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) is indicated as monotherapy for the treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy. This indication is approved based on overall response rate and duration of response. Improvements in overall survival, progression-free survival or health-related quality of life have not been established.

Classical Hodgkin Lymphoma (cHL)

KEYTRUDA® (pembrolizumab) is indicated as monotherapy for the treatment of adult 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 is on the basis of objective response rate (ORR). 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.

Microsatellite instability-high cancer

**Colorectal**

KEYTRUDA® (pembrolizumab) is indicated in adult and paediatric patients for the treatment of unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer 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 single-arm trials. 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, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumours 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 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, 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.

## 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

Select patients for treatment with KEYTRUDA, as a single agent, based on the presence of positive PD-L1 expression, using a validated test conducted by an experienced laboratory in:

- stage III NSCLC who are not candidates for surgical resection or definitive chemoradiation (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials).
- metastatic NSCLC (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials).
- previously untreated locally advanced or metastatic urothelial carcinoma, cisplatin ineligible (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials).

### Recommended Dosing

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

- The recommended dose of KEYTRUDA in paediatric patients is 2 mg/kg (up to a maximum of 200 mg) for PMBCL or MSI-H/dMMR cancers.

When administering KEYTRUDA as part of a combination with chemotherapy, KEYTRUDA should be administered first. See also the Product Information for the chemotherapy agents administered in combination.

Patients should be treated with KEYTRUDA until disease progression or unacceptable toxicity. Patients with urothelial carcinoma, NSCLC, PMBCL or MSI-H/dMMR cancers without disease progression can be treated for up to 24 months or 35 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 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

**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 Grade 0-1* |
| | Severe or life-threatening (Grade 3 or 4) or recurrent moderate (Grade 2) | Permanently discontinue |
| Immune-mediated colitis | Moderate or severe (Grade 2 or 3) | Withhold until adverse reactions recover to Grade 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 Grade 0-1* |
| | Severe or life-threatening (Grade 3 or 4) | Permanently discontinue |
| Immune-mediated endocrinopathies | Severe or life-threatening (Grade 3 or 4) | Withhold until adverse reactions recover to Grade 0-1*<br><br>For patients with severe (Grade 3) or life-threatening (Grade 4) endocrinopathy that improves to Grade 2 or lower and is controlled with |

| Adverse reactions | Severity | Dose modification |
|---|---|---|
| | | hormone replacement, continuation of KEYTRUDA may be considered. |
| Immune-mediated hepatitis | 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 Grade 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 Grade 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 Grade 0-1* |
| | Severe or life-threatening (Grade 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 (Grade 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 Grade 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 hematological toxicity, KEYTRUDA should be withheld until adverse reactions recover to Grade 0-1.

When administering KEYTRUDA in combination with lenvatinib for the treatment of endometrial carcinoma,

| Adverse reactions | Severity | Dose modification |
|---|---|---|

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.

## 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 solutions 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 24 hours. If refrigerated, allow the vials and/or IV bags to come to room temperature prior to use.
- 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 PMBCL and MSI-H/dMMR 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.

**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

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].

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

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

Monitor patients for signs and symptoms of hypophysitis (including hypopituitarism and secondary adrenal insufficiency) and exclude other causes. Administer corticosteroids to treat secondary 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) 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 and myasthenic syndrome/myasthenia gravis (including exacerbation). The following were reported in other clinical studies with KEYTRUDA or in post-marketing use: myocarditis, pericarditis and pericardial effusion, and peripheral neuropathy.

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); 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.

For subjects with relapsed or refractory classical Hodgkin lymphoma, clinical data for the use of pembrolizumab in patients ineligible to ASCT due to reasons other than failure to salvage chemotherapy are limited (see section 5.1 Pharmacodynamic Properties).

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

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 a study, 87 paediatric patients (36 children ages 9 months to less than 12 years and 51 adolescents ages 12 years to 18 years) with advanced melanoma, lymphoma, or PD-L1 positive advanced, relapsed, or refractory solid tumours were administered KEYTRUDA 2 mg/kg every 3 weeks. Patients received KEYTRUDA for a median of 3 doses (range 1-26 doses), with 71 patients (82%) 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, vomiting, fatigue, constipation, abdominal pain and nausea.

Efficacy for paediatric patients with PMBCL or MSI-H/dMMR 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 23 patients with cHL who proceeded to allogeneic HSCT after treatment with KEYTRUDA on any trial, 6 patients (26%) developed graft-versus-host-disease (GVHD), one of which was fatal, and 2 patients (9%) developed severe hepatic veno-occlusive disease (VOD) after reduced-intensity conditioning, one of which was fatal. 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].

## 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 |
| 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 patients with HNSCC (n=192) the incidence of hypothyroidism was 14.6% (all Grades) with 0.5.% Grade 3. In patients with cHL (n=241) the incidence of hypothyroidism was 14.1% (all Grades) with 0.4% Grade 3.
† 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%.

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 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 summarizes 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 %** |
| **Hematology** | | | | |
| 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** | | | | |

| | **KEYTRUDA 2 mg/kg every 3 weeks n=178** | | **Chemotherapy n=171** | |
|---|---|---|---|---|
| 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 |

| | **KEYTRUDA 2 mg/kg every 3 weeks n=178** | | **Chemotherapy n=171** | |
|---|---|---|---|---|
| Hypoalbuminemia | 43 | 4 | 39 | 1 |
| Increased Aspartate Aminotransferase | 26 | 2 | 17 | 1 |
| Increased Alkaline Phosphatase | 35 | 4 | 28 | 2 |
| **Hematology** | | | | |
| Anemia | 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 summarizes 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** | | | | |
| Diarrhea | 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 summarizes 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 dyspnea 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** | | | | |
| Dyspnea | 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

Adverse events occurring in patients with HNSCC were generally similar to those occurring in patients with melanoma or NSCLC, except with respect to the higher rate of hypothyroidism observed in patients with HNSCC (see Table 2). Of these 28 patients, 15 had no prior history of hypothyroidism.

Classical Hodgkin Lymphoma

In patients with cHL, a higher incidence of pyrexia (24%) possibly due to B-symptoms, hypothyroidism (14.1%) and upper respiratory tract infection (13%) have been noted. Other adverse events were generally similar to those occurring in patients with melanoma or NSCLC.

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 diarrhea. 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, diarrhea, 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 9 summarizes the incidence of adverse reactions occurring in at least 10% of patients receiving KEYTRUDA.

**Table 9: Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-052**

| | **KEYTRUDA**<br>**200mg every 3 weeks**<br>**N=370** | |
|---|---|---|
| **Adverse Reaction** | **All Grades* (%)** | **Grades 3 – 4 (%)** |
| All Adverse Reactions | 96 | 49 |
| **Blood and Lymphatic System Disorders** | | |

| | | |
|---|---|---|
| Anemia | 17 | 7 |
| **Gastrointestinal Disorders** | | |
| Constipation | 21 | 1.1 |
| Diarrhea† | 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 |
| Dyspnea | 11 | 0.5 |
| **Skin and Subcutaneous Tissue Disorders** | | |
| Rash[Þ] | 21 | 0.5 |
| Pruritis | 19 | 0.3 |
| Edema peripheral | 14 | 1.1 |

- * Graded per NCI CTCAE v4.0
- † Includes diarrhea, 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 multicenter, 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%), diarrhea (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, anemia, and pneumonitis.

Table 10 summarizes the incidence of adverse reactions occurring in at least 10% of patients receiving KEYTRUDA. Table 11 summarizes the incidence of laboratory abnormalities that occurred in at least 20% of patients receiving KEYTRUDA.

**Table 10: 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 |
| Diarrhea‡ | 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 |
| Dyspneaß | 14 | 1.9 | 12 | 1.2 |
| **Skin and Subcutaneous Tissue Disorders** | | | | |
| Pruritus | 23 | 0 | 6 | 0.4 |

| | | | | |
|---|---|---|---|---|
| Rash[à] | 20 | 0.4 | 13 | 0.4 |

- [*] Chemotherapy: paclitaxel, docetaxel, or vinflunine
- [†] Graded per NCI CTCAE v4.0
- [‡] Includes diarrhea, 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
- [Þ] Includes cough, productive cough
- [ß] Includes dyspnea, dyspnea 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 11: 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

MSI-H/dMMR cancer

Adverse events occurring in patients with MSI-H/dMMR cancer 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%), decreased weight (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 12 and 13 summarise adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in combination with lenvatinib.

**Table 12: 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** | | |
| Decreased weight | 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 13: Laboratory abnormalities worsened from baseline occurring in ≥3% 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 |

| **Laboratory Test*** | **KEYTRUDA 200 mg every 3 weeks with lenvatinib** | |
|---|---|---|
| | **All Grades %†** | **Grade 3-4 %†** |
| 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).

### Postmarketing 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.

*Musculoskeletal and connective tissue disorders:* arthritis

*Eye disorders:* Vogt-Koyanagi-Harada syndrome

*Immune system disorders:* haemophagocytic lymphohistiocytosis

**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.

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 multicenter, 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). Randomization 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 14 summarizes key efficacy measures.

**Table 14: Response to KEYTRUDA 10 mg/kg every 2 or 3 weeks in patients with ipilimumab-naïve advanced melanoma in KEYNOTE-006**

| **Endpoint** | **KEYTRUDA**<br><br>**10 mg/kg every 3 weeks n=277** | **KEYTRUDA**<br><br>**10 mg/kg every 2 weeks n=279** | **Ipilimumab**<br><br>**n=278** |
|---|---|---|---|
| **OS*** | | | |
| Number (%) of patients with event | 92 (33%) | 85 (30%) | 112 (40%) |

| **Endpoint** | **KEYTRUDA**<br>**10 mg/kg every 3 weeks n=277** | **KEYTRUDA**<br>**10 mg/kg every 2 weeks n=279** | **Ipilimumab**<br>**n=278** |
|---|---|---|---|
| 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<br>(NA, NA) | Not reached<br>(NA, NA) | Not reached<br>(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<br>(2.0+, 22.8+) | Not reached<br>(1.8+, 22.8) | Not reached<br>(1.1+, 23.8+) |
| % ongoing at 12 monthsᵖ | 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)**

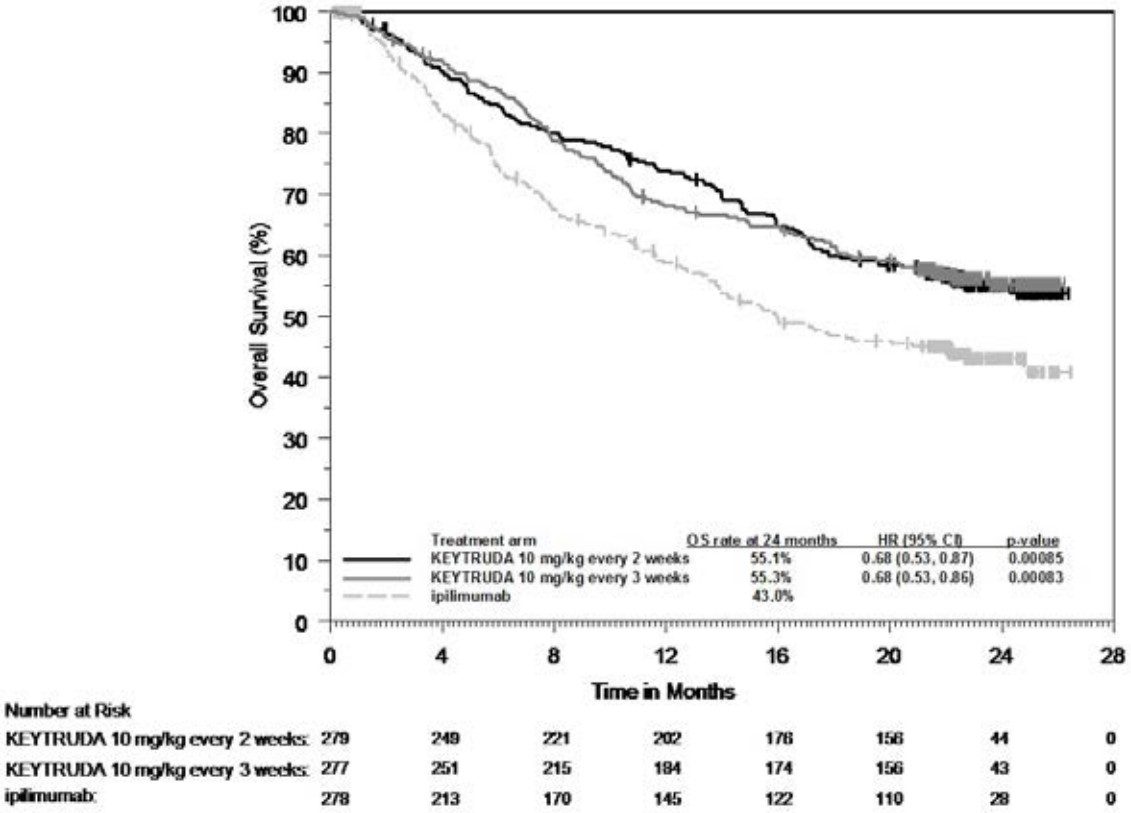
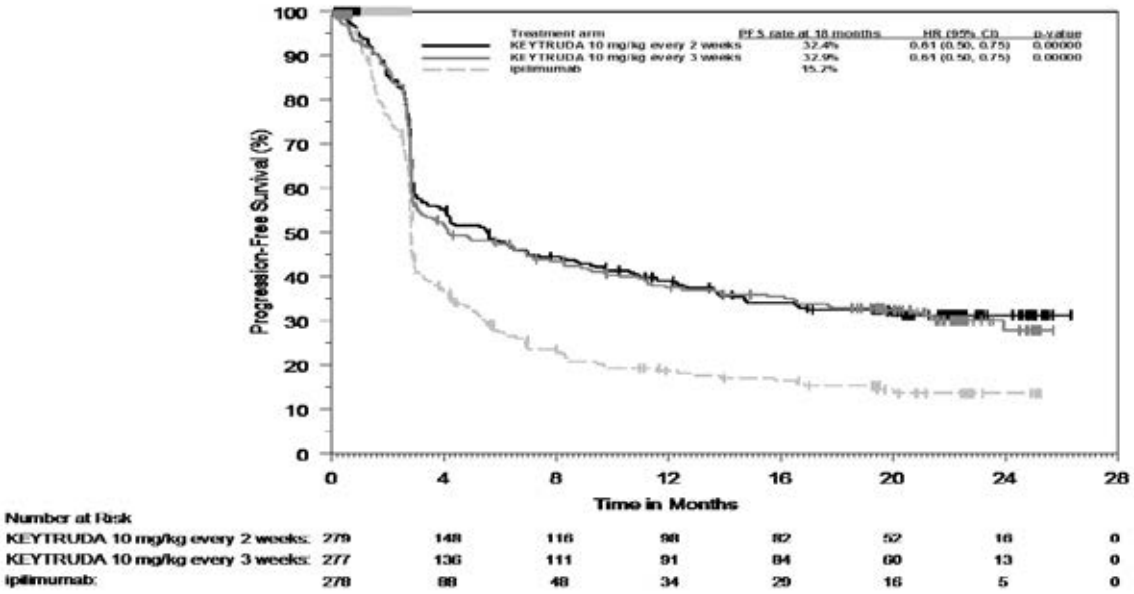


**Figure 2: Kaplan-Meier curve for progression-free survival (based on IRO) by treatment arm in KEYNOTE-006 (intent to treat population)**




*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 multicenter, 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 15 summarizes key efficacy measures in patients previously treated with ipilimumab, and the Kaplan-Meier curve for PFS is shown in Figure 3. 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 15: 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**<br><br>**2 mg/kg every 3 weeks**<br><br>**n=180** | **KEYTRUDA**<br><br>**10 mg/kg every 3 weeks**<br><br>**n=181** | **Chemotherapy**<br><br>**n=179** |
|---|---|---|---|
| **OS*** | | | |
| Number (%) of patients with event | 123 (68%) | 117 (65%) | 128 (72%) |

| **Endpoint** | **KEYTRUDA**<br>**2 mg/kg every 3 weeks**<br>**n=180** | **KEYTRUDA**<br>**10 mg/kg every 3 weeks**<br>**n=181** | **Chemotherapy**<br>**n=179** |
|---|---|---|---|
| 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) |

| **Endpoint** | **KEYTRUDA**<br>**2 mg/kg every 3 weeks**<br>**n=180** | **KEYTRUDA**<br>**10 mg/kg every 3 weeks**<br>**n=181** | **Chemotherapy**<br>**n=179** |
|---|---|---|---|
| Complete response % | 2% | 3% | 0% |
| Partial response % | 19% | 23% | 4% |
| **Response durationß by IRO¶** | | | |
| Median in months (range) | 22.8<br>(1.4+, 25.3+) | Not reached<br>(1.1+, 28.3+) | 6.8<br>(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

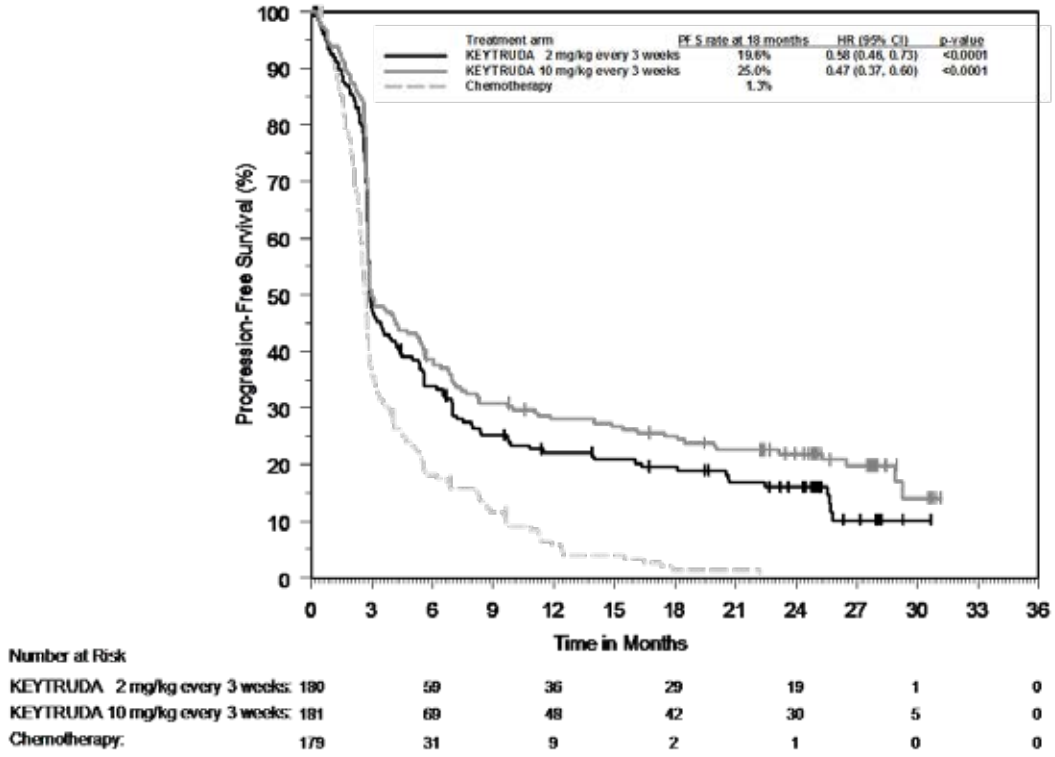
à Based on Kaplan-Meier estimates

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 16 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 16: 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 multicenter, 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 17 and Figure 4.

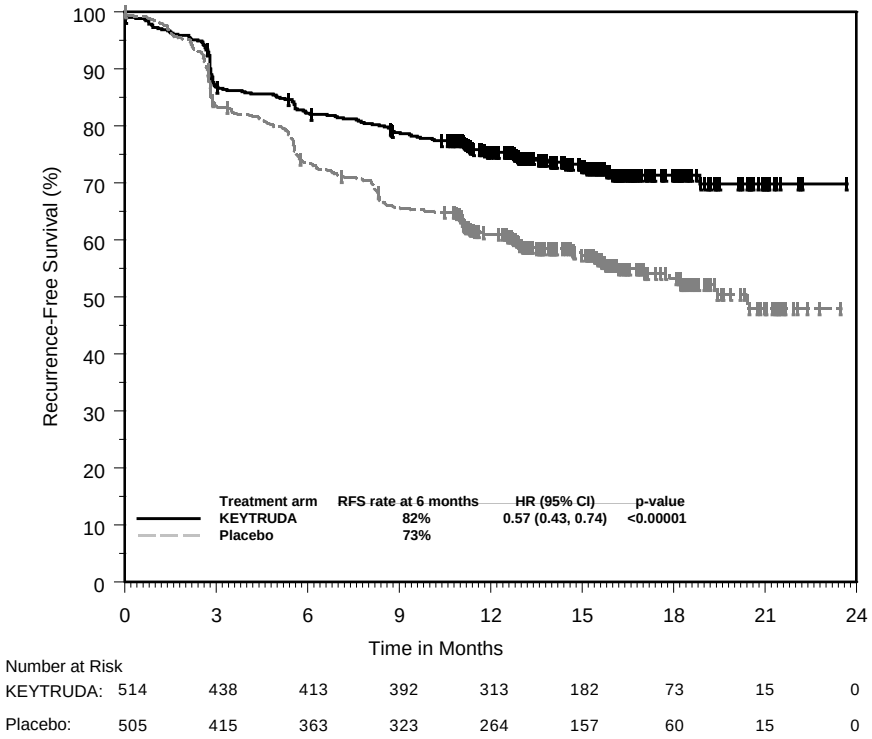
**Table 17: Efficacy Results in KEYNOTE-054**

| **Endpoint** | **KEYTRUDA**<br>**200 mg every 3 weeks**<br>**n=514** | **Placebo**<br>**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 Carcinoma (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 multicenter, 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 18 summarizes key efficacy measures.

**Table 18: Response to KEYTRUDA, pemetrexed, and platinum chemotherapy in patients with non-squamous NSCLC in KEYNOTE-189**

| **Endpoint** | • **KEYTRUDA + Pemetrexed + Platinum Chemotherapy**<br>**n=410** | • **Placebo + Pemetrexed + Platinum Chemotherapy**<br>**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<br>(NA, NA) | 11.3<br>(8.7, 15.1) |
| **PFS** | | |
| Number (%) of patients with event | 244 (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<br>(1.1+, 18.0+) | 7.8<br>(2.1+, 16.4+) |
| % with duration ≥6 months¶ | 81% | 63% |
| % with duration ≥9 months¶ | 60% | 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

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

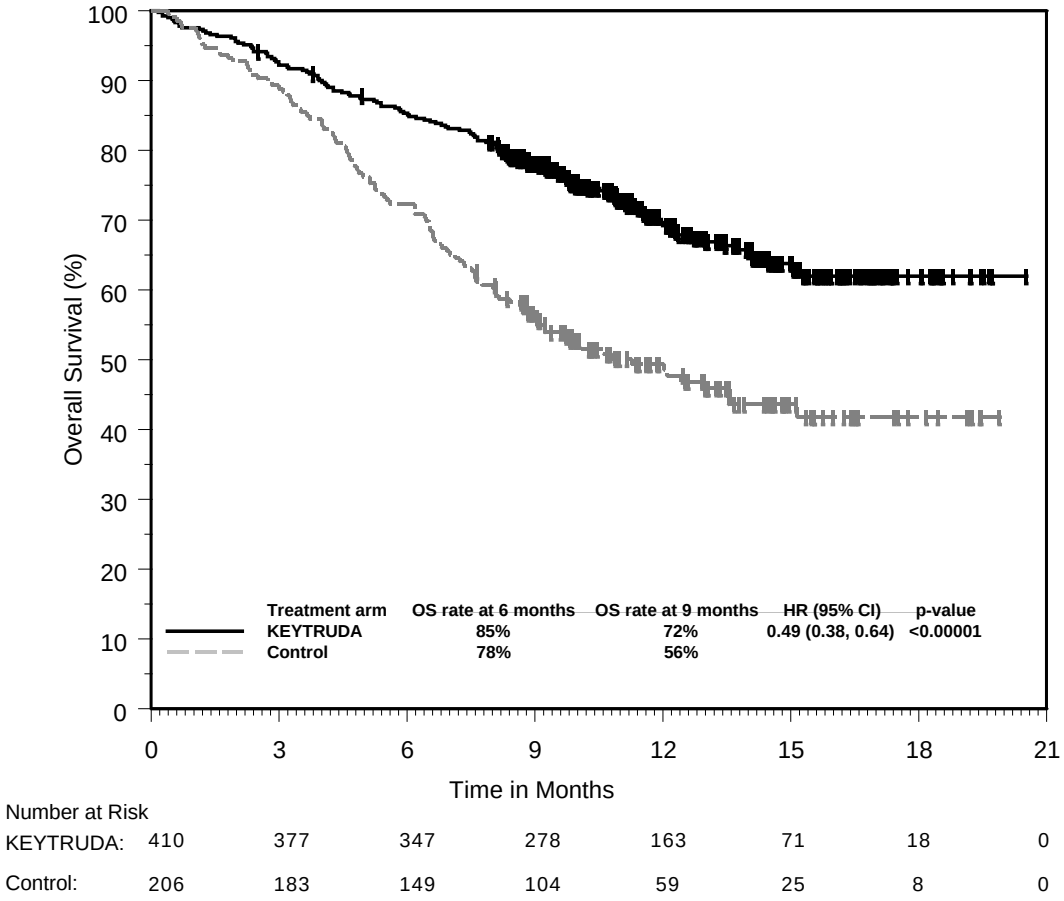
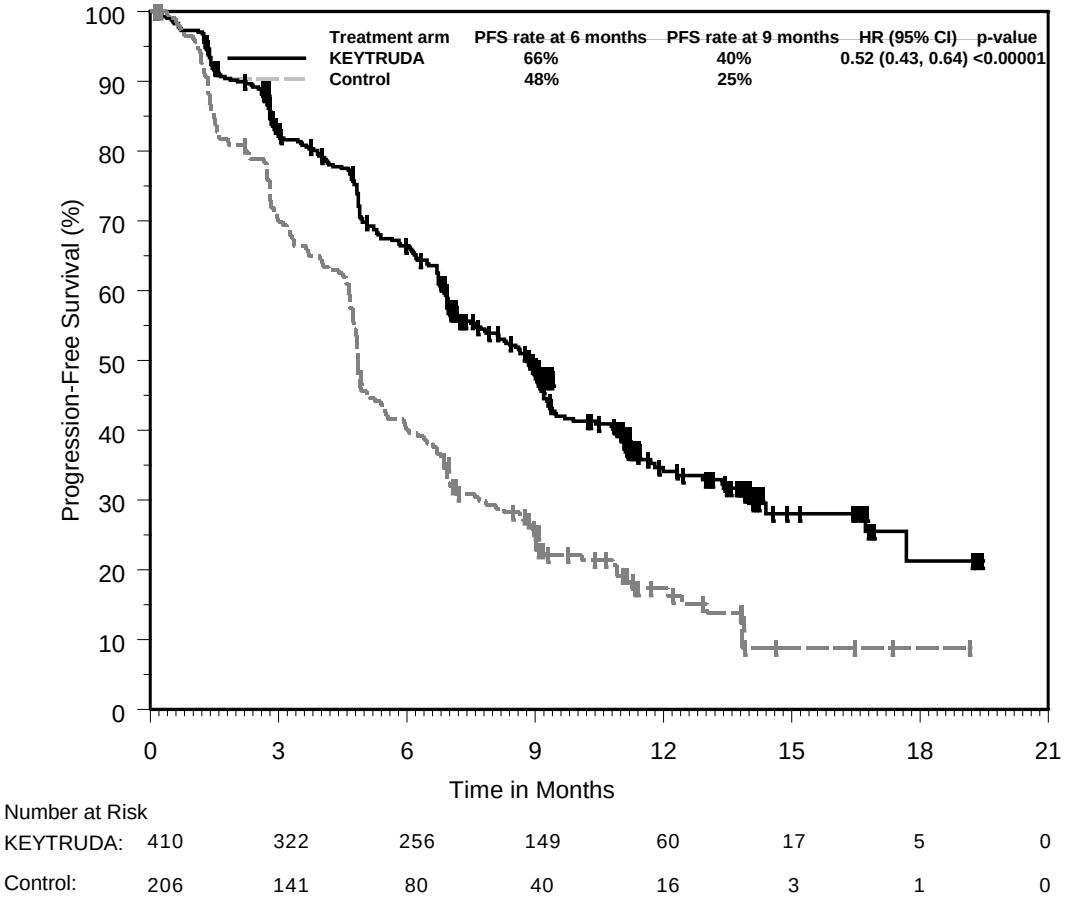


**Figure 6: Kaplan-Meier curve for progression-free survival by treatment arm in KEYNOTE-189 (intent to treat population)**




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, dyspnea 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, multicenter, 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. Randomization 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 single agent at the time of disease progression.

Assessment of tumour status was performed every 6 weeks through Week 18, every 9 weeks through Week 45 and every 12 weeks thereafter. 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 19 and Figures 7 and 8).

**Table 19: Efficacy Results in KEYNOTE-407**

| **Endpoint** | • **KEYTRUDA**<br>• **Carboplatin**<br>• **Paclitaxel/Nab-paclitaxel** | • **Placebo**<br>• **Carboplatin**<br>• **Paclitaxel/Nab-paclitaxel** |
|---|---|---|

| | **n=278** | **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 (4.3, 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

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

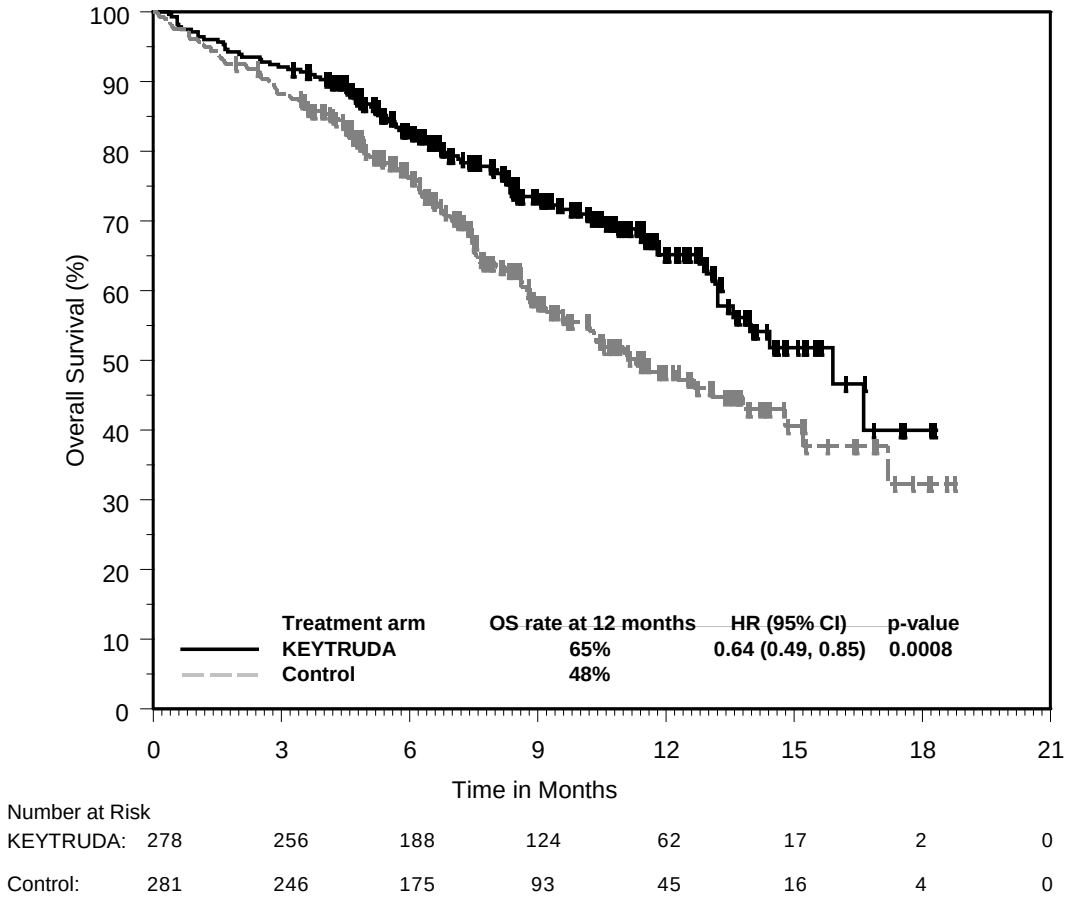
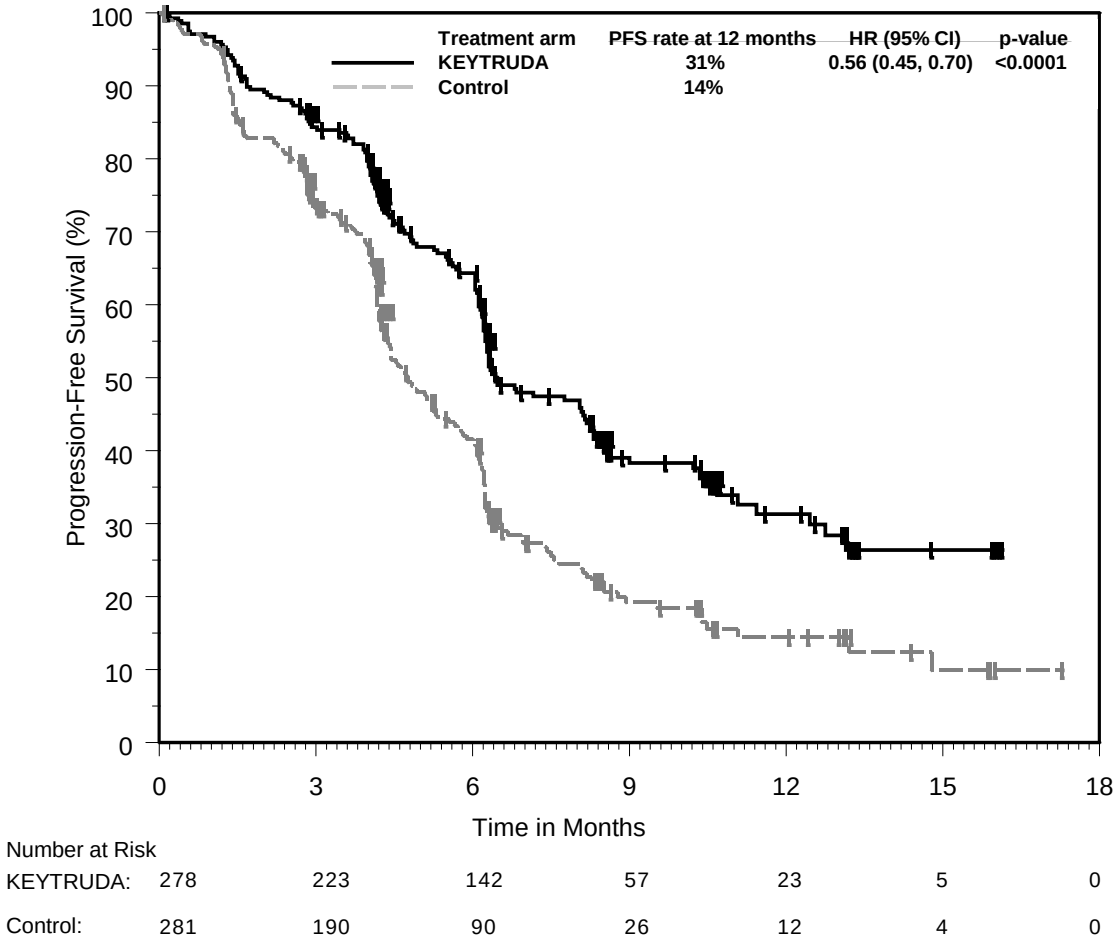


**Figure 8: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-407**




*KEYNOTE-042: Controlled trial of NSCLC patients naïve to treatment*

The efficacy of KEYTRUDA was investigated in KEYNOTE-042, a multicenter, randomized, 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 randomized (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.

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 20 summarizes key efficacy measures for the subgroup of patients with TPS ≥ 50% and the entire ITT population (TPS ≥ 1%).

**Table 20: 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) | | 0.81 (0.67, 0.99) | |
| Median in months (95% CI) | 5.4 (4.3, 6.2) | 6.5 (6.3, 7.0) | 7.1 (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<br>(2.1+, 31.2+) | 8.3<br>(1.8+, 28.1) | 22.0<br>(2.1+, 36.5+) | 10.8<br>(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

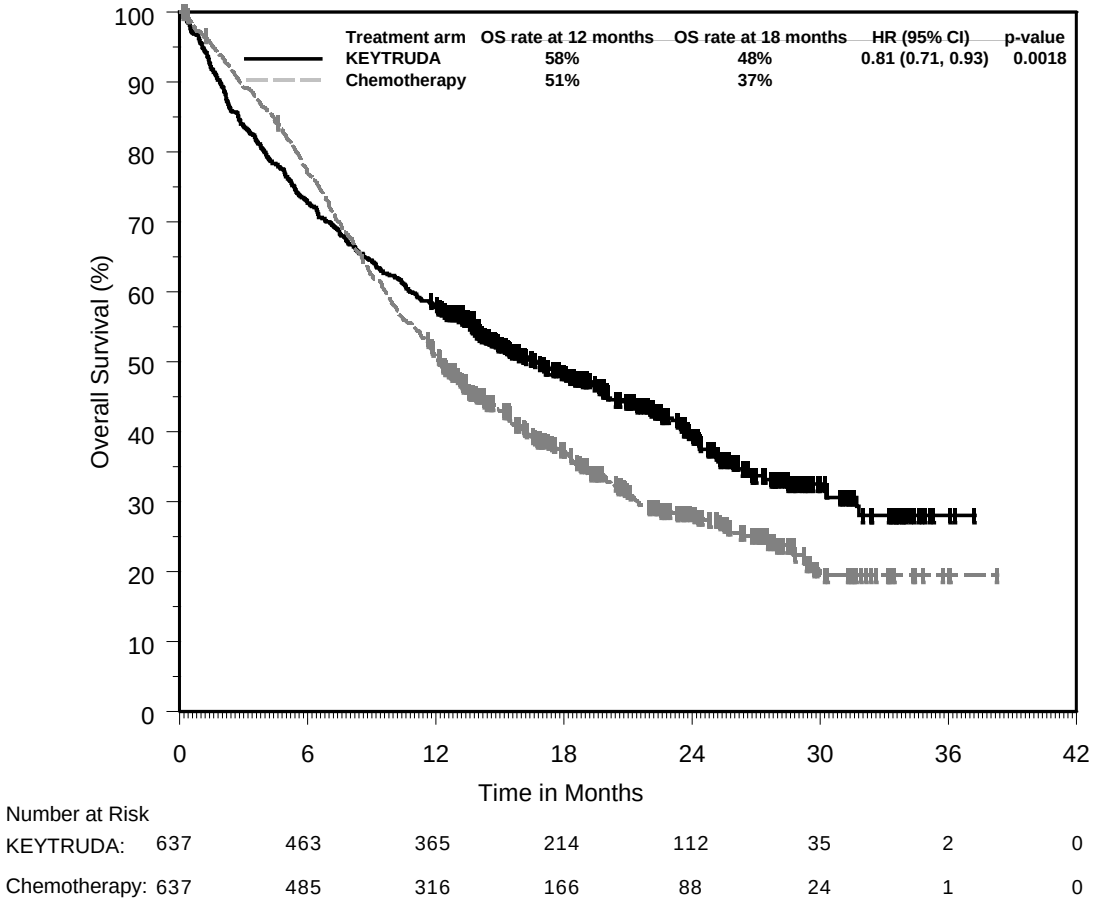
‡ Assessed by BICR using RECIST 1.1

§ 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 multicenter, 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.

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 21 summarizes key efficacy measures for the entire ITT population.

**Table 21: 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<br>(1.9+, 14.5+) | 6.3<br>(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)**

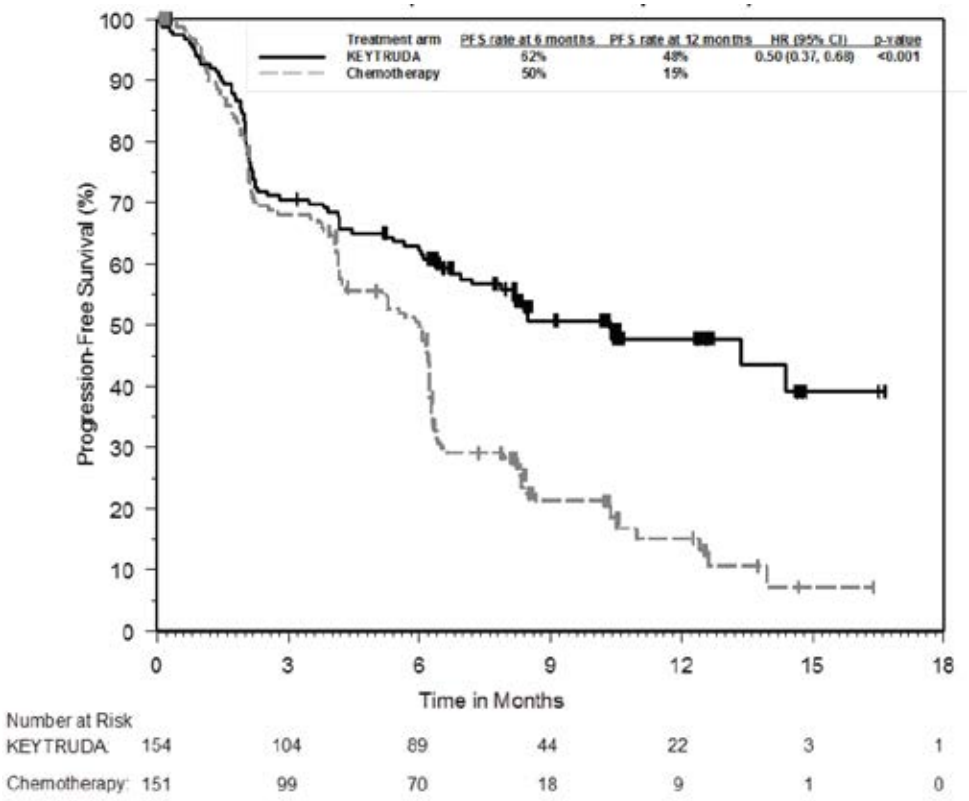
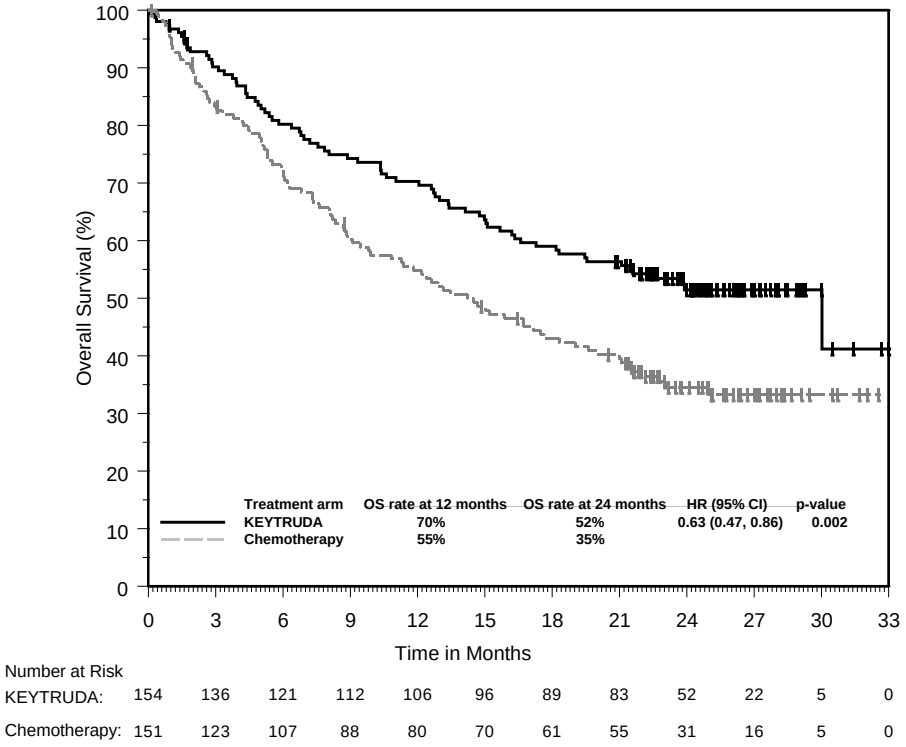


**Figure 11: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-024 (Intent to Treat Population)**




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, dyspnea, 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 multicenter, 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 22 summarizes 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 22: Response to KEYTRUDA 2 or 10 mg/kg every 3 Weeks in Previously Treated Patients with NSCLC in KEYNOTE-010**

| **Endpoint** | **KEYTRUDA**<br>**2 mg/kg every 3 weeks** | **KEYTRUDA**<br>**10 mg/kg every 3 weeks** | **Docetaxel**<br>**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<br>(0.7+, 16.8+) | Not reached<br>(2.1+, 17.8+) | 8.1<br>(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

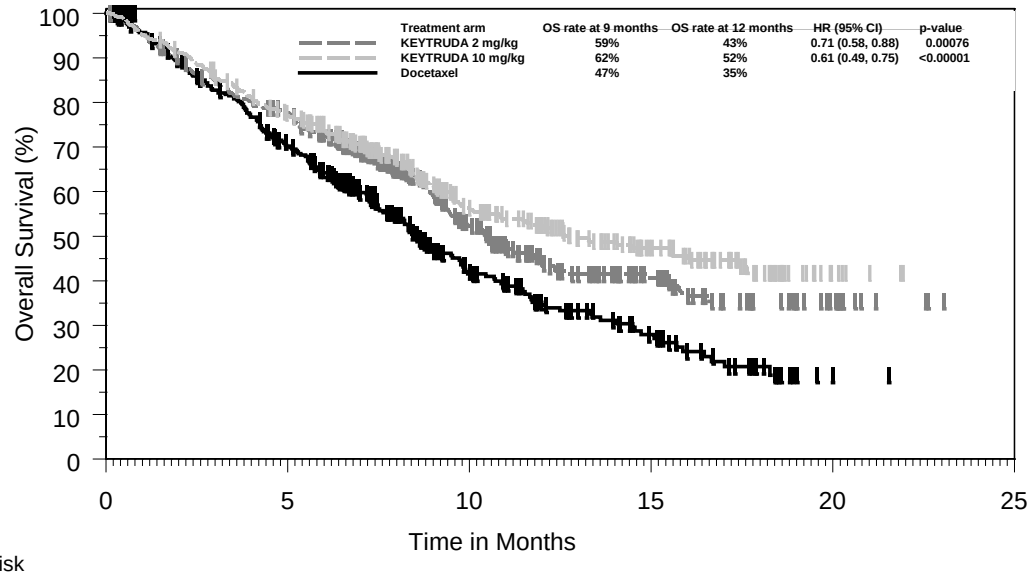
§ All responses were partial responses

¶ 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

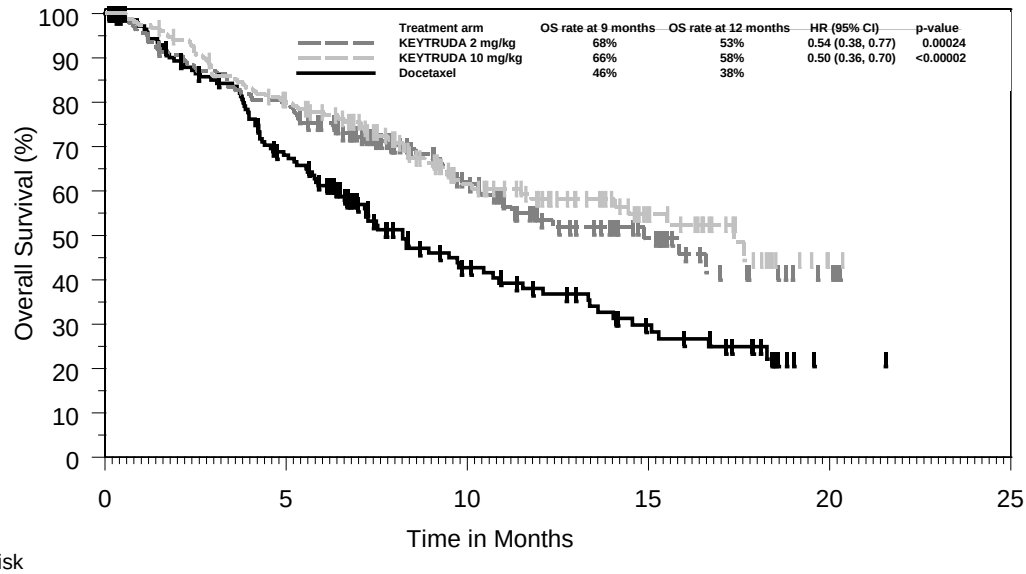
Þ Includes 22, 24, and 1 patients with ongoing responses of 6 months or longer in the KEYTRUDA 2 mg/kg, KEYTRUDA 10 mg/kg, and docetaxel groups respectively

**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

KEYTRUDA is approved based on overall response rate and duration of response from two single-arm, open label studies. The results of a randomised, active-controlled, ongoing, phase 3 study are awaited.

*KEYNOTE-012: Open-label study in HNSCC patients previously treated with chemotherapy*

The efficacy of KEYTRUDA was investigated in 192 patients with recurrent and/or metastatic HNSCC, regardless of tumour human papilloma virus (HPV) status (33% positive), enrolled in a multicentre, nonrandomised, open-label multi-cohort study (KEYNOTE-012). One cohort (n=132) was included regardless of PD-L1 tumour status. Efficacy is reported for 174 patients with recurrent and/or metastatic HNSCC that progressed on or after treatment with platinum-containing chemotherapy. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible.

Patients received KEYTRUDA 10 mg/kg every 2 weeks (n=53), or 200 mg every 3 weeks (n=121) until disease progression or unacceptable toxicity. Assessment of tumour status was performed every 8 weeks. The major efficacy outcome measures were ORR according to RECIST 1.1, as assessed by blinded independent central review, and duration of response.

Among the 174 patients, the baseline characteristics were median age 60 years (32% age 65 or older); 82% male; 75% White, 16% Asian, and 6% Black; 87% had M1 disease; 33% had HPV positive tumours; 63% had prior cetuximab; 29% had an ECOG PS of 0 and 71% had an ECOG PS of 1; and the median number of prior lines of therapy administered for the treatment of HNSCC was 2.

Efficacy results are summarized in Table 23.

**Table 23 Efficacy Results in Patients with HNSCC**

| | **Previously treated with platinum** |
|---|---|
| **Endpoint** | n=174 |
| **Objective Response Rate*** | |
| ORR %, (95% CI) | 16.1% (11, 22.4) |
| Complete Response | 4.6% |
| Partial Response | 11.5% |
| **Response Duration** | |
| Median in months (range) | Not Reached (2.4+, 27.7+)† |
| % with duration ≥ 6-months | 85%¶ |
| **Time to Response** | |
| Median in months (range) | 2.9 (1.6, 16.7)† |
| **PFS*** | |
| Median in months (95% CI) | 2 (1.9, 2.1) |
| 6-month PFS rate | 24.3% |
| **OS*** | |
| Median in months (95% CI) | 8.5 (6.2, 10.2) |
| 6-month OS rate | 58.7% |
| 12-month OS rate | 38.3% |

- * Assessed by blinded independent central review using RECIST 1.1
- † Based on patients (n=28) with a confirmed response by independent review
- ¶ Based on Kaplan-Meier estimates; includes 23 patients with responses of 6 months or longer including 14 patients with response of 12 months or longer.

There were objective responses in patients regardless of HPV tumour status.

Classical Hodgkin Lymphoma

*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 multicenter, 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 35% 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 36% of patients had prior radiation therapy.

Efficacy results are summarized in Table 24.

**Table 24: 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) | 69% (62.3, 75.2) |
| Complete Remission | 19% | 22% |
| Partial Remission | 39% | 47% |
| **Response Duration*** | | |
| Median in months (range) | Not reached (0.0+, 26.1+)† | 11.1 (0.0+, 11.1) ‡ |
| % with duration ≥ 6-months | 80%§ | 76%¶ |
| % with duration ≥ 12-months | 70%# | --- |
| **Time to Response** | | |
| Median in months (range) | 2.8 (2.4, 8.6) † | 2.8 (2.1, 8.8) ‡ |
| **PFS*** | | |
| Median in months (95% CI) | 11.4 (4.9, 27.8) | 11.3 (10.8, Not reached) |
| 6-month PFS rate | 66% | 72% |
| 9-month PFS rate | --- | 62% |
| 12-month PFS rate | 48% | --- |

| **OS** | | |
|---|---|---|
| 6-month OS rate | 100% | 99.5% |
| 12-month OS rate | 87.1% | 97.6% |

[a] Median follow-up time of 28.7 months

[b] Median follow-up time of 10.1 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=145) 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 31 patients with responses of 6 months or longer.

# Based on Kaplan-Meier estimation; includes 7 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 multicenter, 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 25.

**Table 25: 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.

Clinical Studies in Advanced or Metastatic 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 multicenter, 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.

The median follow-up time for 370 patients treated with KEYTRUDA was 11.5 months. Efficacy results are summarised in Table 26. The data presented for subjects with PD-L1 CPS ≥10 are based on a subgroup analysis.

**Table 26: Efficacy Results in Patients with Urothelial Carcinoma Ineligible for Cisplatin-Containing Chemotherapy**

| Endpoint | All Subjects<br>n=370 | PD-L1 CPS < 10<br>N=251 | PD-L1 CPS ≥10<br>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

Previously Untreated Urothelial Carcinoma

KEYNOTE-361 (NCT02853305) is an ongoing, multicenter, randomized 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 to stop 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 randomized 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 multicenter, 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 randomization, 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 27 and Figure 14). There was no statistically significant difference between KEYTRUDA and chemotherapy with respect to PFS. Efficacy results are summarised in Table 27.

**Table 27: Efficacy Results in Patients with Urothelial Carcinoma Previously Treated with Chemotherapy**

| **Endpoint** | **KEYTRUDA**<br>**200 mg every 3 weeks**<br>**n=270** | **Chemotherapy**<br>**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

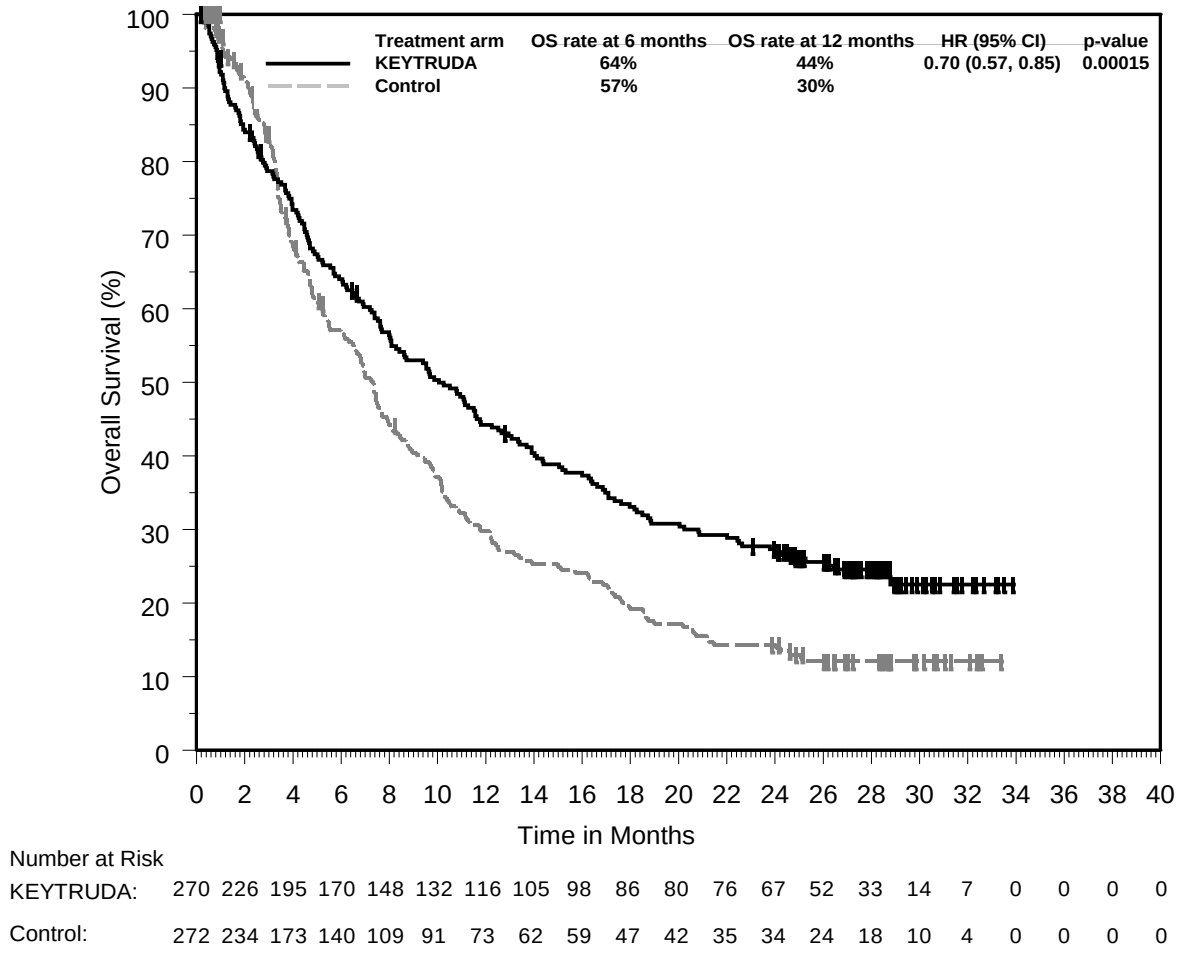
# Based on Kaplan-Meier estimation

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 14. 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 14: 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.

Microsatellite Instability-High 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 multicenter, nonrandomized, 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 summarized in Table 28 and Table 29.

**Table 28: 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 29: 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

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 with 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 30.

**Table 30: 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

**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**

17 September 2019

**Summary table of changes**

| Section changed | Summary of new information |
|---|---|
| 4.1 | Added indication for KEYTRUDA in combination with lenvatinib for endometrial carcinoma that is not MSI-H or dMMR |
| 4.2 | Updated dose recommendations for combination with lenvatinib |
| 4.8 | Added safety outcomes for KEYNOTE-146 |
| 5.1 | Added efficacy outcomes for KEYNOTE-146 |