▼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

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 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 for the adjuvant treatment of adult and adolescent (12 years and older) patients with Stage IIB, IIC, or III melanoma 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.

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

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

Malignant Pleural Mesothelioma

KEYTRUDA® (pembrolizumab), in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of adult patients with unresectable advanced or metastatic malignant pleural mesothelioma (MPM).

Head and neck squamous cell cancer (HNSCC)

KEYTRUDA® (pembrolizumab) is indicated for the treatment of adult patients with resectable locally advanced HNSCC whose tumours express PD-L1 with a CPS ≥1, as determined by a validated test, as a single agent as neoadjuvant treatment, continued as adjuvant treatment in combination with radiotherapy (RT) with or without cisplatin and then as a single agent.

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

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

Classical Hodgkin lymphoma (cHL)

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

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

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

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

Urothelial carcinoma
KEYTRUDA® (pembrolizumab), in combination with enfortumab vedotin, is indicated for the first-line treatment of adult patients with locally advanced or metastatic urothelial carcinoma (mUC).

KEYTRUDA® (pembrolizumab) is indicated as monotherapy for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for any platinum-containing chemotherapy. This indication is approved based on overall response rate and duration of response in a single-arm study. Improvements in overall survival, progression-free survival, or health-related quality of life have not been established.

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

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

Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) cancer
KEYTRUDA® (pembrolizumab) is indicated for the treatment of adult and paediatric patients with unresectable or metastatic solid tumours that are MSI-H or dMMR, as determined by a validated test, that have progressed following prior treatment and when there are no satisfactory alternative treatment options.

Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer
KEYTRUDA® (pembrolizumab) is indicated for the treatment of patients with unresectable or metastatic colorectal cancer (CRC) that is MSI-H or dMMR as determined by a validated test.

Biliary tract carcinoma (BTC)
KEYTRUDA® (pembrolizumab), in combination with gemcitabine and cisplatin, is indicated for the treatment of patients with locally advanced unresectable or metastatic biliary tract carcinoma (BTC).

Endometrial carcinoma
KEYTRUDA® (pembrolizumab), in combination with carboplatin and paclitaxel, followed by KEYTRUDA as a single agent, is indicated for the treatment of adult patients with primary advanced or recurrent 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 in any setting and are not candidates for curative surgery or radiation.

Cervical cancer

KEYTRUDA® (pembrolizumab), in combination with chemoradiotherapy (CRT), is indicated for the treatment of patients with high-risk, locally advanced cervical cancer (FIGO 2014 Stage IB2-IIB and node-positive, or Stage III-IVA).

KEYTRUDA® (pembrolizumab) in combination with platinum chemotherapy and paclitaxel, with or without bevacizumab, is indicated for the treatment of patients with persistent, recurrent, or metastatic cervical cancer whose tumours express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by a validated test.

Merkel Cell Carcinoma (MCC)

KEYTRUDA® (pembrolizumab), as monotherapy, is indicated for the treatment of adult and adolescent (12 years and older) patients with recurrent locally advanced or metastatic Merkel cell carcinoma (MCC).

Renal cell carcinoma (RCC)

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

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

KEYTRUDA® (pembrolizumab), as monotherapy, is indicated for the adjuvant treatment of patients with RCC with a clear cell component who are at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions (see section 5.1, Clinical Trials: Renal Cell Carcinoma).

Cutaneous squamous cell carcinoma (cSCC)

KEYTRUDA® (pembrolizumab) is indicated as monotherapy for the treatment of adult patients with recurrent or metastatic cutaneous squamous cell carcinoma (cSCC) or locally advanced cSCC that is not curable by surgery or radiation.

Gastric cancer

KEYTRUDA® (pembrolizumab), in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of patients with locally advanced unresectable or metastatic gastric or gastroesophageal junction (GOJ) adenocarcinoma that is not HER2-positive.

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

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

Tumour mutational burden-high (TMB-H) cancer
KEYTRUDA® (pembrolizumab) is indicated for the treatment of adult and paediatric patients with unresectable or metastatic tumour mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumours, as determined by a validated test, that have progressed following prior treatment and who have no satisfactory alternative treatment options. This indication was approved via the **provisional approval** pathway, based on the pooling of data on objective response rate and response duration across multiple different tissue types in a single-arm trial. The assumption that TMB-H status is predictive of the treatment effect of KEYTRUDA for every tissue type has not been verified. Full registration for this indication depends on verification and description of clinical benefit in confirmatory trials.

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

KEYTRUDA® (pembrolizumab), in combination with chemotherapy, is indicated for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumours express PD-L1 (CPS ≥10) as determined by a validated test and who have not received prior chemotherapy for metastatic disease.

Ovarian Cancer
KEYTRUDA® (pembrolizumab), in combination with paclitaxel, with or without bevacizumab, is indicated for the treatment of patients with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal carcinoma whose tumours express PD-L1 (CPS≥1) as determined by a validated test, and who have received one or two prior systemic treatment regimens.

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

For safe and effective use of KEYTRUDA in some indications, *in vitro* diagnostic (IVD) companion diagnostic (CDx) testing for biomarkers (such as PD-L1, MSI-H/dMMR, and TMB-H) is essential (see Section 4.1 THERAPEUTIC INDICATIONS). Testing used in clinical practice should be adequately comparable to the testing used in the pivotal studies (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials).

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

chemotherapy in patients with high grade gliomas.

Recommended dosing

The recommended dosage and duration of treatment for KEYTRUDA-containing treatment is presented in Table 1. When assessing disease progression to determine if treatment should cease, consider the possibility of pseudoprogression (i.e., an initial transient increase in tumour size or small new lesions within the first few months, followed by tumour shrinkage). 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).

Table 1: Recommended dosage and duration of treatment with KEYTRUDA

Indication	Recommended dosage of KEYTRUDA*	Duration/timing of treatment
Monotherapy		
Adult patients with unresectable or metastatic melanoma	200 mg every 3 weeks or 400 mg every 6 weeks†	Until disease progression or unacceptable toxicity
Adjuvant treatment of adult patients with melanoma, NSCLC, or RCC	200 mg every 3 weeks or 400 mg every 6 weeks†	Until disease recurrence, unacceptable toxicity, or up to 12 months
Adult patients with NSCLC, HNSCC, cHL, PMBCL, locally advanced or metastatic urothelial carcinoma, MSI-H or dMMR cancer, MSI-H or dMMR CRC, MCC, TMB-H cancer, or cSCC	200 mg every 3 weeks or 400 mg every 6 weeks†	Until disease progression, unacceptable toxicity, or up to 24 months
Adult patients with high-risk BCG-unresponsive NMIBC	200 mg every 3 weeks or 400 mg every 6 weeks†	Until persistent or recurrent high-risk NMIBC, disease progression, unacceptable toxicity, or up to 24 months
Paediatric patients with cHL, PMBCL, MSI-H or dMMR cancer, or TMB-H cancer	2 mg/kg every 3 weeks (up to a maximum of 200 mg)	Until disease progression, unacceptable toxicity, or up to 24 months
Adolescent patients (12 years and older) with MCC	2 mg/kg every 3 weeks (up to a maximum of 200 mg)	Until disease progression, unacceptable toxicity, or up to 24 months
Adolescent patients (12 years and older) for adjuvant treatment of melanoma.	2 mg/kg every 3 weeks (up to a maximum of 200 mg)	Until disease recurrence, unacceptable toxicity, or up to 12 months
Combination therapy‡		
Adult patients with resectable NSCLC	200 mg every 3 weeks or 400 mg every 6 weeks† Administer KEYTRUDA prior to chemotherapy when given on the same day.	Neoadjuvant treatment in combination with chemotherapy for 12 weeks or until disease progression that precludes definitive surgery or unacceptable toxicity, followed by adjuvant treatment with KEYTRUDA as a single agent after surgery for 39 weeks or until disease recurrence or unacceptable toxicity

Indication	Recommended dosage of KEYTRUDA*	Duration/timing of treatment
Adult patients with NSCLC, MPM, HNSCC, non-HER2-positive gastric cancer, oesophageal cancer, or BTC	200 mg every 3 weeks or 400 mg every 6 weeks† Administer KEYTRUDA prior to chemotherapy when given on the same day.	Until disease progression, unacceptable toxicity, or up to 24 months
Adult patients with locally advanced or metastatic urothelial cancer	200 mg every 3 weeks or 400 mg every 6 weeks† Administer KEYTRUDA after enfortumab vedotin§ when given on the same day.	Until disease progression, unacceptable toxicity, or up to 24 months
Adult patients with resectable locally advanced HNSCC	200 mg every 3 weeks or 400 mg every 6 weeks† Administer KEYTRUDA prior to cisplatin when given on the same day.	Neoadjuvant treatment with KEYTRUDA for 2 doses of 200 mg every 3 weeks or 1 dose of 400 mg every 6 weeks or until disease progression that precludes definitive surgery or unacceptable toxicity, continued as adjuvant treatment in combination with RT with or without cisplatin for 3 doses of 200 mg every 3 weeks or 2 doses of 400 mg every 6 weeks followed by 12 doses of 200 mg every 3 weeks or 6 doses of 400 mg every 6 weeks as monotherapy or until disease recurrence or unacceptable toxicity.
Adult patients with HER2-positive gastric cancer	200 mg every 3 weeks or 400 mg every 6 weeks† Administer KEYTRUDA prior to trastuzumab and chemotherapy when given on the same day.	Until disease progression, unacceptable toxicity, or up to 24 months
Adult patients with cervical cancer	200 mg every 3 weeks or 400 mg every 6 weeks† Administer KEYTRUDA prior to chemoradiotherapy or prior to chemotherapy with or without bevacizumab when given on the same day.	Until disease progression, unacceptable toxicity, or for KEYTRUDA, up to 24 months
Adult patients with RCC	200 mg every 3 weeks or 400 mg every 6 weeks† Administer KEYTRUDA in combination with axitinib 5 mg orally twice daily¶ or Administer KEYTRUDA in combination with lenvatinib 20 mg orally once daily.	Until disease progression, unacceptable toxicity, or for KEYTRUDA, up to 24 months

Indication	Recommended dosage of KEYTRUDA*	Duration/timing of treatment
Adult patients with endometrial carcinoma	200 mg every 3 weeks or 400 mg every 6 weeks† Administer KEYTRUDA prior to carboplatin and paclitaxel when given on the same day. or Administer KEYTRUDA in combination with lenvatinib 20 mg orally once daily.	Until disease progression, unacceptable toxicity, or for KEYTRUDA, up to 24 months
Adult patients with high-risk early-stage TNBC	200 mg every 3 weeks or 400 mg every 6 weeks† Administer KEYTRUDA prior to chemotherapy when given on the same day.	Neoadjuvant treatment in combination with chemotherapy for 24 weeks (8 doses of 200 mg every 3 weeks or 4 doses of 400 mg every 6 weeks) or until disease progression or unacceptable toxicity, followed by adjuvant treatment with KEYTRUDA as a single agent for up to 27 weeks (9 doses of 200 mg every 3 weeks or 5 doses of 400 mg every 6 weeks) or until disease recurrence or unacceptable toxicity#
Adult patients with locally recurrent unresectable or metastatic TNBC	200 mg every 3 weeks or 400 mg every 6 weeks† Administer KEYTRUDA prior to chemotherapy when given on the same day.	Until disease progression, unacceptable toxicity, or up to 24 months
Adult patients with ovarian cancer	200 mg every 3 weeks or 400 mg every 6 weeks† Administer KEYTRUDA prior to paclitaxel with or without bevacizumab when given on the same day.	Until disease progression, unacceptable toxicity, or up to 24 months

* Each dose of KEYTRUDA is administered as an intravenous (IV) infusion over 30 minutes.

† KEYTRUDA was originally developed using an every-three-weeks monotherapy dosing regimen (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials). Subsequent approval of the every-six-weeks dosing regimen was based on pharmacokinetic and exposure-response modelling and simulations, supported by observed pharmacokinetic data. Clinical endpoint data (such as PFS or OS) from randomised controlled trials of every-three-weeks versus every-six-weeks dosing of KEYTRUDA is not available.

‡ Refer to the Product Information for the agents administered in combination with KEYTRUDA for recommended dosing information, as appropriate. For additional detail regarding studied regimens, refer to Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials.

§ The recommended initial dose of enfortumab vedotin is 1.25 mg/kg (up to a maximum of 125 mg for patients ≥100 kg) as an intravenous solution on Days 1 and 8 of a 21-day cycle until disease progression or unacceptable toxicity.

¶ When axitinib is used in combination with KEYTRUDA, dose escalation of axitinib above the initial 5 mg dose may be considered at intervals of six weeks or longer.

\# Patients who experience disease progression or unacceptable toxicity related to KEYTRUDA with neoadjuvant treatment in combination with chemotherapy should not receive adjuvant single agent KEYTRUDA.

Dose modifications

No dose reductions of KEYTRUDA are recommended. Withhold or discontinue KEYTRUDA to manage adverse reactions as described in Table 2.

Table 2: Recommended dose modifications [see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE]

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

Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	TEN	1*
	Severe skin reactions (Grade 4) or confirmed SJS or TEN	Permanently discontinue
Other immune-mediated adverse reactions	Based on severity and type of reaction (Grade 2 or Grade 3)	Withhold until adverse reactions recover to Grades 0-1*
	Severe or life-threatening (Grades 3 or 4) myocarditis, encephalitis, or Guillain-Barré syndrome	Permanently discontinue
	Life-threatening (Grade 4) or recurrent severe (Grade 3)	Permanently discontinue
Infusion-related reactions	Severe or life-threatening (Grades 3 or 4)	Permanently discontinue

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

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

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

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

When administering KEYTRUDA in combination with lenvatinib, interrupt one or both to manage adverse reactions as appropriate. No dose reductions are recommended for KEYTRUDA. For management of adverse reactions, withhold, dose reduce, or discontinue lenvatinib in accordance with the instructions in the lenvatinib Product Information.

Geriatric dosing

No dose adjustment is necessary in this population (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE, Use in the elderly).

Dosing in renal impairment

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

Dosing in hepatic impairment

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].

Preparation and administration

- Protect from light. Do not freeze. Do not shake.
- Equilibrate the vial of KEYTRUDA to room temperature.
- Prior to dilution, the vial of liquid can be out of refrigeration (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.
- Do not freeze the infusion solution.
- The product does not contain preservative. Aseptic handling should be ensured during the preparation of infusion. The diluted product should be used immediately. If not used immediately, diluted solutions of KEYTRUDA may be stored at room temperature for up to 12 hours. Diluted solutions of KEYTRUDA may also be stored under refrigeration at 2°C to 8°C; however, the total time from dilution of KEYTRUDA to completion of infusion should not exceed 7 days. If refrigerated, allow the vials and/or IV bags to come to room temperature prior to use.
- Translucent to white proteinaceous particles may be seen in the diluted solution, and are not of concern, as particles will be removed by the filter during administration. Administer infusion solution intravenously over 30 minutes using a sterile, non-pyrogenic, low-protein binding 0.2 to 5 µm in-line or add-on filter.
- Do not co-administer other drugs through the same infusion line.
- Product is for single use in one patient only. Discard any residue.

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 recurrent severe (Grade 3) or life-threatening (Grade 4) colitis [See Section 4.2 DOSE AND METHOD OF ADMINISTRATION, Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) and Immune-mediated Adverse Reactions above]. The potential risk of gastrointestinal perforation should be taken into consideration.

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

Immune-mediated hepatitis

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

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

Hepatotoxicity in Combination with Axitinib

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

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

Immune-mediated nephritis

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

Immune-mediated endocrinopathies

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

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

Thyroid disorders, including hyperthyroidism, hypothyroidism and thyroiditis, have been reported in patients receiving KEYTRUDA and can occur at any time during treatment, therefore monitor patients for changes in thyroid function (at the start of treatment, periodically

during treatment and as indicated based on clinical evaluation) and clinical signs and symptoms of thyroid disorders. Hypothyroidism may be managed with replacement therapy without treatment interruption and without corticosteroids. Hyperthyroidism may be managed symptomatically. Withhold or discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) hyperthyroidism [See Section 4.2 DOSE AND METHOD OF ADMINISTRATION, Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) and Immune-mediated Adverse Reactions above].

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

Severe skin reactions

Immune-mediated severe skin reactions have been reported in patients treated with KEYTRUDA. Monitor patients for suspected severe skin reactions and exclude other causes. Based on the severity of the adverse reaction, withhold or permanently discontinue KEYTRUDA and administer corticosteroids [See Section 4.2 DOSE AND METHOD OF ADMINISTRATION].

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

Other immune-mediated adverse reactions

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

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.

Patients with pre-existing autoimmune disease (AID)

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

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

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

Infusion-related reactions

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

Patients excluded from clinical trials

Patients with the following conditions were excluded from clinical trials: active CNS metastases; ECOG PS ≥ 2 (except for urothelial carcinoma and advanced RCC); HIV, hepatitis B or hepatitis C infection; active systemic autoimmune disease; interstitial lung disease; prior pneumonitis requiring systemic corticosteroid therapy; a history of severe hypersensitivity to another monoclonal antibody; receiving immunosuppressive therapy and a history of severe immune-related adverse reactions from treatment with ipilimumab, defined as any Grade 4 toxicity or Grade 3 toxicity requiring corticosteroid treatment (> 10 mg/day prednisone or equivalent) for greater than 12 weeks. Patients with active infections were excluded from clinical trials and were required to have their infection treated prior to receiving pembrolizumab. Patients with active infections occurring during treatment with pembrolizumab were managed with appropriate medical therapy. Patients with clinically significant renal (creatinine > 1.5 x ULN) or hepatic (bilirubin > 1.5 x ULN, ALT, AST > 2.5 x ULN in the absence of liver metastases) abnormalities at baseline were excluded from clinical trials, therefore information is limited in patients with severe renal and moderate to severe hepatic impairment.

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

Patient Alert Card

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

Paediatric use

In KEYNOTE-051, 173 paediatric patients (65 children ages 6 months to less than 12 years and 108 adolescents ages 12 years to 17 years) with advanced melanoma, lymphoma, or PD-L1 positive or MSI-H advanced, relapsed, or refractory solid tumours were administered KEYTRUDA 2 mg/kg every 3 weeks. The cHL population (n=30) included patients 6 to 17 years of age. Patients received KEYTRUDA for a median of 4 doses (range 1-52 doses), with 147 patients (85%) receiving KEYTRUDA for 2 doses or more. The concentrations of pembrolizumab in paediatric patients were comparable to those observed in adult patients at the same dose regimen of 2 mg/kg every 3 weeks.

The safety profile in these paediatric patients was similar to that seen in adults treated with pembrolizumab. The most common adverse reactions (reported in at least 20% of paediatric patients) were pyrexia (33%), vomiting (30%), headache (25%), abdominal pain (23%), anaemia (21%) and cough (20%). The majority of adverse reactions reported for monotherapy were of Grades 1 or 2 severity. Eighty (46%) patients had 1 or more Grades 3 to 5 adverse reactions of which 5 (2.9%) patients had 1 or more adverse reactions that resulted in death. The frequencies are based on all reported adverse drug reactions, regardless of the investigator assessment of causality. No new immune-mediated AEs causally associated with pembrolizumab are identified in this population.

Efficacy for paediatric patients with melanoma, relapsed or refractory cHL, PMBCL, MCC, MSI-H/dMMR cancers, or TMB-H cancers, is extrapolated from the results in the respective adult populations and supported by data from KEYNOTE-051 [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). There is limited data regarding the safety of combination therapy with pembrolizumab and axitinib in patients ≥75 years of age with advanced RCC.

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 4.2 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 haematopoietic stem cell transplantation (HSCT) after being treated with KEYTRUDA.

Of 14 patients in KEYNOTE-013 who proceeded to allogeneic HSCT after treatment with pembrolizumab, 6 patients reported acute GVHD and 1 patient reported chronic GVHD, none of which were fatal. Two patients experienced hepatic VOD, one of which was fatal. One patient experienced engraftment syndrome post-transplant.

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

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

Cases of fatal hyperacute GVHD after allogeneic HSCT have also been reported in patients with lymphoma who received a PD-1 receptor blocking antibody before transplantation. These complications may occur despite intervening therapy between PD-1 blockade and allogeneic

HSCT. Follow patients closely for early evidence of transplant-related complications such as hyperacute GVHD, severe (Grade 3 to 4) acute GVHD, steroid-requiring febrile syndrome, hepatic VOD, and other immune mediated adverse reactions, and intervene promptly.

Allogeneic HSCT prior to treatment with KEYTRUDA

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

Use of pembrolizumab in urothelial carcinoma patients who have received prior platinum-containing chemotherapy

Physicians should consider the delayed onset of pembrolizumab effect before initiating treatment in patients with poorer prognostic features and/or aggressive disease. In urothelial cancer, a higher number of deaths within 2 months was observed in pembrolizumab compared to chemotherapy (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials). Factors associated with early deaths were fast progressive disease on prior platinum therapy and liver metastases.

Use of pembrolizumab in combination with chemotherapy for first-line treatment of patients with NSCLC

In general, the frequency of adverse reactions for pembrolizumab combination therapy is observed to be higher than for pembrolizumab monotherapy or chemotherapy alone, reflecting the contributions of each of these components (see sections 4.2 DOSE AND METHOD OF ADMINISTRATION and 4.8 ADVERSE EFFECTS). A direct comparison of the safety of pembrolizumab when used in combination with pemetrexed and platinum chemotherapy to pembrolizumab monotherapy is not available.

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

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

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

Use in pregnancy

Category D. There are no clinical data on the use of pembrolizumab in pregnancy. 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 fetus and to result in an increase in fetal loss. These results indicate a potential risk, based on its mechanism of action, that administration of KEYTRUDA during pregnancy could cause fetal 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 fetus. KEYTRUDA is not recommended during pregnancy unless the clinical benefit outweighs the potential risk to the fetus. Patients who could become pregnant should use effective contraception during treatment with KEYTRUDA and for at least 4 months following the last dose of KEYTRUDA.

Use in lactation

There is no information regarding the presence of pembrolizumab in human milk, the absorption and effects on the breast-fed infant, or the effects on milk production. Human IgG is excreted in human milk. Because of the lack of data to support safety for the breastfed child, patients should be advised not to breast-feed during treatment and for at least 4 months after the last dose.

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

Advanced melanoma and NSCLC (pooled analysis)

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.

The incidences of immune-mediated adverse reactions in this pooled population of patients with advanced melanoma or NSCLC (n=2799) are presented by CTCAE Grade in Table 3.

Table 3: Immune-Mediated Adverse Reactions

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

* In individual studies of patients with HNSCC treated with KEYTRUDA as monotherapy (n=909) the incidence of hypothyroidism was 16.1% (all Grades) with 0.3% Grade 3. In patients with HNSCC treated with KEYTRUDA in combination with platinum and 5-FU chemotherapy (n=276) the incidence of hypothyroidism was 15.2%, all of which were Grade 1 or 2. In patients with cHL (n=389) the incidence of hypothyroidism was 17%, all of which were Grade 1 or 2. In the adjuvant study of patients with resected RCC treated with KEYTRUDA as monotherapy (n=488) the incidence of hypothyroidism was 21% (all Grades) with 0.2% Grade 3.

† In the adjuvant study of patients with resected RCC treated with KEYTRUDA as monotherapy (n=488) the incidence of hyperthyroidism was 12% (all Grades) with 0.2% Grade 3.

‡In individual studies of patients with NSCLC treated with KEYTRUDA as monotherapy (total n=2602), the incidence of pneumonitis (all Grades) ranged from 3.8% to 8.3%. In cHL patients treated with KEYTRUDA as monotherapy, the incidence of pneumonitis (all Grades) ranged from 5.2% to 10.8% for cHL patients in KEYNOTE-087 (n=210) and KEYNOTE-204 (n=148), respectively.

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

***Endocrinopathies*:** The median time to onset of adrenal insufficiency was 5.3 months (range 26 days to 16.6 months). The median duration was not reached (range 4 days to 1.9+ years). Adrenal insufficiency led to discontinuation of KEYTRUDA in 1 (<0.1%) patient. Adrenal insufficiency resolved in 5 patients. The median time to onset of hypophysitis was 3.7 months (range 1 day to 11.9 months). The median duration was 4.7 months (range 8+ days to 12.7+ months). Hypophysitis led to discontinuation of KEYTRUDA in 4 (0.1%) patients. Hypophysitis resolved in 7 patients. The median time to onset of hyperthyroidism was 1.4 months (range 1 day to 21.9 months). The median duration was 2.1 months (range 3 days to 15.0+ months). Hyperthyroidism led to discontinuation of KEYTRUDA in 2 (<0.1%) patients. Hyperthyroidism resolved in 71 patients. The median time to onset of hypothyroidism was 3.5 months (range 1 day to 18.9 months). The median duration was not reached (range 2 days

to 27.7+ months). One (<0.1%) patient discontinued KEYTRUDA due to hypothyroidism.
***Pneumonitis*:** The median time to onset of pneumonitis was 3.3 months (range 2 days to 19.3 months). The median duration was 1.5 months (range 1 day to 17.2+ months). Pneumonitis led to discontinuation of KEYTRUDA in 36 (1.3%) patients. Pneumonitis resolved in 55 patients.
***Colitis*:** The median time to onset of colitis was 3.5 months (range 10 days to 16.2 months). The median duration was 1.3 months (range 1 day to 8.7+ months). Colitis led to discontinuation of KEYTRUDA in 15 (0.5%) patients. Colitis resolved in 41 patients.
***Hepatitis*:** The median time to onset of hepatitis was 1.3 months (range 8 days to 21.4 months). The median duration was 1.8 months (range 8 days to 20.9+ months). Hepatitis led to discontinuation of KEYTRUDA in 6 (0.2%) patients. Hepatitis resolved in 15 patients.
***Nephritis*:** The median time to onset of nephritis was 5.1 months (range 12 days to 12.8 months). The median duration was 3.3 months (range 12 days to 8.9+ months). Nephritis led to discontinuation of KEYTRUDA in 3 (0.1%) patients. Nephritis resolved in 5 patients. In patients with non-squamous NSCLC treated with pembrolizumab in combination with pemetrexed and platinum chemotherapy (n=405), the incidence of nephritis was 1.7% (all Grades) with 1.0% Grade 3 and 0.5% Grade 4.

Melanoma

Advanced melanoma

Table 4 summarises the adverse events that occurred in at least 10% of patients with melanoma treated with KEYTRUDA in KEYNOTE-006. The most common adverse events (reported in at least 15% of patients) were arthralgia and cough.

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

	KEYTRUDA 10 mg/kg every 2 or 3 weeks n=555		Ipilimumab n=256	
Laboratory Test	**All Grades %**	**Grades 3-4 %**	**All Grades %**	**Grades 3-4 %**
Haematology				

Lymphopenia	45	5	36	5
Chemistry				
Hypertriglyceridemia	40	2	33	1

Table 6 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 6: Adverse Events Occurring in ≥10% of Patients Treated with KEYTRUDA and at a Higher Incidence than in the Chemotherapy Arm (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-4]) (KEYNOTE-002)

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

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

Table 7: Laboratory Abnormalities Worsened from Baseline in ≥20% of Patients with Unresectable or Metastatic Melanoma and at a Higher Incidence than in the Chemotherapy Arm (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-4]) (KEYNOTE-002)

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

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

Resected melanoma

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

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

Among the 969 patients with resected melanoma enrolled in KEYNOTE-716, the adverse reactions were generally similar to those occurring in patients with unresectable or metastatic melanoma and NSCLC.

Non-small cell lung carcinoma (NSCLC)

In combination with chemotherapy for advanced NSCLC

Table 8 summarises the adverse events that occurred in at least 20% of patients treated with KEYTRUDA, pemetrexed, and platinum chemotherapy in KEYNOTE-189. Adverse events occurring in previously untreated patients with NSCLC receiving KEYTRUDA in combination with carboplatin and either paclitaxel or nab-paclitaxel in KEYNOTE-407 were generally similar to those occurring in patients in KEYNOTE-189 with the exception of alopecia (46%) and arthralgia (21%).

Table 8: Adverse events occurring in ≥20% of patients receiving KEYTRUDA with pemetrexed and platinum chemotherapy and at a higher incidence than in patients receiving placebo with pemetrexed and platinum chemotherapy (between-arm difference of ≥5% [All Grades] or ≥2% [Grades 3-4]) (KEYNOTE-189)

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

* Graded per NCI CTCAE v4.03

Monotherapy for advanced NSCLC

Table 9 summarises the adverse events that occurred in at least 10% of previously untreated patients with NSCLC receiving KEYTRUDA in KEYNOTE-042. The most common adverse events (reported in at least 15% of patients) were dyspnoea and cough. Adverse events occurring in previously untreated patients with NSCLC receiving KEYTRUDA in KEYNOTE-024 and previously treated patients in KEYNOTE-010 were generally similar to those occurring in patients in KEYNOTE-042.

Table 9: Adverse Events Occurring in ≥10% of NSCLC Patients Treated with KEYTRUDA and at a Higher Incidence than in the Chemotherapy Arm (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-5]) (KEYNOTE-042)

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

* Graded per NCI CTCAE v4.03

Adjuvant therapy for resected NSCLC

Among the 580 patients with resected NSCLC treated with KEYTRUDA in KEYNOTE-091, the adverse reactions were generally similar to those occurring in other patients with NSCLC receiving KEYTRUDA as monotherapy with the exception of hypothyroidism (21%) and hyperthyroidism (11%).

Neoadjuvant followed by adjuvant therapy for resectable NSCLC

Adverse events occurring in patients with resectable NSCLC receiving KEYTRUDA in combination with platinum-containing chemotherapy, given as neoadjuvant treatment and continued as monotherapy adjuvant treatment in KEYNOTE-671, were generally similar to those occurring in patients in other clinical trials across tumour types receiving KEYTRUDA in combination with chemotherapy. Patients with active autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were not eligible for this study.

Neoadjuvant phase of KEYNOTE-671

A total of 396 patients received at least 1 dose of KEYTRUDA in combination with platinum-containing chemotherapy as neoadjuvant treatment and 399 patients received at least 1 dose of placebo in combination with platinum-containing chemotherapy as neoadjuvant treatment. Serious adverse events occurred in 34% of patients who received KEYTRUDA in combination with platinum-containing chemotherapy as neoadjuvant treatment; the most frequent (≥2%) serious adverse events were pneumonia (4.8%), venous thromboembolism (3.3%), and anaemia (2%). Fatal adverse events occurred in 1.3% of patients, including death due to unknown cause (0.8%), sepsis (0.3%), and immune-mediated lung disease (0.3%).

Permanent discontinuation of any study drug due to an adverse event occurred in 18% of patients who received KEYTRUDA in combination with platinum-containing chemotherapy as neoadjuvant treatment; the most frequent (≥1%) adverse events that led to permanent discontinuation of any study drug were acute kidney injury (1.8%), interstitial lung disease (1.8%), anaemia (1.5%), neutropenia (1.5%), and pneumonia (1.3%).

Of the 396 KEYTRUDA-treated patients and 399 placebo-treated patients who received neoadjuvant treatment, 6% (n=25) and 4.3% (n=17), respectively, did not receive surgery due to adverse events. The most frequent (≥1%) adverse event that led to cancellation of surgery in the KEYTRUDA arm was interstitial lung disease (1%).

Of the 325 KEYTRUDA-treated patients who received surgery, 3.1% (n=10) experienced delay of surgery (surgery more than 8 weeks from last neoadjuvant treatment if patient received less than 4 cycles of neoadjuvant therapy or more than 20 weeks after first dose of neoadjuvant treatment if patient received 4 cycles of neoadjuvant therapy) due to adverse events. Of the 317 placebo-treated patients who received surgery, 2.5% (n=8) experienced delay of surgery due to adverse events.

Of the 325 KEYTRUDA-treated patients who received surgery, 7% (n=22) did not receive adjuvant treatment due to adverse events. Of the 317 placebo-treated patients who received surgery, 3.2% (n=10) did not receive adjuvant treatment due to adverse events.

Adjuvant Phase of KEYNOTE-671

A total of 290 patients in the KEYTRUDA arm and 267 patients in the placebo arm received at least 1 dose of adjuvant treatment.

Of the patients who received single agent KEYTRUDA as adjuvant treatment, 14% experienced serious adverse events; the most frequent serious adverse event was pneumonia (3.4%). One fatal adverse event of pulmonary haemorrhage occurred. Permanent discontinuation of adjuvant KEYTRUDA due to an adverse event occurred in 12% of patients; the most frequent (≥1%) adverse reactions that led to permanent discontinuation of adjuvant KEYTRUDA were diarrhoea (1.7%), interstitial lung disease (1.4%), AST increased (1%), and musculoskeletal pain (1%).

Malignant Pleural Mesothelioma

Among the 241 patients with MPM treated with KEYTRUDA in combination with pemetrexed and platinum chemotherapy in KEYNOTE-483, the adverse events were generally similar to those occurring in other patients receiving KEYTRUDA in combination with pemetrexed and platinum chemotherapy.

Head and neck cancer

Neoadjuvant and Adjuvant Treatment of Locally Advanced HNSCC

The safety of KEYTRUDA as neoadjuvant and adjuvant treatment added to standard of care (SOC) therapy was evaluated in KEYNOTE-689, a multicentre, randomised(1:1), open-label, active-controlled trial in patients with resectable locally advanced (Stage III-IVA by AJCC 8th edition) head and neck squamous cell carcinoma (HNSCC) [see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials]. KEYTRUDA was administered as single-agent neoadjuvant therapy before definitive surgery, during adjuvant radiotherapy (RT) with or without concurrent cisplatin, and then as single agent adjuvant therapy. Concurrent cisplatin was added to KEYTRUDA and adjuvant RT for high-risk disease pathology. A total of 361 patients received treatment on the KEYTRUDA arm and 315 patients received treatment on the SOC therapy arm.

The median duration of exposure to KEYTRUDA in the neoadjuvant phase was 3.1 weeks (range: 1 day to 4.9 weeks). The median duration of exposure to KEYTRUDA in the adjuvant phase was 42 weeks (range: 1 day to 82 weeks).

The median age of patients who received KEYTRUDA was 60 years (range: 29 to 82), 32% age 65 or older, 6% age 75 or older; 79% male; 78% White, 14% Asian, 2.2% Black or African American, 2% Other races, 2.7% unknown race; and 15% Hispanic or Latino.

The most common adverse events (≥ 20%) on the KEYTRUDA arm were stomatitis (48%), radiation skin injury (40%), weight loss (36%), fatigue (33%), dysphagia (29%), constipation (27%), hypothyroidism (26%), nausea (24%), rash (22%), dry mouth (22%), diarrhoea (22%), and musculoskeletal pain (22%).
Table 10 and Table 11 summarise adverse events and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-689.

Table 10: Adverse Events Occurring in ≥20% of Patients Receiving KEYTRUDA in KEYNOTE-689

Adverse Events	KEYTRUDA Neoadjuvant then adjuvant beginning with RT with or without cisplatin n=361		Standard of Care Adjuvant RT with or without cisplatin n=315	
	All Grades* (%)	Grade 3 or 4 (%)	All Grades* (%)	Grade 3 or 4 (%)
Gastrointestinal				
Stomatitis†	48	14	60	13
Dysphagia	29	12	32	11
Constipation	27	0.3	22	0.3
Nausea	24	1.9	28	2.9
Dry mouth	22	1.4	26	1.6
Diarrhoea‡	22	4.2	11	0.6
Injury, poisoning and procedural complications				
Radiation skin injury	40	4.2	48	5.7
Investigations				
Weight loss	36	14	27	10
Endocrine disorders				
Hypothyroidism§	26	0	6	0
General				
Fatigue¶	33	2.2	27	1.6
Skin and subcutaneous tissue disorders				
Rash#	22	1.9	10	1.9
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain Þ	22	1.9	16	0.6

* Graded per NCI CTCAE v4.03

† Includes pharyngeal inflammation, cheilitis, oral mucosal erythema, mucosal inflammation, glossitis, mouth ulceration, tongue ulceration

‡ Includes colitis, enteritis, hemorrhagic diarrhoea

§ Includes blood thyroid stimulating hormone increased

¶ Includes asthenia

Includes dermatitis, skin exfoliation, dermatitis acneiform, eczema, rash macular, rash maculo-papular, erythema multiforme, dermatitis exfoliative, urticarial dermatitis, eczema asteatotic, exfoliative rash, rash pruritic, rash pustular

Þ Includes neck pain, arthralgia, pain in extremity, back pain, myalgia, bone pain, arthritis, non-cardiac chest pain, musculoskeletal chest pain, musculoskeletal stiffness, spinal pain

Table 11: Select Laboratory Abnormalities (≥20%) that Worsened from Baseline in Patients with HNSCC Who Received KEYTRUDA in KEYNOTE-689

Laboratory Test*	KEYTRUDA Neoadjuvant then adjuvant beginning with radiation with or without cisplatin		Radiation with or without cisplatin	
	All Grades† (%)	Grades 3-4 (%)	All Grades† (%)	Grades 3-4 (%)
Haematology				
Lymphopenia	76	50	86	55
Anaemia	75	12	74	12
Neutropenia	32	13	35	19
Thrombocytopenia	22	1.7	29	1.9
Chemistry				
Hyperglycemia	57	5.7	47	2.7
Hyponatremia	47	16	36	11
Increased ALT	42	6.2	37	2.0
Hypoalbuminemia	40	1.4	38	1.0
Increased AST	38	4.8	23	2.0
Hypomagnesemia	34	1.2	22	1.3
Hypokalemia	29	6.8	20	7.4
Hyperkalemia	29	3.4	24	2.3
Increased alkaline phosphatase	27	2.5	19	0.0
Hypocalcemia	27	2.6	26	3.3
Hypophosphatemia	23	6.1	15	7.0
Increased creatinine	22	2.0	27	2.9
Hypercalcemia	21	2.0	14	1.3

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA + CRT/RT (range: 342 to 357 patients) and CRT/RT (range: 300 to 309 patients)

† Graded per NCI CTCAE v4.03

Neoadjuvant Phase of KEYNOTE-689

Of the 361 patients who received at least one dose of single agent KEYTRUDA as neoadjuvant treatment, 11% of patients experienced serious adverse events. Serious adverse events that occurred in more than one patient were pneumonia (1.4%), tumour haemorrhage (0.8%), dysphagia (0.6%), immune mediated hepatitis (0.6%), cellulitis (0.6%), and dyspnoea (0.6%). Fatal adverse events occurred in 1.1% of patients who received neoadjuvant KEYTRUDA including respiratory failure, clostridium infection, septic shock, and myocardial infarction (one patient each).

Permanent discontinuation of KEYTRUDA due to an adverse event occurred in 2.8% of patients who received KEYTRUDA as neoadjuvant treatment. The most frequent adverse event which resulted in permanent discontinuation of neoadjuvant KEYTRUDA in more than one patient was arthralgia (0.6%).

Of the 361 patients who received KEYTRUDA as neoadjuvant treatment, 11% (n=38) did not receive surgery. Surgical cancellation on the KEYTRUDA arm was due to disease progression

in 4% (n=15), patient decision in 3% (n=10), adverse events in 1.4% (n=5), physician's decision in 1.1% (n=4), unresectable tumour in 0.6% (n=2), loss of follow-up in 0.3% (n=1), and use of non-study anti-cancer therapy in 0.3% (n=1).

Of the 351 patients randomised to SOC, 12% (n=43) did not receive surgery. Surgical cancellation on the SOC arm was due to patient decision in 7% (n=24), physician's decision in 2.3% (n=8), disease progression in 1.7% (n=6), and adverse reactions in 1.4% (n=5).

Of the 323 KEYTRUDA-treated patients who received surgery, 1.2% (n=4) experienced delay of surgery (defined as on-study surgery occurring ≥ 9 weeks after initiation of neoadjuvant KEYTRUDA) due to adverse events. Of the 307 patients randomised to SOC who received surgery on study, 0.3% (n=1) experienced delay of surgery (defined as surgery occurring ≥ 6 weeks after randomisation) due to adverse events.

Among the KEYTRUDA-treated patients who received surgery, 2.8% (n=9) did not receive adjuvant treatment due to adverse events. Among the SOC-treated patients who received surgery, 3.6% (n=11) did not receive adjuvant RT or chemoradiation due to adverse events.

Adjuvant Phase of KEYNOTE-689

A total of 275 patients in the KEYTRUDA arm and 275 patients in the SOC arm started the adjuvant phase of treatment. On the KEYTRUDA arm, 100 patients received KEYTRUDA and cisplatin with concurrent RT, 154 patients received KEYTRUDA alone with concurrent RT, 7 patients received cisplatin alone with concurrent RT, and 13 patients received RT alone. One patient received KEYTRUDA alone. On the SOC arm, 139 patients received cisplatin with concurrent RT while 136 patients received RT alone. For the KEYTRUDA arm, a total of 222 patients received single-agent KEYTRUDA following RT.

Of the 255 patients who received at least one dose of KEYTRUDA in the adjuvant phase, 38% experienced serious adverse events. The most frequent serious adverse events reported in ≥ 1% of KEYTRUDA-treated patients were pneumonia (2.7%), pyrexia (2.4%), stomatitis (2.4%), acute kidney injury (2.0%), pneumonitis (1.6%), COVID-19 (1.2%), death not otherwise specified (1.2%), diarrhoea (1.2%), dysphagia (1.2%), gastrostomy tube site complication (1.2%), and immune-mediated hepatitis (1.2%).

Fatal adverse events occurred in 5% including death not otherwise specified (1.2%), acute renal failure (0.4%), hypercalcemia (0.4%), pulmonary haemorrhage (0.4%), dysphagia/malnutrition (0.4%), mesenteric thrombosis (0.4%), sepsis (0.4%), pneumonia (0.4%), COVID-19 (0.4%), respiratory failure (0.4%), cardiovascular disorder (0.4%) and gastrointestinal haemorrhage (0.4%).

Permanent discontinuation of adjuvant KEYTRUDA due to an adverse event occurred in 17% of patients. The most frequent (≥1%) adverse events that led to permanent discontinuation of adjuvant KEYTRUDA were pneumonitis, colitis, immune-mediated hepatitis and death not otherwise specified. Of the 275 patients who received SOC in the adjuvant phase, 23% experienced serious adverse events.

The most frequent serious adverse events reported in >1% of SOC-treated patients were pneumonia (3.6%) and acute kidney injury (3.3%). Fatal adverse events occurred in 4.7% including pneumonia (0.7%), septic shock (0.4%), death not otherwise specified (0.4%), sudden death (0.4%), myocardial infarction (0.4%), pancreatic neoplasm (0.4%) and other infections (2.9%).

First-line treatment of metastatic or unresectable, recurrent HNSCC
The safety of KEYTRUDA, as a single agent and in combination with platinum (cisplatin or carboplatin) and 5-FU chemotherapy, was investigated in KEYNOTE-048, a multicentre, open-label, randomised (1:1:1), active-controlled trial in patients with previously untreated, recurrent or metastatic HNSCC *[see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials]*. Patients with autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. A total of 576 patients received KEYTRUDA 200 mg every 3 weeks either as a single agent (n=300) or in combination with platinum and 5-FU (n=276) every 3 weeks for 6 cycles followed by KEYTRUDA, compared to 287 patients who received cetuximab weekly in combination with platinum and 5-FU every 3 weeks for 6 cycles followed by cetuximab.

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

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

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

Tables 12 and 13 summarise adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-048.

Table 12: Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-048

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

* Graded per NCI CTCAE v4.0

† Includes fatigue, asthenia

‡ Includes diarrhoea, colitis, haemorrhagic diarrhoea, microscopic colitis

§ Includes dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis bullous, dermatitis contact, dermatitis exfoliative, drug eruption, erythema, erythema multiforme, rash, erythematous rash, generalized rash, macular rash, maculo-papular rash, pruritic rash, seborrheic dermatitis

¶ Includes cough, productive cough

Includes dyspnoea, exertional dyspnoea

Þ Includes pneumonia, atypical pneumonia, bacterial pneumonia, staphylococcal pneumonia, aspiration pneumonia, lower respiratory tract infection, lung infection, lung infection pseudomonal

ß Includes peripheral sensory neuropathy, peripheral neuropathy, hypoesthesia, dysesthesia

à Includes back pain, musculoskeletal chest pain, musculoskeletal pain, myalgia

Table 13: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients Receiving KEYTRUDA in KEYNOTE-048

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks		KEYTRUDA 200 mg every 3 weeks Platinum 5-FU		Cetuximab Platinum 5-FU	
	All Grades† (%)	Grades 3-4 (%)	All Grades† (%)	Grades 3-4 (%)	All Grades† (%)	Grades 3-4 (%)
Haematology						
Lymphopenia	54	25	70	35	75	46
Anaemia	52	7	89	29	79	20
Thrombocytopenia	12	3.8	73	18	76	18
Neutropenia	8	1.4	68	37	73	43
Chemistry						
Hyperglycemia	47	3.8	54	6	65	4.7
Hyponatremia	46	18	55	20	59	20
Hypoalbuminemia	44	3.5	46	3.9	49	1.1
Increased AST	28	3.1	25	1.9	37	3.6
Increased ALT	25	2.1	22	1.5	38	1.8
Increased alkaline phosphatase	25	2.1	26	1.1	33	1.1
Hypercalcemia	22	4.5	16	4.2	13	2.5
Hypocalcemia	22	1.0	32	3.8	58	6
Hyperkalemia	21	2.8	28	4.2	29	4.6
Hypophosphatemia	20	5	34	12	49	20
Hypokalemia	19	5	33	12	47	15
Increased creatinine	17	1.0	36	2.3	27	2.1
Hypomagnesemia	15	0.4	40	1.7	76	9

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA/chemotherapy (range: 240 to 267 patients), KEYTRUDA (range: 245 to 292 patients), cetuximab/chemotherapy (range: 249 to 282 patients).

† Graded per NCI CTCAE v4.0

Relapsed or refractory Classical Hodgkin lymphoma

KEYNOTE-204

The safety of KEYTRUDA for the treatment of patients with relapsed or refractory cHL was

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

The median duration of exposure to KEYTRUDA was 10.0 months (range: 1 day to 26.7 months). KEYTRUDA was discontinued due to adverse reactions in 14% of patients and treatment was interrupted due to adverse reactions in 30%. Thirty-eight percent of patients had an adverse reaction requiring systemic corticosteroid therapy. Serious adverse reactions occurred in 30% of patients receiving KEYTRUDA. The most frequent serious adverse reactions (≥1%) included pneumonia, pneumonitis, interstitial lung disease, pyrexia, myocarditis, acute kidney injury, and febrile neutropenia. Three patients died from causes other than disease progression; one from pneumonia, one from hypovolemic shock, and one due to unknown cause. Table 14 and Table 15 summarise adverse reactions and laboratory abnormalities, respectively, in patients in KEYNOTE-204.

Table 14: Adverse Reactions (≥10%) in Patients with cHL who Received KEYTRUDA in KEYNOTE-204

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

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

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

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

Laboratory Abnormality*	KEYTRUDA 200 mg every 3 weeks		Brentuximab Vedotin 1.8 mg/kg every 3 weeks	
	All Grades† (%)	Grades 3-4 (%)	All Grades† (%)	Grades 3-4 (%)
Chemistry				
Hyperglycemia	45	4.1	36	2.0
Increased AST	38	4.7	38	2.0
Increased ALT	31	5	43	2.6
Hypophosphatemia	31	4.9	17	2.8
Increased creatinine	26	3.4	13	2.6
Hypomagnesemia	23	0	13	0
Hyponatremia	24	4.1	20	3.3
Hypocalcemia	21	2.0	15	0
Increased alkaline phosphatase	19	2.1	21	2.0
Hypoalbuminemia	16	0.7	18	0.7
Hyperbilirubinemia	15	1.4	8	0.7
Haematology				
Lymphopenia	34	8	32	13
Thrombocytopenia	32	9	24	4.0
Neutropenia	27	8	42	16
Anaemia	22	4.1	32	7

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (range: 143 to 148 patients) and BV (range: 145 to 152 patients); hypomagnesemia: KEYTRUDA n=52 and BV n=47.
† Graded per NCI CTCAE v4.0

KEYNOTE-087
Among the 210 patients with cHL who received KEYTRUDA in KEYNOTE-087 (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials), the median duration of exposure to KEYTRUDA was 8.4 months (range: 1 day to 15.2 months). Serious adverse reactions occurred in 16% of patients who received KEYTRUDA. Serious adverse reactions that

occurred in ≥1% of patients included pneumonia, pneumonitis, pyrexia, dyspnoea, graft versus host disease (GVHD) and herpes zoster. Two patients died from causes other than disease progression; one from GVHD after subsequent allogeneic HSCT and one from septic shock.

Permanent discontinuation of KEYTRUDA due to an adverse reaction occurred in 5% of patients and dosage interruption due to an adverse reaction occurred in 26%. Fifteen percent of patients had an adverse reaction requiring systemic corticosteroid therapy. Table 16 and Table 17 summarise adverse reactions and laboratory abnormalities, respectively, in KEYNOTE-087.

Table 16: Adverse Reactions (≥10%) in Patients with cHL who Received KEYTRUDA in KEYNOTE-087

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

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

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

Table 17: Select Laboratory Abnormalities (≥15%) That Worsened from Baseline in Patients with cHL who Received KEYTRUDA in KEYNOTE-087

Laboratory Abnormality*	KEYTRUDA 200 mg every 3 weeks	
	All Grades† (%)	Grades 3-4 (%)
Chemistry		
Hypertransaminasemia‡	35	2.4
Increased alkaline phosphatase	17	0
Increased creatinine	15	0.5
Haematology		
Anaemia	30	6
Thrombocytopenia	27	4.3
Neutropenia	25	7

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

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

Primary mediastinal B-cell lymphoma

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

Urothelial carcinoma

Combination Therapy

The safety of KEYTRUDA in combination with enfortumab vedotin was investigated in KEYNOTE-A39 in patients with locally advanced or metastatic urothelial cancer [see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials]. A total of 440 patients received KEYTRUDA 200 mg on Day 1 and enfortumab vedotin 1.25 mg/kg on Days 1 and 8 of each 21-day cycle compared to 433 patients who received gemcitabine on Days 1 and 8 and investigator's choice of cisplatin or carboplatin on Day 1 of each 21-day cycle. Among patients who received KEYTRUDA and enfortumab vedotin, the median duration of exposure to KEYTRUDA was 8.5 months (range: 9 days to 28.5 months).

Fatal adverse reactions occurred in 3.9% of patients treated with KEYTRUDA in combination with enfortumab vedotin including acute respiratory failure (0.7%), pneumonia (0.5%), and pneumonitis/ILD (0.2%).

Serious adverse reactions occurred in 50% of patients receiving KEYTRUDA in combination with enfortumab vedotin. Serious adverse reactions in ≥2% of patients receiving KEYTRUDA in combination with enfortumab vedotin were rash (6%), acute kidney injury (5%), pneumonitis/ILD (4.5%), urinary tract infection (3.6%), diarrhoea (3.2%), pneumonia (2.3%), pyrexia (2%), and hyperglycemia (2%).

Permanent discontinuation of KEYTRUDA occurred in 27% of patients. The most common adverse reactions (≥2%) resulting in permanent discontinuation of KEYTRUDA were

pneumonitis/ILD (4.8%) and rash (3.4%).

Dose interruptions of KEYTRUDA occurred in 61% of patients. The most common adverse reactions (≥2%) resulting in interruption of KEYTRUDA were rash (17%), peripheral neuropathy (7%), COVID-19 (5%), diarrhoea (4.3%), pneumonitis/ILD (3.6%), neutropenia (3.4%), fatigue (3%), alanine aminotransferase increased (2.7%), hyperglycemia (2.5%), pneumonia (2%), and pruritus (2%).

Table 18 and Table 19 summarise adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in combination with enfortumab vedotin in KEYNOTE-A39.

Table 18: Adverse Reactions ≥20% (All Grades) in Patients Treated with KEYTRUDA in Combination with Enfortumab Vedotin in KEYNOTE-A39

	KEYTRUDA in combination with Enfortumab Vedotin n=440		Chemotherapy n=433	
Adverse Reaction	**All Grades* %**	**Grades 3-4 %**	**All Grades* %**	**Grades 3-4 %**
Skin and subcutaneous tissue disorders				
Rash†	68	15	15	0
Pruritus	41	1.1	7	0
Alopecia	35	0.5	8	0.2
General disorders and administration site conditions				
Fatigue†	51	6	57	7
Nervous system disorders				
Peripheral neuropathy†	67	8	14	0
Dysgeusia	21	0	9	0
Metabolism and nutrition disorders				
Decreased appetite	33	1.8	26	1.8
Gastrointestinal disorders				
Diarrhea	38	4.5	16	1.4
Nausea	26	1.6	41	2.8
Constipation	26	0	34	0.7
Investigations				
Weight loss	33	3.6	9	0.2
Eye disorders				
Dry eye†	24	0	2.1	0
Infections and infestations				
Urinary tract infection	21	5	19	8

* Graded per NCI CTCAE v4.03
† Includes multiple terms

Clinically relevant adverse reactions (<20%) include pyrexia (18%), dry skin (17%), vomiting (12%), pneumonitis/ILD (10%), hypothyroidism (10%), blurred vision (6%), infusion site extravasation (2%), and myositis (0.5%).

Table 19: Selected Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients in KEYNOTE-A39

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks and Enfortumab Vedotin		Chemotherapy	
	All Grades† %	Grades 3-4 %	All Grades† %	Grades 3-4 %
Chemistry				
Increased aspartate aminotransferase	75	4.6	39	3.3
Increased creatinine	71	3.2	68	2.6
Hyperglycemia	66	14	54	4.7
Increased alanine aminotransferase	59	5	49	3.3
Hyponatremia	46	13	47	13
Hypophosphatemia	44	9	36	9
Hypoalbuminemia	39	1.8	35	0.5
Hypokalemia	26	5	16	3.1
Hyperkalemia	24	1.4	36	4.0
Hypercalcemia	21	1.2	14	0.2
Hematology				
Lymphopenia	58	15	59	17
Anemia	53	7	89	33
Neutropenia	30	9	80	50

* 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: 407 to 439 patients)

† Graded per NCI CTCAE v4.03

Cisplatin-ineligible patients with urothelial carcinoma (KEYNOTE-052)

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

The most common adverse reactions (reported in at least 20% of patients) were fatigue, musculoskeletal pain, decreased appetite, constipation, rash and diarrhoea. KEYTRUDA was discontinued due to adverse reactions in 11% of patients. Eighteen patients (5%) died from causes other than disease progression. Five patients (1.4%) who were treated with KEYTRUDA experienced sepsis which led to death, and three patients (0.8%) experienced pneumonia which led to death. Adverse reactions leading to interruption of KEYTRUDA occurred in 22% of patients; the most common (≥1%) were liver enzyme increase, diarrhoea, urinary tract infection, acute kidney injury, fatigue, joint pain, and pneumonia. Serious adverse reactions occurred in 42% of patients. The most frequent serious adverse reactions (≥2%) were urinary tract infection, haematuria, 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 20 summarises the incidence of adverse reactions occurring in at least 10% of patients

receiving KEYTRUDA.

Table 20: Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-052

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

* Graded per NCI CTCAE v4.0
† Includes diarrhoea, colitis, enterocolitis, gastroenteritis, frequent bowel movements
‡ Includes abdominal pain, pelvic pain, flank pain, abdominal pain lower, tumour pain, bladder pain, hepatic pain, suprapubic pain, abdominal discomfort, abdominal pain upper
§ Includes autoimmune hepatitis, hepatitis, hepatitis toxic, liver injury, transaminases increased, hyperbilirubinemia, blood bilirubin increased, alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzymes increased, liver function tests increased
¶ Includes fatigue, asthenia
# Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, pain in extremity, spinal pain
ᵖ 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 (KEYNOTE-045)

The safety of KEYTRUDA for the treatment of patients with locally advanced or metastatic

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

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

Table 21 summarises the incidence of adverse reactions occurring in at least 10% of patients receiving KEYTRUDA. Table 22 summarises the incidence of laboratory abnormalities that occurred in at least 20% of patients receiving KEYTRUDA.

Table 21: Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-045

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

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

Table 22: 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
Haemoglobin decreased	52	13	68	18
Lymphocytes decreased	45	15	55	26
Albumin decreased	43	1.7	50	3.8
Sodium decreased	37	9	47	13
Alkaline phosphatase increased	37	7	33	4.9
Creatinine increased	35	4.4	28	2.9
Phosphate decreased	29	8	34	14
Aspartate aminotransferase increased	28	4.1	20	2.5
Potassium increased	28	0.8	27	6
Calcium decreased	26	1.6	34	2.1

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

BCG-unresponsive, high-risk NMIBC

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

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

KEYTRUDA was discontinued due to adverse reactions in 10% of patients. The most common adverse (>1%) reaction resulting in permanent discontinuation of KEYTRUDA was pneumonitis (1.4%). Adverse reactions leading to interruption of KEYTRUDA occurred in 24% of patients; the most common (≥2%) were diarrhoea (2%) and urinary tract infection (2%). Serious adverse reactions occurred in 27% of KEYTRUDA-treated patients. The most frequent serious adverse reactions (≥2%) in KEYTRUDA-treated patients were pneumonia (3%), colitis (2%), pulmonary embolism (2%), and urinary tract infection (2%). Table 23 and Table 24 summarise adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-057.

Table 23: Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-057

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

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

Table 24: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of BCG-unresponsive NMIBC Patients Receiving KEYTRUDA in KEYNOTE-057

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks	
	All Grades† (%)	Grades 3-4 (%)
Chemistry		
Hyperglycemia	61	7
Increased ALT	25	2.7
Hyponatremia	25	7
Hypophosphatemia	24	6
Hypoalbuminemia	25	1.4
Hyperkalemia	23	1.4
Hypocalcemia	22	0.7
Increased AST	21	2.7
Increased creatinine	20	0.7
Haematology		
Anaemia	35	1.4
Lymphopenia	30	1.6

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

† Graded per NCI CTCAE v4.03

MSI-H/dMMR cancer

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

Endometrial carcinoma

In Combination with Chemotherapy (KEYNOTE-868/NRG-GY018)

In patients with endometrial carcinoma receiving KEYTRUDA plus chemotherapy (paclitaxel and carboplatin), adverse events were generally similar to those observed with KEYTRUDA alone or chemotherapy alone with the exception of rash maculo-papular (13% all Grades; 2% Grades 3-4).

In Combination with Lenvatinib (KEYNOTE-775)

The safety of KEYTRUDA in combination with lenvatinib was investigated in KEYNOTE-775, a multicentre, open-label, randomised (1:1), active-controlled trial in patients with advanced endometrial carcinoma previously treated with at least one prior platinum-based chemotherapy regimen in any setting, including in the neoadjuvant and adjuvant settings. Patients with endometrial carcinoma that is not MSI-H or dMMR received KEYTRUDA 200 mg every 3 weeks in combination with lenvatinib 20 mg orally once daily (n=342) or received doxorubicin or paclitaxel (n=325).

For patients with not MSI-H or dMMR tumour status, the median duration of study treatment was 7.2 months (range: 1 day to 26.8 months) and the median duration of exposure to KEYTRUDA was 6.8 months (range: 1 day to 25.8 months).

Fatal adverse reactions among these patients occurred in 4.7% of those treated with KEYTRUDA and lenvatinib, including 2 cases of pneumonia, and 1 case of the following: acute kidney injury, acute myocardial infarction, colitis, decreased appetite, intestinal perforation, lower gastrointestinal haemorrhage, malignant gastrointestinal obstruction, multiple organ

dysfunction syndrome, myelodysplastic syndrome, pulmonary embolism, and right ventricular dysfunction.

Serious adverse reactions occurred in 50% of these patients receiving KEYTRUDA and lenvatinib. Serious adverse reactions (≥3%) were hypertension (4.4%) and urinary tract infections (3.2%).

Discontinuation of KEYTRUDA due to an adverse reaction occurred in 15% of these patients. The most common adverse reaction leading to discontinuation of KEYTRUDA (≥1%) was increased ALT (1.2%).

Dose interruptions of KEYTRUDA due to an adverse reaction occurred in 48% of these patients. The most common adverse reactions leading to interruption of KEYTRUDA (≥3%) were: diarrhoea (8%), increased ALT (4.4%), increased AST (3.8%), and hypertension (3.5%).

Table 25 and Table 26 summarise adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in combination with lenvatinib in KEYNOTE-775.

Table 25: Adverse Reactions Occurring in ≥20% of Patients with Endometrial Carcinoma in KEYNOTE-775

Adverse Reaction	Endometrial Carcinoma (not MSI-H or dMMR)			
	KEYTRUDA 200 mg every 3 weeks and Lenvatinib n=342		Doxorubicin or Paclitaxel n=325	
	All Grades* (%)	Grades 3-4 (%)	All Grades* (%)	Grades 3-4 (%)
Endocrine				
Hypothyroidism†	67	0.9	0.9	0
Vascular				
Hypertension‡	67	39	6	2.5
Haemorrhagic events§	25	2.6	15	0.9
General				
Fatigue¶	58	11	54	6
Gastrointestinal				
Diarrhoea#	55	8	20	2.8
Nausea	49	2.9	47	1.5
Vomiting	37	2.3	21	2.2
Stomatitisᵇ	35	2.6	26	1.2
Abdominal painß	34	2.6	21	1.2
Constipation	27	0	25	0.6
Musculoskeletal and Connective Tissue				
Musculoskeletal disordersà	53	5	27	0.6
Metabolism				
Decreased appetiteè	44	7	21	0
Investigations				
Weight loss	34	10	6	0.3
Renal and Urinary				
Proteinuriaδ	29	6	3.4	0.3
Infections				
Urinary tract infectionø	31	5	13	1.2
Nervous System				
Headache	26	0.6	9	0.3
Respiratory, Thoracic and Mediastinal				
Dysphonia	22	0	0.6	0
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysesthesiaý	23	2.9	0.9	0
Rash£	20	2.3	4.9	0

* Graded per NCI CTCAE v4.03

† Includes hypothyroidism, blood thyroid stimulating hormone increased, thyroiditis, secondary hypothyroidism

‡ Includes hypertension, blood pressure increased, secondary hypertension, blood pressure abnormal, hypertensive encephalopathy, blood pressure fluctuation

§ Includes epistaxis, vaginal haemorrhage, haematuria, gingival bleeding, metrorrhagia, rectal haemorrhage, contusion, haematochezia, cerebral haemorrhage, conjunctival haemorrhage, gastrointestinal haemorrhage, haemoptysis, haemorrhage urinary tract, lower gastrointestinal haemorrhage, mouth haemorrhage, petechiae, uterine haemorrhage, anal haemorrhage, blood blister, eye haemorrhage, haematoma, haemorrhage intracranial, haemorrhagic stroke, melena, stoma site haemorrhage, upper gastrointestinal haemorrhage, wound haemorrhage, blood urine present, ecchymosis, haematemesis, haemorrhage subcutaneous, hepatic haematoma, injection site bruising, intestinal haemorrhage, laryngeal haemorrhage, pulmonary haemorrhage, subdural haematoma, umbilical haemorrhage, vessel puncture site bruise

¶ Includes fatigue, asthenia, malaise, lethargy

Includes diarrhoea, gastroenteritis

Þ Includes stomatitis, mucosal inflammation, oropharyngeal pain, aphthous ulcer, mouth ulceration, cheilitis, oral mucosal erythema, tongue ulceration

ß Includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, gastrointestinal pain, abdominal tenderness, epigastric discomfort

à Includes arthralgia, myalgia, back pain, pain in extremity, bone pain, neck pain, musculoskeletal pain, arthritis, musculoskeletal chest pain, musculoskeletal stiffness, non-cardiac chest pain, pain in jaw

è Includes decreased appetite, early satiety

ð Includes proteinuria, protein urine present, haemoglobinuria

ø Includes urinary tract infection, cystitis, pyelonephritis

ý Includes palmar-plantar erythrodysesthesia syndrome, palmar erythema, plantar erythema

£ Includes rash, rash maculo-papular, rash pruritic, rash erythematous, rash macular, rash pustular, rash papular, rash vesicular, application site rash

Table 26: Laboratory Abnormalities Worsened from Baseline* Occurring in ≥20% (All Grades) or ≥3% (Grades 3-4) of Patients with Endometrial Carcinoma in KEYNOTE-775

Laboratory Test†	Endometrial Carcinoma (not MSI-H or dMMR)			
	KEYTRUDA 200 mg every 3 weeks and Lenvatinib		Doxorubicin or Paclitaxel	
	All Grades‡ %	Grades 3-4 %	All Grades‡ %	Grades 3-4 %
Chemistry				
Hypertriglyceridemia	70	6	45	1.7
Hypoalbuminemia	60	2.7	42	1.6
Increased aspartate aminotransferase	58	9	23	1.6
Hyperglycemia	58	8	45	4.4
Hypomagnesemia	46	0	27	1.3
Increased alanine aminotransferase	55	9	21	1.2
Hypercholesteremia	53	3.2	23	0.7
Hyponatremia	46	15	28	7
Increased alkaline phosphatase	43	4.7	18	0.9
Hypocalcemia	40	4.7	21	1.9
Increased lipase	36	14	13	3.9
Increased creatinine	35	4.7	18	1.9
Hypokalemia	34	10	24	5
Hypophosphatemia	26	8	17	3.2
Increased amylase	25	7	8	1
Hyperkalemia	23	2.4	12	1.2
Increased creatine kinase	19	3.7	7	0
Increased bilirubin	18	3.6	6	1.6
Haematology				
Lymphopenia	51	18	66	23
Thrombocytopenia	50	8	30	4.7
Anaemia	49	8	84	14
Leukopenia	43	3.5	83	43
Neutropenia	34	8	80	60

* With at least one 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: KEYTRUDA/lenvatinib (range: 263 to 340 patients) and doxorubicin or paclitaxel (range: 240 to 322 patients).
‡ Graded per NCI CTCAE v4.03

Gastric or GOJ adenocarcinoma

In combination with chemotherapy for gastric or gastroesophageal junction (GOJ) adenocarcinoma (KEYNOTE-859)

The safety of KEYTRUDA was evaluated in 1572 patients with gastric or GOJ cancer enrolled in KEYNOTE-859, which included 785 patients treated with KEYTRUDA 200 mg and FP (n=106) or CAPOX (n=674) every 3 weeks, and 787 patients who received placebo and FP (n=107) or CAPOX (n=679) every 3 weeks [see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials]. Patients with HER2-positive tumours were excluded from this study.

The median duration of exposure to KEYTRUDA was 6.2 months (range: 1 day to 33.7 months).

Serious adverse events occurred in 45% of patients receiving KEYTRUDA. Serious adverse events in >2% of patients included pneumonia (4.1%), diarrhoea (3.9%), haemorrhage (3.9%), and vomiting (2.4%). Fatal adverse events occurred in 8% of patients receiving KEYTRUDA, including infection (2.3%) and thromboembolism (1.3%). Permanent discontinuation of KEYTRUDA due to adverse reactions occurred in 15% of patients. Adverse reaction resulting in permanent discontinuation of KEYTRUDA in ≥1% were infections (1.8%) and diarrhoea (1.0%). Dosage interruptions of KEYTRUDA due to an adverse reaction occurred in 65% of patients. Adverse reactions leading to interruption of KEYTRUDA (≥2%) were neutropenia (21%), thrombocytopenia (13%), diarrhoea (5.5%), fatigue (4.8%), infection (4.8%), anaemia (4.5%), increased AST (4.3%), increased ALT (3.8%), increased blood bilirubin (3.3%), white blood cell count decreased (2.2%), nausea (2%), palmar-plantar erythrodysaesthesia syndrome (2%), and vomiting (2%).

The adverse events occurring in at least 20% of patients and with a difference of ≥5% incidence between patients treated with KEYTRUDA versus placebo were vomiting (34% vs. 27%). Grade 3-5 adverse events were generally similar between arms, except for events consistent with known toxicities of pembrolizumab [see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE].

The laboratory abnormalities occurring in at least 20% of patients and with a difference of ≥5% incidence were lymphopenia (57% vs. 51%), increased AST (57% vs. 48%), increased alkaline phosphatase (48% vs. 41%), increased ALT (40% vs. 29%), hypokalemia (35% vs. 27%), and hypomagnesemia (29% vs. 22%).

In combination with chemotherapy and trastuzumab for HER2-positive gastric or gastroesophageal junction adenocarcinoma (KEYNOTE-811)

The safety of KEYTRUDA was evaluated in 696 patients with HER2-positive gastric or GOJ cancer enrolled in KEYNOTE-811, which included 350 patients treated with KEYTRUDA 200 mg, trastuzumab, and CAPOX (n=297) or FP (n=53) every 3 weeks, compared to 346 patients treated with placebo, trastuzumab, and CAPOX (n=298) or FP (n=48) every 3 weeks [see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials].

The median duration of exposure to KEYTRUDA was 9.2 months (range: 1 day to 33.6 months).

Fatal adverse reactions occurred in 3 patients who received KEYTRUDA in combination with trastuzumab and CAPOX or FP and included pneumonitis in 2 patients and hepatitis in 1 patient.

KEYTRUDA was discontinued due to adverse reactions in 13% of patients. Adverse reactions resulting in permanent discontinuation of KEYTRUDA in ≥1% of patients were pneumonitis (2.0%) and pneumonia (1.1%).

Adverse reactions leading to interruption of KEYTRUDA occurred in 71% of patients; the most common adverse reactions or laboratory abnormalities leading to interruption of KEYTRUDA (≥2%) were neutropenia (21%), thrombocytopenia (13%), diarrhoea (7%), pneumonia (5%), anaemia (4.9%), COVID-19 (3.1%), hypokalaemia (3.1%), fatigue/aesthenia (4.9%), decreased appetite (4%), increased AST (3.7%), increased blood bilirubin (4.6%), increased ALT (2.9%), vomiting (2.6%), pneumonitis (2.3%), pyrexia (2.3%), increased blood creatinine (2%), and colitis (2%).

In the KEYTRUDA arm versus placebo, there was a difference of ≥5% incidence between patients treated with KEYTRUDA versus standard of care for diarrhoea (53% vs. 47%), rash

(35% vs. 28%), hypothyroidism (11% vs. 5%), and pneumonia (11% vs. 5%). There were no clinically meaningful differences in incidence of Grade 3-4 toxicity between arms.

For laboratory abnormalities, there was a difference of ≥5% incidence between patients treated with KEYTRUDA versus standard of care for decreased leukocytes (60% vs. 54%), decreased calcium (56% vs. 46%), decreased lymphocytes (59% vs. 51%), decreased potassium (41% vs. 36%), increased bilirubin (33% vs. 25%), increased creatinine (28% vs. 18%), and decreased glucose (17% vs. 11%). There were no clinically meaningful differences in incidence of Grade 3-4 toxicity between arms.

Cervical cancer

High-Risk, Locally Advanced Cervical Cancer

The safety of KEYTRUDA in combination with CRT (cisplatin plus external beam radiation therapy [EBRT] followed by brachytherapy [BT]) was investigated in KEYNOTE-A18, a placebo-controlled, randomised (1:1), multicentre, double-blind trial including 1058 patients with high-risk, locally advanced cervical cancer. A total of 528 patients received KEYTRUDA in combination with chemoradiotherapy compared to 530 patients who received placebo in combination with chemoradiotherapy.

KEYTRUDA was discontinued for adverse reactions in 9% of patients, with no single adverse reaction accounting for the majority. Serious adverse reactions occurred in 33% of patients receiving KEYTRUDA in combination with chemoradiotherapy. Serious adverse reactions occurring in ≥1% of patients included urinary tract infection (3.2%), anaemia (3%), pyrexia (2.7%), diarrhoea (1.9%), hydronephrosis (1.1%), sepsis (1.1%), and vaginal haemorrhage (1.1%). Fatal adverse reactions occurred in 0.9% of patients receiving KEYTRUDA in combination with chemoradiotherapy, including 1 case each (0.2%) of immune-mediated gastritis, large intestinal perforation, urosepsis, sepsis, and vaginal haemorrhage.

Table 27 and Table 28 summarise adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-A18.

Table 27: Adverse Reactions Occurring in ≥10% of Patients Receiving KEYTRUDA in KEYNOTE-A18

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks and 400 mg every 6 weeks with chemoradiotherapy n=528		Placebo with chemoradiotherapy n=530	
	All Grades* (%)	Grades 3-4 (%)	All Grades* (%)	Grades 3-4 (%)
Gastrointestinal				
Nausea	61	1.5	64	1.9
Diarrhoea	57	5.1	56	4.7
Vomiting	30	0.9	33	1.3
Constipation	22	0.2	23	0.4
Abdominal pain	15	0.9	15	1.3
General				
Fatigue†	35	1.1	33	1.3
Pyrexia	16	0.9	15	0.8
Infections				
Urinary tract infection‡	29	4.4	32	3.4
Endocrine				
Hypothyroidism§	23	0.6	7	0
Hyperthyroidism	12	0.4	2.8	0

Metabolism and Nutrition				
Decreased appetite	18	0.6	20	0.4
Investigations				
Weight loss	16	1.7	15	0.6
Renal and Urinary				
Dysuria	15	0.2	14	0
Skin and Subcutaneous Tissue				
Rash¶	15	1.1	9	0.2
Nervous system				
Headache	13	0.2	14	0.2
Musculoskeletal and connective tissue disorders				
Arthralgia	12	0.4	12	0
Infectious and infestations				
COVID-19	11	0	10	0.6

* Graded per NCI CTCAE v5.0
† Includes fatigue, asthenia
‡ Includes urinary tract infection, urinary tract infection pseudomonal, pyelonephritis acute, cystitis, escherichia urinary tract infection
§ Includes hypothyroidism, autoimmune hypothyroidism
¶ Includes erythema multiforme, dermatitis, drug eruption, eczema, rash, skin exfoliation, dermatitis bullous, rash maculo-papular, lichen planus, dyshidrotic eczema, dermatitis acneiform

Table 28: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients Receiving KEYTRUDA in KEYNOTE-A18

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks and 400 mg every 6 weeks with chemoradiotherapy		Placebo with chemoradiotherapy	
	All Grades† (%)	Grades 3-4 (%)	All Grades† (%)	Grades 3-4 (%)
Haematology				
Lymphopenia	99	97	99	94
Leukopenia	96	51	95	51
Anaemia	86	26	84	25
Neutropenia	79	35	78	36
Thrombocytopenia	65	8.4	64	7.2
Chemistry				
Hypomagnesemia	61	3.5	64	3.3
Increased ALT	54	3.8	50	1.5
Hyponatremia	52	4.2	50	3.4
Increased AST	52	2.7	43	1.5
Hypokalemia	44	13	40	12
Hypocalcemia	41	4.6	41	5.1
Increased creatinine	40	4.9	41	4.4
Hypoalbuminemia	34	1.7	34	1.5
Increased alkaline phosphatase	34	0.6	32	0.2

* 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: KEYTRUDA + chemoradiotherapy (range: 512 to 527 patients) and placebo + chemoradiotherapy (range: 520 to 527 patients)
† Graded per NCI CTCAE v5.0

Persistent, Recurrent, or Metastatic Cervical Cancer

The safety of KEYTRUDA in combination with chemotherapy (paclitaxel and cisplatin or paclitaxel and carboplatin) with or without bevacizumab was investigated in KEYNOTE-826,

a multicentre, double-blind, randomised, placebo-controlled trial in 616 patients with persistent, recurrent, or first-line metastatic cervical cancer (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials).

KEYTRUDA was discontinued due to adverse reactions in 15% of patients and treatment was interrupted due to adverse reactions in 66% of patients. Serious adverse reactions occurred in 50% of patients receiving KEYTRUDA plus chemotherapy, with or without bevacizumab. The most frequently occurring serious adverse reactions (≥3%) included febrile neutropenia, urinary tract infection, anaemia, acute kidney injury and sepsis. Fatal adverse reactions were reported in 4.6% of patients receiving KEYTRUDA plus chemotherapy, with or without bevacizumab, including 3 cases of hemorrhage, 2 cases of sepsis, 2 cases due to unknown causes, and 1 case each of acute myocardial infarction, autoimmune encephalitis, cardiac arrest, cerebrovascular accident, femur fracture with perioperative pulmonary embolus, intestinal perforation, and pelvic infection.

Table 29 and Table 30 summarise adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-826.

Table 29: Adverse Reactions Occurring in ≥20% of Patients Receiving KEYTRUDA in KEYNOTE-826

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks and chemotherapy* with or without bevacizumab n=307		Placebo and chemotherapy* with or without bevacizumab n=309	
	All Grades† (%)	Grades 3-4 (%)	All Grades† (%)	Grades 3-4 (%)
Nervous System				
Peripheral neuropathy‡	58	4.2	57	6
Skin and Subcutaneous Tissue				
Alopecia	56	0	58	0
Rash§	22	3.6	15	0.3
General				
Fatigue¶	47	7	46	6
Gastrointestinal				
Nausea	40	2	44	1.6
Diarrhoea	36	2	30	2.6
Constipation	28	0.3	33	1
Vomiting	26	2.6	27	1.9
Musculoskeletal and Connective Tissue				
Arthralgia	27	0.7	26	1.3
Vascular				
Hypertension	24	9	23	11
Infections				
Urinary tract infection	24	9	26	8

* Chemotherapy (paclitaxel and cisplatin or paclitaxel and carboplatin)
† Graded per NCI CTCAE v4.0
‡ Includes neuropathy peripheral, peripheral sensory neuropathy, peripheral motor neuropathy, peripheral sensorimotor neuropathy, paresthesia
§ Includes rash, rash maculo-papular, rash erythematous, rash macular, rash papular, rash pruritic, rash pustular
¶ Includes fatigue, asthenia

Table 30: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients Receiving KEYTRUDA in KEYNOTE-826

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks and chemotherapy† with or without bevacizumab n=307		Placebo and chemotherapy† with or without bevacizumab n=309	
	All Grades‡ (%)	Grades 3-4 (%)	All Grades‡ (%)	Grades 3-4 (%)
Haematology				
Anaemia	80	35	77	33
Leukopenia	76	27	69	19
Neutropenia	73	43	62	32
Lymphopenia	64	35	59	35
Thrombocytopenia	57	19	53	15
Chemistry				
Hyperglycemia	51	4.7	46	2.3
Hypoalbuminemia	46	1.4	37	5
Hyponatremia	39	14	38	11
Increased ALT	40	7	38	6
Increased AST	40	6	36	3.0
Increased alkaline phosphatase	38	3.4	40	2.3
Hypocalcemia	37	4.1	31	5
Increased creatinine	34	5	32	6
Hypokalemia	29	7	26	7
Hyperkalemia	23	3.7	27	4.7
Hypercalcemia	21	1.0	20	1.3

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA plus chemotherapy (range: 296 to 301 patients) and placebo plus chemotherapy (range: 299 to 302 patients)
† Chemotherapy (paclitaxel and cisplatin or paclitaxel and carboplatin)
‡ Graded per NCI CTCAE v4.0

Merkel Cell Carcinoma

Among the 105 patients with MCC enrolled in KEYNOTE-017 and KEYNOTE-913 [see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials], the median duration of exposure to KEYTRUDA was 6.3 months (range 1 day to 28 months). Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible. Adverse reactions occurring in patients with MCC were similar to those occurring in 2799 patients with melanoma or NSCLC treated with KEYTRUDA as a single agent. Laboratory abnormalities (Grades 3-4) that occurred at a higher incidence included increased lipase (17%).

Renal cell carcinoma

In combination with axitinib (KEYNOTE-426)

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

Table 31: Adverse Reactions Occurring in ≥20% of Patients Receiving KEYTRUDA with Axitinib in KEYNOTE-426

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

* Graded per NCI CTCAE v4.03

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

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

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

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

Table 32: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients Receiving KEYTRUDA with Axitinib in KEYNOTE-426

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks and Axitinib		Sunitinib	
	All Grades† %	Grades 3-4 %	All Grades %	Grades 3-4 %
Chemistry				
Hyperglycaemia	62	9	54	3.2
Increased ALT	60	20	44	5
Increased AST	57	13	56	5
Increased creatinine	43	4.3	40	2.4
Hyponatremia	35	8	29	8
Hyperkalaemia	34	6	22	1.7
Hypoalbuminemia	32	0.5	34	1.7
Hypercalcemia	27	0.7	15	1.9
Hypophosphatemia	26	6	49	17
Increased alkaline phosphatase	26	1.7	30	2.7
Hypocalcaemia‡	22	0.2	29	0.7
Blood bilirubin increased	22	2.1	21	1.9
Activated partial thromboplastin time prolonged§	22	1.2	14	0
Haematology				
Lymphopenia	33	11	47	9
Anaemia	29	2.1	65	8
Thrombocytopenia	27	1.4	78	14

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA/axitinib (range: 342 to 425 patients) and sunitinib (range: 345 to 421 patients).
† Graded per NCI CTCAE v4.03
‡ Corrected for albumin
§ Two patients with a Grade 3 elevated activated partial thromboplastin time prolonged (aPTT) were also reported as having an adverse reaction of hepatotoxicity.

In combination with lenvatinib for advanced renal cell carcinoma (KEYNOTE-581)

Table 33 summarises the adverse events that occurred in at least 20% of patients treated with KEYTRUDA and lenvatinib in KEYNOTE-581.

Table 33: Adverse Events Occurring in ≥20% of Patients Receiving KEYTRUDA with Lenvatinib and at a Higher Incidence than in Patients Receiving Sunitinib (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-4]) (KEYNOTE-581)

	KEYTRUDA + lenvatinib n=352		Sunitinib n=340	
Adverse Events	**All Grades* (%)**	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
Gastrointestinal Disorders				
Diarrhoea	61	10	49	5
Nausea	36	2.6	33	0.6
Vomiting	26	3.4	20	1.5
Constipation	25	0.9	19	0
Abdominal pain	21	2.0	8	0.9
Vascular Disorders				

Hypertension	55	28	41	19
Endocrine Disorders				
Hypothyroidism	47	1.4	26	0
Metabolism and Nutrition Disorders				
Decreased appetite	40	4.0	31	1.5
Respiratory, Thoracic and Mediastinal Disorders				
Dysphonia	30	0	4.1	0
Investigations				
Decreased weight	30	8	9	0.3
Renal and Urinary Disorders				
Proteinuria	30	8	13	2.9
Skin and Subcutaneous Tissue Disorders				
Rash	27	3.7	14	0.6
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	28	1.4	15	0.3
Nervous System Disorders				
Headache	23	0.6	16	0.9

* Graded per NCI CTCAE v4.03

Monotherapy for resected renal cell carcinoma (KEYNOTE-564)
In patients receiving KEYTRUDA as monotherapy for adjuvant treatment of RCC, adverse events were generally similar to those occurring in patients with melanoma or NSCLC.

Cutaneous squamous cell carcinoma (cSCC)

Among the 159 patients with advanced cSCC (recurrent or metastatic, or locally advanced disease) enrolled in KEYNOTE-629, the median duration of exposure to KEYTRUDA was 6.9 months (range 1 day to 28.9 months). Patients with autoimmune disease or a medical condition that required systemic corticosteroids or other immunosuppressive medications were ineligible. Adverse events occurring in patients with recurrent or metastatic cSCC or locally advanced cSCC were generally similar to those occurring in patients with melanoma or NSCLC treated with KEYTRUDA as a single agent.

Oesophageal Cancer

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

TMB-H cancer

The safety of KEYTRUDA was investigated in 105 adult patients with TMB-H cancer enrolled in KEYNOTE-158 (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials). The median duration of exposure to KEYTRUDA was 4.9 months (range: 0.03 to 35.2 months). Adverse reactions occurring in patients with TMB-H cancer were similar to those occurring in patients with other solid tumours who received KEYTRUDA as a single agent.

Triple-negative breast cancer (TNBC)

KEYNOTE-522: Controlled study of neoadjuvant and adjuvant treatment of patients with high-risk early-stage TNBC
The safety of KEYTRUDA in combination with neoadjuvant chemotherapy (carboplatin and paclitaxel followed by doxorubicin or epirubicin and cyclophosphamide) followed by surgery

and continued adjuvant treatment with KEYTRUDA as a single agent was investigated in KEYNOTE-522, a randomised (2:1), multicentre, double-blind, placebo-controlled trial in patients with newly diagnosed, previously untreated, high-risk early-stage TNBC.

A total of 778 patients on the KEYTRUDA arm received at least 1 dose of KEYTRUDA in combination with neoadjuvant chemotherapy followed by KEYTRUDA as adjuvant treatment after surgery, compared to 389 patients who received at least 1 dose of placebo in combination with neoadjuvant chemotherapy followed by placebo as adjuvant treatment after surgery *[see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials].*

The median duration of exposure to KEYTRUDA 200 mg every 3 weeks was 13.3 months (range: 1 day to 21.9 months).

Fatal adverse reactions occurred in 0.9% of patients receiving KEYTRUDA, including 1 each of adrenal crisis, autoimmune encephalitis, hepatitis, pneumonia, pneumonitis, pulmonary embolism, and sepsis in association with multiple organ dysfunction syndrome and myocardial infarction.

Serious adverse reactions occurred in 44% of patients receiving KEYTRUDA. Serious adverse reactions in ≥2% of patients who received KEYTRUDA included febrile neutropenia (15%), pyrexia (3.7%), anaemia (2.6%), and neutropenia (2.2%).

KEYTRUDA was discontinued for adverse reactions in 20% of patients. The most common adverse reactions (≥1%) resulting in permanent discontinuation of KEYTRUDA were increased ALT (2.7%), increased AST (1.5%), and rash (1%). Adverse reactions leading to the interruption of KEYTRUDA occurred in 57% of patients. The most common adverse reactions leading to interruption of KEYTRUDA (≥2%) were neutropenia (26%), thrombocytopenia (6%), increased ALT (6%), increased AST (3.7%), anaemia (3.5%), rash (3.2%), febrile neutropenia (2.8%), leukopenia (2.8%), upper respiratory tract infection (2.6%), pyrexia (2.2%), and fatigue (2.1%).

Tables 32 and 33 summarise the adverse reactions and laboratory abnormalities, respectively, in patients treated with KEYTRUDA in KEYNOTE-522.

Table 34: Adverse Events Occurring in ≥20% of Patients Receiving KEYTRUDA in KEYNOTE-522

Adverse Event	KEYTRUDA 200 mg every 3 weeks with chemotherapy*/KEYTRUDA n=778		Placebo with chemotherapy*/Placebo n=389	
	All Grades† (%)	Grades 3-4 (%)	All Grades† (%)	Grades 3-4 (%)
General				
Fatigue‡	70	8	66	3.9
Pyrexia	28	1.3	19	0.3
Gastrointestinal				
Nausea	67	3.7	66	1.8
Constipation	42	0	39	0.3
Diarrhoea	41	3.2	34	1.8
Stomatitis§	34	2.7	29	1
Vomiting	31	2.7	28	1.5
Abdominal pain¶	24	0.5	23	0.8
Skin and Subcutaneous Tissue				
Alopecia	61	0	58	0
Rash#	52	5	41	0.5
Nervous System				
Peripheral neuropathyÞ	41	3.3	42	2.3
Headache	30	0.5	29	1
Musculoskeletal and Connective Tissue				
Arthralgia	29	0.5	31	0.3
Myalgia	20	0.5	19	0
Respiratory, Thoracic and Mediastinal				
Coughß	26	0.1	24	0
Metabolism and Nutrition				
Decreased appetite	23	0.9	17	0.3
Psychiatric				
Insomnia	21	0.5	19	0

* Chemotherapy: carboplatin and paclitaxel followed by doxorubicin or epirubicin and cyclophosphamide

† Graded per NCI CTCAE v4.0

‡ Includes asthenia, fatigue

§ Includes aphthous ulcer, cheilitis, lip pain, lip ulceration, mouth ulceration, mucosal inflammation, oral mucosal eruption, oral pain, stomatitis, tongue blistering, tongue ulceration

¶ Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness

Includes dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis bullous, dermatitis exfoliative generalized, drug eruption, eczema, incision site rash, injection site rash, rash, rash erythematous, rash follicular, rash macular, rash maculo-papular, rash morbilliform, rash papular, rash pruritic, rash pustular, rash rubelliform, skin exfoliation, skin toxicity, toxic skin eruption, urticaria, vasculitic rash, viral rash

Þ Includes neuropathy peripheral, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy

ß Includes cough, productive cough, upper-airway cough syndrome

Table 35: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients Receiving KEYTRUDA in KEYNOTE-522

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks with chemotherapy†/KEYTRUDA		Placebo with chemotherapy†/Placebo	
	All Grades‡ %	Grades 3-4 %	All Grades‡ %	Grades 3-4 %
Haematology				
Anaemia	97	22	96	19
Leukopenia	93	41	91	32
Neutropenia	88	62	89	62
Lymphopenia	79	28	74	22
Thrombocytopenia	57	10	56	8
Chemistry				
Increased ALT	70	9	67	3.9
Increased AST	65	6	56	1.5
Hyperglycemia	63	4.3	61	2.8
Increased alkaline phosphatase	37	1	35	0.5
Hyponatremia	35	9	25	4.6
Hypoalbuminemia	34	1.0	30	1.3
Hypocalcemia	31	2.2	28	3.1
Hypokalemia	31	6	22	2.8
Hypophosphatemia	20	6	15	4.2

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA in combination with chemotherapy followed by KEYTRUDA as a single agent (range: 762 to 777 patients) and placebo in combination with chemotherapy followed by placebo (range: 381 to 389 patients).

† Chemotherapy: carboplatin and paclitaxel followed by doxorubicin or epirubicin and cyclophosphamide

‡ Graded per NCI CTCAE v4.0

KEYNOTE-355: Controlled study of combination therapy in patients with locally recurrent unresectable or metastatic TNBC

The safety of KEYTRUDA in combination with paclitaxel, paclitaxel protein-bound, or gemcitabine and carboplatin was investigated in KEYNOTE-355, a multicentre, double-blind, randomised (2:1), placebo-controlled trial in patients with locally recurrent unresectable or metastatic TNBC who had not been previously treated with chemotherapy in the metastatic setting *[see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials]*. A total of 596 patients (including 34 patients from a safety run-in) received KEYTRUDA 200 mg every 3 weeks in combination with paclitaxel, paclitaxel protein-bound, or gemcitabine and carboplatin.

The median duration of exposure to KEYTRUDA was 5.7 months (range: 1 day to 33.0 months).

Fatal adverse reactions occurred in 2.5% of patients receiving KEYTRUDA in combination with chemotherapy, including cardio-respiratory arrest (0.7%) and septic shock (0.3%).

Serious adverse reactions occurred in 30% of patients receiving KEYTRUDA in combination with paclitaxel, paclitaxel protein-bound, or gemcitabine and carboplatin. Serious adverse reactions in ≥2% of patients were pneumonia (2.9%), anaemia (2.2%), and thrombocytopenia (2%).

KEYTRUDA was discontinued for adverse reactions in 11% of patients. The most common

adverse reactions resulting in permanent discontinuation of KEYTRUDA (≥1%) were increased ALT (2.2%), increased AST (1.5%), and pneumonitis (1.2%). Adverse reactions leading to the interruption of KEYTRUDA occurred in 50% of patients. The most common adverse reactions leading to interruption of KEYTRUDA (≥2%) were neutropenia (22%), thrombocytopenia (14%), anaemia (7%), increased ALT (6%), leukopenia (5%), increased AST (5%), decreased white blood cell count (3.9%), and diarrhoea (2%).

Tables 34 and 35 summarise the adverse reactions and laboratory abnormalities in patients on KEYTRUDA in KEYNOTE-355.

Table 36: Adverse Events Occurring in ≥20% of Patients Receiving KEYTRUDA with Chemotherapy in KEYNOTE-355

Adverse Event	KEYTRUDA 200 mg every 3 weeks with chemotherapy n=596		Placebo every 3 weeks with chemotherapy n=281	
	All Grades* (%)	Grades 3-4 (%)	All Grades* (%)	Grades 3-4 (%)
General				
Fatigue†	48	5	49	4.3
Gastrointestinal				
Nausea	44	1.7	47	1.8
Diarrhoea	28	1.8	23	1.8
Constipation	28	0.5	27	0.4
Vomiting	26	2.7	22	3.2
Skin and Subcutaneous Tissue				
Alopecia	34	0.8	35	1.1
Rash‡	26	2	16	0
Respiratory, Thoracic and Mediastinal				
Cough§	23	0	20	0.4
Metabolism and Nutrition				
Decreased appetite	21	0.8	14	0.4
Nervous System				
Headache¶	20	0.7	23	0.7

* Graded per NCI CTCAE v4.03
† Includes fatigue and asthenia
‡ Includes rash, rash maculo-papular, rash pruritic, rash pustular, rash macular, rash papular, butterfly rash, rash erythematous, eyelid rash
§ Includes cough, productive cough, upper-airway cough syndrome
¶ Includes headache, migraine, tension headache

Table 37: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients Receiving KEYTRUDA with Chemotherapy in KEYNOTE-355

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks with chemotherapy		Placebo every 3 weeks with chemotherapy	
	All Grades† %	Grades 3-4 %	All Grades† %	Grades 3-4 %
Haematology				
Anaemia	90	20	85	19
Leukopenia	85	39	86	39
Neutropenia	78	50	79	53
Lymphopenia	73	28	71	19
Thrombocytopenia	54	19	53	21
Chemistry				
Increased ALT	60	11	58	8
Increased AST	57	9	55	6
Hyperglycemia	52	4.4	51	2.2
Hypoalbuminemia	36	2.0	32	2.2
Increased alkaline phosphatase	35	3.9	39	2.2
Hypocalcemia	29	3.3	27	1.8
Hyponatremia	28	5	26	6
Hypophosphatemia	21	7	18	4.8
Hypokalemia	20	4.4	18	4.0

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA + chemotherapy (range: 566 to 592 patients) and placebo + chemotherapy (range: 269 to 280 patients).

† Graded per NCI CTCAE v4.03

Biliary tract carcinoma (BTC)

In patients with BTC receiving KEYTRUDA plus chemotherapy (gemcitabine and cisplatin) in KEYNOTE-966, the median duration of exposure to KEYTRUDA was 6 months (range: 1 day to 28 months). In the KEYTRUDA plus chemotherapy versus placebo plus chemotherapy arms, there was a difference of ≥5% incidence in adverse events between patients treated with KEYTRUDA versus placebo for pyrexia (26% vs. 20%), rash (21% vs. 13%), pruritus (15% vs. 10%) and hypothyroidism (9% vs. 2.6%). There were no clinically meaningful differences in incidence of Grade 3-4 toxicity between arms. KEYTRUDA was discontinued due to adverse events in 15% of patients. The most common adverse event resulting in permanent discontinuation of KEYTRUDA (≥1%) was pneumonitis (1.3%). Adverse events leading to the interruption of KEYTRUDA occurred in 55% of patients. The most common adverse events or laboratory abnormalities leading to interruption of KEYTRUDA (≥2%) were decreased neutrophil count (18%), decreased platelet count (10%), anaemia (6%), decreased white blood count (4%), pyrexia (3.8%), fatigue (3.0%), cholangitis (2.8%), increased ALT (2.6%), increased AST (2.5%), and biliary obstruction (2.3%).

Ovarian Cancer

The safety of KEYTRUDA in combination with paclitaxel with or without bevacizumab was investigated in 638 patients with epithelial ovarian, fallopian tube, or primary peritoneal carcinoma enrolled in KEYNOTE-B96 (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical Trials).

Among patients who received KEYTRUDA, the median duration of exposure was 7.5 months (range: 1 day to 35.9 months).

Fatal adverse events occurred in 4.7% of patients receiving KEYTRUDA and paclitaxel with or without bevacizumab, including assisted suicide (0.6%), death (0.6%), intestinal perforation (0.6%), sepsis (0.6%), COVID-19 (0.3%), cardio-respiratory arrest (0.3%), colitis (0.3%), duodenal obstruction (0.3%), embolic stroke (0.3%), gastrointestinal hemorrhage (0.3%) and interstitial lung disease (0.3%).

Serious adverse events occurred in 56% of patients receiving KEYTRUDA and paclitaxel with or without bevacizumab. Serious adverse events in ≥2% of patients were urinary tract infection (4.7%), pneumonia (4.4%), pulmonary embolism (2.8%), hyponatremia (2.5%), pyrexia (2.5%), abdominal pain (2.2%), adrenal insufficiency (2.2%), anaemia (2.2%), COVID-19 (2.2%), diarrhoea (2.2%), febrile neutropenia (2.2%), decreased neutrophil count (2.2%), small intestinal obstruction (2.2%) and vomiting (2.2%).

KEYTRUDA was discontinued for adverse events in 15% of patients. The most common adverse events resulting in permanent discontinuation of KEYTRUDA (≥0.5%) were increased alanine aminotransferase (0.9%), colitis (0.9%), arthritis (0.6%), haemolytic anaemia (0.6%), interstitial lung disease (0.6%), intestinal perforation (0.6%), pneumonia (0.6%) and sepsis (0.6%).

Table 38 and Table 39 summarise the adverse events and laboratory abnormalities in patients on KEYTRUDA in KEYNOTE-B96.

Table 38: Adverse Events Occurring in ≥20% of Patients Receiving KEYTRUDA in KEYNOTE-B96

Adverse Event	KEYTRUDA 400 mg every 6 weeks and chemotherapy with or without bevacizumab n=320		Placebo every 6 weeks and chemotherapy with or without bevacizumab n=318	
	All Grades* (%)	Grades 3-4† (%)	All Grades* (%)	Grades 3-4† (%)
General				
Fatigue	41	7	37	6
Pyrexia	21	0.6	12	0.6
Infections and infestations				
Urinary tract infection	28	6	23	2.8
Gastrointestinal				
Diarrhoea	44	5	40	1.3
Nausea	41	2.5	36	2.5
Abdominal pain	24	2.5	26	2.2
Constipation	24	0	26	0.6
Vomiting	24	2.8	23	1.9
Skin and Subcutaneous Tissue				
Alopecia	38	0	35	0
Rash	21	0	13	0.6
Respiratory, Thoracic and Mediastinal				
Epistaxis	32	0.3	25	0
Cough	20	0	15	0
Metabolism and Nutrition				
Decreased appetite	24	2.2	20	1.6
Nervous System				
Peripheral neuropathy	39	5	33	6
Vascular Disorders				
Hypertension	20	7	19	5

* Graded per NCI CTCAE v5

† Of these ≥20% adverse events, none was reported as Grade 4 in patients who received KEYTRUDA. Hypertension was reported as Grade 4 in one patient in the control arm.

Table 39: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients Receiving KEYTRUDA in KEYNOTE-B96

Laboratory Test*	KEYTRUDA 400 mg every 6 weeks and chemotherapy with or without bevacizumab		Placebo every 6 weeks and chemotherapy with or without bevacizumab	
	All Grades† %	Grades 3-4 %	All Grades† %	Grades 3-4 %
Haematology				
Anaemia	84	15	79	11
Leukopenia	83	24	78	20
Neutropenia	72	39	67	32
Lymphopenia	59	27	60	19
Hypomagnesemia	43	2.3	38	2.3
Chemistry				
Hyponatremia	51	6	39	4.8
Hypoalbuminemia	51	4.1	44	2.6
Aspartate aminotransferase increased	42	3.8	33	1.3
Alanine aminotransferase increased	41	7	31	1.6
Hypocalcemia	39	3.2	28	1.9
Alkaline phosphatase increased	31	1.9	27	1.9
Creatinine increased	30	3.8	24	2.9
Hypokalemia	28	7	20	4.1
Hyperkalemia	21	1.9	20	2.9

* Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA + chemotherapy (range: 310 to 319 patients) and placebo + chemotherapy (range: 303 to 316 patients).

† Graded per NCI CTCAE v5

Post-marketing experience

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

Blood and lymphatic disorders: autoimmune haemolytic anaemia
Eye disorders: Vogt-Koyanagi-Harada syndrome
Gastrointestinal disorders: coeliac disease
Immune system disorders: haemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, infusion-related reactions (including cytokine release syndrome)
Musculoskeletal and connective tissue disorders: arthritis (including immune-mediated arthritis), Sjögren's syndrome, tenosynovitis, polymyalgia rheumatica and myositis (including polymyositis)
Nervous system disorders: optic neuritis

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 preclinical murine models, combinations of an anti-mouse PD-1 antibody plus a tyrosine kinase inhibitor (TKI) have demonstrated enhanced anti-tumour activity compared to either agent alone.

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

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

Clinical trials

Melanoma

KEYNOTE-006: Controlled trial in melanoma patients naïve to treatment with ipilimumab

The safety and efficacy of KEYTRUDA were investigated in KEYNOTE-006, a multicentre, controlled, Phase III study for the treatment of unresectable or metastatic melanoma in patients who were naïve to ipilimumab and who received no or one prior systemic therapy. Patients were randomised (1:1:1) to receive KEYTRUDA at a dose of 10 mg/kg every 2 (n=279) or 3 weeks (n=277) or ipilimumab (n=278). Randomisation was stratified by line of therapy, ECOG performance status, and PD-L1 expression status. The study excluded patients with autoimmune disease or those receiving immunosuppression; previous severe

hypersensitivity to other monoclonal antibodies; and HIV, hepatitis B or hepatitis C infection. Patients with BRAF V600E mutant melanoma were not required to have received prior BRAF inhibitor therapy.

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

Of the 834 patients in KEYNOTE-006, 60% were male, 44% were ≥65 years (median age was 62 years [range 18-89]) and 98% were white. Sixty-six percent had no prior systemic therapies and thus received study therapy as first-line treatment whereas 34% had one prior therapy and thus received study therapy as second-line treatment. Thirty-one percent had an ECOG PS of 1 and 69% had an ECOG PS of 0. Eighty percent of patients were PD-L1 positive (PD-L1 membrane expression in ≥1% of tumour and associated immune cells as assessed prospectively by an immunohistochemistry assay with the 22C3 anti-PD-L1 antibody) and 18% were PD-L1 negative. Sixty-five percent of patients had M1c stage, 32% had elevated LDH and 9% had brain metastases. BRAF mutations were reported in 302 (36%) patients. Among patients with BRAF mutant tumours, 139 (46%) were previously treated with a BRAF inhibitor. Baseline characteristics were well-balanced across treatment arms.

The primary efficacy outcome measures were overall survival (OS) and progression free survival (PFS; as assessed by Integrated Radiology and Oncology Assessment [IRO] review using Response Evaluation Criteria in Solid Tumours [RECIST 1.1]). Secondary efficacy outcome measures were overall response rate (ORR) and response duration.
Table 40 summarises key efficacy measures.

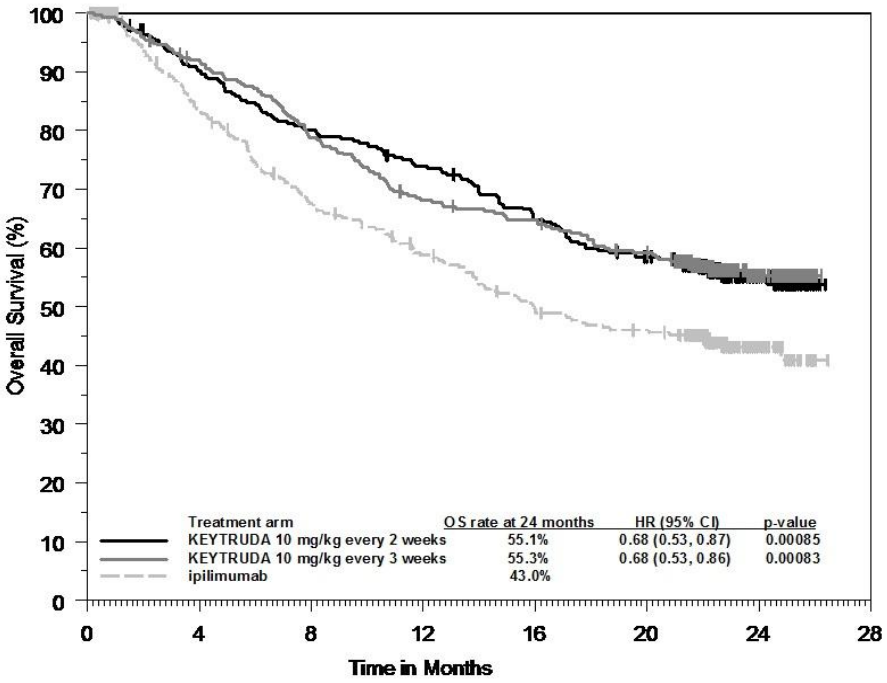
Table 40: Response to KEYTRUDA 10 mg/kg every 2 or 3 weeks in patients with ipilimumab-naïve advanced melanoma in KEYNOTE-006

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

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

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

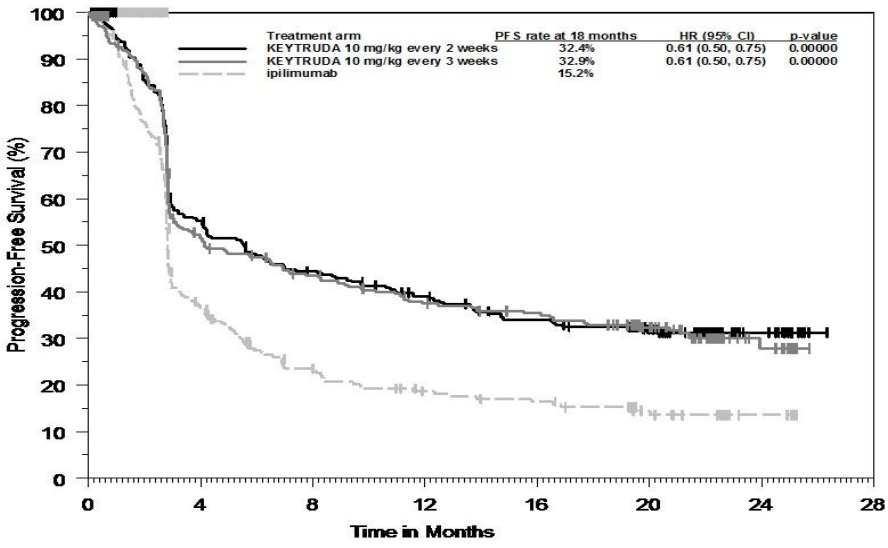
Figure 1: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-006 (intent to treat population)



Number at Risk

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

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



Number at Risk

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

Sub-population analysis by BRAF mutation status

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

Sub-population analysis by PD-L1 status

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

KEYNOTE-002: Controlled trial in melanoma patients previously treated with ipilimumab

The safety and efficacy of KEYTRUDA were investigated in KEYNOTE-002, a multicentre, controlled study for the treatment of unresectable or metastatic melanoma in patients previously treated with ipilimumab and if BRAF V600 mutation-positive, a BRAF or MEK inhibitor. Patients were randomised (1:1:1) to receive KEYTRUDA at a dose of 2 (n=180) or 10 mg/kg (n=181) every 3 weeks or chemotherapy (n=179; including dacarbazine, temozolomide, carboplatin, paclitaxel, or carboplatin+paclitaxel). The study excluded patients with autoimmune disease or those receiving immunosuppression; a history of severe or life-threatening immune-mediated adverse reactions from treatment with ipilimumab, defined as any Grade 4 toxicity or Grade 3 toxicity requiring corticosteroid treatment (greater than 10 mg/day prednisone or equivalent dose) for greater than 12 weeks; previous severe hypersensitivity to other monoclonal antibodies; a history of pneumonitis or interstitial lung disease; HIV, Hepatitis B or Hepatitis C infection.

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

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

The primary efficacy outcome measures were PFS (as assessed by IRO review using RECIST 1.1) and overall survival (OS). Secondary efficacy outcome measures were PFS as assessed by Investigator using RECIST 1.1, ORR and response duration. Table 41 summarises key

efficacy measures in patients previously treated with ipilimumab. There was no statistically significant difference between KEYTRUDA and chemotherapy in the final OS analysis that was not adjusted for the potentially confounding effects of crossover. Of the patients randomised to the chemotherapy arm, 55% crossed over and subsequently received treatment with KEYTRUDA.

Table 41: Response to KEYTRUDA 2 mg/kg or 10 mg/kg every 3 weeks in patients with unresectable or metastatic melanoma in KEYNOTE-002

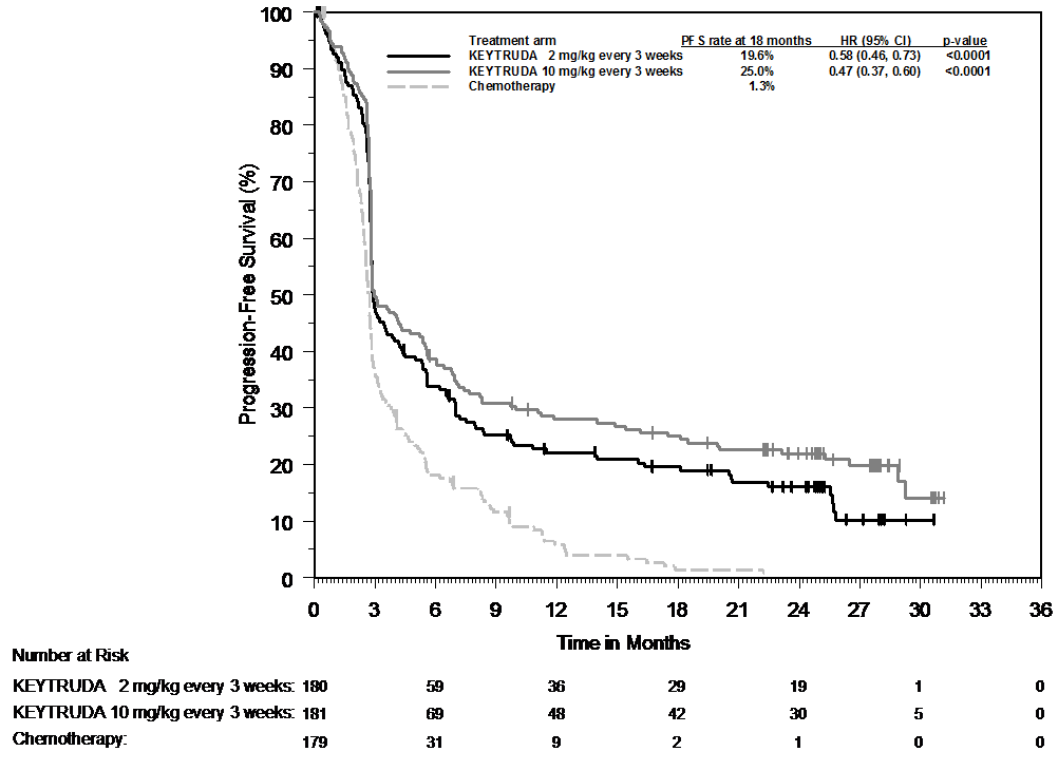
Endpoint	KEYTRUDA 2 mg/kg every 3 weeks n=180	KEYTRUDA 10 mg/kg every 3 weeks n=181	Chemotherapy n=179
OS*			
Number (%) of patients with event	123 (68%)	117 (65%)	128 (72%)
Hazard ratio† (95% CI)	0.86 (0.67, 1.10)	0.74 (0.57, 0.96)	---
p-Value‡	0.117	0.011è	---
Median in months (95% CI)	13.4 (11.0, 16.4)	14.7 (11.3, 19.5)	11.0 (8.9, 13.8)
PFS§ by IRO¶			
Number (%) of patients with event	129 (72%)	126 (70%)	155 (87%)
Hazard ratio† (95% CI)	0.57 (0.45, 0.73)	0.50 (0.39, 0.64)	---
p-Value‡	<0.0001	<0.0001	---
Median in months (95% CI)	2.9 (2.8, 3.8)	2.9 (2.8, 4.7)	2.7 (2.5, 2.8)
Mean in months (95% CI)#	5.4 (4.7, 6.0)	5.8 (5.1, 6.4)	3.6 (3.2, 4.1)
PFS§ by INVÞ			
Number (%) of patients with event	122 (68%)	112 (62%)	157 (88%)
Hazard ratio† (95% CI)	0.49 (0.38, 0.62)	0.41 (0.32, 0.52)	---
p-Value‡	<0.0001	<0.0001	---
Median in months (95% CI)	3.7 (2.9, 5.4)	5.4 (3.8, 6.8)	2.6 (2.4, 2.8)
Mean in months (95% CI) #	5.8 (5.2, 6.4)	6.5 (5.8, 7.1)	3.7 (3.2, 4.1)
Best Overall Response§ by IRO¶			
ORR % (95% CI)	21% (15, 28)	25% (19, 32)	4% (2, 9)
Complete response %	2%	3%	0%
Partial response %	19%	23%	4%
Response durationß by IRO¶			
Median in months (range)	22.8 (1.4+, 25.3+)	Not reached (1.1+, 28.3+)	6.8 (2.8, 11.3)
% ongoing at 12 monthsà	73%	79%	Not reachedð

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

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

patients treated with KEYTRUDA 2 mg/kg every 3 weeks and 0.47 (95% CI: 0.37, 0.60 for patients treated with KEYTRUDA 10 mg/kg every 3 weeks (Figure 3).

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



KEYNOTE-001: Open label study in melanoma patients

The safety and efficacy of KEYTRUDA were also investigated in an uncontrolled, open-label study for the treatment of unresectable or metastatic melanoma. Efficacy was evaluated for 276 patients from two defined cohorts of KEYNOTE-001, one which included patients previously treated with ipilimumab (and if BRAF V600 mutation-positive, a BRAF or MEK inhibitor) and another with included patients naïve to treatment with ipilimumab. Patients were randomised to receive KEYTRUDA at a dose of 2 mg/kg every 3 weeks or 10 mg/kg every 3 weeks. The study excluded patients with autoimmune disease; medical conditions that required immunosuppression; a history of severe immune-mediated adverse reactions with ipilimumab, defined as any Grade 4 toxicity requiring treatment with corticosteroids or Grade 3 toxicity requiring corticosteroid treatment (greater than 10 mg/day prednisone or equivalent dose) for greater than 12 weeks; medical conditions that required systemic corticosteroids or other immunosuppressive medication; a history of pneumonitis or interstitial lung disease; or any active infection requiring therapy, including HIV, HBV or HCV. Patients were treated with KEYTRUDA until disease progression that was symptomatic, was rapidly progressive, required urgent intervention, or occurred with a decline in performance status, at the discretion of the investigator, based on clinical judgment. Patients were also discontinued if disease progression was confirmed at 4 to 6 weeks with repeat imaging or unacceptable toxicity.

Of the 89 patients receiving 2 mg/kg of KEYTRUDA who were previously treated with ipilimumab, 53% were male, 33% were ≥65 years of age and the median age was 59 years (range 18-88). All but two patients were white. Eighty-four percent of patients had M1c stage

and 8% of patients had a history of brain metastases. Seventy-eight percent of patients had at least two and 35% of patients had three or more prior systemic therapies for advanced melanoma. BRAF mutations were reported in 13% of the study population.

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

The primary efficacy outcome measure was ORR as assessed by independent review using confirmed responses and RECIST 1.1. Secondary efficacy outcome measures were disease control rate (DCR; including complete response, partial response and stable disease), response duration, PFS, and OS. Tumour response was assessed at 12-week intervals. Table 42 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 42: 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-716: Placebo-controlled trial for the adjuvant treatment of patients with completely resected Stage IIB or IIC melanoma

The efficacy of KEYTRUDA was investigated in KEYNOTE-716, a multicentre, randomised, double-blind, placebo-controlled trial in patients with completely resected stage IIB or IIC melanoma. A total of 976 patients were randomised (1:1) to receive KEYTRUDA 200 mg or the paediatric (≥12 years old) dose of KEYTRUDA 2 mg/kg intravenously (up to a maximum of 200 mg) every three weeks (n=487) or placebo (n=489) for up to one year until disease recurrence or unacceptable toxicity. Randomisation was stratified by American Joint Committee on Cancer 8th edition (AJCC) T stage. Patients must not have been previously treated for melanoma beyond complete surgical resection for their melanoma prior to study entry. Patients with active autoimmune disease or a medical condition that required immunosuppression or mucosal or ocular melanoma were ineligible. Patients underwent imaging every 6 months for 1 year from randomisation, every 6 months from years 2 to 4, and then once in year 5 from randomisation or until recurrence, whichever came first.

Among the 976 patients, the baseline characteristics were: median age of 61 years (range: 16 to 87), 39% age 65 or older; 60% male; and 93% ECOG PS of 0 and 7% ECOG PS of 1. Sixty-four percent had stage IIB and 35% had stage IIC.

The primary efficacy outcome measure was investigator-assessed recurrence free survival (RFS) in the whole population, where RFS was defined as the time between the date of randomisation and the date of first recurrence (local, regional, or distant metastasis) or death, whichever occurs first. The secondary outcome measures were distant metastasis-free survival (DMFS) and OS in the whole population. OS was not formally assessed at the time of these analyses.

The trial initially demonstrated a statistically significant improvement in RFS and DMFS for patients randomised to the pembrolizumab arm compared with placebo. Results reported from the pre-specified interim analysis for RFS with a median follow-up of 14.3 months are summarised in Table 43. Results reported from the pre-specified interim analysis for DMFS with a median follow-up of 26.9 months are summarised in Table 43 and Figure 5.

Table 43: Efficacy Results in KEYNOTE-716

Endpoint	**KEYTRUDA** **200 mg every 3 weeks n=487**	**Placebo** **n=489**
RFS		
Number (%) of patients with event	54 (11%)	82 (17%)
RFS rate at 18 months	85.8%	77%
Median in months (95% CI)	NR (22.6, NR)	NR (NR, NR)
Hazard ratio* (95% CI)	0.65 (0.46, 0.92)	
p-Value (stratified log-rank)	0.00658	
DMFS		
Number (%) of patients with event	63 (13%)	95 (19%)
DMFS rate at 24 months	88.1%	82.2%
Median in months (95% CI)	NR (NR, NR)	NR (NR, NR)
Hazard ratio* (95% CI)	0.64 (0.47, 0.88)	
p-Value (stratified log-rank)	0.00292	

* Based on the stratified Cox proportional hazard model
NR=not reached

A pre-specified sensitivity analysis of RFS that included new primary melanomas was consistent with the primary RFS analysis, with an HR of 0.64 (95% CI: 0.46, 0.88).

A pre-specified final analysis for RFS performed with a median follow-up of 20.5 months (range: 4.6 to 32.7 months). At the time of this analysis, the hazard ratio in patients randomised to pembrolizumab versus patients randomised to placebo was 0.61 (95% CI: 0.45, 0.82) with 72/487 (14.8%) events and 115/489 (23.5%), respectively. These efficacy results are summarised in Figure 4.Updated RFS results with a median follow-up of 26.9 months were consistent with the final analysis for RFS for patients randomised to the pembrolizumab arm compared with placebo (HR 0.64; 95% CI: 0.50, 0.84).

Figure 4: Kaplan-Meier Curve for Recurrence-Free Survival in KEYNOTE-716 (Intent to Treat Population)

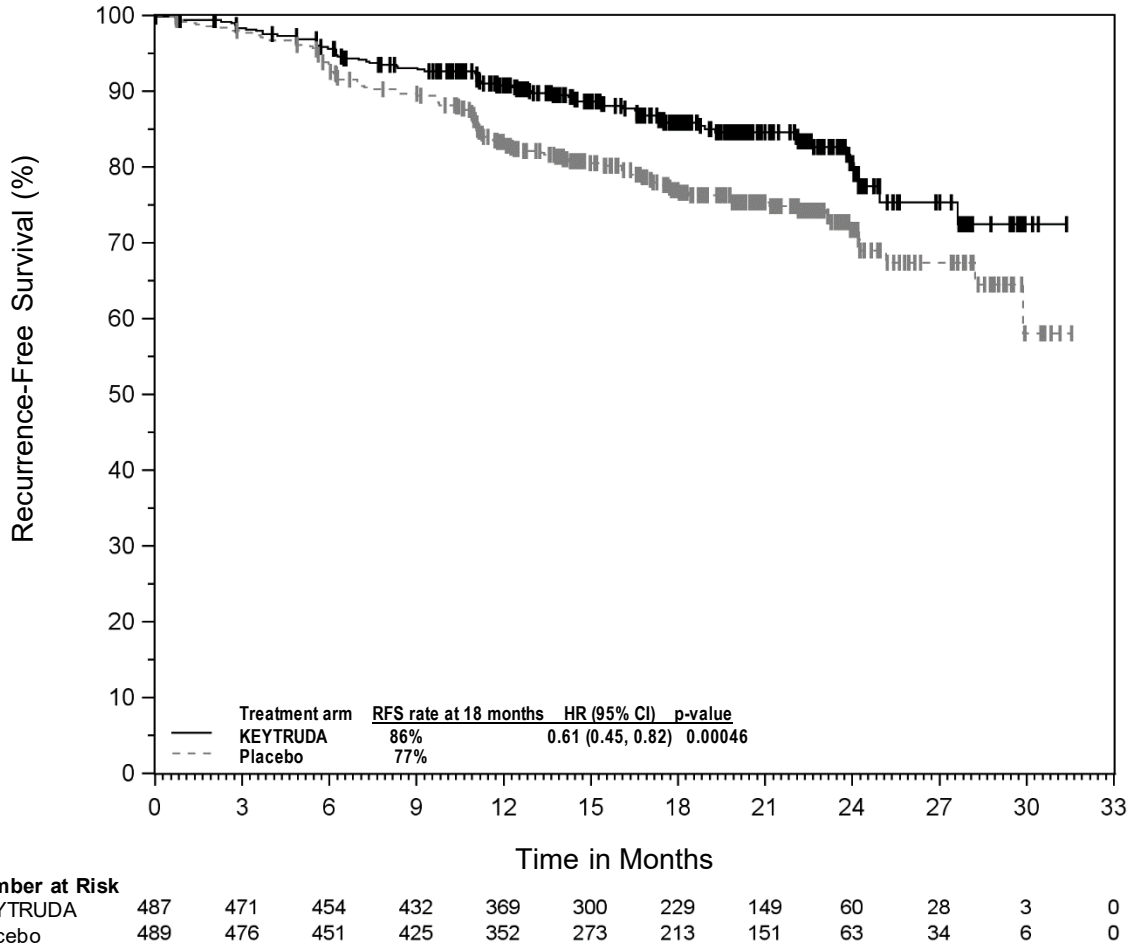
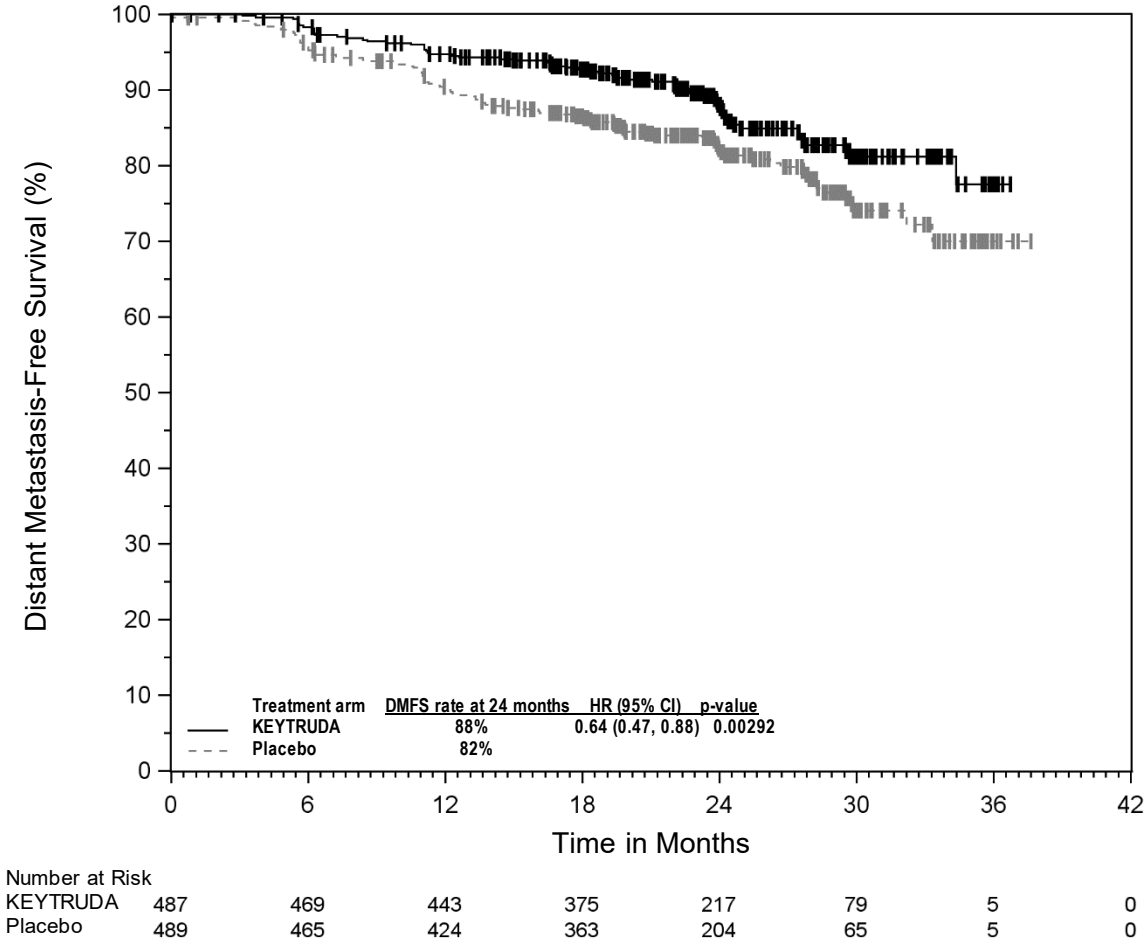


Figure 5: Kaplan-Meier Curve for Distant Metastasis-Free Survival in KEYNOTE 716 (Intent to Treat Population)



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

The efficacy of KEYTRUDA was evaluated in KEYNOTE-054, a multicentre, randomised double-blind, placebo-controlled trial in patients with completely resected stage IIIA (> 1 mm lymph node metastasis), IIIB or IIIC melanoma. A total of 1019 patients were randomised (1:1) to receive KEYTRUDA 200 mg every three weeks (n=514) or placebo (n=505), for up to one year until disease recurrence or unacceptable toxicity. Randomisation was stratified by 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 was investigator-assessed RFS, measured in the intent-to-treat (ITT) population and in the subgroup with PD-L1 positive tumours. The secondary efficacy outcomes included distant metastasis-free survival (DMFS) and overall survival (OS) in the ITT population and in the subgroup with PD-L1 positive tumours. The OS data were not mature at the time of DMFS analysis. The trial demonstrated a statistically significant improvement in RFS and DMFS for patients randomised to the KEYTRUDA arm compared with placebo. RFS efficacy results with a median follow-up time of 16.0 months are summarised in Table 44 and Figure 6. DMFS efficacy results with a median follow-up time of 45.5 months are summarised in Table 44 and Figure 7.

Table 44: Efficacy results in KEYNOTE-054

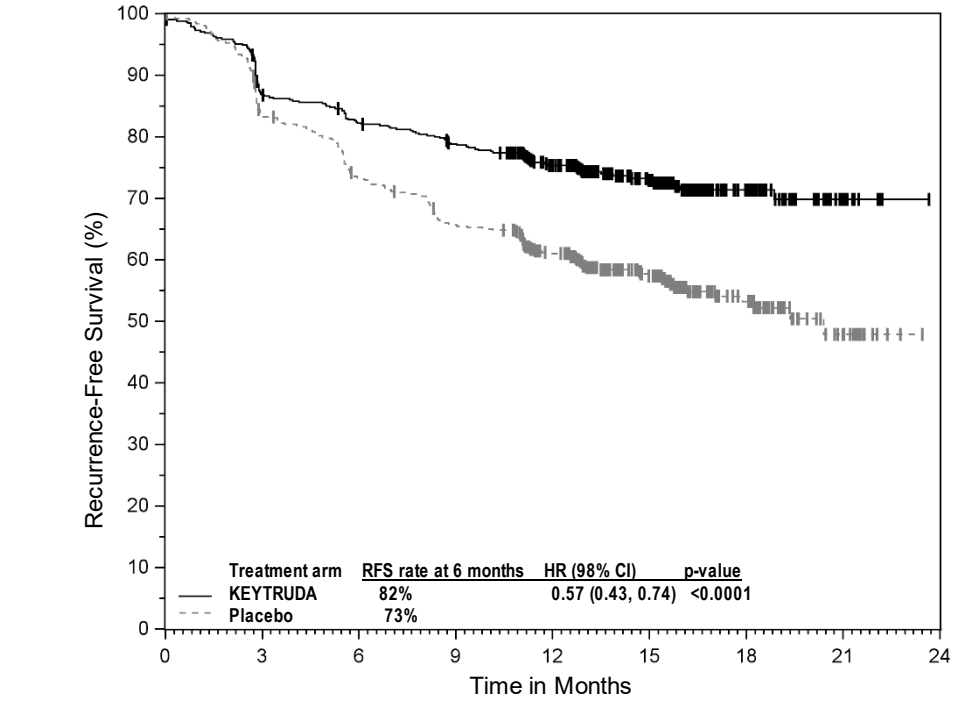
Endpoint	**KEYTRUDA 200 mg every 3 weeks n=514**	**Placebo n=505**
RFS		
Number (%) of patients with event	135 (26%)	216 (43%)
RFS rate at 6 months	82%	73%
Median in months (95% CI)	NR (NR, NR)	20.4 (16.2, NR)
Hazard ratio (HR)* (98.4% CI)	0.57 (0.43, 0.74)	
p-value (stratified log-rank)	<0.0001	
DMFS		
Number (%) of patients with event	173 (34%)	245 (49%)
DMFS rate at 42 months	65%	49%
Median in months (95% CI)	NR (49.6, NR)	40.0 (27.7, NR)
Hazard ratio* (95% CI)	0.60 (0.49, 0.73)	
p-value (stratified log-rank)	< 0.0001	

* Based on the stratified Cox proportional hazard model
NR = not reached

For patients in the ITT population, the RFS rate at 42 months was 60% in the KEYTRUDA arm and 41% in the placebo arm (HR was 0.59 [95% CI: 0.49, 0.70]).

RFS and DMFS benefit was consistently demonstrated across subgroups, including tumour PD-L1 expression, BRAF mutation status, and stage of disease (using AJCC 7th edition). These results were consistent when reclassified in a post-hoc analysis according to the current AJCC 8th edition staging system.

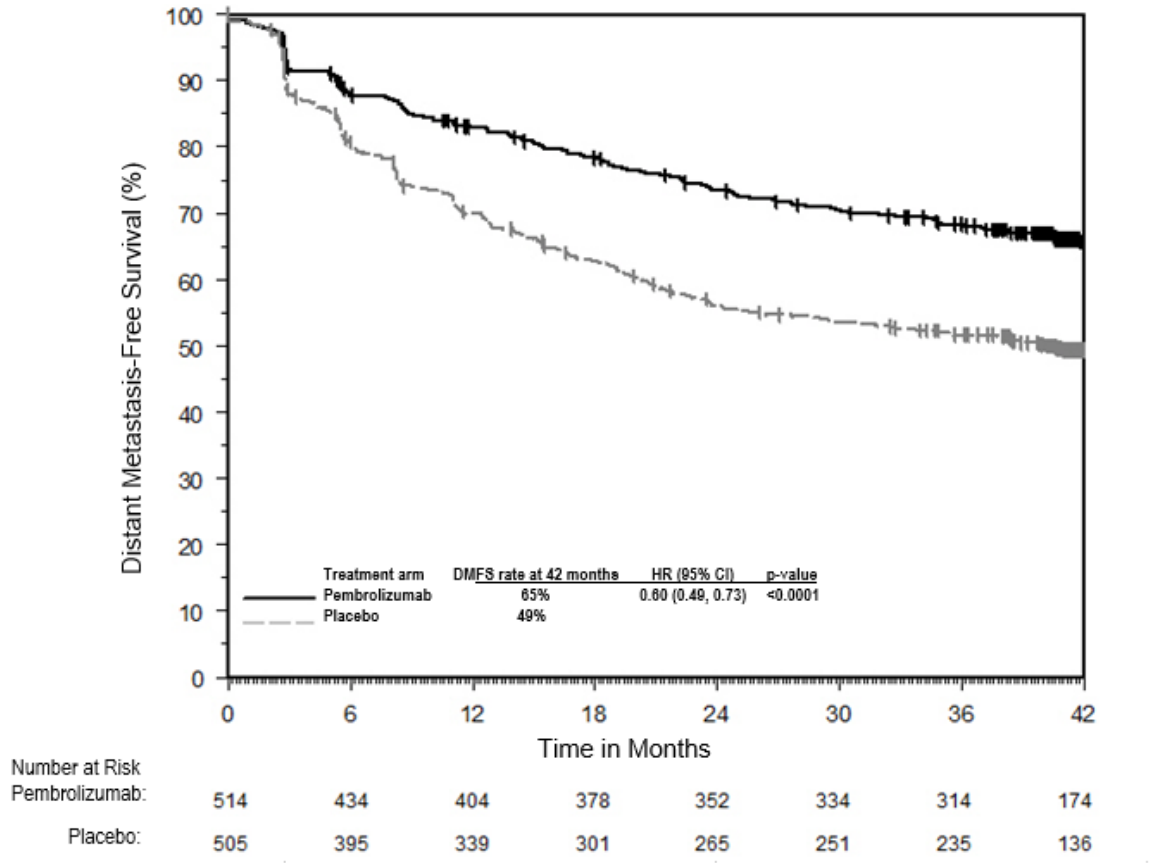
Figure 6: Kaplan-Meier curve for recurrence-free survival in KEYNOTE-054 (ITT population)



Number at Risk

KEYTRUDA	514	438	413	392	313	182	73	15	0
Placebo	505	415	363	323	264	157	60	15	0

Figure 7: Kaplan-Meier curve for distant metastasis free survival in KEYNOTE-054 (ITT population)



Non-small cell lung cancer (NSCLC)

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

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

- KEYTRUDA 200 mg with pemetrexed 500 mg/m^2 and investigator's choice of cisplatin 75 mg/m^2 or carboplatin AUC 5 mg/mL/min intravenously every 3 weeks for 4 cycles followed by KEYTRUDA 200 mg and pemetrexed 500 mg/m^2 intravenously every 3 weeks.
- Placebo with pemetrexed 500 mg/m^2 and investigator's choice of cisplatin 75 mg/m^2 or carboplatin AUC 5 mg/mL/min intravenously every 3 weeks for 4 cycles followed by placebo and pemetrexed 500 mg/m ^{2} intravenously every 3 weeks.

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

therapy or had a complete response, treatment with KEYTRUDA could be reinitiated for disease progression and administered for up to 1 additional year. Assessment of tumour status was performed at Week 6 and Week 12, followed by every 9 weeks thereafter. Patients receiving placebo plus chemotherapy who experienced independently-verified progression of disease were offered KEYTRUDA as monotherapy.

Among the 616 patients in KEYNOTE-189 (410 patients in the KEYTRUDA combination arm and 206 in the placebo plus chemotherapy arm), baseline characteristics were: median age of 64 years (49% age 65 or older); 59% male; 94% White and 3% Asian; 43% and 56% ECOG performance status of 0 or 1 respectively; 31% with PD-L1 TPS <1% (using the PD-L1 IHC 22C3 pharmDx assay); 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 45 summarises key efficacy measures.

Table 45: Response to KEYTRUDA, pemetrexed, and platinum chemotherapy in patients with non-squamous NSCLC in KEYNOTE-189

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

* Based on the stratified Cox proportional hazard model
† Based on stratified log-rank test
‡ Based on patients with a best overall response as confirmed complete or partial response
§ Based on Miettinen and Nurminen method stratified by PD-L1 status, platinum chemotherapy and smoking status
¶ Based on Kaplan-Meier estimation
NA = not available

The final OS analysis was performed at a median duration of follow-up of 18.8 months after 421 patient events (258 for KEYTRUDA combination arm and 163 for the placebo plus chemotherapy arm). Median OS was 22.0 months (95% CI: 19.5, 24.5) for the KEYTRUDA combination arm and 10.6 months (95% CI: 8.7, 13.6) for the placebo plus chemotherapy arm. The OS HR was 0.56 (95% CI: 0.46, 0.69; p<0.00001). At final analysis, a PFS analysis was performed based on 534 patient events (337 for the KEYTRUDA combination arm and 197 for the placebo plus chemotherapy arm). The median PFS was 9.0 months (95% CI: 8.1, 10.4) for the KEYTRUDA combination arm and 4.9 months (95% CI: 4.7, 5.5) for the placebo plus chemotherapy arm. The PFS HR was 0.49 (95% CI: 0.41, 0.59, p<0.00001). See Figures 8 and Figure 9.

The ORR at the final analysis was 48% for the KEYTRUDA combination arm and 20% for the placebo plus chemotherapy arm. The median duration of response was 12.5 months (range 1.1+, 34.9+) for the KEYTRUDA combination arm and 7.1 months (range 2.4, 27.8+) for the placebo plus chemotherapy arm. The percentage of patients with ongoing responses based on Kaplan-Meier estimation was 53% at 12 months or longer, in patients who received KEYTRUDA combination therapy, vs. 27% in patients who received placebo plus

chemotherapy.

Figure 8: Kaplan-Meier Curve for overall survival by treatment arm in KEYNOTE-189 (intent to treat population)

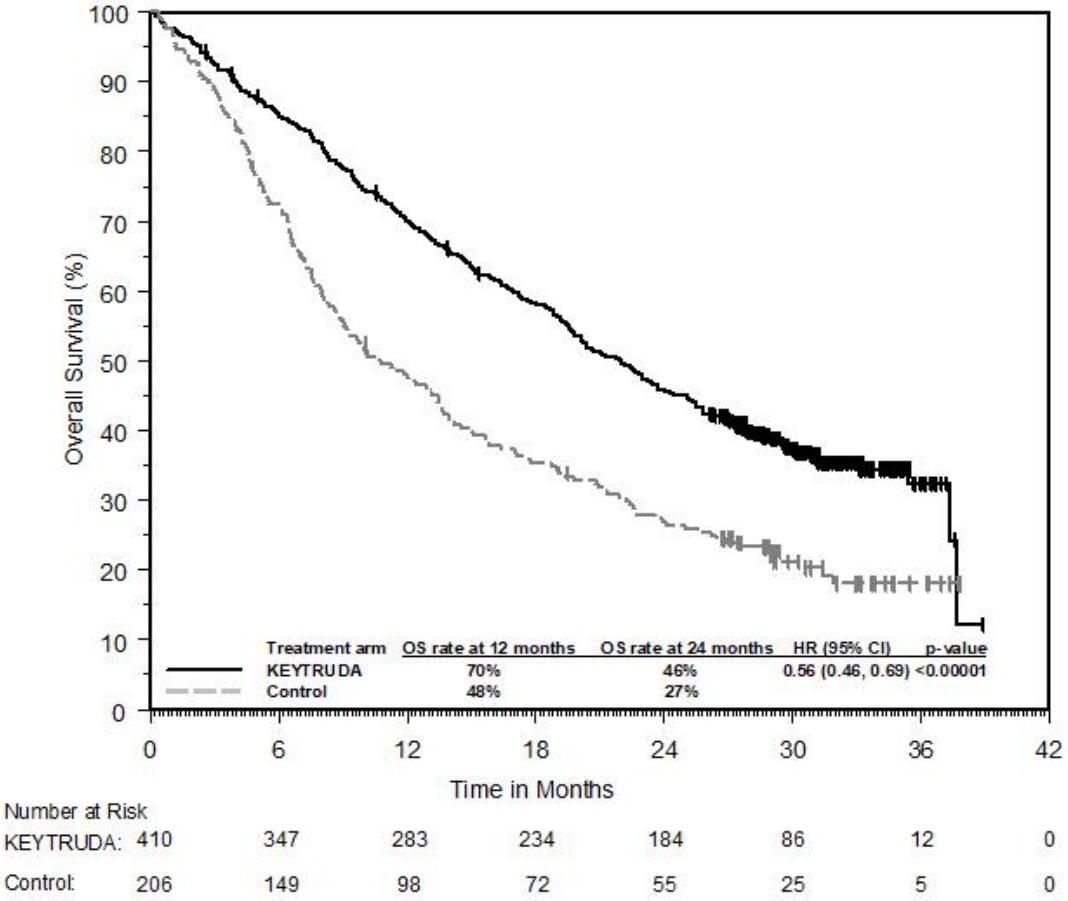
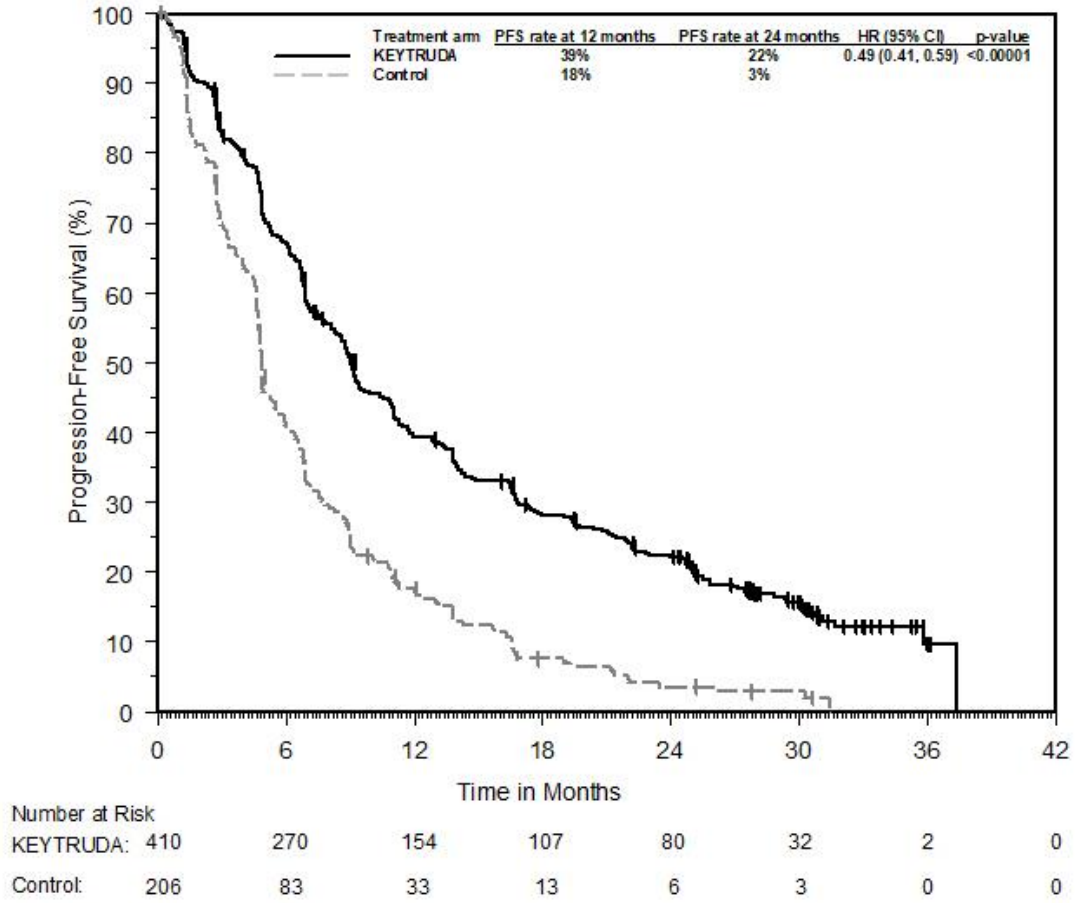


Figure 9: Kaplan-Meier curve for progression-free survival by treatment arm in KEYNOTE-189 (intent to treat population)



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

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

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

- KEYTRUDA 200 mg and carboplatin AUC 6 mg/mL/min on Day 1 of each 21-day cycle for 4 cycles, and paclitaxel 200 mg/m^2 on Day 1 of each 21-day cycle for 4 cycles or

nab-paclitaxel 100 mg/m^2 on Days 1, 8 and 15 of each 21-day cycle for 4 cycles, followed by KEYTRUDA 200 mg every 3 weeks. KEYTRUDA was administered prior to chemotherapy on Day 1.

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

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

Patients in the placebo arm were offered KEYTRUDA as a monotherapy at the time of disease progression.

Assessment of tumour status was performed every 6 weeks through Week 18, every 9 weeks through Week 45 and every 12 weeks thereafter. The major efficacy outcome measures were progression-free survival and objective response rate (ORR) as assessed by BICR using RECIST 1.1 and overall survival. An additional efficacy outcome measure was duration of response as assessed by BICR using RECIST 1.1.

A total of 559 patients were randomised: 278 patients to the KEYTRUDA arm and 281 to the placebo arm. The study population characteristics were: median age of 65 years (range: 29 to 88); 55% age 65 or older; 81% male; 77% White; ECOG performance status of 0 (29%) and 1 (71%); and 8% with brain metastases at baseline. Thirty-five percent had tumour PD-L1 expression TPS <1% [negative]; 19% were from the East Asian region; and 60% received paclitaxel.

In KEYNOTE-407, there was a statistically significant improvement in OS, PFS and ORR in patients randomised to KEYTRUDA in combination with carboplatin and either paclitaxel or nab-paclitaxel compared with patients randomised to placebo with carboplatin and either paclitaxel or nab-paclitaxel (see Table 44).

Table 46: Efficacy Results in KEYNOTE-407

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

* Based on the stratified Cox proportional hazard model

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

‡ Based on Kaplan-Meier estimation

NA = not available

The final OS analysis was performed at a median duration of follow-up of 14.3 months after 365 patient events (168 for KEYTRUDA combination arm and 197 for placebo plus chemotherapy arm). Median OS was 17.1 months (95% CI: 14.4, 19.9) for the KEYTRUDA combination arm and 11.6 months (95% CI: 10.1, 13.7) for the placebo plus chemotherapy arm. The OS HR was 0.71 (95% CI: 0.58, 0.88; p=0.0006). At final analysis, a PFS analysis was performed based on 469 patient events (217 for the KEYTRUDA combination arm and 252 for the placebo plus chemotherapy arm). The median PFS was 8.0 months (95% CI: 6.3, 8.4) for the KEYTRUDA combination arm and 5.1 months (95% CI: 4.3, 6.0) for the placebo plus chemotherapy arm. The PFS HR was 0.57 (95% CI: 0.47, 0.69, p<0.0001). See Figures 10 and 11.

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

Figure 10: Kaplan-Meier Curve for Overall Survival in KEYNOTE-407

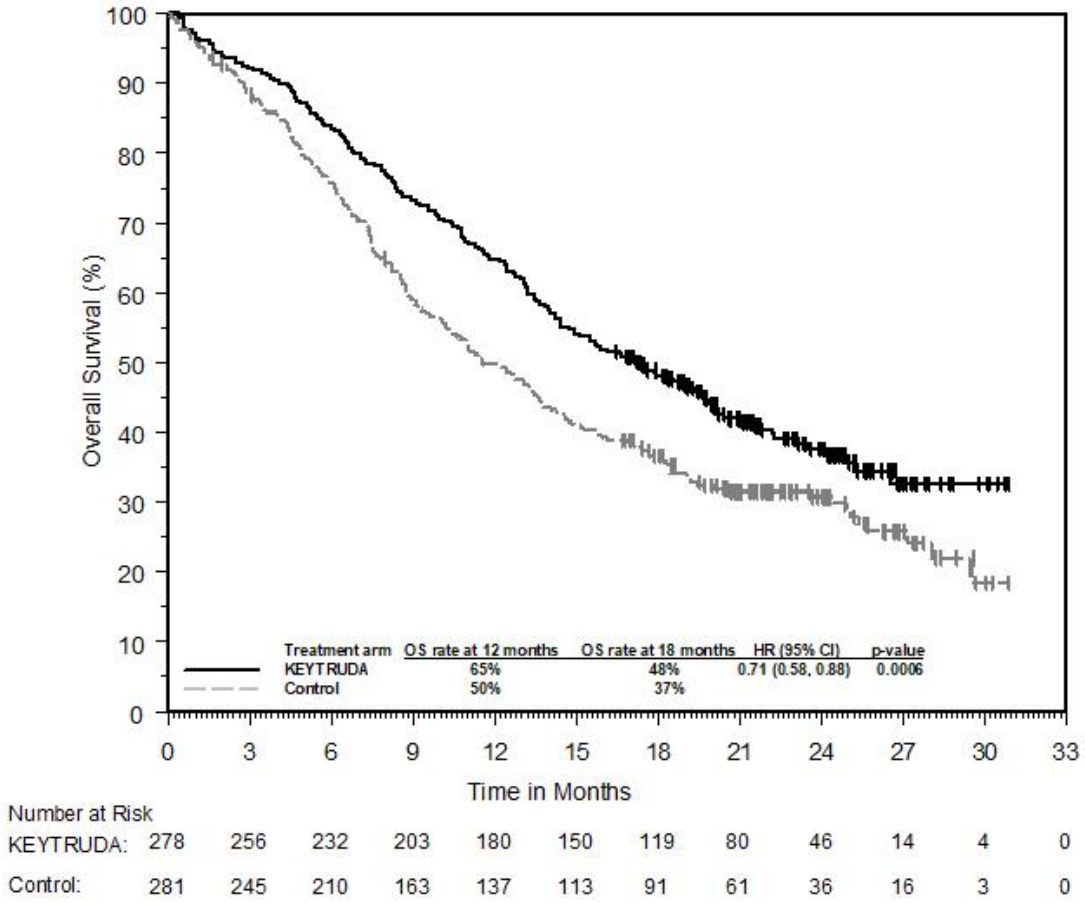
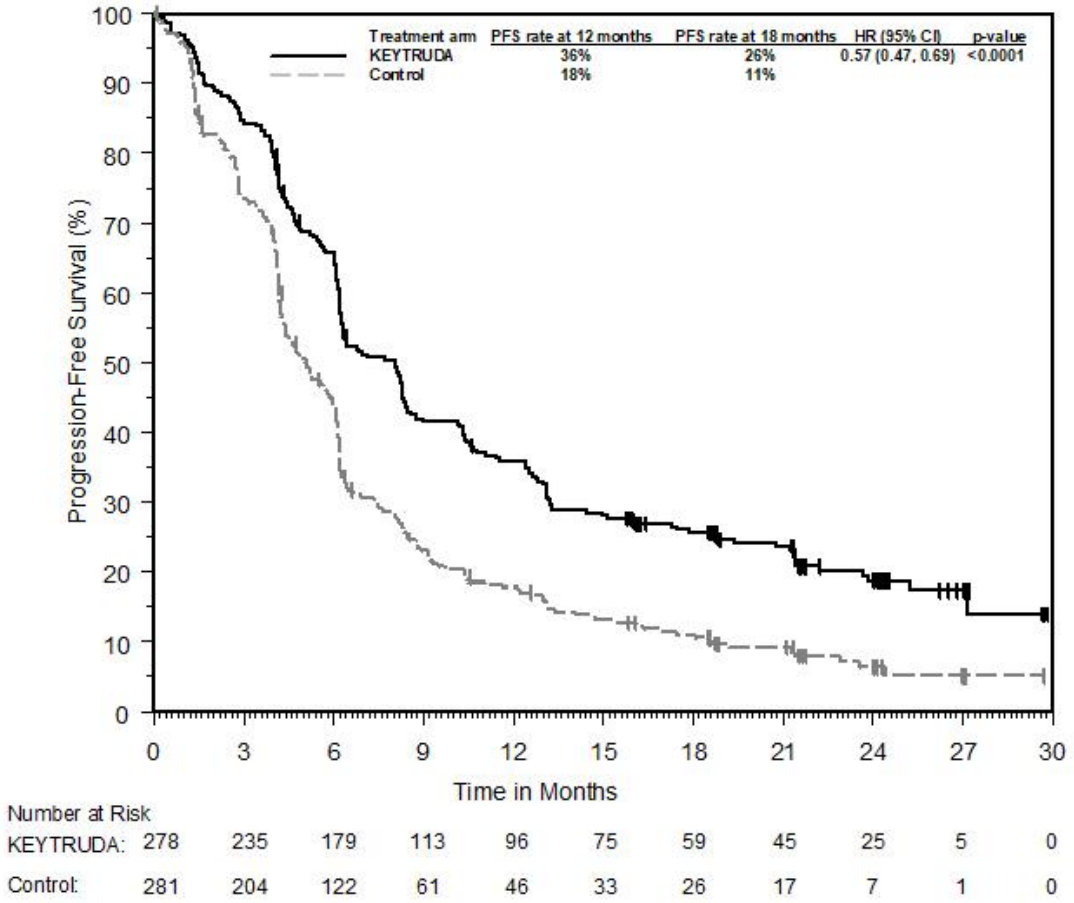


Figure 11: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-407



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

The efficacy of KEYTRUDA was investigated in KEYNOTE-042, a multicentre, randomised, controlled trial conducted in 1274 patients with stage III NSCLC who were not candidates for surgical resection or definitive chemoradiation, or patients with metastatic NSCLC. Only patients whose tumours expressed PD-L1 (TPS ≥ 1%) by an immunohistochemistry assay using the PD-L1 IHC 22C3 pharmDx assay and who had not received prior systemic treatment for metastatic NSCLC were eligible. Patients with EGFR or ALK genomic tumour aberrations; autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Patients were randomised (1:1) to receive KEYTRUDA 200 mg every 3 weeks (n=637) or investigator's choice platinum-containing chemotherapy (n=637; including pemetrexed+carboplatin or paclitaxel+carboplatin. Patients with non-squamous NSCLC could receive pemetrexed maintenance). Patients were treated with KEYTRUDA until unacceptable toxicity or disease progression. Treatment could continue beyond disease progression if the patient was clinically stable and was considered to be deriving clinical benefit by the investigator. Patients without disease progression could be treated for up to 24 months. Treatment with KEYTRUDA could be reinitiated for subsequent disease progression and administered for up to 1 additional year. Assessment of tumour status was performed every 9 weeks for the first 45 weeks, and every 12 weeks thereafter.

Among the 1274 patients in KEYNOTE-042, baseline characteristics were: median age 63 years (45% age 65 or older); 71% male; 64% White and 30% Asian: 19% Hispanic or Latino; and 31% and 69% with an ECOG performance status 0 and 1, respectively. Disease characteristics were squamous (39%) and non-squamous (61%); M0 (13%), M1 (87%); and

treated brain metastases (6%). Forty-seven percent of patients had TPS ≥50%, and 53% had TPS 1 to 49%.

The primary efficacy outcome measure was OS. Secondary efficacy outcome measures were PFS and ORR as assessed by blinded independent central review (BICR) using RECIST 1.1. Table 47 summarises key efficacy measures for the subgroup of patients with TPS ≥ 50% and the entire ITT population (TPS ≥ 1%).

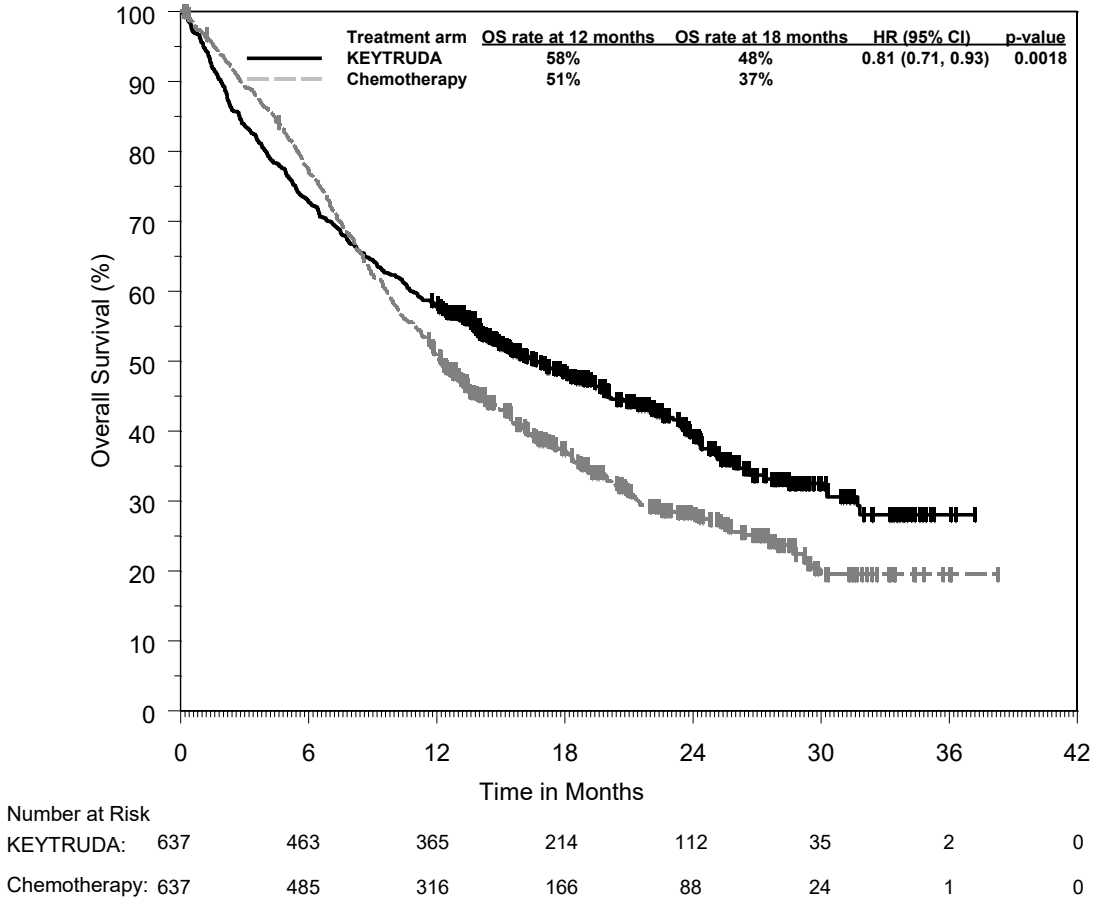
Table 47: Efficacy results of All Randomised Patients (PD-L1 TPS ≥1% and TPS ≥50%) in KEYNOTE-042

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

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

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

Figure 12: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-042 (TPS ≥ 1%, Intent-to-Treat Population)



In KEYNOTE-042, a higher number of deaths within 4 months of treatment initiation followed by a long-term survival benefit was observed with pembrolizumab monotherapy compared to chemotherapy (see Figure 12).

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

The efficacy of KEYTRUDA in previously untreated patients with NSCLC was also investigated in KEYNOTE-024, a multicentre, randomised, controlled trial. The study design was similar to that of KEYNOTE-042, except that only patients with metastatic NSCLC whose tumours expressed PD-L1 with TPS of 50% or greater by an immunohistochemistry assay using the PD-L1 IHC 22C3 pharmDx assay were eligible. Patients with treated brain metastases were eligible if neurologically returned to baseline prior to enrolment and off corticosteroids. Patients were randomised (1:1) to receive KEYTRUDA 200 mg every 3 weeks (n=154) or investigator's choice platinum-containing chemotherapy (n=151; including pemetrexed+carboplatin, pemetrexed+cisplatin, gemcitabine+cisplatin, gemcitabine+carboplatin, or paclitaxel+carboplatin. Patients with non-squamous NSCLC could receive pemetrexed maintenance). Patients on chemotherapy who experienced independently-verified progression of disease were able to crossover and receive KEYTRUDA. Assessment of tumour status was performed every 9 weeks.

Among the 305 patients in KEYNOTE-024, baseline characteristics were: median age 65 years (54% age 65 or older); 61% male; 82% White and 15% Asian; and 35% and 65% with an ECOG performance status 0 and 1, respectively. Subjects with ECOG performance status

> 1 and subjects with significant organ dysfunction were ineligible. Disease characteristics were squamous (18%) and non-squamous (82%); M1 (99%); and brain metastases (9%).

The primary efficacy outcome measure was PFS as assessed by blinded independent central review (BICR) using RECIST 1.1. Secondary efficacy outcome measures were OS and ORR (as assessed by BICR using RECIST 1.1). Table 48 summarises key efficacy measures for the entire ITT population.

Table 48: Efficacy Results in KEYNOTE-024

Endpoint	**KEYTRUDA 200 mg every 3 weeks n=154**	**Chemotherapy n=151**
PFS*		
Number (%) of patients with event	73 (47%)	116 (77%)
Hazard ratio† (95% CI)	0.50 (0.37, 0.68)	
p-Value‡	<0.001	
Median in months (95% CI)	10.3 (6.7, NA)	6.0 (4.2, 6.2)
OS		
Number (%) of patients with event	44 (29%)	64 (42%)
Hazard ratio† (95% CI)	0.60 (0.41, 0.89)	
p-Value‡	0.005	
Median in months (95% CI)	Not reached (NA, NA)	Not reached (9.4, NA)
Objective response rate*		
ORR % (95% CI)	45% (37, 53)	28% (21, 36)
Complete response %	4%	1%
Partial response %	41%	27%
Response Duration§,¶		
Median in months (range)	Not reached (1.9+, 14.5+)	6.3 (2.1+, 12.6+)
% with duration ≥ 6 months	88%	59%

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

The final OS analysis was performed at a median follow-up of 25 months after 169 patient events (73 for KEYTRUDA and 96 for chemotherapy). Median OS was 30.0 months (95% CI: 18.3, NA) for KEYTRUDA and 14.2 months (95% CI: 9.8, 19.0) for chemotherapy. The OS HR was 0.63 (95% CI: 0.47, 0.86; p=0.002). See Figure 14.

Figure 13: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-024 (Intent to Treat Population)

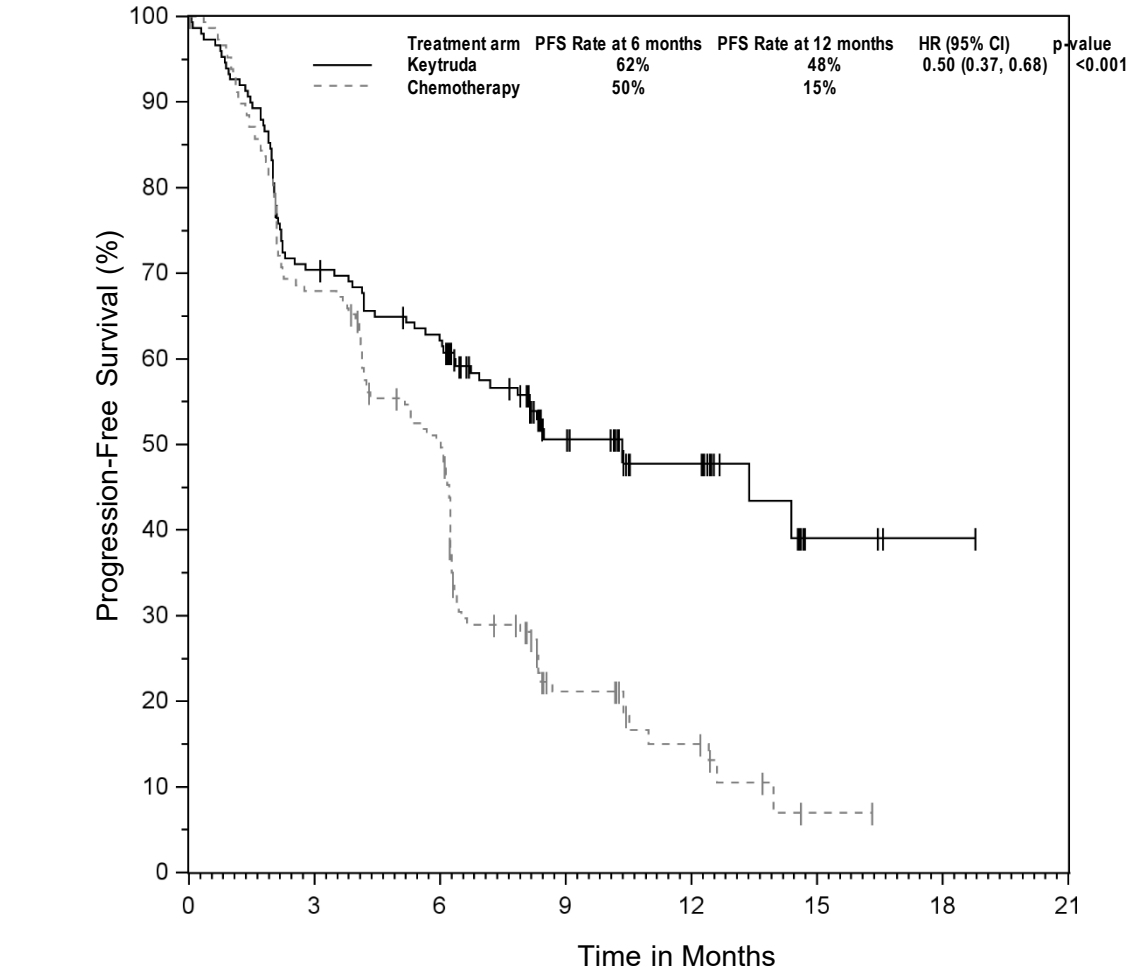
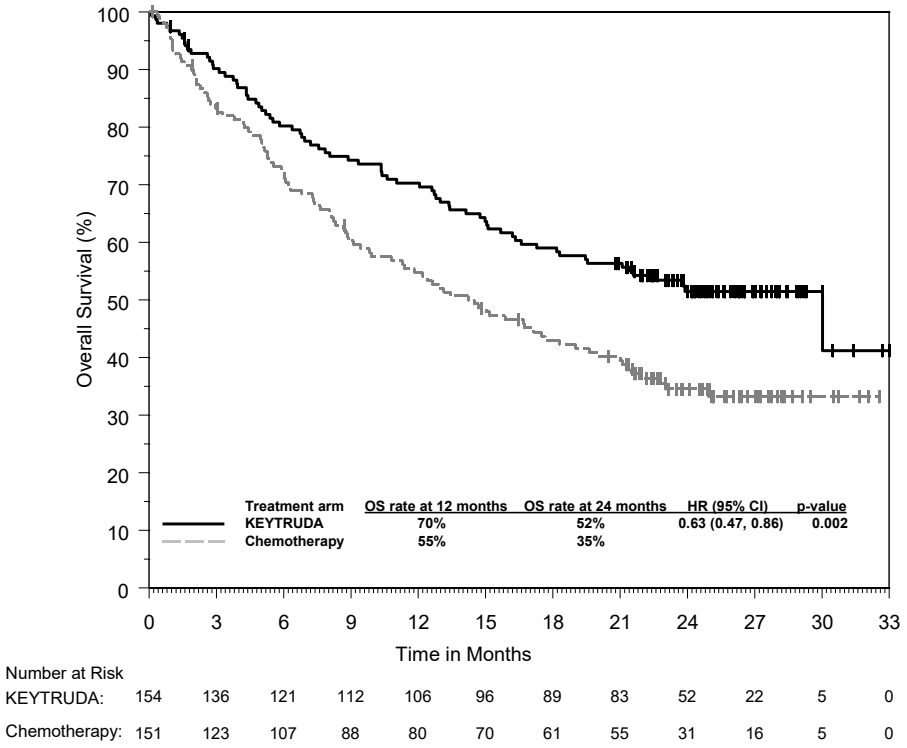


Figure 14: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-024 (Intent to Treat Population)



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

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

The efficacy of KEYTRUDA was investigated in KEYNOTE-010, a multicentre, randomised, controlled trial. Key eligibility criteria were advanced NSCLC that had progressed following platinum-containing chemotherapy, and if appropriate, targeted therapy for ALK or EGFR mutations, and PD-L1 expression TPS of 1% or greater by a clinical trial assay version of the PD-L1 IHC 22C3 pharmDx assay. 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.

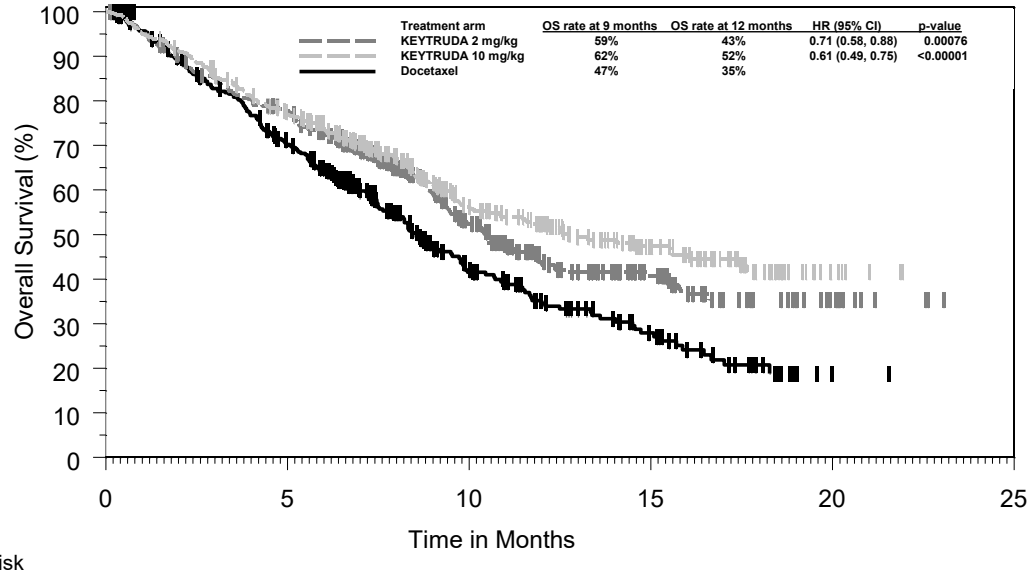
The primary efficacy outcome measures were OS and PFS as assessed by an independent review committee using RECIST 1.1. Secondary efficacy outcome measures were ORR and response duration. Table 49 summarises key efficacy measures for the entire ITT population (TPS ≥1%) and for the subgroup of patients with TPS ≥50%. Kaplan-Meier curves for OS (TPS ≥1% and TPS ≥50%) are shown in Figures 15 and 16.

Table 49: Response to KEYTRUDA 2 or 10 mg/kg Every 3 Weeks in Previously Treated Patients with NSCLC in KEYNOTE-010

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

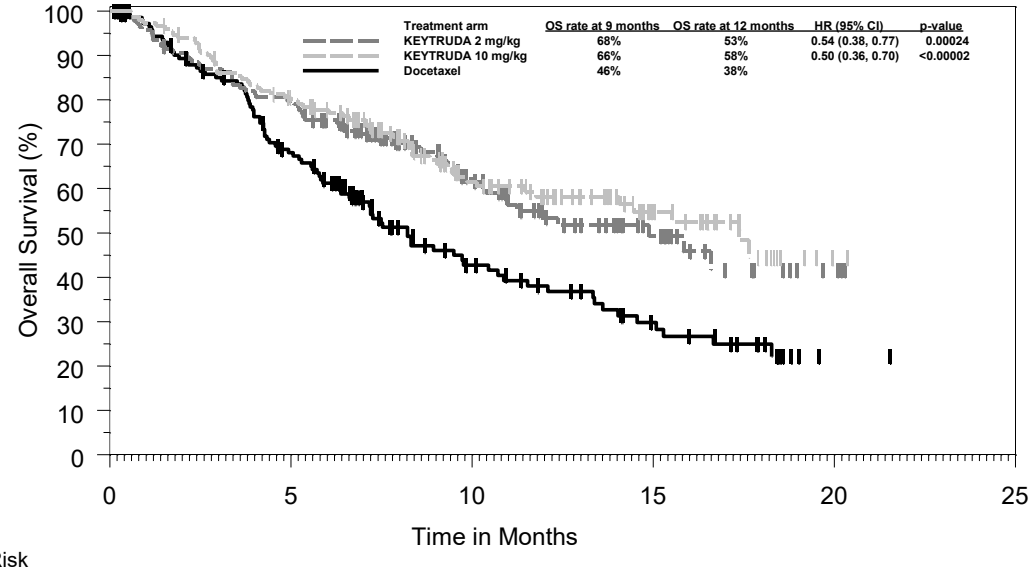
* Hazard ratio (KEYTRUDA compared to docetaxel) based on the stratified Cox proportional hazard model
† Based on stratified log-rank test
‡ Assessed by BICR using RECIST 1.1
§ All responses were partial responses
¶ Based on patients with a best overall response as confirmed complete or partial response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

Figure 15: 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 16: 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.

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

The efficacy of KEYTRUDA in combination with platinum-containing chemotherapy given as neoadjuvant treatment and continued as monotherapy adjuvant treatment was investigated in KEYNOTE-671, a multicentre, randomised, double-blind, placebo-controlled trial. Key eligibility criteria were previously untreated and resectable Stage II, IIIA, or IIIB (N2) NSCLC by AJCC 8th edition, regardless of tumour PD-L1 expression. Patients with active autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Randomisation was stratified by stage (II vs. III), tumour PD-L1 expression (TPS ≥50% or <50%), histology (squamous vs. non-squamous), and geographic region (East Asia vs. non-East Asia).

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

- Treatment Arm A: neoadjuvant KEYTRUDA 200 mg on Day 1 in combination with cisplatin 75 mg/m^2 and either pemetrexed 500 mg/m^2 on Day 1 or gemcitabine 1000 mg/m^2 on Days 1 and 8 of each 21-day cycle for up to 4 cycles. Following surgery, KEYTRUDA 200 mg was administered every 3 weeks for up to 13 cycles.
- Treatment Arm B: neoadjuvant placebo on Day 1 in combination with cisplatin 75 mg/m^2 and either pemetrexed 500 mg/m^2 on Day 1 or gemcitabine 1000 mg/m^2 on Days 1 and 8 of each 21-day cycle for up to 4 cycles. Following surgery, placebo was administered every 3 weeks for up to 13 cycles.

All study medications were administered via intravenous infusion. Treatment with KEYTRUDA or placebo continued until completion of the treatment (17 cycles), disease progression that precluded definitive surgery, disease recurrence in the adjuvant phase, disease progression for those who did not undergo surgery or had incomplete resection and entered the adjuvant phase, or unacceptable toxicity. Assessment of tumour status was performed at baseline, Week 7, and Week 13 in the neoadjuvant phase and within 4 weeks prior to the start of the adjuvant phase. Following the start of the adjuvant phase, assessment of tumour status was performed every 16 weeks through the end of Year 3, and then every 6 months thereafter.

The primary efficacy outcome measures were OS and investigator-assessed event-free survival (EFS). Secondary efficacy outcome measures were pathological complete response (pCR) rate and major pathological response (mPR) rate as assessed by blinded independent

pathology review (BIPR).

A total of 797 patients in KEYNOTE-671 were randomised: 397 patients to the KEYTRUDA arm and 400 to the placebo arm. Baseline characteristics were: median age of 64 years (range: 26 to 83), 45% age 65 or older; 71% male; 61% White, 31% Asian, and 2.0% Black. Sixty-three percent and 37% had ECOG performance of 0 or 1, respectively; 30% had Stage II and 70% had Stage III disease; 33% had TPS ≥50% and 67% had TPS <50%; 43% had tumours with squamous histology and 57% had tumours with non-squamous histology; 31% were from the East Asian region.

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

The key results of KEYNOTE-671 are summarised in Table 50, Figure 17 and Figure 18.

Table 50: Efficacy results in KEYNOTE-671

Endpoint	KEYTRUDA with chemotherapy/KEYTRUDA n=397	Placebo with chemotherapy/Placebo n=400
OS*		
Number of patients with event (%)	110 (28%)	144 (36%)
Median in months† (95% CI)	NR (NR, NR)	52.4 (45.7, NR)
Hazard ratio‡ (95% CI)	0.72 (0.56, 0.93)	
p-Value§	0.00517	
EFS#		
Number of patients with event (%)	139 (35%)	205 (51%)
Median in months† (95% CI)	NR (34.1, NR)	17.0 (14.3, 22.0)
Hazard ratio‡ (95% CI)	0.58 (0.46, 0.72)	
p-Value§	< 0.0001	
pCR#		
Number of patients with pCR	72	16
pCR Rate (%), (95% CI)	18.1 (14.5, 22.3)	4.0 (2.3, 6.4)
Treatment difference estimate (%), (95% CI)¶	14.2 (10.1, 18.7)	
p-Value	< 0.0001	
mPR#		
Number of patients with mPR	120	44
mPR Rate (%), (95% CI)	30.2 (25.7, 35.0)	11.0 (8.1, 14.5)
Treatment difference estimate (%), (95% CI)¶	19.2 (13.9, 24.7)	
p-Value	< 0.0001	

* Median (range) duration of follow-up at this analysis (IA2) was 29.8 (0.4 to 62) months
† Based on Kaplan-Meier estimates
‡ Based on Cox regression model with treatment as a covariate stratified by stage, tumour PD-L1 expression, histology, and geographic region
§ Based on stratified log-rank test
¶ Based on Miettinen and Nurminen method stratified by stage, tumour PD-L1 expression, histology, and geographic region
# Median (range) duration of follow-up at this analysis (IA1) was 21.4 (0.4 to 50.6) months
NR = not reached

A significant difference in EFS was demonstrated at interim analysis 1 (IA1). EFS analysis was repeated at IA2; after 422 patient events (174 for the KEYTRUDA arm and 248 for the

placebo arm). Median EFS at IA2 was 47.2 months (95% CI: 32.9, NR) for the KEYTRUDA arm and 18.3 months (95% CI: 14.8, 22.1) for the placebo arm. The EFS HR at IA2 was 0.59 (95% CI: 0.48, 0.72). The EFS Kaplan-Meier curve for IA2 is presented in Figure 18 rather than the primary EFS analysis.

Figure 17: Kaplan-Meier curve for overall survival by treatment arm in KEYNOTE-671 (Intent to Treat population)

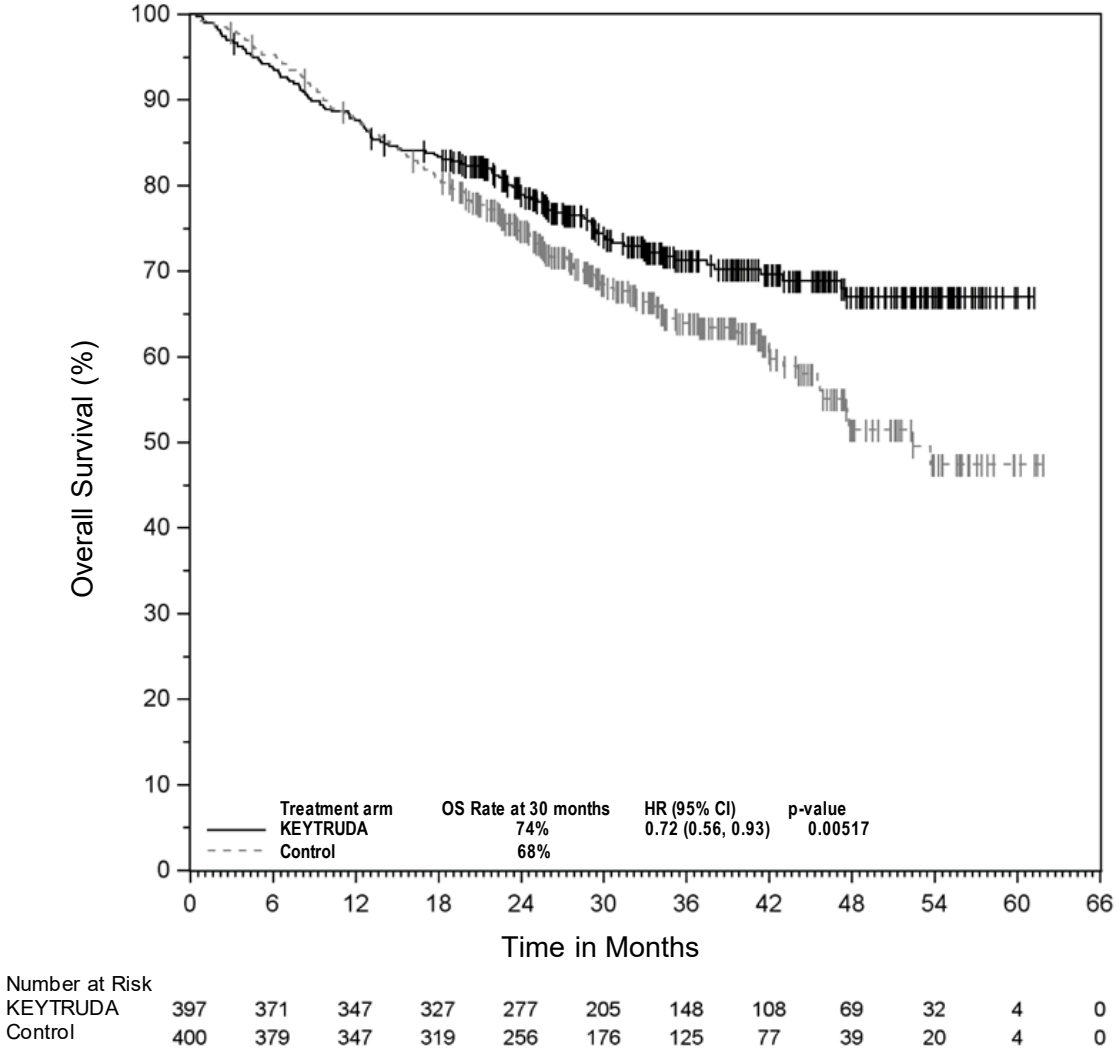
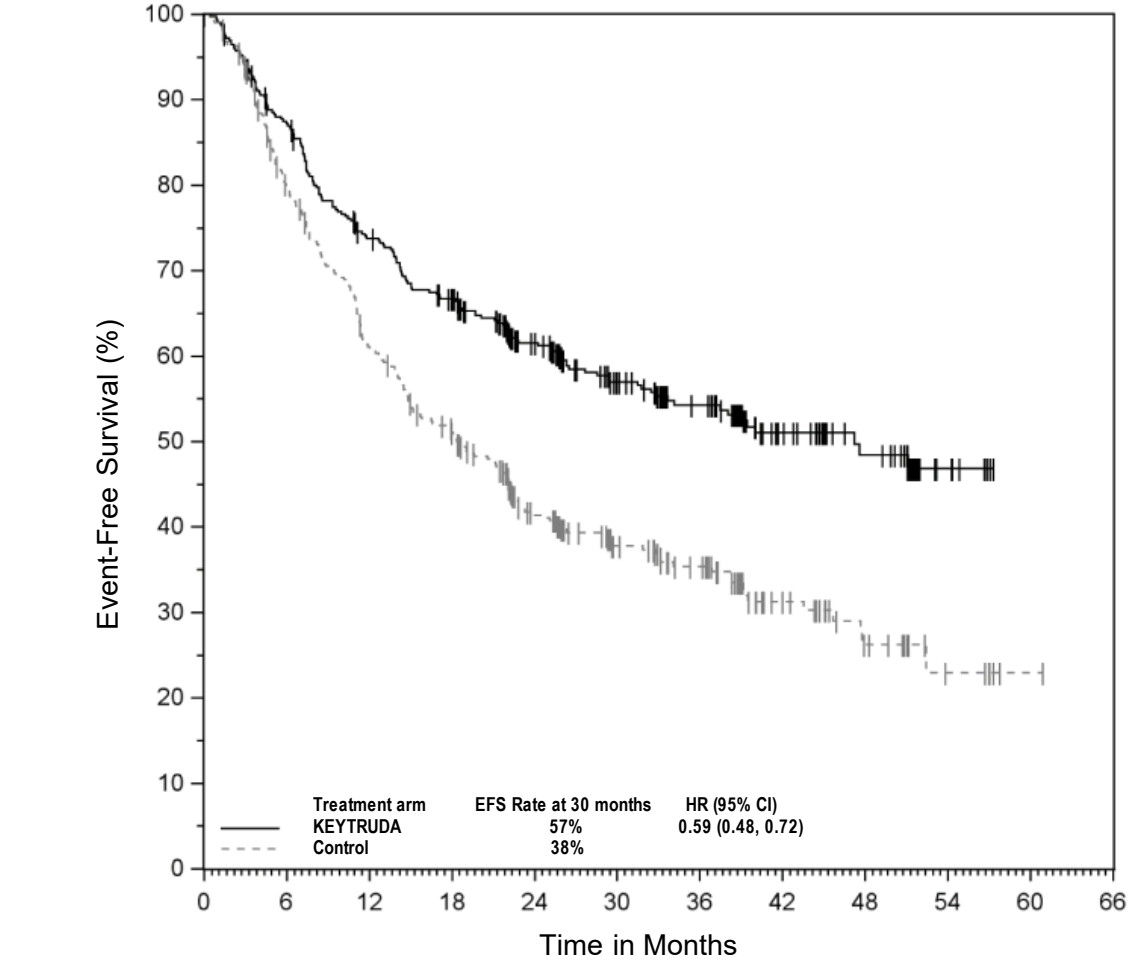


Figure 18: Kaplan-Meier curve for event-free survival by treatment arm in KEYNOTE-671 (Intent to Treat population)



KEYNOTE-091: Controlled trial for the adjuvant treatment of patients with resected NSCLC
The efficacy of KEYTRUDA was investigated in KEYNOTE-091, a multicentre, randomised, triple-blind, placebo-controlled trial in patients with completely resected stage IB (T2a ≥4 cm), II, or IIIA NSCLC by AJCC 7th edition, regardless of tumour PD-L1 expression status. Patients had not received neoadjuvant radiotherapy or chemotherapy, and no prior or planned adjuvant radiotherapy for the current malignancy. Adjuvant chemotherapy of up to 4 cycles was optional.

Patients were ineligible if they had autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; or had a history of interstitial lung disease or pneumonitis.

Randomisation was stratified by stage (IB vs. II vs. IIIA), receipt of adjuvant chemotherapy (yes vs. no), PD-L1 status (TPS <1% [negative] vs. TPS 1-49% vs. TPS ≥50%), and geographic region (Western Europe vs. Eastern Europe vs. Asia vs. Rest of World). Patients were randomised (1:1) to receive KEYTRUDA 200 mg or placebo intravenously every 3 weeks.

Treatment continued until RECIST 1.1-defined disease recurrence as determined by the

investigator, unacceptable toxicity, or approximately one year (18 doses). Tumours were assessed by imaging every 12 weeks after the first dose of KEYTRUDA for the first year, then every 6 months for years 2 to 3, and then annually up to the end of year 5. After year 5, imaging is performed as per local standard of care. The major efficacy outcome measure was investigator-assessed disease-free survival (DFS). An additional efficacy outcome measure was OS.

Of 1177 patients randomised, 1010 (86%) received adjuvant platinum-based chemotherapy following complete resection. Among these 1010 patients, the median age was 64 years (range: 35 to 84), 49% age 65 or older; 68% male; 77% White, 18% Asian; 86% current or former smokers; and 39% with ECOG PS of 1. Eleven percent had Stage IB, 57% had Stage II, and 31% had Stage IIIA disease. Thirty-nine percent had PD-L1 TPS <1% [negative], 33% had TPS 1-49%, and 28% had TPS ≥50%. Fifty-two percent were from Western Europe, 20% from Eastern Europe, 17% from Asia, and 11% from Rest of World.

The trial met its primary endpoint, demonstrating a statistically significant improvement in DFS in the overall population for patients randomised to the KEYTRUDA arm compared to patients randomised to the placebo arm. In an exploratory subgroup analysis of the 167 patients (14%) who did not receive adjuvant chemotherapy, the DFS HR was 1.25 (95% CI: 0.76, 2.05). OS results were not mature with only 42% of pre-specified OS events in the overall population.

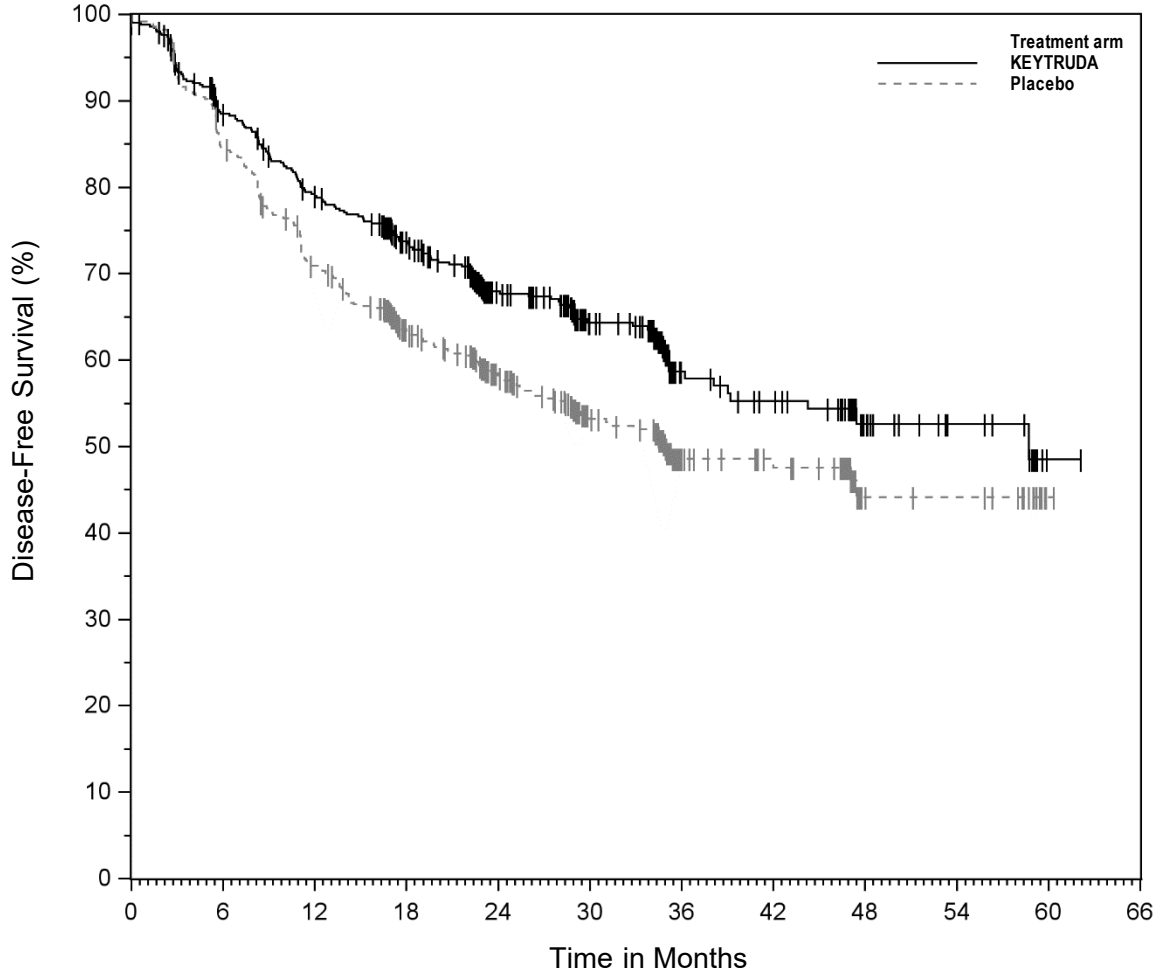
Table 51 and Figure 19 summarise the efficacy results for KEYNOTE-091 in patients who received adjuvant chemotherapy.

Table 51: Efficacy Results in KEYNOTE-091 for Patients Who Received Adjuvant Chemotherapy

Endpoint	**KEYTRUDA 200 mg every 3 weeks n=506**	**Placebo n=504**
DFS		
Number (%) of patients with event	177 (35%)	231 (46%)
Median in months (95% CI)	58.7 (39.2, NR)	34.9 (28.6, NR)
Hazard ratio* (95% CI)	0.73 (0.60, 0.89)	

* Based on the unstratified univariate Cox regression model
NR = not reached

Figure 19: Kaplan-Meier Curve for Disease-Free Survival in KEYNOTE-091 for Patients Who Received Adjuvant Chemotherapy



Number at Risk												
KEYTRUDA	506	422	372	308	227	158	71	61	27	16	1	0
Placebo	504	422	349	272	206	134	58	47	17	15	1	0

Malignant Pleural Mesothelioma

KEYNOTE-483: Controlled trial of combination therapy in patients with untreated unresectable advanced or metastatic MPM

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

- KEYTRUDA 200 mg with pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 or carboplatin AUC 5-6 mg/mL/min on Day 1 of each 21-day cycle for up to 6 cycles, followed by KEYTRUDA 200 mg every 3 weeks. KEYTRUDA was administered prior to chemotherapy on Day 1.
- Pemetrexed 500 mg/m^2 and cisplatin 75 mg/m^2 or carboplatin AUC 5-6 mg/mL/min on Day 1 of each 21-day cycle for up to 6 cycles.

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

Among the 440 patients in KEYNOTE-483 (222 patients in the KEYTRUDA combination arm and 218 in the chemotherapy arm), baseline characteristics were: median age of 70 years (77% age 65 or older); 76% male; 79% White, 21% not reported or unknown; 2% Hispanic or Latino; and 47% and 53% ECOG performance status of 0 or 1, respectively. Seventy-eight percent had epithelioid and 22% had non-epithelioid histology.

The primary efficacy outcome measure was OS. Additional efficacy outcome measures were PFS, ORR, and DoR, as assessed by BICR using mRECIST. The trial demonstrated a statistically significant improvement in OS, PFS, and ORR in patients randomised to KEYTRUDA in combination with chemotherapy compared with patients randomised to chemotherapy alone. The median follow-up time was 17 months (range: 0.8 – 60.3 months). Table 52 summarises key efficacy measures for KEYNOTE-483. Figure 20 and Figure 23 show the Kaplan-Meier curves for OS and PFS, respectively, in the overall population based on the final analysis.

Table 52: Efficacy Results in KEYNOTE-483

Endpoint	**KEYTRUDA 200 mg every 3 weeks + Pemetrexed + Platinum Chemotherapy (n=222)**	**Pemetrexed + Platinum Chemotherapy (n=218)**
OS*		
Number (%) of patients with event	167 (75%)	175 (80%)
Hazard ratio† (95% CI)	0.79 (0.64, 0.98)	
p-Value‡	0.0162	
Median in months (95% CI)	17.3 (14.4, 21.3)	16.1 (13.1, 18.2)
PFS*,§		
Number (%) of patients with event	190 (86%)	166 (76%)
Hazard ratio† (95% CI)	0.80 (0.65, 0.99)	
p-Value‡	0.0194	
Median in months (95% CI)	7.1 (6.9, 8.1)	7.1 (6.8, 7.7)
Objective Response Rate§,¶		
ORR % (95% CI)	52% (45.5, 59.0)	29% (23.0, 35.4)
Number (%) of complete responses	1 (0.5%)	0 (0%)
Number (%) of partial responses	115 (52%)	63 (29%)
p-Value#	<0.00001	
Response Duration*,§,Þ		
Median in months (95% CI)	6.9 (5.8, 8.3)	6.8 (5.5, 8.5)
% with duration ≥12 months$^{\beta}$	23%	13%

* Based on the final analysis

† Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by histological subtype at randomisation (epithelioid vs other subtypes).

‡ Based on stratified log-rank test

§ Assessed by BICR using mRECIST

¶ Based on an interim analysis

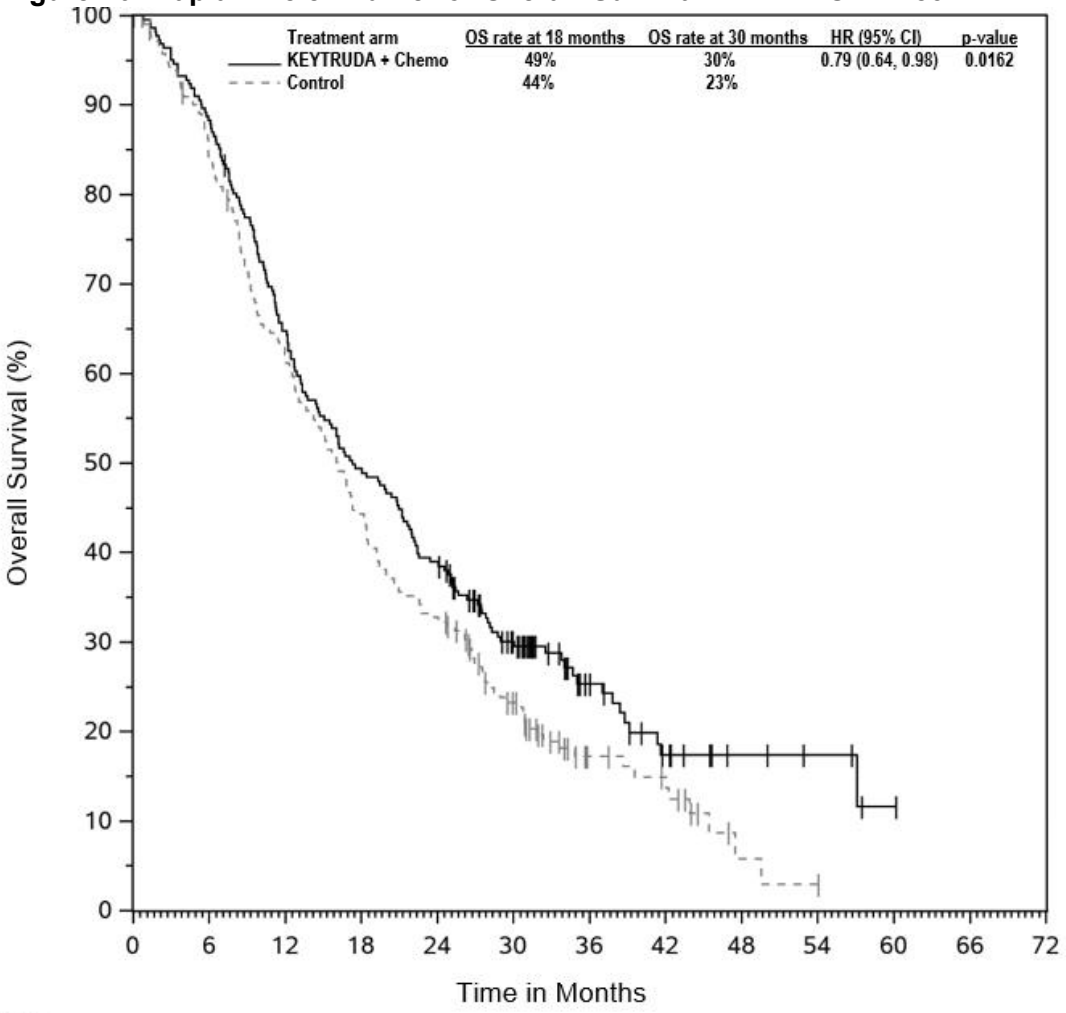
Based on Miettinen and Nurminen method stratified by histological subtype at

randomisation (epithelioid vs other subtypes).

Þ Based on patients with a best overall response as confirmed complete or partial response; n=117 for patients in the KEYTRUDA combination arm; n=64 for patients in the chemotherapy arm

β Based on Kaplan-Meier estimates

Figure 20: Kaplan-Meier Curve for Overall Survival in KEYNOTE-483

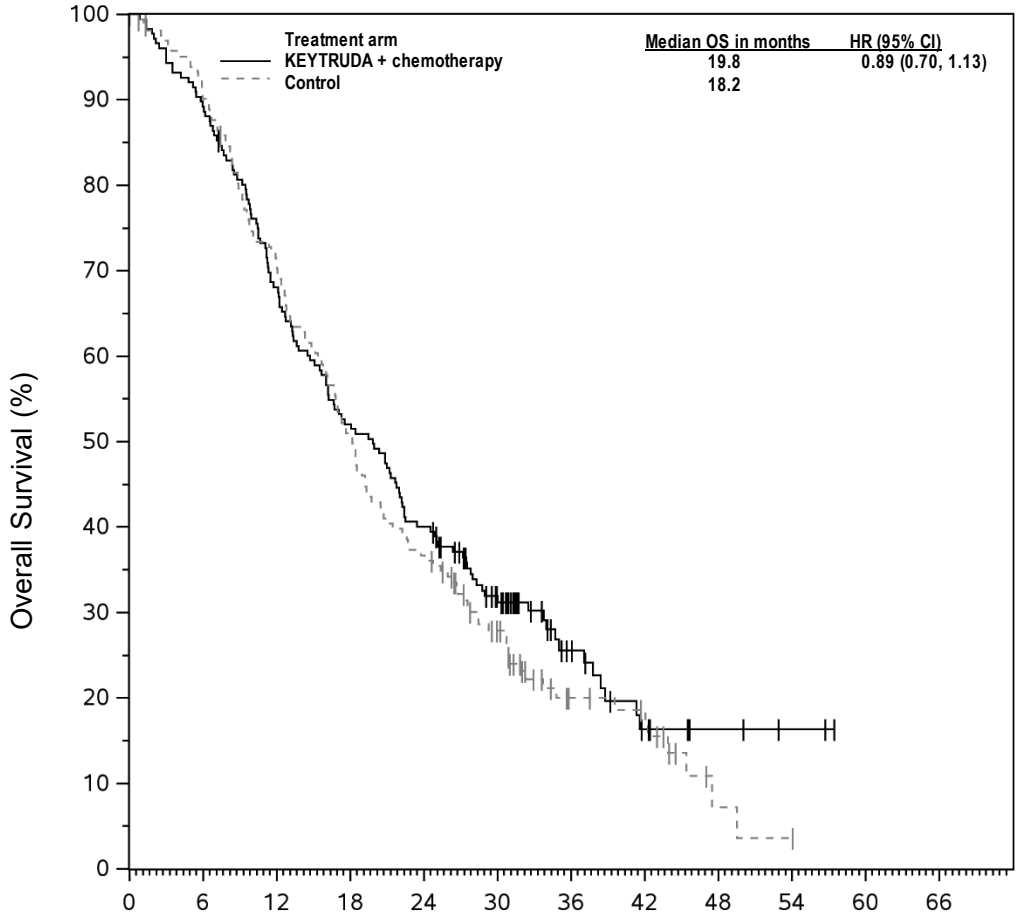


Number at Risk

KEYTRUDA + Chemo	222	196	143	109	86	54	25	13	6	4	1	0	0
Control	218	176	128	92	68	40	16	12	2	1	0	0	0

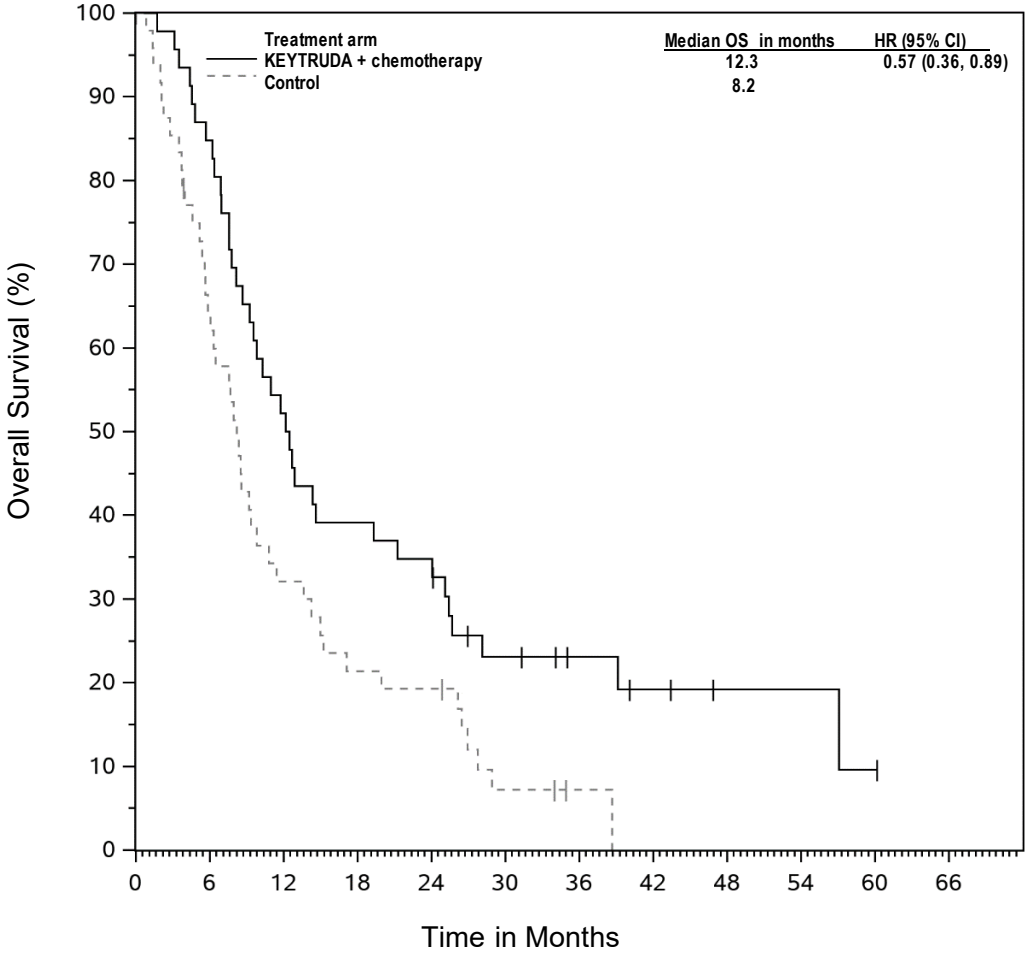
Figure 21 and Figure 22 show the Kaplan-Meier curves for OS for the epithelioid and non-epithelioid histological subgroups based on a pre-specified exploratory analysis. Due to its exploratory nature, the subgroup analysis by histology should be interpreted with caution.

Figure 21: Kaplan-Meier Curve for Overall Survival in Patients with Epithelioid MPM in KEYNOTE-483



Number at Risk												
KEYTRUDA + chemotherapy	176	157	119	91	70	45	19	9	4	2	0	0
Control	169	146	113	82	59	37	15	12	2	1	0	0

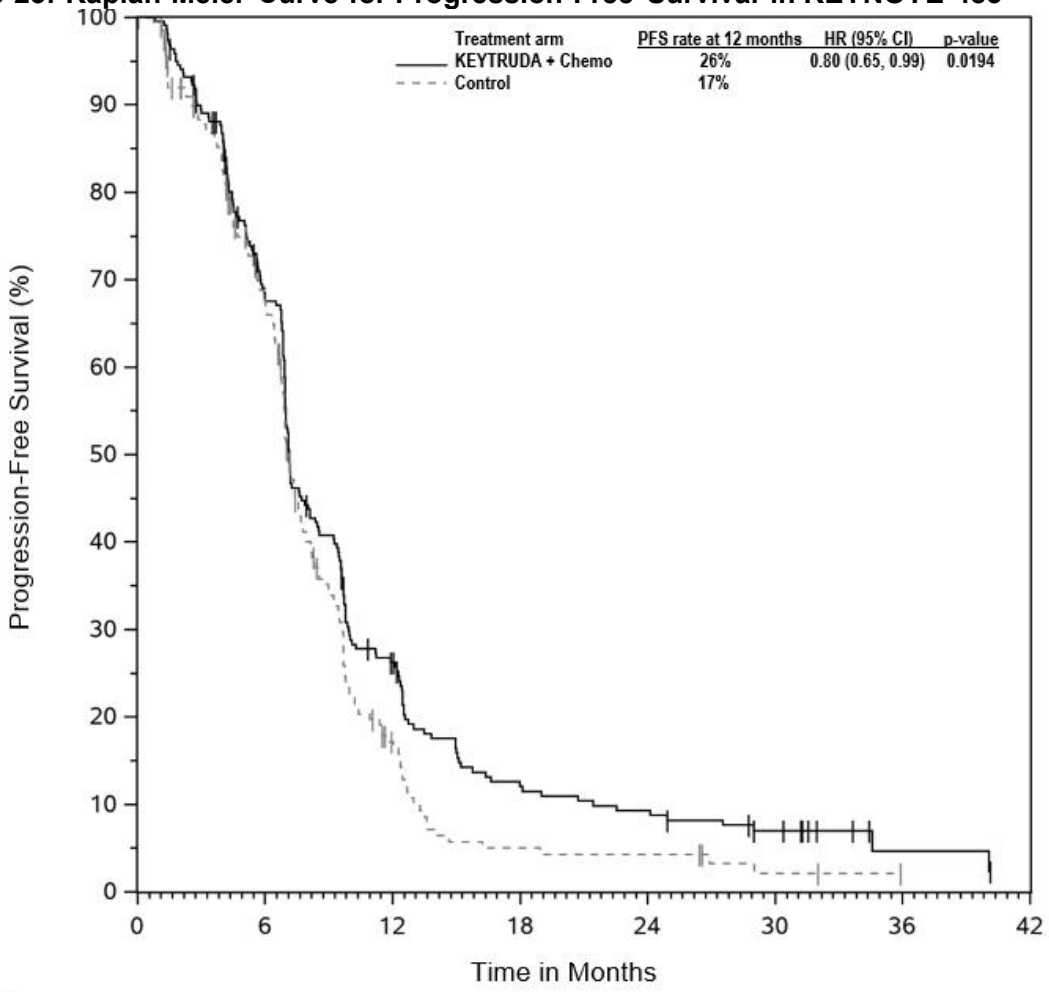
Figure 22: Kaplan-Meier Curve for Overall Survival in Patients with Non-epithelioid MPM in KEYNOTE-483



Number at Risk

KEYTRUDA + chemotherapy	46	39	24	18	16	9	6	4	2	2	1	0
Control	49	30	15	10	9	3	1	0	0	0	0	0

Figure 23: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-483



Number at Risk								
KEYTRUDA + Chemo	222	139	50	22	17	10	2	0
Control	218	121	24	7	6	2	0	0

Head and neck cancer

Neoadjuvant and Adjuvant Treatment of Locally Advanced HNSCC for Tumours Expressing PD-L1 (CPS≥ 1)

The efficacy of KEYTRUDA was investigated in KEYNOTE-689 (NCT02358031), a randomised, multicentre, open-label, active-controlled trial conducted in 714 patients with resectable locally advanced (Stage III-IVA) HNSCC [AJCC, 8th edition]. Patients with active autoimmune disease requiring systemic therapy within two years of treatment or a medical condition that required immunosuppression were ineligible. Randomisation was stratified by primary tumour site (oropharynx/oral cavity vs. larynx vs. hypopharynx), tumour stage (III vs. IVA) and PD-L1 status (TPS ≥ 50% vs. TPS<50%) according to the PD-L1 IHC 22C3 pharmDx assay.

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

- neoadjuvant KEYTRUDA 200 mg for 2 cycles prior to surgical resection. Within 6 weeks following surgery, 3 cycles of adjuvant KEYTRUDA 200 mg every 3 weeks in combination with radiotherapy (RT) with or without 3 cycles of cisplatin 100 mg/m2 every 3 weeks. This was followed by KEYTRUDA 200 mg every 3 weeks for up to 12 cycles.
- no neoadjuvant treatment prior to surgery. Within 6 weeks following surgery, adjuvant RT with or without 3 cycles of concurrent cisplatin 100 mg/m2 every 3 weeks.

  On both treatment arms, patients received cisplatin with adjuvant RT if high-risk pathological features (i.e., positive margins <1 mm or extranodal extension) were present at surgery.

Treatment with KEYTRUDA continued until disease progression by RECIST v1.1 per BICR during the neoadjuvant phase that precluded surgery, local or metastatic recurrence during the adjuvant phase, completion of treatment, or unacceptable toxicity. Assessment of tumour status was performed prior to surgery at Week 6 in the neoadjuvant phase. Following the start of the adjuvant phase, assessment of tumour status was performed 12 weeks after end of RT with or without cisplatin treatment and then every 3 months until the end of year 3; then every 6 months thereafter up to the end of year 5.

The trial was not designed to isolate the effect of KEYTRUDA in each phase (neoadjuvant or adjuvant) of treatment.

The major efficacy outcome measure was event-free survival (EFS) by BICR defined as the time from randomisation to the first occurrence of any of the following events: progression of disease that precludes definitive surgery, local or distant disease progression or recurrence, or death due to any cause. Additional efficacy outcome measures were major pathological response (mPR) as assessed by BIPR, and overall survival (OS).

The demographic and baseline characteristics in the 682 patients with PD-L1 expression of CPS ≥1 were: median age of 60 years (range: 22 to 87), 33% age 65 or older; 79% male; 78% White, 13% Asian and 2.5% Black or African American, 14% were Hispanic or Latino; 43% had ECOG PS of 1, and 79% were former/current smokers. Four percent of patients' tumours were HPV-positive, and 26% had Stage III disease, 74% had Stage IVA disease. Sixty-eight percent of patients' tumours had PD-L1 expression of CPS ≥10.

Eighty-eight percent of patients received definitive surgery in both the KEYTRUDA and the SOC arm.

Seventy-six percent of patients in the KEYTRUDA arm and 78% of patients in the SOC arm started the radiation phase of treatment. In the KEYTRUDA arm, 35% of patients received

KEYTRUDA and cisplatin with concurrent RT, 57% of patients received KEYTRUDA alone with concurrent RT, 3% of patients received cisplatin alone with concurrent RT, 5% of patients received RT alone and one patient (0.4%) received KEYTRUDA alone without concurrent RT. On the SoC arm, 52% of patients received cisplatin with concurrent RT while 48% patients received RT alone.

The trial demonstrated a statistically significant improvement in EFS for patients randomised to the KEYTRUDA arm compared to those randomised to the standard of care (SOC) arm at the first pre-specified interim analysis. Table 53 and Figure 24 summarise efficacy results in KEYNOTE-689 for patients with HNSCC CPS ≥1.

Table 53 Efficacy Results for Perioperative KEYTRUDA with adjuvant RT with or without cisplatin in Patients with HNSCC CPS ≥1 in KEYNOTE-689

Endpoint	**KEYTRUDA 200 mg every 3 weeks with RT with or without cisplatin n=347**	**RT with or without cisplatin n=335**
EFS		
Number of events, n (%)	128 (37%)	156 (47%)
Median in months* (95% CI)	59.7 (37.9, NR)	29.6 (19.5, 41.9)
Hazard ratio† (95% CI)	0.70 (0.55, 0.89)	
p-Value‡,	0.00140	

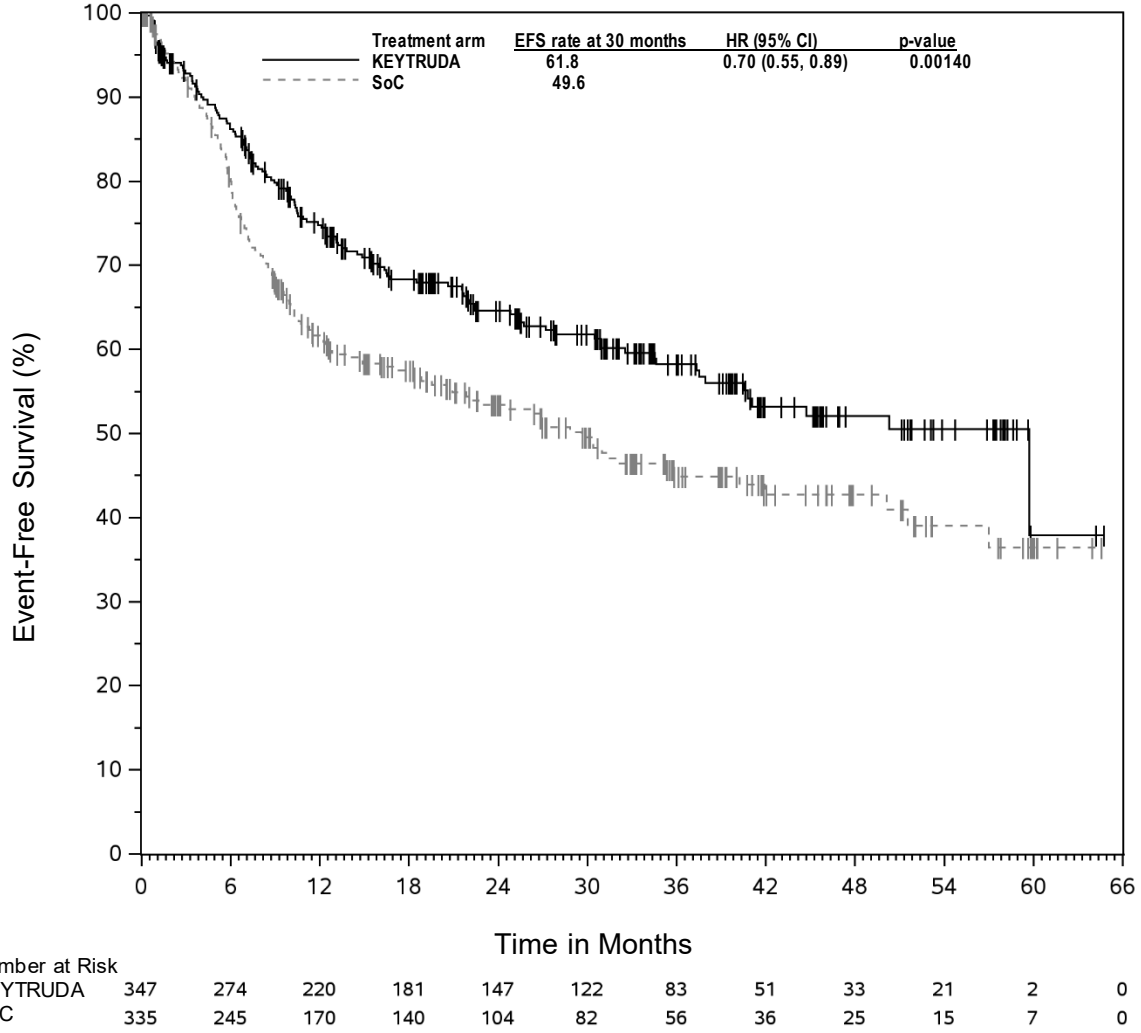
* From product-limit (Kaplan-Meier) method for censored data.

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

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

NR = not reached

Figure 24: Kaplan-Meier Curve for Event-free Survival for KEYTRUDA in Patients with HNSCC CPS ≥1 in KEYNOTE-689



While OS results were not mature at this interim analysis, with 76% of pre-specified OS events in the CPS≥1 population, no trend towards a detriment was observed.

Hypopharyngeal Tumours
In an exploratory subgroup analysis of patients with PD-L1-positive (CPS ≥1) hypopharyngeal tumours who were randomised (n=51), the EFS HR was 2.28 (95% CI: 0.79, 6.56). Among these patients, 23 patients in the KEYTRUDA arm received surgery, of which 17 patients (74%) had R0 resections. On the SOC arm, 23 patients received surgery, of which 20 (87%) had R0 resections.

Oral Cavity, Oropharyngeal and Laryngeal Tumours
In an exploratory subgroup analysis of patients with PD-L1 positive (CPS ≥1) oral cavity, oropharyngeal and laryngeal tumours who received surgery (n=555), 91% of patients on the KEYTRUDA arm had R0 resections while 85% of patients on the SOC arm had R0 resections.

KEYNOTE-048: Controlled trial of first-line monotherapy or combination therapy in HNSCC

The efficacy of KEYTRUDA was investigated in Study KEYNOTE-048, a multicentre, randomised, open-label, active-controlled study in patients with metastatic or recurrent HNSCC who had not previously received systemic therapy for recurrent or metastatic disease

and who were considered incurable by local therapies. Patients with active autoimmune disease that required systemic therapy within two years of treatment or a medical condition that required immunosuppression were ineligible for the study. Patients with nasopharyngeal tumours were excluded. Randomisation was stratified by tumour PD-L1 expression (TPS≥50% or <50%) based on the PD-L1 IHC 22C3 pharmDx assay, HPV status (positive or negative), and ECOG PS (0 vs. 1). A prospective classification of patients' tumour PD-L1 status according to CPS using the PD-L1 IHC 22C3 pharmDx assay was conducted using the tumour specimens used for randomisation. Patients were randomised 1:1:1 to one of the following treatment arms:

- KEYTRUDA 200 mg every 3 weeks
- KEYTRUDA 200 mg every 3 weeks, carboplatin AUC 5 mg/ml/min every 3 weeks or cisplatin 100 mg/m^2 every 3 weeks, and 5-FU 1000 mg/m^2/d 4 days continuous every 3 weeks (maximum of 6 cycles of platinum and 5-FU)
- Cetuximab 400 mg/m^2 load then 250 mg/m^2 once weekly, carboplatin AUC 5 mg/ml/min every 3 weeks or cisplatin 100 mg/m^2 every 3 weeks, and 5-FU 1000 mg/m^2/d 4 days continuous every 3 weeks (maximum of 6 cycles of platinum and 5-FU)

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

A total of 882 patients were randomised; 301 patients to the KEYTRUDA monotherapy arm, 281 patients to the KEYTRUDA plus chemotherapy arm, and 300 patients to the standard treatment arm. The study population characteristics were: median age of 61 years (range: 20 to 94); 36% age 65 or older; 83% male; 73% White and 20% Asian; 61% ECOG PS of 1; and 79% were former/current smokers. Disease characteristics were: 22% HPV positive, 15%, 85%, 43%, and 23% had PD-L1 expression defined as CPS <1, CPS ≥1, CPS ≥20, and TPS ≥50%, respectively, and 95% had Stage IV disease (Stage IVa 19%, Stage IVb 6%, and Stage IVc 70%).

The primary efficacy outcome measures were OS and PFS (assessed by BICR according to RECIST 1.1). ORR, as assessed by BICR according to RECIST 1.1, was a secondary outcome measure. The trial demonstrated a statistically significant improvement in OS for patients randomised to KEYTRUDA in combination with chemotherapy compared to standard treatment. A statistically significant improvement in OS was also demonstrated for patients with PD-L1 CPS ≥1 randomised to KEYTRUDA as monotherapy compared with cetuximab in combination with chemotherapy. Table 54 and Table 55 and Figure 25 and Figure 26 describe key efficacy results for KEYTRUDA in KEYNOTE-048.

Table 54: Efficacy Results for KEYTRUDA plus Chemotherapy in KEYNOTE-048 (CPS≥1)

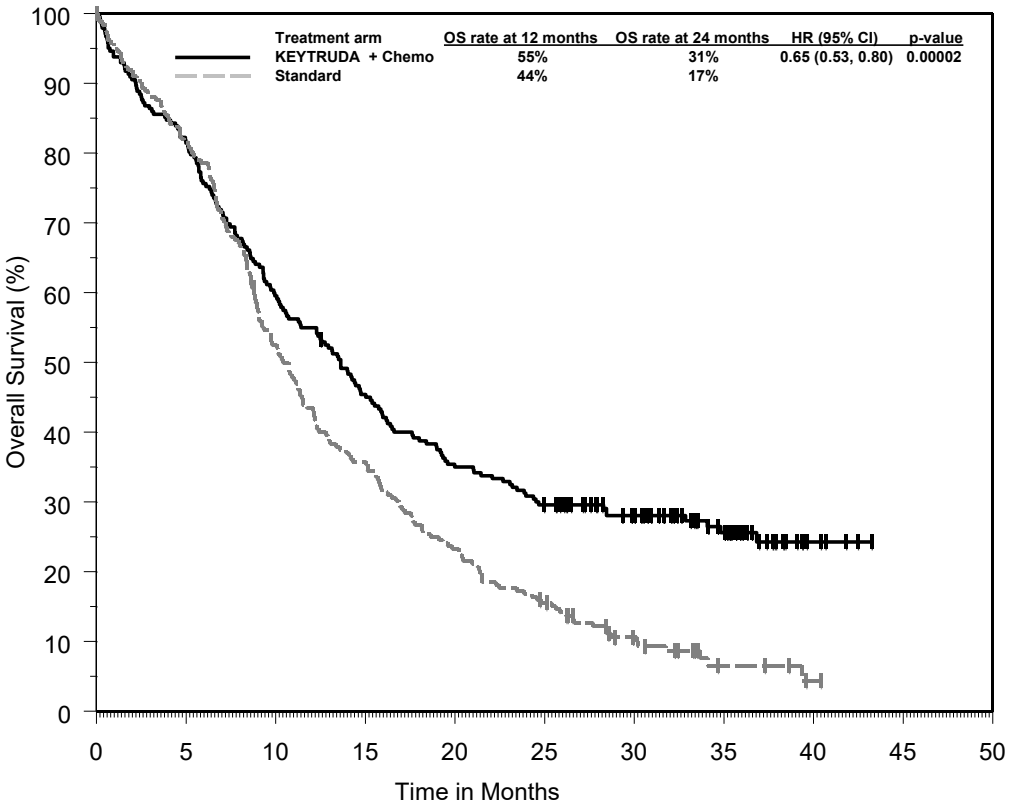
Endpoint	**KEYTRUDA Platinum Chemotherapy 5-FU n=242**	**Standard Treatment* n=235**
OS		
Number (%) of patients with event	177 (73%)	213 (91%)
Median in months (95% CI)	13.6 (10.7, 15.5)	10.4 (9.1, 11.7)
Hazard ratio† (95% CI)	0.65 (0.53, 0.80)	
p-Value‡	0.00002	

PFS		
Number of patients with event (%)	212 (88%)	221 (94%)
Median in months (95% CI)	5.1 (4.7, 6.2)	5.0 (4.8, 6.0)
Hazard ratio† (95% CI)	0.84 (0.69, 1.02)	
p-Value‡	0.0369	
ORR		
Objective response rate§ (95% CI)	36% (30.3, 42.8)	36% (29.6, 42.2)
Complete response	7%	3%
Partial response	30%	33%
p-Value¶	0.4586	
Duration of Response		
Median in months (range)	6.7 (1.6+, 39.0+)	4.3 (1.2+, 31.5+)
% with duration ≥6 months	54%	34%

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

In KEYNOTE-048, OS HRs for patients randomised to KEYTRUDA in combination with chemotherapy, compared with cetuximab in combination with chemotherapy, were similar for all populations regardless of PD-L1 expression in a pre-specified interim analysis: ITT (HR 0.77, 95% CI: 0.63, 0.93), CPS ≥1 (HR 0.71, 95% CI: 0.57, 0.88), CPS ≥20 (HR 0.69, 95% CI: 0.51, 0.94). A positive association was observed between increasing PD-L1 expression and treatment benefit. The trial also demonstrated a statistically significant improvement in OS for the patients expressing PD-L1 CPS ≥1 and CPS ≥20. The OS HRs at final analysis were CPS ≥1 (0.65, 95% CI: 0.53, 0.80), CPS ≥20 (0.60, 95% CI: 0.45, 0.82).

Figure 25: Kaplan-Meier Curve for Overall Survival for KEYTRUDA plus Chemotherapy in KEYNOTE-048 (CPS≥1)*



Number at Risk

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

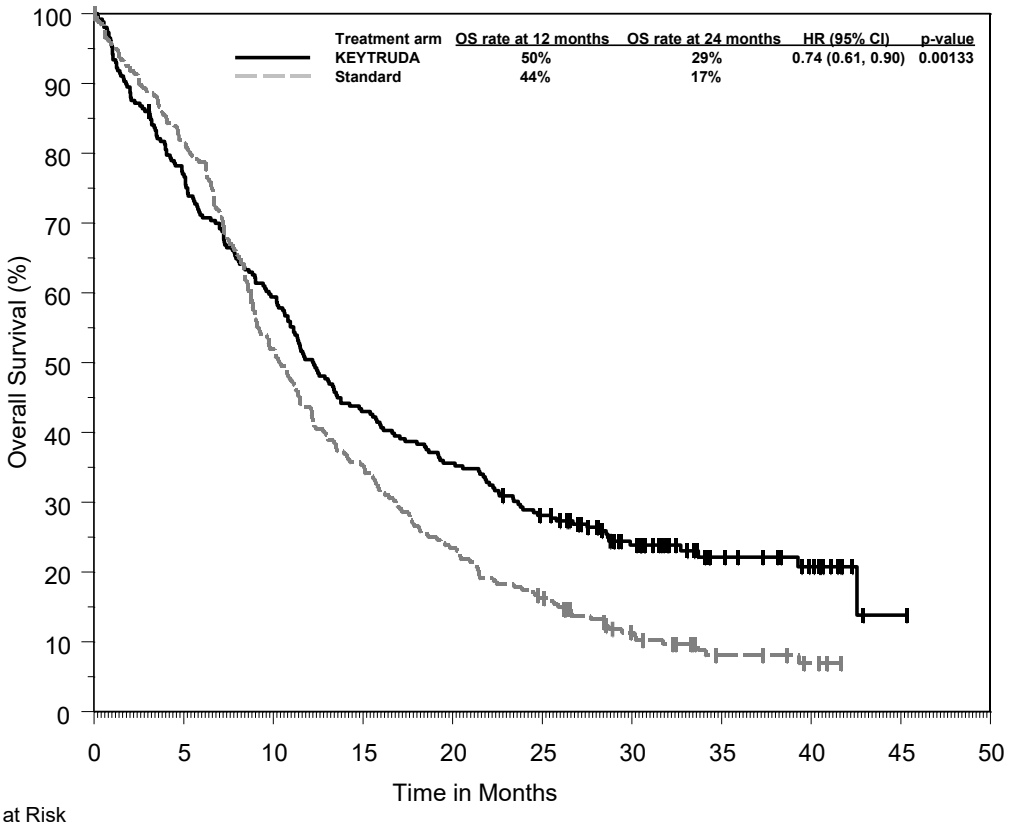
*Median follow-up of 11.5 months at protocol-specified final analysis.

Table 55: Efficacy Results for KEYTRUDA as Monotherapy in KEYNOTE-048 (CPS≥1)

Endpoint	KEYTRUDA n=257	Standard Treatment* n=255
OS		
Number (%) of patients with event	197 (77%)	229 (90%)
Median in months (95% CI)	12.3 (10.8, 14.3)	10.3 (9.0, 11.5)
Hazard ratio† (95% CI)	0.74 (0.61, 0.90)	
p-Value‡	0.00133	
PFS		
Number of patients with event (%)	228 (89%)	237 (93%)
Median in months (95% CI)	3.2 (2.2, 3.4)	5.0 (4.8, 6.0)
Hazard ratio† (95% CI)	1.13 (0.94, 1.36)	
p-Value§	0.8958	
ORR		
Objective response rate¶ (95% CI)	19% (14.5, 24.4)	35% (29.1, 41.1)
Complete response	5%	3%
Partial response	14%	32%
p-Value#	1.0000	
Duration of Response		
Median in months (range)	23.4 (1.5+, 43.0+)	4.5 (1.2+, 38.7+)
% with duration ≥6 months	81%	36%

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

Figure 26: Kaplan-Meier Curve for Overall Survival for KEYTRUDA as Monotherapy in KEYNOTE-048 (CPS≥1)*



Number at Risk

KEYTRUDA:	257	197	152	110	91	70	43	21	13	1	0
Standard:	255	207	131	89	59	40	21	9	5	0	0

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

Additional OS analyses based on PD-L1 expression (CPS ≥1 and CPS ≥20) were performed in KEYNOTE-048. The trial demonstrated a statistically significant improvement in OS at the protocol-specified interim analysis for patients randomised to KEYTRUDA monotherapy compared to standard treatment for PD-L1 expression CPS ≥1 and CPS ≥20. OS for patients who had PD-L1 CPS ≥1 or CPS ≥20 for KEYTRUDA monotherapy compared to standard treatment is summarised in Table 54.

Table 56: OS by PD-L1 Expression at Protocol-specified Interim Analysis

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

* Cetuximab, platinum, and 5-FU

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

‡ Based on stratified log-rank test

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

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

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

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

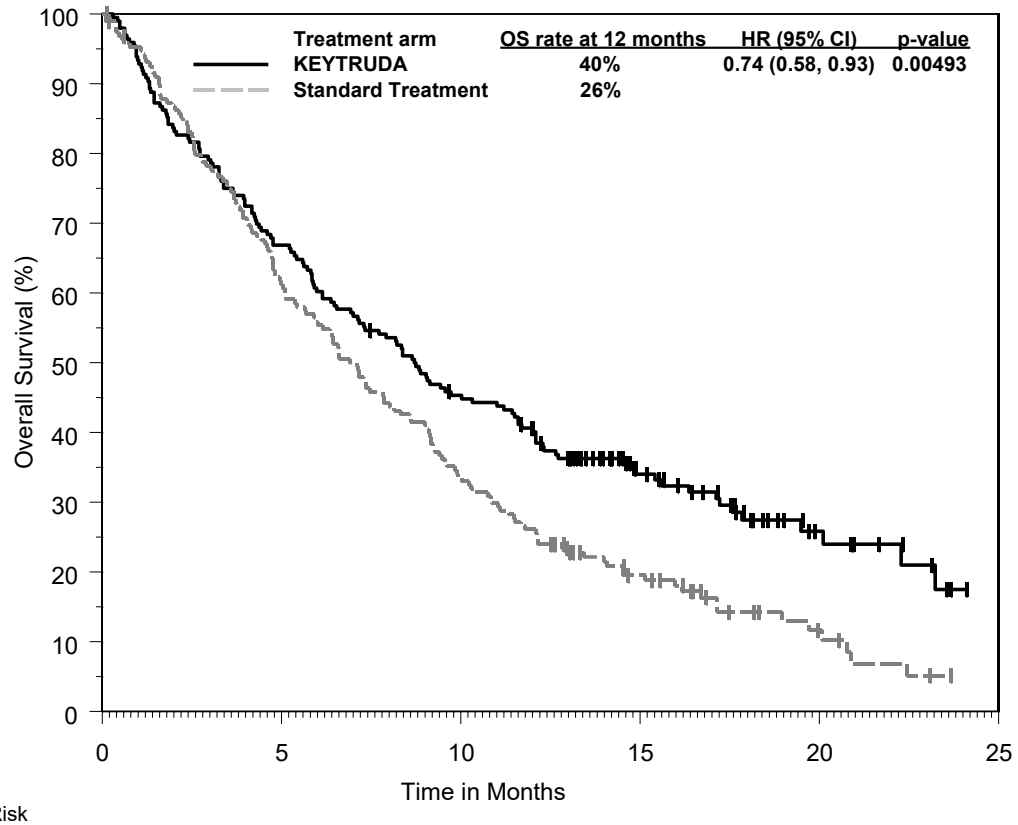
The primary efficacy outcome was OS. There was no statistically significant difference between KEYTRUDA and standard treatment. Secondary efficacy outcome measures were PFS, ORR, and duration of response (as assessed by BICR using RECIST 1.1). Efficacy measures for KEYNOTE-040 for the CPS ≥1 population are summarised in Table 55, and the Kaplan-Meier curve for OS is shown in Figure 27.

Table 57: Efficacy Results in KEYNOTE-040 (CPS≥1)

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

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

Figure 27: Kaplan-Meier Curve for Overall Survival in KEYNOTE-040 (CPS≥1)*



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

Relapsed or refractory Classical Hodgkin lymphoma

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

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

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

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

Among KEYNOTE-204 patients, the baseline characteristics were median age 35 years (16% age 65 or older); 57% male; 77% White; and 61% and 38% had an ECOG performance status 0 and 1, respectively. The median number of prior lines of therapy administered for the

treatment of cHL was 2 (range 1 to 11). Forty-two percent were refractory to the last prior therapy and 29% had primary refractory disease. Thirty-seven percent had undergone prior auto-HSCT, 5% had received prior BV, and 39% had prior radiation therapy.

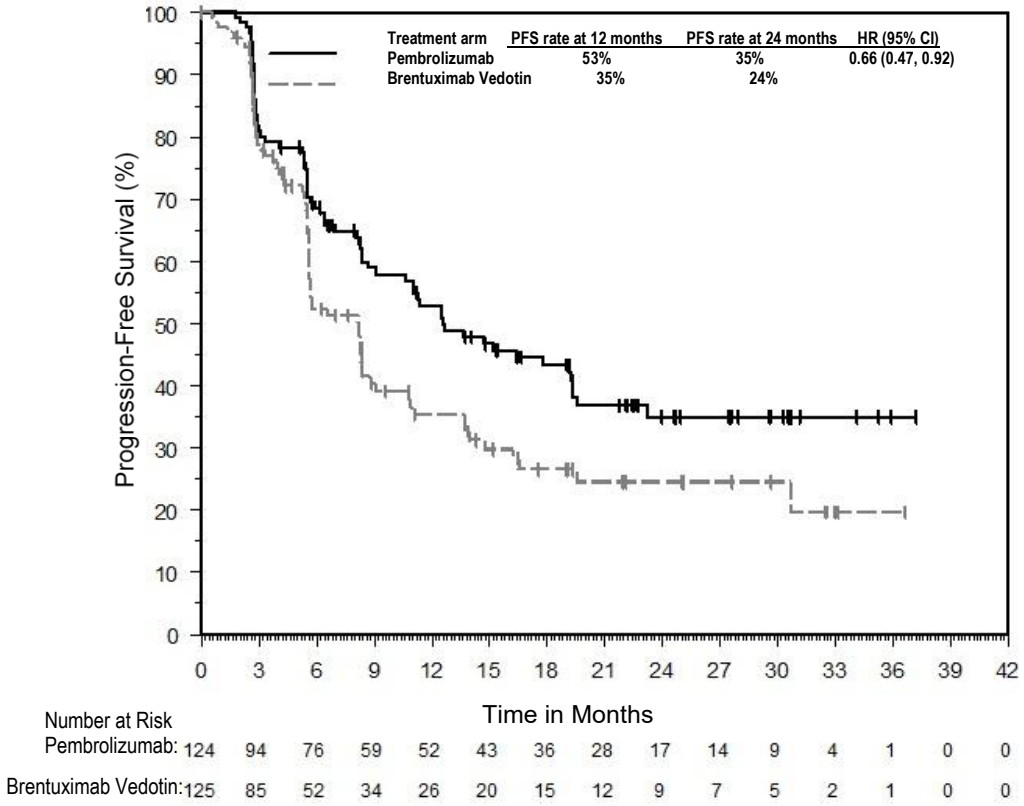
In the ITT population, the median follow-up time for 151 patients treated with pembrolizumab was 24.9 months (range: 1.8 to 42.0 months). The initial analysis resulted in a HR for PFS of 0.65 (95% CI: 0.48, 0.88) with a one-sided p value of 0.0027. The ORR was 66% for pembrolizumab compared to 54% for standard treatment with a p-value of 0.0225. Table 58 summarises the efficacy results in a subpopulation consisting of 112 patients who failed a transplant before enrolling and 137 who failed 2 or more prior therapies and were ineligible for ASCT at the time of enrolment; 124 patients received pembrolizumab and 125 patients received BV. Efficacy results in this subpopulation were consistent with the ITT population. The Kaplan-Meier curve for PFS for this subpopulation is shown in Figure 28.

Table 58: Efficacy Results in cHL Patients Who Failed a Transplant Before Enrolling or Who Failed 2 or More Prior Therapies and Were Ineligible for ASCT in KEYNOTE-204

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

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

Figure 28: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in cHL Patients Who Failed a Transplant Before Enrolling or Who Failed 2 or More Prior Therapies and Were Ineligible for ASCT in KEYNOTE-204



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

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

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

Among KEYNOTE-013 patients, the baseline characteristics were median age 32 years (6%

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

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

Efficacy results are summarised in Table 57.

Table 59: Efficacy Results in Patients with refractory or relapsed classical Hodgkin Lymphoma

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

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

The improved benefit as assessed by ORR, CRR, and response duration in the KEYNOTE-087 population was accompanied by overall improvements in health-related quality of life (HRQoL) as assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and the European Quality of Life Five Dimensions Questionnaire (EQ-5D). Relative to subjects with stable disease or progressive disease, subjects with a complete or partial response had the largest improvement

and the highest proportion with a 10 point or greater increase in their EORTC QLQ-C30 global health status/QoL score, as well as, had the largest improvement in their EQ-5D utility and VAS scores from baseline to Week 12.

Primary mediastinal B-cell lymphoma

KEYNOTE-170: Open-label study in patients with relapsed or refractory PMBCL

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

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

Efficacy results for KEYNOTE-170 are summarised in Table 58.

Table 60: Efficacy Results in Patients with refractory or relapsed PMBCL

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

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

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

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

Urothelial carcinoma

KEYNOTE-A39: Controlled trial of combination therapy with enfortumab vedotin in urothelial carcinoma patients

The efficacy of KEYTRUDA in combination with enfortumab vedotin was investigated in KEYNOTE-A39, an open-label, multicenter, randomised, active-controlled trial that enrolled 886 platinum-eligible patients with locally advanced or metastatic urothelial carcinoma. The trial excluded patients with autoimmune disease or a medical condition that required immunosuppression, active CNS metastases, ongoing sensory or motor neuropathy Grade ≥2, or uncontrolled diabetes defined as hemoglobin A1C (HbA1c) ≥8% or HbA1c ≥7% with associated diabetes symptoms. Patients were considered cisplatin-ineligible if they had at least one of the following criteria: glomerular filtration rate 30-59 mL/min, ECOG PS ≥2, Grade ≥2 hearing loss, or NYHA Class III heart failure. Patients randomised to the gemcitabine and platinum-based chemotherapy arm were permitted to receive maintenance immunotherapy. Randomisation was stratified by cisplatin eligibility (eligible or ineligible), PD-L1 expression [high (CPS ≥10) or low (CPS <10)], and liver metastases (present or absent). Patients were randomised (1:1) to one of the following treatment arms; all study medications were administered via intravenous infusion.

- KEYTRUDA 200 mg over 30 minutes on Day 1 and enfortumab vedotin 1.25 mg/kg on Days 1 and 8 of each 21-day cycle.
- Gemcitabine 1000 mg/m^2 on Days 1 and 8 and investigator's choice of cisplatin 70 mg/m^2 or carboplatin (AUC 4.5 or 5 mg/mL/min according to local guidelines) on Day 1 of each 21-day cycle.

Treatment with KEYTRUDA and enfortumab vedotin continued until RECIST v1.1-defined progression of disease, unacceptable toxicity or, for KEYTRUDA, a maximum of 35 cycles (up to approximately 2 years). Treatment was permitted beyond RECIST v1.1-defined disease progression if the treating investigator considered the patient to be deriving clinical benefit and the treatment was tolerated. Assessment of tumour status was performed every 9 weeks for 18 months and then every 12 weeks thereafter. The major efficacy outcome measures were PFS as assessed by BICR according to RECIST v1.1 and OS. Additional outcome measures included ORR and DoR as assessed by BICR according to RECIST v1.1.

The median age was 69 years (range 22 to 91); 77% were male; and 67% were White. Ninety-five percent had M1 disease, and 5% had M0 disease. Seventy-three percent had a primary tumour in the lower tract, and 27% of patients had a primary tumour in the upper tract. Fifty-four percent were cisplatin-eligible, 58% were PD-L1 high, and 72% of patients had visceral metastases, including 22% with liver metastases. Twenty percent had normal renal function, and 37%, 41% and 2% were characterised with mild, moderate, or severe renal impairment, respectively. Ninety-seven percent had ECOG PS of 0-1 and 3% had ECOG PS of 2. Eighty-five percent of patients had transitional cell carcinoma (TCC) histology, 2% had TCC with other histology, and 6% had TCC with squamous differentiation.

Thirty-two percent of patients receiving KEYTRUDA in combination with enfortumab vedotin went on to receive subsequent cancer-related therapies, compared to 70% in the gemcitabine and platinum-based chemotherapy arm. Thirty-two percent of patients in the gemcitabine and platinum-based chemotherapy arm received maintenance immunotherapy, and 26% received immunotherapy as first subsequent therapy after disease progression.

The trial demonstrated a statistically significant improvement in OS, PFS, and ORR in patients randomised to KEYTRUDA in combination with enfortumab vedotin compared with patients randomised to gemcitabine and platinum-based chemotherapy. Efficacy results were consistent across all pre-specified patient subgroups.

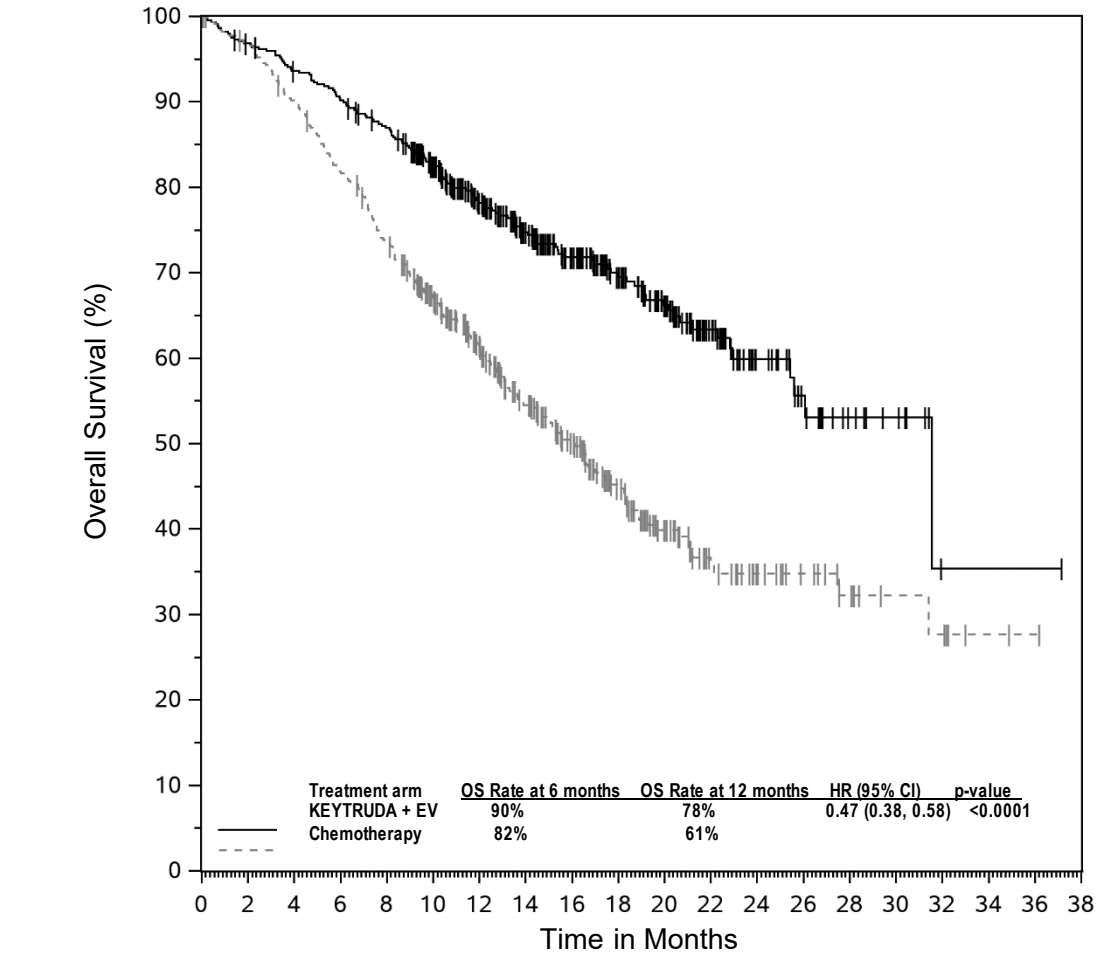
The median follow-up time for 442 patients treated with KEYTRUDA and enfortumab vedotin was 17.3 months (range: 0.3 to 37.2 months). Efficacy results are summarised in Table 61 and Figure 29 and Figure 30.

Table 61: Efficacy Results in KEYNOTE-A39

Endpoint	**KEYTRUDA 200 mg every 3 weeks in combination with enfortumab vedotin n=442**	**Gemcitabine + Platinum Chemotherapy with or without maintenance immunotherapy n=444**
OS		
Number (%) of patients with event	133 (30%)	226 (51%)
Median in months (95% CI)	31.5 (25.4, NR)	16.1 (13.9, 18.3)
Hazard ratio* (95% CI)	0.47 (0.38, 0.58)	
p-Value†	<0.0001	
PFS		
Number (%) of patients with event	223 (50%)	307 (69%)
Median in months (95% CI)	12.5 (10.4, 16.6)	6.3 (6.2, 6.5)
Hazard ratio* (95% CI)	0.45 (0.38, 0.54)	
p-Value†	<0.0001	
Objective Response Rate‡		
ORR§ % (95% CI)	68% (63.1, 72.1)	44% (39.7, 49.2)
p-Value¶	<0.0001	
Complete response	29%	12%
Partial response	39%	32%
Stable Disease	19%	34%
Disease Control Rate#	86%	78%
Response Duration		
Median in months (range)	NR (2.0+, 28.3+)	7.0 (1.5+, 30.9+)
% with duration ≥6 monthsÞ	86%	61%
% with duration ≥12 monthsÞ	67%	35%
% with duration ≥18 monthsÞ	60%	19%

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

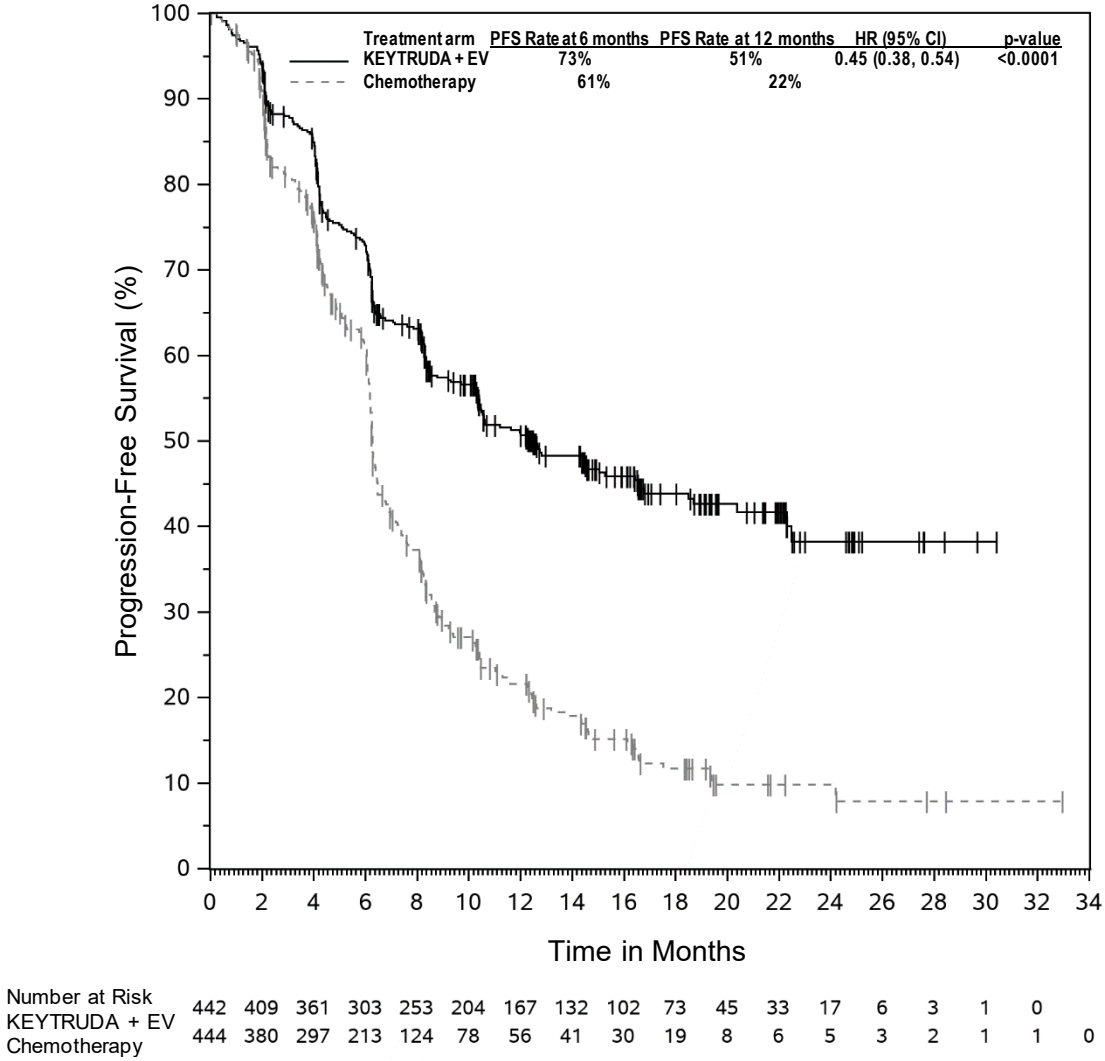
Figure 29: Kaplan-Meier Curve for Overall Survival in KEYNOTE-A39



Number at Risk

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

Figure 30: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-A39



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

The efficacy of KEYTRUDA was investigated in KEYNOTE-052, a multicentre, open-label single-arm trial of patients with locally advanced or metastatic urothelial carcinoma who were not eligible for cisplatin-containing chemotherapy. Patients with creatinine clearance ≥30ml/min were eligible for treatment. Patients with an ECOG higher than 2, 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.

At a pre-specified interim analysis, the median follow-up time for 370 patients treated with KEYTRUDA was 11.5 months. Efficacy results are summarised in Table 62.

Table 62: Efficacy Results in Patients with Urothelial Carcinoma Ineligible for Cisplatin-Containing Chemotherapy

Endpoint	**All Subjects n=370**
Objective Response Rate*	
ORR %, (95% CI)	29% (24, 34)
Disease Control Rate†	47%
Complete response	8%
Partial response	21%
Stable disease	18%
Response Duration	
Median in months (range)	Not reached (1.4+, 27.9+)
% with duration ≥ 6-months	82%‡
Time to Response	
Median in months (range)	2.1 (1.3, 9.0)
PFS*	
Median in months (95% CI)	2.3 (2.1, 3.4)
6-month PFS rate	34%
OS	
Median in months (95% CI)	11.5 (10.0, 13.3)
6-month OS rate	67%
12-month OS rate	48%

* 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

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

81% and 82%, respectively for all subjects and subjects with CPS ≥10.

KEYNOTE-361: Controlled trial in previously untreated urothelial carcinoma patients

The efficacy of KEYTRUDA for the first-line treatment of platinum-eligible patients with locally advanced or metastatic urothelial carcinoma was investigated in KEYNOTE-361, a multicentre, randomised, open-label, active-controlled study in 1,010 previously untreated patients. The safety and efficacy of KEYTRUDA in combination with platinum-based chemotherapy for previously untreated patients with locally advanced or metastatic urothelial carcinoma has not been established.

The study compared KEYTRUDA with or without platinum-based chemotherapy (i.e., cisplatin or carboplatin with gemcitabine) to platinum-based chemotherapy alone. Among the patients receiving KEYTRUDA plus platinum-based chemotherapy, 44% received cisplatin and 56% received carboplatin.

The study did not meet its primary efficacy outcome measures of improved PFS or OS in the KEYTRUDA plus chemotherapy arm compared to the chemotherapy-alone arm. Additional efficacy endpoints, including improvement of OS in the KEYTRUDA monotherapy arm, could not be formally tested.

KEYNOTE-045: Controlled trial in urothelial carcinoma patients previously treated with platinum-containing chemotherapy

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

Patients were randomised to receive either KEYTRUDA 200 mg every 3 weeks (n=270) or investigator's choice of any of the following chemotherapy regimens all given intravenously every 3 weeks (n=272): paclitaxel 175 mg/m2 (n=84), docetaxel 75 mg/m2 (n=84), or vinflunine 320 mg/m2 (n=87). Patients received KEYTRUDA until unacceptable toxicity or disease progression. Clinically stable patients with initial evidence of disease progression were permitted to remain on treatment until disease progression was confirmed. Patients without disease progression were treated for up to 24 months. While this trial permitted re-initiation of treatment with pembrolizumab for subsequent disease progression and administration for up to 1 additional year, due to limited data at the time of data cutoff any benefit remains unknown. Assessment of tumour status was performed at 9 weeks after randomisation, then every 6 weeks through the first year, followed by every 12 weeks thereafter. The primary efficacy outcomes were OS and PFS as assessed by BICR per RECIST v1.1. Secondary efficacy outcome measures were ORR as assessed by BICR per RECIST v1.1 and duration of response.

Among the 542 randomised patients, the study population characteristics were: median age 66 years (range: 26 to 88), 58% age 65 or older; 74% male; 72% White and 23% Asian; 42% ECOG PS of 0, 56% ECOG PS of 1, <2% of patients were ECOG PS of 2 with no patients ECOG PS > 2; and 96% M1 disease and 4% M0 disease. Eighty-seven percent of patients had visceral metastases, including 34% with liver metastases. Eighty-six percent had a primary tumour in the lower tract and 14% had a primary tumour in the upper tract. Fifteen percent of patients had disease progression following prior platinum-containing neoadjuvant or adjuvant chemotherapy as the most recent line of therapy. Twenty-one percent had received 2 or more prior systemic regimens in the metastatic setting. Seventy-six percent of

patients received prior cisplatin, 23% had prior carboplatin, and 1% were treated with other platinum-based regimens.

At a pre-specified interim analysis, the median follow-up time for 270 patients treated with KEYTRUDA was 10.3 months. The study demonstrated statistically significant improvements in OS and ORR for patients randomised to KEYTRUDA as compared to chemotherapy where the ORR for patients on KEYTRUDA was approximately two-fold greater than those on chemotherapy alone (21% versus 11%, p=0.001) (Table 61). There was no statistically significant difference between KEYTRUDA and chemotherapy with respect to PFS. Efficacy results are summarised in Table 61.

Table 63: Efficacy Results in Patients with Urothelial Carcinoma Previously Treated with Chemotherapy

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

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

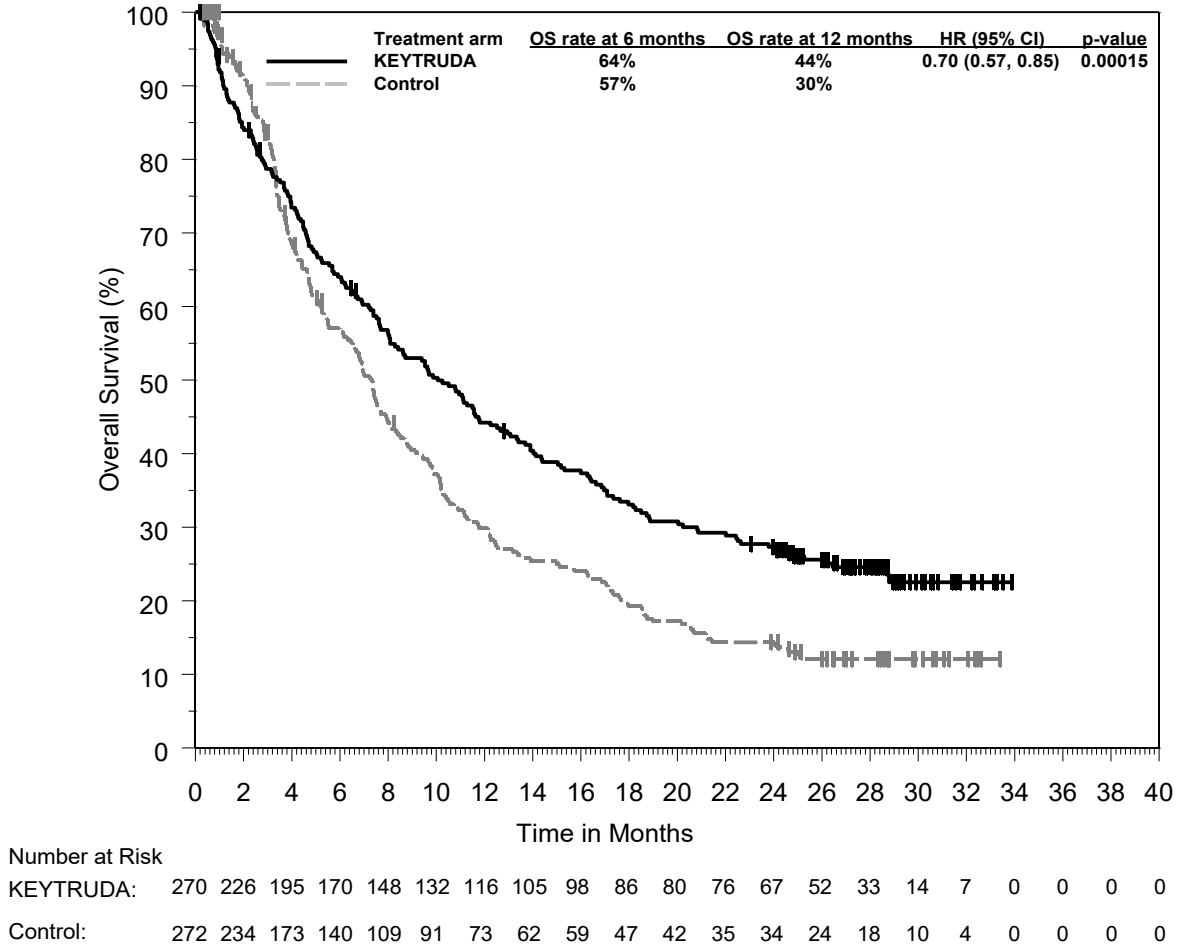
At the interim analysis, median duration of response was not reached in the KEYTRUDA arm (range 1.6+ to 15.6+ months) and was 4.3 months (range: 1.4+ to 15.4+ months) in the chemotherapy arm. At the time of the analysis, responses were ongoing in 41 and 14 patients at 6 and 12 months respectively, in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

The final OS analysis was performed 13.6 months after the interim analysis with 419 patient events (200 for KEYTRUDA and 219 for chemotherapy). Median OS was 10.1 months (95% CI: 8.0, 12.3) for KEYTRUDA and 7.3 months (95% CI: 6.1, 8.1) for chemotherapy. The OS HR was 0.70 (95% CI: 0.57, 0.85; p<0.001). See Figure 31. 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 31: 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.

In KEYNOTE-045, a higher number of deaths within 2 months was observed in pembrolizumab compared to chemotherapy, followed by a long-term survival benefit (see Figure 31). Factors associated with early deaths were fast progressive disease on prior platinum therapy and liver metastases.

KEYNOTE-057: BCG-unresponsive, high-risk, non-muscle invasive bladder cancer

The efficacy of KEYTRUDA was investigated in KEYNOTE-057, a multicentre, open-label, single-arm trial in 96 patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in-situ (CIS) with or without papillary tumours who were ineligible for or had elected not to undergo cystectomy. BCG-unresponsive high-risk NMIBC is defined as persistent disease despite adequate BCG therapy, disease recurrence after an initial tumour-free state following adequate BCG therapy, or T1 disease following a single induction course of BCG. Prior to treatment, all patients had received adequate BCG therapy, had undergone recent cystoscopic procedure(s) and transurethral resection of bladder tumour (TURBT) to remove all resectable disease (Ta and T1 components) and assure the absence of muscle invasive disease. Residual CIS (Tis components) not amenable to complete resection was acceptable. The trial excluded patients with muscle invasive (i.e., T2, T3, T4) locally advanced non-resectable or metastatic urothelial carcinoma, concurrent extra-vesical (i.e., urethra, ureter or renal pelvis) non-muscle invasive transitional cell carcinoma of the urothelium, autoimmune disease or a medical condition that required immunosuppression.

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

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

The median follow-up time was 28.0 months (range: 4.6 to 40.5 months). Efficacy results are summarised in Table 64.

Table 64: Efficacy results for patients with BCG-unresponsive, high-risk NMIBC

Endpoint	**n=96**
Complete response (CR) rate* (95% CI)	41% (31, 51)
Response duration†	
Median in months (range)	16.2 (0.0+, 30.4+)
% with duration ≥ 6 months	78%‡
% with duration ≥ 12 months	57%§

* Based on negative cystoscopy (with TURBT/biopsies as applicable), urine cytology, and computed tomography urography (CTU imaging)

† Duration reflects period from the time complete response was achieved

‡ Based on Kaplan-Meier estimates; includes 27 patients with responses of 6 months or longer

§ Based on Kaplan-Meier estimates; includes 18 patients with responses of 12 months or longer

Results remained similar at a final analysis, when the median follow-up time was 69 months. Out of the 96 patients, 44 eventually underwent radical cystectomy at various times after discontinuation of KEYTRUDA (range: 1.4 to 46.5 months). The rate of pathological upstaging to muscle invasive disease or non-organ confined disease at the time of radical cystectomy was 14% (n=6).

Microsatellite instability-high (MSI-H) cancer

KEYNOTE-164, KEYNOTE-158, and KEYNOTE-051: Open-label studies in patients with MSI-H or dMMR cancer

The efficacy of KEYTRUDA was investigated in 504 patients with MSI-H or dMMR cancer enrolled in three multicentre, non-randomised, open-label, multi-cohort studies (KEYNOTE-164, KEYNOTE-158, and KEYNOTE-051). All studies excluded patients with autoimmune disease or a medical condition that required immunosuppression. Regardless of histology, MSI or MMR tumour status was determined using polymerase chain reaction (PCR) or immunohistochemistry (IHC), respectively.

- KEYNOTE-164 enrolled 124 patients with advanced MSI-H or dMMR colorectal cancer (CRC) that progressed following treatment with a fluoropyrimidine and either oxaliplatin or irinotecan +/- anti-VEGF/EGFR mAb-based therapy.
- KEYNOTE-158 enrolled 373 patients with advanced MSI-H or dMMR non-colorectal cancer (non-CRC) who had disease progression following prior therapy.
- KEYNOTE-051 enrolled 7 paediatric patients with MSI-H or dMMR cancers.

Adult patients received KEYTRUDA 200 mg every 3 weeks (paediatric patients received 2 mg/kg 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. In KEYNOTE-164 and KEYNOTE-158, assessment of tumour status was performed every 9 weeks through the first year, then every 12 weeks thereafter. In KEYNOTE-051, assessment of tumour status was performed every 8 weeks for 24 weeks, and then every 12 weeks thereafter. The major efficacy outcome measures were ORR and duration of response as assessed by BICR according to RECIST 1.1 and as assessed by the investigator according to RECIST 1.1 in KEYNOTE-051.

In KEYNOTE-164 and KEYNOTE-158, the baseline characteristics were: median age of 60 years (36% age 65 or older); 44% male; 78% White, 14% Asian; and ECOG PS 0 (45%) and 1 (55%). Ninety-two percent of patients had M1 disease and 4% had M0 disease. Thirty-seven percent of patients received one prior line of therapy and 61% received two or more prior lines of therapy.

In KEYNOTE-051, the baseline characteristics were: median age of 11 years (range: 3 to 16); 71% female; 86% White and 14% Asian; and 57% had a Lansky/Karnofsky Score of 100. Seventy-one percent of patients had Stage IV and 14% had Stage III disease. Fifty-seven percent of patients received one prior line of therapy and 29% received two prior lines of therapy.

The median follow-up time for 497 adult and 7 paediatric patients treated with KEYTRUDA was 20.5 months and 5.2 months, respectively. Efficacy results are summarised in Table 63 and Table 64.

Table 65: Efficacy Results for Patients with MSI-H/dMMR Cancer

Endpoint	n=497
Objective Response Rate*	
ORR %, (95% CI)	34% (30, 38)
Complete response	11%
Partial response	23%
Response Duration*	
Median in months (range)	63.2 (1.9+, 63.9+)
% with duration ≥ 36-months	75%†

*Assessed by BICR using RECIST 1.1
† Based on Kaplan-Meier estimates, includes 65 patients with response of 36 months or longer
+ Denotes ongoing response

Table 66: Response by Tumour Type

	N	Objective response rate n (%)	95% CI	DOR range (months)
CRC	124	42 (34%)	(26%, 43%)	(4.4, 58.5+)
Non-CRC	373	126 (34%)	(29%, 39%)	(1.9+, 63.9+)
Endometrial	94	47 (50%)	(40%, 61%)	(2.9, 63.2)
Gastric or GE junction	51	20 (39%)	(26%, 54%)	(1.9+, 63.0+)
Small Intestinal	27	16 (59%)	(39%, 78%)	(3.7+, 57.3+)
Ovarian	25	8 (32%)	(15%, 54%)	(4.2, 56.6+)
Biliary	22	9 (41%)	(21%, 64%)	(6.2, 49.0+)
Pancreatic	22	4 (18%)	(5%, 40%)	(8.1, 24.3+)
Brain	21	1 (5%)	(0%, 24%)	18.9
Sarcoma	14	3 (21%)	(5%, 51%)	(35.4+, 57.2+)
Breast	13	1 (8%)	(0%,36%)	24.3+
Other*	12	4 (33%)	(10%, 65%)	(6.2+, 32.3+)
Cervical	11	1 (9%)	(0%, 41%)	63.9+
Neuroendocrine	11	1 (9%)	(0%, 41%)	13.3
Prostate	8	1 (13%)	(0%, 53%)	24.5+
Adrenocortical	7	1 (14%)	(0%, 58%)	4.2
Mesothelioma	7	0 (0%)	(0%, 41%)	
Thyroid	7	1 (14%)	(0%, 58%)	8.2
Small cell lung	6	2 (33%)	(4%, 78%)	(20.0, 47.5)
Bladder	6	3 (50%)	(12%, 88%)	(35.6+, 57.5+)
Salivary	5	2 (40%)	(5%, 85%)	(42.6+, 57.8+)
Renal Cell	4	1 (25%)	(0%, 81%)	22.0

* Includes tumour type (n): anal (3), HNSCC (1), nasopharyngeal (1), retroperitoneal (1), testicular (1), vaginal (1), vulvar (1), appendiceal adenocarcinoma, NOS (1), hepatocellular carcinoma (1), and carcinoma of unknown origin (1).
+ Denotes ongoing response

Among the 7 paediatric patients from KEYNOTE-051 (6 with brain cancer, 1 with abdominal adenocarcinoma), 1 patient with brain cancer had a response per irRECIST.

KEYNOTE-177: Controlled trial for first-line treatment of patients with MSI-H or dMMR CRC

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

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

- mFOLFOX6 (oxaliplatin, leucovorin, and 5-FU) or mFOLFOX6 in combination with either bevacizumab or cetuximab: Oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2 (or levoleucovorin 200 mg/m^2), and 5-FU 400 mg/m^2 bolus on Day 1, then 5-FU 2400 mg/m^2 over 46-48 hours. Bevacizumab 5 mg/kg on Day 1 or cetuximab 400 mg/m^2 on first infusion, then 250 mg/m^2 weekly.
- FOLFIRI (irinotecan, leucovorin, and 5-FU) or FOLFIRI in combination with either bevacizumab or cetuximab: Irinotecan 180 mg/m^2, leucovorin 400 mg/m^2 (or levoleucovorin 200 mg/m^2), and 5-FU 400 mg/m^2 bolus on Day 1, then 5-FU 2400 mg/m^2 over 46-48 hours. Bevacizumab 5 mg/kg on Day 1 or cetuximab 400 mg/m^2 on first infusion, then 250 mg/m^2 weekly.

Treatment with KEYTRUDA or chemotherapy continued until RECIST v1.1-defined progression of disease as determined by the investigator or unacceptable toxicity. Patients treated with KEYTRUDA without disease progression could be treated for up to 24 months. Assessment of tumour status was performed every 9 weeks. Patients randomised to chemotherapy were offered KEYTRUDA at the time of disease progression. The primary efficacy outcome measures were PFS (assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ) and OS. Secondary outcome measures were ORR and DoR.

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

The trial demonstrated a statistically significant improvement in PFS for patients randomised to KEYTRUDA compared with chemotherapy at an interim analysis. There was no statistically significant difference between KEYTRUDA and chemotherapy in the final OS analysis, with an additional 12 months of follow-up, in which 60% of the patients who had been randomised to receive chemotherapy had crossed over to receive subsequent anti-PD-1/PD-L1 therapies including KEYTRUDA. The median follow-up time was 38.1 months (range: 0.2 to 58.7 months). Table 65, Figure 32 and Figure 33 summarise the key efficacy measures for KEYNOTE-177.

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

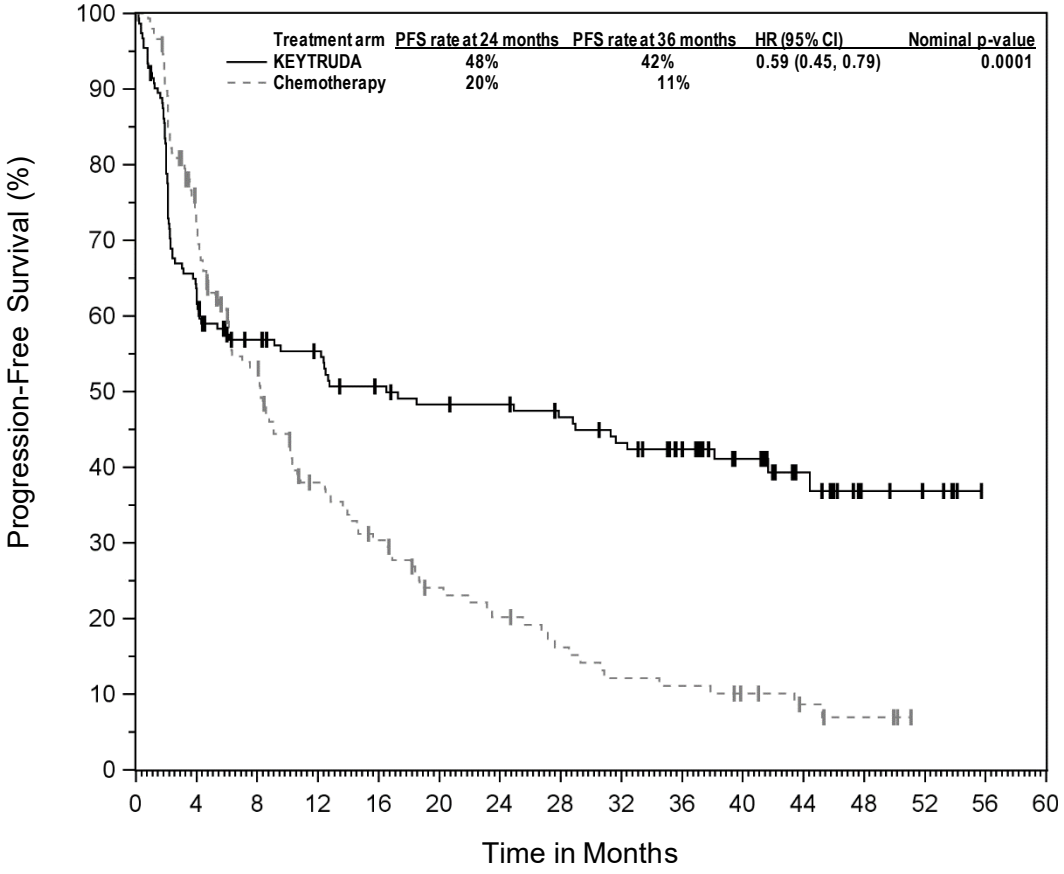
Table 67: Efficacy Results for First-line Treatment in Patients with Metastatic MSI-H CRC in KEYNOTE-177

Endpoint	KEYTRUDA 200 mg every 3 weeks n=153	Chemotherapy n=154
PFS		
Number (%) of patients with event	82 (54%)	113 (73%)
Median in months (95% CI)	16.5 (5.4, 32.4)	8.2 (6.1, 10.2)
Hazard ratio* (95% CI)	0.60 (0.45, 0.80)	
p-Value†	0.0004	
OS‡		
Number (%) of patients with event	62 (41%)	78 (51%)
Median in months (95% CI)	NR (49.2, NR)	36.7 (27.6, NR)
Hazard ratio* (95% CI)	0.74 (0.53, 1.03)	
p-Value§	0.0718	
Objective Response Rate ¶		
ORR (95% CI)	44% (35.8, 52.0)	33% (25.8, 41.1)
Complete response rate	11%	4%
Partial response rate	33%	29%
Response Duration ¶,#		
Median in months (range) Þ	NR (2.3+ - 41.4+)	10.6 (2.8 - 37.5+)
% of patients with duration ≥ 6 months β	91%	84%
% of patients with duration ≥ 12 months β	75%	37%
% of patients with duration ≥ 24 months β, à	43%	18%

* Based on Cox regression model
† Two-sided, based on log-rank test (significance level 0.0234)
‡ Final OS analysis
§ Two-sided, based on log-rank test (significance level 0.0492)
¶ Based on confirmed response by BICR review
# Based on n=67 patients with a response in the KEYTRUDA arm and n=51 patients with a response in the chemotherapy arm
Þ At the final analysis, the median duration of response was not reached (range: 2.3+, 53.5+) for the KEYTRUDA arm and 10.6 months (range: 2.8, 48.3+) for the chemotherapy arm.
β Based on observed duration of response
à At the final analysis, the percentage of patients with ongoing responses based on Kaplan-Meier estimation was 84% at 24 months or longer in the KEYTRUDA arm vs. 34% in the chemotherapy arm.
\+ Denotes ongoing response
NR = not reached

At the final analysis, the PFS and ORR results were consistent with the primary analysis.

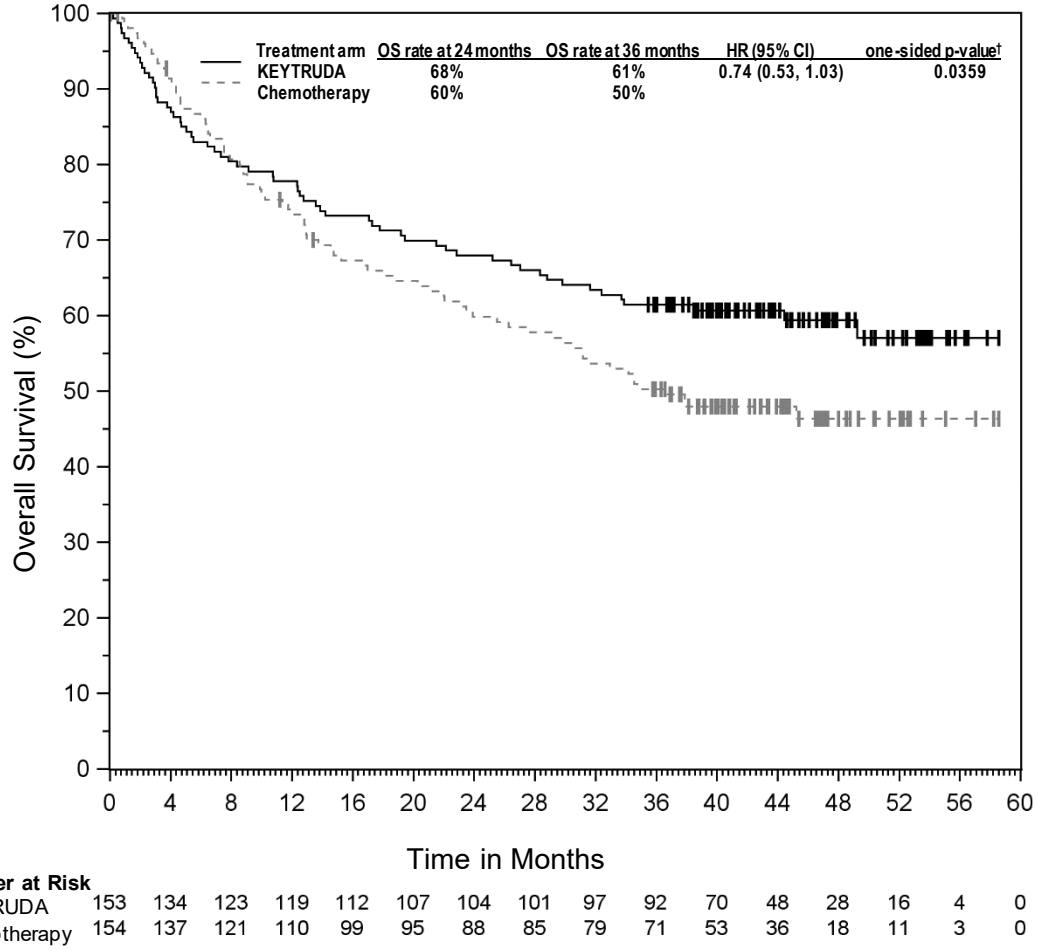
Figure 32: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-177 (Intent to Treat Population)*



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

* At the time of the protocol-specified final analysis.

Figure 33: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-177 (Intent to Treat Population)*



* At the time of the protocol-specified final analysis.
† Not statistically significant after adjustment for multiplicity.

Biliary tract carcinoma (BTC)

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

The efficacy of KEYTRUDA in combination with gemcitabine and cisplatin was investigated in KEYNOTE-966, a multicentre, randomised, double-blind, placebo-controlled trial that enrolled 1069 patients with locally advanced unresectable or metastatic BTC, who had not received prior systemic therapy in the advanced disease setting. Patients with autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Randomisation was stratified by region (Asia vs. non-Asia), locally advanced versus metastatic, and site of origin (gallbladder, intrahepatic or extrahepatic cholangiocarcinoma).

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

- KEYTRUDA 200 mg on Day 1 plus gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2 on Day 1 and Day 8 every 3 weeks.
- Placebo on Day 1 plus gemcitabine 1000 mg/m^2 and cisplatin 25 mg/m^2 on Day 1 and Day 8 every 3 weeks

All study medications were administered via intravenous infusion. Treatment continued until

unacceptable toxicity or disease progression. For pembrolizumab, treatment continued for a maximum of 35 cycles, or approximately 24 months. For cisplatin, treatment could be administered for a maximum of 8 cycles and for gemcitabine, treatment could be continued beyond 8 cycles.

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

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

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

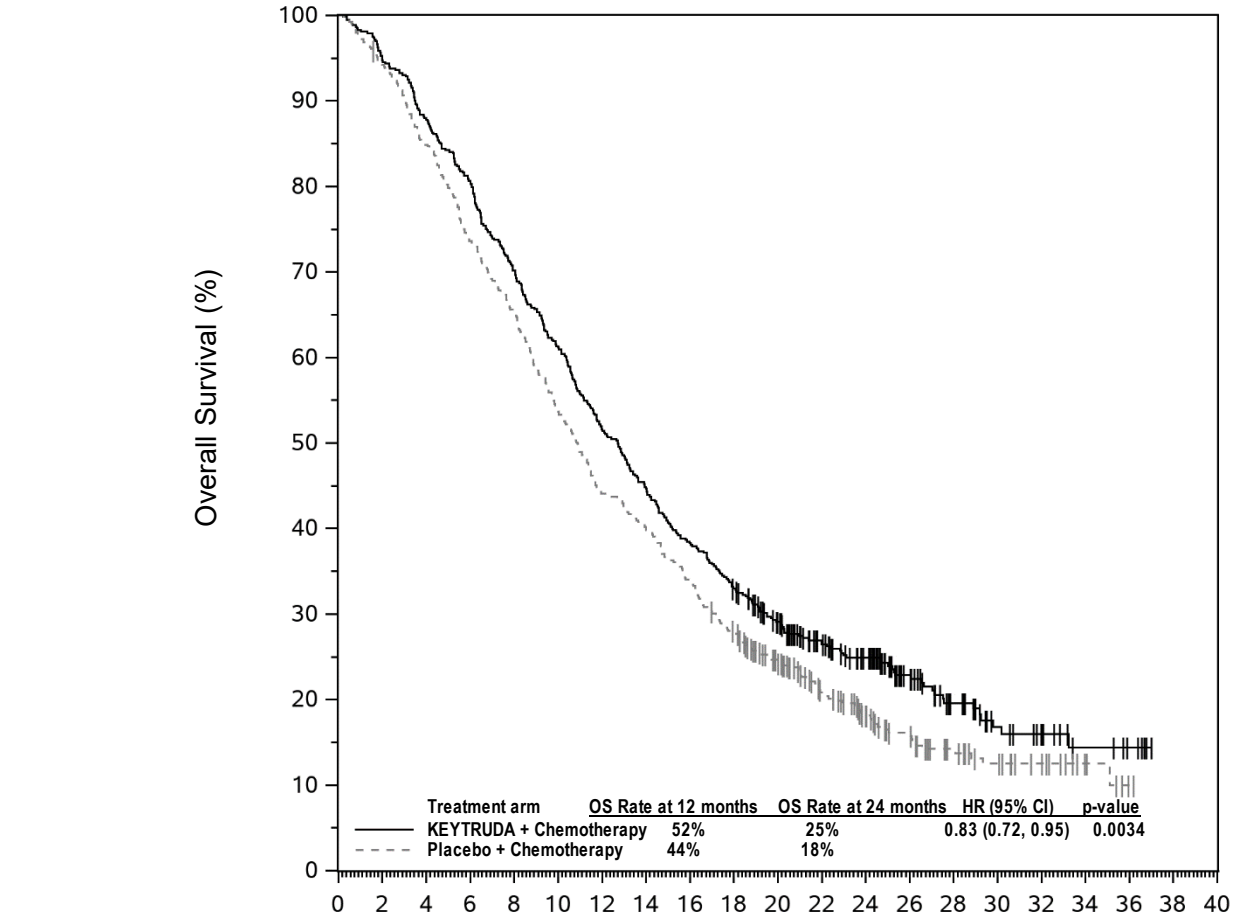
Table 68 and Figure 34 summarise the efficacy results for KEYNOTE-966.

Table 68: Efficacy Results in Patients with BTC in KEYNOTE-966

Endpoint	KEYTRUDA 200 mg every 3 weeks with gemcitabine/cisplatin n=533	Placebo with gemcitabine/cisplatin n=536
OS*		
Number (%) of patients with event	414 (78%)	443 (83%)
Median in months (95% CI)	12.7 (11.5, 13.6)	10.9 (9.9, 11.6)
Hazard ratio† (95% CI)	0.83 (0.72, 0.95)	
p-Value‡	0.0034	
PFS§		
Number (%) of patients with event	361 (68%)	391 (73%)
Median in months (95% CI)	6.5 (5.7, 6.9)	5.6 (5.1, 6.6)
Hazard ratio† (95% CI)	0.86 (0.75, 1.00)	
p-Value‡	NS	
Objective Response Rate§		
ORR¶ (95% CI)	29% (25, 33)	29% (25, 33)
Number (%) of complete responses	11 (2.1%)	7 (1.3%)
Number (%) of partial responses	142 (27%)	146 (27%)
p-Value#	NS	
Duration of Response*	n=156	n=152
Median in months Þ (95%)	8.3 (6.9, 10.2)	6.8 (5.7, 7.1)

* Results at the pre-specified final OS analysis
† Based on the stratified Cox proportional hazard model
‡ One-sided p-Value based on a stratified log-rank test
§ Results at pre-specified final analysis of PFS and ORR
¶ Confirmed complete response or partial response
# One-sided p-Value based on the stratified Miettinen and Nurminen analysis
Þ Based on Kaplan-Meier estimate
NS = not significant

Figure 34: Kaplan-Meier Curve for Overall Survival in KEYNOTE-966*



*Based on the pre-specified final OS analysis

There was no statistically significant improvement in progression-free survival, objective response rate or duration of response in patients receiving pembrolizumab plus gemcitabine and cisplatin or placebo plus gemcitabine and cisplatin.

Endometrial carcinoma

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

The efficacy of KEYTRUDA in combination with paclitaxel and carboplatin was investigated in KEYNOTE-868, a multicentre, randomised, double-blind, placebo-controlled trial in 810 patients with advanced or recurrent endometrial carcinoma including those with dMMR and pMMR tumours. Patients had not received prior systemic therapy or had received prior chemotherapy in the adjuvant setting. Patients who had received prior adjuvant chemotherapy were eligible if their chemotherapy-free interval was at least 12 months. Patients with endometrial sarcoma, including carcinosarcoma, or patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible. Randomisation was stratified according to MMR status, ECOG PS (0 or 1 vs. 2), and prior adjuvant chemotherapy. Patients were randomised (1:1) to one of the following treatment arms:

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

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

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

The dMMR population characteristics were: median age of 66 years (range: 37 to 86), 55% age 65 or older; 79% White, 9% Black, and 3% Asian; 5% Hispanic or Latino; 64% ECOG PS of 0, 33% ECOG PS of 1, and 3% ECOG PS of 2; 61% had recurrent disease and 39% had primary or persistent disease; 5% received prior adjuvant chemotherapy and 43% received prior radiotherapy. The histologic subtypes were endometrioid carcinoma (24% grade 1, 43% grade 2, 14% grade 3), adenocarcinoma NOS (11%), and other (8% including dedifferentiated/undifferentiated, serous, and mixed epithelial).

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

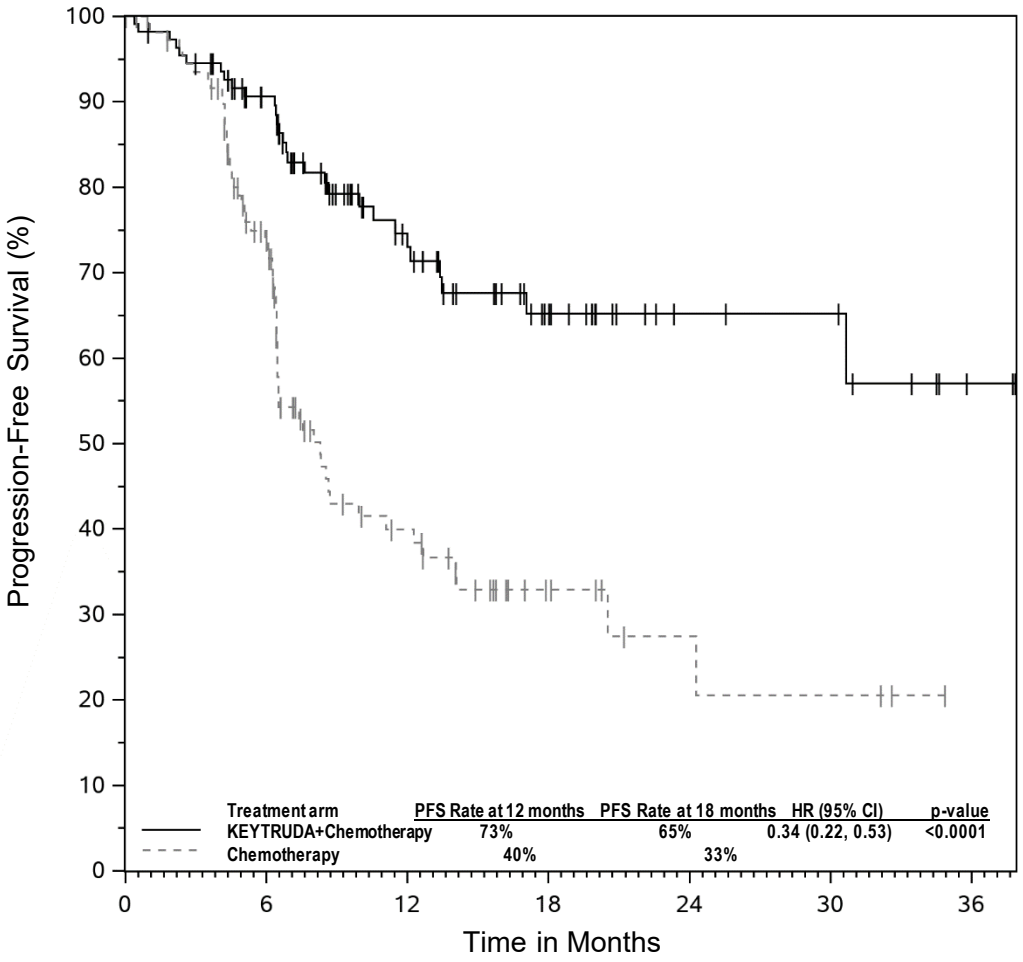
The primary efficacy outcome measure was PFS as assessed by the investigator according to RECIST 1.1 in the dMMR and pMMR populations. Secondary efficacy outcome measures included OS, ORR, and response duration in the dMMR and pMMR populations. The study demonstrated statistically significant improvements in PFS for patients randomised to pembrolizumab in combination with chemotherapy compared to placebo in combination with chemotherapy in both the dMMR and pMMR populations. The median follow-up time was 13.6 months (range: 0.6 to 39.4 months) and 8.7 months (range: 0.1 to 37.2 months) in the dMMR and pMMR populations, respectively. OS endpoint was not formally assessed within multiplicity control. OS results were not mature. Efficacy results by MMR status are summarised in Table 69. The Kaplan-Meier curves for PFS by MMR status are shown in Figure 35 and Figure 36, respectively.

Table 69: Efficacy Results in KEYNOTE-868

Endpoint	dMMR Population		pMMR Population	
	KEYTRUDA with chemotherapy* n=110	**Placebo with chemotherapy* n=112**	**KEYTRUDA with chemotherapy* n=294**	**Placebo with chemotherapy* n=294**
PFS				
Number (%) of patients with event	29 (26%)	60 (54%)	95 (32%)	138 (47%)
Median in months (95% CI)	NR (30.7, NR)	8.3 (6.5, 12.3)	13.1 (10.6, 19.5)	8.7 (8.4, 11.0)
Hazard ratio† (95% CI)	0.34 (0.22, 0.53)		0.57 (0.44, 0.74)	
p-Value‡	<0.0001		<0.0001	
OS				
Number (%) of patients with event	10 (9%)	17 (15%)	45 (15%)	54 (18%)
Median in months (95% CI)	NR (NR, NR)	NR (NR, NR)	28.0 (21.4, NR)	27.4 (19.5, NR)
Hazard ratio† (95% CI)	0.55 (0.25, 1.19)		0.79 (0.53, 1.17)	
p-Value§	0.0617		0.1157	
Objective Response Rate				
Number of participants with measurable disease at baseline	n=95	n=95	n=220	n=235
ORR¶ % (95% CI)	78% (68, 86)	69% (59, 79)	61% (55, 68)	51% (45, 58)
Complete response	28%	12%	11%	7%
Response Duration				
Median in months (range)	NR (0.0+, 33.0+)	4.4 (0.0+, 32.8+)	7.1 (0.0+, 32.8+)	6.4 (0.0+, 20.1+)
% with duration ≥12 months#	79%	21%	35%	16%

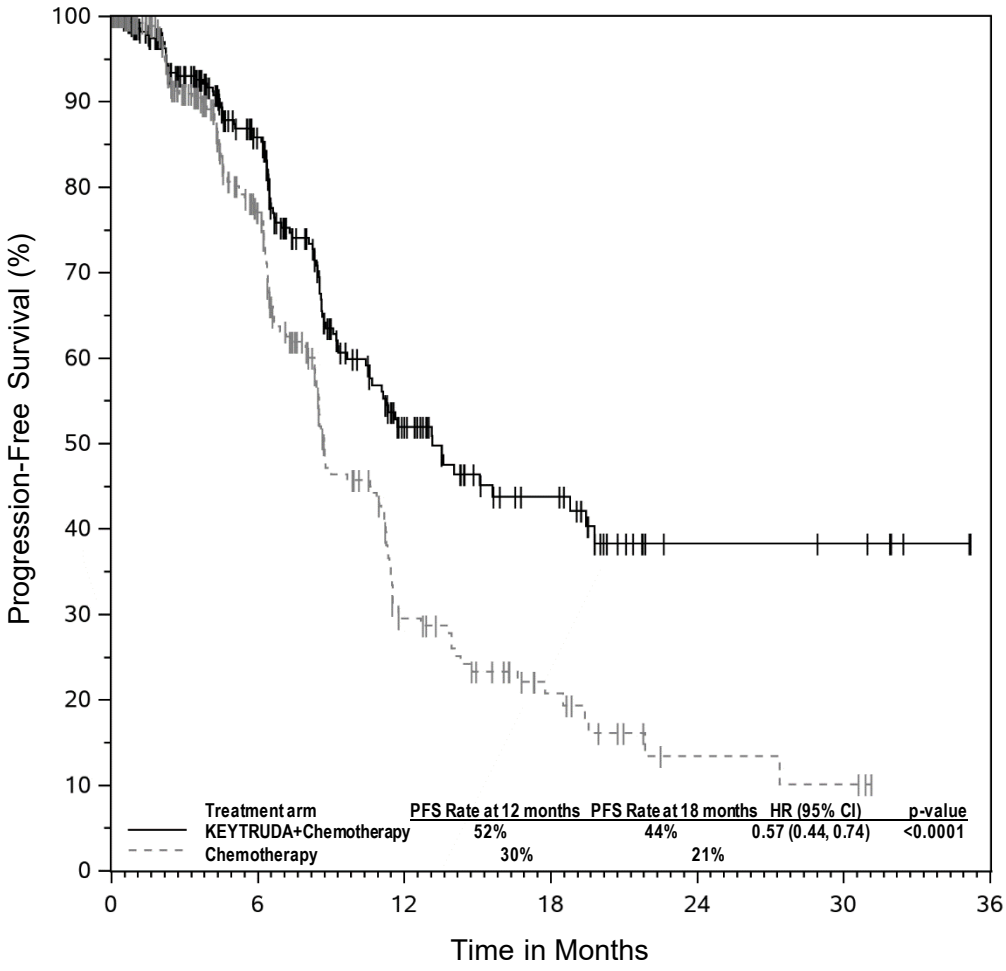
* Chemotherapy (paclitaxel and carboplatin)
† Based on the stratified Cox proportional hazard model
‡ Based on stratified log-rank test (compared to an alpha boundary of 0.00207 for dMMR and 0.00116 for pMMR)
§ Nominal p-Value; no multiplicity adjustment
¶ Response: Best objective response as confirmed complete response or partial response
# Based on Kaplan-Meier estimation
NR=not reached

Figure 35: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-868 (dMMR Population)



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

Figure 36: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-868 (pMMR Population)



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

KEYNOTE-775: Controlled trial of combination therapy in advanced endometrial carcinoma patients previously treated with systemic therapy

The efficacy of KEYTRUDA in combination with lenvatinib was investigated in KEYNOTE-775 (NCT03517449), a multicentre, open-label, randomised, active-controlled trial that enrolled 827 patients with advanced endometrial carcinoma who had been previously treated with at least one prior platinum-based chemotherapy regimen in any setting, including in the neoadjuvant and adjuvant settings. Patients with endometrial sarcoma, including carcinosarcoma, or patients who had active autoimmune disease or a medical condition that required immunosuppression were ineligible. Patients with endometrial carcinoma that were not MSI-H or dMMR were stratified by ECOG performance status, geographic region, and history of pelvic radiation. Patients were randomised (1:1) to one of the following treatment arms:

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

Treatment with KEYTRUDA and lenvatinib continued until RECIST v1.1-defined progression

of disease as verified by BICR, unacceptable toxicity, or for KEYTRUDA, a maximum of 24 months. Treatment was permitted beyond RECIST v1.1-defined disease progression if the treating investigator considered the patient to be deriving clinical benefit, and the treatment was tolerated. Assessment of tumour status was performed every 8 weeks. The major efficacy outcome measures were OS and PFS as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Additional efficacy outcome measures included ORR and DoR, as assessed by BICR. Among the 697 not dMMR patients, 346 patients were randomised to KEYTRUDA in combination with lenvatinib, and 351 patients were randomised to investigator's choice of doxorubicin (n=254) or paclitaxel (n=97). The not dMMR population characteristics were: median age of 65 years (range: 30 to 86), 52% age 65 or older; 62% White, 22% Asian, and 3% Black; 60% ECOG PS of 0 and 40% ECOG PS of 1. The histologic subtypes were endometrioid carcinoma (55%), serous (30%), clear cell carcinoma (7%), mixed (4%), and other (3%). All 697 of these patients received prior systemic therapy for endometrial carcinoma: 67% had one, 30% had two, and 3% had three or more prior systemic therapies. Thirty-seven percent of patients received only prior neoadjuvant or adjuvant therapy.

Efficacy results from the first interim analysis, in the not MSI-H or dMMR population, are summarised in Table 70. Kaplan-Meier curves for final OS and updated PFS analyses are shown in Figure 37 and Figure 38, respectively.

Table 70: Efficacy Results* in KEYNOTE-775

	Endometrial Carcinoma (not MSI-H or dMMR)	
Endpoint	**KEYTRUDA 200 mg every 3 weeks and Lenvatinib n=346**	**Doxorubicin or Paclitaxel n=351**
OS		
Number (%) of patients with event	165 (48%)	203 (58%)
Median in months (95% CI)	17.4 (14.2, 19.9)	12.0 (10.8, 13.3)
Hazard ratio† (95% CI)	0.68 (0.56, 0.84)	
p-Value‡	0.0001	
PFS		
Number (%) of patients with event	247 (71%)	238 (68%)
Median in months (95% CI)	6.6 (5.6, 7.4)	3.8 (3.6, 5.0)
Hazard ratio† (95% CI)	0.60 (0.50, 0.72)	
p-Value‡	<0.0001	
Objective Response Rate		
ORR§ (95% CI)	30% (26, 36)	15% (12, 19)
Complete response rate	5%	3%
Partial response rate	25%	13%
p-Value¶	<0.0001	
Duration of Response	n=105	n=53
Median in months (range)	9.2 (1.6+, 23.7+)	5.7 (0.0+, 24.2+)

* Based on pre-specified interim analysis

† Based on the stratified Cox regression model

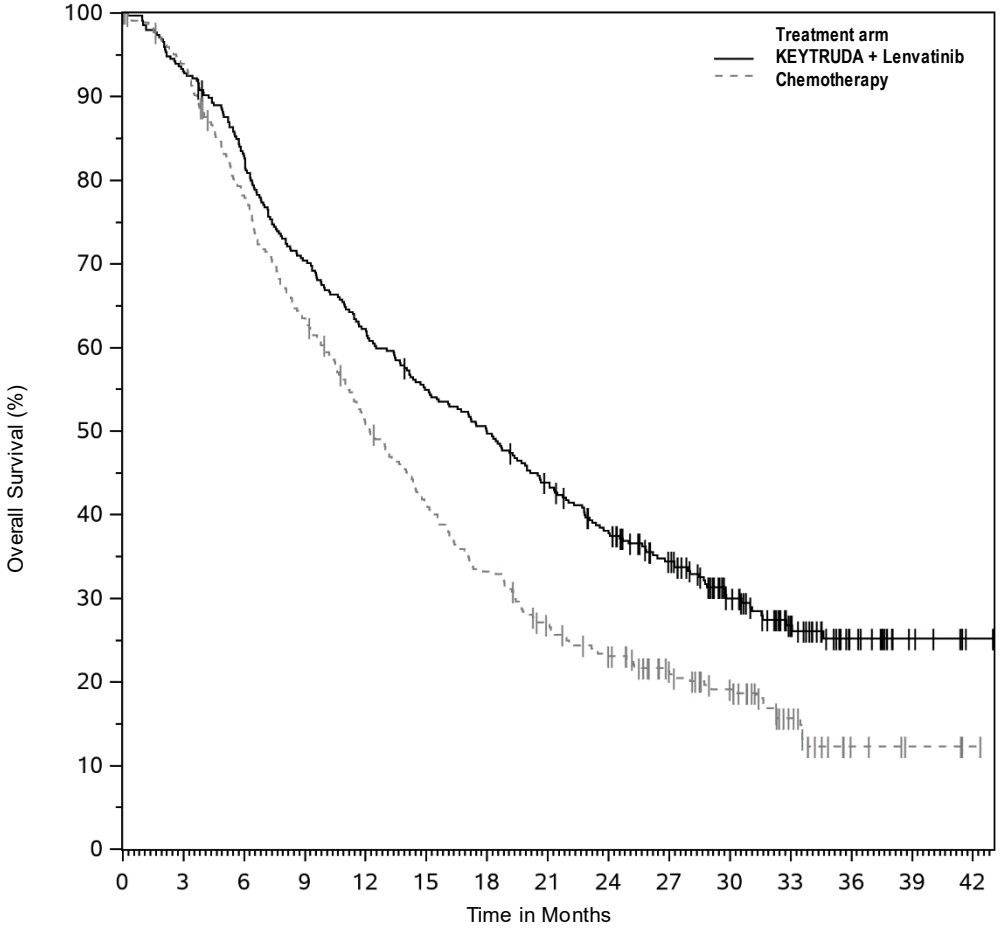
‡ Based on stratified log-rank test

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

¶ Based on Miettinen and Nurminen method stratified by ECOG performance status, geographic region, and history of pelvic radiation

The protocol-specified final OS analysis with approximately 16 months of additional follow-up duration from the interim analysis (overall median follow-up time of 14.7 months [range: 0.3 to 43.0 months]) was performed without statistical inferential testing, which was not required after the success criteria for study hypotheses was met at the pre-specified interim analysis for OS. The median OS for KEYTRUDA in combination with lenvatinib was 18.0 months (95% CI: 14.9, 20.5) compared to 12.2 months (95%CI: 11.0, 14.1) for doxorubicin or paclitaxel, with an HR of 0.70 (95% CI: 0.58, 0.83). At the time of the protocol-specified final OS analysis, the median PFS for KEYTRUDA in combination with lenvatinib was 6.7 months (95% CI: 5.6, 7.4) compared to 3.8 months (95% CI: 3.6, 5.0) for doxorubicin or paclitaxel, with an HR of 0.60 (95% CI: 0.50, 0.72).

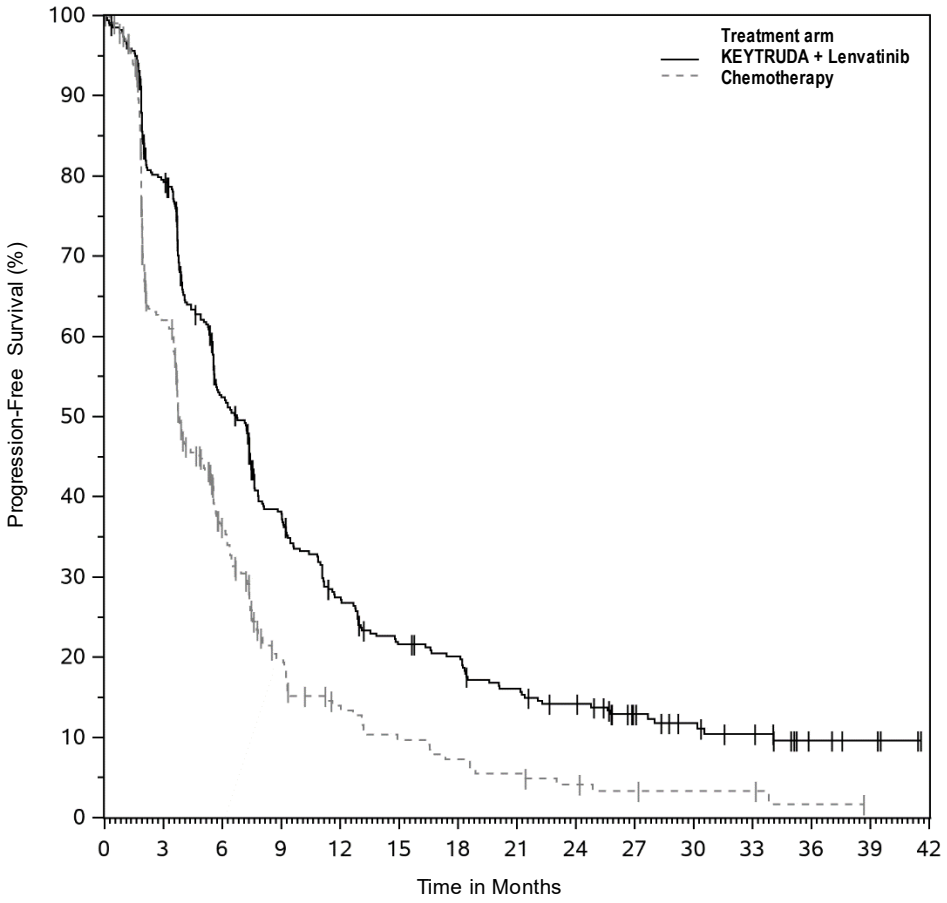
Figure 37: Kaplan-Meier Curve for Overall Survival in KEYNOTE-775 (Not MSI-H or dMMR)*



Number at Risk															
KEYTRUDA + Lenvatinib	346	322	285	242	214	188	171	148	124	95	65	41	20	7	2
Chemotherapy	351	324	267	217	171	138	111	86	71	53	40	21	6	3	1

*Based on the protocol-specified final OS analysis

Figure 38: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-775 (Not MSI-H or dMMR)*



Number at Risk															
KEYTRUDA + Lenvatinib	346	265	166	116	80	61	55	43	36	24	18	14	6	4	0
Chemotherapy	351	177	83	38	23	16	12	9	6	4	3	3	1	0	0

* Based on updated PFS analysis conducted at the time of the protocol-specified OS final analysis

Cervical cancer

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

The efficacy of KEYTRUDA in combination with cisplatin and external beam radiation therapy (EBRT) followed by brachytherapy (BT) was investigated in KEYNOTE-A18, a multicentre, randomised, double-blind, placebo-controlled trial that enrolled 1060 patients with high-risk, locally advanced cervical cancer (LACC) who had not previously received any definitive surgery, radiation, or systemic therapy for cervical cancer. To be eligible, patients required either:

- FIGO 2014 Stage III-IVA disease (tumour involvement of the lower vagina with or without extension onto pelvic sidewall or hydronephrosis/nonfunctioning kidney or has spread to adjacent pelvic organs), regardless of node status, or
- Node-positive, FIGO 2014 Stage IB2-IIB disease (tumour lesions >4 cm or clinically visible lesions that have spread beyond the uterus but have not extended onto the pelvic wall or to the lower third of vagina) [consistent with FIGO 2018 Stage IIIC].

Eligible patients enrolled are consistent with FIGO 2018 Stage III or IV (Stage IIIC patients must have at least two or more positive pelvic lymph nodes or 1 positive para-aortic lymph

node and clinical lesions greater than 4 cm in size when confined to the cervix). Patients with autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Randomisation was stratified by planned type of EBRT (Intensity-modulated radiation therapy [IMRT] or volumetric modulated arc therapy [VMAT] vs. non-IMRT and non-VMAT), planned total radiotherapy dose ([EBRT + BT dose] of <70 Gy vs. ≥70 Gy as per equivalent dose [EQD2]), and FIGO 2014 stage of cervical cancer at screening (IB2-IIB vs. III-IVA). Patients were randomised (1:1) to one of two treatment arms:

- KEYTRUDA 200 mg IV every 3 weeks (5 cycles) concurrent with cisplatin 40 mg/m^2 IV weekly (5 cycles, an optional sixth infusion could be administered per local practice) and radiotherapy (EBRT followed by BT), followed by KEYTRUDA 400 mg IV every 6 weeks (15 cycles)
- Placebo IV every 3 weeks (5 cycles) concurrent with cisplatin 40 mg/m^2 IV weekly (5 cycles, an optional sixth infusion could be administered per local practice), and radiotherapy (EBRT followed by BT), followed by placebo IV every 6 weeks (15 cycles).

Treatment continued until RECIST v1.1-defined progression of disease as determined by investigator or unacceptable toxicity. Assessment of tumour status was performed every 12 weeks for the first two years, every 24 weeks in year 3, and then annually. The primary efficacy outcomes were PFS as assessed by investigator according to RECIST v1.1 (modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, or histopathologic confirmation), or histopathologic confirmation, and OS.

Among the 1060 patients enrolled in KEYNOTE-A18, the baseline characteristics were: median age of 50 years (range: 22 to 87); 13% age 65 or older, 49% White, 2% Black, 29% Asian; 32% Hispanic or Latino; 73% ECOG PS 0 and 27% ECOG PS 1; 94% with CPS ≥1; 43% were FIGO 2014 Stage IB2 to IIB, 57% were FIGO 2014 Stage III to IVA, 83% had positive pelvic and/or positive para-aortic lymph node(s), 17% had neither positive pelvic nor para-aortic lymph node. Eighty-three percent had squamous cell carcinoma and 17% had non-squamous histology. Regarding radiation, 89% of patients received IMRT or VMAT EBRT, and the median EQD2 dose was 87 Gy (range: 3 to 207).

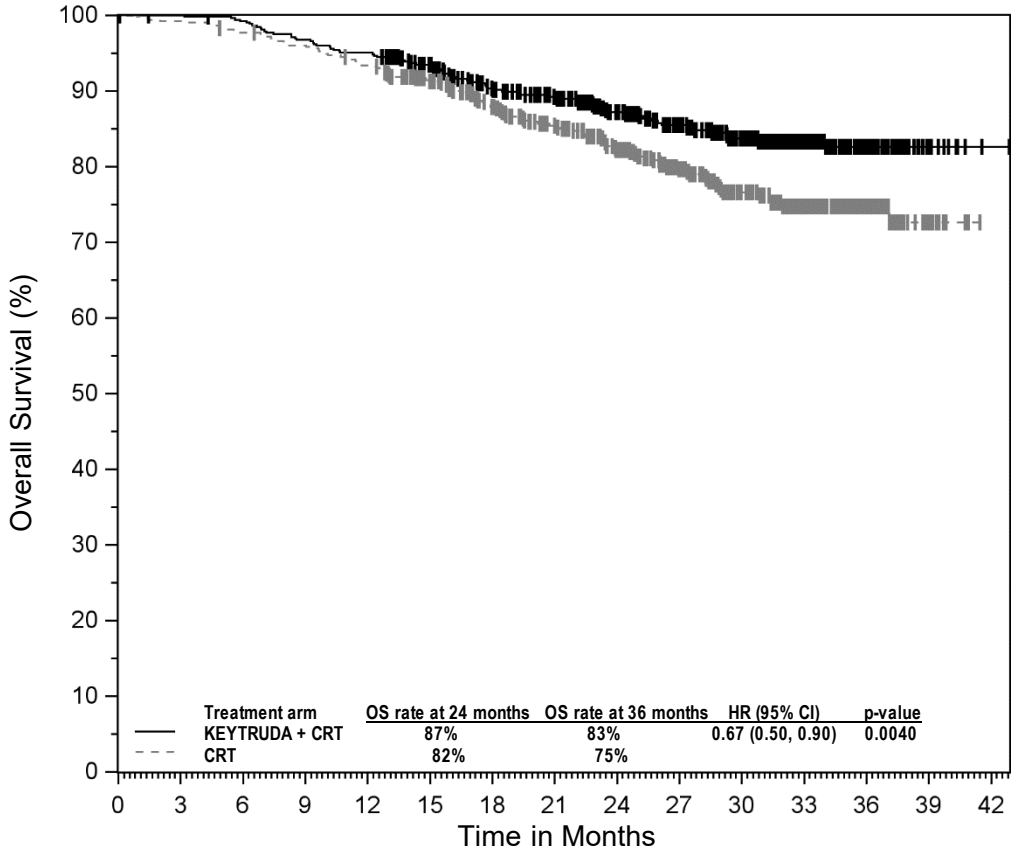
The trial demonstrated statistically significant improvements in PFS at the first prespecified interim analysis (IA1) and OS at the second pre-specified interim analysis (IA2) for patients randomised to KEYTRUDA with CRT compared to placebo with CRT. At the first pre-specified interim analysis (IA1), the HR for PFS was 0.70 (95% CI: 0.55, 0.89; p-Value 0.0020) and median follow-up time was 17 months (range: 0.9 to 31 months). Results reported from the pre-specified interim analysis for OS (IA2) with a median follow up of 28 months (range 0.9 to 43 months) are summarised in Table 71, Figure 39 and Figure 40.

Table 71: Efficacy Results* for Patients with High-Risk, Locally Advanced Cervical Cancer treated with KEYTRUDA plus Chemoradiotherapy in KEYNOTE-A18

	KEYTRUDA 200 mg every 3 weeks and 400 mg every 6 weeks with CRT n=529	Placebo with CRT n=531
OS		
Number of patients with event (%)	75 (14%)	109 (21%)
Median in months (95% CI)	NR (NR, NR)	NR (NR, NR)
24-month OS rate (95% CI)	87% (84, 90)	82% (78, 85)
36-month OS rate (95% CI)	83% (78, 86)	75% (70, 79)
Hazard ratio† (95% CI)	0.67 (0.50, 0.90)	
p-Value‡	0.0040	
PFS by Investigator		
Number of patients with event (%)	155 (29%)	210 (40%)
Median in months (95% CI)	NR (NR, NR)	NR (32, NR)
12-month PFS rate (95% CI)	80% (76, 83)	73% (69, 77)
24-month PFS rate (95% CI)	71% (66, 75)	59% (54, 63)
Hazard ratio† (95% CI)	0. 68 (0.56, 0. 84)	

* Based on a pre-specified interim OS analysis (IA2; data cut-off 08-JAN-2024)
† Based on the stratified Cox proportional hazard model
‡ One-sided p-Value based on stratified log-rank test
CRT = Chemoradiotherapy
NR = Not reached

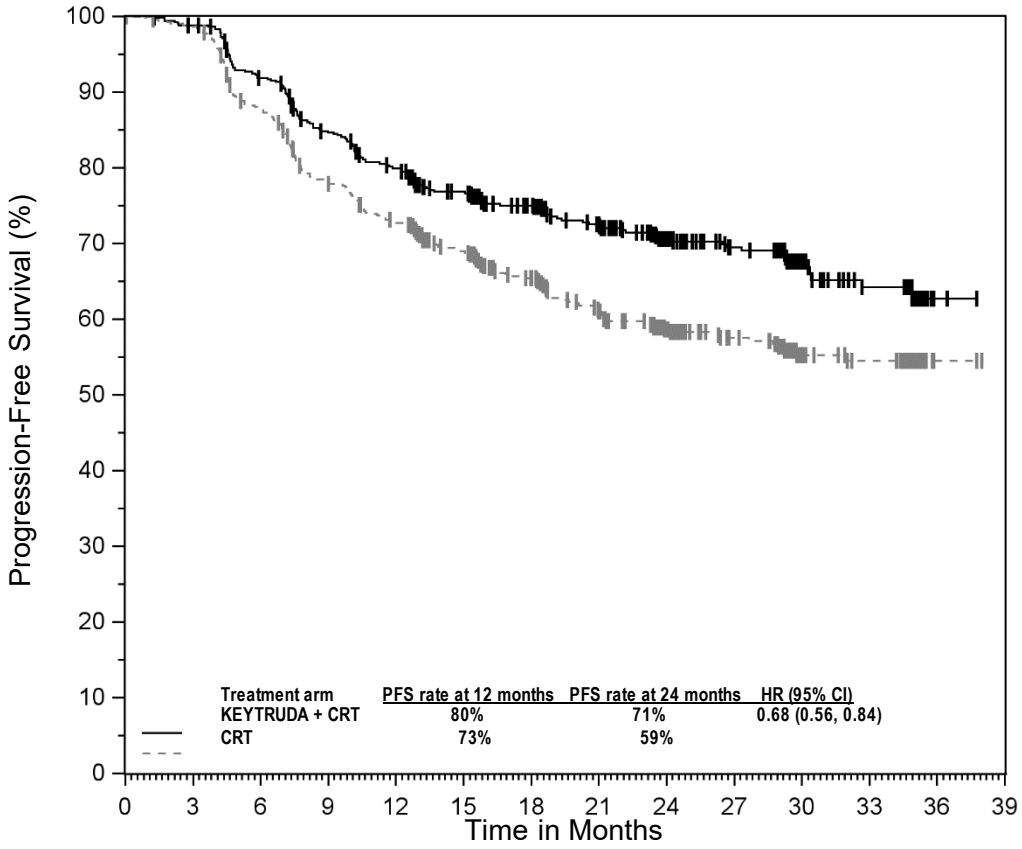
Figure 39: Kaplan-Meier Curve for Overall Survival in KEYNOTE-A18



Number at Risk

KEYTRUDA + CRT	529	527	522	509	500	463	412	374	326	273	210	136	63	11	1
CRT	531	527	518	508	493	455	405	366	316	259	194	125	58	12	0

Figure 40: Kaplan-Meier Curve for Progression Free Survival by Treatment Arm in KEYNOTE-A18*



Number at Risk

KEYTRUDA + CRT	529	515	474	430	402	353	317	280	217	179	86	69	2	0
CRT	531	513	452	395	366	325	283	241	178	148	78	69	2	0

*Based on pre-specified OS interim analysis

At IA2, PFS and OS hazard ratios (HR; with 95% CI) by stage stratum were as follows:

- FIGO 2014 Stage III-IVA:
  - PFS HR: 0.57 (0.43, 0.76)
  - OS HR: 0.57 (0.39, 0.83)
- Node-positive FIGO 2014 Stage IB2-IIB (FIGO 2018 Stage IIIC):
  - PFS HR: 0.85 (0.62, 1.16)
  - OS HR: 0.89 (0.55, 1.44)

Subgroup analyses were uninformative regarding a predictive effect of PD-L1 at a cut-off of CPS 1 (PD-L1 positive), as only 4.7% of the study population had a CPS <1.

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

The efficacy of KEYTRUDA in combination with paclitaxel and cisplatin or paclitaxel and carboplatin, with or without bevacizumab, was investigated in KEYNOTE-826, a multicentre, randomised, double-blind, placebo-controlled trial that enrolled 617 patients with persistent, recurrent, or first-line metastatic cervical cancer who had not been treated with chemotherapy except when used concurrently as a radio-sensitizing agent. Patients were enrolled regardless of tumour PD-L1 expression status. Patients with autoimmune disease that required systemic

therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Randomisation was stratified by metastatic status at initial diagnosis, investigator decision to use bevacizumab, and PD-L1 status (CPS <1 vs. CPS 1 to <10 vs. CPS ≥10). Patients were randomised (1:1) to one of the two treatment groups:

- Treatment Group 1: KEYTRUDA 200 mg plus chemotherapy
- Treatment Group 2: Placebo plus chemotherapy

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

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

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

Of the 617 enrolled patients, 548 patients (89%) had tumours expressing PD-L1 with a CPS ≥1. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx assay. Among these 548 enrolled patients with tumours expressing PD-L1, 273 patients were randomised to KEYTRUDA in combination with chemotherapy with or without bevacizumab, and 275 patients were randomised to placebo in combination with chemotherapy with or without bevacizumab. The baseline characteristics of these 548 patients were: median age of 51 years (range: 22 to 82), 16% age 65 or older; 59% White, 18% Asian, and 1% Black; 37% Hispanic or Latino; 56% and 43% ECOG performance status of 0 or 1, respectively; 63% received bevacizumab as study treatment; 21% with adenocarcinoma and 5% with adenosquamous histology; for patients with persistent or recurrent disease with or without distant metastases, 39% had received prior chemoradiation only and 17% had received prior chemoradiation plus surgery. The median follow-up time was 17.2 months (range: 0.3 to 29.4 months).

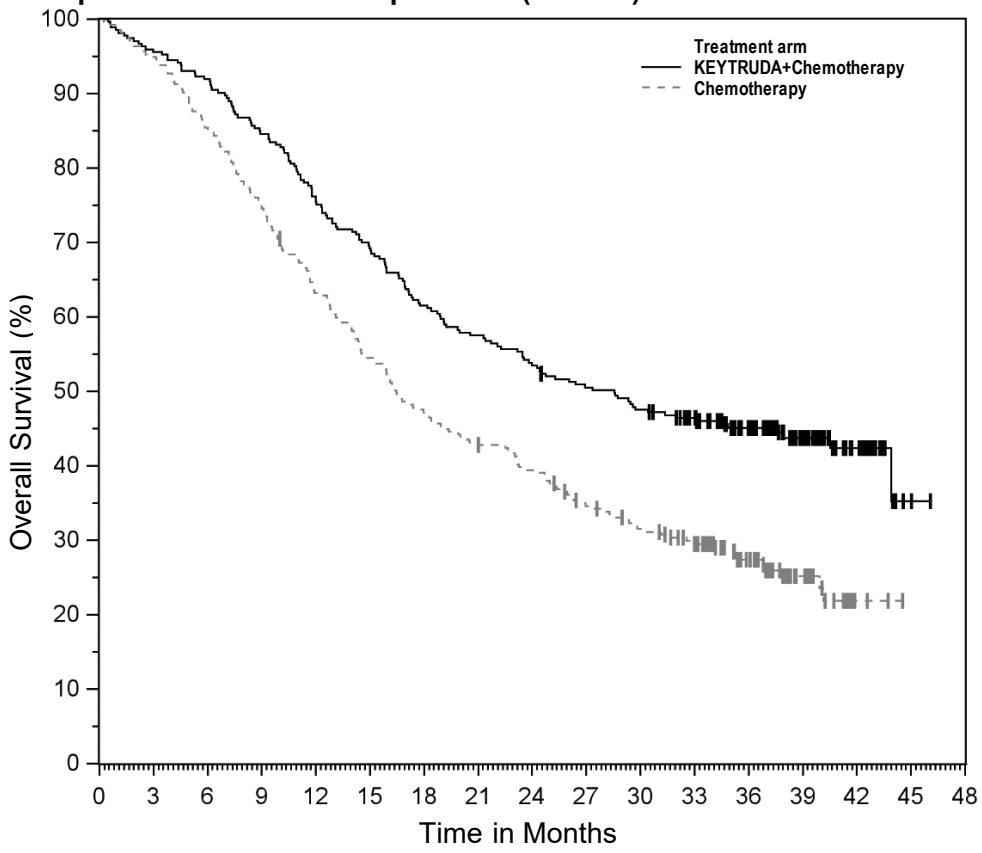
A statistically significant improvement in OS and PFS was demonstrated in patients randomised to receive KEYTRUDA compared with patients randomised to receive placebo. An updated OS analysis was conducted at the time of final analysis when 354 deaths in the CPS ≥1 population were observed. Efficacy results for patients with tumours expressing PD-L1 (CPS ≥1) in KEYNOTE-826 are summarised in Table 72 and Figure 41.

Table 72: Efficacy Results in KEYNOTE-826 for patients with PD-L1 expression (CPS ≥1)

Endpoint	KEYTRUDA 200 mg every 3 weeks plus Chemotherapy* with or without bevacizumab n=273	Placebo plus Chemotherapy* with or without bevacizumab n=275
OS		
Number of patients with event (%)	118 (43)	154 (56)
Median in months (95% CI)	NR (19.8, NR)	16.3 (14.5, 19.4)
Hazard ratio† (95% CI)	0.64 (0.50, 0.81)	
p-Value‡	0.0001	
Updated OS		
Number of patients with event (%)	153 (56.0%)	201 (73.1%)
Median in months (95% CI)	28.6 (22.1, 38.0)	16.5 (14.5, 20.0)
Hazard ratio† (95% CI)	0.60 (0.49, 0.74)	
PFS		
Number of patients with event (%)	157 (58)	198 (72)
Median in months (95% CI)	10.4 (9.7, 12.3)	8.2 (6.3, 8.5)
Hazard ratio† (95% CI)	0.62 (0.50, 0.77)	
p-Value§	<0.0001	
Objective Response Rate		
ORR¶ (95% CI)	68% (62, 74)	50% (44, 56)
Complete response rate	23%	13%
Partial response rate	45%	37%
Duration of Response		
Median in months (range)	18.0 (1.3+, 24.2+)	10.4 (1.5+, 22.0+)
% of patients with duration ≥12 months#	56	46
% of patients with duration ≥18 months#	50	35

* Chemotherapy (paclitaxel and cisplatin or paclitaxel and carboplatin)
† Based on the stratified Cox proportional hazard model
‡ Based on stratified log-rank test (compared to an alpha boundary of 0.00549)
§ Based on stratified log-rank test (compared to an alpha boundary of 0.00144)
¶ Response: Best objective response as confirmed complete response or partial response
# Based on Kaplan-Meier estimation
NR = not reached

Figure 41: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-826 patients with PD-L1 expression (CPS ≥1)*, †



Number at Risk

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

* Chemotherapy (paclitaxel and cisplatin or paclitaxel and carboplatin) with or without bevacizumab
† Based on the protocol-specified final OS analysis

Merkel Cell Carcinoma

The efficacy of KEYTRUDA was investigated in KEYNOTE-017 and KEYNOTE-913, two multicenter, non-randomised, open-label trials that enrolled 105 patients with recurrent locally advanced or metastatic MCC who had not received prior systemic therapy for their advanced disease. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible.

Patients received KEYTRUDA 2 mg/kg (KEYNOTE-017) or 200 mg (KEYNOTE-913) every 3 weeks until unacceptable toxicity or disease progression that was symptomatic, rapidly progressive, required urgent intervention, occurred with a decline in performance status, or was confirmed at least 4 weeks later with repeat imaging. Patients without disease progression were treated for up to 24 months.

The major efficacy outcome measures were ORR and DoR as assessed by BICR per RECIST v1.1.

Among the 105 patients enrolled, the median age was 73 years (range: 38 to 91), 79% were age 65 or older; 62% were male; 80% were White, race in 19% was unknown or missing, and 1% were Asian; 53% had ECOG PS of 0, and 47% had ECOG PS of 1. Thirteen percent had stage IIIB disease and 84% had stage IV. Seventy-six percent of patients had prior surgery

and 51% had prior radiation therapy.

Efficacy results are summarised in Table 73.

Table 73: Efficacy Results in KEYNOTE 017 and KEYNOTE 913

Endpoint	**KEYNOTE-017 KEYTRUDA 2 mg/kg every 3 weeks n=50**	**KEYNOTE-913 KEYTRUDA 200 mg or 2 mg/kg every 3 weeks n=55**
Objective Response Rate		
ORR (95% CI)	56% (41, 70)	49% (35, 63)
Complete responses, n (%)	12 (24%)	9 (16%)
Partial responses, n (%)	16 (32%)	18 (33%)
Duration of Response	**n=28**	**n=27**
Median DoR in months (range)	NR (5.9, 34.5+)	NR (4.8, 25.4+)
Patients with duration ≥6 months, n (%)	27 (96%)	25 (93%)
Patients with duration ≥12 months, n (%)	15 (54%)	19 (70%)

+ Denotes ongoing response
NR = not reached

Renal cell carcinoma

KEYNOTE-426: Controlled trial of combination therapy with axitinib for first-line treatment of patients with advanced RCC

The efficacy of KEYTRUDA in combination with axitinib was investigated in a randomised, multicentre, open-label, active-controlled trial KEYNOTE-426, conducted in patients with advanced RCC, regardless of PD-L1 tumour status and International Metastatic RCC Database Consortium (IMDC) risk group categories. The trial excluded patients with a history of severe autoimmune disease, patient with a medical condition that required immunosuppression within 2 years of pembrolizumab-axitinib therapy, or those who had experienced a significant cardiac, cardiovascular, or cerebrovascular event within 12 months of pembrolizumab-axitinib therapy. Randomisation was stratified by risk categories (favourable versus intermediate versus poor) and geographic region (North America versus Western Europe versus “Rest of the World”). Patients were randomised (1:1) to one of the following treatment arms:

- KEYTRUDA 200 mg intravenously every 3 weeks in combination with axitinib 5 mg orally, twice daily. Patients who tolerated axitinib 5 mg twice daily for 2 consecutive treatment cycles (i.e. 6 weeks) with no > Grade 2 treatment-related adverse events to axitinib and with blood pressure well controlled to ≤ 150/90 mm Hg were permitted dose escalation of axitinib to 7 mg twice daily. Dose escalation of axitinib to 10 mg twice daily was permitted using the same criteria. Axitinib could be interrupted or reduced to 3 mg twice daily and subsequently to 2 mg twice daily to manage toxicity.
- Sunitinib 50 mg orally, once daily for 4 weeks and then off treatment for 2 weeks.

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

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

The primary efficacy outcome measures were OS and PFS (as assessed by BICR according to RECIST 1.1). Secondary efficacy outcome measures were ORR and response duration, as assessed by BICR using RECIST 1.1. The median follow-up time for 432 patients treated with KEYTRUDA and axitinib was 13.2 months (range: 0.1 – 21.5 months). Table 72 summarises key efficacy measures. Improvements in OS, PFS and ORR were shown consistently across all tested subgroups, including subgroups by IMDC risk category and PD-L1 tumour expression status.

Table 74: Response to KEYTRUDA and Axitinib in Patients with Advanced RCC in KEYNOTE-426

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

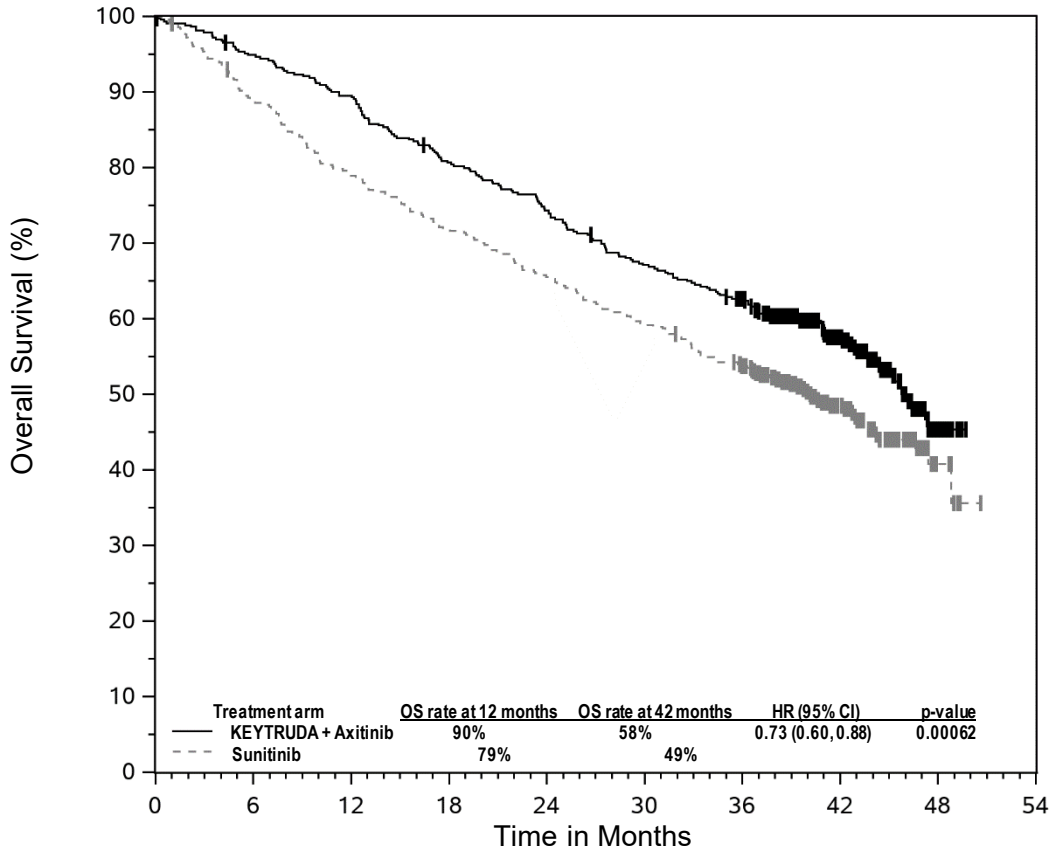
* Based on the stratified Cox proportional hazard model
† Based on stratified log-rank test.
‡ Based on patients with a best overall response as confirmed complete or partial response
§ Based on Miettinen and Nurminen method stratified by IMDC risk group and geographic region
¶ Based on Kaplan-Meier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

The protocol-specified final OS analysis was performed at a median duration of follow-up of 37.7 months after 418 patient events (193 in the KEYTRUDA and axitinib arm and 225 in the sunitinib arm). Median OS was 45.7 months (95% CI: 43.6, NA) in the KEYTRUDA and axitinib arm and 40.1 months (95% CI: 34.3, 44.2) in the sunitinib arm. The OS HR was 0.73 (95% CI: 0.60, 0.88). The 12-month OS rates were 90% (95% CI: 86, 92) in the KEYTRUDA and axitinib arm and 79% (95% CI: 75, 83) in the sunitinib arm. The 24-month OS rates were 74% (95% CI: 70, 78) in the KEYTRUDA and axitinib arm and 66% (95% CI: 61, 70) in the sunitinib arm. The 36-month OS rates were 63% (95% CI: 58, 67) in the KEYTRUDA and axitinib arm and 54% (95% CI: 49, 58) in the sunitinib arm. The 42-month OS rates were 58% (95% CI: 53, 62) in the KEYTRUDA and axitinib arm and 49% (95% CI: 44, 53) in the sunitinib arm. At final analysis, a PFS analysis was performed based on 587 patient events (286 in the KEYTRUDA and axitinib arm and 301 in the sunitinib arm). The median PFS was 15.7 months (95% CI: 13.6, 20.2) in the KEYTRUDA and axitinib arm and 11.1 months (95% CI: 8.9, 12.5) in the sunitinib arm. The PFS HR was 0.68 (95% CI: 0.58, 0.80).

The ORR at the final analysis was 60% in the KEYTRUDA and axitinib arm and 40% in the sunitinib arm. The median duration of response was 23.6 months (range: 1.4+ to 43.4+) in the KEYTRUDA and axitinib arm and 15.3 months (range: 2.3 to 42.8+) in the sunitinib arm. The percentage of patients with ongoing responses based on Kaplan-Meier estimation were 71%, 59%, 49%, and 45% at 12, 18, 24, and 30 months, respectively, in patients with confirmed response in the KEYTRUDA and axitinib arm, vs. 62%, 46%, 37%, and 32% in patients with

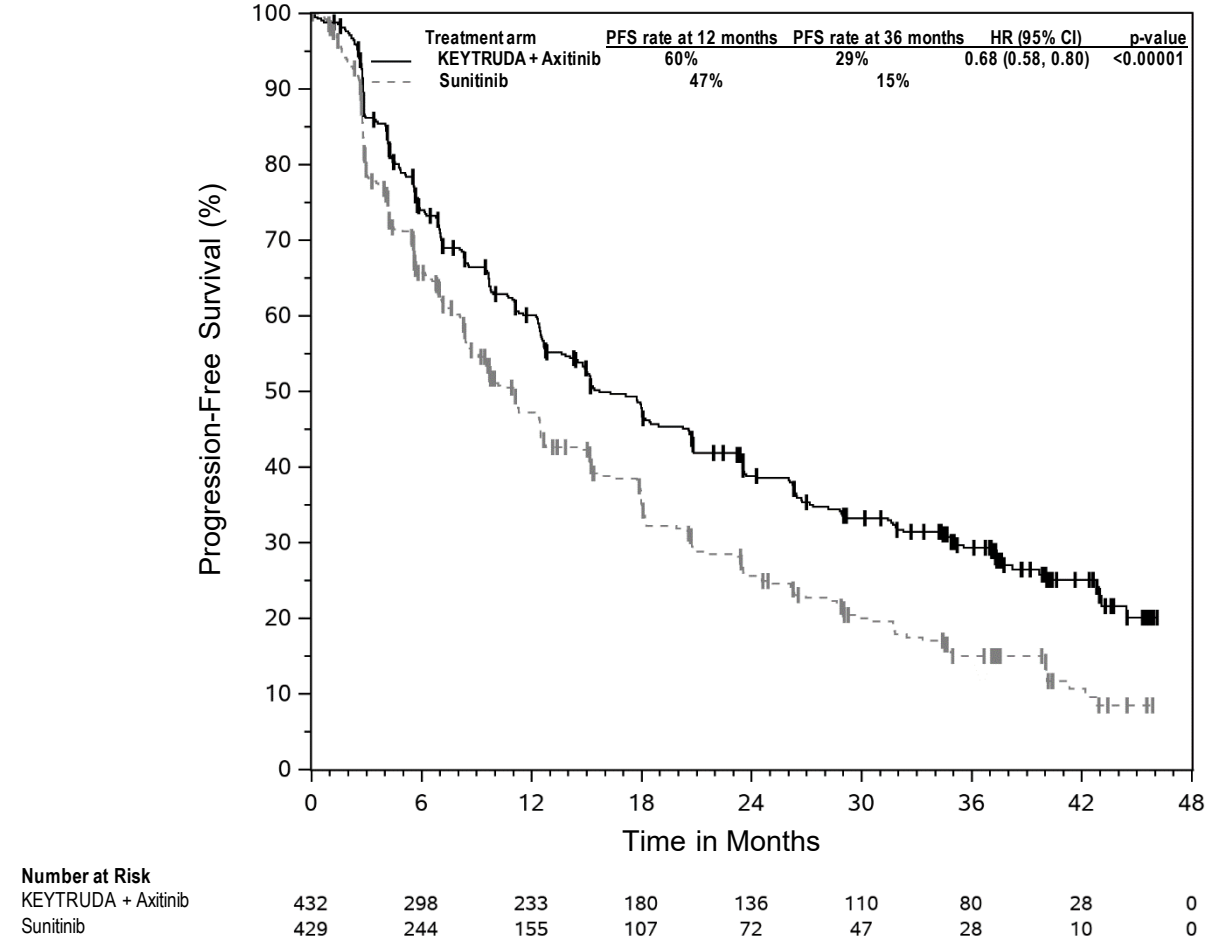
confirmed response in the sunitinib arm.

Figure 42: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-426 (Intent to Treat population)



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

Figure 43: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-426 (Intent to Treat population)



KEYNOTE-581: Controlled trial of combination therapy with lenvatinib for first-line treatment of patients with advanced RCC

The efficacy of KEYTRUDA in combination with lenvatinib was investigated in KEYNOTE-581 (CLEAR), a multicentre, open-label, randomised trial conducted in 1069 patients with advanced RCC in the first-line setting. Patients were enrolled regardless of PD-L1 tumour expression status. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible. Randomisation was stratified by geographic region (North America versus Western Europe versus "Rest of the World") and Memorial Sloan Kettering Cancer Center (MSKCC) prognostic groups (favourable versus intermediate versus poor risk).
Patients were randomised (1:1:1) to one of the following treatment arms:

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

Treatment continued until unacceptable toxicity or disease progression as determined by the investigator and confirmed by BICR using RECIST 1.1. Administration of KEYTRUDA with lenvatinib was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered by the investigator to be deriving clinical benefit. KEYTRUDA was continued for a maximum of 24 months; however, treatment with lenvatinib could be continued beyond 24 months. Assessment of tumour status was performed at baseline and

then every 8 weeks.

Among the 1069 patients in KEYNOTE 581 (355 patients in the KEYTRUDA with lenvatinib arm, 357 patients in the lenvatinib with everolimus arm, and 357 patients in the sunitinib arm), the study population characteristics were: median age of 62 years (range: 29 to 88 years); 42% age 65 or older; 75% male; 74% White, 21% Asian, 1% Black, and 2% other races; 18% and 82% of patients had a baseline KPS of 70 to 80 and 90 to 100, respectively; patient distribution by IMDC risk categories was 33% favourable, 56% intermediate and 10% poor, and by MSKCC risk categories was 27% favourable, 64% intermediate and 9% poor. Common sites of metastases in patients were lung (68%), lymph node (45%), and bone (25%).

The primary efficacy outcome measure was PFS based on BICR using RECIST 1.1. Key secondary efficacy outcome measures included OS and ORR. The trial demonstrated statistically significant longer PFS and OS, and a higher ORR, amongst patients randomised to receive KEYTRUDA in combination with lenvatinib compared with those randomised to receive sunitinib. The main efficacy results for KEYNOTE-581 (with a median OS follow-up time of 26.6 months) are summarised in Table 75 and Figure 44. Consistent results were observed across pre-specified subgroups, MSKCC prognostic groups and PD-L1 tumour expression status. OS analyses were not adjusted to account for subsequent therapies.

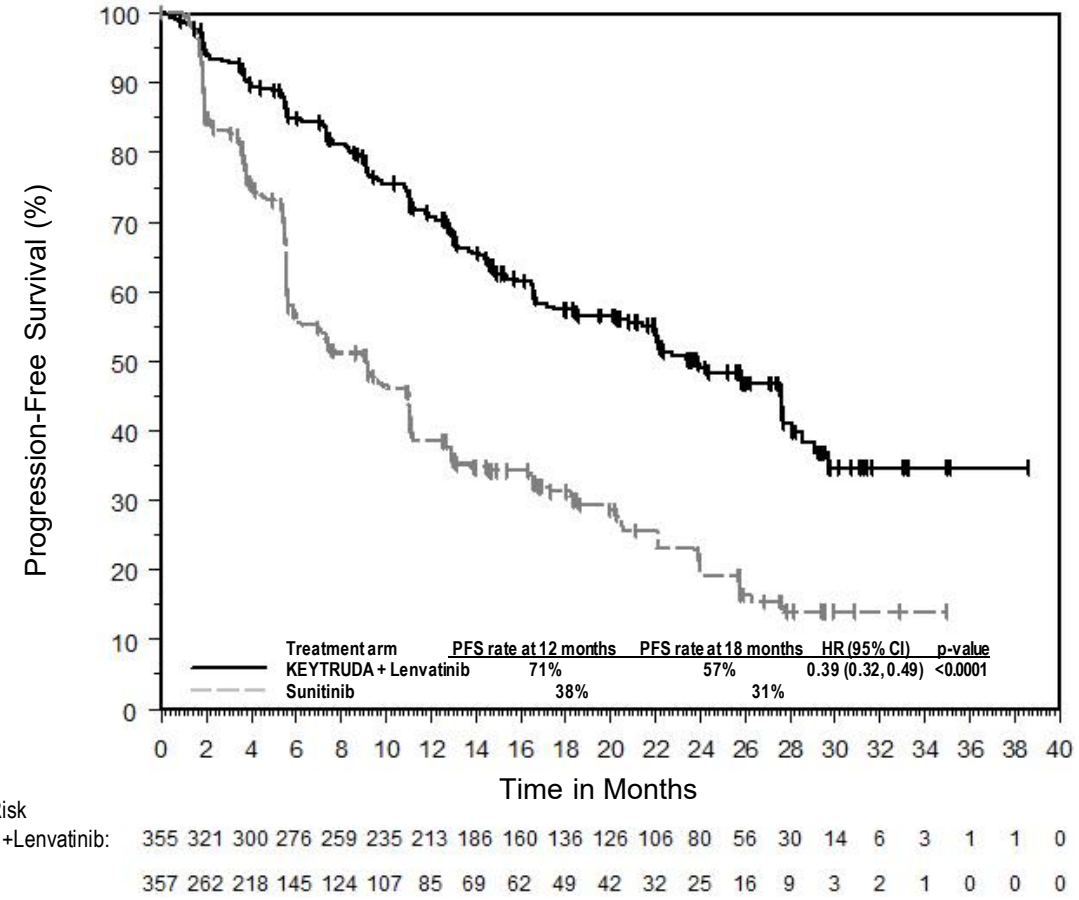
Table 75: Efficacy Results in KEYNOTE-581

Endpoint	**KEYTRUDA 200 mg every 3 weeks and Lenvatinib n=355**	**Sunitinib n=357**
PFS		
Number of patients with event (%)	160 (45%)	205 (57%)
Median in months (95% CI)	23.9 (20.8, 27.7)	9.2 (6.0, 11.0)
Hazard ratio* (95% CI)	0.39 (0.32, 0.49)	
p-Value†	<0.0001	
OS		
Number of patients with event (%)	80 (23%)	101 (28%)
Median in months (95% CI)	NR (33.6, NR)	NR (NR, NR)
Hazard ratio* (95% CI)	0.66 (0.49, 0.88)	
p-Value†	0.0049	
12-month OS rate (95% CI)	91% (88, 94)	80% (76, 84)
18-month OS rate (95% CI)	87% (83, 90)	74% (69, 79)
24-month OS rate (95% CI)	79% (74, 83)	70% (65, 75)
Objective Response Rate		
ORR‡ (95% CI)	71% (66, 76)	36% (31, 41)
Complete response rate	16%	4%
Partial response rate	55%	32%
p-Value§	<0.0001	
Response Duration¶		
Median in months (range)	26 (1.6+, 36.8+)	15 (1.6+, 33.2+)

Data cutoff date = 28 Aug 2020. + Denotes ongoing response. CI = confidence interval; NE = Not estimable; NR = not reached.

* Based on the stratified Cox proportional hazard model
† Two-sided p-Value based on stratified log-rank test
‡ Response: Best objective response as confirmed complete response or partial response
§ Nominal p-Value. At the earlier pre-specified final analysis of ORR (median follow-up time of 17.3 months), statistically significant superiority was achieved for ORR comparing KEYTRUDA plus lenvatinib with sunitinib, (odds ratio: 3.84 (95% CI: 2.81, 5.26), p-Value <0.0001)
¶ Based on Kaplan-Meier estimates

Figure 44: Kaplan-Meier Curve for Progression-Free Survival* by Treatment Arm in KEYNOTE-581



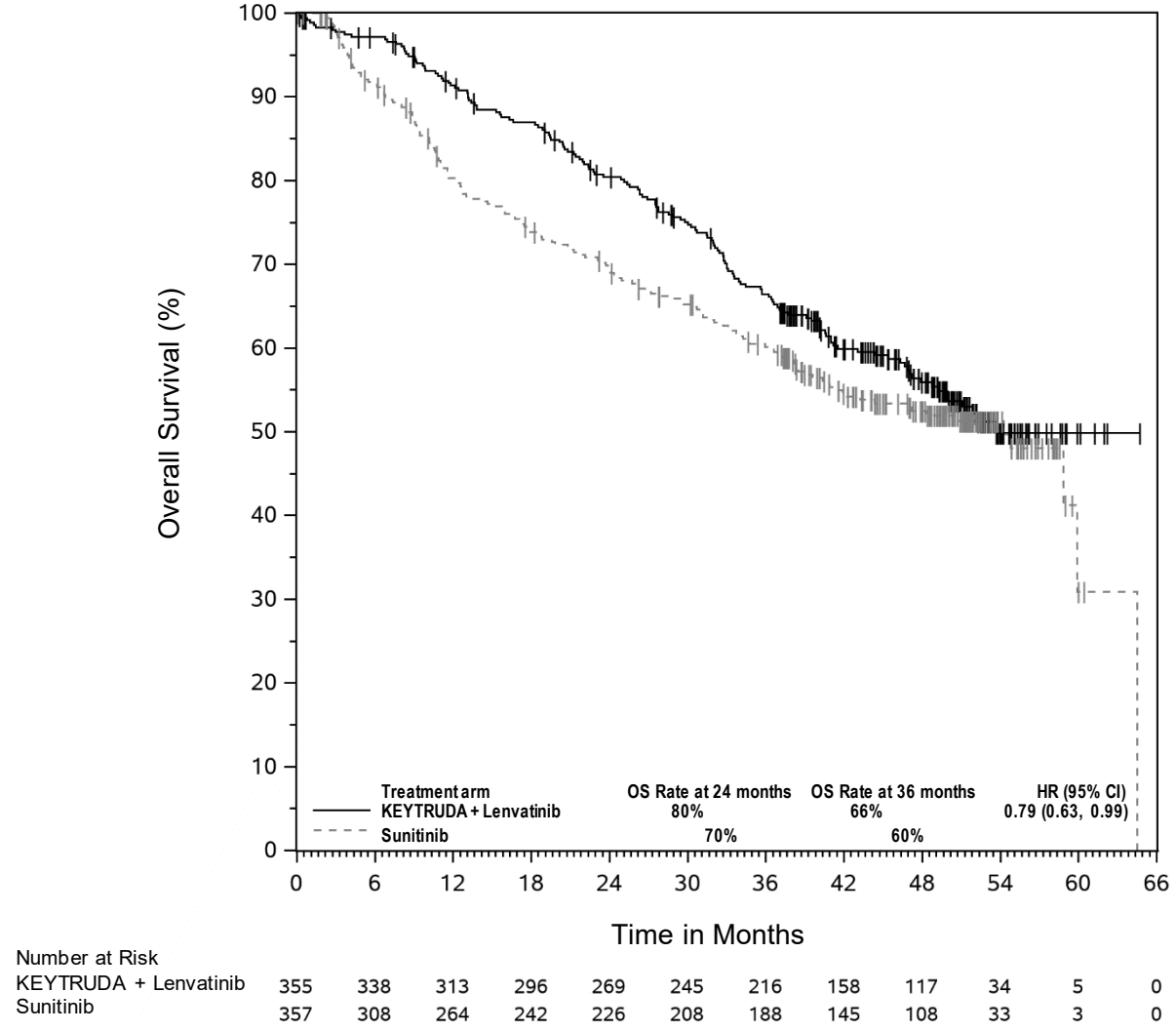
Number at Risk

KEYTRUDA +Lenvatinib:	355	321	300	276	259	235	213	186	160	136	126	106	80	56	30	14	6	3	1	1	0
Sunitinib:	357	262	218	145	124	107	85	69	62	49	42	32	25	16	9	3	2	1	0	0	0

* Data cutoff date 28 AUG 2020

The final OS analysis was conducted at an updated data cut-off date of 31 July 2022 (median OS follow-up 49.4 months). The median duration of treatment was 22.6 months (range: 2 days – 62.1 months) in the KEYTRUDA in combination with lenvatinib arm and 7.8 months (range: 3 days – 57.5 months) in the sunitinib arm. Median OS for KEYTRUDA in combination with lenvatinib was 53.7 months (95% CI: 48.7, NE) compared to 54.3 months (95% CI: 40.9, NE) for sunitinib, with a HR 0.79 (95% CI: 0.63, 0.99). See Figure 45. Subsequent to their participation in KEYNOTE-581, 55% of patients in the sunitinib arm and 16% of patients in the KEYTRUDA plus lenvatinib arm received subsequent systemic anti-PD-1/PD-L1 therapy. OS analyses were not adjusted to account for subsequent therapies.

Figure 45: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-581 at Final Analysis*



*Data cutoff date 31 JUL 2022

KEYNOTE-B61

The efficacy of KEYTRUDA in combination with lenvatinib was investigated in KEYNOTE-B61 (NCT04704219), a multicentre, single-arm trial that enrolled 160 patients with advanced/metastatic non-clear cell RCC in the first-line setting. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible.

Patients received KEYTRUDA 400 mg every 6 weeks in combination with lenvatinib 20 mg orally once daily. KEYTRUDA was continued for a maximum of 24 months; however, lenvatinib could be continued beyond 24 months. Treatment continued until unacceptable toxicity or disease progression. Administration of KEYTRUDA with lenvatinib was permitted beyond RECIST-defined disease progression if the patient was considered by the investigator to be deriving clinical benefit.

Among the 158 treated patients, the baseline characteristics were: median age of 60 years (range: 24 to 87 years); 71% male; 86% White, 8% Asian, and 3% Black; <1% Hispanic or Latino; 22% and 78% of patients had a baseline KPS of 70 to 80 and 90 to 100, respectively;

histologic subtypes were 59% papillary, 18% chromophobe, 4% translocation, <1% medullary, 13% unclassified, and 6% other; patient distribution by IMDC risk categories was 35% favourable, 54% intermediate, and 10% poor. Common sites of metastases in patients were lymph node (65%), lung (35%), bone (30%), and liver (21%).

The major efficacy outcome measure was ORR as assessed by BICR using RECIST 1.1. Additional efficacy outcome measures included DOR as assessed by BICR using RECIST 1.1. Efficacy results are summarised in Table 76.

Table 76: Efficacy Results in KEYNOTE-B61

Endpoint	**KEYTRUDA 400 mg every 6 weeks and Lenvatinib n=158**
Objective Response Rate (Confirmed)	
ORR (95% CI)	51% (43, 59)
Complete response	8%
Partial response	42%
Duration of Response*	
Median in months (range)	19.5 (1.5+, 23.5+)

CI = confidence interval
* Based on Kaplan-Meier estimates
\+ Denotes ongoing response

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

The efficacy of KEYTRUDA was investigated as adjuvant therapy for RCC in KEYNOTE-564, a multicentre randomised, double-blind, placebo-controlled study in 994 patients with intermediate-high or high risk of recurrence of RCC, or M1 no evidence of disease (NED). The intermediate high-risk category included: pT2 with Grade 4 or sarcomatoid features; pT3, any Grade without nodal involvement (N0) or distant metastases (M0). The high-risk category included: pT4, any Grade N0 and M0; any pT, any Grade with nodal involvement and M0. The M1 NED category included patients with metastatic disease who had undergone complete resection of primary and metastatic lesions. Patients must have undergone a partial nephroprotective or radical complete nephrectomy (and complete resection of solid, isolated, soft tissue metastatic lesion(s) in M1 NED participants) with negative surgical margins ≥4 weeks prior to the time of screening. A clear cell component to the RCC histology was required for trial inclusion. Patients with active autoimmune disease, with a medical condition that required immunosuppression, or who had received prior systemic therapy for advanced RCC were ineligible. Patients were randomised (1:1) to receive KEYTRUDA 200 mg every 3 weeks (n=496) or placebo (n=498) for up to 1 year until disease recurrence or unacceptable toxicity. Randomisation was stratified by metastasis status (M0, M1 NED), within M0 group, further stratified by ECOG PS (0,1), and geographic region (US, non-US). Patients underwent imaging every 12 weeks for the first 2 years from randomisation, then every 16 weeks from year 3 to 5, and then every 24 weeks annually.

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

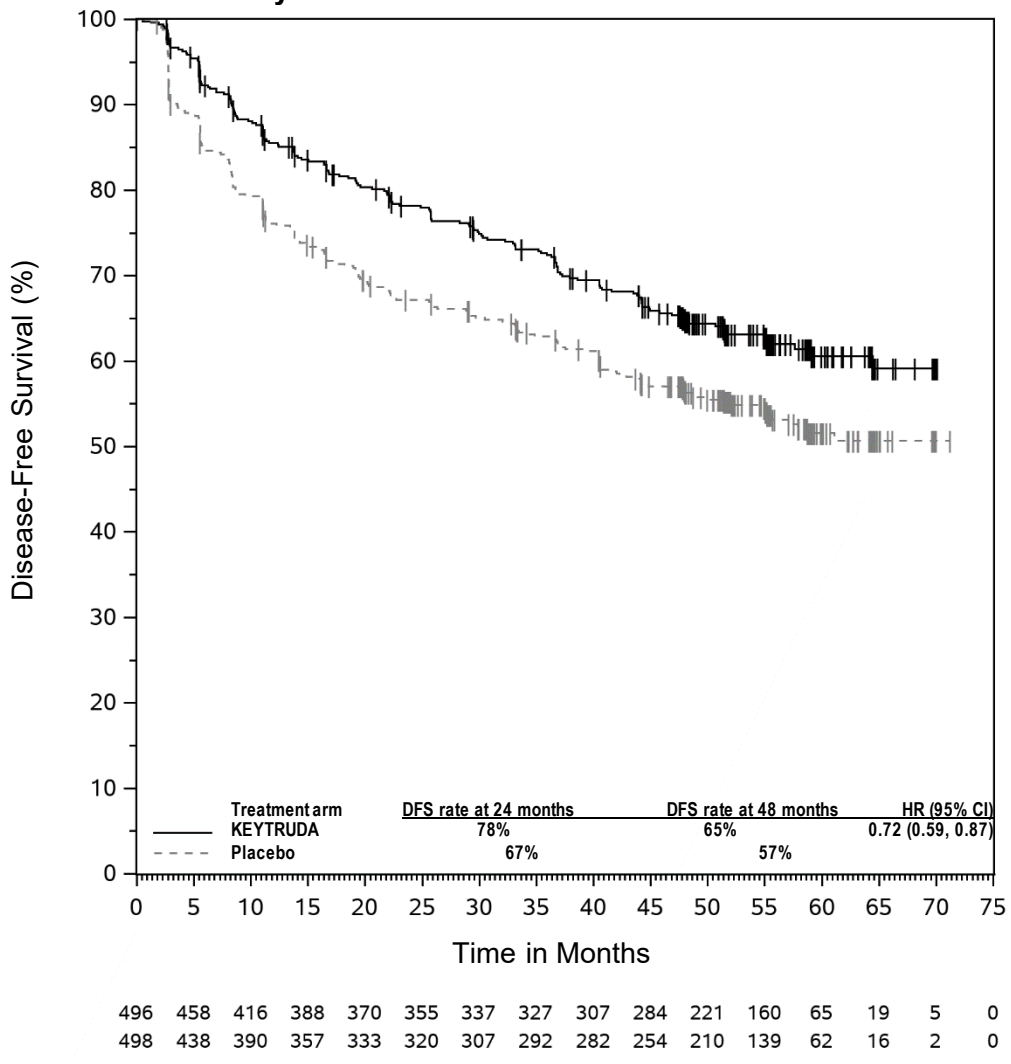
The primary efficacy outcome measure was investigator-assessed disease-free survival (DFS). The key secondary outcome measure was OS. The study demonstrated statistically significant improvements in DFS and OS for patients randomised to the KEYTRUDA arm compared with placebo. Generally consistent results were observed across pre-specified subgroups. Efficacy results are summarised in Table 77 and Figure 46 and Figure 47.

Table 77: Efficacy Results in KEYNOTE-564

Endpoint	**KEYTRUDA 200 mg every 3 weeks n=496**	**Placebo n=498**
DFS*		
Number (%) of patients with event	109 (22%)	151 (30%)
Median in months (95% CI)	NR	NR
Hazard ratio‡ (95% CI)	0.68 (0.53, 0.87)	
p-Value	0.0010§	
OS†		
Number (%) of patients with event	55 (11%)	86 (17%)
Median in months (95% CI)	NR	NR
Hazard ratio (95% CI)‡	0.62 (0.44, 0.87)	
p-Value	0.0024§	

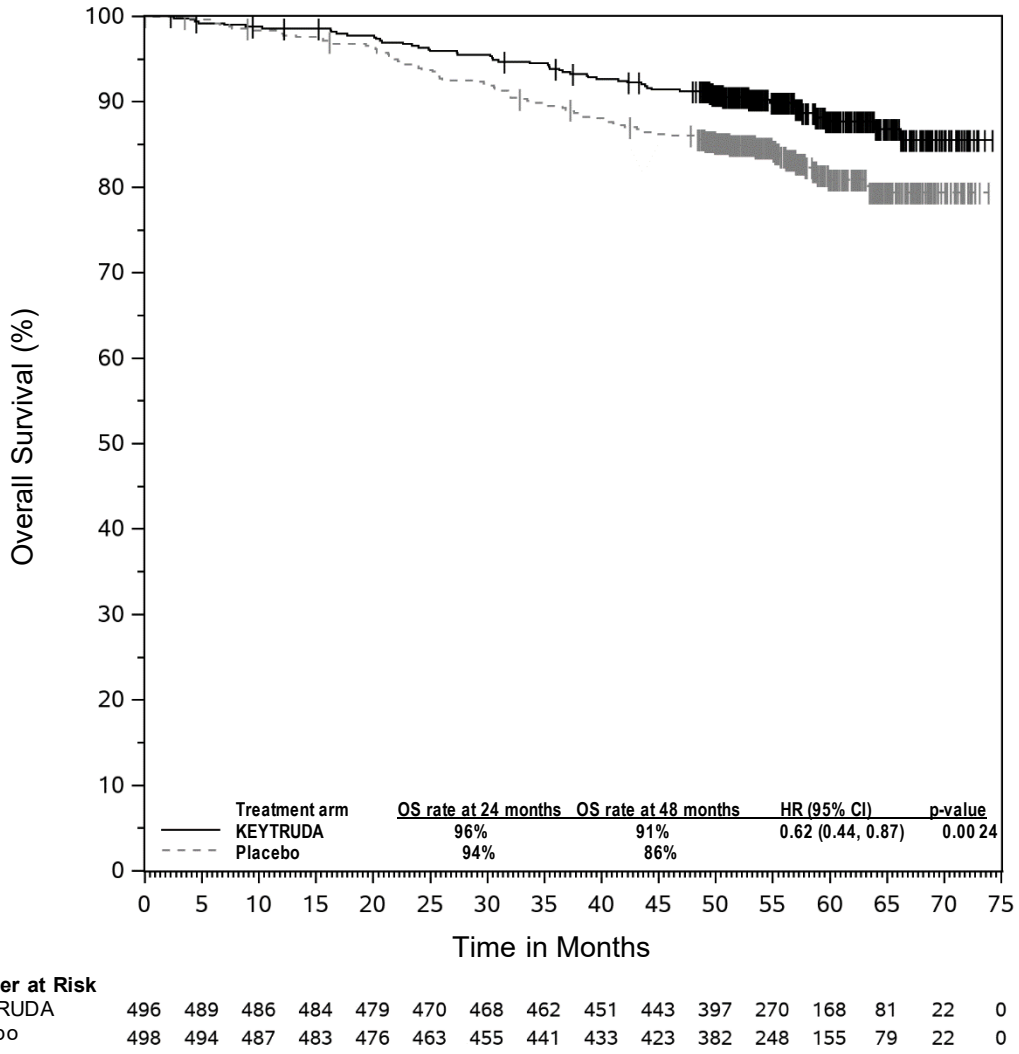
* Median follow-up time was 23.9 months (range: 2.5 to 41.5 months)
† Median follow-up time was 55.8 months (range: 2.5 to 74.5 months).
‡ Based on the stratified Cox proportional hazard model
§ Based on stratified log-rank test
NR = not reached

Figure 46: Kaplan-Meier Curve for Disease-Free Survival by Treatment Arm at Interim Analysis 3* in KEYNOTE-564



*Median follow-up time: 55.8 months, data cutoff date 15 SEP 2023.

Figure 47: Kaplan-Meier Curve for Overall Survival by Treatment Arm at Interim Analysis 3* in KEYNOTE-564



*Median follow-up time: 55.8 months, data cutoff date 15 SEP 2023.

Cutaneous squamous cell carcinoma (cSCC)

KEYNOTE 629: Open-label trial of monotherapy in cSCC

The efficacy of KEYTRUDA was investigated in KEYNOTE-629, a multicentre, multi-cohort, non-randomised, open-label, single-arm trial that enrolled 159 patients with recurrent or metastatic cSCC or locally advanced cSCC.

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

Assessment of tumour status was performed every 6 weeks during the first year, and every 9 weeks during the second year. The major efficacy outcome measures were ORR and DoR as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

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

Among the 54 patients with locally advanced cSCC treated, the study population characteristics were: median age of 76 years (range: 35 to 95), 80% age 65 or older; 72% male; 83% White, 13% race unknown; 41% ECOG PS of 0 and 59% ECOG PS of 1. Twenty-two percent received one or more prior lines of therapy; 63% received prior radiation therapy.

Efficacy results are summarised in Table 78.

Table 78: Efficacy Results in KEYNOTE-629

Endpoint	**KEYTRUDA Recurrent or Metastatic cSCC n=105**	**KEYTRUDA Locally Advanced cSCC n=54**	**Combined cSCC n=159**
Objective Response Rate			
ORR (95% CI)	35% (26, 45)	52% (38, 66)	41% (33, 49)
Complete response rate	12%	22%	16%
Partial response rate	23%	30%	25%
Time to Response			
Median in months (range)	1.6 (1.2, 24.7)	2.7 (1.1, 12.3)	2.0 (1.1, 24.7)
Duration of Response*	n=37	n=28	n=65
Median in months (range)	NR (2.7, 64.2+)†	47.2 (1.0+, 49.9+)‡	52.5 (1.0+, 64.2+)§
% with duration ≥6 months	81%	93%	86%
% with duration ≥12 months	78%	85%	81%

* Median follow-up time: recurrent or metastatic cSCC: 23.8 months; locally advanced cSCC: 48.0 months
† Based on patients (n=37) with a confirmed response by independent review
‡ Based on patients (n=28) with a confirmed response by independent review
§ Based on patients (n=65) with a confirmed response by independent review
\+ Denotes ongoing response

Gastric or GOJ adenocarcinoma

KEYNOTE-859: In combination with chemotherapy as first-line treatment for advanced HER2-negative gastric or gastroesophageal junction (GOJ) adenocarcinoma

The efficacy of KEYTRUDA in combination with fluoropyrimidine and platinum chemotherapy was investigated in KEYNOTE-859, a multicentre, randomised, double-blind, placebo-controlled trial that enrolled 1579 patients with locally advanced unresectable or metastatic gastric or gastroesophageal junction (GOJ) adenocarcinoma that was HER2-negative (not HER2-positive per local standards), regardless of PD-L1 expression status, who had not previously received systemic therapy for metastatic disease. Patients with an autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Randomisation was stratified by PD-L1 expression (CPS ≥1 or <1), chemotherapy regimen (5-FU plus cisplatin [FP] or capecitabine plus oxaliplatin [CAPOX]), and geographic region (Europe/ Israel/ North America/ Australia, Asia or Rest of the World).

All study medications, except oral capecitabine, were administered as an intravenous infusion,

in 3-week cycles. All patients received investigators choice of combination chemotherapy: either cisplatin 80 mg/m^2 and 5-FU 800 mg/m^2/day for 5 days (FP), or oxaliplatin 130 mg/m^2 and capecitabine 1000 mg/m^2 bid for 14 days (CAPOX). Patients were randomised (1:1) to receive either KEYTRUDA 200 mg or a matching placebo prior to chemotherapy on Day 1 of each cycle. Treatment continued until radiographic progression of disease, unacceptable toxicity, or for a maximum of 24 months. Tumour status was assessed by BICR using RECIST v1.1 (modified to allow up to 10 target lesions total/5 per organ), with imaging taken at 6 week intervals. The primary efficacy outcome measure was OS. Additional secondary efficacy outcome measures included BICR-assessed PFS, ORR, and DOR.

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

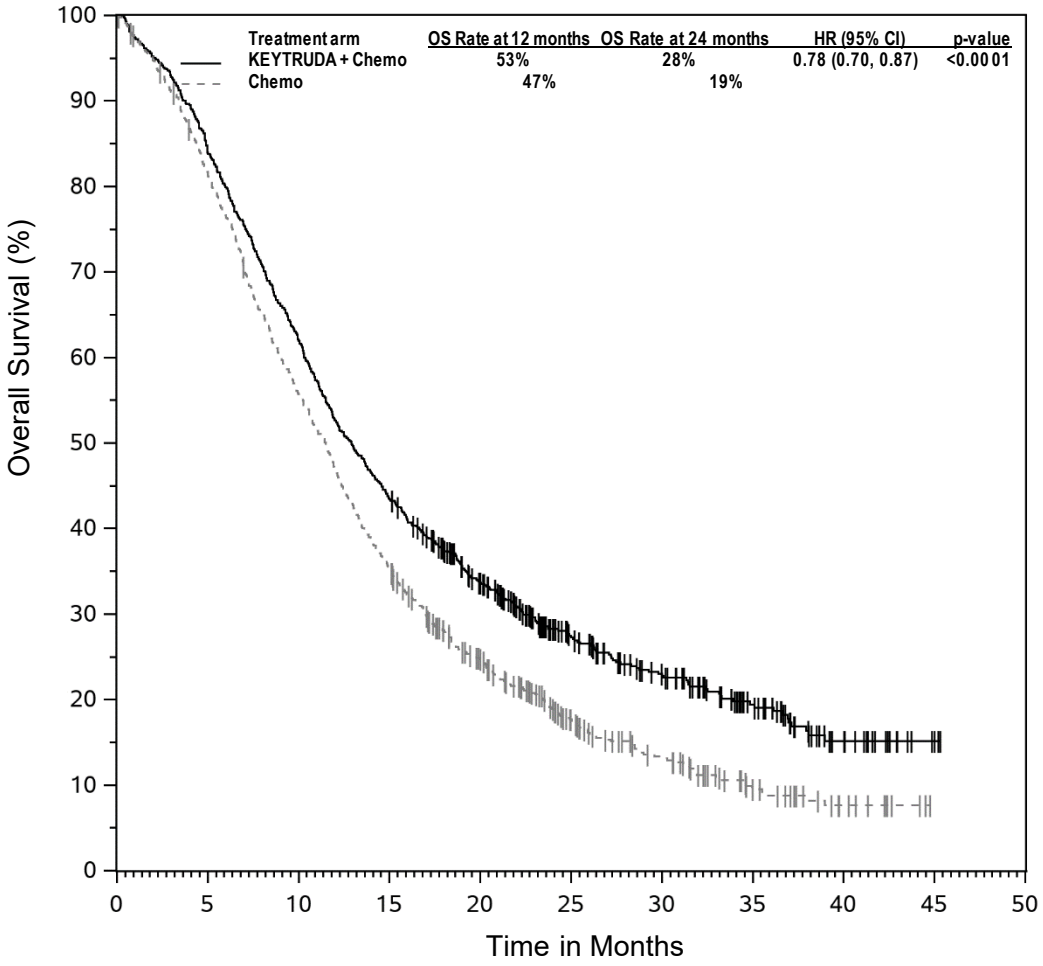
A statistically significant improvement in OS, PFS and ORR was demonstrated in patients randomised to KEYTRUDA in combination with chemotherapy compared with placebo in combination with chemotherapy. Efficacy results are summarised in Table 79.

Table 79: Efficacy Results for KEYNOTE-859

Endpoint	KEYTRUDA 200 mg every 3 weeks FP or CAPOX n=790	Placebo FP or CAPOX n=789
OS		
Number (%) of patients with event	603 (76)	666 (84)
Median in months* (95% CI)	12.9 (11.9,14.0)	11.5 (10.6,12.1)
Hazard ratio† (95% CI)	0.78 (0.70, 0.87)	
p-Value (stratified log-rank)‡	<0.0001	
PFS		
Number (%) of patients with event	572 (72)	608 (77)
Median in months* (95% CI)	6.9 (6.3, 7.2)	5.6 (5.5, 5.7)
Hazard ratio† (95% CI)	0.76 (0.67, 0.85)	
p-Value (stratified log-rank)‡	<0.0001	
Objective Response Rate		
ORR§ (95% CI)	51% (47.7, 54.8)	42% (38.5, 45.5)
Complete response rate	9%	6%
Partial response rate	42%	36%
Difference (95% CI)	9% (4.4, 14.1)	
p-Value¶	0.00009	
Response Duration	n=405	n=331
Median in months (range)	8.0 (1.2+ - 41.5+)	5.7 (1.3+ - 34.7+)
% with duration ≥ 12 months*	39%	26%
% with duration ≥ 24 months*	27%	13%

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

Figure 48: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-859

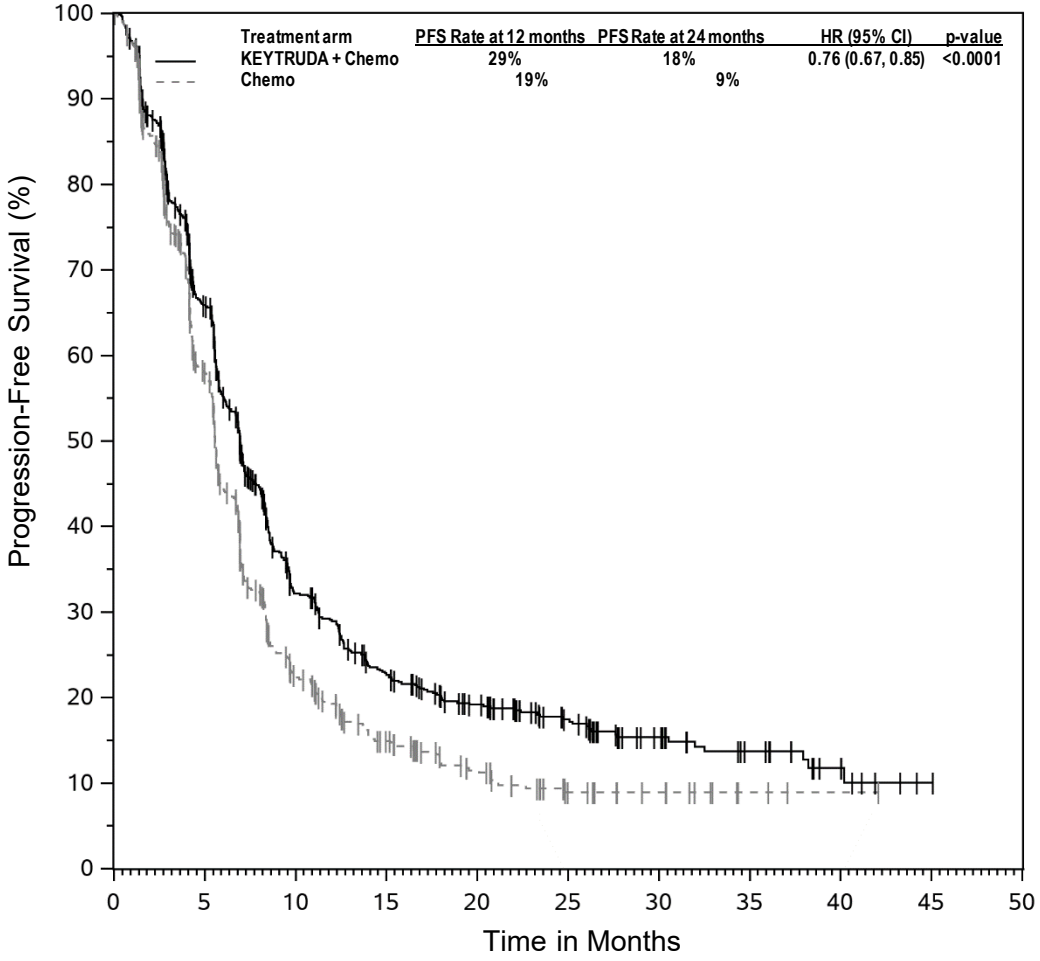


Number at Risk

KEYTRUDA + Chemo	790	663	490	343	240	143	95	55	19	3	0
Chemo	789	636	434	274	169	95	58	26	10	0	0

In an exploratory subgroup analysis in patients with PD-L1 CPS < 1 (n=344): The median OS was 12.7 months (95% CI: 11.4, 15.0) for the KEYTRUDA arm and 12.2 months (95% CI: 9.5, 14.0) for the placebo arm, with a HR of 0.92 (95% CI: 0.73, 1.17); The median PFS was 7.2 months (95% CI: 6.0, 8.5) for the KEYTRUDA arm and 5.8 months (95% CI: 5.4, 6.9) for the placebo arm, with a HR of 0.90 (95% CI: 0.70, 1.15).

Figure 49: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-859



Number at Risk

KEYTRUDA + Chemo	790	461	199	131	94	63	36	22	9	1	0
Chemo	789	407	130	71	41	19	11	3	1	0	0

KEYNOTE-811: In combination with trastuzumab and chemotherapy as first-line treatment for advanced HER2-positive gastric or gastroesophageal junction (GOJ) adenocarcinoma

The efficacy of KEYTRUDA in combination with trastuzumab plus fluoropyrimidine and platinum chemotherapy was investigated in KEYNOTE-811, a multicentre, randomised, double-blind, placebo-controlled trial that enrolled 698 patients with HER2-positive locally advanced unresectable or metastatic gastric or gastroesophageal junction (GOJ) adenocarcinoma regardless of PD-L1 expression status, who had not previously received systemic therapy for metastatic disease. Patients with an autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Randomisation was stratified by PD-L1 expression (CPS ≥1 or <1), chemotherapy regimen (5-FU plus cisplatin [FP] or capecitabine plus oxaliplatin [CAPOX]), and geographic region (Europe/ Israel/ North America/ Australia, Asia or Rest of the World).

All study medications, except oral capecitabine, were administered as an intravenous infusion in 3-week cycles. All patients received trastuzumab (8 mg/kg on first infusion and 6 mg/kg in subsequent cycles), followed by investigator's choice of combination chemotherapy: either cisplatin 80 mg/m^2 for up to 6 cycles and 5-FU 800 mg/m^2/day for 5 days (FP) or oxaliplatin 130 mg/m^2 up to 6-8 cycles and capecitabine 1000 mg/m^2 bid for 14 days (CAPOX). Patients

were randomised (1:1) to additionally receive either KEYTRUDA 200 mg or a matching placebo, given on Day 1 of each cycle prior to trastuzumab and chemotherapy. Treatment continued until radiographic progression of disease, unacceptable toxicity, or for a maximum of 24 months. Tumour status was assessed by BICR using RECIST v1.1 (modified to allow up to 10 target lesions total/5 per organ), with imaging taken at 6 week intervals.

Among the 698 patients randomised in KEYNOTE-811, 594 (85%) had tumours that expressed PD-L1 with a CPS ≥1. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx assay. The population characteristics of these 594 patients were: median age of 63 years (range: 19 to 85), 43% age 65 or older; 80% male; 63% White, 33% Asian, and 0.7 % Black; 42% ECOG PS of 0 and 58% ECOG PS of 1. Ninety-eight percent of patients had metastatic disease (stage IV) and 2% had locally advanced unresectable disease. Ninety-five percent (n=562) had tumours that were not MSI-H, 1% (n=8) had tumours that were MSI-H, and in 4% (n=24) the MSI status was not known. Eighty-five percent of patients received CAPOX.

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

In the overall population, a statistically significant improvement in OS (HR 0.80; 95% CI: 0.67, 0.94; p-Value=0.004), at final analysis, and PFS (HR 0.72; 95% CI: 0.60, 0.87; p-Value=0.0002), at a pre-specified interim analysis, was demonstrated in patients randomised to KEYTRUDA in combination with trastuzumab and chemotherapy compared with placebo in combination with trastuzumab and chemotherapy.

At a pre-specified interim analysis, conducted on the first 264 patients randomised in the overall population (133 patients in the KEYTRUDA arm and 131 in the placebo arm), a statistically significant improvement in the objective response rate (74.4% vs. 51.9%, representing a 22.7% difference; 95% CI: (11.2, 33.7); p-Value <0.0001) was demonstrated in patients randomised to KEYTRUDA in combination with trastuzumab and chemotherapy compared with placebo in combination with trastuzumab and chemotherapy.

A pre-specified subgroup analysis indicated that adding KEYTRUDA to trastuzumab and chemotherapy demonstrated an improvement in OS and PFS in the population of patients whose tumours express PD-L1 with a CPS of ≥1. An exploratory analysis of OS and PFS in the PD-L1 CPS <1 population showed a HR of 1.10 (95% CI: 0.72, 1.68) and 0.99 (95% CI: 0.62 , 1.56), respectively. This indicates that the improvement in the ITT population was primarily attributed to the results observed in the subgroup of patients with PD-L1 CPS ≥1.
Efficacy results at the final analysis for the pre-specified subgroup of patients whose tumours expressed PD-L1 with a CPS ≥1 are summarised in Table 80 and Figure 50 and Figure 51.

Table 80: Efficacy Results for KEYNOTE-811 with PD-L1 Expression CPS ≥1

Endpoint	KEYTRUDA 200 mg every 3 weeks Trastuzumab Fluoropyrimidine and Platinum Chemotherapy n=298	Placebo Trastuzumab Fluoropyrimidine and Platinum Chemotherapy n=296
OS		
Number (%) of patients with event	226 (76%)	244 (82%)
Median in months (95% CI)	20.1 (17.9, 22.9)	15.7 (13.5, 18.5)
Hazard ratio* (95% CI)	0.79 (0.66, 0.95)	
p-Value†	0.0062	
PFS		
Number (%) of patients with event	221 (74%)	226 (76%)
Median in months (95% CI)	10.9 (8.5, 12.5)	7.3 (6.8, 8.4)
Hazard ratio* (95% CI)	0.72 (0.60, 0.87)	
p-Value†	0.0003	
Objective Response Rate		
ORR‡ (95% CI)	73% (68, 78)	58% (53, 64)
Complete response rate	17%	10%
Partial response rate	56%	48%
Difference (95% CI)§	15% (7.1, 22.2)	
p-Value§	<0.0001	
Response Duration	n=218	n=173
Median in months (range)	11.3 (1.1+, 60.8+)	9.5 (1.4+, 60.5+)
% with duration ≥ 6 months¶	75%	68%
% with duration ≥ 12 months¶	49%	42%

* Based on the unstratified Cox proportional hazard model

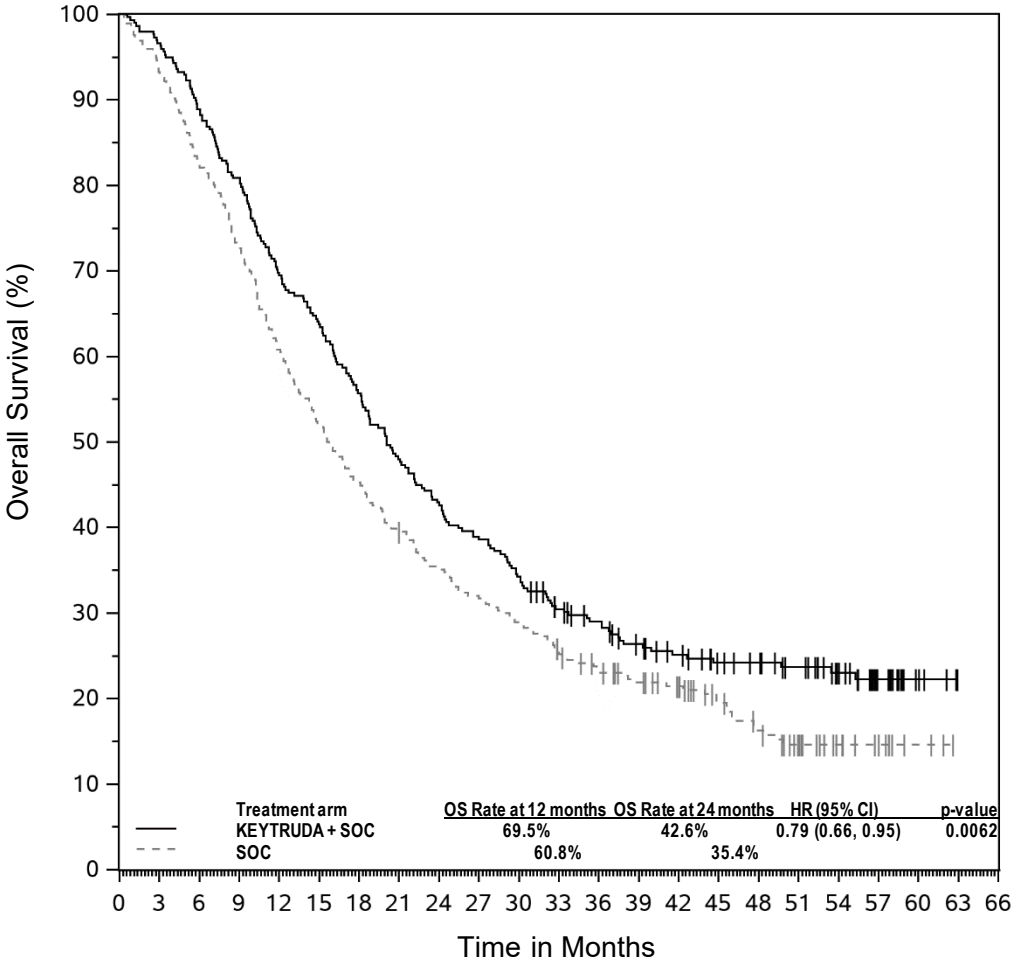
† Based on unstratified log-rank test; p-Value is nominal as no formal test was performed in patients with PD-L1 expression (CPS ≥1)

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

§ Based on unstratified Miettinen and Nurminen method; p-Value is nominal as no formal test was performed in patients with PD-L1 expression (CPS ≥1)

¶ Based on Kaplan-Meier estimation

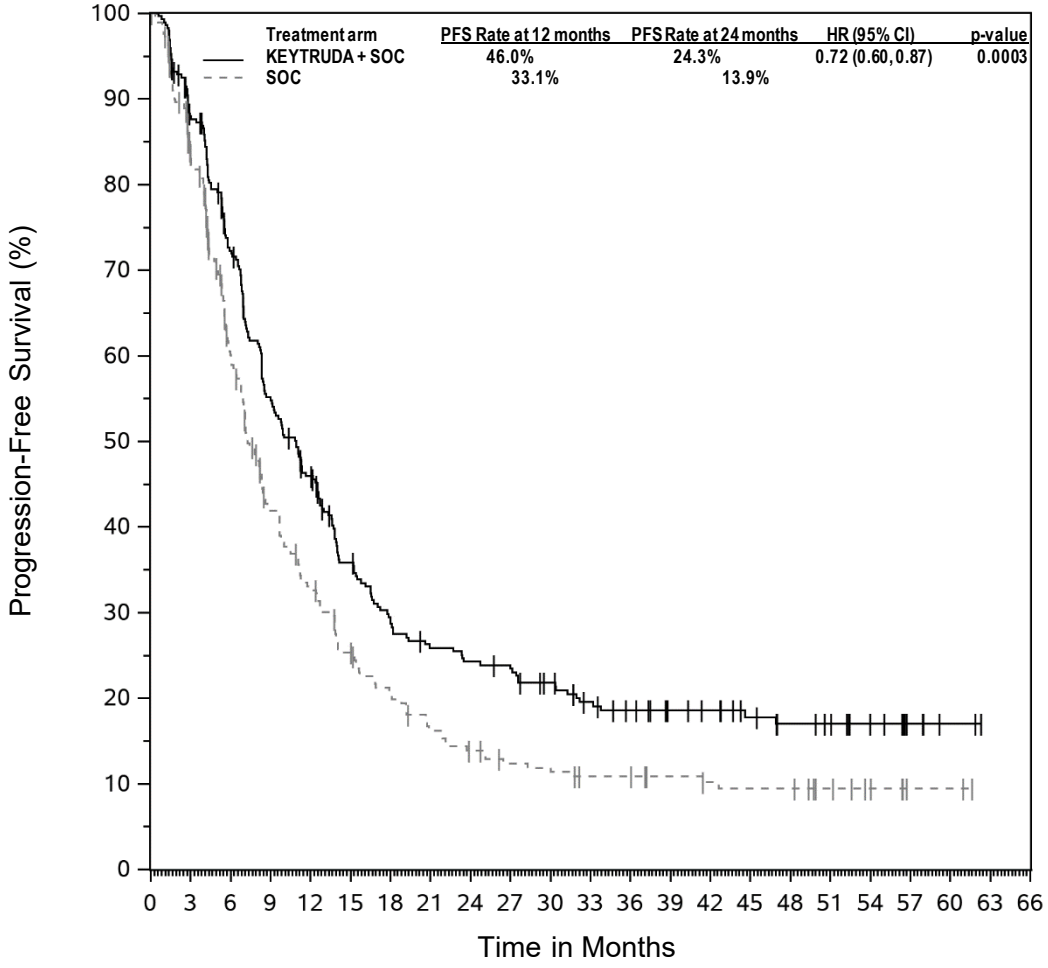
Figure 50: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-811 (CPS ≥1)



Number at Risk																					
KEYTRUDA + SOC	298	288	265	241	207	190	166	143	127	115	102	86	78	67	59	51	48	42	32	18	5	0	0
SOC	296	276	244	215	180	154	135	117	104	93	85	73	63	56	50	38	30	21	13	9	3	0	0

*Based on the pre-specified final analysis

Figure 51: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-811 (CPS ≥1)



*Based on the pre-specified final analysis

Oesophageal Cancer

KEYNOTE-590: First-line treatment of locally advanced unresectable or metastatic oesophageal/gastroesophageal junction cancer

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

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

- KEYTRUDA 200 mg on Day 1 of each three-week cycle in combination with cisplatin 80 mg/m^2 IV on Day 1 of each three-week cycle for up to six cycles and FU 800 mg/m^2 IV per day on Day 1 to Day 5 of each three-week cycle, or per local standard for FU administration, for up to 24 months.
- Placebo on Day 1 of each three-week cycle in combination with cisplatin 80 mg/m^2 IV on Day 1 of each three-week cycle for up to six cycles and FU 800 mg/m^2 IV per day on Day 1 to Day 5 of each three-week cycle, or per local standard for FU administration, for up to 24 months.

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

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

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

Table 81 summarises the key efficacy measures for KEYNOTE-590. The Kaplan-Meier curves for OS and PFS are shown in Figure 52-Figure 57.

Table 81: Efficacy Results in Patients with Locally Advanced Unresectable or Metastatic Oesophageal Cancer in KEYNOTE-590

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

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

Figure 52: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-590

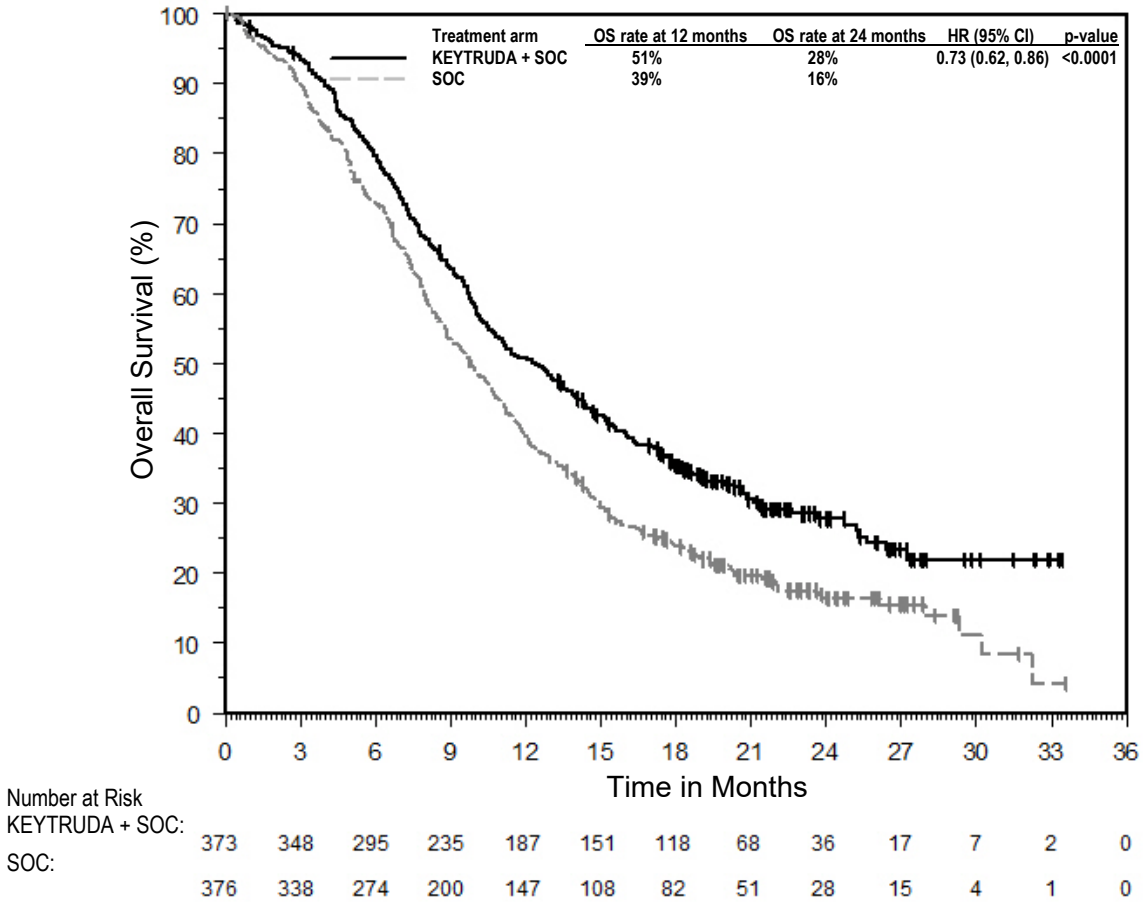


Figure 53: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-590 with PD-L1 expression (CPS ≥ 10)

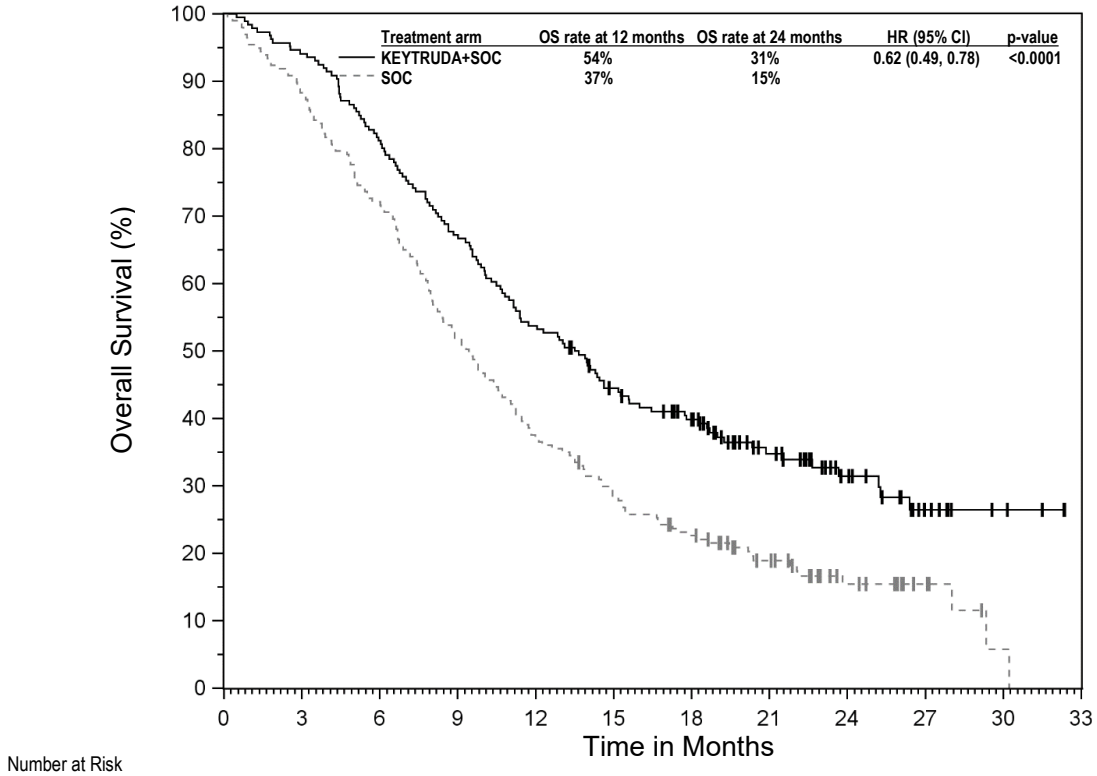
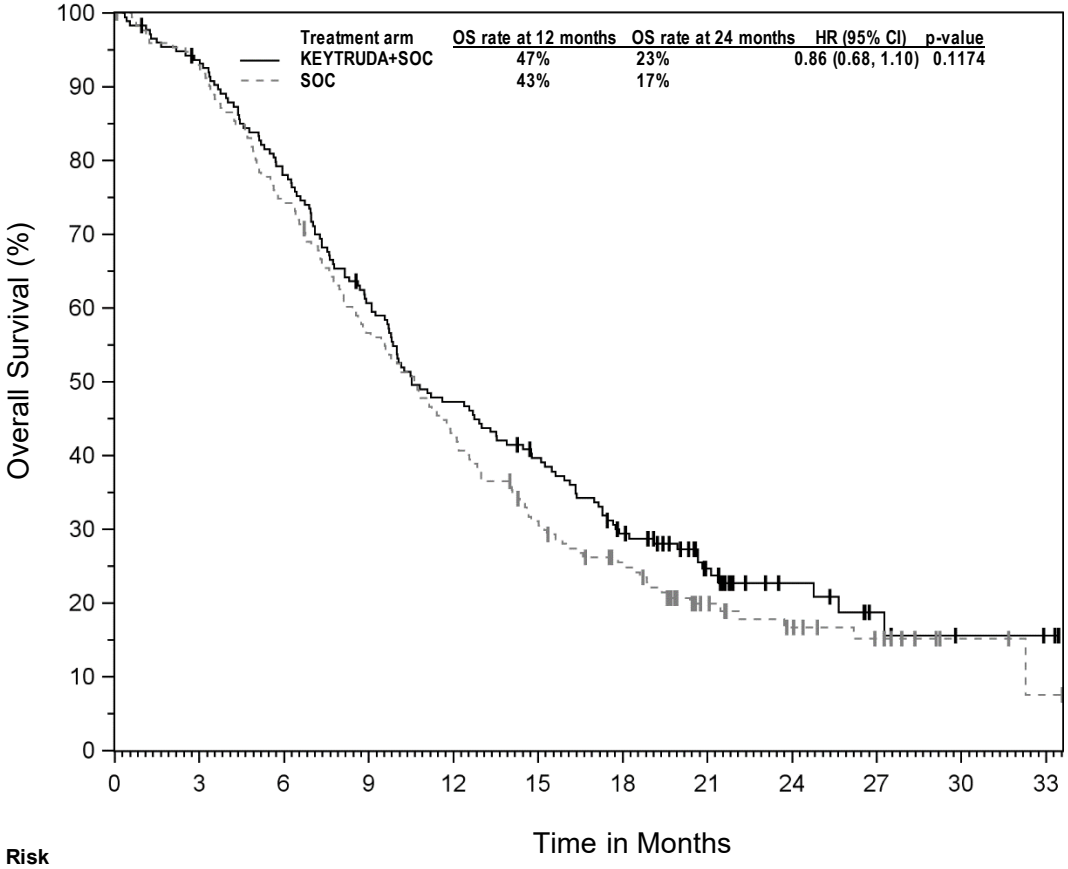


Figure 54: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-590 with PD-L1 expression (CPS < 10)



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

Figure 55: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-590

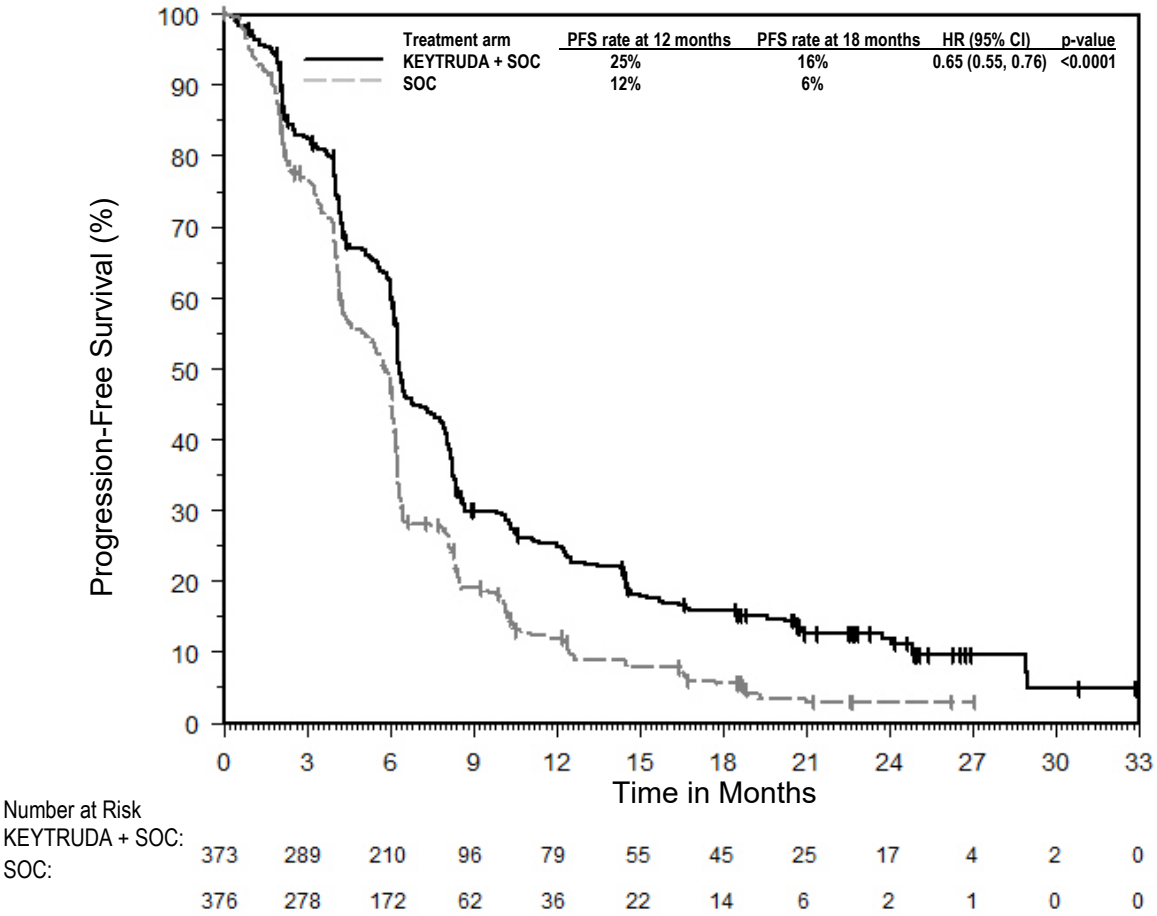
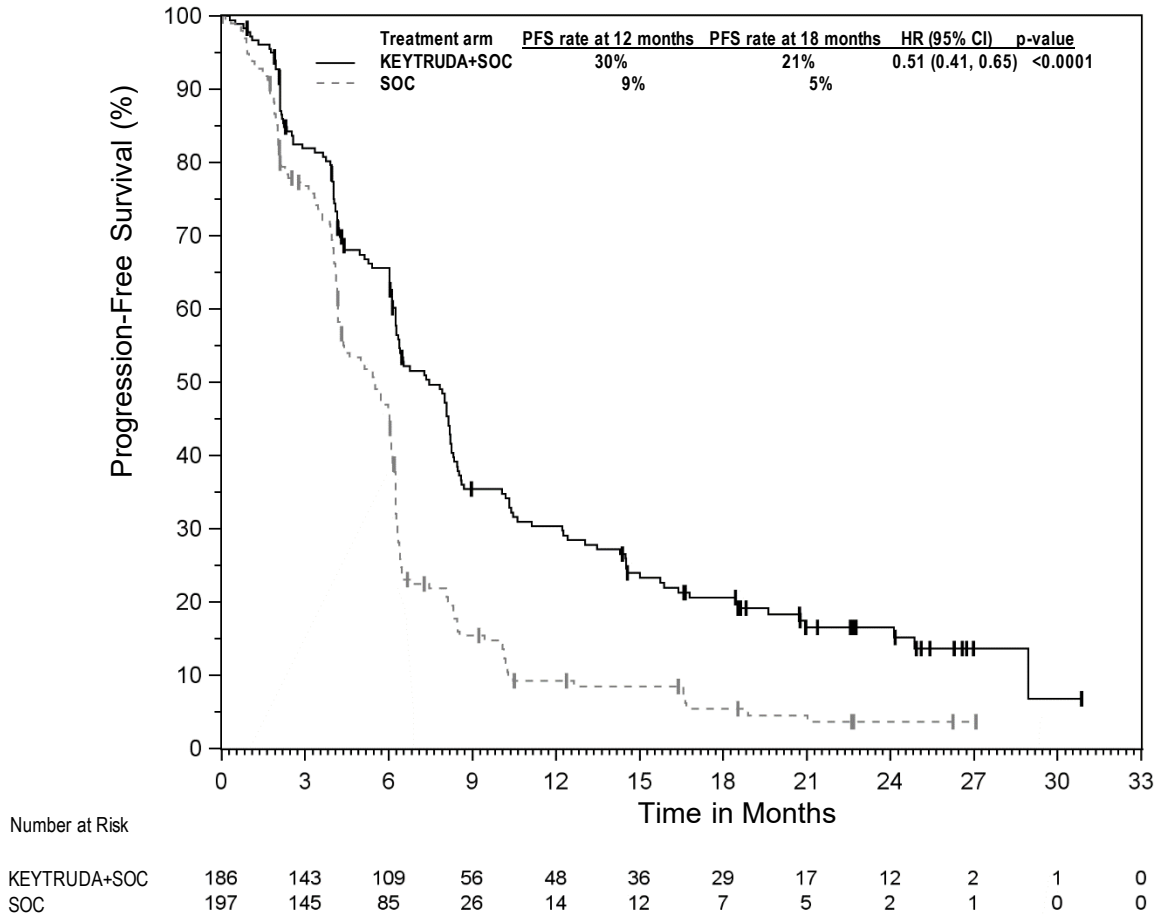


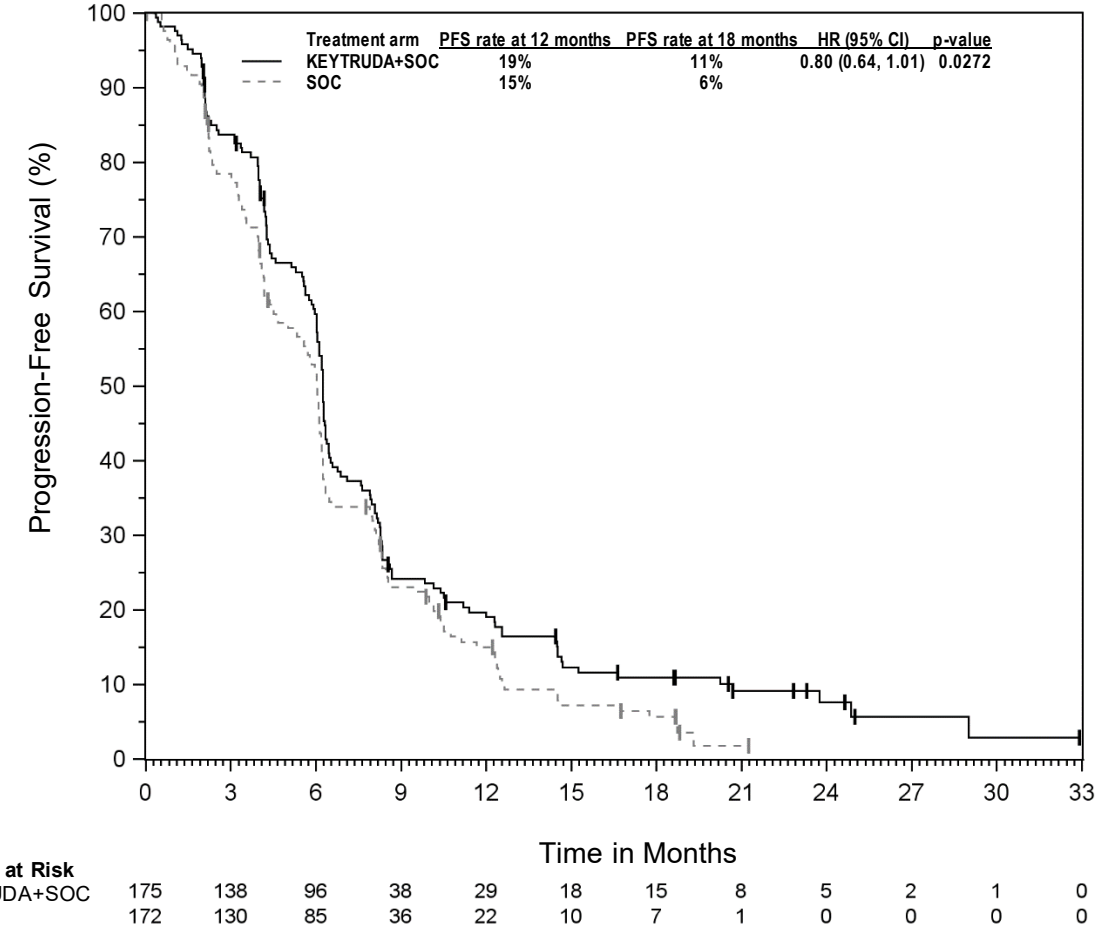
Figure 56: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-590 with PD-L1 expression (CPS ≥ 10)



Number at Risk

KEYTRUDA+SOC	186	143	109	56	48	36	29	17	12	2	1	0
SOC	197	145	85	26	14	12	7	5	2	1	0	0

Figure 57: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-590 with PD-L1 expression (CPS < 10)



Tumour mutational burden-high (TMB-H) cancer

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

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

of 5 target lesions per organ.

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

Efficacy results are summarised in Tables 82 and 83.

Table 82: Efficacy results for patients with TMB-H cancer in KEYNOTE-158

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

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

Table 83: Responses by tumour type (TMB-H)

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

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

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

Triple-negative breast cancer (TNBC)

KEYNOTE-522: Controlled study of neoadjuvant and adjuvant treatment of patients with high-risk early-stage TNBC

The efficacy of KEYTRUDA in combination with carboplatin and paclitaxel followed by doxorubicin or epirubicin and cyclophosphamide, given as a neoadjuvant treatment and continued as monotherapy adjuvant treatment was investigated in Study KEYNOTE-522, a randomised, double-blind, multicentre, placebo-controlled study. The key eligibility criteria for this study were newly diagnosed previously untreated high-risk early-stage TNBC (tumour size >1 cm but ≤2 cm in diameter with nodal involvement or tumour size >2 cm in diameter regardless of nodal involvement), regardless of tumour PD-L1 expression. Patients with active autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible for the study. Randomisation was stratified by nodal status (positive vs. negative), tumour size (T1/T2 vs. T3/T4), and choice of carboplatin (dosed every 3 weeks vs. weekly).

Patients were randomised (2:1) to one of the following treatment arms; all study medications were administered via intravenous infusion.

- **Arm 1:**
  - Four cycles of preoperative KEYTRUDA 200 mg every 3 weeks on Day 1 of cycles 1-4 of treatment regimen in combination with:
    - Carboplatin
      - AUC 5 mg/mL/min every 3 weeks on Day 1 of cycles 1-4 of treatment regimen

        or AUC 1.5 mg/mL/min every week on Day 1, 8, and 15 of cycles 1-4 of treatment regimen **and**
    - Paclitaxel 80 mg/m^2 every week on Day 1, 8, and 15 of cycles 1-4 of treatment regimen
  - Followed by four additional cycles of preoperative KEYTRUDA 200 mg every 3 weeks on Day 1 of cycles 5-8 of treatment regimen in combination with:
    - Doxorubicin 60 mg/m^2 **or** epirubicin 90 mg/m^2 every 3 weeks on Day 1 of cycles 5-8 of treatment regimen **and**
    - Cyclophosphamide 600 mg/m^2 every 3 weeks on Day 1 of cycles 5-8 of treatment regimen
  - Following surgery, 9 cycles of KEYTRUDA 200 mg every 3 weeks were administered.

- **Arm 2:**
  - Four cycles of preoperative placebo every 3 weeks on Day 1 of cycles 1-4 of treatment regimen in combination with:
    - Carboplatin
      - AUC 5 mg/mL/min every 3 weeks on Day 1 of cycles 1-4 of treatment regimen

        or AUC 1.5 mg/mL/min every week on Day 1, 8, and 15 of cycles 1-4 of treatment regimen **and**
    - Paclitaxel 80 mg/m^2 every week on Day 1, 8, and 15 of cycles 1-4 of treatment regimen
  - Followed by four additional cycles of preoperative placebo every 3 weeks on Day 1 of cycles 5-8 of treatment regimen in combination with:

- Doxorubicin 60 mg/m^2 **or** epirubicin 90 mg/m^2 every 3 weeks on Day 1 of cycles 5-8 of treatment regimen **and**
- Cyclophosphamide 600 mg/m^2 every 3 weeks on Day 1 of cycles 5-8 of treatment regimen

- Following surgery, 9 cycles of placebo every 3 weeks were administered.

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

The major efficacy outcome measures were pathological complete response (pCR) rate and event-free survival (EFS). pCR was defined as absence of invasive cancer in the breast and lymph nodes (ypT0/Tis ypN0) and was assessed by the blinded local pathologist at the time of definitive surgery. EFS was defined as the time from randomisation to the first occurrence of any of the following events: progression of disease that precludes definitive surgery, local or distant recurrence, second primary malignancy, or death due to any cause. An additional efficacy outcome measure was OS.

A total of 1174 patients were randomised: 784 patients to the KEYTRUDA arm and 390 patients to the placebo arm. The study population characteristics were: median age of 49 years (range: 22 to 80), 11% age 65 or older; 99.9% female; 64% White, 20% Asian, 5% Black, and 2% American Indian or Alaska Native; 87% ECOG PS of 0 and 13% ECOG PS of 1; 56% were pre-menopausal status and 44% were post-menopausal status; 7% were primary Tumour 1 (T1), 68% T2, 19% T3, and 7% T4; 49% were nodal involvement 0 (N0), 40% N1, 11% N2, and 0.2% N3; 75% of patients were overall stage II and 25% were stage III.

The trial demonstrated a statistically significant improvement in pCR, EFS and OS at pre-specified analyses for patients randomised to KEYTRUDA in combination with chemotherapy followed by KEYTRUDA monotherapy compared with patients randomised to placebo in combination with chemotherapy followed by placebo alone. Efficacy results are summarised in Table 84, Figure 58 and Figure 59.

Table 84: Efficacy Results in Patients with High-Risk Early-Stage TNBC in KEYNOTE-522

Endpoint	KEYTRUDA with chemotherapy/KEYTRUDA	Placebo with chemotherapy/Placebo
pCR (ypT0/Tis ypN0)*, †	**n=669**	**n=333**
Number of patients with pCR	428	182
pCR Rate (%), (95% CI)	64.0 (60.2, 67.6)	54.7 (49.1, 60.1)
Treatment difference (%) estimate (95% CI) ‡, §	9.2 (2.8, 15.6)	
p-Value	0.00221	
EFS¶	**n=784**	**n=390**
Number of patients with event (%)	123 (16%)	93 (24%)
24 month EFS rate (%), (95% CI)	88 (85, 90)	81 (77, 85)
Hazard ratio (95% CI) #	0.63 (0.48, 0.82)	
p-Value Þ	0.00031	
OS##	**n=784**	**n=390**
Number of patients with event (%)	115 (15%)	85 (22%)
36-month OS rate (%), (95% CI)	90 (87, 91)	87 (83, 90)
60-month OS rate (%), (95% CI)	87 (84, 89)	82 (77, 85)
Hazard ratio (95% CI) §	0.66 (0.50, 0.87)	
p-Value Þ	0.00150	

* Based on a pre-specified pCR final analysis (compared to a significance level of 0.0028)

† At the pre-specified pCR interim analysis at IA1 (n=602), the pCR rates were 64.8 (59.9, 69.5) in the KEYTRUDA arm and 51.2 (44.1, 58.3) in the placebo arm. The estimated pCR rate difference was 13.6 (5.4, 21.8).

‡ In a supportive analysis conducted on the complete ITT population (n = 1174) at IA4, the estimated pCR rate difference was 7.5 (95% CI: 1.6,13.4).

§ Based on Miettinen and Nurminen method stratified by nodal status, tumour size, and choice of carboplatin

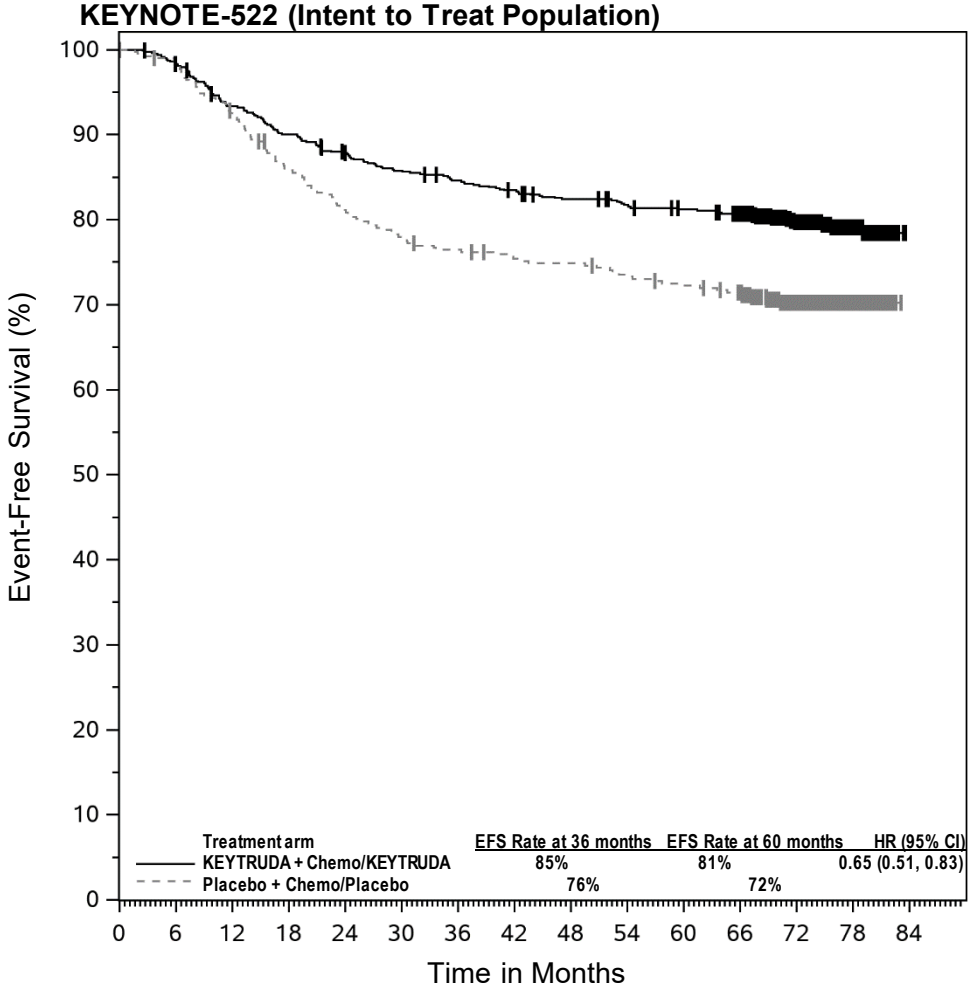
¶ Based on a pre-specified EFS interim analysis (compared to a significance level of 0.0052) with a median follow-up time of 37.8 months (range: 2.7 to 48 months)

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

Þ Based on log-rank test stratified by nodal status, tumour size, and choice of carboplatin

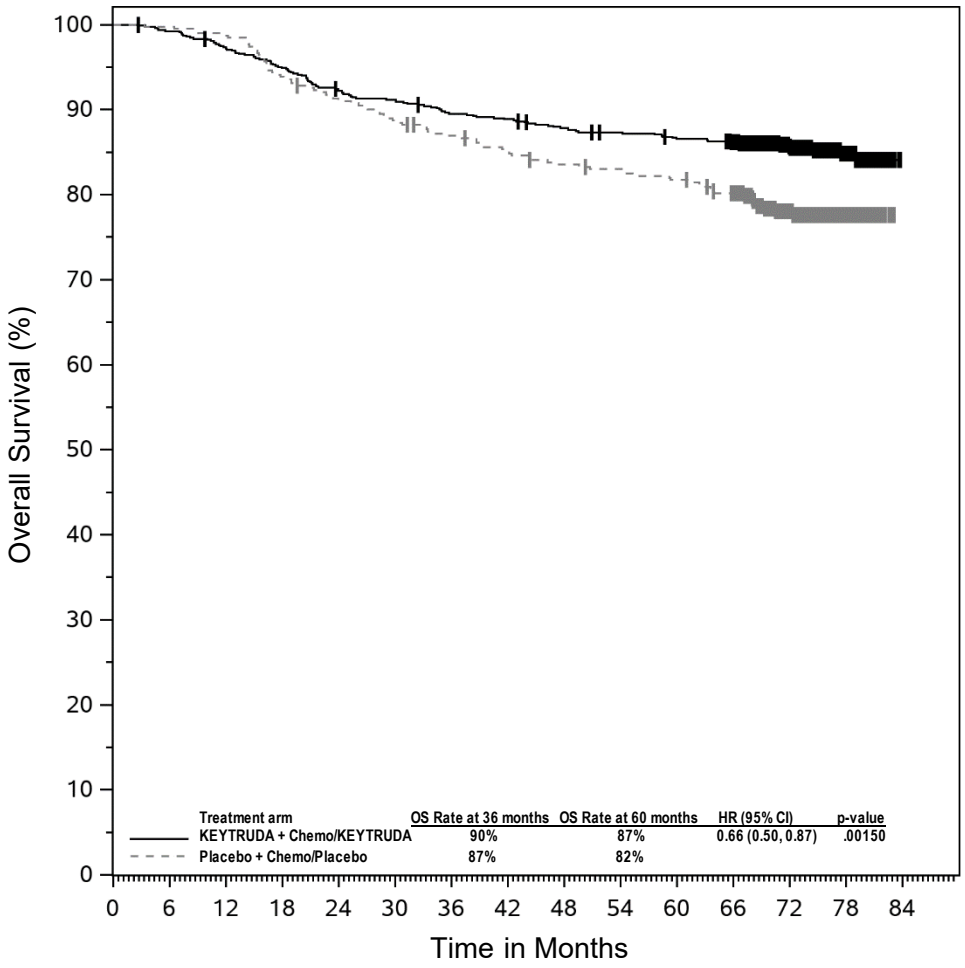
Based on a pre-specified OS interim analysis (compared to a significance level of 0.0050) with a median follow-up time of 73.1 months (range: 2.7 to 83.9 months)

Figure 58: Kaplan-Meier Curve for Event-Free Survival by Treatment Arm in KEYNOTE-522 (Intent to Treat Population)



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

Figure 59: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-522 (Intent to Treat Population)



Number at Risk

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

KEYNOTE-355: Controlled study of combination therapy in patients with locally recurrent unresectable or metastatic TNBC

The efficacy of KEYTRUDA in combination with paclitaxel, nab-paclitaxel, or gemcitabine and carboplatin was investigated in Study KEYNOTE-355, a randomised, double-blind, multicentre, placebo-controlled study. The key eligibility criteria for this study were locally recurrent unresectable or metastatic TNBC, regardless of tumour PD-L1 expression, and which had not been previously treated with chemotherapy in the metastatic setting. Patients with active autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible for the study. Randomisation was stratified by chemotherapy treatment (paclitaxel or nab-paclitaxel vs. gemcitabine and carboplatin), tumour PD-L1 expression (CPS ≥1 vs. CPS <1) based on the PD-L1 IHC 22C3 pharmDx assay, and prior treatment with the same class of chemotherapy in the neoadjuvant setting (yes vs. no).

Patients were randomised (2:1) to one of the following treatment arms; all study medications were administered via intravenous infusion.

- KEYTRUDA 200 mg on Day 1 every 3 weeks in combination with nab-paclitaxel 100 mg/m^2 on Days 1, 8 and 15 every 28 days, or paclitaxel 90 mg/m^2 on Days 1, 8, and 15 every 28 days, or gemcitabine 1000 mg/m^2 and carboplatin AUC 2 mg/mL/min on Days 1 and 8 every 21 days.
- Placebo on Day 1 every 3 weeks in combination with nab-paclitaxel 100 mg/m^2 on Days 1, 8 and 15 every 28 days, or paclitaxel 90 mg/m^2 on Days 1, 8, and 15 every 28 days, or gemcitabine 1000 mg/m^2 and carboplatin AUC 2 mg/mL/min on Days 1 and 8 every 21 days.

Treatment with KEYTRUDA or placebo continued until RECIST 1.1-defined progression of disease as determined by the investigator, unacceptable toxicity, or a maximum of 24 months. Administration of KEYTRUDA was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Assessment of tumour status was performed at Weeks 8, 16, and 24, then every 9 weeks for the first year, and every 12 weeks thereafter.

The major efficacy outcome measures were OS and PFS as assessed by BICR using RECIST 1.1, in patients with tumour PD-L1 expression CPS ≥10. Additional efficacy outcome measures were ORR, DOR, and DCR (stable disease for at least 24 weeks, or complete response, or partial response) in patients with tumour PD-L1 expression CPS ≥10 as assessed by BICR using RECIST 1.1.

A total of 847 patients were randomised: 566 patients to the KEYTRUDA arm and 281 patients to the placebo arm. The study population characteristics were: median age of 53 years (range: 22 to 85), 21% age 65 or older; 100% female; 68% White, 21% Asian, and 4% Black; 60% ECOG PS of 0 and 40% ECOG PS of 1; and 68% were post-menopausal status. Seventy-five percent of the patients had tumour PD-L1 expression defined as CPS ≥1 and 38% had tumour PD-L1 expression CPS ≥10.

In KEYNOTE-355, there was a statistically significant improvement in OS and PFS in patients with tumour PD-L1 expression CPS ≥10 randomised to KEYTRUDA in combination with paclitaxel, nab-paclitaxel, or gemcitabine and carboplatin compared with patients randomised to placebo in combination with paclitaxel, nab-paclitaxel, or gemcitabine and carboplatin.

Efficacy results are summarised in Table 85 and Figure 60 and Figure 61.

Table 85: Efficacy Results in Patients with Locally Recurrent Unresectable or Metastatic TNBC with PD-L1 Expression CPS ≥10 in KEYNOTE-355

Endpoint	KEYTRUDA with chemotherapy* n=220	Placebo with chemotherapy* n=103
OS†		
Number of patients with event (%)	155 (70%)	84 (82%)
Median in months (95% CI)	23.0 (19.0, 26.3)	16.1 (12.6, 18.8)
Hazard ratio‡ (95% CI)	0.73 (0.55, 0.95)	
p-Value§	0.0093	
24-month OS rate (95% CI)	48.2 (41.4, 54.6)	34.0 (25.0, 43.1)
PFS¶,#		
Number of patients with event (%)	136 (62%)	79 (77%)
Median in months (95% CI)	9.7 (7.6, 11.3)	5.6 (5.3, 7.5)
Hazard ratio‡ (95% CI)	0.65 (0.49, 0.86)	
p-Value§	0.0012	
Objective Response Rate†,#		
ORR, (95% CI)	53% (46, 59)	41% (31, 51)
Complete response	17%	14%
Partial response	35%	27%
Response Duration†,#		
Median in months (95% CI)	12.8 (9.9, 25.9)	7.3 (5.5, 15.4)
% with duration ≥6 monthsβ	82%	60%
% with duration ≥12 monthsβ	56%	38%

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

† Based on the pre-specified final analysis

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

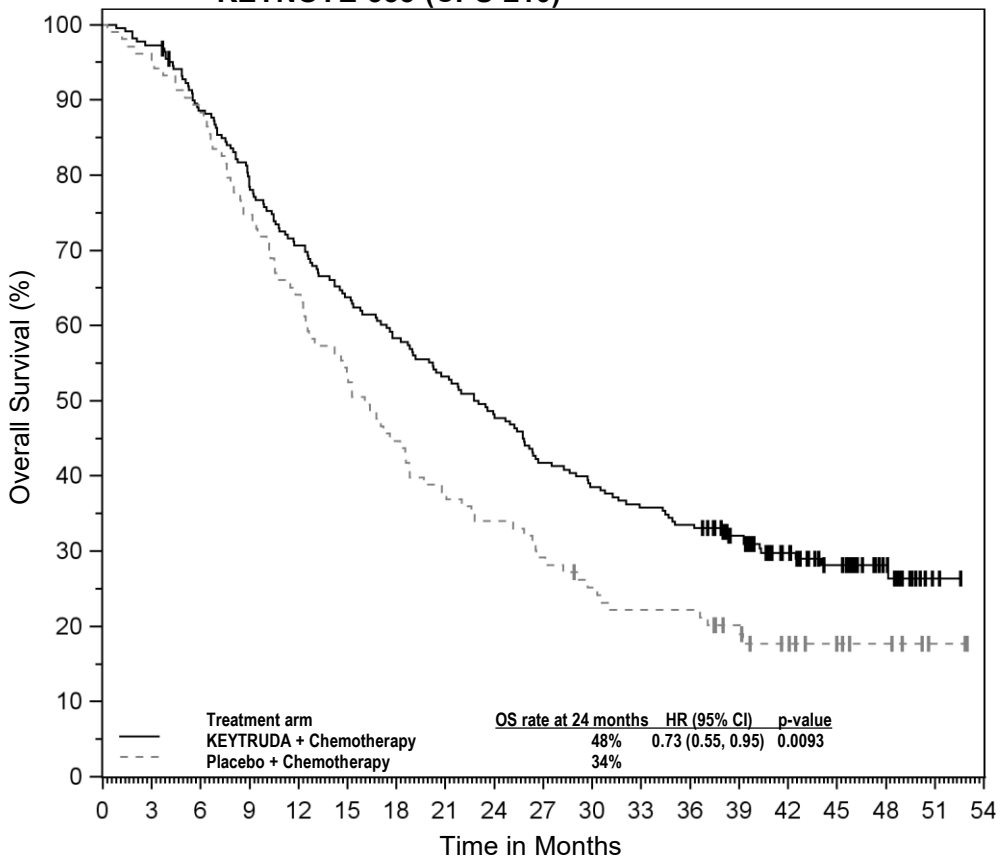
§ One-sided p-Value based on log-rank test stratified by chemotherapy on study (taxane vs. gemcitabine and carboplatin) and prior treatment with same class of chemotherapy in the neoadjuvant setting (yes vs. no)

¶ Assessed by BICR using RECIST 1.1

Based on a pre-specified interim analysis

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

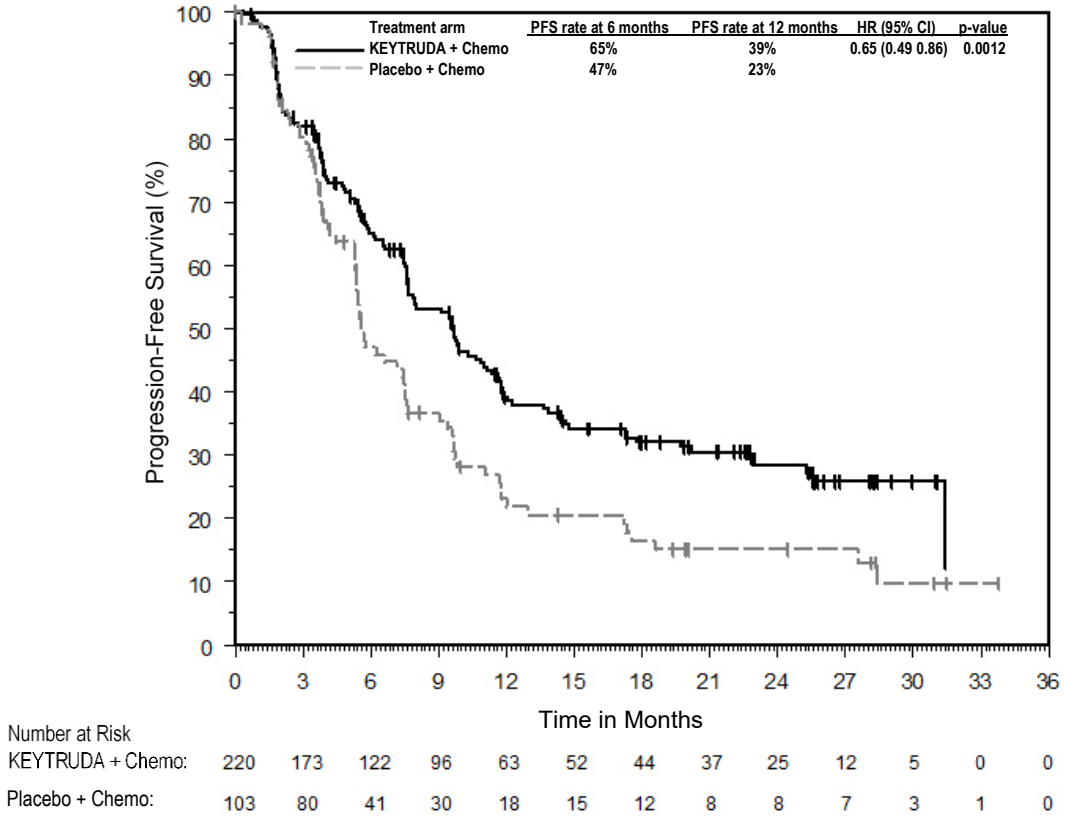
Figure 60: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-355 (CPS ≥10)*



Number at Risk																		
KEYTRUDA + Chemotherapy	220	214	193	171	154	139	127	116	105	91	84	78	73	59	43	31	17	2	0
Placebo + Chemotherapy	103	98	91	77	66	55	46	39	35	30	25	22	22	17	12	8	6	2	0

*Based on the pre-specified final analysis

Figure 61: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-355 (CPS ≥10)



*Based on a pre-specified interim analysis

Ovarian Cancer

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

The efficacy of KEYTRUDA in combination with paclitaxel, with or without bevacizumab, was investigated in KEYNOTE-B96, a multicentre, randomised, double-blind, placebo-controlled trial that enrolled 643 patients with histologically-confirmed epithelial ovarian, fallopian tube, or primary peritoneal carcinoma who had received one or two prior lines of systemic therapy for ovarian carcinoma. Patients must have received at least one line of platinum-based chemotherapy for ovarian cancer with radiographic evidence of disease progression within 6 months after the last dose. Prior therapy with an anti-PD-1/PD-L1 inhibitor, PARP inhibitor, or bevacizumab was permitted. Patients with primary platinum-refractory disease (radiographic progression while receiving or within 28 days of the last dose of first-line platinum-based therapy) were excluded from the trial. Patients with autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Randomisation was stratified by investigator decision to use bevacizumab, geographic region, and PD-L1 status (CPS <1 vs. CPS 1 to <10 vs. CPS ≥10). Patients were randomised (1:1) to one of the two treatment groups:

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

All study medications were administered as an intravenous infusion. KEYTRUDA 400 mg or placebo were administered on Day 1 of each 6-week treatment cycle and paclitaxel 80 mg/m^2 was administered on Days 1, 8, and 15 of each 3-week treatment cycle. The option to use bevacizumab was by investigator choice prior to randomisation. Bevacizumab 10 mg/kg was administered on Day 1 of a 2-week treatment cycle. Treatment with KEYTRUDA continued until RECIST v1.1-defined progression of disease, unacceptable toxicity, or a maximum of 24 months. Administration of KEYTRUDA was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Assessment of tumour status was performed at Week 9 and then every 9 weeks for the first year, followed by every 12 weeks thereafter. The primary efficacy outcome measure was PFS as assessed by investigator according to RECIST v1.1. A secondary efficacy outcome measure was OS.

Of the 643 enrolled patients, 466 patients (72%) had tumours expressing PD-L1 with a CPS ≥1. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx assay. Among these 466 enrolled patients with tumours expressing PD-L1 with a CPS ≥1, 234 patients were randomised to KEYTRUDA in combination with paclitaxel with or without bevacizumab, and 232 patients were randomised to placebo in combination with paclitaxel with or without bevacizumab. The baseline characteristics of the 466 patients were: median age of 62 years (range: 37 to 85), 38% age 65 or older; 67% White, 20% Asian, and 2% Black; 13% Hispanic or Latino; 55% and 44% ECOG performance status of 0 or 1, respectively; 73% received bevacizumab as study treatment; 36% of patients received 1 prior line and 64% received 2 prior lines of therapy; prior systemic therapy includes: 46% with bevacizumab; 39% with a PARP inhibitor, or 3% with an anti-PD-1/PD-L1 inhibitor. The platinum-free interval following the most recent line of therapy was <3 months in 47% of patients, and 3 to 6 months in 53% of patients. Eighty-nine percent had high grade serous and 6% had clear cell histology.

The study demonstrated statistically significant improvement in PFS and OS for patients randomised to KEYTRUDA in combination with paclitaxel with or without bevacizumab compared to placebo in combination with paclitaxel with or without bevacizumab in patients whose tumours expressed PD-L1 CPS ≥1.

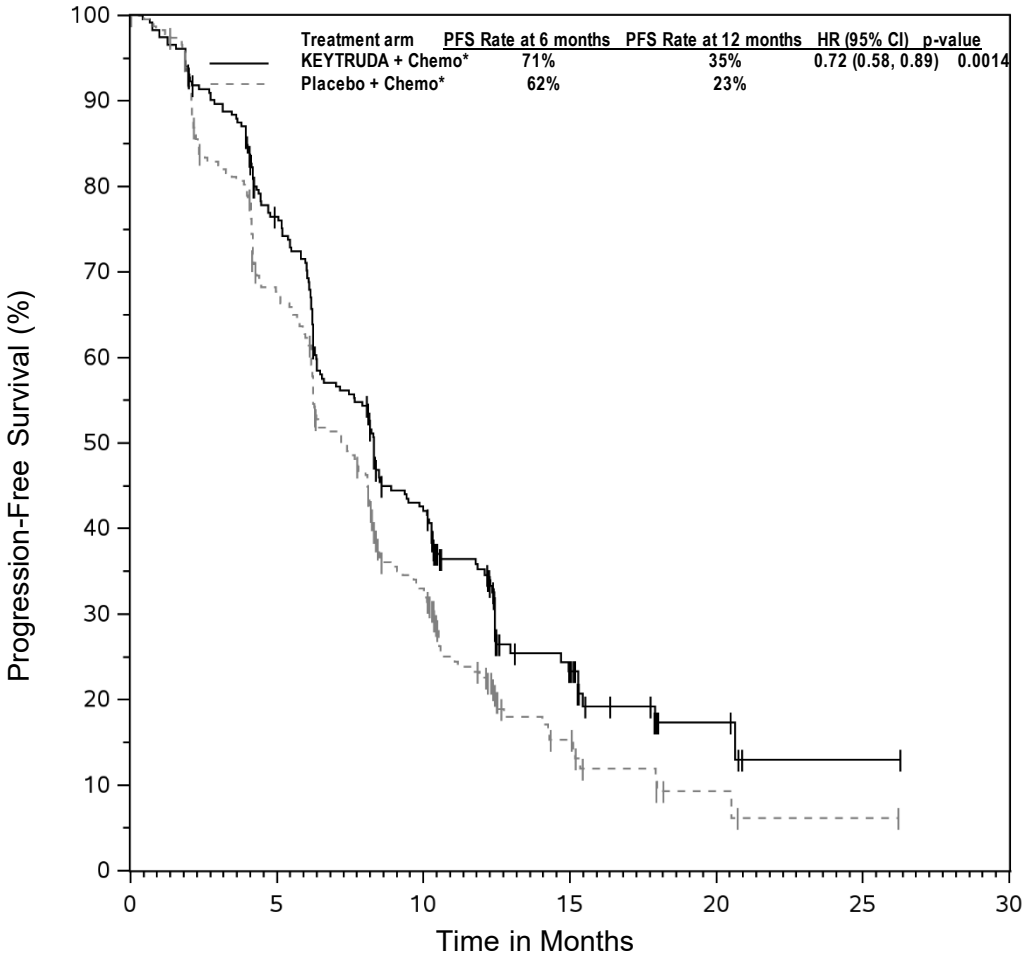
Efficacy results are summarised in Table 86 and Figure 62 and Figure 63.

Table 86: Efficacy Results in Patients with Ovarian Cancer with PD-L1 Expression CPS ≥1

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

* Based on pre-specified interim analysis with a median follow-up time of 12 months (range: 0.5 to 27 months)
† Based on stratified log-rank test (p-Value [one-sided] is compared to an alpha boundary of 0.0116)
‡ Based on pre-specified interim analysis with a median follow-up time of 15.8 months (range: 0.5 to 38 months)
§ Based on stratified log-rank test (p-Value [one-sided] is compared to an alpha boundary of 0.0083)

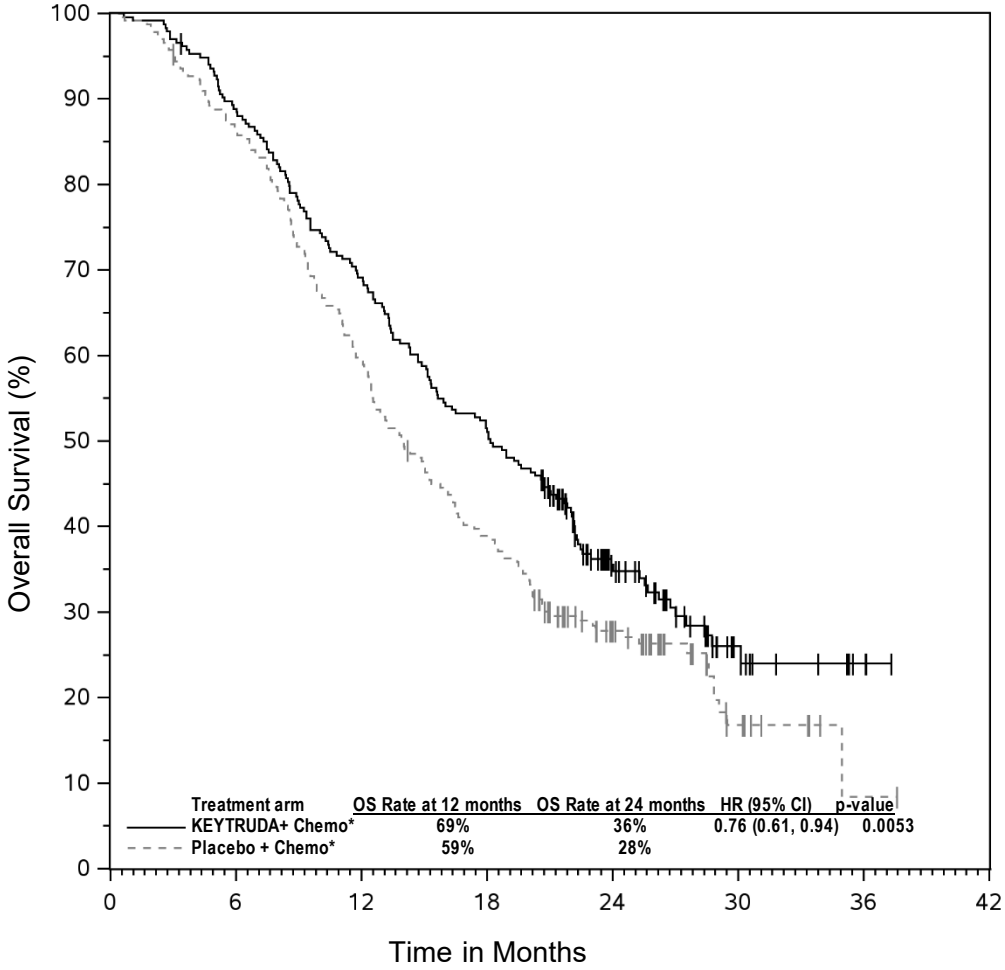
Figure 62: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-B96 (CPS ≥1)



Number at Risk							
KEYTRUDA + Chemo*	234	170	87	21	5	1	0
Placebo + Chemo*	232	150	64	16	3	1	0

*Chemotherapy (paclitaxel) with or without bevacizumab

Figure 63: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-B96 (CPS ≥1)



Number at Risk

KEYTRUDA+ Chemo*	234	207	161	120	49	13	3	0
Placebo + Chemo*	232	200	137	89	41	10	1	0

*Chemotherapy (paclitaxel) with or without bevacizumab

Paediatric population

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

Immunogenicity

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

of an altered pharmacokinetic or safety profile with anti-pembrolizumab binding antibody development.

5.2 PHARMACOKINETIC PROPERTIES

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

Absorption

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

Distribution

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

Metabolism

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

Excretion

Pembrolizumab clearance (CV%) is approximately 23% lower [geometric mean, 195 mL/day (40%)] after achieving maximal change at steady state compared with the first dose (252 mL/day [CV%: 37%]); this decrease in clearance with time is not considered clinically important. The geometric mean value (CV%) for the terminal half-life ($t_{½}$) 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 dilution of the medicinal product, see Section 4.2 DOSE AND METHOD OF ADMINISTRATION.

6.5 NATURE AND CONTENTS OF CONTAINER

Carton of 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

25 August 2026

Summary table of changes

Section changed	Summary of new information
4.2	Update to the storage conditions after reconstitution.

RCN: 000027014-AU

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