCC
The efficacy of KEYTRUDA was investigated in Study KEYNOTE-048, a multicentre, randomised, open-label, active-controlled study in patients with metastatic or recurrent HNSCC who had not previously received systemic therapy for recurrent or metastatic disease and who were considered incurable by local therapies. Patients with active autoimmune disease that required systemic therapy within two years of treatment or a medical condition that required immunosuppression were ineligible for the study. Patients with nasopharyngeal tumours were excluded. Randomisation was stratified by tumour PD-L1 expression (TPS≥50% or <50%) based on the PD-L1 IHC 22C3 pharmDx™ kit, HPV status (positive or negative), and ECOG PS (0 vs. 1). A prospective classification of patients' tumour PD-L1 status according to CPS using the PD-L1 IHC 22C3 pharmDx™ kit was conducted using the tumour specimens used for randomisation. Patients were randomised 1:1:1 to one of the following treatment arms:

- KEYTRUDA 200 mg every 3 weeks
- KEYTRUDA 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 1000 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 1000 mg/m^2/d 4 days continuous every 3 weeks (maximum of 6 cycles of platinum and 5-FU)

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

A total of 882 patients were randomised; 301 patients to the KEYTRUDA monotherapy arm,

281 patients to the KEYTRUDA plus chemotherapy arm, and 300 patients to the standard treatment arm. The study population characteristics were: median age of 61 years (range: 20 to 94); 36% age 65 or older; 83% male; 73% White and 20% Asian; 61% ECOG PS of 1; and 79% were former/current smokers. Disease characteristics were: 22% HPV positive, 15%, 85%, 43%, and 23% had PD-L1 expression defined as CPS <1, CPS ≥1, CPS ≥20, and TPS ≥50%, respectively, and 95% had Stage IV disease (Stage IVa 19%, Stage IVb 6%, and Stage IVc 70%).

The primary efficacy outcome measures were OS and PFS (assessed by BICR according to RECIST 1.1). ORR, as assessed by BICR according to RECIST 1.1, was a secondary outcome measure. The trial demonstrated a statistically significant improvement in OS for patients randomised to KEYTRUDA in combination with chemotherapy compared to standard treatment. A statistically significant improvement in OS was also demonstrated for patients with PD-L1 CPS ≥1 randomised to KEYTRUDA as monotherapy compared with cetuximab in combination with chemotherapy. Tables 33 and 34 and Figures 14 and 15 describe key efficacy results for KEYTRUDA in KEYNOTE-048.

Table 33: Efficacy Results for KEYTRUDA plus Chemotherapy in KEYNOTE-048 (CPS≥1)

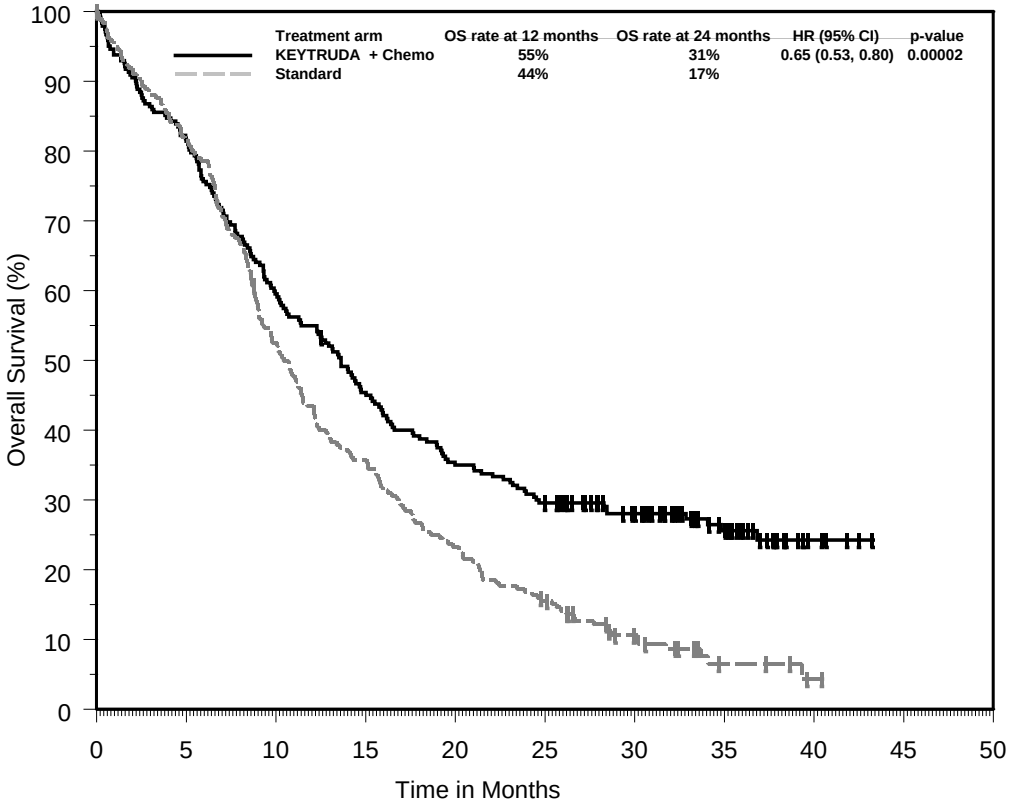
Endpoint	**KEYTRUDA Platinum Chemotherapy 5-FU n=242**	**Standard Treatment* n=235**
OS		
Number (%) of patients with event	177 (73%)	213 (91%)
Median in months (95% CI)	13.6 (10.7, 15.5)	10.4 (9.1, 11.7)
Hazard ratio† (95% CI)	0.65 (0.53, 0.80)	
p-Value‡	0.00002	
PFS		
Number of patients with event (%)	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‡	0.0369	
ORR		
Objective response rate§ (95% CI)	36% (30.3, 42.8)	36% (29.6, 42.2)
Complete response	7%	3%
Partial response	30%	33%
p-Value¶	0.4586	
Duration of Response		
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)

In KEYNOTE-048, OS HRs for patients randomised to KEYTRUDA in combination with chemotherapy, compared with cetuximab in combination with chemotherapy, were similar for all populations regardless of PD-L1 expression in a pre-specified interim analysis: ITT (HR 0.77, 95% CI: 0.63, 0.93), CPS ≥1 (HR 0.71, 95% CI: 0.57, 0.88), CPS ≥20 (HR 0.69, 95% CI: 0.51, 0.94). A positive association was observed between increasing PD-L1 expression and

treatment benefit. The trial also demonstrated a statistically significant improvement in OS for the patients expressing PD-L1 CPS ≥1 and CPS ≥20. The OS HRs at final analysis were CPS ≥1 (0.65, 95% CI: 0.53, 0.80), CPS ≥20 (0.60, 95% CI: 0.45, 0.82).

Figure 14: Kaplan-Meier Curve for Overall Survival for KEYTRUDA plus Chemotherapy in KEYNOTE-048 (CPS≥1)*



Number at Risk

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

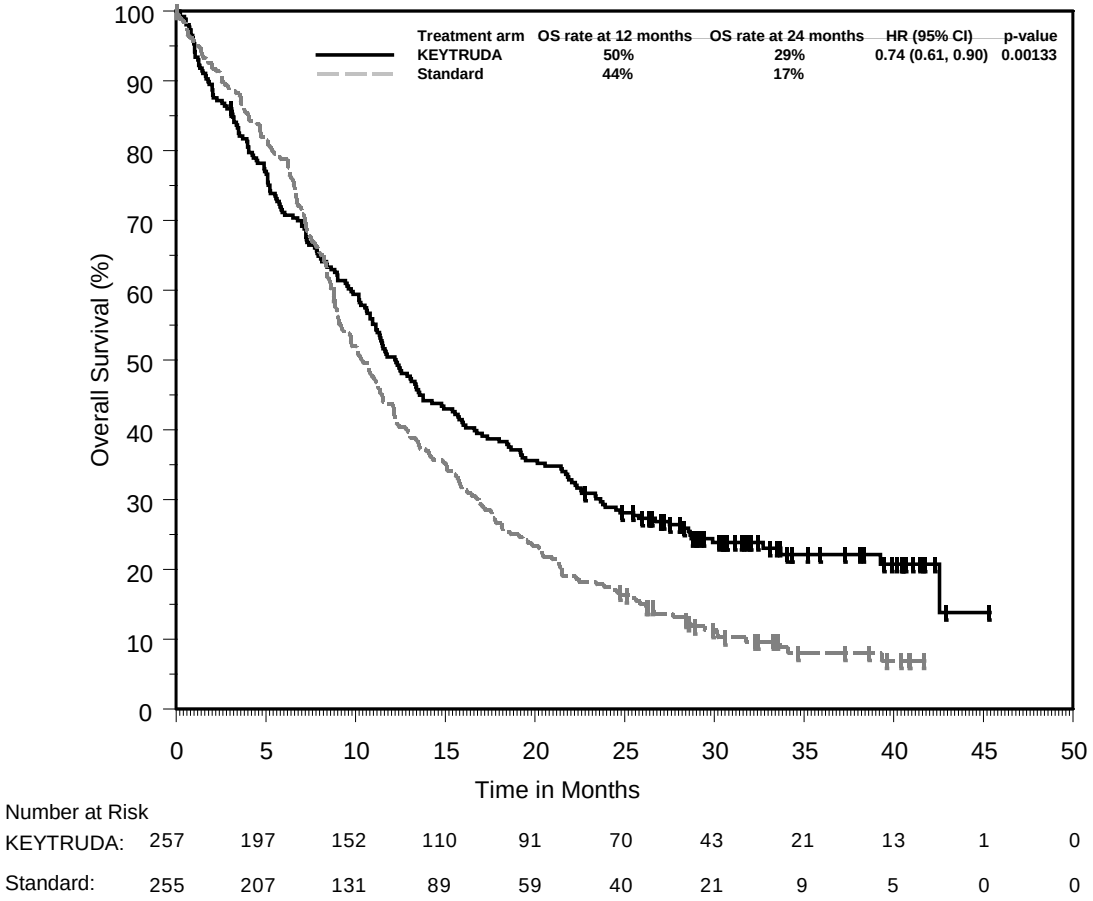
*Median follow-up of 11.5 months at protocol-specified final analysis.

Table 34: Efficacy Results for KEYTRUDA as Monotherapy in KEYNOTE-048 (CPS≥1)

Endpoint	KEYTRUDA 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§	0.8958	
ORR		
Objective response rate¶ (95% CI)	19% (14.5, 24.4)	35% (29.1, 41.1)
Complete response	5%	3%
Partial response	14%	32%
p-Value#	1.0000	
Duration of Response		
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
‡ Non-inferiority p-Value
§ Based on stratified log-rank test
¶ Response: Best objective response as confirmed complete response or partial response
# Based on Miettinen and Nurminen method stratified by ECOG (0 vs. 1), HPV status (positive vs. negative), and PD-L1 status (strongly positive vs. not strongly positive)

Figure 15: Kaplan-Meier Curve for Overall Survival for KEYTRUDA as Monotherapy in KEYNOTE-048 (CPS≥1)*



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

Additional OS analyses based on PD-L1 expression (CPS ≥1 and CPS ≥20) were performed in KEYNOTE-048. The trial demonstrated a statistically significant improvement in OS at the protocol-specified interim analysis for patients randomised to KEYTRUDA monotherapy compared to standard treatment for PD-L1 expression CPS ≥1 and CPS ≥20. OS for patients who had PD L1 CPS ≥1 or CPS ≥20 for KEYTRUDA monotherapy compared to standard treatment is summarised in Table 35.

Table 35: OS by PD-L1 Expression at Protocol-specified Interim Analysis

	CPS ≥1		CPS ≥20	
	KEYTRUDA n=257	**Standard Treatment* n=255**	**KEYTRUDA n=133**	**Standard Treatment* n=122**
Number of events (%)	177 (69%)	206 (81%)	82 (62%)	95 (78%)
Median in months (95% CI)	12.3 (10.8, 14.9)	10.3 (9.0, 11.5)	14.9 (11.6, 21.5)	10.7 (8.8, 12.8)
Hazard ratio† (95% CI)	0.78 (0.64, 0.96)		0.61 (0.45, 0.83)	
p-Value‡	0.0085		0.0007	

* Cetuximab, platinum, and 5-FU

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

‡ Based on stratified log-rank test

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

The efficacy of KEYTRUDA was investigated in KEYNOTE-040, a multicentre, open-label, randomised, active-controlled study for the treatment of recurrent or metastatic HNSCC in patients with disease progression who received prior platinum-containing chemotherapy. The study excluded patients with active autoimmune disease that required systemic therapy within 2 years of treatment, a medical condition that required immunosuppression, or who were previously treated with 3 or more systemic regimens for recurrent and/or metastatic HNSCC.

Patients were stratified by PD-L1 expression, HPV status and ECOG performance status and then randomised (1:1) to receive either KEYTRUDA 200 mg every 3 weeks (n=247) or one of three standard treatments (n=248): methotrexate 40 mg/m2 once weekly (n=64), docetaxel 75 mg/m2 once every 3 weeks (n=99), or cetuximab 400 mg/m2 loading dose and then 250 mg/m2 once weekly (n=71). Patients were treated with KEYTRUDA for up to 24 months or until unacceptable toxicity or disease progression. Treatment could continue beyond progression if the patient was clinically stable and was considered to be deriving clinical benefit by the investigator. Assessment of tumour status was performed at 9 weeks, then every 6 weeks through week 52, followed by every 9 weeks through 24 months.

Among the 495 randomised patients in KEYNOTE-040, the baseline characteristics included: median age 60 years (33% age 65 or older); 83% male; 84% White, 6% Asian, and 2% Black; and 28% and 72% with an ECOG performance status 0 or 1, respectively. Disease characteristics were: HPV positive (24%) and PD-L1 expression defined as CPS <1 (20%), CPS ≥1 (79%) and TPS ≥50% (26%). Seventy-one percent (71%) of patients had M1 disease and the majority had Stage IV disease (Stage IV 33%, Stage IVa 11%, Stage IVb 5%, and Stage IVc 45%). Fifteen percent (15%) had disease progression following platinum-containing neoadjuvant or adjuvant chemotherapy, and 84% had received 1-2 prior systemic regimens for metastatic disease.

The primary efficacy outcome was OS. There was no statistically significant difference between KEYTRUDA and standard treatment. Secondary efficacy outcome measures were PFS, ORR, and duration of response (as assessed by BICR using RECIST 1.1). Efficacy measures for KEYNOTE-040 for the CPS ≥1 population are summarised in Table 36, and the Kaplan-Meier curve for OS is shown in Figure 16.

Table 36: Efficacy Results in KEYNOTE-040 (CPS≥1)

Endpoint	Pembrolizumab 200 mg every 3 weeks n=196	Standard Treatment* n=191
OS		
Number (%) of patients with event	138 (70%)	162 (85%)
Hazard ratio† (95% CI)	0.74 (0.58, 0.93)	
p-Value‡	0.0049	
Median in months (95% CI)	8.7 (6.9, 11.4)	7.1 (5.7, 8.3)
PFS§		
Number (%) of patients with event	170 (87%)	170 (89%)
Hazard ratio† (95% CI)	0.86 (0.69, 1.06)	
p-Value‡	0.0774	
Median in months (95% CI)	2.2 (2.1, 3.0)	2.3 (2.1, 3.0)
Rate (%) at 6 months	28.7 (22.5, 35.2)	20.5 (15.0, 26.7)
Overall Response Rate§		
ORR (95% CI)	17% (12.3, 23.4)	10% (6.1, 15.1)
p-Value¶	0.0171	
Complete response	2%	0.5%
Partial response	15%	9%
Stable disease	24%	28%
Response Duration§,#		
Median in months (range)	18.4 (2.7, 18.4)	9.6 (1.4+, 18.8)
Number (%Þ) of patients with duration ≥6 months	16 (72%)	5 (51%)

* Methotrexate, docetaxel, and cetuximab

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

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

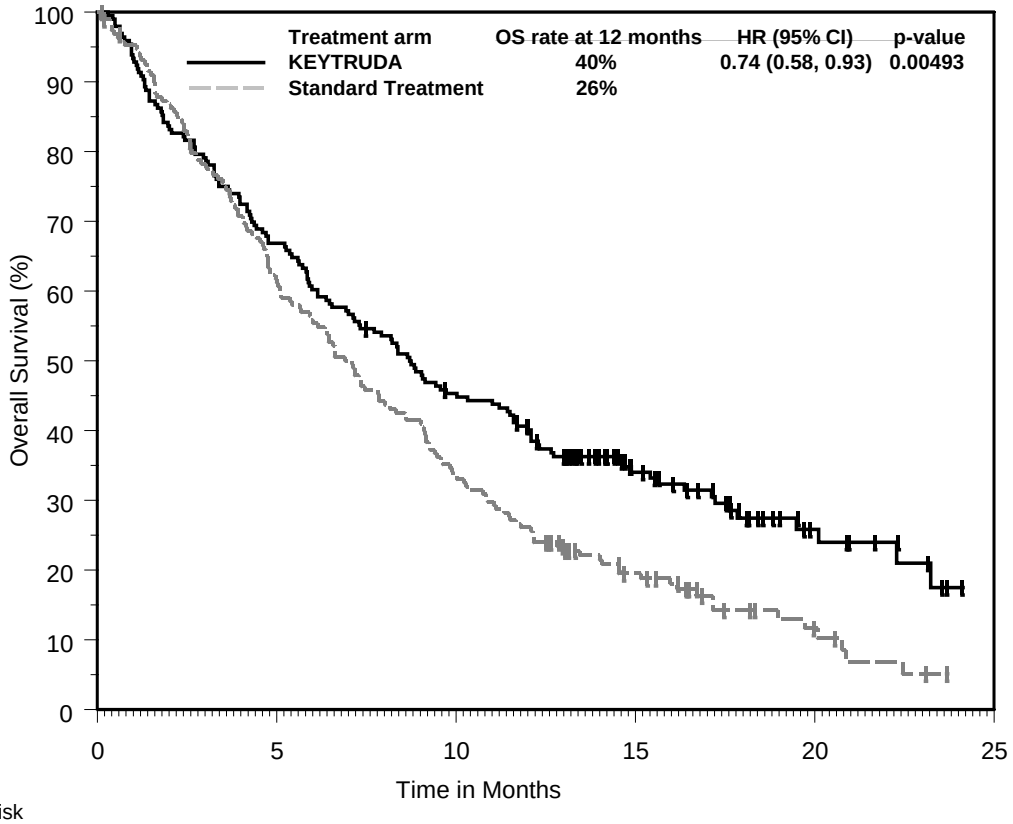
§ Assessed by BICR using RECIST 1.1

¶ Based on method by Miettinen and Nurminen

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

Þ Based on Kaplan-Meier estimation

Figure 16: Kaplan-Meier Curve for Overall Survival in KEYNOTE-040 (CPS≥1)*



Number at Risk

KEYTRUDA:	196	131	87	43	14	2
Standard Treatment:	191	115	63	28	8	1

*Median follow-up of 7.9 months at protocol-specified final analysis.

Classical Hodgkin Lymphoma

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

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

- KEYTRUDA 200 mg intravenously every 3 weeks
- Brentuximab vedotin 1.8 mg/kg intravenously every 3 weeks

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

Among KEYNOTE-204 patients, the baseline characteristics were median age 35 years (16% age 65 or older); 57% male; 77% White; and 61% and 38% had an ECOG performance status 0 and 1, respectively. The median number of prior lines of therapy administered for the treatment of cHL was 2 (range 1 to 11). Forty-two percent were refractory to the last prior therapy and 29% had primary refractory disease. Thirty-seven percent had undergone prior auto-HSCT, 5% had received prior BV, and 39% had prior radiation therapy.

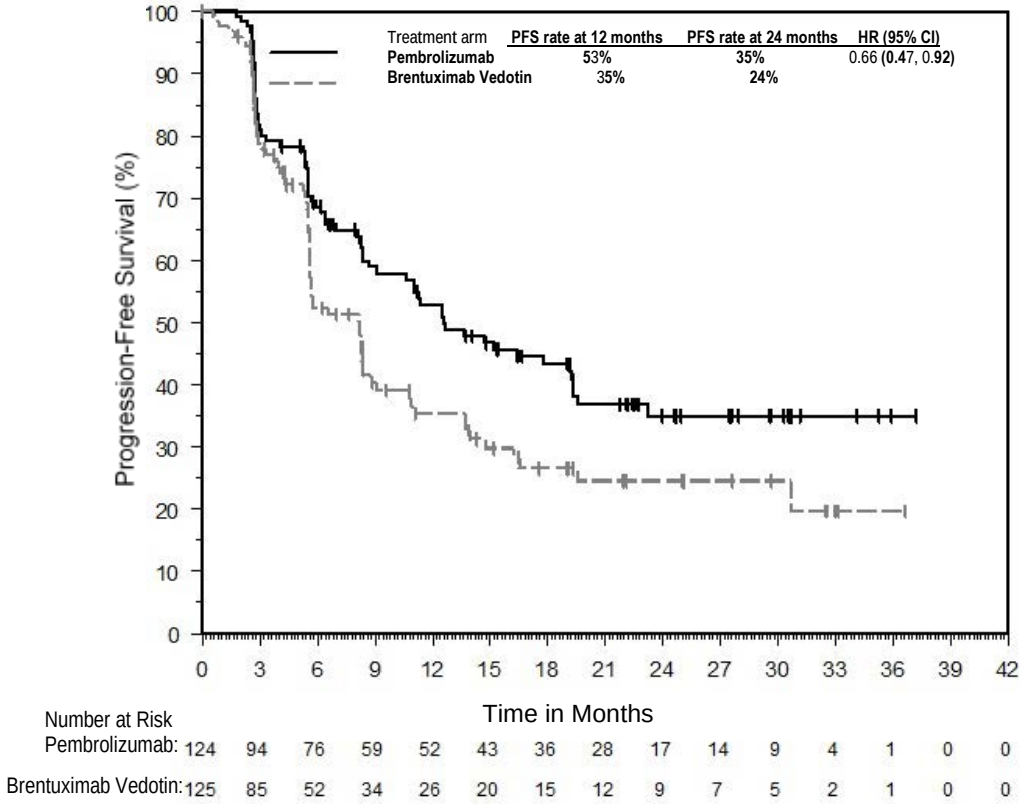
In the ITT population, the median follow-up time for 151 patients treated with pembrolizumab was 24.9 months (range: 1.8 to 42.0 months). The initial analysis resulted in a HR for PFS of 0.65 (95% CI: 0.48, 0.88) with a one-sided p value of 0.0027. The ORR was 66% for pembrolizumab compared to 54% for standard treatment with a p-value of 0.0225. Table 37 summarises the efficacy results in 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; 124 patients received pembrolizumab and 125 patients received BV. Efficacy results in this subpopulation were consistent with the ITT population. The Kaplan-Meier curve for PFS for this subpopulation is shown in Figure 17.

Table 37: Efficacy Results in cHL Patients Who Failed a Transplant Before Enrolling or Who Failed 2 or More Prior Therapies and Were Ineligible for ASCT in KEYNOTE 204

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

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

Figure 17: 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



Patient-reported outcomes (PROs) were assessed using EORTC QLQ-C30. A prolonged time to deterioration in EORTC QLQ C30 global health status/QoL was observed for patients treated with pembrolizumab compared to BV (HR 0.40; 95% CI: 0.22-0.74). Over 24 weeks of follow-up, patients treated with pembrolizumab had an improvement in global health status/QoL compared to BV which showed a decline (difference in Least Square (LS) means=8.60; 95% CI: 3.89, 13.31; nominal two-sided p=0.0004). These results should be interpreted in the context of the open-label study design and therefore taken cautiously.

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

The efficacy of KEYTRUDA was investigated in 241 patients with refractory classical Hodgkin Lymphoma, or who have relapsed after 3 or more prior lines of therapy, enrolled in two multicentre, nonrandomised, open-label studies (KEYNOTE-013 and KEYNOTE-087). Both studies included patients regardless of PD-L1 expression. Patients with active, non-infectious pneumonitis, an allogeneic hematopoietic stem cell transplant within the past 5 years (or greater than 5 years but with GVHD), active autoimmune disease or a medical condition that required immunosuppression were ineligible for either trial. Patients received KEYTRUDA 10 mg/kg every 2 weeks (n=31) or 200 mg every 3 weeks (n=210) until unacceptable toxicity or documented disease progression. Response was assessed using the revised lymphoma criteria by PET CT scans, with the first planned post-baseline assessment at week 12. The major efficacy outcome measures (ORR, CRR, and duration of response) were assessed by blinded independent central review according to the 2007 revised International Working Group (IWG) criteria. Secondary efficacy outcome measures were PFS and OS.

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

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

Efficacy results are summarised in Table 38.

Table 38: Efficacy Results in Patients with refractory or relapsed classical Hodgkin Lymphoma

	KEYNOTE-013[a]	KEYNOTE-087[b]
Endpoint	n=31	n=210
Objective Response Rate*		
ORR %, (95% CI)	58% (39.1, 75.5)	71% (64, 77)
Complete remission	19%	28%
Partial remission	39%	43%
Response Duration*		
Median in months (range)	Not reached (0.0+, 26.1+)[†]	16.6 (0.0+, 39.1+) [‡]
% with duration ≥ 6-months	80%[§]	74%[¶]
% with duration ≥ 12-months	70%[#]	59%[Þ]
Time to Response		
Median in months (range)	2.8 (2.4, 8.6) [†]	2.8 (2.1, 16.5) [‡]
PFS*		
Median in months (95% CI)	11.4 (4.9, 27.8)	13.6 (11.1, 16.7)
6-month PFS rate	66%	72%
9-month PFS rate	---	61%
12-month PFS rate	48%	52%
OS		
6-month OS rate	100%	99.5%
12-month OS rate	87.1%	96.1%

[a] Median follow-up time of 28.7 months
[b] Median follow-up time of 39.5 months
* Assessed by blinded independent central review according to the 2007 revised International Working Group (IWG) criteria
† Based on patients (n=18) with a response by independent review.
‡ Based on patients (n=149) with a response by independent review.
§ Based on Kaplan-Meier estimation; includes 9 patients with responses of 6 months or longer.
¶ Based on Kaplan-Meier estimation; includes 84 patients with responses of 6 months or longer.
# Based on Kaplan-Meier estimation; includes 7 patients with responses of 12 months or longer.
Þ Based on Kaplan-Meier estimation; includes 60 patients with responses of 12 months or longer

The improved benefit as assessed by ORR, CRR, and response duration in the KEYNOTE-

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

Primary Mediastinal B-Cell Lymphoma

KEYNOTE-170: Open-label study in patients with relapsed or refractory PMBCL
The efficacy of KEYTRUDA was investigated in KEYNOTE-170, a multicentre, open-label, single-arm trial in 53 patients with relapsed or refractory PMBCL. Patients with active, non-infectious pneumonitis, an allogeneic HSCT within the past 5 years (or greater than 5 years but with symptoms of GVHD), active autoimmune disease, a medical condition that required immunosuppression, or an active infection requiring systemic therapy were ineligible for the trial. Patients received KEYTRUDA 200 mg every 3 weeks until unacceptable toxicity or documented disease progression, or for up to 24 months in patients that did not progress. Disease assessment was performed every 12 weeks. The major efficacy outcome measures (ORR, CRR, PFS, and duration of response) were assessed by blinded independent central review according to the 2007 revised IWG criteria.

Among the 53 patients, the baseline characteristics were: median age 33 years (range: 20 to 61 years), 43% male; 92% White; 43% had an ECOG performance status (PS) of 0 and 57% had an ECOG PS of 1. The median number of prior lines of therapy administered for the treatment of PMBCL was 3 (range 2 to 8). Seventy-seven percent were refractory to the last prior therapy, 40% had primary refractory disease, and 89% had disease that was chemo-refractory to any prior regimen. Twenty-six percent of patients had undergone prior auto-HSCT, 74% did not receive prior transplant; and 32% of patients had prior radiation therapy.

Efficacy results for KEYNOTE-170 are summarised in Table 39.

Table 39: Efficacy Results in Patients with refractory or relapsed PMBCL

Endpoint	**KEYNOTE-170**
	n=53
Objective Response Rate*	
ORR %, (95% CI)	45% (32, 60)
Complete remission	11%
Partial remission	34%
Response Duration*	
Median in months (range)	Not reached (1.1+,19.2+)†
% with duration ≥ 6-months	85%‡
Time to Response	
Median in months (range)	2.8 (2.1-8.5)†
PFS*	
Median in months (95% CI)	4.7 (2.8, 11.0)
6-month PFS rate	45%
12-month PFS rate	34%
OS	
6-month OS rate	70%
12-month OS rate	58%

* Assessed by blinded independent central review according to the 2007 revised IWG criteria

† Based on patients (n=24) with a response by independent review

‡ Based on Kaplan-Meier estimation, includes 12 patients with response of 6 months or longer including 5 patients with a response of 12 months or longer.

Urothelial Carcinoma

KEYNOTE-052: Open label trial in urothelial carcinoma patients ineligible for cisplatin-containing chemotherapy

The efficacy of KEYTRUDA was investigated in KEYNOTE-052, a multicentre, open-label single-arm trial of patients with locally advanced or metastatic urothelial carcinoma who were not eligible for cisplatin-containing chemotherapy. Patients with creatinine clearance ≥30ml/min were eligible for treatment. Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible for treatment.

Patients received KEYTRUDA 200 mg every 3 weeks until unacceptable toxicity or disease progression. Clinically stable patients with initial evidence of disease progression were permitted to remain on treatment until disease progression was confirmed. Patients without disease progression were treated for up to 24 months. Treatment with pembrolizumab could be reinitiated for subsequent disease progression and administered for up to 1 additional year. 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. The primary efficacy outcome measure was ORR according to RECIST 1.1 and a secondary efficacy outcome measure was duration of response. Efficacy is reported for patients who had the opportunity for at least 2 post-baseline scans representing at least 4 months of follow-up.

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, 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.

Among the 370 patients, 30% (n = 110) had tumours that expressed PD-L1 with a combined positive score (CPS) of greater than or equal to 10. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx Kit. The baseline characteristics of these 110 patients were: median age 73 years, 68% male, and 87% White. Eighty-two percent had M1 disease, and 18% had M0 disease. Eighty-one percent had a primary tumour in the lower tract, and 18% of patients had a primary tumour in the upper tract. Seventy-six percent of patients had visceral metastases, including 11% with liver metastases. Reasons for cisplatin ineligibility included: 45% with baseline creatinine clearance of <60 mL/min, 37% with ECOG performance status of 2, 10% with ECOG 2 and baseline creatinine clearance of <60 mL/min, and 8% with other reasons (Class III heart failure, Grade 2 or greater peripheral neuropathy, and Grade 2 or greater hearing loss). Ninety percent of patients were treatment naïve, and 10% received prior adjuvant or neoadjuvant platinum-based chemotherapy.

At a pre-specified interim analysis, the median follow-up time for 370 patients treated with KEYTRUDA was 11.5 months. Efficacy results are summarised in Table 40. The data presented for subjects with PD-L1 CPS ≥10 are based on a subgroup analysis.

Table 40: Efficacy Results in Patients with Urothelial Carcinoma Ineligible for Cisplatin-Containing Chemotherapy

Endpoint	All Subjects n=370	PD-L1 CPS < 10 N=251	PD-L1 CPS ≥10 N=110
Objective Response Rate*			
ORR %, (95% CI)	29% (24, 34)	21% (16, 26)	47% (38, 57)
Disease Control Rate†	47%	38%	67%
Complete response	8%	3%	19%
Partial response	21%	18%	28%
Stable disease	18%	18%	20%
Response Duration			
Median in months (range)	Not reached (1.4+, 27.9+)	Not reached (1.6+, 27.9+)	Not reached (1.4+, 26.5+)
% with duration ≥ 6-months	82%‡	80%§	82%§
Time to Response			
Median in months (range)	2.1 (1.3, 9.0)	2.1 (1.6, 9.0)	2.1 (1.3, 4.7)
PFS*			
Median in months (95% CI)	2.3 (2.1, 3.4)	2.1 (2.0, 2.1)	4.9 (3.8, 10.8)
6-month PFS rate	34%	27%	49%
OS			
Median in months (95% CI)	11.5 (10.0, 13.3)	10 (8, 12)	18.5 (12.2, NA¶)
6-month OS rate	67%	63%	76%
12-month OS rate	48%	42%	61%

** Assessed by BICR using RECIST 1.1
† Based on best response of stable disease or better
‡ Based on Kaplan-Meier estimates; includes 85 patients with responses of 6 months or longer
§ Based on Kaplan-Meier estimates; includes 41 patients with responses of 6 months or longer
¶ Not available

The final ORR analysis was performed 9.9 months after the interim analysis with 106 ORR events for all patients [median follow-up of 11.4 months (range: 0.1, 41.2 months)]. ORR was 29% (95% CI: 24, 34) and 47% (95% CI: 38, 57), respectively for all subjects and subjects with CPS ≥10. The complete and partial response rates were 9% and 20%, respectively in all subjects and 20% and 27%, respectively in subjects with CPS ≥10. At the final analysis among the responding patients, the median response duration was 30.1 months (range 1.4+ to 35.9+ months) in all subjects (n=106) and not reached (range 1.4+ to 35.4+ months) in subjects with CPS ≥10 (n=52). Responses of 6 months or longer (based on Kaplan-Meier estimation) were 81% and 82%, respectively for all subjects and subjects with CPS ≥10.

KEYNOTE-361: Controlled trial in previously untreated urothelial carcinoma patients
KEYNOTE-361 is an ongoing, multicentre, randomised study in previously untreated patients with metastatic urothelial carcinoma who are eligible for platinum containing chemotherapy. The study compares KEYTRUDA with or without platinum-based chemotherapy (i.e., cisplatin or carboplatin with gemcitabine) to platinum-based chemotherapy alone. The trial also enrolled a third arm of monotherapy with KEYTRUDA to compare to platinum-based chemotherapy alone. The independent Data Monitoring Committee (iDMC) for the study conducted a review of early data and found that in patients classified as having low PD-L1 expression (CPS <10), those treated with KEYTRUDA monotherapy had decreased survival compared to those who

received platinum-based chemotherapy. The iDMC recommended tostop further accrual of patients with low PD-L1 expression in the monotherapy arm, however, no other changes were recommended, including any change of therapy for patients who had already been randomised to and were receiving treatment in the monotherapy arm.

KEYNOTE-045: Controlled trial in urothelial carcinoma patients previously treated with platinum-containing chemotherapy
The efficacy of KEYTRUDA was evaluated in KEYNOTE-045, a multicentre, randomised (1:1), active-controlled trial in patients with locally advanced or metastatic urothelial carcinoma with disease progression on or after platinum-containing chemotherapy. Patients with creatinine clearance ≥30ml/min were eligible for treatment. Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible for treatment.

Patients were randomised to receive either KEYTRUDA 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/m2 (n=84), docetaxel 75 mg/m2 (n=84), or vinflunine 320 mg/m2 (n=87). Patients received KEYTRUDA 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. While this trial permitted re-initiation of treatment with pembrolizumab for subsequent disease progression and administration for up to 1 additional year, due to limited data at the time of data cutoff any benefit remains unknown. Assessment of tumour status was performed at 9 weeks after randomisation, then every 6 weeks through the first year, followed by every 12 weeks thereafter. The primary efficacy outcomes were OS and PFS as assessed by BICR per RECIST v1.1. Secondary efficacy outcome measures were ORR as assessed by BICR per RECIST v1.1 and duration of response.

Among the 542 randomised patients, the study population characteristics were: median age 66 years (range: 26 to 88), 58% age 65 or older; 74% male; 72% White and 23% Asian; 42% ECOG PS of 0, 56% ECOG PS of 1, <2% of patients were ECOG PS of 2 with no patients ECOG PS > 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 as the most recent line of therapy. Twenty-one percent had received 2 or more prior systemic regimens in the metastatic setting. Seventy-six percent of patients received prior cisplatin, 23% had prior carboplatin, and 1% were treated with other platinum-based regimens.

At a pre-specified interim analysis, the median follow-up time for 270 patients treated with KEYTRUDA was 10.3 months. The study demonstrated statistically significant improvements in OS and ORR for patients randomised to KEYTRUDA as compared to chemotherapy where the ORR for patients on KEYTRUDA was approximately two-fold greater than those on chemotherapy alone (21% versus 11%, p=0.001) (Table 41). There was no statistically significant difference between KEYTRUDA and chemotherapy with respect to PFS. Efficacy results are summarised in Table 41.

Table 41: Efficacy Results in Patients with Urothelial Carcinoma Previously Treated with Chemotherapy

Endpoint	KEYTRUDA 200 mg every 3 weeks n=270	Chemotherapy n=272
OS		
Number (%) of patients with event	155 (57%)	179 (66%)
Hazard ratio* (95% CI)	0.73 (0.59, 0.91)	
p-Value†	0.002	
Median in months (95% CI)	10.3 (8.0, 11.8)	7.4 (6.1, 8.3)
PFS‡		
Number (%) of patients with event	218 (81%)	219 (81%)
Hazard ratio* (95% CI)	0.98 (0.81, 1.19)	
p-Value†	0.416	
Median in months (95% CI)	2.1 (2.0, 2.2)	3.3 (2.3, 3.5)
Objective Response Rate‡		
ORR % (95% CI)	21% (16, 27)	11% (8, 16)
Complete response	7%	3%
Partial response	14%	8%
p-Value§,	0.001	

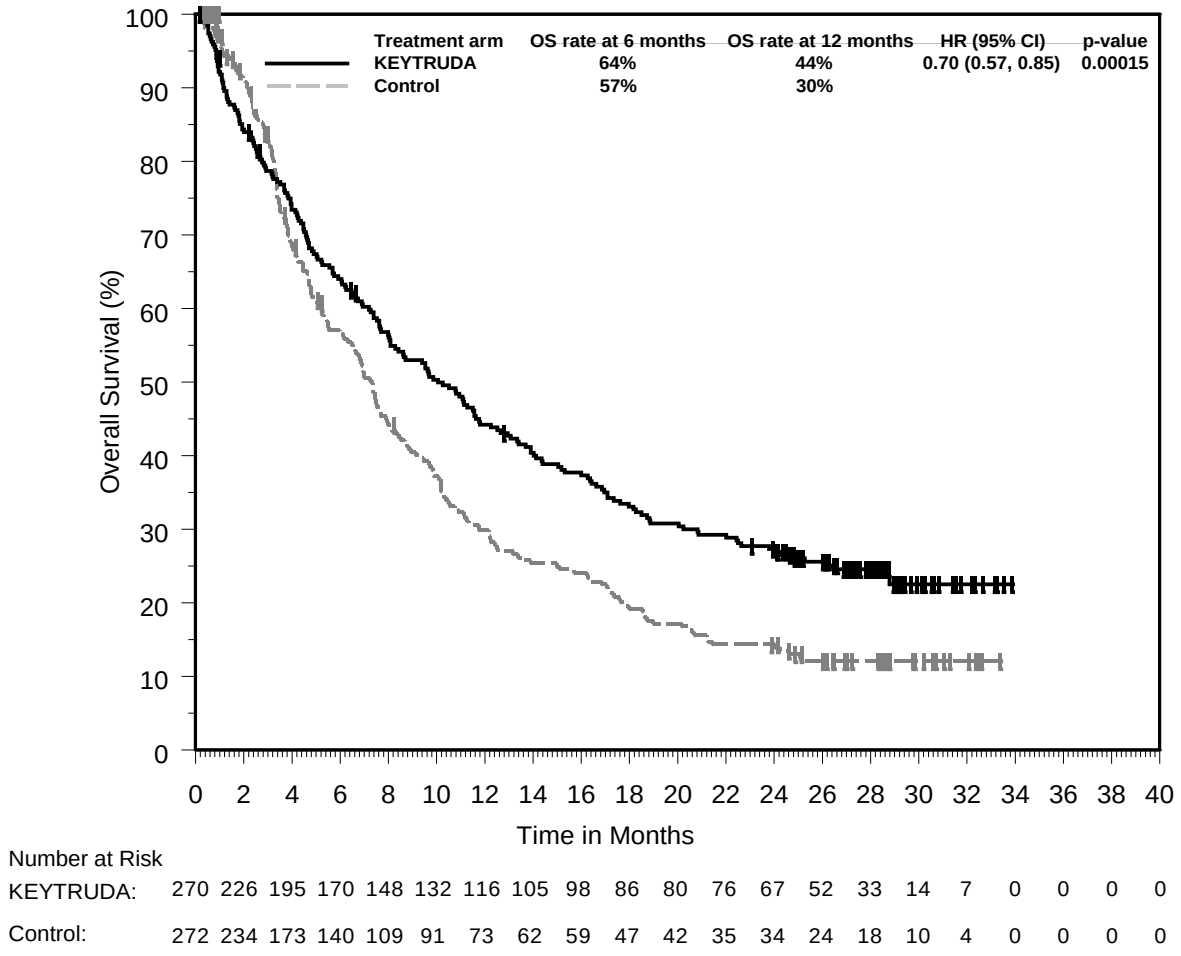
* Hazard ratio (KEYTRUDA compared to chemotherapy) based on the stratified Cox proportional hazard model
† Based on stratified log-rank test
‡ Assessed by BICR using RECIST 1.1
§ Based on method by Miettinen and Nurminen
¶ Based on patients with a best overall response as confirmed complete or partial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

At the interim analysis, median duration of response was not reached in the KEYTRUDA arm (range 1.6+ to 15.6+ months) and was 4.3 months (range: 1.4+ to 15.4+ months) in the chemotherapy arm. At the time of the analysis, responses were ongoing in 41 and 14 patients at 6 and 12 months respectively, in the KEYTRUDA arm, and 7 and 3 patients at 6 and 12 months respectively, in the chemotherapy arm.

The final OS analysis was performed 13.6 months after the interim analysis with 419 patient events (200 for KEYTRUDA and 219 for chemotherapy). Median OS was 10.1 months (95% CI: 8.0, 12.3) for KEYTRUDA and 7.3 months (95% CI: 6.1, 8.1) for chemotherapy. The OS HR was 0.70 (95% CI: 0.57, 0.85; p<0.001). See Figure 18. In the final analysis there was no statistically significant difference between KEYTRUDA and chemotherapy with respect to PFS.

At the final analysis, among the 57 responding patients who received KEYTRUDA vs. 30 responding patients who received chemotherapy, the median response duration was not reached (range 1.6+ to 30.0+ months) in patients who received KEYTRUDA, vs. 4.4 months (range 1.4+ to 29.9+ months) in patients who received chemotherapy. In patients who received KEYTRUDA, 84% had responses of 6 months or longer and 68% had responses of 12 months or longer (based on Kaplan-Meier estimation) vs. 47% who had responses of 6 months or longer and 35% who had responses of 12 months or longer (based on Kaplan-Meier estimation) in patients who received chemotherapy. The complete and partial response rates were 9% and 12%, respectively in patients who received KEYTRUDA vs. 3% and 8%, respectively in patients who received chemotherapy.

Figure 18: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-045 (Intent to Treat Population)



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-057: BCG-unresponsive High-Risk Non-Muscle Invasive Bladder Cancer

The efficacy of KEYTRUDA was investigated in KEYNOTE 057, a multicenter, open-label, single-arm trial in 96 patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in-situ (CIS) with or without papillary tumours who are ineligible for or have elected not to undergo cystectomy. BCG-unresponsive high-risk NMIBC is defined as persistent disease despite adequate BCG therapy, disease recurrence after an initial tumour-free state following adequate BCG therapy, or T1 disease following a single induction course of BCG. Prior to treatment, all patients had received adequate BCG therapy, had undergone recent cystoscopic procedure(s) and transurethral resection of bladder tumour (TURBT) to remove all resectable disease (Ta and T1 components) and assure the absence of muscle invasive disease. Residual CIS (Tis components) not amenable to complete resection was acceptable. The trial excluded patients

with muscle invasive (i.e., T2, T3, T4) locally advanced non-resectable or metastatic urothelial carcinoma, concurrent extra-vesical (i.e., urethra, ureter or renal pelvis) non-muscle invasive transitional cell carcinoma of the urothelium, autoimmune disease or a medical condition that required immunosuppression.

Patients received KEYTRUDA 200 mg every 3 weeks until unacceptable toxicity, persistent or recurrent high-risk NMIBC, or progressive disease. Assessment of tumour status was performed every 12 weeks, and patients without disease progression could be treated for up to 24 months. The major efficacy outcome measures were complete response (as defined by negative results for cystoscopy [with TURBT/biopsies as applicable], urine cytology, and computed tomography urography [CTU] imaging) and duration of response. Patients who have completed a minimum of 18 months of treatment with KEYTRUDA and who have remained without evidence of disease at 2 or more consecutive 3-monthly evaluation visits were permitted to electively discontinue treatment.

The study population characteristics were: median age 73 years (69% age 65 or older); 84% male; 67% White; and 73% and 27% with an ECOG performance status of 0 or 1, respectively. Tumour pattern at study entry was CIS with T1 (13%), CIS with high grade TA (25%), and CIS (63%). Baseline high-risk NMIBC disease status was 27% persistent and 73% recurrent. The median number of prior instillations of BCG was 12.

The median follow-up time was 28.0 months (range: 4.6 to 40.5 months). Efficacy results are summarised in Table 42.

Table 42: Efficacy Results for Patients with BCG-unresponsive, high risk NMIBC

Endpoint	**n=96**
Complete Response Rate*	41%
Response Duration†	
Median in months (range)	16.2 (0.0+, 30.4+)
% with duration ≥ 6 months	78%‡
% with duration ≥ 12 months	57%§

* Based on negative cystoscopy (with TURBT/biopsies as applicable), urine cytology, and computed tomography urography (CTU imaging)
† Duration reflects period from the time complete response was achieved
‡ Based on Kaplan-Meier estimates; includes 27 patients with responses of 6 months or longer
§ Based on Kaplan-Meier estimates; includes 18 patients with responses of 12 months or longer

At the time of analysis, among the 96 patients there were no occurrences of progression to muscle-invasive disease (T2) or metastatic bladder cancer while on KEYTRUDA.

Microsatellite Instability-High (MSI-H) Cancer

KEYNOTE-164 and KEYNOTE-158 Open-label studies in patients with MSI-H, including mismatch repair deficient (dMMR), cancer who have received prior therapy
The efficacy of KEYTRUDA was investigated in 155 patients with MSI-H or dMMR cancer enrolled in two multicentre, nonrandomised, open-label, multi-cohort, single-arm, Phase II studies (KEYNOTE-164 and KEYNOTE-158). Regardless of histology, MSI or MMR tumour status was determined using polymerase chain reaction (PCR) or immunohistochemistry (IHC), respectively. Efficacy was evaluated in 61 patients enrolled in KEYNOTE-164 with advanced MSI-H or dMMR colorectal cancer (CRC) that progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. Efficacy was also evaluated in 94 patients enrolled in KEYNOTE-158 with advanced MSI-H or dMMR non-colorectal cancer (non-CRC)

who had disease progression following prior therapy. Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible for either trial. Enrolled patients were required to have an ECOG PS of 0 or 1.

Patients received KEYTRUDA 200 mg every 3 weeks until unacceptable toxicity or disease progression. Clinically stable patients with initial evidence of disease progression were permitted to remain on treatment until disease progression was confirmed. Patients without disease progression were treated for up to 24 months. Treatment with pembrolizumab could be reinitiated for subsequent disease progression and administered for up to 1 additional year. Assessment of tumour status in KEYNOTE-164 was performed every 9 weeks and in KEYNOTE-158 every 9 weeks through the first year, then every 12 weeks thereafter. The major efficacy outcome measures were ORR and duration of response according to RECIST 1.1.

Among the 155 patients with MSI-H cancer, the baseline characteristics were: median age 60 years (40% age 65 or older); 55% male; 78% White, 20% Asian; and ECOG PS 0 (49%) and 1 (51%). Ninety-three percent of patients had M1 disease and 6% had M0 disease. Ninety percent of patients with CRC and 51% of patients with non-CRC received two or more prior lines of therapy.

The median follow-up time for 155 patients treated with KEYTRUDA was 9.7 months. Efficacy results are summarised in Table 43 and Table 44.

Table 43: Efficacy Results for Patients with MSI-H/dMMR Cancer

Endpoint	**n=155**
Objective Response Rate*	
ORR %, (95% CI)	34% (26, 42)
Complete response	3%
Partial response	31%
Response Duration*	
Median in months (range)	Not reached (2.1+, 12.5+)
% with duration ≥ 6-months	98%†

*Assessed by BICR using RECIST 1.1

† Based on Kaplan-Meier estimates, includes 32 patients with response of 6 months or longer

Table 44: Response by Tumour Type

	N	Objective response rate n (%)	95% CI	DOR range (months)
CRC	61	17 (28%)	(17%, 41%)	2.9+ - 12.5+
Non-CRC	94	35 (37%)	(28%, 48%)	2.1+ - 10.7+
Endometrial	24	13 (54%)	(33%, 74%)	2.1+ - 8.4+
Gastric	13	6 (46%)	(19%, 75%)	4.0+ - 8.6+
Small intestinal	13	4 (31%)	(9%, 61%)	2.2+ - 10.4+
Pancreatic	10	1 (10%)	(0.3%, 45%)	8.1
Cholangiocarcinoma	9	2 (22%)	(3%, 60%)	4.2+ - 6.5+
Adrenocortical	3	1 (33%)	(0.8%, 91%)	2.1+
Mesothelioma	3	SD, PD, PD		
Small cell lung	3	2 (67%)	(9%, 99%)	6.7+ - 10.7+
Cervical	2	PR, PD		6.9+
Neuroendocrine	2	SD, PD		
Thyroid	2	SD, PD		
Urothelial	2	PR, PD		8.3+
Brain	1	PD		
Ovarian	1	PD		
Prostate cancer	1	SD		
Retroperitoneal	1	PR		6.2+
Salivary	1	PR		10.7+
Sarcoma	1	PR		4.2
Testicular	1	PD		
Tonsillar	1	PR		4.2+

CR = complete response
PR = partial response
SD = stable disease
PD = progressive disease

KEYNOTE-177: Controlled trial for first-line treatment of patients with MSI-H or dMMR CRC
The efficacy of KEYTRUDA was investigated in KEYNOTE-177, a multicentre, randomised, open-label, active-controlled trial that enrolled 307 patients with previously untreated metastatic MSI-H or dMMR CRC. MSI or MMR tumour status was determined locally using polymerase chain reaction (PCR) or immunohistochemistry (IHC), respectively. Patients with autoimmune disease, or a medical condition that required immunosuppression were ineligible.

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

- mFOLFOX6 (oxaliplatin, leucovorin, and 5-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 5-FU 400 mg/m^2 bolus on Day 1, then 5-FU 2400 mg/m^2 over 46-48 hours. Bevacizumab 5 mg/kg on Day 1 or cetuximab 400 mg/m^2 on first infusion, then 250 mg/m^2 weekly.
- FOLFIRI (irinotecan, leucovorin, and 5-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 5-FU 400 mg/m^2 bolus on Day 1, then 5-FU 2400 mg/m^2 over 46-48 hours. Bevacizumab 5 mg/kg on Day 1 or cetuximab 400 mg/m^2 on first infusion, then 250 mg/m^2 weekly.

Treatment with KEYTRUDA or chemotherapy continued until RECIST v1.1-defined

progression of disease as determined by the investigator or unacceptable toxicity. Patients treated with KEYTRUDA 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 KEYTRUDA at the time of disease progression. The primary efficacy outcome measures were PFS (assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ) and OS. Secondary outcome measures were ORR and DoR.

A total of 307 patients were enrolled and randomised to KEYTRUDA (n=153) or chemotherapy (n=154). The baseline characteristics of these 307 patients were: median age of 63 years (range: 24 to 93), 47% age 65 or older; 50% male; 75% White and 16% Asian; 52% had an ECOG PS of 0 and 48% had an ECOG PS of 1; 25% had a BRAF V600E mutation and 24% had a KRAS/NRAS mutation; and 27% had received prior adjuvant or neoadjuvant chemotherapy. Of the 154 patients randomised to receive chemotherapy, 143 were treated: 56% of them received mFOLFOX6 and 44% received FOLFIRI; with bevacizumab added for 70% of regimens and cetuximab for 11%.

The trial demonstrated a statistically significant improvement in PFS for patients randomised to KEYTRUDA compared with chemotherapy. The median follow-up time was 27.6 months (range: 0.2 to 48.3 months). Table 45 and Figure 19 summarise the key efficacy measures for KEYNOTE-177. Overall survival data were not mature at the time of analysis, with 66% of the required events having occurred.

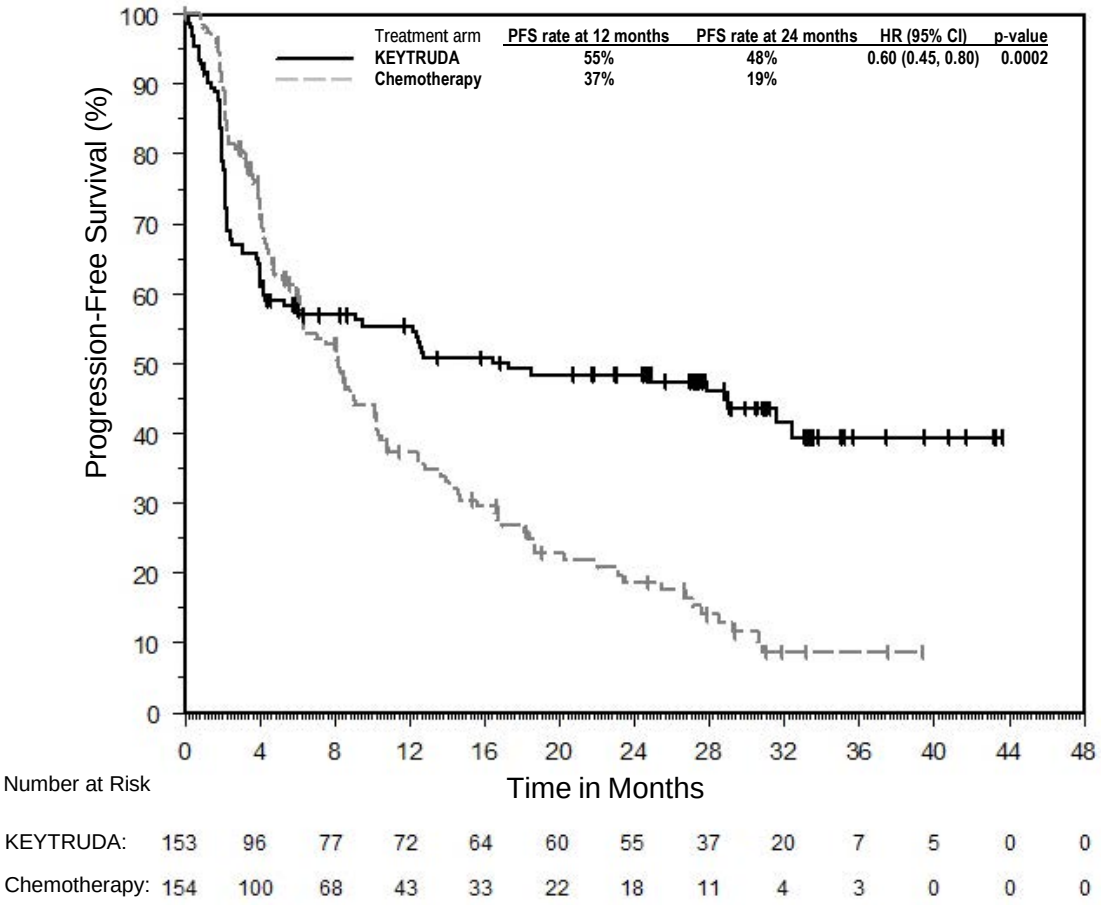
It is not known how KEYTRUDA compares with platinum-based chemotherapy as the first-line treatment for patients with unresectable non-metastatic MSI-H/dMMR CRC to induce tumour regression sufficient to allow for resection with curative intent.

Table 45: Efficacy Results for First-line Treatment in Patients with Metastatic MSI-H CRC in KEYNOTE-177

Endpoint	KEYTRUDA 200 mg every 3 weeks n=153	Chemotherapy n=154
PFS		
Number (%) of patients with event	82 (54%)	113 (73%)
Median in months (95% CI)	16.5 (5.4, 32.4)	8.2 (6.1, 10.2)
Hazard ratio* (95% CI)	0.60 (0.45, 0.80)	
p-Value†	0.0004	
Objective Response Rate‡		
ORR (95% CI)	44% (35.8, 52.0)	33% (25.8, 41.1)
Complete response rate	11%	4%
Partial response rate	33%	29%
Response Duration‡§		
Median in months (range)	NR (2.3+ - 41.4+)	10.6 (2.8 - 37.5+)
% of patients with duration ≥ 6 months§¶	91%	84%
% of patients with duration ≥ 12 months§¶	75%	37%
% of patients with duration ≥ 24 months§¶	43%	18%

* Based on Cox regression model
† Two-sided, based on log-rank test (significance level 0.0234)
‡ Based on confirmed response by BICR review
§ Based on n=67 patients with a response in the KEYTRUDA arm and 51 patients with a response in the chemotherapy arm
¶ Based on observed duration of response
\+ Denotes ongoing response
NR = not reached

Figure 19: Kaplan-Meier curve for Progression-free Survival by treatment arm in KEYNOTE-177 (intent to treat population)



Endometrial Carcinoma

KEYNOTE-146: an open-label, multi-cohort trial in patients with endometrial carcinoma that had progressed following at least one prior systemic therapy

The efficacy of KEYTRUDA in combination with lenvatinib was investigated in KEYNOTE-146, a single-arm, multicentre, open-label, multi-cohort trial that enrolled 108 patients with metastatic endometrial carcinoma that had progressed following at least one prior systemic therapy in any setting. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible. Patients were treated with KEYTRUDA 200 mg intravenously every 3 weeks in combination with lenvatinib 20 mg orally once daily until unacceptable toxicity or disease progression as determined by the investigator. The major efficacy outcome measures were ORR and DOR by independent radiologic review committee (IRC) using RECIST v1.1.

Administration of KEYTRUDA and lenvatinib was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered by the investigator to be deriving clinical benefit. KEYTRUDA dosing 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 6 weeks until week 24, followed by every 9 weeks thereafter.

Among the 108 patients, 87% (n=94) had tumours that were not MSI-H or dMMR, 10% (n=11) had tumours that were MSI-H or dMMR, and in 3% (n=3) the status was not known. Tumour MSI status was determined using a polymerase chain reaction (PCR) test. Tumour MMR status was determined using an immunohistochemistry (IHC) test. The baseline characteristics of the 94 patients with tumours that were not MSI-H or dMMR were: median age of 66 years, 62% age 65 or older; and 86% White, 6% Black, 4% Asian, 3% other races; and ECOG PS of 0 (52%) or 1 (48%). All 94 of these patients received prior systemic therapy for endometrial carcinoma: 51% had one, 38% had two, and 11% had three or more prior systemic therapies.

Efficacy results are summarised in Table 46.

Table 46: Efficacy results in KEYNOTE-146

Endpoint	**KEYTRUDA with lenvatinib n=94***
Objective Response Rate	
ORR (95% CI)	38.3% (29, 49)
Complete response rate	10.6%
Partial response rate	27.7%
Response duration	
Median in months (range)	NR (1.2+, 33.1+)†
% with duration ≥6 months	69%

* Median follow-up time of 18.7 months
† Based on patients (n=36) with a response by independent review
\+ Denotes ongoing
NR = not reached

Renal Cell Carcinoma

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

The efficacy of KEYTRUDA in combination with axitinib was investigated in a randomised, multicentre, open-label, active-controlled trial KEYNOTE-426, conducted in patients with advanced RCC, regardless of PD-L1 tumour status and International Metastatic RCC Database Consortium (IMDC) risk group categories. The trial excluded patients with a history of severe autoimmune disease, patient with a medical condition that required immunosuppression within 2 years of pembrolizumab-axitinib therapy, or those who had experienced a significant cardiac, cardiovascular, or cerebrovascular event within 12 months of pembrolizumab-axitinib therapy. 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:

- KEYTRUDA 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 KEYTRUDA and axitinib continued until RECIST 1.1-defined progression of disease as verified by BICR or confirmed by the investigator, unacceptable toxicity, or for KEYTRUDA, a maximum of 24 months. Administration of KEYTRUDA and axitinib was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Assessment of tumour status was performed at baseline, after randomisation at Week 12, then every 6 weeks thereafter until Week 54, and then every 12 weeks thereafter. Chemistry and haematology laboratory tests were performed at each cycle.

Among the 861 patients in KEYNOTE-426 (432 patients in the KEYTRUDA combination arm and 429 in the sunitinib arm), baseline characteristics were: median age of 62 years (range: 26 to 90); 38% age 65 or older; 73% male; 79% White and 16% Asian; 99.9% had a Karnofsky Performance Score (KPS) of ≥70%; patient distribution by IMDC risk categories was 31% favorable, 56% intermediate and 13% poor.

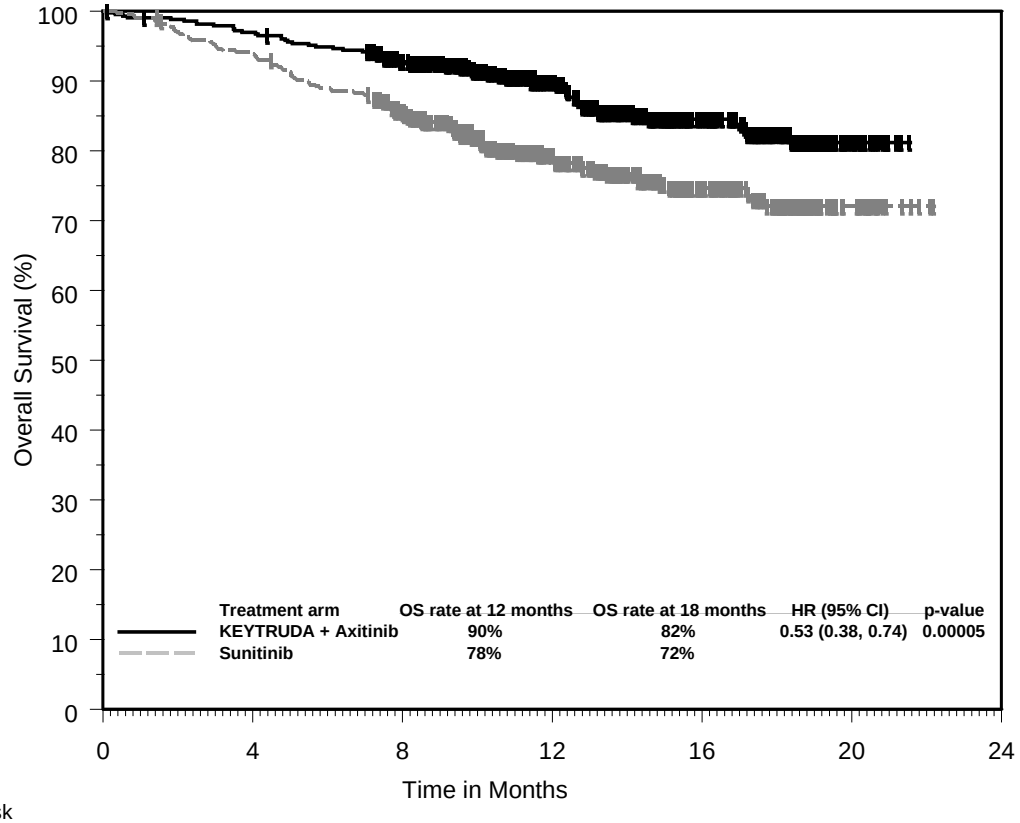
The primary efficacy outcome measures were OS and PFS (as assessed by BICR according to RECIST 1.1). Secondary efficacy outcome measures were ORR and response duration, as assessed by BICR using RECIST 1.1. The median follow-up time for 432 patients treated with KEYTRUDA and axitinib was 13.2 months (range: 0.1 – 21.5 months). Table 47 summarises key efficacy measures. Improvements in OS, PFS and ORR were shown consistently across all tested subgroups, including subgroups by IMDC risk category and PD-L1 tumour expression status.

Table 47: Response to KEYTRUDA and Axitinib in Patients with Advanced RCC in KEYNOTE-426

Endpoint	KEYTRUDA with axitinib n=432	Sunitinib n=429
OS		
Number of patients with event (%)	59 (14%)	97 (23%)
Median in months (95% CI)	Not reached (NA, NA)	Not reached (NA, NA)
Hazard ratio* (95% CI)	0.53 (0.38, 0.74)	
p-Value†	0.00005	
12-month OS rate (95% CI)	90% (86, 92)	78% (74, 82)
18-month OS rate (95% CI)	82% (77, 86)	72% (66, 77)
PFS		
Number of patients with event (%)	183 (42%)	213 (50%)
Median in months (95% CI)	15.1 (12.6, 17.7)	11.0 (8.7, 12.5)
Hazard ratio* (95% CI)	0.69 (0.56, 0.84)	
p-Value†	0.00012	
ORR		
Overall response rate‡ (95% CI)	59% (54, 64)	36% (31, 40)
Complete response	6%	2%
Partial response	53%	34%
p-Value§	<0.0001	
Duration of Response		
Median in months (range)	Not reached (1.4+, 18.2+)	15.2 (1.1+, 15.4+)
Number (%¶) of patients with duration ≥6 months	161 (88%)	84 (81%)
Number (%¶) of patients with duration ≥12 months	58 (71%)	26 (62%)

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

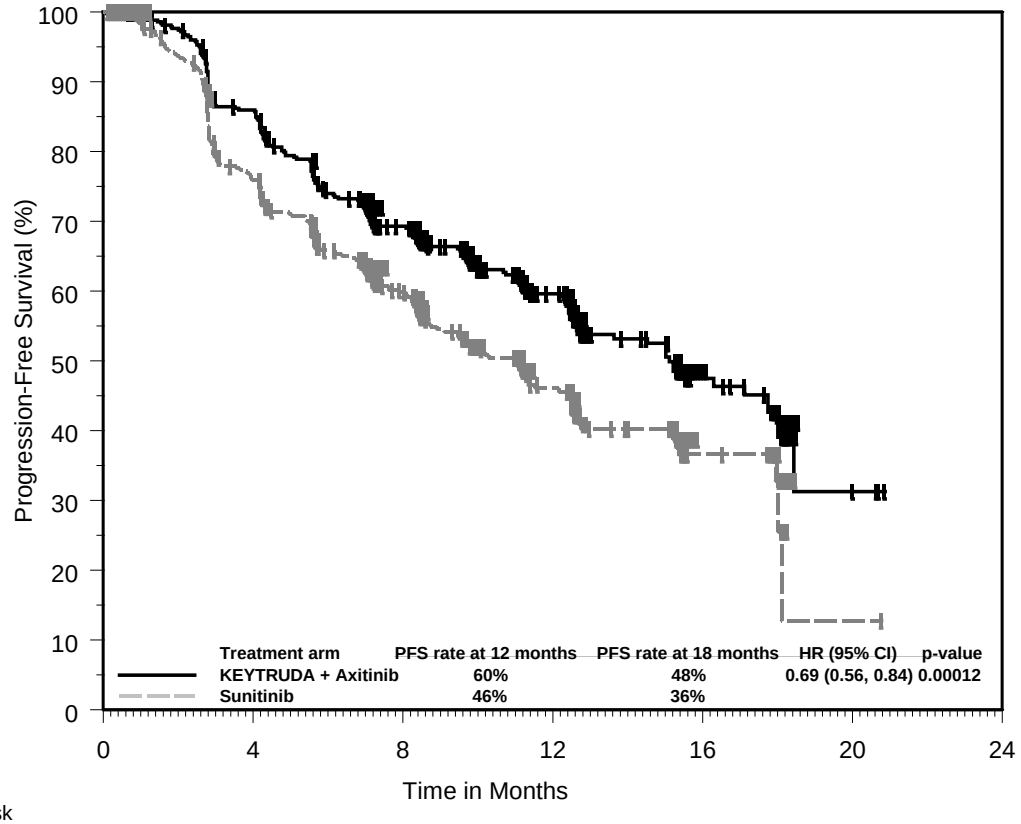
Figure 20: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-426 (Intent to Treat population)



Number at Risk

KEYTRUDA + Axitinib:	432	417	378	256	136	18	0
Sunitinib:	429	401	341	211	110	20	0

Figure 21: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-426 (Intent to Treat population)



Number at Risk

KEYTRUDA + Axitinib:	432	357	251	140	42	3	0
Sunitinib:	429	302	193	89	29	1	0

Cutaneous Squamous Cell Carcinoma

KEYNOTE 629: Open-label trial of monotherapy in cutaneous cSCC patients naïve to treatment

The efficacy of KEYTRUDA was investigated in KEYNOTE-629, a multicentre, multi-cohort, non-randomised, open-label, single-arm trial that enrolled 105 patients with cutaneous squamous cell carcinoma. The trial excluded patients with autoimmune disease or a medical condition that required immunosuppression.

Patients received KEYTRUDA 200 mg intravenously every 3 weeks until documented disease progression, unacceptable toxicity, or a maximum of 24 months. Patients with initial radiographic disease progression could receive additional doses of KEYTRUDA during confirmation of progression unless disease progression was symptomatic, rapidly progressive, required urgent intervention, or occurred with a decline in performance status.

Assessment of tumour status was performed every 6 weeks during the first year, and every 9 weeks during the second year. The major efficacy outcome measures were ORR and DoR as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target

lesions and a maximum of 5 target lesions per organ.

Among the 105 patients treated, the study population characteristics were: median age of 72 years (range: 29 to 95); 71% age 65 or older; 76% male; 71% White; 25% race unknown; 34% ECOG PS of 0 and 66% ECOG PS of 1. Forty-five percent of patients had locally recurrent only cSCC, 24% had metastatic only cSCC, and 31% had both locally recurrent and metastatic cSCC. Eighty-seven percent received one or more prior lines of therapy; 74% received prior radiation therapy.

Efficacy results are summarised in Table 48.

Table 48: Efficacy Results for Patients with Cutaneous Squamous Cell Carcinoma

Endpoint	**n=105***
Objective Response Rate[†]	
ORR % (95% CI)	34% (25, 44)
Complete response rate	4%
Partial response rate	31%
Response duration	
Median in months (range)	Not reached (2.7, 13.1+)[‡]
% with duration ≥6 months	80%[§]

* Median follow-up time of 9.5 months
[†] Assessed by BICR using RECIST 1.1
[‡] Based on patients (n=36) with a response by independent review
[§] Based on Kaplan-Meier estimates; includes 22 patients with responses of 6 months or longer

Oesophageal Cancer

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

KEYNOTE-590
The efficacy of KEYTRUDA was investigated in KEYNOTE-590, a multicenter, randomised, placebo-controlled trial that enrolled 749 patients as a first-line treatment in patients with locally advanced unresectable or metastatic carcinoma of the oesophagus or gastroesophageal junction. All patients were required to have tumour specimens for PD-L1 testing at a central laboratory; PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx kit. Patients with active autoimmune disease, a medical condition that required immunosuppression, or known HER-2 positive GEJ adenocarcinoma patients were ineligible. Randomisation was stratified by tumour histology (squamous cell carcinoma vs. adenocarcinoma), geographic region (Asia vs. ex-Asia), and ECOG performance status (0 vs. 1).

Patients were randomised (1:1) to one of the following treatment arms; all study medications were administered via intravenous infusion:

- KEYTRUDA 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 FU 800 mg/m^2 IV per day on Day 1 to Day 5 of each three-week cycle, or per local standard for FU administration, for up to 24 months.
- Placebo on Day 1 of each three-week cycle in combination with cisplatin 80 mg/m^2 IV on Day 1 of each three-week cycle for up to six cycles and FU 800 mg/m^2 IV per day

on Day 1 to Day 5 of each three-week cycle, or per local standard for FU administration, for up to 24 months.

Treatment with KEYTRUDA or chemotherapy continued until unacceptable toxicity or disease progression. Patients randomised to KEYTRUDA were permitted to continue beyond the first RECIST v1.1-defined disease progression if clinically stable until the first radiographic evidence of disease progression was confirmed at least 4 weeks later with repeat imaging. Patients treated with KEYTRUDA without disease progression could be treated for up to 24 months. Assessment of tumour status was performed every 9 weeks. The major efficacy outcome measures were OS and PFS as assessed by the investigator according to RECIST v1.1. Secondary efficacy outcome measures were ORR and DoR, according to RECIST v1.1, as assessed by the investigator.

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

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

Table 49 summarises the key efficacy measures for KEYNOTE-590. The Kaplan-Meier curves for OS and PFS are shown in Figures 22-27.

Table 49: Efficacy Results in Patients with Locally Advanced Unresectable or Metastatic Oesophageal Cancer in KEYNOTE 590

Endpoint	KEYTRUDA 200 mg every 3 weeks Cisplatin 5-FU n=373	Placebo Cisplatin 5-FU n=376
OS		
Number (%) of patients with event	262 (70%)	309 (82%)
Median in months* (95% CI)	12.4 (10.5, 14.0)	9.8 (8.8, 10.8)
Hazard ratio† (95% CI)	0.73 (0.62, 0.86)	
p-Value (stratified log-rank)	<0.0001	
PFS‡		
Number (%) of patients with event	297 (79.6%)	333 (88.6%)
Median in months* (95% CI)	6.3 (6.2, 6.9)	5.8 (5.0, 6.0)
Hazard ratio†(95% CI)	0.65 (0.55, 0.76)	
p-Value (stratified log-rank)	<0.0001	
Objective Response Rate‡		
ORR % (95% CI)	45% (39.9, 50.2)	29.3% (24.7,34.1)
Complete response rate	6.4%	2.4%
Partial response rate	38.6%	26.9%
p-Value (Miettinen-Nurminen)	<0.0001	
Response Duration‡,§		
Median duration of response in months (range)	8.3 (1.2+, 31.0+)	6.0 (1.5+, 25.0+)
% of patients with duration ≥6 months*	73.5%	50.4%
% of patients with duration ≥12 months*	38.6%	17.8%
% of patients with duration ≥18 months*	29.4%	7.7%

* Based on Kaplan-Meier estimation
† Based on the stratified Cox proportional hazard model
‡ Assessed by investigator using RECIST 1.1
§ Based on patients with a best overall response as confirmed complete or partial response

Figure 22: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-590

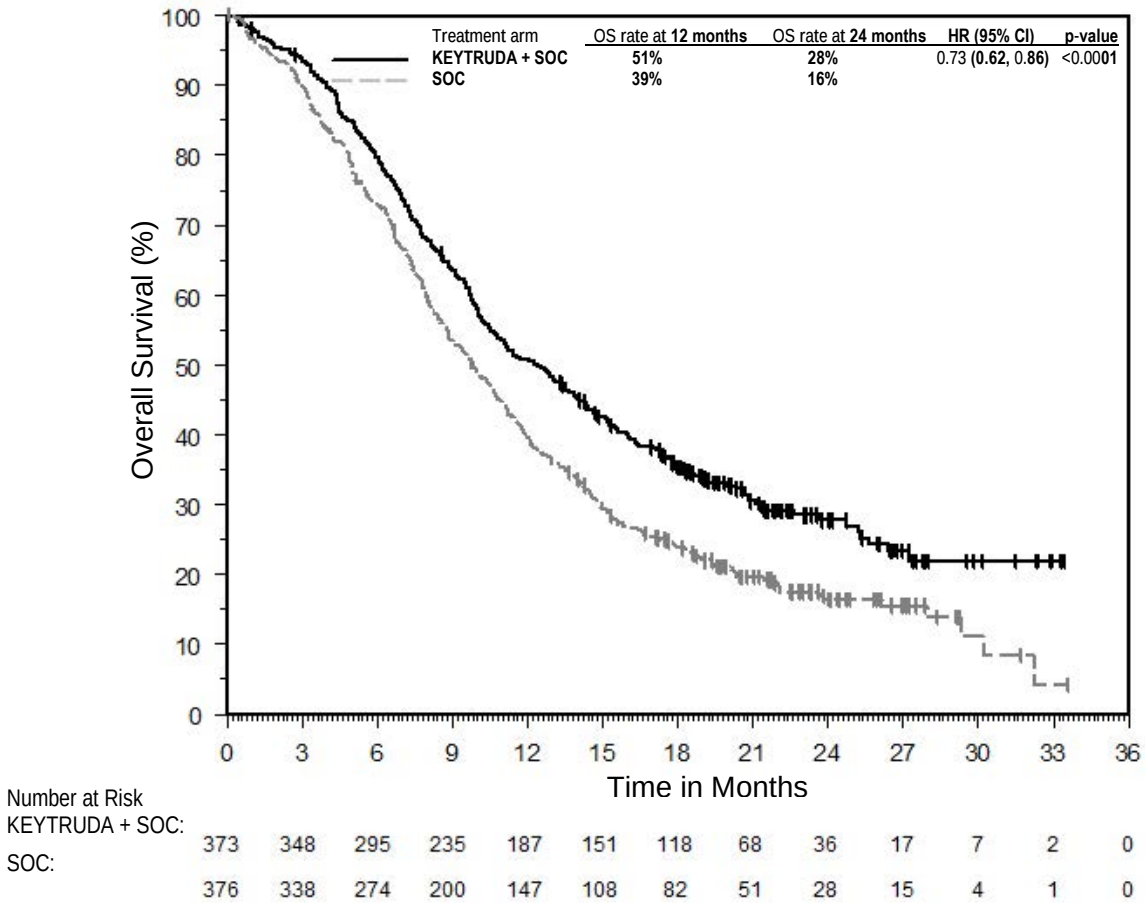


Figure 23: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-590 with PD-L1 expression (CPS ≥ 10)

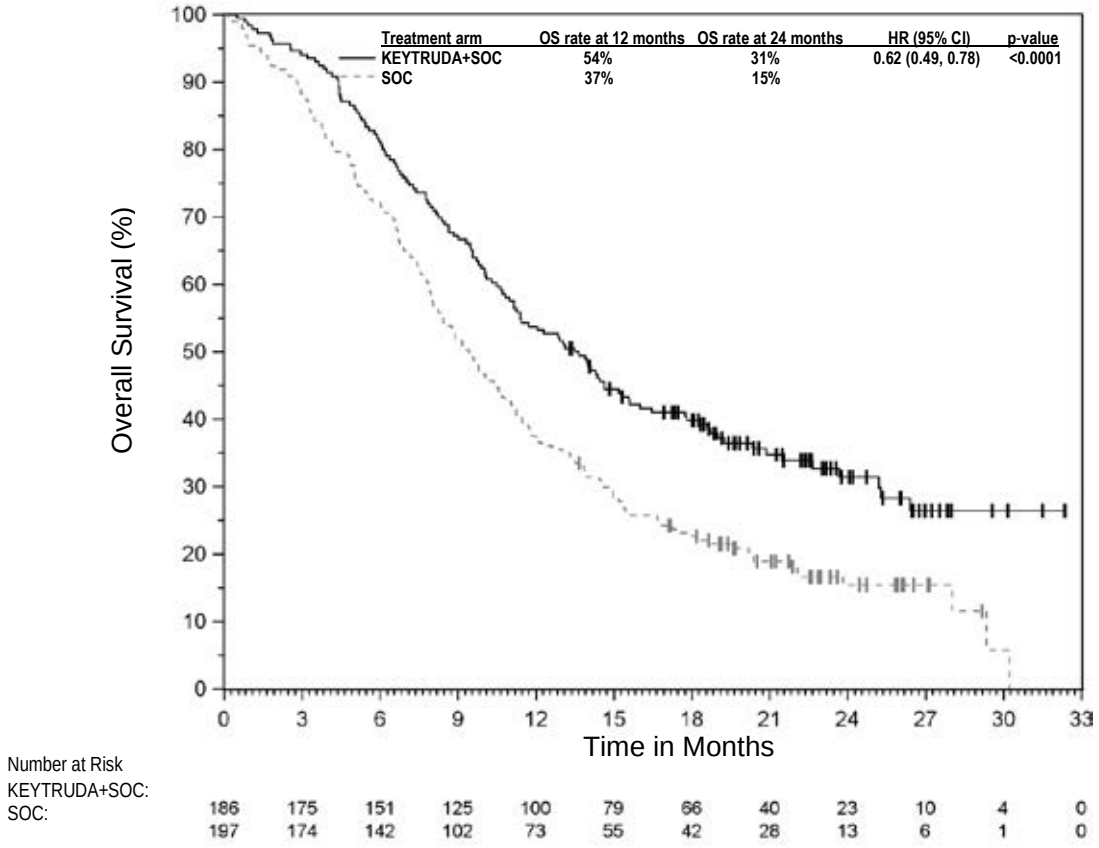
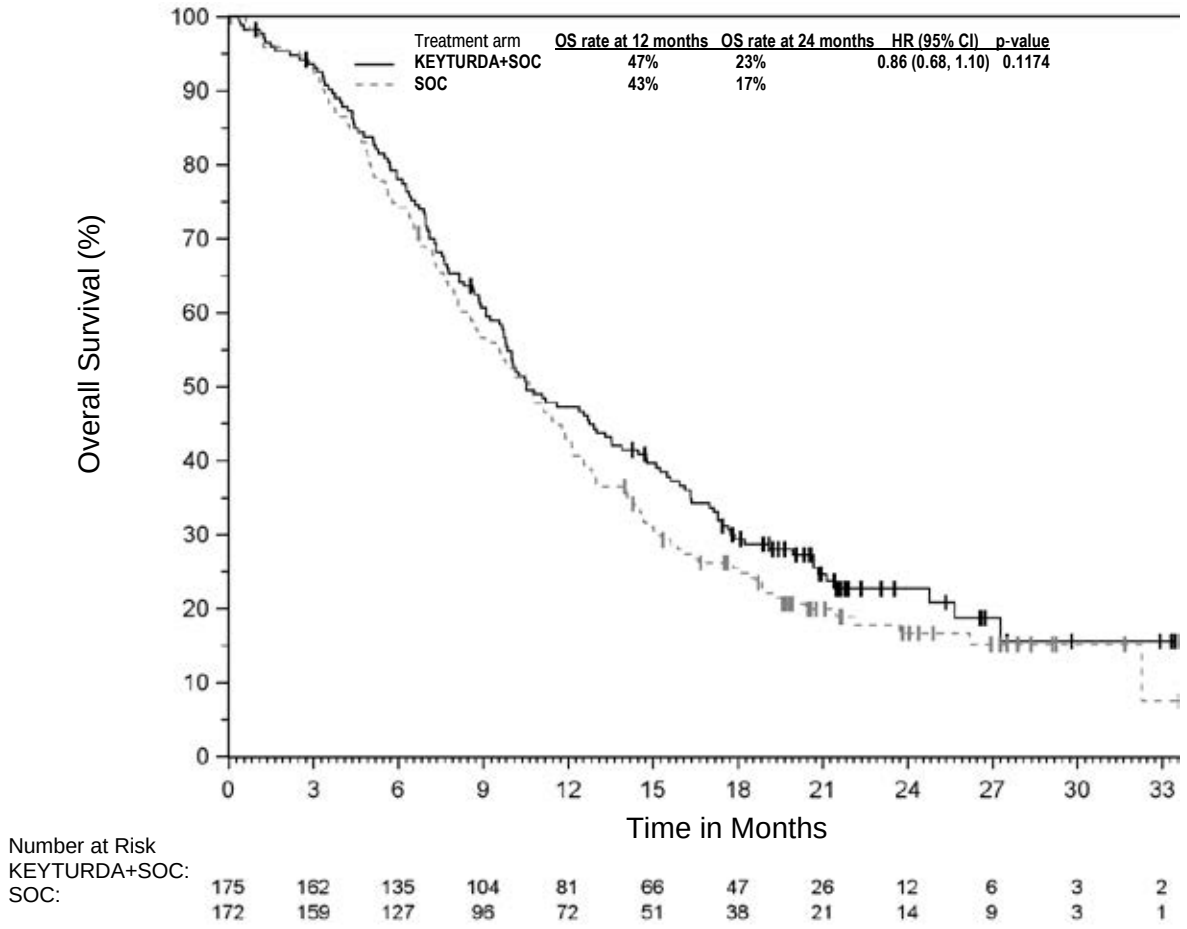
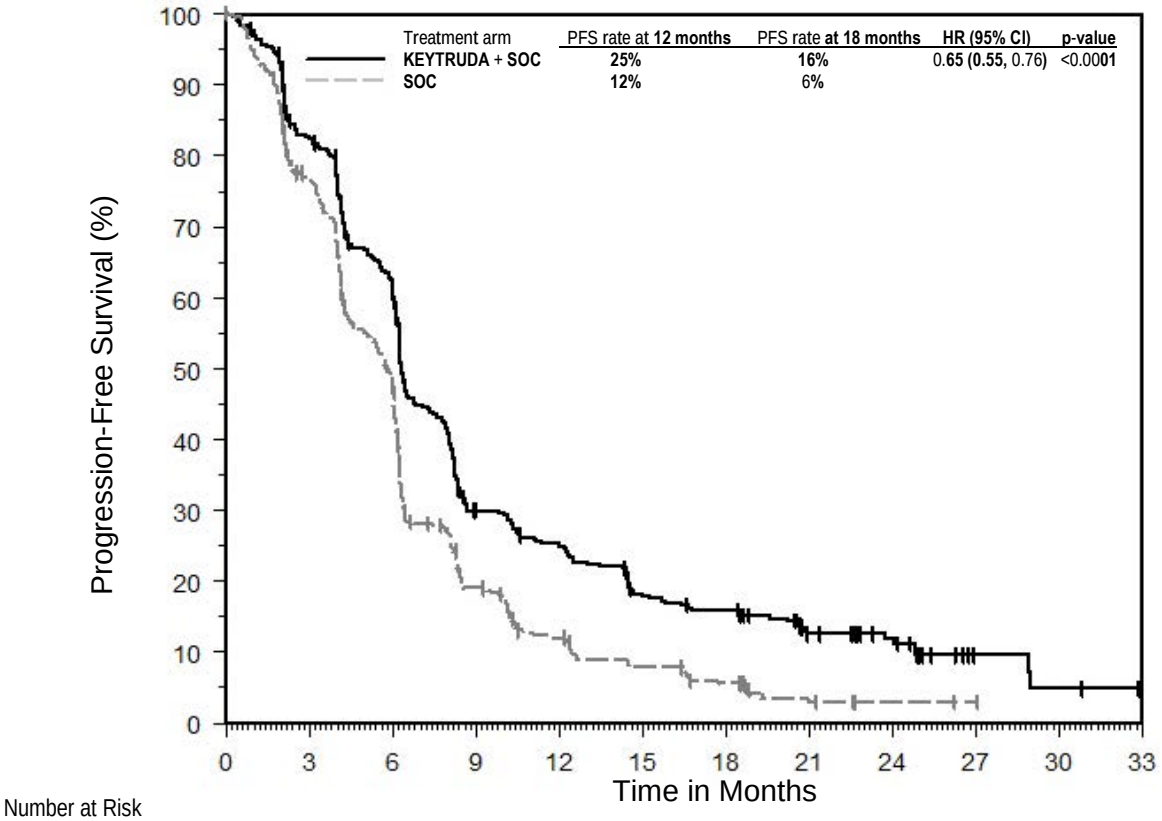


Figure 24: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-590 with PD-L1 expression (CPS < 10)



In a pre-specified formal test of OS in patients with PD-L1 CPS ≥ 10 (n=383), the median was 13.5 months (95% CI: 11.1, 15.6) for the KEYTRUDA arm and 9.4 months (95% CI: 8.0, 10.7) for the placebo arm, with a HR of 0.62 (95% CI: 0.49, 0.78; p-Value < 0.0001). In an exploratory analysis, in patients with PD-L1 CPS < 10 (n=347), the median OS was 10.5 months (95% CI: 9.7, 13.5) for the KEYTRUDA arm and 10.6 months (95% CI: 8.8, 12.0) for the placebo arm, with a HR of 0.86 (95% CI: 0.68, 1.10).

Figure 25: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-590



Number at Risk

KEYTRUDA + SOC:	373	289	210	96	79	55	45	25	17	4	2	0
SOC:	376	278	172	62	36	22	14	6	2	1	0	0

Figure 26: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-590 with PD-L1 expression (CPS ≥ 10)

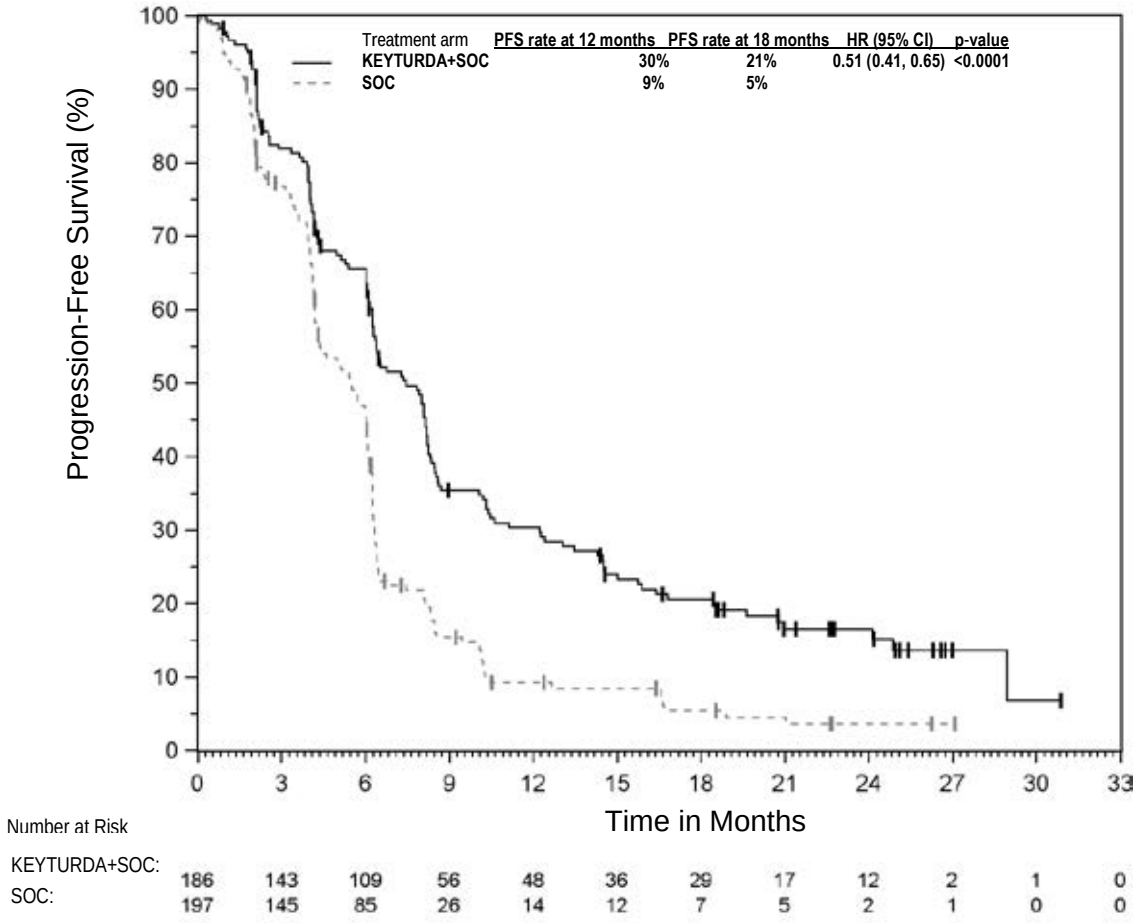
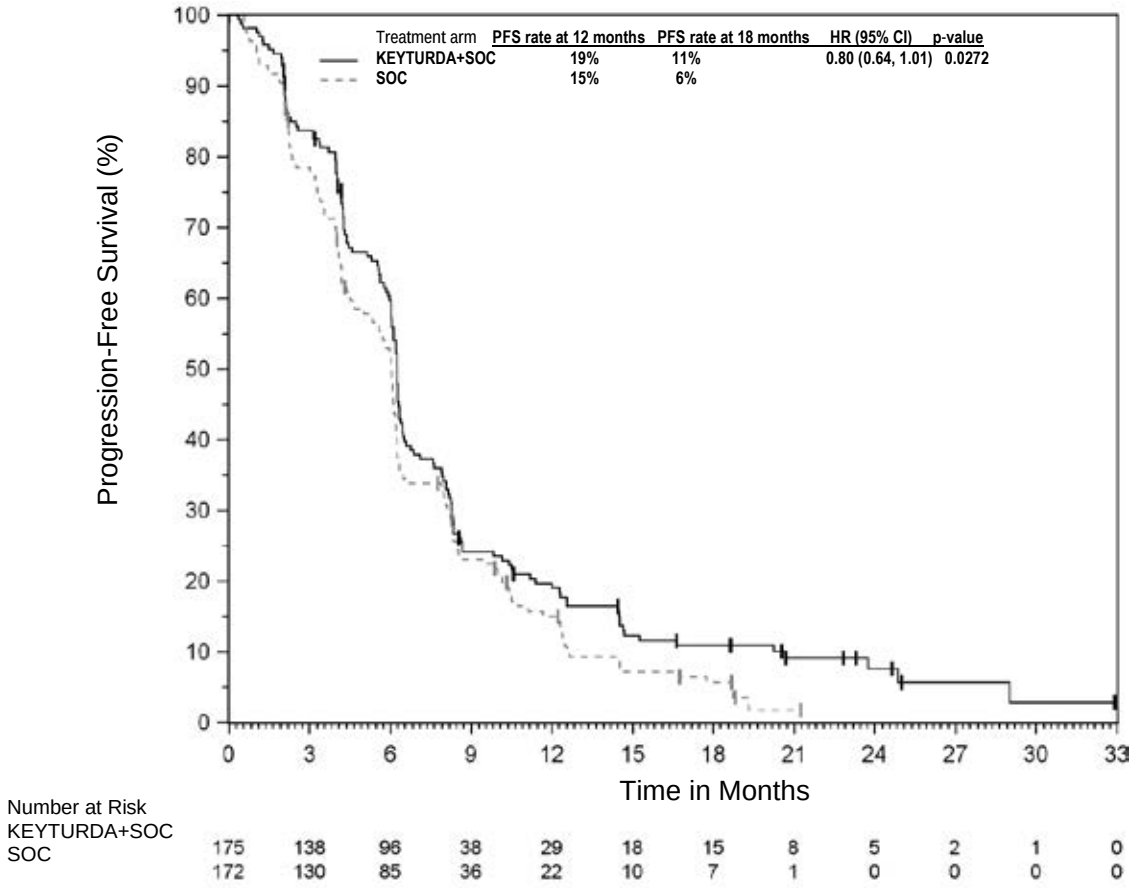


Figure 27: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-590 with PD-L1 expression (CPS < 10)



Tumour Mutational Burden High (TMB-H) cancer

The efficacy of KEYTRUDA was investigated in a prospectively-planned retrospective analysis of 102 adult patients with certain previously treated, unresectable or metastatic solid tumours with high tumour mutational burden (TMB-H), who were enrolled in Cohorts A through J of KEYNOTE-158, a multicentre, non-randomised, open-label, multi-cohort trial. Tumour types eligible for enrolment in Cohorts A through J were anal squamous cell carcinoma, cholangiocarcinoma, neuroendocrine carcinoma, endometrial carcinoma, cervical squamous cell carcinoma, vulvar squamous cell carcinoma, small cell lung carcinoma, mesothelioma, thyroid carcinoma and salivary gland carcinoma. The trial excluded patients who had previously received an anti-PD-1 or other immune-modulating monoclonal antibody, or who had an autoimmune disease or a medical condition that required immunosuppression. Patients received KEYTRUDA 200 mg intravenously every 3 weeks until unacceptable toxicity or documented disease progression. Assessment of tumour status was performed every 9 weeks for the first 12 months, and every 12 weeks thereafter.

The statistical analysis plan pre-specified ≥10 and ≥13 mutations per megabase (mut/Mb) using the FoundationOne CDx assay as cutpoints to assess TMB. Testing of TMB was blinded with respect to clinical outcomes. The primary efficacy outcome measures were ORR and DoR in patients who received at least one dose of KEYTRUDA as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum

of 5 target lesions per organ.

In KEYNOTE-158, 1050 patients were included in the efficacy analysis population. TMB was analysed in the subset of 790 patients with sufficient tissue for testing based on protocol-specified testing requirements. Of the 790 patients, 102 (13%) had tumours identified as TMB-H, defined as TMB ≥10 mut/Mb. Among the 102 patients with TMB-H advanced solid tumours, the study population characteristics were: median age of 61 years (range: 27 to 80), 34% age 65 or older; 34% male; 81% White; and 41% ECOG PS of 0 and 58% ECOG PS of 1. Fifty-six percent of patients had at least two prior lines of therapy.

Efficacy results are summarised in Tables 50 and 51.

Table 50: Efficacy results for patients with TMB-H cancer in KEYNOTE-158

	KEYTRUDA 200 mg every 3 weeks	
	TMB ≥10 mut/Mb n=102*	**TMB ≥13 mut/Mb n=70**
Objective response rate (ORR)		
ORR (95% CI)	29% (21, 39)	37% (26, 50)
Complete response rate	4%	3%
Partial response rate	25%	34%
Duration of response (DOR)		
Responders, n	30	26
Median in months (range) †	NR (2.2+, 34.8+)	NR (2.2+, 34.8+)
% with duration ≥6 months	87%	88%
% with duration ≥12 months	57%	58%
% with duration ≥24 months	50%	50%

* Median follow-up time of 11.1 months
† From product-limit (Kaplan-Meier) method for censored data
\+ Denotes ongoing
NR = not reached

Table 51: Responses by tumour type (TMB-H)

	N	**Objective responses n (ORR)**	**95% CI**	**DOR range** (months)
Overall*	102	30 (29%)	(21%, 39%)	(2.2+, 34.8+)
Small cell lung cancer	34	10 (29%)	(15%, 47%)	(4.1, 32.5+)
Cervical cancer	16	5 (31%)	(11%, 59%)	(3.7+, 34.8+)
Endometrial cancer	15	7 (47%)	(21%, 73%)	(8.4+, 33.9+)
Anal cancer	14	1 (7%)	(0.2%, 34%)	(18.8+, 18.8+)
Vulvar cancer	12	2 (17%)	(2%, 48%)	(8.8, 11.0+)
Neuroendocrine cancer	5	2 (40%)	(5%, 85%)	(2.2+, 32.6+)
Salivary cancer	3	PR, SD, PD		(31.3, 31.3+)
Thyroid cancer	2	CR, CR		(8.2, 33.2+)
Mesothelioma cancer	1	PD		

* No patients with TMB ≥10 mut/Mb were identified in the cholangiocarcinoma cohort
\+ denotes ongoing
CR = complete response
PR = partial response
SD = stable disease
PD = progressive disease

In an exploratory analysis in 32 patients enrolled in KEYNOTE-158 whose cancer had TMB ≥10 mut/Mb and <13 mut/Mb, the ORR was 13% (95% CI: 4%, 29%), including two complete responses and two partial responses.

Paediatric population

KEYNOTE-051, a study of pembrolizumab in the paediatric population, 22 patients aged 11 years to 17 years with Hodgkin Lymphoma. The baseline characteristics were median age 15 years; 64% male; 68% White; 77% had a Lansky/Karnofsky scale 90-100 and 23% had scale 70-80. Eighty-six percent had two or more prior lines of therapy and 91% had Stage 3 or higher. In these paediatric patients with cHL, the ORR assessed by BICR according to the IWG 2007 criteria was 54.5%, 1 patient (4.5%) had a complete response and 11 patients (50.0%) had a partial response, and the ORR assessed by the Lugano 2014 criteria was 63.6%, 4 patients (18.2%) had a complete response and 10 patients (45.5%) had a partial response. Efficacy in this population was supported by extrapolation from adult data in Hodgkin Lymphoma.

Immunogenicity

In clinical studies in patients treated with pembrolizumab at a dose of 2 mg/kg every 3 weeks, 200 mg every 3 weeks or 10 mg/kg every 2 or 3 weeks, 36 (1.8%) of 2034 evaluable patients tested positive for treatment-emergent antibodies against pembrolizumab of which 9 (0.4%) patients had neutralizing antibodies against pembrolizumab. There was no evidence of an altered pharmacokinetic or safety profile with anti-pembrolizumab binding antibody development.

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics of pembrolizumab was studied in 2993 patients with various cancers who received doses in the range of 1 to 10 mg/kg every 2 weeks, 2 to 10 mg/kg every 3 weeks, or 200 mg every 3 weeks. There are no clinically meaningful differences in pharmacokinetics of pembrolizumab across indications.

Absorption

KEYTRUDA is dosed via the IV route and therefore is immediately and completely bioavailable.

Distribution

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

Metabolism

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

Excretion

Pembrolizumab clearance (CV%) is approximately 23% lower [geometric mean, 195 mL/day

(40%)] after achieving maximal change at steady state compared with the first dose (252 mL/day [CV%: 37%]); this decrease in clearance with time is not considered clinically important. The geometric mean value (CV%) for the terminal half-life (t½) is 22 days (32%).

Steady-state concentrations of pembrolizumab were reached by 16 weeks of repeated dosing with an every 3 week regimen and the systemic accumulation was 2.1 fold. The peak concentration (C_{max}), trough concentration (C_{min}), and area under the plasma concentration versus time curve at steady state (AUC_{ss}) of pembrolizumab increased dose proportionally in the dose range of 2 to 10 mg/kg every 3 weeks.
Following administration of pembrolizumab 200 mg every 3 weeks in patients with cHL, the observed median C_{min} at steady-state was up to 40% higher than that in other tumour types treated with the same dosage; however, the range of trough concentrations is similar. There are no notable differences in the median C_{max} between cHL and other tumour types. Based on available safety data in cHL and other tumour types, these differences are not considered clinically meaningful.

Special populations

The effects of various covariates on the pharmacokinetics of pembrolizumab were assessed in population pharmacokinetic analyses. The following factors had no clinically important effect on the clearance of pembrolizumab: age (range 15-94 years), gender, race, mild or moderate renal impairment, mild hepatic impairment, and tumour burden. The relationship between body weight and clearance supports the use of either fixed dose or body weight-based dosing to provide adequate and similar control of exposure. Pembrolizumab concentrations with weight-based dosing at 2 mg/kg every 3 weeks in paediatric patients (6 to 17 years) are comparable to those of adults at the same dose. For patients aged < 2 years, systemic exposure is predicted to be approximately 120% greater than in adults; this should be interpreted with caution as it is based on PK extrapolation.

Renal Impairment

The effect of renal impairment on the clearance of pembrolizumab was evaluated by population pharmacokinetic analysis in patients with mild (GFR <90 and ≥60 mL/min/1.73 m2) or moderate (GFR <60 and ≥30 mL/min/1.73 m2) renal impairment compared to patients with normal (GFR ≥90 mL/min/1.73 m2) renal function. No clinically important differences in the clearance of pembrolizumab were found between patients with mild or moderate renal impairment and patients with normal renal function. KEYTRUDA has not been studied in patients with severe (GFR <30 and ≥15 mL/min/1.73 m2) renal impairment [See Section 4.2 DOSE AND METHOD OF ADMINISTRATION].

Hepatic Impairment

The effect of hepatic impairment on the clearance of pembrolizumab was evaluated by population pharmacokinetic analysis in patients with mild hepatic impairment (total bilirubin (TB) 1.0 to 1.5 x ULN or AST >ULN as defined using the National Cancer Institute criteria of hepatic dysfunction) compared to patients with normal hepatic function (TB and AST ≤ULN). No clinically important differences in the clearance of pembrolizumab were found between patients with mild hepatic impairment and normal hepatic function. KEYTRUDA has not been studied in patients with moderate (TB >1.5 to 3 x ULN and any AST) or severe (TB >3 x ULN and any AST) hepatic impairment [See Section 4.2 DOSE AND METHOD OF ADMINISTRATION].

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

The genotoxic potential of pembrolizumab has not been evaluated. As a large protein molecule, pembrolizumab is not expected to interact directly with DNA or other chromosomal material.

Carcinogenicity

The carcinogenic potential of pembrolizumab has not been evaluated in long-term animal studies.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Histidine
Histidine hydrochloride monohydrate
Sucrose
Polysorbate 80
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 4.2 DOSE AND METHOD OF ADMINISTRATION.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in a refrigerator (2°C to 8°C).
Protect from light. Do not freeze. Do not shake.
For storage conditions after reconstitution or dilution of the medicinal product, see Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

6.5 NATURE AND CONTENTS OF CONTAINER

Carton of one 50 mg powder for injection or one 100 mg/4 mL concentrated injection single-use vial.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

KEYTRUDA (pembrolizumab) is a selective humanised monoclonal antibody designed to block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab is an IgG4 kappa immunoglobulin with an approximate molecular weight of 149 kDa. Pembrolizumab is produced in Chinese hamster ovary cells by recombinant DNA technology.

CAS number

1374853-91-4

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only medicine (Schedule 4)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

16 April 2015

10 DATE OF REVISION

21 October 2021

Summary table of changes

Section changed	Summary of new information
4.1	Added new paediatric indication for cHL
4.2	Added relapsed or refractory cHL for paediatric use
4.4	Deleted text regarding limited clinical data for the use of pembrolizumab in patients ineligible to ASCT; Updated Paediatric Use section; Updated data for Complications of allogeneic HSCT after treatment with KEYTRUDA in cHL
4.8	Added Sjögren's syndrome as AE term in Post-marketing Experience; Updated AE data for cHL patients (Table 2 - footnote); Added safety information for patients with relapsed or refractory cHL based on KEYNOTE-204 and KEYNOTE-087
5.1	Updated efficacy information based on KEYNOTE-204; Updated data of prior therapies and efficacy results based on latest outcome from KEYNOTE-087; Added a new section of paediatric population to include data from KEYNOTE-051
All	Mnior editorial revision

RCN: 000015213-AU