PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

KEYTRUDA®

pembrolizumab

powder for solution for infusion 50 mg
solution for infusion 100 mg/4 mL vial

Antineoplastic agent, monoclonal antibody

KEYTRUDA® has been issued marketing authorization **with conditions**, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for KEYTRUDA®, please refer to Health Canada's Notice of Compliance with conditions – drug products website: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php

KEYTRUDA® is indicated for the treatment of:

- Adult and pediatric patients with refractory or relapsed classical Hodgkin Lymphoma (cHL), as monotherapy, who have failed autologous stem cell transplant (ASCT) or who are not candidates for multi-agent salvage chemotherapy and ASCT.

- Adult and pediatric patients with refractory Primary Mediastinal B-cell Lymphoma (PMBCL) or who have relapsed after 2 or more lines of therapy, as monotherapy.

- Adult patients with locally advanced unresectable or metastatic urothelial carcinoma, as monotherapy, who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by a validated test, or in adults who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.

- Adult 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.

- Adult patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)
  - colorectal cancer whose tumours have progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, as monotherapy, or
  - endometrial cancer whose tumours have progressed following prior therapy and who have no satisfactory alternative treatment options, as monotherapy.

- Adult patients in combination with lenvatinib with advanced endometrial carcinoma that is not microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior platinum-based systemic therapy, and are not candidates for curative surgery or radiation.

KEYTRUDA® has been issued marketing authorization **without conditions** for:

- Treatment of adult patients with unresectable or metastatic melanoma who have not received prior treatment with ipilimumab. Subjects with BRAF V600 mutant melanoma may have received prior BRAF inhibitor therapy.

- Treatment of adult patients with unresectable or metastatic melanoma and disease progression following ipilimumab therapy and, if BRAF V600 mutation positive, following a BRAF or MEK inhibitor.

- Adjuvant treatment of adult patients with Stage III melanoma with lymph node involvement who have undergone complete resection.

- First-line treatment, as monotherapy, of adult patients with metastatic non-small cell lung carcinoma (NSCLC) or stage III disease where patients are not candidates for surgical resection or definitive chemoradiation, expressing PD-L1 [Tumour Proportion Score (TPS ≥1%)] as determined by a validated test, with no EGFR or ALK genomic tumour aberrations.

- Treatment of adult patients with metastatic non-squamous NSCLC in combination with pemetrexed and platinum chemotherapy, with no EGFR or ALK genomic tumour aberrations, and no prior systemic chemotherapy treatment for metastatic NSCLC.

- Treatment of adult patients with metastatic squamous NSCLC in combination with carboplatin and either paclitaxel or nab-paclitaxel, with no prior systemic chemotherapy treatment for metastatic NSCLC.

- Treatment of adult patients with metastatic NSCLC as monotherapy, whose tumours express PD-L1 [(Tumour Proportion Score (TPS) ≥ 1%)] as determined by a validated test and who have disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have received authorized therapy for these aberrations prior to receiving KEYTRUDA®.

- Treatment of adult patients with locally advanced or metastatic urothelial carcinoma, as monotherapy, who have disease progression during or following platinum-containing chemotherapy or within 12 months of completing neoadjuvant or adjuvant platinum-containing chemotherapy.

- Treatment of adult patients with advanced or metastatic renal cell carcinoma (RCC) in combination with axitinib, with no prior systemic therapy for metastatic RCC.

- First-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) as monotherapy, in adult patients whose tumours have PD-L1 expression (Combined Positive Score [CPS] ≥ 1) as determined by a validated test.

- First-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) in combination with platinum and fluorouracil (FU) chemotherapy, in adult patients.

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Submission Control No: 239505

This product has been authorized under the Notice of Compliance with Conditions (NOC/c) for one or all of its indicated uses.

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market authorization granted to a product on the basis of **promising** evidence of clinical effectiveness following review of the submission by Health Canada.

Products authorized under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

What will be different about this Product Monograph?
The following Product Monograph will contain boxed text at the beginning of each major section clearly stating the nature of the market authorization. Sections for which NOC/c status holds particular significance will be identified in the left margin by the symbol NOC/c. These sections may include, but are not limited to, the following:
- Indications;
- Action and Clinical Pharmacology;
- Warnings and Precautions;
- Adverse Reactions;
- Dosage and Administration; and
- Clinical Trials.

Adverse Reaction Reporting and Re-Issuance of the Product Monograph
Health care providers are encouraged to report Adverse Reactions associated with normal use of these and all drug products to Health Canada's Canada Vigilance Program at 1-866-234-2345. The Product Monograph will be re-issued in the event of serious safety concerns previously unidentified or at such time as the sponsor provides the additional data in support of the product's clinical benefit. Once the latter has occurred, and in accordance with the NOC/c policy, the conditions associated with market authorization will be removed.

RECENT MAJOR LABEL CHANGES

Indications (1)	01/2021
Dosage and Administration, Recommended Dose and Dosage Adjustment (4.2)	01/2021

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PART I: HEALTH PROFESSIONAL INFORMATION

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- Adult and pediatric patients with refractory Primary Mediastinal B-cell Lymphoma (PMBCL) or who have relapsed after 2 or more lines of therapy, as monotherapy.

- Adult patients with locally advanced unresectable or metastatic urothelial carcinoma, as monotherapy, who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 [Combined Positive Score (CPS) ≥ 10] as determined by a validated test, or in adults who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.

- Adult 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.

- Adult patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)
    - colorectal cancer whose tumours have progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, as monotherapy, or
    - endometrial cancer whose tumours have progressed following prior therapy and who have no satisfactory alternative treatment options, as monotherapy.

- Adult patients in combination with lenvatinib with advanced endometrial carcinoma that is not microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior platinum-based systemic therapy, and are not candidates for curative surgery or radiation.

KEYTRUDA® has been issued marketing authorization **without conditions** for:

- Treatment of adult patients with unresectable or metastatic melanoma who have not received prior treatment with ipilimumab. Subjects with BRAF V600 mutant melanoma may have received prior BRAF inhibitor therapy.

- Treatment of adult patients with unresectable or metastatic melanoma and disease progression following ipilimumab therapy and, if BRAF V600 mutation positive, following a BRAF or MEK inhibitor.

- Adjuvant treatment of adult patients with Stage III melanoma with lymph node involvement who have undergone complete resection.

- First-line treatment, as monotherapy, of adult patients with metastatic non-small cell lung carcinoma (NSCLC) or stage III disease where patients are not candidates for surgical resection or definitive chemoradiation, expressing PD-L1 [Tumour Proportion Score (TPS ≥1%)] as determined by a validated test, with no EGFR or ALK genomic tumour aberrations.

- Treatment of adult patients with metastatic non-squamous NSCLC in combination with pemetrexed and platinum chemotherapy, with no EGFR or ALK genomic tumour aberrations, and no prior systemic chemotherapy treatment for metastatic NSCLC.

- Treatment of adult patients with metastatic squamous NSCLC in combination with carboplatin and either paclitaxel or nab-paclitaxel, with no prior systemic chemotherapy treatment for metastatic NSCLC.

- Treatment of adult patients with metastatic NSCLC as monotherapy, whose tumours express PD-L1 [(Tumour Proportion Score (TPS) ≥ 1%)] as determined by a validated test and who have disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have received authorized therapy for these aberrations prior to receiving KEYTRUDA®.

- Treatment of adult patients with locally advanced or metastatic urothelial carcinoma, as monotherapy who have disease progression during or following platinum-containing chemotherapy or within 12 months of completing neoadjuvant or adjuvant platinum-containing chemotherapy.

- Treatment of adult patients with advanced or metastatic renal cell carcinoma (RCC) in combination with axitinib, with no prior systemic therapy for metastatic RCC.

- First-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) as monotherapy, in adult patients whose tumours have PD-L1 expression (Combined Positive Score [CPS) ≥ 1] as determined by a validated test.
- First-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) in combination with platinum and fluorouracil (FU) chemotherapy, in adult patients.

1 INDICATIONS

Melanoma

KEYTRUDA® is indicated for the treatment of adult patients with unresectable or metastatic melanoma who have not received prior treatment with ipilimumab. Subjects with BRAF V600 mutant melanoma may have received prior BRAF inhibitor therapy.

KEYTRUDA® is indicated for the treatment of adult patients with unresectable or metastatic melanoma and disease progression following ipilimumab therapy and, if BRAF V600 mutation positive, following a BRAF or MEK inhibitor.

KEYTRUDA® is indicated for the adjuvant treatment of adult patients with Stage III melanoma with lymph node involvement who have undergone complete resection.

Non-Small Cell Lung Carcinoma

KEYTRUDA® as monotherapy is indicated for the first-line treatment of adult patients with metastatic non-small cell lung carcinoma (NSCLC) or stage III disease where patients are not candidates for surgical resection or definitive chemoradiation, expressing PD-L1 [Tumour Proportion Score (TPS) ≥1%] as determined by a validated test, with no EGFR or ALK genomic tumour aberrations.

A positive association was observed between the level of PD-L1 expression and the magnitude of the treatment benefit (See CLINICAL TRIALS).

KEYTRUDA®, in combination with pemetrexed and platinum chemotherapy, is indicated for the treatment of adult patients with metastatic non-squamous NSCLC with no EGFR or ALK genomic tumour aberrations, and no prior systemic chemotherapy treatment for metastatic NSCLC.

KEYTRUDA®, in combination with carboplatin and either paclitaxel or nab-paclitaxel, is indicated for the treatment of adult patients with metastatic squamous NSCLC with no prior systemic chemotherapy treatment for metastatic NSCLC.

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

NOC/c **Hodgkin Lymphoma**
KEYTRUDA® as monotherapy is indicated for the treatment of adult and pediatric patients with refractory or relapsed classical Hodgkin Lymphoma (cHL) who have failed autologous stem cell transplant (ASCT), or who are not candidates for multi-agent salvage chemotherapy and ASCT. An improvement in overall survival has not yet been established.

NOC/c **Primary Mediastinal B-cell Lymphoma**
KEYTRUDA® as monotherapy is indicated for the treatment of adult and pediatric patients with refractory primary mediastinal B-cell lymphoma (PMBCL), or who have relapsed after 2 or more lines of therapy. An improvement in survival or disease-related symptoms has not been established.

Urothelial Carcinoma
KEYTRUDA® is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma as monotherapy who have disease progression during or following platinum-containing chemotherapy or within 12 months of completing neoadjuvant or adjuvant platinum-containing chemotherapy.

NOC/c KEYTRUDA® is indicated for the treatment of adult patients with locally advanced unresectable or metastatic urothelial carcinoma, as monotherapy who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by a validated test, or in adults who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status. An improvement in survival or disease-related symptoms has not been established.

NOC/c KEYTRUDA® is indicated for the treatment of adult 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.

- The indication is authorized based on tumour complete response rate and durability of response (See CLINICAL TRIALS).

Renal Cell Carcinoma
KEYTRUDA®, in combination with axitinib, is indicated for the treatment of adult patients with advanced or metastatic renal cell carcinoma (RCC) with no prior systemic therapy for metastatic RCC (See CLINICAL TRIALS).

NOC/c Microsatellite Instability-High Cancer (MSI-H)

KEYTRUDA® is indicated as monotherapy for the treatment of adult patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) for:

- colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan; or
- endometrial cancer that has progressed following prior therapy and who have no satisfactory alternative treatment options.

NOC/c Endometrial Carcinoma

KEYTRUDA®, in combination with lenvatinib, is indicated for the treatment of adult patients with advanced endometrial carcinoma that is not microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior platinum-based systemic therapy, and are not candidates for curative surgery or radiation.

The indication is authorized based on tumour response rate and durability of response. An improvement in survival or disease-related symptoms has not been established (See CLINICAL TRIALS).

Head and Neck Cancer

KEYTRUDA® is indicated for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) as monotherapy, in adult patients whose tumours have PD-L1 expression (Combined Positive Score [CPS] ≥ 1) as determined by a validated test.

KEYTRUDA® is indicated for the first-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) in combination with platinum and fluorouracil (FU) chemotherapy, in adult patients.

1.1 Pediatrics

NOC/c Pediatrics (<18 years of age): KEYTRUDA® as monotherapy is indicated for the treatment of pediatric patients with:

- relapsed or refractory cHL who have failed ASCT, or who are not candidates for multi-agent salvage chemotherapy and ASCT.
- refractory PMBCL, or pediatric PMBCL patients whose disease has relapsed after 2 or more prior lines of therapy

(See WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS & DOSAGE AND ADMINISTRATION). The safety and efficacy of KEYTRUDA® has not been established for pediatric patients with conditions other than relapsed or refractory cHL or relapsed or refractory PMBCL.

1.2 Geriatrics

Geriatrics (> 65 years of age): No overall differences in safety or efficacy were reported between elderly patients (65 years and over) and younger patients (less than 65 years). Limited safety and efficacy information is available for KEYTRUDA® in cHL ≥ 65 years of age (n=20) (See WARNINGS AND PRECAUTIONS; Geriatrics).

NOC/c

2 CONTRAINDICATIONS

KEYTRUDA® is contraindicated in patients who have experienced a severe hypersensitivity reaction (See WARNINGS AND PRECAUTIONS) to this drug or to any ingredient in the formulation or component of the container closure system. For a complete listing, See Dosage Forms, Strengths, Composition and Packaging.

NOC/c

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Patient Selection

For treatment of Non-Small Cell Lung Carcinoma as Monotherapy and Urothelial Carcinoma

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

- metastatic NSCLC or stage III disease where patients are not candidates for surgical resection or definitive chemoradiation, using the Tumour Proportion Score (TPS) (See CLINICAL TRIALS, NSCLC); or
- locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy, using the Combined Positive Score (CPS). CPS is the number of PD-L1 staining cells (tumour cells, lymphocytes, macrophages) divided by the total number of viable tumour cells, multiplied by 100 (See CLINICAL TRIALS, Urothelial Carcinoma).

A test authorized by Health Canada which is equivalent to that used in clinical trials should be required (See CLINICAL TRIALS).

Colorectal cancer or endometrial cancer that is MSI-H or dMMR and endometrial cancer that is not MSI-H or dMMR.

Patients should be selected for treatment based on MSI-H or dMMR tumour status as determined by an accredited laboratory using validated testing methods (See CLINICAL TRIALS).

4.2 Recommended Dose and Dosage Adjustment

Recommended Dosage for Unresectable or Metastatic Melanoma

The current recommended dose of KEYTRUDA® is a 200 mg fixed dose administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity. It is expected that the patient will continue to experience a similar safety and efficacy profile on this new regimen as they have had on the previous one of 2 mg/kg Q3W.

Recommended Dosage for Adjuvant Treatment of Melanoma

The recommended dose of KEYTRUDA® is a 200 mg fixed dose administered as an intravenous infusion over 30 minutes every 3 weeks for up to one year or until disease recurrence or unacceptable toxicity.

Recommended Dosage for – Previously Untreated NSCLC as Monotherapy or in Combination with Chemotherapy
The recommended dose of KEYTRUDA® is a 200 mg fixed dose administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity or up to 24 months in patients without disease progression.

When administering KEYTRUDA® as part of a combination with pemetrexed and platinum chemotherapy, KEYTRUDA® should be administered first. See also the Product Monographs for pemetrexed and the selected platinum chemotherapy.

Recommended Dosage for NSCLC – Previously Treated
The current recommended dose of KEYTRUDA® is a 200 mg fixed dose administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity. It is expected that the patient will continue to experience a similar safety and efficacy profile on this new regimen as they have had on the previous one of 2 mg/kg Q3W.

NOC/c **Recommended Dosage for Hodgkin Lymphoma**
The recommended dose of KEYTRUDA® administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression:

- in adult patients is 200 mg; and
- in pediatric patients is 2 mg/kg (up to a maximum of 200 mg).

NOC/c **Recommended Dosage for PMBCL**
The recommended dose of KEYTRUDA® administered as an intravenous infusion over 30 minutes every 3 weeks:

- in adult patients is 200 mg; and
- in pediatric patients is 2 mg/kg (up to a maximum of 200 mg).

Recommended Dosage for Urothelial Carcinoma – Previously Treated
The recommended dose of KEYTRUDA® is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

NOC/c **Recommended Dosage for Urothelial Carcinoma – Not Eligible for Cisplatin-Containing Chemotherapy**
The recommended dose of KEYTRUDA® is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity or up to 24 months in patients without disease progression.

NOC/c **Recommended Dosage for BCG-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC)**
The recommended dose of KEYTRUDA® is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity or up to 24 months or 35 doses, whichever is longer, in patients without disease progression.

NOC/c **Recommended Dosage for MSI-H colorectal or endometrial cancer patients**
The recommended dose of KEYTRUDA® for adult patients is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

NOC/c **Recommended Dosage for Endometrial Carcinoma (not MSI-H or dMMR)**

For adult patients with endometrial carcinoma that is not MSI-H or dMMR, the recommended dosing is:

- KEYTRUDA® – 200 mg administered as an intravenous infusion over 30 minutes once every 3 weeks until unacceptable toxicity, disease progression, or for up to 24 months, in combination with;
- Lenvatinib – 20 mg orally once daily until unacceptable toxicity or disease progression.

Refer to the lenvatinib Product Monograph for recommended lenvatinib dosing information.

Recommended Dosage for RCC

For adult patients with RCC, the recommended dosing is:

- KEYTRUDA® – 200 mg administered as an intravenous infusion over 30 minutes once every 3 weeks until unacceptable toxicity, disease progression, or for up to 24 months or 35 doses, whichever is longer, in combination with;

- Axitinib – 5 mg axitinib orally twice daily until unacceptable toxicity or disease progression. As in KEYNOTE-426, when axitinib is used in combination with KEYTRUDA®, dose escalation may be considered for patients who tolerated the initial 5 mg axitinib dose at intervals of six weeks or longer (i.e., at least 2 treatment cycles).

Refer to the axitinib Product Monograph for recommended axitinib dose information.

Recommended Dosage for HNSCC – Previously Untreated as Monotherapy or in Combination with Chemotherapy

The recommended dose of KEYTRUDA® is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity or up to 24 months in patients without disease progression.

When administering KEYTRUDA® in combination with chemotherapy, administer KEYTRUDA® prior to chemotherapy when given on the same day. Refer to the Product Monographs for the chemotherapy agents administered in combination with KEYTRUDA® for recommended dosing information, as appropriate.

Atypical responses (i.e., an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed. Clinically stable patients with initial evidence of disease progression may remain on treatment until disease progression is confirmed.

Recommended Treatment Modifications

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

Table 1: Recommended Treatment Modifications for KEYTRUDA®.

Immune-related adverse reactions	Severity	Treatment modification
Pneumonitis	Moderate (Grade 2)	Withhold until adverse reactions recover to Grade 0-1*

Immune-related adverse reactions	Severity	Treatment modification
	Severe or life-threatening (Grade 3 or 4), or recurrent moderate (Grade 2)	Permanently discontinue
Colitis	Moderate or severe (Grade 2 or 3)	Withhold until adverse reactions recover to Grade 0-1*
	Life-threatening (Grade 4) or recurrent severe (Grade 3)	Permanently discontinue
Nephritis	Moderate (Grade 2) with creatinine > 1.5 to ≤ 3 times upper limit of normal (ULN)	Withhold until adverse reactions recover to Grade 0-1*
	Severe or life-threatening (Grade 3 or 4) (Grade ≥ 3 with creatinine > 3 times ULN)	Permanently discontinue
Endocrinopathies	Severe or life-threatening (Grade 3 or 4) symptomatic hypophysitis Type 1 diabetes associated with Grade >3 hyperglycemia (glucose >250 mg/dL or >13.9 mmol/L) or associated with ketoacidosis Hyperthyroidism Grade ≥ 3	Withhold until adverse reactions recover to Grade 0-1* For patients with severe (Grade 3) or life-threatening (Grade 4) endocrinopathy that improved to Grade 2 or lower and is controlled with hormone replacement, if indicated, continuation of KEYTRUDA® may be considered after corticosteroid taper, if needed. Otherwise treatment should be discontinued. Hypothyroidism may be managed with replacement therapy without treatment interruption.
Hepatitis For liver enzyme elevations in RCC patients treated with combination therapy. See dosing guidelines following this table.	Moderate (Grade 2) with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 to 5 times upper limit of normal (ULN) or total bilirubin >1.5 to 3 times ULN	Withhold until adverse reactions recover to Grade 0-1*
	Grade ≥ 3 with AST or ALT >5 times ULN or total bilirubin >3 times ULN	Permanently discontinue
	For patients with liver metastasis 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
Skin reactions or Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Severe skin reactions (Grade 3) or suspected SJS or TEN	Withhold until adverse reactions recover to Grade 0-1*
	Severe skin reactions (Grade 4) or confirmed SJS or TEN	Permanently discontinue
Other immune-related adverse reactions	Based on severity and type of reaction (Grade 2 or Grade 3)	Withhold until adverse reactions recover to Grade 0-1*
	Severe or life-threatening (Grade 3 or 4) myocarditis, encephalitis, or Guillain-Barré syndrome	Permanently discontinue
	Life-threatening (Grade 4) or recurrent severe (Grade 3)	Permanently discontinue
Infusion-related reactions	Severe or life-threatening (Grade 3 or 4)	Permanently discontinue

Immune-related adverse reactions	Severity	Treatment modification

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

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

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 Monograph.

- 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.

Renal Impairment: No dose adjustment is needed for patients with mild (eGFR) <90 and ≥ 60 mL/min/1.73 m^2) or moderate (eGFR <60 and ≥ 30 mL/min/1.73 m^2) renal impairment. KEYTRUDA® has not been studied in patients with severe (eGFR <30 and ≥ 15 mL/min/1.73 m^2) renal impairment.

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.

Eastern Cooperative Oncology Group (ECOG) performance status score ≥ 2: Patients with ECOG performance status score ≥ 2 were excluded from the clinical trials (See CLINICAL TRIALS).

Recommended Dose Modification for Lenvatinib used in combination with KEYTRUDA®:
See manufacturer's Product Monograph for the coadministered product, lenvatinib for toxicity management, dose adjustment guidelines for special populations, and contraindications. When administering KEYTRUDA® in combination with lenvatinib for the treatment of endometrial carcinoma, interrupt one or both as appropriate. No dose reductions are recommended for KEYTRUDA®. Withhold, dose reduce, or discontinue lenvatinib in accordance with the instructions in the lenvatinib Product Monograph.

Recommended Dose Modification for Axitinib used in combination with KEYTRUDA®:
See manufacturer's Product Monograph for the coadministered product, axitinib for toxicity management, dose adjustment guidelines for special populations, and contraindications. When administering KEYTRUDA® in combination with axitinib for the treatment of RCC, interrupt one or both as appropriate. No dose reductions are recommended for KEYTRUDA®. Withhold, dose reduce, or discontinue axitinib in accordance with the instructions in the axitinib Product Monograph.

4.3 Administration

- Translucent to white proteinaceous particles may be seen in the diluted solution.
- Administer infusion solution intravenously over 30 minutes using a sterile, non-pyrogenic, low-protein binding 0.2 to 5 µm in-line or add-on filter.
- Do not co-administer other drugs through the same infusion line.
- Discard any unused portion left in the vial.

4.4 Reconstitution

Reconstitution of KEYTRUDA® (Lyophilized Powder)

- Prior to reconstitution, the vial of lyophilized powder can be out of refrigeration (temperatures at or below 25°C) for up to 24 hours.
- Aseptically add 2.3 mL of sterile water for injection to yield a 25 mg/mL (pH 5.2-5.8) solution of KEYTRUDA®.
- To avoid foaming, deliver the water along the walls of the vial and not directly on the lyophilized powder.
- Slowly swirl the vial to allow reconstitution of the lyophilized powder. Allow up to 5 minutes for the bubbles to clear. Do not shake the vial.

Preparation for Intravenous Infusion

- 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. Dilute KEYTRUDA® solution or reconstituted lyophilized powder prior to intravenous administration.
- Withdraw the required volume from the vial(s) 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.

Storage of Reconstituted and Diluted Solutions

- Do not freeze the infusion solution.
- The product does not contain preservative. The reconstituted and/or diluted product should be used immediately. If not used immediately, reconstituted and diluted solutions of KEYTRUDA® may be stored at room temperature for a cumulative time of up to 6 hours. Reconstituted and diluted solutions of KEYTRUDA® may also be stored under refrigeration at 2°C to 8°C; however, the total time from reconstitution or dilution of KEYTRUDA® to completion of infusion should not exceed 96 hours. If refrigerated, allow the vials and/or IV bags to come to room temperature prior to use.

4.5 Missed Dose

If a planned dose of KEYTRUDA® is missed, it should be administered as soon as possible. The schedule of administration should be adjusted to maintain the prescribed dosing interval.

5 OVERDOSAGE

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 management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 – Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous infusion	Powder for solution for infusion 50 mg	L-histidine, polysorbate 80, L-histidine monohydrochloride monohydrate, sucrose, and sterile water for injection.
	Solution for infusion 100 mg/4 mL vial	

KEYTRUDA® is supplied as

- Powder for Solution for Infusion: 50 mg lyophilized powder of pembrolizumab in a single-use vial, white to off-white lyophilized powder for reconstitution.
  One vial contains 50 mg of pembrolizumab with a controlled excess fill of 20% (total content per vial 60 mg). After reconstitution with 2.3 mL of sterile water for injection, each 1 mL of solution contains 25 mg of pembrolizumab.
- Solution for Infusion: 100 mg/4 mL (25 mg/mL) solution in a single-use vial, clear to slightly opalescent, colorless to slightly yellow solution.
  Each vial of 4 mL contains 100 mg of pembrolizumab with a controlled excess fill of 0.25 mL (total content per vial 4.25 mL).

NOC/c

7 WARNINGS AND PRECAUTIONS

General

KEYTRUDA® (pembrolizumab) should be administered under the supervision of physicians experienced in the treatment of cancer.

When KEYTRUDA® is to be administered in combination with lenvatinib, refer to the Product Monograph for lenvatinib prior to the initiation of treatment.

The data described in the WARNINGS AND PRECAUTIONS section reflect exposure to KEYTRUDA® as monotherapy in 2799 patients in three randomized, open-label, active-controlled clinical trials (KEYNOTE-002, KEYNOTE-006, and KEYNOTE-010), which enrolled 912 patients with melanoma and 682 patients with NSCLC, and one single-arm trial (KEYNOTE-001) which enrolled 655 patients with melanoma and 550 patients with NSCLC (See CLINICAL TRIALS). This is termed the Reference Safety Data set and will be referred to as the data set against which safety data from other indicated populations were compared.

Driving and Operating Machinery

Exercise caution when driving or operating a vehicle or potentially dangerous machinery.

Hepatic/Biliary/Pancreatic

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 DOSAGE AND ADMINISTRATION).

Immune

Immune-mediated adverse reactions, including severe and fatal cases, have occurred in patients receiving KEYTRUDA®. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of KEYTRUDA®, administration of corticosteroids and/or supportive care. Immune-mediated adverse reactions have also occurred after the last dose of 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-mediated adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered. KEYTRUDA® may be restarted within 12 weeks after last dose of KEYTRUDA® if the adverse reaction remains at Grade ≤ 1 and corticosteroid dose has been reduced to ≤ 10 mg prednisone or equivalent per day. KEYTRUDA® must be permanently discontinued for any Grade 3 immune-mediated adverse reaction that recurs and for any Grade 4 immune-mediated adverse reaction toxicity, except for endocrinopathies that are controlled with replacement hormones (See DOSAGE AND ADMINISTRATION and ADVERSE REACTIONS).

Immune-mediated pneumonitis

KEYTRUDA® can cause immune-mediated pneumonitis, including fatal cases. Monitor patients for signs and symptoms of pneumonitis. Evaluate patients with suspected pneumonitis with radiographic imaging and administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper) for Grade 2 or greater pneumonitis. 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 DOSAGE AND ADMINISTRATION and ADVERSE REACTIONS).

Immune-mediated colitis

KEYTRUDA® can cause immune-mediated colitis. Monitor patients for signs and symptoms of colitis. Administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper) for Grade 2 or greater colitis. Withhold KEYTRUDA® for moderate (Grade 2) or severe (Grade 3) colitis, and permanently discontinue KEYTRUDA® for life-threatening (Grade 4) colitis (See DOSAGE AND ADMINISTRATION and ADVERSE REACTIONS).

Immune-mediated hepatitis

KEYTRUDA® can cause immune-mediated hepatitis. Monitor patients for changes in liver function. Administer corticosteroids (initial dose of 0.5 to 1 mg/kg/day [for Grade 2 hepatitis] and 1 to 2 mg/kg/day [for Grade 3 or greater hepatitis] prednisone or equivalent followed by a taper) and, based on severity of liver enzyme elevations, withhold or discontinue KEYTRUDA® (See DOSAGE AND ADMINISTRATION and ADVERSE REACTIONS).

Immune-mediated nephritis and renal dysfunction
KEYTRUDA® can cause immune-mediated nephritis. Monitor patients for changes in renal function. Administer corticosteroids (initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper) for Grade 2 or greater nephritis. Withhold KEYTRUDA® for moderate (Grade 2), and permanently discontinue KEYTRUDA® for severe (Grade 3) or life-threatening (Grade 4) nephritis (See DOSAGE AND ADMINISTRATION and ADVERSE REACTIONS).

Immune mediated endocrinopathies
Severe endocrinopathies, including adrenal insufficiency (primary and secondary), hypophysitis, type 1 diabetes mellitus, diabetic ketoacidosis, hypothyroidism, and hyperthyroidism have been observed with KEYTRUDA® treatment.

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

Adrenal insufficiency:
KEYTRUDA® can cause adrenal insufficiency (primary and secondary). Monitor for signs and symptoms of adrenal insufficiency. Administer corticosteroids and hormone replacement as clinically indicated. Withhold KEYTRUDA® for moderate (Grade 2) adrenal insufficiency and withhold or discontinue KEYTRUDA® for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency (See DOSAGE AND ADMINISTRATION and ADVERSE REACTIONS).

Hypophysitis:
KEYTRUDA® can cause hypophysitis. Monitor patients for signs and symptoms of hypophysitis (including hypopituitarism). Administer corticosteroids and hormone replacement as clinically indicated. Withhold KEYTRUDA® for moderate (Grade 2) hypophysitis and withhold or discontinue KEYTRUDA® for severe (Grade 3) or life-threatening (Grade 4) hypophysitis (See DOSAGE AND ADMINISTRATION and ADVERSE REACTIONS).

Type 1 diabetes mellitus:
KEYTRUDA® can cause type 1 diabetes mellitus, including diabetic ketoacidosis, which have been reported in 6 (0.2%) of 2799 patients receiving KEYTRUDA®. Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Administer insulin for type 1 diabetes and withhold KEYTRUDA® in cases of severe hyperglycemia until metabolic control is achieved.

Thyroid disorders:
KEYTRUDA® can cause thyroid disorders, including hyperthyroidism, hypothyroidism, and thyroiditis, which 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 (see ADVERSE REACTIONS). 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 DOSAGE AND ADMINISTRATION and Immune-mediated adverse reactions below).

Severe skin reactions
KEYTRUDA® can cause immune-mediated severe skin reactions. 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 DOSAGE AND ADMINISTRATION).

Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some with fatal outcomes, have been reported in patients treated with KEYTRUDA®. 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 DOSAGE AND ADMINISTRATION).

Other immune-mediated adverse reactions
KEYTRUDA® can cause other clinically important immune-mediated adverse reactions including severe and fatal cases.

Based on the severity of the adverse reaction, KEYTRUDA® should be withheld and corticosteroids administered.

The following additional clinically significant, immune-mediated adverse reactions were reported in less than 1% (unless otherwise indicated) of the 2799 patients treated with KEYTRUDA® in the Reference Safety Data set: uveitis; arthritis (1.5%); myositis; encephalitis; sarcoidosis; myasthenic syndrome/myasthenia gravis (including exacerbation); vasculitis; Guillain-Barré syndrome; hemolytic anemia; pancreatitis; and myelitis.

The following was reported in other clinical studies with KEYTRUDA® or in post-marketing use: myocarditis.

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.

Elevated liver enzymes when KEYTRUDA® is given in combination with axitinib for RCC
When KEYTRUDA® is given with axitinib, higher than expected frequencies of Grades 3 and 4 ALT and AST elevations have been reported in patients with advanced RCC (See ADVERSE REACTIONS). Monitor liver enzymes before initiation of and periodically throughout treatment. Consider more frequent monitoring of liver enzymes as compared to when the drugs are used in monotherapy. Follow medical management guidelines for both drugs. (See DOSAGE AND ADMINISTRATION and the Product Monograph for axitinib).

Increased mortality in patients with multiple myeloma when KEYTRUDA® is added to a thalidomide analogue and dexamethasone
In two randomized clinical trials in patients with multiple myeloma, the addition of KEYTRUDA® to a thalidomide analogue plus dexamethasone, a use for which no PD-1 or PD-L1 blocking antibody is indicated, resulted in increased mortality. Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

Complications of allogeneic Hematopoietic Stem Cell Transplant (HSCT)
Allogeneic HSCT after treatment with KEYTRUDA®
Cases of graft-versus-host-disease (GVHD) and hepatic veno-occlusive disease (VOD) have been observed in patients with classical Hodgkin lymphoma undergoing allogeneic HSCT after previous exposure to KEYTRUDA®. Until further data become available, careful consideration to

the potential benefits of HSCT and the possible increased risk of transplant-related complications should be made case by case (See ADVERSE REACTIONS).

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 an 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.

Infusion-related reactions:
KEYTRUDA® can cause severe (>=Grade 3) infusion-related reactions, including hypersensitivity and anaphylaxis, which have been reported in 6 (0.2%) of 2799 patients receiving KEYTRUDA® in the Reference Safety Data set. For severe or life-threatening infusion reactions, stop infusion and permanently discontinue KEYTRUDA® (See DOSAGE AND ADMINISTRATION). Patients with mild or moderate infusion reaction may continue to receive KEYTRUDA® with close monitoring; premedication with antipyretic and antihistamine may be considered.

Monitoring and Laboratory Tests
Liver function tests (hepatic transaminase and bilirubin levels), thyroid function tests and serum electrolytes should be monitored at the start of treatment, periodically during treatment and as indicated based on clinical evaluation. Patients should be closely monitored during treatment for signs and symptoms of immune-mediated adverse reactions, including but not limited to: dyspnea; hypoxia; increased frequency of bowel movements; diarrhea; elevated transaminase and bilirubin levels; elevated creatinine levels; rash; pruritus; headache; fatigue; hypotension; mental status changes; visual disturbances; muscle pain or weakness; paresthesias (See DOSAGE AND ADMINISTRATION and WARNINGS AND PRECAUTIONS).

Renal
Renal Impairment
No dose adjustment is needed for patients with mild (estimated Glomerular Filtration Rate (eGFR) <90 and ≥ 60 mL/min/1.73 m^2) or moderate (eGFR <60 and ≥ 30 mL/min/1.73 m^2) renal impairment. KEYTRUDA® has not been studied in patients with severe (eGFR <30 and ≥ 15 mL/min/1.73 m^2) renal impairment (See DOSAGE AND ADMINISTRATION).
Reproductive Health: Female and Male Potential
- **Teratogenic Risk**

KEYTRUDA® can cause fetal harm. Pregnant women or women with childbearing potential should be advised of the potential risk to the fetus (See Special Populations, Pregnant Women).

7.1 Special Populations
7.1.1 Pregnant Women
There are no data on the use of pembrolizumab in pregnant women. Animal reproduction studies have not been conducted with pembrolizumab; however, blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to result in an increase in fetal loss (See NON-CLINICAL TOXICOLOGY). 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. Women of childbearing potential should use effective contraception during treatment with KEYTRUDA® and for 4 months after the last dose of KEYTRUDA®.

7.1.2 Breast-feeding

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

7.1.3 Pediatrics

Pediatrics (< 18 years of age): There is limited experience with KEYTRUDA® in pediatric patients compared with in adult patients. The mechanism of action of pembrolizumab in pediatric patients is expected to be similar to that in adult patients. Therefore, adverse reactions of KEYTRUDA® reported in adult patients can occur in pediatric patients. In a single Phase I/II trial that enrolled pediatric patients with advanced tumours, immune-mediated adverse reactions were observed. The observed immune-mediated adverse reactions included pneumonitis, colitis, thyroid disorders (hyperthyroidism, hypothyroidism and thyroiditis) and skin reactions. Infusion reactions were also observed (see ADVERSE REACTIONS). The developmental effect of KEYTRUDA® on pediatric patients has not been established. Monitor pediatric patients for signs and symptoms of immune-mediated adverse reactions and/or infusion reactions and manage as is described throughout the WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION sections.

Efficacy for pediatric patients with cHL and PMBCL is extrapolated from the results in the respective adult populations (see CLINICAL TRIALS).

7.1.4 Geriatrics

No overall differences in safety or efficacy were reported between elderly patients (65 years and over) and younger patients (less than 65 years). No dose adjustment is necessary in this population. Limited safety and efficacy information is available for KEYTRUDA® in cHL patients ≥ 65 years of age (n=46).

NOC/c

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety and efficacy of KEYTRUDA® was investigated in 2799 patients treated with KEYTRUDA® in the Reference Safety Data set for the treatment of unresectable or metastatic melanoma or metastatic NSCLC. Overall, 1567 patients with melanoma (699 previously treated with ipilimumab and 868 naïve to ipilimumab) and 1232 patients with NSCLC were treated. Safety is described for the pooled population of the 2799 patients that composed the Reference Safety Data set (studied across three doses; 2 mg/kg every 3 weeks and 10 mg/kg every 2 or 3 weeks). 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 melanoma and NSCLC patients.

Treatment-related serious adverse events (SAEs) reported up to 90 days after the last dose occurred in 10% of patients receiving KEYTRUDA® (See WARNINGS AND PRECAUTIONS). Of these treatment-related SAEs, those occurring in more than ten patients (out of 2799) were: pneumonitis (n=44); colitis (n=25); diarrhea (n=17); and pyrexia (n=10).

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Immune-mediated adverse reactions

Immune-mediated adverse reactions are presented based on the 2799 patients treated with KEYTRUDA® in the Reference Safety Data set..

Table 3 presents the incidence of immune-mediated adverse reactions by Grade that occurred in patients receiving KEYTRUDA®.

Table 3: Immune-Mediated Adverse Reactions

Adverse Reaction	KEYTRUDA® 2 mg/kg every 3 weeks or 10 mg/kg every 2 or 3 weeks n=2799				
	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 patients with cHL (n=389) treated with KEYTRUDA® as monotherapy, the incidence of hypothyroidism was 17% (all of which were Grade 1 or 2). In patients with completely resected stage III melanoma, the incidence of hypothyroidism was 14.7% (all Grades) with 0% Grade 3 and hyperthyroidism was 10.4% (all Grades) with 0.2% Grade 3.

In patients with HNSCC treated with KEYTRUDA® as monotherapy (n=909) the incidence of hypothyroidism was 16.1% (all Grades) with 0.3% Grade 3. In patients with HNSCC treated with KEYTRUDA in combination with platinum and FU chemotherapy (n=276) the incidence of hypothyroidism was 15.9%, all of which were Grade 1 or 2.

In individual studies of patients with NSCLC treated with KEYTRUDA® as monotherapy (total n=2022), the incidence of pneumonitis (all Grades) ranged from 3.8% to 8.3%. In cHL patients treated with KEYTRUDA as monotherapy, the incidence of pneumonitis (all Grades) ranged from 5.2% to 10.8% for cHL patients in KEYNOTE-087 (n=210) and KEYNOTE-204 (n=148), respectively.

In patients with non-squamous NSCLC treated with KEYTRUDA® 200 mg 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.

In patients with endometrial carcinoma treated with KEYTRUDA® 200 mg in combination with lenvatinib (n=94), the incidence of hypothyroidism was 51.1% (all Grades) with 1.1% of cases Grade 3. Pancreatitis was reported in 3 patients (3.2%) with 2.1% Grade 3. Nephritis occurred in 2.1% of patients with 1.1% Grade 3.

The following information on Immune-mediated adverse reactions is based on patients treated with KEYTRUDA® in the Reference Safety Data set (n=2799).

Pneumonitis:
The median time to onset of pneumonitis was 3.3 months (range 2 days to 19.3 months), and the median duration was 1.5 months (range 1 day to 17.2+ months). Pneumonitis occurred more frequently in patients with a history of prior thoracic radiation (6.9%) than in patients who did not receive prior thoracic radiation (2.9%). Pneumonitis led to discontinuation of KEYTRUDA® in 36 (1.3%) patients. Pneumonitis resolved in 55/94 patients (59%).

Colitis:
The median time to onset of colitis was 3.5 months (range 10 days to 16.2 months), and 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 41/48 patients (85%).

Hepatitis:
The median time to onset of hepatitis was 1.3 months (range 8 days to 21.4 months), and 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 15/19 patients (79%).

Nephritis and renal dysfunction:
The median time to onset of nephritis was 5.1 months (range 12 days to 12.8 months), and 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 5/9 patients (56%).

Endocrinopathies:
Adrenal Insufficiency:
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 5/22 patients (23%).

Hypophysitis:
The median time to onset of hypophysitis was 3.7 months (range 1 day to 11.9 months), and 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 7/17 patients (41%).

Hyperthyroidism:
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 71/96 patients (74%).

Hypothyroidism:
The median time to onset of hypothyroidism was 3.5 months (range 1 day to 18.9 months), and the median duration was not reached (range 2 days to 27.7+ months). One (<0.1%) patient discontinued KEYTRUDA® due to hypothyroidism.

See Warnings and Precautions section for serious immune-mediated skin reactions and other clinically important immune-mediated reactions.

Melanoma
Treatment was discontinued for treatment-related adverse events in 5.4% of the 555 patients receiving KEYTRUDA® and in 9.4% of the 256 patients receiving ipilimumab.

In KEYNOTE-002, the adverse reaction profile was similar for the 2 mg/kg dose and 10 mg/kg dose, therefore summary safety results are provided in a pooled analysis (n=357) of both KEYTRUDA® arms. Adverse reactions resulting in permanent discontinuation occurred in 12% of patients receiving KEYTRUDA®; the most common (≥ 1%) were general physical health deterioration (1%), asthenia (1%), dyspnea (1%), pneumonitis (1%), and generalized edema (1%). Adverse reactions leading to interruption of KEYTRUDA® occurred in 14% of patients. The most common (≥ 1%) were: dyspnea (1%); diarrhea (1%); and maculo-papular rash (1%). The most common adverse reactions (reported in at least 20% of patients) of KEYTRUDA® were: fatigue; pruritus; rash; constipation; nausea; diarrhea; and decreased appetite.

There were no new safety signals observed at the final analysis and therefore with additional follow-up, no meaningful changes occurred in the safety profile of pembrolizumab.

Table 4 summarizes the treatment-related adverse events that occurred in at least 1% of patients with melanoma treated with KEYTRUDA® in KEYNOTE-006. The most common treatment-related adverse events (reported in at least 15% of patients) were diarrhea and fatigue.

In KEYNOTE-006, the adverse reaction profile was similar for the every 2 week and every 3 week schedule, therefore summary safety results are provided in a pooled analysis (n=555) of both KEYTRUDA® arms. Adverse reactions leading to permanent discontinuation of KEYTRUDA® occurred in 9% of patients. Adverse reactions leading to discontinuation of KEYTRUDA® in more than one patient were: colitis (1.4%); autoimmune hepatitis (0.7%); allergic reaction (0.4%); polyneuropathy (0.4%); and cardiac failure (0.4%). Adverse reactions leading to interruption of KEYTRUDA® occurred in 21% of patients. The most common (≥ 1%) was diarrhea (2.5%). The most common adverse reactions (reported in at least 20% of patients) were fatigue and diarrhea.

There were no new safety signals observed at the final analysis. After 9 additional months of follow-up from the second interim analysis to final analysis, no meaningful changes occurred in the safety profile of pembrolizumab.

Table 4: Treatment-Related Adverse Events (incidence ≥ 1%) KEYTRUDA® Treatment Groups Combined, All patients as treated (APaT) Population in KEYNOTE 006.

Adverse Reaction	KEYTRUDA® 10 mg/kg every 2 or 3 weeks n=555			Ipilimumab 3 mg/kg every 3 weeks n=256		
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Blood and lymphatic system disorders						
Anemia	9 (1.6)	2 (0.4)	0	1 (0.4)	1 (0.4)	0
Endocrine disorders						
Hyperthyroidism	24 (4.3)	0	0	6 (2.3)	1 (0.4)	0
Hypothyroidism	46 (8.3)	1 (0.2)	0	2 (0.8)	0	0
Gastrointestinal disorders						
Abdominal pain	15 (2.7)	0	0	15 (5.9)	0	0
Abdominal pain upper	7 (1.3)	0	0	1 (0.4)	0	0
Colitis	12 (2.2)	7 (1.3)	2 (0.4)	19 (7.4)	14 (5.5)	2 (0.8)
Constipation	12 (2.2)	0	0	5 (2.0)	0	0
Diarrhea	87 (15.7)	10 (1.8)	0	58 (22.7)	8 (3.1)	0
Dry mouth	31 (5.6)	0	0	1 (0.4)	0	0
Nausea	59 (10.6)	1 (0.2)	0	22 (8.6)	1 (0.4)	0
Vomiting	15 (2.7)	1 (0.2)	0	14 (5.5)	0	0
General disorders and administration site conditions						
Asthenia	63 (11.4)	1 (0.2)	0	16 (6.3)	2 (0.8)	0
Fatigue	111 (20.0)	1 (0.2)	0	39 (15.2)	3 (1.2)	0
Influenza like illness	8 (1.4)	0	0	4 (1.6)	1 (0.4)	0
Pyrexia	14 (2.5)	0	0	6 (2.3)	0	0
Injury, poisoning and procedural complications						
Infusion related reaction	6 (1.1)	0	0	0	0	0
Investigations						
Alanine aminotransferase increased	16 (2.9)	1 (0.2)	0	9 (3.5)	1 (0.4)	1 (0.4)
Aspartate aminotransferase increased	20 (3.6)	0	1 (0.2)	6 (2.3)	2 (0.8)	0
Blood bilirubin increased	7 (1.3)	0	0	0	0	0
Blood creatinine increased	7 (1.3)	0	0	1 (0.4)	0	0
Blood thyroid stimulating hormone decreased	6 (1.1)	0	0	2 (0.8)	1 (0.4)	0
Weight decreased	6 (1.1)			5 (2.0)	1 (0.4)	0
Metabolism and nutrition disorders						
Decreased appetite	35 (6.3)	0	0	20 (7.8)	0	0
Hypocalcemia	8 (1.4)	0	0	0	0	0
Musculoskeletal and connective tissue disorders						
Arthralgia	58 (10.5)	1 (0.2)	0	13 (5.1)	2 (0.8)	0
Arthritis	6 (1.1)	0	0	0	0	0
Back pain	12 (2.2)	0	0	0 (0.0)	0	0
Muscle spasms	7 (1.3)	0	0	1 (0.4)	0	0
Myalgia	25 (4.5)	1 (0.2)	0	5 (2.0)	1 (0.4)	0
Pain in extremity	7 (1.3)	2 (0.4)	0	1 (0.4)	0	0
Nervous system disorders						
Dizziness	9 (1.6)	0	0	2 (0.8)	0	0
Dysgeusia	15 (2.7)	0	0	3 (1.2)	0	0
Headache	15 (2.7)	0	0	9 (3.5)	0	0

Adverse Reaction	KEYTRUDA® 10 mg/kg every 2 or 3 weeks n=555			Ipilimumab 3 mg/kg every 3 weeks n=256		
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Psychiatric disorders						
Insomnia	7 (1.3)	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders						
Cough	22 (4.0)	0	0	0	0	0
Dyspnea	12 (2.2)	1 (0.2)	0	3 (1.2)	1 (0.4)	0
Skin and subcutaneous tissue disorders						
Dry skin	14 (2.5)	0	0	3 (1.2)	0	0
Eczema	7 (1.3)	0	0	1 (0.4)	0	0
Erythema	11 (2.0)	0	0	5 (2.0)	0	0
Hair colour changes	6 (1.1)	0	0	0	0	0
Papule	6 (1.1)	0	0	0	0	0
Pruritus	79 (14.2)	0	0	65 (25.4)	1 (0.4)	0
Rash	78 (14.1)	0	0	37 (14.5)	1 (0.4)	1 (0.4)
Rash maculo-papular	16 (2.9)	1 (0.2)	0	7 (2.7)	1 (0.4)	0
Rash pruritic	7 (1.3)	0	0	4 (1.6)	0	0
Skin hypopigmentation	9 (1.6)	0	0	0	0	0
Vitiligo	56 (10.1)	0	0	4 (1.6)	0	0
Vascular disorders						
Flushing	6 (1.1)	0	0	2 (0.8)	0	0

Treatment-related adverse events reported in <1% patients with melanoma treated with KEYTRUDA® 10 mg/kg every 2 or 3 weeks (n=555) by system organ class (SOC) are shown below.

Endocrine disorders: adrenal insufficiency, hypophysitis, hypopituitarism
Eye disorders: uveitis
Gastrointestinal disorders: pancreatitis
Hepatobiliary disorders: hepatitis
Metabolism and nutrition disorders: Type 1 diabetes mellitus
Musculoskeletal and connective tissue disorders: myositis
Nervous system disorders: Guillain-Barré syndrome
Respiratory, thoracic and mediastinal disorders: pneumonitis

Table 5: Treatment-Related Adverse Events (incidence ≥ 1%) KEYTRUDA® Treatment Groups Combined, APaT Population in KEYNOTE 002.

Adverse Reaction	KEYTRUDA® 2 or 10 mg/kg every 3 weeks n=357			Chemotherapy n=171		
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Blood and lymphatic system disorders						
Anemia	12 (3.4)	1 (0.3)	0	35 (20.5)	9 (5.3)	0
Ear and labyrinth disorders						
Vertigo	5 (1.4)	0	0	2 (1.2)	0	0

Adverse Reaction	KEYTRUDA® 2 or 10 mg/kg every 3 weeks n=357			Chemotherapy n=171		
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Endocrine disorders						
Hyperthyroidism	8 (2.2)	0	0	0	0	0
Hypothyroidism	22 (6.2)	0	0	0	0	0
Gastrointestinal disorders						
Abdominal pain	10 (2.8)	1 (0.3)	0	4 (2.3)	0	0
Colitis	4 (1.1)	2 (0.6)	0	0		0
Constipation	14 (3.9)	0	0	14 (8.2)	0	0
Diarrhea	34 (9.5)	2 (0.6)	0	14(8.2)	3 (1.8)	0
Dry mouth	6 (1.7)	0	0	0	0	0
Nausea	24 (6.7)	1 (0.3)	0	56 (32.7)	3 (1.8)	1 (0.6)
Vomiting	12 (3.4)	2 (0.6)	0	26 (15.2)	3 (1.8)	1 (0.6)
General disorders and administration site conditions						
Asthenia	14 (3.9)	2 (0.6)	0	10 (5.8)	1 (0.6)	0
Chills	11 (3.1)	0	0	6 (3.5)	0	0
Fatigue	92 (25.8)	3 (0.8)	0	62 (36.3)	8 (4.7)	0
Influenza like illness	9 (2.5)	0	0	1 (0.6)	0	0
Malaise	4 (1.1)	0	0	1 (0.6)	0	0
Edema peripheral	8 (2.2)	0	0	4 (2.3)	0	0
Pyrexia	17 (4.8)	0	0	8 (4.7)	1 (0.6)	0
Investigations						
Alanine aminotransferase increased	11 (3.1)	1 (0.3)	0	3 (1.8)	0	0
Aspartate aminotransferase increased	10 (2.8)	2 (0.6)	0	0	0	0
Blood alkaline phosphatase increased	6 (1.7)	0	0	0	0	0
Blood bilirubin increased	4 (1.1)	0	0	3 (1.8)	0	0
Lymphocyte count decreased	4 (1.1)	1 (0.3)	0	7 (4.1)	2 (1.2)	0
Metabolism and nutrition disorders						
Decreased appetite	25 (7.0)	2 (0.6)	0	26 (15.2)	0	0
Musculoskeletal and connective tissue disorders						
Arthralgia	25 (7.0)	2 (0.6)	0	9 (5.3)	1 (0.6)	0
Back pain	5 (1.4)	0	0	2 (1.2)	1 (0.6)	0
Joint stiffness	4 (1.1)	0	0	1 (0.6)	0	0
Myalgia	16 (4.5)	2 (0.6)	0	10 (5.8)	1 (0.6)	0
Pain in extremity	4 (1.1)	0	0	3 (1.8)	0	0
Nervous system disorders						
Dysgeusia	4 (1.1)	0	0	7 (4.1)	0	0
Headache	12 (3.4)	0	0	6 (3.5)	0	0
Respiratory, thoracic and mediastinal disorders						
Cough	12 (3.4)	0	0	1 (0.6)	0	0
Dyspnea	12 (3.4)	0	1 (0.3)	4 (2.3)	0	0
Pneumonitis	4 (1.1)	2 (0.6)	0	0	0	0
Skin and subcutaneous tissue disorders						
Alopecia	6 (1.7)	0	0	35 (20.5)	1 (0.6)	0
Dermatitis acneiform	4 (1.1)	0	0	0	0	0
Dry skin	18 (5.0)	0	0	2 (1.2)	0	0
Eczema	7 (2.0)	0	0	0	0	0

Adverse Reaction	KEYTRUDA® 2 or 10 mg/kg every 3 weeks n=357			Chemotherapy n=171		
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Erythema	4 (1.1)	0	0	4 (2.3)	0	0
Hyperhidrosis	4 (1.1)	0	0	2 (1.2)	0	0
Pruritus	79 (22.1)	0	0	6 (3.5)	0	0
Rash	39 (10.9)	0	0	8 (4.7)	0	0
Rash generalized	4 (1.1)	0	0	1 (0.6)	0	0
Rash maculo-papular	15 (4.2)	2 (0.6)	0	0	0	0
Skin hypopigmentation	6 (1.7)	0	0	0	0	0
Vitiligo	19 (5.3)	0	0	2 (1.2)	0	0

Treatment-related adverse events reported in <1% patients with melanoma treated with KEYTRUDA® 2 mg/kg or 10 mg/kg every 3 weeks (n=357) by SOC are shown below.

Blood and lymphatic system disorders: hemolytic anemia
Endocrine disorders: hypophysitis, hypopituitarism
Eye disorders: uveitis
Gastrointestinal disorders: pancreatitis
Hepatobiliary disorders: hepatitis
Musculoskeletal and connective tissue disorders: arthritis

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

Abnormal Hematologic and Clinical Chemistry Findings
Laboratory abnormalities (worsened from baseline in ≥ 10% of patients), reported in KEYNOTE-006 in patients with advanced melanoma are presented in Table 6.

Table 6: Laboratory Abnormalities Worsened from Baseline in ≥ 10% of Patients with Unresectable or Metastatic Melanoma Treated with KEYTRUDA® and at a Higher Incidence than in the Ipilimumab Arm (Between Arm Difference of ≥ 5% [All Grades] or ≥ 2% [Grades 3-4]) (KEYNOTE-006).

Laboratory Test	KEYTRUDA® 10 mg/kg every 2 or 3 weeks n=555		Ipilimumab n=256	
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
Hematology				
Lymphopenia	33	6	25	6
Leukopenia	12	0	5	0
Thrombocytopenia	11	1	6	1
Chemistry				
Hypertriglyceridemia	42	3	33	1
Hypercholesterolemia	22	1	17	0

Laboratory abnormalities (worsened from baseline in ≥ 10% of patients), reported in KEYNOTE-002 in patients with advanced melanoma are presented in Table 7.

Table 7: Laboratory Abnormalities Worsened from Baseline in ≥10% of Patients with Unresectable or Metastatic Melanoma 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).

Laboratory Test	KEYTRUDA® 2 or 10 mg/kg every 3 weeks n=357		Chemotherapy n=171	
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
Chemistry				
Hyperglycemia	48	6	42	6
Hypoalbuminemia	35	2	30	1
Hyponatremia	36	7	24	4
Increased Alkaline Phosphatase	26	3	17	2
Increased Aspartate Aminotransferase	23	2	16	1
Hypercholesterolemia	20	1	11	0
Increased Alanine Aminotransferase	20	2	15	1
Bicarbonate decreased	18	0	10	0
Hyperkalemia	15	1	8	1
Creatinine increased	14	1	9	1

Adjuvant Melanoma

Among the 1019 patients with resected melanoma enrolled in KEYNOTE-054, the adverse reactions were generally similar to those occurring in patients with unresectable or metastatic melanoma or NSCLC.

Table 8 summarizes the treatment-related adverse events that occurred in at least 1% of patients with resected melanoma treated with KEYTRUDA® in KEYNOTE-054. The most common treatment-related adverse events (reported in at least 15% of patients) were diarrhea, fatigue, and pruritis.

KEYTRUDA® was discontinued for treatment-related adverse events in 12% of patients in KEYNOTE 054. The most common treatment-related adverse event leading to study drug discontinuation was: pneumonitis (n=7, 1.4%). The median time to discontinuation for treatment-related adverse events was 5.8 months. There were 2 (0.4%) deaths reported in the KEYTRUDA® arm: drug reaction with eosinophilia and systemic symptoms (n=1); and autoimmune myositis with respiratory failure (n=1).

Table 8: Treatment-Related Adverse Events (incidence ≥ 1%) in patients treated with KEYTRUDA® APaT Population in KEYNOTE 054.

Adverse Reaction	KEYTRUDA® 200 mg every 3 weeks n=509			Placebo n=502		
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Blood and lymphatic system disorders						
Eosinophilia	5 (1.0)	0	0	1 (0.2)	0	0
Lymphopenia	5 (1.0)	1 (0.2)	0	1 (0.2)	0	0
Endocrine disorders						

Adverse Reaction	KEYTRUDA® 200 mg every 3 weeks n=509			Placebo n=502		
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Hyperthyroidism	49 (9.6)	1 (0.2)	0	4 (0.8)	0	0
Hypophysitis	8 (1.6)	2 (0.4)	0	0	0	0
Hypothyroidism	73 (14.3)	0	0	13 (2.6)	0	0
Thyroiditis	12 (2.4)	0	0	0	0	0
Eye disorders						
Dry eye	7 (1.4)	0	0	4 (0.8)	0	0
Gastrointestinal disorders						
Abdominal pain	20 (3.9)	0	0	15 (3.0)	0	0
Abdominal pain upper	9 (1.8)	1 (0.2)	0	10 (2.0)	0	0
Autoimmune colitis	5 (1.0)	3 (0.6)	0	1 (0.2)	1 (0.2)	0
Colitis	13 (2.6)	6 (1.2)	0	1 (0.2)	0	0
Constipation	12 (2.4)	0	0	8 (1.6)	0	0
Diarrhea	94 (18.5)	3 (0.6)	1 (0.2)	82 (16.3)	3 (0.6)	0
Dry mouth	23 (4.5)	0	0	10 (2.0)	0	0
Dyspepsia	8 (1.6)	0	0	2 (0.4)	0	0
Gastritis	5 (1.0)	1 (0.2)	0	0	0	0
Nausea	58 (11.4)	0	0	43 (8.6)	0	0
Vomiting	17 (3.3)	0	0	9 (1.8)	0	0
General disorders and administration site conditions						
Asthenia	48 (9.4)	0	0	34 (6.8)	0	0
Chills	6 (1.2)	0	0	4 (0.8)	0	0
Fatigue	143 (28.1)	4 (0.8)	0	135 (26.9)	2 (0.4)	0
Influenza like illness	14 (2.8)	0	0	9 (1.8)	0	0
Pyrexia	6 (1.2)	1 (0.2)	0	6 (1.2)	0	0
Immune system disorders						
Sarcoidosis	6 (1.2)	0	0	0	0	0
Investigations						
Alanine aminotransferase increased	26 (5.1)	3 (0.6)	0	16 (3.2)	1 (0.2)	0
Investigations						
Aspartate aminotransferase increased	19 (3.7)	1 (0.2)	0	14 (2.8)	1 (0.2)	0
Blood alkaline phosphatase increased	6 (1.2)	0	0	2 (0.4)	0	0
Blood bilirubin increased	7 (1.4)	0	0	4 (0.8)	0	0
Blood creatine phosphokinase increased	6 (1.2)	1 (0.2)	1 (0.2)	2 (0.4)	0	0
Blood creatinine increased	6 (1.2)	0	0	1 (0.2)	0	0
Blood thyroid stimulating hormone decreased	7 (1.4)	0	0	1 (0.2)	0	0
Eosinophil count increased	5 (1.0)	0	0	0	0	0
Gamma-glutamyltransferase increased	9 (1.8)	2 (0.4)	0	4 (0.8)	1 (0.2)	0
Lipase increased	7 (1.4)	3 (0.6)	1 (0.2)	3 (0.6)	3 (0.6)	0

Adverse Reaction	KEYTRUDA® 200 mg every 3 weeks n=509			Placebo n=502		
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Lymphocyte count decreased	5 (1.0)	0	0	2 (0.4)	0	0
Weight decreased	12 (2.4)	0	0	11 (2.2)	0	0
Weight increased	15 (2.9)	0	0	4 (0.8)	0	0
Metabolism and nutrition disorders						
Decreased appetite	25 (4.9)	1 (0.2)	0	8 (1.6)	0	0
Hypophosphatemia	5 (1.0)	1 (0.2)	0	1 (0.2)	0	0
Type 1 diabetes mellitus	5 (1.0)	5 (1.0)	0	0	0	0
Musculoskeletal and connective tissue disorders						
Arthralgia	51 (10.0)	3 (0.6)	0	47 (9.4)	0	0
Arthritis	5 (1.0)	0	0	0	0	0
Musculoskeletal and connective tissue disorders						
Muscle spasms	5 (1.0)	0	0	1 (0.2)	0	0
Musculoskeletal pain	5 (1.0)	0	0	3 (0.6)	0	0
Myalgia	26 (5.1)	0	0	15 (3.0)	0	0
Pain in extremity	7 (1.4)	0	0	3 (0.6)	0	0
Nervous system disorders						
Dizziness	10 (2.0)	0	0	13 (2.6)	0	0
Dysgeusia	9 (1.8)	0	0	10 (2.0)	0	0
Headache	37 (7.3)	0	0	33 (6.6)	1 (0.2)	0
Respiratory, thoracic and mediastinal disorders						
Cough	17 (3.3)	0	0	16 (3.2)	0	0
Dyspnea	27 (5.3)	1 (0.2)	0	14 (2.8)	0	0
Pneumonitis	15 (2.9)	3 (0.6)	0	3 (0.6)	0	0
Skin and subcutaneous tissue disorders						
Alopecia	10 (2.0)	0	0	8 (1.6)	0	0
Dermatitis acneiform	8 (1.6)	0	0	5 (1.0)	0	0
Dry skin	20 (3.9)	0	0	8 (1.6)	0	0
Eczema	11 (2.2)	0	0	3 (0.6)	0	0
Erythema	6 (1.2)	0	0	4 (0.8)	0	0
Lichenoid keratosis	5 (1.0)	1 (0.2)	0	0	0	0
Pruritus	85 (16.7)	0	0	49 (9.8)	0	0
Pruritus generalized	6 (1.2)	0	0	3 (0.6)	0	0
Rash	49 (9.6)	0	0	32 (6.4)	0	0
Rash maculo-papular	24 (4.7)	1 (0.2)	0	21 (4.2)	0	0
Skin hypopigmentation	8 (1.6)	0	0	3 (0.6)	0	0
Vitiligo	23 (4.5)	0	0	7 (1.4)	0	0
Vascular disorders						
Hypertension	5 (1.0)	1 (0.2)	0	5 (1.0)	2 (0.4)	0

Treatment-related adverse events reported in <1% of patients with complete resection of Stage IIIA (>1 mm metastasis), IIIB and IIIC melanoma treated with KEYTRUDA® (n=509) by SOC are shown below.

Cardiac disorders: myocarditis
Endocrine disorders: adrenal insufficiency
Eye disorders: uveitis

Gastrointestinal disorders: pancreatitis
Hepatobiliary disorders: hepatitis
Injury, poisoning and procedural complications: infusion related reaction
Metabolism and nutrition disorders: diabetic ketoacidosis
Musculoskeletal and connective tissue disorders: myositis

Abnormal Hematologic and Clinical Chemistry Findings
Laboratory abnormalities (worsened from baseline in ≥ 10% of patients), reported in KEYNOTE-054 in patients with lymph node involvement who have undergone complete resection are presented in Table 9.

Table 9: Laboratory Abnormalities Worsened from Baseline in ≥ 10% Treated with KEYTRUDA® and at a Higher Incidence than in Control Arm (Between Arm Difference of ≥ 5% [All Grades] or ≥ 2% [Grades 3-4]) APaT Population.

Laboratory Test	KEYTRUDA® 200 mg every 3 weeks n=509		Placebo n=502	
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
Alanine aminotransferase increased	27	2	16	0.2
Aspartate aminotransferase increased	24	2	15	0.4
Lymphocyte count decreased	23	1	16	1
Creatinine increased	15	0.6	10	0
Hypocalcemia	13	0	8	0.2
Hypoalbuminemia	13	0	4	0.2
Alkaline phosphatase increased	13	0.2	5	0.2

NSCLC
Table 10 summarizes the treatment-related adverse events that occurred in at least 1% of patients with NSCLC treated with KEYTRUDA® in KEYNOTE-024. The most common treatment-related adverse events (reported in at least 10% of patients) were diarrhea, fatigue, and pyrexia. The most common Grade 3-5 treatment-related adverse events for patients treated with KEYTRUDA® in KEYNOTE-024 were diarrhea (3.9%), pneumonitis (2.6%), and anemia (1.9%).

Treatment was discontinued for treatment related adverse events in 7.1% of the 154 patients receiving KEYTRUDA® and in 10.7% of the 150 patients receiving chemotherapy. The most common treatment-related adverse event leading to study drug discontinuation (occurring in more than 2 patients) was: pneumonitis (n=6). The median time to discontinuation for treatment-related adverse events was 0.7 months. There were 9 (5.8%) deaths reported in the KEYTRUDA® arm: pneumonia (n=2); respiratory failure (n=2); cardiac arrest (n=1); hemorrhagic stroke (n=1); sepsis (n=1); general physical health deterioration (n=1); and sudden death (n=1). One of the deaths (sudden death) was considered by the investigator to be related to treatment. There were 7 (4.7%) death in the chemotherapy arm: cardiac arrest/failure (n=3); sepsis (n=1); pulmonary embolism (n=1); pulmonary alveolar hemorrhage (n=1); and not specified (n=1). Three of the deaths (sepsis, pulmonary alveolar hemorrhage, and not specified) were considered to be treatment related.

There were no new safety signals observed at the final analysis and therefore with additional follow-up, no meaningful changes occurred in the safety profile of pembrolizumab.

Table 10: Treatment-Related Adverse Events (incidence ≥ 1%) in Patients Treated with KEYTRUDA®, APaT Population in KEYNOTE 024.

Adverse Reaction	KEYTRUDA® 200 mg every 3 weeks n=154			Chemotherapy n=150		
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Blood and lymphatic system disorders						
Anemia	8 (5.2)	3 (1.9)	0	66 (44.0)	29 (19.3)	0
Eosinophilia	3 (1.9)	0	0	0	0	0
Lymphopenia	2 (1.3)	0	0	0	0	0
Endocrine disorders						
Hyperthyroidism	11 (7.1)	0	0	0	0	0
Hypothyroidism	12 (7.8)	0	0	1 (0.7)	0	0
Thyroiditis	3 (1.9)	0	0	0	0	0
Gastrointestinal disorders						
Abdominal pain	4 (2.6)	0	0	3 (2.0)	0	0
Abdominal distention	2 (1.3)	0	0	0	0	0
Colitis	2 (1.3)	2 (1.3)	0	0	0	0
Constipation	6 (3.9)	0	0	17 (11.3)	0	0
Diarrhea	22(14.3)	6 (3.9)	0	20 (13.3)	2 (1.3)	0
Dyspepsia	2 (1.3)	0	0	4 (2.7)	0	0
Nausea	15 (9.7)	0	0	65 (43.3)	3 (2.0)	0
Stomatitis	4 (2.6)	0	0	18 (12.0)	2 (1.3)	0
Vomiting	4 (2.6)	1 (0.6)	0	30 (20.0)	1(0.7)	0
General disorders and administration site conditions						
Asthenia	5 (3.2)	1 (0.6)	0	11 (7.3)	2 (1.3)	0
Chills	3 (1.9)	0	0	0	0	0
Fatigue	16 (10.4)	2 (1.3)	0	43 (28.7)	5 (3.3)	0
Edema	2 (1.3)	0	0	2 (1.3)	0	0
Edema peripheral	4 (2.6)	1 (0.6)	0	6 (4.0)	0	0
Pyrexia	16 (10.4)	0	0	8 (5.3)	0	0
Lower respiratory tract infection	2 (1.3)	2 (1.3)				
Infusion related reaction	3 (1.9)	0	0	0	0	0
Investigations						
Alanine aminotransferase increased	10 (6.5)	0	0	7 (4.7)	0	0
Aspartate aminotransferase increased	8 (5.2)	2 (1.3)	0	5 (3.3)	0	0
Blood creatinine increased	3 (1.9)	0	0	15 (10.0)	1 (0.7)	0
Blood thyroid stimulating hormone increased	5 (3.2)	0	0	0	0	0
Blood thyroid stimulating hormone decreased	4 (2.6)	0	0	0	0	0

Adverse Reaction	KEYTRUDA® 200 mg every 3 weeks n=154			Chemotherapy n=150		
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Gamma-glutamyltransferase increased	3 (1.9)	1 (0.6)	0	4 (2.7)	0	0
Hepatic enzyme increased	2 (1.3)	1 (0.6)	0	0	0	0
Transaminase increased	3 (1.9)	2 (1.3)	0	0	0	0
Weight decreased	5 (3.2)	0	0	4 (2.7)	0	0
Metabolism and nutrition disorders						
Decreased appetite	14 (9.1)	0	0	39 (26.0)	4 (2.7)	0
Diabetes Mellitus	2 (1.3)	2 (1.3)	0	0	0	0
Hyperglycemia	2 (1.3)	0	1 (0.6)	2 (1.3)	0	0
Hyperkalemia	3 (1.9)	0	0	1 (0.7)	0	0
Hypoalbuminemia	3 (1.9)	2 (1.3)	0	4 (2.7)	2 (1.3)	0
Hyponatremia	5 (3.2)	0	0	2 (1.3)	1 (0.7)	0
Musculoskeletal and connective tissue disorders						
Arthralgia	13 (8.4)	0	0	4 (2.7)	0	0
Arthritis	2 (1.3)	0	0	0	0	0
Back pain	2 (1.3)	0	0	1 (0.7)	0	0
Myalgia	3 (1.9)	0	0	1 (0.7)	0	0
Nervous system disorders						
Dizziness	2 (1.3)	0	0	3 (2.0)	0	0
Neuropathy peripheral	2 (1.3)	0	0	9 (6.0)	1 (0.7)	0
Paresthesia	2 (1.3)	0	0	2 (1.3)	0	0
Renal and urinary disorders						
Dysuria	2 (1.3)	0	0	1 (0.7)	0	0
Respiratory, thoracic and mediastinal disorders						
Cough	5 (3.2)	0	0	0	0	0
Dyspnea	4 (2.6)	1 (0.6)	0	5 (3.3)	1 (0.7)	0
Hiccups	2 (1.3)	0	0	7 (4.7)	0	0
Pneumonitis	8 (5.2)	2 (1.3)	2 (1.3)	1 (0.7)	1 (0.7)	0
Skin and subcutaneous tissue disorders						
Dry skin	8 (5.2)	0	0	1 (0.7)	0	0
Erythema	3 (1.9)	0	0	0	0	0
Night sweats	3 (1.9)	0	0	0	0	0
Pruritus	12 (7.8)	0	0	3 (2.0)	0	0
Pruritus generalized	3 (1.9)	0	0	1 (0.7)	0	0
Psoriasis	2 (1.3)	1 (0.6)	0	0	0	0
Rash	11 (7.1)	1 (0.6)	0	3 (2.0)	0	0
Rash maculo-papular	5 (3.2)	1 (0.6)	0	1 (0.7)	0	0
Rash pruritic	2 (1.3)	0	0	1 (0.7)	0	0
Skin exfoliation	2 (1.3)	0	0	0	0	0
Urticaria	2 (1.3)	0	0	1 (0.7)	0	0

Treatment-related adverse events reported in <1% patients with NSCLC treated with KEYTRUDA® 200 mg every 3 weeks (n=154) by SOC are shown below.

Endocrine disorders: hypophysitis
Gastrointestinal disorders: pancreatitis

Metabolism and nutrition disorders: diabetic ketoacidosis
Musculoskeletal and connective tissue disorders: myositis

Table 11 summarizes the treatment-related adverse events that occurred in at least 1% of patients with NSCLC treated with KEYTRUDA® in KEYNOTE-042. The most common treatment-related adverse event (reported in at least 10% of patients) was hypothyroidism. The most common Grade 3-5 treatment-related adverse events for patients treated with KEYTRUDA® in KEYNOTE-042 were pneumonitis (3.1%) and alanine aminotransferase increased (1.4%).

Treatment was discontinued for treatment related adverse events in 9.0% of the 636 patients receiving KEYTRUDA® and in 9.4% of the 615 patients receiving chemotherapy. The most common treatment-related adverse events leading to study drug discontinuation (occurring in more than 2 patients) were: pneumonitis (n=19); alanine aminotransferase increased (n=6); and aspartate aminotransferase increased (n=3). The median time to discontinuation for treatment-related adverse events was 2.8 months.

Table 11: Treatment-Related Adverse Events (incidence ≥ 1%) in Patients Treated with KEYTRUDA®, APaT Population in KEYNOTE-042

	KEYTRUDA® 200 mg every 3 weeks n=636				Chemotherapy n=615			
Adverse Reaction	**Any Grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**	**Any Grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**
Blood and lymphatic system disorders								
Anemia	35 (5.5)	4 (0.6)	0	0	229(37.2)	73 (11.9)	7 (1.1)	0
Leukopenia	10 (1.6)	0	0	0	35 (5.7)	6 (1.0)	4 (0.7)	0
Endocrine disorders								
Hyperthyroidism	37 (5.8)	1 (0.2)	0	0	1 (0.2)	0	0	0
Hypothyroidism	69 (10.8)	1 (0.2)	0	0	2 (0.3)	0	0	0
Gastrointestinal disorders								
Constipation	8 (1.3)	0	0	0	68 (11.1)	0	0	0
Diarrhea	34(5.3)	5 (0.8)	0	0	46 (7.5)	1 (0.2)	0	0
Dry mouth	10 (1.6)	0	0	0	4 (0.7)	0	0	0
Nausea	31 (4.9)	0	0	0	184 (29.9)	7 (1.1)	0	0
Stomatitis	7 (1.1)	0	0	0	31 (5.0)	0	0	0
Vomiting	15 (2.4)	0	0	0	97 (15.8)	2(0.3)	0	0
General disorders and administration site conditions								
Asthenia	27 (4.2)	3 (0.5)	0	0	60 (9.8)	10 (1.6)	0	0
Fatigue	50 (7.9)	3 (0.5)	0	0	102 (16.6)	8 (1.3)	0	0
Edema peripheral	9 (1.4)	1 (0.2)	0	0	14 (2.3)	0	0	0
Pyrexia	24 (3.8)	0	0	0	19 (3.1)	0	0	0
Hepatobiliary disorders								
Hepatic function abnormal	8 (1.3)	1 (0.2)	1 (0.2)	0	4 (0.7)	2 (0.3)	0	0
Investigations								
Alanine aminotransferase increased	45 (7.1)	9 (1.4)	0	0	53 (8.6)	5 (0.8)	0	0
Aspartate aminotransferase increased	41 (6.4)	4 (0.6)	0	0	42 (6.8)	2 (0.3)	0	0

	KEYTRUDA® 200 mg every 3 weeks n=636				Chemotherapy n=615			
Adverse Reaction	**Any Grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**	**Any Grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**
Blood alkaline phosphatase increased	17 (2.7)	2 (0.3)	0	0	17 (2.8)	2 (0.3)	0	0
Blood bilirubin increased	12 (1.9)	0	0	0	8 (1.3)	0	0	0
Blood thyroid stimulating hormone decreased	11 (1.7)	0	0	0	1 (0.2)	0	0	0
Blood thyroid stimulating hormone increased	14 (2.2)	0	0	0	1 (0.2)	0	0	0
Gamma-glutamyltransferase increased	8 (1.3)	2 (0.3)	0	0	4 (0.7)	1 (0.2)	0	0
Tri-iodothyronine decreased	9 (1.4)	0	0	0	3 (0.5)	0	0	0
Weight decreased	17 (2.7)	2 (0.3)	0	0	19 (3.1)	0	0	0
Metabolism and nutrition disorders								
Decreased appetite	40 (6.3)	5 (0.8)	0	0	109 (17.7)	9 (1.5)	0	0
Musculoskeletal and connective tissue disorders								
Arthralgia	27 (4.2)	0	0	0	46 (7.5)	0	0	0
Myalgia	20 (3.1)	1 (0.2)	0	0	50 (8.1)	0	0	0
Nervous system disorders								
Dysgeusia	7 (1.1)	0	0	0	20 (3.3)	0	0	0
Respiratory, thoracic and mediastinal disorders								
Cough	9 (1.4)	0	0	0	6 (1.0)	0	0	0
Dyspnea	16 (2.5)	2 (0.3)	0	0	18 (2.9)	0	0	1 (0.2)
Hemoptysis	7 (1.1)	0	0	1 (0.2)	2 (0.3)	0	0	0
Pleural effusion	10 (1.6)	4 (0.6)	0	0	0	0	0	0
Pneumonitis	43 (6.8)	15 (2.4)	4 (0.6)	1 (0.2)	0	0	0	0
Skin and subcutaneous tissue disorders								
Dry skin	11 (1.7)	1 (0.2)	0	0	6 (1.0)	0	0	0
Pruritus	46 (7.2)	2 (0.3)	0	0	15 (2.4)	0	0	0
Rash	46 (7.2)	3 (0.5)	0	0	27(4.4)	0	0	0
Rash maculo-papular	12 (1.9)	4 (0.6)	0	0	5 (0.8)	1 (0.2)	0	0

Treatment-related adverse events reported in <1% patients with NSCLC treated with KEYTRUDA® 200 mg every 3 weeks (n=636) by SOC are shown below.

Cardiac disorders: myocarditis
Endocrine disorders: adrenal insufficiency, hypophysitis, hypopituitarism, thyroiditis
Gastrointestinal disorders: colitis, pancreatitis
Hepatobiliary disorders: hepatitis

Injury, poisoning and procedural complications: infusion related reaction, including hypersensitivity
Musculoskeletal and connective tissue disorders: arthritis
Renal and urinary disorders: nephritis

Table 12 summarizes the treatment-related adverse events that occurred in at least 1% of patients with NSCLC treated with KEYTRUDA® in KEYNOTE-189. The most common treatment-related adverse events (reported in at least 20% of patients) were nausea, anemia, fatigue, neutropenia, and decreased appetite. The most common Grade 3-5 treatment-related adverse events for patients treated with KEYTRUDA® in KEYNOTE-189 were neutropenia (14.6%), anemia (13.6%), thrombocytopenia (7.7%) and febrile neutropenia (5.9%).

Treatment was discontinued for treatment-related adverse events in 9.6% of the 405 patients receiving KEYTRUDA®, pemetrexed, and chemotherapy and in 4.0% of the 202 patients receiving placebo, pemetrexed, and chemotherapy. The most common treatment-related adverse events leading to study drug discontinuation (occurring in more than 3 patients) were acute kidney injury (n=7) and pneumonitis (n=7). The median time to discontinuation for treatment-related adverse events was 4.0 months.

Table 12: Treatment-Related Adverse Events (Incidence ≥ 1%) in Patients Treated with KEYTRUDA® in Combination with Pemetrexed and Platinum Chemotherapy, APaT Population in KEYNOTE-189.

Adverse Reaction	KEYTRUDA® + Pemetrexed + Platinum chemotherapy n=405				Placebo + Pemetrexed + Platinum chemotherapy n=202			
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Blood and lymphatic system disorders								
Anemia	154 (38.0)	53 (13.1)	2 (0.5)	0	77 (38.1)	27 (13.4)	0	0
Febrile neutropenia	25 (6.2)	16 (4.0)	8 (2.0)	0	4 (2.0)	2 (1.0)	2 (1.0)	0
Leukopenia	22 (5.4)	6 (1.5)	2 (0.5)	0	12 (5.9)	1 (0.5)	0	0
Neutropenia	101 (24.9)	34 (8.4)	25 (6.2)	0	45 (22.3)	16 (7.9)	6 (3.0)	0
Pancytopenia	6 (1.5)	4 (1.0)	2 (0.5)	0	2 (1.0)	0	2 (1.0)	0
Thrombocytopenia	69 (17.0)	16 (4.0)	15 (3.7)	0	27 (13.4)	6 (3.0)	7 (3.5)	0
Ear and labyrinth disorders								
Tinnitus	9 (2.2)	0	0	0	9 (4.5)	0	0	0
Endocrine disorders								
Hyperthyroidism	13 (3.2)	0	0	0	6 (3.0)	0	0	0
Hypothyroidism	22 (5.4)	2 (0.5)	0	0	3 (1.5)	0	0	0
Eye disorders								
Dry eye	10 (2.5)	0	0	0	2 (1.0)	0	0	0
Eye pruritus	5 (1.2)	0	0	0	1 (0.5)	0	0	0
Lacrimation increased	51 (12.6)	0	0	0	14 (6.9)	0	0	0
Vision blurred	5 (1.2)	0	0	0	1 (0.5)	0	0	0
Gastrointestinal disorders								
Abdominal pain	10 (2.5)	1 (0.2)	0	0	4 (2.0)	1 (0.5)	0	0

Adverse Reaction	KEYTRUDA® + Pemetrexed + Platinum chemotherapy n=405				Placebo + Pemetrexed + Platinum chemotherapy n=202			
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Abdominal pain upper	9 (2.2)	0	0	0	0	0	0	0
Colitis	5 (1.2)	2 (0.5)	0	0	0	0	0	0
Constipation	67 (16.5)	0	0	0	24 (11.9)	0	0	0
Diarrhea	78 (19.3)	15 (3.7)	0	0	22 (10.9)	4 (2.0)	0	0
Dry mouth	7 (1.7)	0	0	0	2 (1.0)	0	0	0
Dyspepsia	15 (3.7)	0	0	0	3 (1.5)	0	0	0
Nausea	187 (46.2)	12 (3.0)	0	0	90 (44.6)	4 (2.0)	0	0
Stomatitis	26 (6.4)	2 (0.5)	0	0	15 (7.4)	1 (0.5)	0	0
Vomiting	74 (18.3)	7 (1.7)	0	0	39 (19.3)	4 (2.0)	0	0
General disorders and administration site conditions								
Asthenia	53 (13.1)	16 (4.0)	0	0	31 (15.3)	3 (1.5)	0	0
Fatigue	134 (33.1)	20 (4.9)	0	0	62 (30.7)	3 (1.5)	0	0
General physical health deterioration	7 (1.7)	4 (1.0)	0	0	2 (1.0)	2 (1.0)	0	0
Mucosal inflammation	30 (7.4)	3 (0.7)	0	0	14 (6.9)	1 (0.5)	0	0
Edema	7 (1.7)	0	0	0	2 (1.0)	0	0	0
Edema peripheral	27 (6.7)	0	0	0	12 (5.9)	0	0	0
Pyrexia	24 (5.9)	1 (0.2)	0	0	4 (2.0)	0	0	0
Infections and infestations								
Cellulitis	7 (1.7)	5 (1.2)	0	0	0	0	0	0
Conjunctivitis	20 (4.9)	1 (0.2)	0	0	10 (5.0)	0	0	0
Oral candidiasis	11 (2.7)	1 (0.2)	0	0	2 (1.0)	0	0	0
Pneumonia	7 (1.7)	3 (0.7)	0	1 (0.2)	1 (0.5)	0	0	1 (0.5)
Upper respiratory tract infection	6 (1.5)	2 (0.5)	0	0	0	0	0	0
Urinary tract infection	5 (1.2)	0	0	0	0	0	0	0
Investigations								
Alanine aminotransferase increased	38 (9.4)	2 (0.5)	0	0	16 (7.9)	3 (1.5)	0	0
Aspartate aminotransferase increased	28 (6.9)	0	0	0	10 (5.0)	1 (0.5)	0	0
Blood alkaline phosphatase increased	6 (1.5)	0	0	0	3 (1.5)	1 (0.5)	0	0

Adverse Reaction	KEYTRUDA® + Pemetrexed + Platinum chemotherapy n=405				Placebo + Pemetrexed + Platinum chemotherapy n=202			
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Blood creatinine increased	32 (7.9)	1 (0.2)	0	0	12 (5.9)	0	0	0
Blood thyroid stimulating hormone decreased	9 (2.2)	0	0	0	2 (1.0)	0	0	0
Blood thyroid stimulating hormone increased	5 (1.2)	0	0	0	1 (0.5)	0	0	0
Gamma-glutamyltransferase increased	8 (2.0)	2 (0.5)	1 (0.2)	0	4 (2.0)	1 (0.5)	0	0
Lymphocyte count decreased	8 (2.0)	1 (0.2)	0	0	4 (2.0)	0	1 (0.5)	0
Neutrophil count decreased	11 (2.7)	4 (1.0)	3 (0.7)	0	3 (1.5)	2 (1.0)	0	0
Platelet count decreased	10 (2.5)	3 (0.7)	2 (0.5)	0	0	0	0	0
Weight decreased	15 (3.7)	2 (0.5)	0	0	5 (2.5)	0	0	0
White blood cell count decreased	22 (5.4)	7 (1.7)	0	0	12 (5.9)	6 (3.0)	0	0
Metabolism and nutrition disorders								
Decreased appetite	84 (20.7)	4 (1.0)	0	0	42 (20.8)	1 (0.5)	0	0
Dehydration	8 (2.0)	3 (0.7)	0	0	4 (2.0)	1 (0.5)	0	0
Hypocalcemia	6 (1.5)	0	0	0	1 (0.5)	0	0	0
Hypokalemia	9 (2.2)	2 (0.5)	0	0	4 (2.0)	1 (0.5)	0	0
Hypomagnesemia	22 (5.4)	4 (1.0)	1 (0.2)	0	3 (1.5)	0	0	0
Hyponatremia	5 (1.2)	2 (0.5)	0	0	3 (1.5)	1 (0.5)	0	0
Hypophosphatemia	8 (2.0)	3 (0.7)	0	0	2 (1.0)	1 (0.5)	0	0
Musculoskeletal and connective tissue disorders								
Arthralgia	15 (3.7)	1 (0.2)	0	0	8 (4.0)	1 (0.5)	0	0
Muscular weakness	7 (1.7)	1 (0.2)	0	0	2 (1.0)	1 (0.5)	0	0
Myalgia	10 (2.5)	1 (0.2)	0	0	2 (1.0)	0	0	0
Nervous system disorders								
Dizziness	10 (2.5)	0	0	0	5 (2.5)	0	0	0
Dysgeusia	37 (9.1)	1 (0.2)	0	0	14 (6.9)	0	0	0
Headache	9 (2.2)	0	0	0	3 (1.5)	0	0	0
Hypoasthesia	5 (1.2)	0	0	0	0	0	0	0
Lethargy	7 (1.7)	0	0	0	1 (0.5)	0	0	0
Neuropathy peripheral	10 (2.5)	0	0	0	3 (1.5)	0	0	0

Adverse Reaction	KEYTRUDA® + Pemetrexed + Platinum chemotherapy n=405				Placebo + Pemetrexed + Platinum chemotherapy n=202			
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Paresthesia	12 (3.0)	0	0	0	6 (3.0)	0	0	0
Peripheral sensory neuropathy	7 (1.7)	0	0	0	2 (1.0)	0	0	0
Renal and urinary disorders								
Acute kidney injury	14 (3.5)	5 (1.2)	0	2 (0.5)	0	0	0	0
Renal failure	9 (2.2)	2 (0.5)	0	0	4 (2.0)	0	0	0
Respiratory, thoracic and mediastinal disorders								
Cough	8 (2.0)	0	0	0	5 (2.5)	0	0	0
Dyspnea	16 (4.0)	3 (0.7)	1 (0.2)	0	7 (3.5)	1 (0.5)	0	0
Epistaxis	10 (2.5)	0	0	0	3 (1.5)	0	0	0
Hiccups	12 (3.0)	0	0	0	2 (1.0)	0	0	0
Oropharyngeal pain	5 (1.2)	0	0	0	1 (0.5)	0	0	0
Pneumonitis	16 (4.0)	6 (1.5)	1 (0.2)	3 (0.7)	3 (1.5)	3 (1.5)	0	0
Rhinorrhea	12 (3.0)	0	0	0	4 (2.0)	0	0	0
Skin and subcutaneous tissue disorders								
Alopecia	20 (4.9)	0	0	0	9 (4.5)	0	0	0
Dermatitis acneiform	7 (1.7)	0	0	0	2 (1.0)	0	0	0
Dry skin	11 (2.7)	0	0	0	12 (5.9)	0	0	0
Erythema	10 (2.5)	0	0	0	2 (1.0)	0	0	0
Pruritus	37 (9.1)	0	0	0	12 (5.9)	0	0	0
Rash	51 (12.6)	5 (1.2)	0	0	17 (8.4)	3 (1.5)	0	0
Rash maculo-papular	8 (2.0)	0	0	0	7 (3.5)	1 (0.5)	0	0
Rash pruritic	5 (1.2)	0	0	0	1 (0.5)	0	0	0

Treatment-related adverse events attributable to KEYTRUDA® and reported in <1% patients with non-squamous NSCLC treated with KEYTRUDA® in combination with pemetrexed and platinum chemotherapy (n=405) by SOC are shown below.

Endocrine disorders: adrenal insufficiency, hypophysitis, hypopituitarism, thyroiditis
Gastrointestinal disorders: pancreatitis
Hepatobiliary disorders: hepatitis
Injury, poisoning and procedural complications: infusion related reaction
Metabolism and nutrition disorders: Type 1 diabetes mellitus
Musculoskeletal and connective tissue disorders: arthritis
Renal and urinary disorders: nephritis

Table 13 summarizes the treatment-related adverse events that occurred in at least 1% of patients with NSCLC treated with KEYTRUDA® in KEYNOTE-407. The most common treatment-related adverse events (reported in at least 20% of patients) were alopecia, anemia,

neutropenia, nausea, thrombocytopenia, and diarrhea. The most common Grade 3-5 treatment-related adverse events for patients treated with KEYTRUDA® in KEYNOTE-407 were neutropenia (21.2%), anemia (13.7%), thrombocytopenia (6.5%), neutrophil count decreased (6.1%), and febrile neutropenia (5.0%).

Treatment was discontinued for treatment-related adverse events in 9.0% of the 278 patients receiving KEYTRUDA®, carboplatin and either paclitaxel or nab-paclitaxel and in 3.2% of the 280 patients receiving placebo, carboplatin and either paclitaxel or nab-paclitaxel. The most common treatment-related adverse events leading to study discontinuation (occurring in more than 3 patients) were pneumonitis (n=4) and sepsis (n=3). The median time to discontinuation for treatment-related adverse events was 1.9 months.

Table 13: Treatment-Related Adverse Events (Incidence ≥ 1%) in Patients Treated with KEYTRUDA® in Combination with Carboplatin and Either Paclitaxel or Nab-paclitaxel, APaT Population in KEYNOTE-407.

	KEYTRUDA® + Carboplatin + Paclitaxel or Nab-Paclitaxel n=278				Placebo + Carboplatin + Paclitaxel or Nab-Paclitaxel n=280			
Adverse Reaction	**Any Grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**	**Any Grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**
Blood and lymphatic system disorders								
Anemia	123 (44.2)	38 (13.7)	0	0	117 (41.8)	43 (15.4)	0	0
Febrile neutropenia	14 (5.0)	12 (4.3)	2 (0.7)	0	10 (3.6)	8 (2.9)	2 (0.7)	0
Leukopenia	23 (8.3)	8 (2.9)	4 (1.4)	0	19 (6.8)	12 (4.3)	0	0
Lymphopenia	5 (1.8)	1 (0.4)	1 (0.4)	0	4 (1.4)	2 (0.7)	0	0
Neutropenia	97 (34.9)	35 (12.6)	24 (8.6)	0	86 (30.7)	40 (14.3)	23 (8.2)	0
Thrombocytopenia	81 (29.1)	12 (4.3)	6 (2.2)	0	58 (20.7)	12 (4.3)	4 (1.4)	0
Endocrine disorders								
Hyperthyroidism	17 (6.1)	1 (0.4)	0	0	2 (0.7)	0	0	0
Hypothyroidism	16 (5.8)	0	0	0	3 (1.1)	0	0	0
Gastrointestinal disorders								
Abdominal pain	4 (1.4)	0	0	0	3 (1.1)	0	0	0
Abdominal pain upper	4 (1.4)	0	0	0	2 (0.7)	0	0	0
Colitis	6 (2.2)	4 (1.4)	2 (0.7)	0	3 (1.1)	2 (0.7)	0	0
Constipation	31 (11.2)	1 (0.4)	0	0	25 (8.9)	0	0	0
Diarrhea	61 (21.9)	8 (2.9)	0	0	47 (16.8)	4 (1.4)	0	0
Dry mouth	4 (1.4)	0	0	0	1 (0.4)	0	0	0
Gastroesophageal reflux disease	3 (1.1)	0	0	0	1 (0.4)	0	0	0
Nausea	85 (30.6)	2 (0.7)	0	0	71 (25.4)	3 (1.1)	0	0
Retching	3 (1.1)	0	0	0	0	0	0	0

	KEYTRUDA® + Carboplatin + Paclitaxel or Nab-Paclitaxel n=278				Placebo + Carboplatin + Paclitaxel or Nab-Paclitaxel n=280			
Adverse Reaction	**Any Grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**	**Any Grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**
Stomatitis	9 (3.2)	0	0	0	11 (3.9)	1 (0.4)	0	0
Vomiting	36 (12.9)	1 (0.4)	0	0	25 (8.9)	3 (1.1)	0	0
General disorders and administration site conditions								
Asthenia	46 (16.5)	3 (1.1)	0	0	41 (14.6)	6 (2.1)	0	0
Fatigue	54 (19.4)	7 (2.5)	0	0	52 (18.6)	6 (2.1)	1 (0.4)	0
Malaise	10 (3.6)	0	0	0	12 (4.3)	1 (0.4)	0	0
Mucosal inflammation	8 (2.9)	1 (0.4)	0	0	6 (2.1)	0	0	0
Edema peripheral	7 (2.5)	0	0	0	6 (2.1)	1 (0.4)	0	0
Pain	3 (1.1)	1 (0.4)	0	0	3 (1.1)	0	0	0
Pyrexia	8 (2.9)	2 (0.7)	0	0	11 (3.9)	0	0	0
Hepatobiliary disorders								
Autoimmune hepatitis	5 (1.8)	4 (1.4)	1 (0.4)	0	0	0	0	0
Infections and infestations								
Pneumonia	9 (3.2)	6 (2.2)	2 (0.7)	0	4 (1.4)	2 (0.7)	0	1 (0.4)
Rhinitis	3 (1.1)	0	0	0	0	0	0	0
Sepsis	4 (1.4)	0	0	3 (1.1)	0	0	0	0
Upper respiratory tract infection	3 (1.1)	0	0	0	2 (0.7)	0	0	0
Urinary tract infection	4 (1.4)	0	0	0	0	0	0	0
Injury, poisoning and procedural complications								
Infusion related reaction	4 (1.4)	2 (0.7)	1 (0.4)	0	3 (1.1)	0	1 (0.4)	0
Investigations								
Alanine aminotransferase increased	11 (4.0)	1 (0.4)	0	0	8 (2.9)	1 (0.4)	0	0
Aspartate aminotransferase increased	14 (5.0)	0	0	0	5 (1.8)	1 (0.4)	0	0
Blood alkaline phosphatase increased	6 (2.2)	0	0	4 (1.4)	0	0	0	0
Blood bilirubin increased	3 (1.1)	0	0	0	3 (1.1)	1 (0.4)	0	0
Blood creatinine increased	9 (3.2)	0	0	0	6 (2.1)	1 (0.4)	0	0
Lymphocyte count decreased	3 (1.1)	2 (0.7)	0	0	7 (2.5)	2 (0.7)	0	0
Neutrophil count decreased	24 (8.6)	5 (1.8)	12 (4.3)	0	28 (10.0)	12 (4.3)	12 (4.3)	0

	KEYTRUDA® + Carboplatin + Paclitaxel or Nab-Paclitaxel n=278				Placebo + Carboplatin + Paclitaxel or Nab-Paclitaxel n=280			
Adverse Reaction	**Any Grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**	**Any Grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**
Platelet count decreased	23 (8.3)	5 (1.8)	0	0	16 (5.7)	6 (2.1)	0	0
Weight decreased	10 (3.6)	1 (0.4)	0	0	8 (2.9)	1 (0.4)	0	0
White blood cell count decreased	30 (10.8)	7 (2.5)	4 (1.4)	0	28 (10.0)	10 (3.6)	0	0
Metabolism and nutrition disorders								
Decreased appetite	47 (16.9)	5 (1.8)	0	0	57 (20.4)	4 (1.4)	0	0
Dehydration	4 (1.4)	2 (0.7)	0	0	5 (1.8)	1 (0.4)	1 (0.4)	0
Hyperglycemia	3 (1.1)	0	0	0	1 (0.4)	0	0	0
Hypomagnesemia	15 (5.4)	1 (0.4)	0	0	9 (3.2)	2 (0.7)	0	0
Hyponatremia	6 (2.2)	5 (1.8)	0	0	4 (1.4)	0	1 (0.4)	0
Hypophosphatemia	4 (1.4)	1 (0.4)	0	0	4 (1.4)	1 (0.4)	0	0
Musculoskeletal and connective tissue disorders								
Arthralgia	36 (12.9)	1 (0.4)	0	0	24 (8.6)	2 (0.7)	0	0
Bone pain	4 (1.4)	0	0	0	5 (1.8)	0	0	0
Musculoskeletal pain	5 (1.8)	1 (0.4)	0	0	5 (1.8)	0	0	0
Myalgia	32 (11.5)	2 (0.7)	0	0	26 (9.3)	1 (0.4)	0	0
Pain in extremity	8 (2.9)	0	0	0	12 (4.3)	0	0	0
Nervous system disorders								
Dizziness	6 (2.2)	0	0	0	7 (2.5)	0	0	0
Dysgeusia	23 (8.3)	0	0	0	7 (2.5)	0	0	0
Headache	7 (2.5)	0	0	0	7 (2.5)	0	0	0
Hypoasthesia	6 (2.2)	0	0	0	4 (1.4)	0	0	0
Lethargy	4 (1.4)	0	0	0	0	0	0	0
Neuropathy peripheral	55 (19.8)	3 (1.1)	0	0	37 (13.2)	2 (0.7)	0	0
Neurotoxicity	7 (2.5)	0	0	0	2 (0.7)	0	0	0
Paresthesia	15 (5.4)	1 (0.4)	0	0	13 (4.6)	1 (0.4)	0	0
Peripheral motor neuropathy	3 (1.1)	0	0	0	4 (1.4)	0	0	0
Peripheral sensory neuropathy	31 (11.2)	0	0	0	36 (12.9)	2 (0.7)	0	0
Polyneuropathy	6 (2.2)	1 (0.4)	0	0	5 (1.8)	1 (0.4)	0	0
Psychiatric disorders								
Insomnia	4 (1.4)	0	0	0	0	0	0	0
Renal and urinary disorders								
Acute kidney injury	5 (1.8)	1 (0.4)	0	0	4 (1.4)	2 (0.7)	0	1 (0.4)
Respiratory, thoracic and mediastinal disorders								
Dyspnea	4 (1.4)	0	0	0	5 (1.8)	0	0	0

	KEYTRUDA® + Carboplatin + Paclitaxel or Nab-Paclitaxel n=278				Placebo + Carboplatin + Paclitaxel or Nab-Paclitaxel n=280			
Adverse Reaction	**Any Grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**	**Any Grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**
Epistaxis	11 (4.0)	0	0	0	9 (3.2)	1 (0.4)	0	0
Hiccups	11 (4.0)	0	0	0	4 (1.4)	0	0	0
Interstitial lung disease	3 (1.1)	0	0	0	2 (0.7)	1 (0.4)	1 (0.4)	0
Pneumonitis	11 (4.0)	4 (1.4)	0	1 (0.4)	3 (1.1)	0	0	0
Skin and subcutaneous tissue disorders								
Alopecia	126 (45.3)	1 (0.4)	0	0	100 (35.7)	3 (1.1)	0	0
Dry skin	9 (3.2)	0	0	0	5 (1.8)	1 (0.4)	0	0
Pruritus	29 (10.4)	0	0	0	15 (5.4)	0	0	0
Rash	28 (10.1)	0	0	0	20 (7.1)	0	0	0
Rash maculo-papular	6 (2.2)	0	0	0	3 (1.1)	0	0	0
Rash papular	3 (1.1%)	0	0	0	0	0	0	0
Vascular disorders								
Hot flush	3 (1.1)	0	0	0	0	0	0	0
Hypotension	5 (1.8)	2 (0.7)	0	0	7 (2.5)	3 (1.1)	0	0

Treatment–related adverse events attributable to KEYTRUDA® and reported in <1% patients with squamous NSCLC treated with KEYTRUDA® in combination with carboplatin and either paclitaxel or nab-paclitaxel (n=278) by SOC are shown below.

Endocrine disorders: hypophysitis, hypopituitarism
Renal and urinary disorders: nephritis

Table 14 summarizes the treatment-related adverse events that occurred in at least 1% of patients with NSCLC treated with KEYTRUDA® in KEYNOTE-010. Clinically important adverse events regardless of the investigator assessment of causality occurring in patients receiving KEYTRUDA® were fatigue (25%), diarrhea (14%), asthenia (11%) and pyrexia (11%). The most common treatment-related adverse events (reported in at least 10% of patients) were fatigue, decreased appetite, rash, and nausea. The most common Grade 3-5 treatment-related adverse events for patients treated with KEYTRUDA® in KEYNOTE-010 were pneumonitis (1.8%) and fatigue (1.5%).

In KEYNOTE-010, the adverse reaction profile was similar for the 2 mg/kg and 10 mg/kg dose, therefore summary safety results are provided in a pooled analysis (n=682). Treatment was discontinued for treatment-related adverse events in 5% of patients receiving KEYTRUDA®. The most common treatment-related adverse event resulting in permanent discontinuation of KEYTRUDA® was pneumonitis (1.8%, n =12). The median time to discontinuation for treatment-related adverse events was 2.5 months. Treatment-related adverse events leading to

interruption of KEYTRUDA® occurred in 13% of patients; the most common (≥ 1%) were fatigue (1.2%) and decreased appetite (1%).

Table 14: Treatment-Related Adverse Events (incidence ≥ 1%) KEYTRUDA® Treatment Groups Combined, APaT Population in KEYNOTE 010.

Adverse Reaction	KEYTRUDA® 2 or 10 mg/kg every 3 weeks n=682				Docetaxel 75 mg/m^2 every 3 weeks n=309			
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Blood and lymphatic system disorders								
Anemia	24 (3.5)	4 (0.6)	0	0	40 (12.9)	5 (1.6)	0	0
Endocrine disorders								
Hyperthyroidism	25 (3.7)	1 (0.1)	0	0	0	0	0	0
Hypothyroidism	48 (7.0)	0	0	0	1 (0.3)	0	0	0
Eye disorders								
Dry eye	10 (1.5)	0	0	0	1 (0.3)	0	0	0
Gastrointestinal disorders								
Abdominal pain	7 (1.0)	0	0	0	4 (1.3)	0	0	0
Constipation	23 (3.4)	0	0	0	14 (4.5)	0	0	0
Diarrhea	46 (6.7)	2 (0.3)	0	0	56 (18.1)	6 (1.9)	1 (0.3)	0
Dry mouth	8 (1.2)	0	0	0	3 (1.0)	0	0	0
Nausea	68 (10.0)	3 (0.4)	0	0	45 (14.6)	1 (0.3)	0	0
Stomatitis	20 (2.9)	1 (0.1)	0	0	43 (13.9)	3 (1.0)	0	0
Vomiting	25 (3.7)	1 (0.1)	0	0	24 (7.8)	2 (0.6)	0	0
General disorders and administration site conditions								
Asthenia	39 (5.7)	3 (0.4)	0	0	35 (11.3)	6 (1.9)	0	0
Fatigue	95(13.9)	10 (1.5)	0	0	76 (24.9)	11 (3.6)	0	0
Influenza like illness	7 (1.0)	0	0	0	0	0	0	0
Malaise	14 (2.1)	0	0	0	11 (3.6)	0	0	0
Edema peripheral	9 (1.3)	0	0	0	21 (6.8)	0	0	0
Pyrexia	24 (3.5)	1 (0.1)	0	0	17 (5.5)	1 (0.3)	0	0
Infections and infestations								
Pneumonia	10 (1.5)	4 (0.6)	0	2 (0.3)	5 (1.6)	2 (0.6)	2 (0.6)	0
Investigations								
Alanine aminotransferase increased	24 (3.5)	3 (0.4)	0	0	4 (1.3)	0	0	0
Aspartate aminotransferase increased	17 (2.5)	2 (0.3)	0	0	3 (1.0)	0	0	0

Adverse Reaction	KEYTRUDA® 2 or 10 mg/kg every 3 weeks n=682				Docetaxel 75 mg/m^2 every 3 weeks n=309			
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Blood alkaline phosphatase increased	11 (1.6)	2 (0.3)	0	0	2 (0.6)	0	0	0
Blood creatinine increased	13 (1.9)	0	0	0	0	0	0	0
Blood thyroid stimulating hormone increased	7 (1.0)	0	0	0	0	0	0	0
Weight decreased	15 (2.2)	1 (0.1)	0	0	2 (0.6)	0	0	0
Metabolism and nutrition disorders								
Decreased appetite	79 (11.6)	4 (0.6)	0	0	49 (15.9)	3 (1.0)	0	0
Hypertriglyceridemia	10 (1.5)	2 (0.3)	2 (0.3)	0	0	0	0	0
Musculoskeletal and connective tissue disorders								
Arthralgia	32 (4.7)	2 (0.3)	0	0	18 (5.8)	0 (0.0)	0	0
Back pain	9 (1.3)	1 (0.1)	0	0	0	0	0	0
Musculoskeletal pain	8 (1.2)	0	0	0	4 (1.3)	0	0	0
Myalgia	19 (2.8)	0	0	0	29 (9.4)	0	0	0
Nervous system disorders								
Dizziness	11 (1.6)	0	0	0	5 (1.6)	1 (0.3)	0	0
Dysgeusia	11 (1.6)	0	0	0	16 (5.2)	0	0	0
Headache	14 (2.1)	0	0	0	2 (0.6)	0	0	0
Respiratory, thoracic and mediastinal disorders								
Cough	11 (1.6)	0	0	0	3 (1.0)	0	0	0
Dyspnea	21 (3.1)	4 (0.6)	0	0	13 (4.2)	4 (1.3)	0	0
Pneumonitis	26 (3.8)	5 (0.7)	4 (0.6)	3 (0.4)	3 (1.0)	1 (0.3)	0	0
Skin and subcutaneous tissue disorders								
Dry skin	18 (2.6)	0	0	0	4 (1.3)	0	0	0
Pruritus	57 (8.4)	0	0	0	5 (1.6)	1 (0.3)	0	0
Rash	73 (10.7)	2 (0.3)	0	0	14 (4.5)	0	0	0
Rash maculo-papular	9 (1.3)	1 (0.1)	0	0	0	0	0	0

Treatment-related adverse events reported in <1% patients with NSCLC treated with pembrolizumab 2 mg/kg or 10 mg/kg every 3 weeks (n=682) by SOC are shown below.

Endocrine disorders: hypopituitarism, adrenal insufficiency
Gastrointestinal disorders: colitis, pancreatitis
Injury, poisoning and procedural complications: infusion related reaction
Metabolism and nutrition disorders: diabetic ketoacidosis, Type 1 diabetes mellitus
Musculoskeletal and connective tissue disorders: arthritis
Skin and subcutaneous tissue disorders: pemphigoid

Abnormal Hematologic and Clinical Chemistry Findings
Laboratory abnormalities (worsened from baseline in ≥ 10% of patients), reported in KEYNOTE-024 in patients with NSCLC, are presented in Table 15.

Table 15: Laboratory Abnormalities Worsened from Baseline in ≥ 10% of Patients with NSCLC 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]), APaT population in KEYNOTE 024.

Laboratory Test	KEYTRUDA® 200 mg every 3 weeks n=154		Chemotherapy n=150	
	All Grades n (%)	Grades 3-4 n (%)	All Grades n (%)	Grades 3-4 n (%)
Chemistry				
Glucose Increased	80 (51.9)	12 (7.8)	69 (46.0)	9 (6.0)
Alanine Aminotransferase Increased	47 (30.5)	7 (4.5)	46 (30.7)	0
Calcium Decreased	39 (25.3)	0	30 (20.0)	0
Aspartate Aminotransferase Increased	38 (24.7)	6 (3.9)	49 (32.7)	0
Alkaline Phosphatase Increased	34 (22.1)	4 (2.6)	36 (24.0)	0

Laboratory abnormalities (worsened from baseline in ≥ 10% of patients), reported in KEYNOTE-042 in patients with NSCLC, are presented in Table 16.

Table 16: Laboratory Abnormalities Worsened from Baseline in ≥ 10% of Patients with NSCLC 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]), APaT population in KEYNOTE-042

	KEYTRUDA® 200 mg every 3 weeks n=636		Chemotherapy n=615	
Laboratory Test	All Grades n (%)	Grades 3-4 n (%)	All Grades n (%)	Grades 3-4 n (%)
Chemistry				
Calcium Decreased	200 (25.3)	17 (2.2)	146 (19.1)	6 (0.8)

Laboratory abnormalities (worsened from baseline in ≥ 10% of patients), reported in KEYNOTE-189 in patients with non-squamous NSCLC treated with KEYTRUDA® in combination with pemetrexed and platinum chemotherapy, are presented in Table 17.

Table 17: Laboratory Abnormalities Worsened from Baseline in ≥ 10% of Patients with Non-squamous NSCLC Treated with KEYTRUDA® in Combination with Pemetrexed and Platinum Chemotherapy and at a Higher Incidence than in the Placebo, Pemetrexed and Platinum Chemotherapy Arm (Between Arm Difference of ≥ 5% [All Grades] or ≥ 2% [Grades 3-4]) (KEYNOTE-189).

Laboratory Test	KEYTRUDA® + Pemetrexed + Platinum chemotherapy n=405		Placebo + Pemetrexed + Platinum chemotherapy n=202	
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
Hematology				
Neutropenia	48	20	39	18
Platelet count decreased	29	11	28	7
Chemistry				
Hyperglycemia	62	9	57	7
Alanine aminotransferase increased	46	4	40	2
Aspartate aminotransferase increased	46	3	38	1
Creatinine increased	36	4	24	1
Hyponatremia	32	7	22	5
Hyperkalemia	24	3	18	3
Hypocalcemia	23	3	16	<1

Laboratory abnormalities (worsened from baseline in ≥ 10% of patients), reported in KEYNOTE-407 in patients with squamous NSCLC treated with KEYTRUDA® in combination with carboplatin and either paclitaxel or nab-paclitaxel are presented in Table 18.

Table 18: Laboratory Abnormalities Worsened from Baseline in ≥ 10% of Patients with Squamous NSCLC Treated with KEYTRUDA® in Combination with Carboplatin and either Paclitaxel or Nab-Paclitaxel and at a Higher Incidence than in the Placebo, Carboplatin and Either Paclitaxel or Nab-Paclitaxel Arm (Between Arm Difference of ≥ 5% [All Grades] or ≥ 2% [Grades 3-4] (KEYNOTE-407).

	KEYTRUDA® + Carboplatin + Paclitaxel or Nab-Paclitaxel n=278		Placebo + Carboplatin + Paclitaxel or Nab-Paclitaxel n=280	
Laboratory Test	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Hematology				
White blood cell decreased	65	20	58	20
Platelet count decreased	64	10	53	10
Lymphocyte count decreased	49	17	46	12
Hypoalbuminemia	36	3	32	1
Chemistry				
Aspartate aminotransferase increased	29	4	18	2
Alanine aminotransferase increased	27	3	20	2

Laboratory abnormalities (worsened from baseline in ≥ 10% of patients), reported in KEYNOTE-010, in patients with NSCLC, are presented in Table 19. Patients were treated with pembrolizumab at 2 mg/kg or 10 mg/kg every 3 weeks.

Table 19: Laboratory Abnormalities Worsened from Baseline in ≥ 10% of Patients with NSCLC Treated with KEYTRUDA® and at a Higher Incidence than in the Docetaxel Arm (Between Arm Difference of ≥ 5% [All Grades] or ≥ 2% [Grades 3-4]) (KEYNOTE-010).

Laboratory Test	KEYTRUDA® 2 or 10 mg/kg every 3 weeks n=682		Docetaxel 75 mg/m² every 3 weeks n=309	
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
Chemistry				
Hyponatremia	31	8	25	3
Increased alkaline phosphatase	28	3	16	0.6
Increased aspartate aminotransferase	25	2	12	0.6
Alanine aminotransferase increased	21	2	9	0.3
Hypomagnesemia	19	0.3	13	0.3
Creatinine increased	18	0.9	9	0.6

Hodgkin Lymphoma

Table 20 summarizes the treatment-related adverse events that occurred in at least 1% of patients with Hodgkin Lymphoma in KEYNOTE-204 (see CLINICAL TRIALS). The median duration of exposure to KEYTRUDA and brentuximab vedotin was 10 months (range: 1 day to 2.2 years) and 4.8 months (range: 1 day to 2.2 years), respectively. The most common adverse events (reported in at least 10% of patients treated with KEYTRUDA®) were hypothyroidism, pyrexia and pruritus. The most common Grade 3-5 treatment-related adverse events for patients treated with KEYTRUDA® in KEYNOTE-204 were thrombocytopenia (4.1%), neutropenia (2.0%) and pneumonitis (2.0%).

Serious adverse events occurred in 30% of patients who received KEYTRUDA®. Serious adverse events in ≥1% included pneumonitis, pneumonia, pyrexia, myocarditis, acute kidney injury, febrile neutropenia, and sepsis. Three patients (2%) died from causes other than disease progression: two from complications after allogeneic HSCT, and one from unknown cause.

KEYTRUDA® was discontinued for adverse events in 14% of patients with Hodgkin Lymphoma; 7% of patients discontinued treatment due to pneumonitis. Dosage interruption of KEYTRUDA® due to an adverse event occurred in 30% of patients. Adverse events which required dosage interruption in ≥ 3% of patients were upper respiratory tract infection, pneumonitis, transaminase increase, and pneumonia.

Thirty-eight percent of patients had an adverse event requiring systemic corticosteroid therapy.

Table 20: Treatment-Related Adverse Events Occurring in ≥ 1% of Patients with Hodgkin Lymphoma in KEYNOTE-204.

Adverse Event	KEYTRUDA® 200 mg every 3 weeks N=148			Brentuximab vedotin 1.8 mg/kg every 3 weeks N=152		
	Any Grade n (%)	Grade 3 n (%)	Grade 4 / Grade 5 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Blood and lymphatic system disorders						
Anemia	1 (0.7)	1 (0.7)	0	7 (4.6)	1 (0.7)	0
Immune thrombocytopenic purpura	3 (2.0)	0	2 (1.4)	0	0	0
Leukopenia	0	0	0	4 (2.6)	3 (2.0)	0
Lymphopenia	4 (2.7)	0	0	2 (1.3)	0	0
Neutropenia	5 (3.4)	3 (2.0)	0	15 (9.9)	8 (5.3)	3 (2.0)
Thrombocytopenia	6 (4.1)	2 (1.4)	0	5 (3.3)	0	0
Cardiac disorders						
Myocarditis	2 (1.4)	0	1 (0.7)	0	0	0
Endocrine disorders						
Hyperthyroidism	8 (5.4)	0	0	0	0	0
Hypothyroidism	23 (15.5)	0	0	2 (1.3)	0	0
Thyroiditis	2 (1.4)	0	0	0	0	0
Gastrointestinal disorders						
Abdominal pain	3 (2.0)	1 (0.7)	0	4 (2.6)	0	0
Constipation	3 (2.0)	0	0	8 (5.3)	0	0
Diarrhea	14 (9.5)	2 (1.4)	0	7 (4.6)	0	0
Dyspepsia	2 (1.4)	0	0	4 (2.6)	0	0
Nausea	6 (4.1)	0	0	20 (13.2)	0	0
Stomatitis	1 (0.7)	0	0	3 (2.0)	0	0
Vomiting	6 (4.1)	1 (0.7)	0	15 (9.9)	0	0
General disorders and administration site conditions						
Asthenia	3 (2.0)	0	0	2 (1.3)	0	0
Chest pain	2 (1.4)	0	0	1 (0.7)	0	0
Chills	7 (4.7)	0	0	2 (1.3)	0	0
Fatigue	13 (8.8)	0	0	16 (10.5)	0	0
Feeling Cold	2 (1.4)	0	0	0	0	0
Edema Peripheral	2 (1.4)	0	0	0	0	0
Pain	1 (0.7)	0	0	2 (1.3)	0	0
Pyrexia	19 (12.8)	1 (0.7)	0	9 (5.9)	0	0
Infections and infestations						
Ear Infection	2 (1.4)	0	0	1 (0.7)	0	0
Herpes zoster	1 (0.7)	0	0	3 (2.0)	0	0
Nasopharyngitis	2 (1.4)	0	0	1 (0.7)	0	0
Pneumonia	3 (2.0)	2 (1.4)	0 Gr 5: 1 (0.7)	5 (3.3)	2 (1.3)	0
Rhinitis	1 (0.7)	0	0	2 (1.3)	0	0
Upper respiratory tract infection	5 (3.4)	0	0	4 (2.6)	0	0
Injury, poisoning and procedural complications						
Infusion related reaction	5 (3.4)	0	0	12 (7.9)	3 (2.0)	0

Adverse Event	KEYTRUDA® 200 mg every 3 weeks N=148			Brentuximab vedotin 1.8 mg/kg every 3 weeks N=152		
	Any Grade n (%)	Grade 3 n (%)	Grade 4 / Grade 5 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Investigations						
Alanine aminotransferase increased	5 (3.4)	0	0	6 (3.9)	1 (0.7)	0
Aspartate aminotransferase increased	6 (4.1)	0	0	5 (3.3)	1 (0.7)	0
Blood alkaline phosphate increased	3 (2.0)	0	0	3 (2.0)	0	0
Blood Creatinine increased	2 (1.4)	0	0	2 (1.3)	0	0
Blood thyroid stimulating hormone decreased	4 (2.7)	0	0	0	0	0
Blood Thyroid Stimulating Hormone increased	3 (2.0)	0	0	0	0	0
Gamma-glutamyltransferase increased	1 (0.7)	1 (0.7)	0	2 (1.3)	1 (0.7)	0
Neutrophil count decreased	3 (2.0)	1 (0.7)	0	10 (6.6)	6 (3.9)	1 (0.7)
Tri-iodothyronine free increased	2 (1.4)	0	0	0	0	0
Weight decreased	2 (1.4)	0	0	4 (2.6)	0	0
Metabolism and nutrition disorders						
Decreased appetite	6 (4.1)	0	0	6 (3.9)	0	0
Musculoskeletal and connective tissue disorders						
Arthralgia	7 (4.7)	0	0	7 (4.6)	0	0
Back pain	2 (1.4)	0	0	4 (2.6)	0	0
Bone pain	0	0	0	2 (1.3)	0	0
Muscle spasms	1 (0.7)	0	0	2 (1.3)	0	0
Musculoskeletal pain	4 (2.7)	0	0	2 (1.3)	0	0
Myalgia	1 (0.7)	0	0	5 (3.3)	0	0
Neck pain	0	0	0	3 (2.0)	0	0
Pain in extremity	4 (2.7)	0	0	4 (2.6)	0	0
Neoplasms benign, malignant and unspecified						
Tumour flare	2 (1.4)	1 (0.7)	0	0	0	0
Nervous system disorders						
Headache	3 (2.0)	0	0	4 (2.6)	0	0
Hypoesthesia	0	0	0	2 (1.3)	0	0
Neuropathy peripheral	3 (2.0)	1 (0.7)	0	28 (18.4)	5 (3.3)	0
Paraesthesia	2 (1.4)	0	0	10 (6.6)	2 (1.3)	0
Peripheral motor neuropathy	0	0	0	4 (2.6)	-0	0
Peripheral sensorimotor neuropathy	0	0	0	4 (2.6)	1 (0.7)	0
-Peripheral sensory neuropathy	3 (2.0)	0	0	20 (13.2)	2 (1.3)	0

Adverse Event	KEYTRUDA® 200 mg every 3 weeks N=148			Brentuximab vedotin 1.8 mg/kg every 3 weeks N=152		
	Any Grade n (%)	Grade 3 n (%)	Grade 4 / Grade 5 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Psychiatric disorders						
Confusional state	2 (1.4)	0	0	0	0	0
Renal and urinary disorders						
Acute kidney injury	2 (1.4)	0	2 (1.4)	0	0	0
Hematuria	2 (1.4)	0	0	1 (0.7)	0	0
Leukocyturia	0	0	0	2 (1.3)	0	0
Respiratory, thoracic and mediastinal disorders						
Cough	5 (3.4)	0	0	5 (3.3)	0	0
Dyspnea extertional	3 (2.0)	0	0	0	0	0
Interstitual lung disease	3 (2.0)	2 (1.4)	0	1 (0.7)	1 (0.7)	0
Nasal congestion	3 (2.0)	0	0	0	0	0
Oropharyngeal pain	4 (2.7)	0	0	1 (0.7)	0	0
Pleural effusion	2 (1.4)	0	0	0	0	0
Pneumonitis	12 (8.1)	3 (2.0)	3 (2.0)	1 (0.7)	1 (0.7)	0
Productive cough	1 (0.7)	0	0	3 (2.0)	0	0
Skin and subcutaneous tissue disorders						
Alopecia	1 (0.7)	0	0	7 (4.6)	0	0
Dermatitis acneiform	2 (1.4)	0	0	1 (0.7)	0	0
Dermatitis allergic	2 (1.4)	0	0	0	0	0
Dry skin	1 (0.7)	0	0	2 (1.3)	0	0
Eczema	3 (2.0)	0	0	1 (0.7)	1 (0.7)	0
Erythema	3 (2.0)	0	0	2 (1.3)	0	0
Pruritus	16 (10.8)	0	0	8 (5.3)	0	0
Rash	8 (5.4)	0	0	7 (4.6)	0	0
Rash maculo-papular	3 (2.0)	0	0	4 (2.6)	0	0
Urticaria	2 (1.4)	1 (0.7)	0	0	0	0

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 3patients reported chronic GVHD, none of which were fatal. No patients experienced hepatic VOD. One patient experienced engraftment syndrome post-transplant.
Of the 389 patients in the Hodgkin Lymphoma Safety Data set, 6 (1.5%) patients reported Cytokine release syndrome (CRS) following treatment with KEYTRUDA®. One patient experienced a Grade 3 CRS reaction.

Treatment related adverse events reported in <1% patients with HL treated with KEYTRUDA® 200 mg every 3 weeks (n=148) by SOC are shown below:

Endocrine disorders: adrenal insufficiency
Eye disorders: uveitis
Gastrointestinal disorder: pancreatitis
Immune system disorder: drug hypersensitivity
Nervous system disorder: encephalitis autoimmune
Metabolism and nutrition disorder: hyperglycemia
Musculoskeletal and connective tissue disorders: rhabdomyolysis
Renal and urinary disorders: nephritis, renal impairment

Abnormal Hematologic and Clinical Chemistry Findings

Laboratory abnormalities (worsened from baseline in ≥ 20% of patients), reported in KEYNOTE-204 in patients with Hodgkin Lymphoma are presented in Table 21.

Table 21: Laboratory Abnormalities Increased from Baseline in ≥ 20% of Patients with Hodgkin Lymphoma Treated with KEYTRUDA®.

Laboratory Test	KEYTRUDA® 200 mg every 3 weeks n=148		Brentuximab vedotin 1.8 mg/kg every 3 weeks n=152	
	All Grades n (%)	Grades 3-4 n (%)	All Grades n (%)	Grades 3-4 n (%)
Alanine Aminotransferase Increased	50 (33.8)	9 (6.1)	69 (45.4)	7 (4.6)
Alkaline Phosphatase Increased	31 (20.9)	4 (2.7)	34 (22.4)	4 (2.6)
Aspartate Aminotransferase Increased	57 (38.5)	8 (5.4)	62 (40.8)	6 (3.9)
Calcium Decreased	32 (21.6)	3 (2.0)	24 (15.8)	0
Creatinine Increased	42 (28.4)	5 (3.4)	21(13.8)	4 (2.6)
Glucose Increased	68 (45.9)	6 (4.1)	55 (36.2)	3 (2.0)
Hemoglobin Decreased	35 (23.6)	7 (4.7)	50 (32.9)	12 (7.9)
Leukocytes Decreased	46 (31.1)	7 (4.7)	67 (44.1)	17 (11.2)
Lymphocytes Decreased	51 (34.5)	13 (8.8)	48 (31.6)	20 (13.2)
Neutrophils Decreased	41 (27.7)	12 (8.1)	64 (42.1)	25 (16.4)
Phosphate Decreased	47 (31.8)	8 (5.4)	29 (19.1)	5 (3.3)
Platelet Decreased	50 (33.8)	15 (10.1)	39 (25.7)	7 (4.6)
Sodium Decreased	37 (25.0)	6 (4.1)	30 (19.7)	5 (3.3)

Primary Mediastinal B-cell Lymphoma (PMBCL)
Table 22 summarizes the treatment-related adverse events that occurred in at least 1% of patients with PMBCL treated with KEYTRUDA® in KEYNOTE-170. The most common adverse event (reported in at least 10% of patients) was neutropenia.

KEYTRUDA® was discontinued for treatment-related adverse events in 2.0% (1/49) of patients with PMBCL: increased AST after one dose of KEYTRUDA®.

Table 22: Treatment-Related Adverse Events Occurring in ≥ 1% of Patients with PMBCL treated with KEYTRUDA® in KEYNOTE-170.

Adverse Event	KEYTRUDA® 200 mg every 3 weeks N=49	
	Any Grade n (%)	Grade 3/Grade 4 n (%)
Blood and lymphatic system disorders		
Neutropenia	9 (18.4)	5 (10.2) Grade 4: 1 (2.0)
Anemia	1 (2.0)	0
Leukopenia	1 (2.0)	0
Cardiac disorders		
Pericarditis	1 (2.0)	0
Endocrine disorders		
Hypothyroidism	3 (6.1)	0
Hyperthyroidism	1 (2.0)	0
Thyroiditis	1 (2.0)	0
Gastrointestinal disorders		
Abdominal pain	1 (2.0)	0
Diarrhea	1 (2.0)	0
Nausea	1 (2.0)	0
General disorders and administration site conditions		
Fatigue	2 (4.1)	0
Pyrexia	3 (6.1)	0
Asthenia	3 (6.1)	1 (2.0) 0
Hepatobiliary disorders		
Hepatic necrosis	1 (2.0)	0
Infections and infestations		
Clostridium difficile infection	1 (2.0)	1 (2.0) 0
Herpes zoster	1 (2.0)	0
Pneumonia	1 (2.0)	1 (2.0) 0
Upper respiratory tract infection	1 (2.0)	0
Vulvovaginal mycotic infection	1 (2.0)	0
Investigations		
Alanine aminotransferase increased	1 (2.0)	0
Aspartate aminotransferase increased	2 (4.1)	1 (2.0) 0
Hepatic enzyme increased	1 (2.0)	1 (2.0) 0
White blood cell count decreased	1 (2.0)	0
Metabolism and nutrition disorders		
Hyperglycemia	1 (2.0)	0
Musculoskeletal and connective tissue disorders		
Myalgia	2 (4.1)	0
Arthralgia	1 (2.0)	0
Back pain	1 (2.0)	0
Muscle spasms	1 (2.0)	0
Neoplasm benign, malignant and unspecified (includes cysts and polyps)		
Tumour flare	1 (2.0)	1 (2.0) 0
Nervous system disorders		
Paresthesia	1 (2.0)	0
Psychiatric disorders		
Fear	1 (2.0)	0
Respiratory, thoracic and mediastinal disorders		
Pleural effusion	1 (2.0)	0

Adverse Event	KEYTRUDA® 200 mg every 3 weeks N=49	
	Any Grade n (%)	Grade 3/Grade 4 n (%)
Respiratory disorder	1 (2.0)	0
Skin and subcutaneous tissue disorders		
Erythema	1 (2.0)	0
Dermatitis allergic	1 (2.0)	0
Swelling Face	1 (2.0)	0

Two deaths due to adverse events regardless of relationship to therapy were reported among the 49 patients with PMBCL in KEYNOTE -170. Causes of death for these patients were *Aspergillus* infection and myocardial infarction.

Abnormal Hematologic and Clinical Chemistry Findings
Laboratory abnormalities (worsened from baseline in ≥ 20% of patients), reported in KEYNOTE-170 in patients with PMBCL are presented in Table 23.

Table 23: Laboratory Abnormalities Increased from Baseline in ≥ 20% of Patients with PMBCL.

Laboratory Test	KEYTRUDA® 200 mg every 3 weeks n=49	
	All Grades n (%)	Grades 3-4 n (%)
Glucose Increased	16 (32.7)	2 (4.1)
Hemoglobin Decreased	16 (32.7)	0
Leukocytes Decreased	16 (32.7)	4 (8.2)
Lymphocytes Decreased	13 (26.5)	7 (14.3)
Neutrophils Decreased	12 (24.5)	4 (8.2)
Phosphate Decreased	11 (22.4)	4 (8.2)

Urothelial Carcinoma
Table 24 summarizes the treatment-related adverse events that occurred in at least 1% of patients with urothelial carcinoma treated with KEYTRUDA® in KEYNOTE-045. The most common treatment-related adverse events (reported in at least 10% of patients) were pruritus, fatigue and nausea. Fifteen percent of patients had ≥ Grade 3 treatment-related adverse events. The most common ≥ Grade 3 adverse reactions (occurring in more than 2 patients) were: pneumonitis (n=4); diarrhea (n=3); fatigue (n=3); and aspartate aminotransferase increase (n=3).

KEYTRUDA® was discontinued for treatment-related adverse events in 5.6% of patients in KEYNOTE 045. The most common treatment-related adverse event leading to study drug discontinuation (occurring in more than 2 patients) was: pneumonitis (n=5). The median time to discontinuation for treatment-related adverse events was 0.7 months.

Table 24: Treatment-Related Adverse Events Occurring in ≥ 1% of Patients with Urothelial Carcinoma treated with KEYTRUDA® in KEYNOTE-045.

Adverse Reaction	KEYTRUDA® 200 mg every 3 weeks n=266				Chemotherapy n=255			
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Blood and lymphatic system disorders								
Anemia	9 (3.4)	2 (0.8)	0 (0)	0 (0)	63 (24.7)	20 (7.8)	0 (0)	0 (0)
Endocrine disorders								
Hyperthyroidism	10 (3.8)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Hypothyroidism	15 (5.6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Gastrointestinal disorders								
Abdominal pain	4 (1.5)	0 (0)	0 (0)	0 (0)	10 (3.9)	0 (0)	0 (0)	0 (0)
Colitis	5 (1.9)	2 (0.8)	0 (0)	0 (0)	1 (0.4)	0 (0)	0 (0)	0 (0)
Constipation	6 (2.3)	0 (0)	0 (0)	0 (0)	52 (20.4)	7 (2.7)	0 (0)	0 (0)
Diarrhea	24 (9.0)	3 (1.1)	0 (0)	0 (0)	33 (12.9)	1 (0.4)	1 (0.4)	0 (0)
Dry mouth	4 (1.5)	0 (0)	0 (0)	0 (0)	2 (0.8)	0 (0)	0 (0)	0 (0)
Flatulence	3 (1.1)	0 (0)	0 (0)	0 (0)	1 (0.4)	0 (0)	0 (0)	0 (0)
Nausea	29 (10.9)	1 (0.4)	0 (0)	0 (0)	62 (24.3)	4 (1.6)	0 (0)	0 (0)
Stomatitis	4 (1.5)	1 (0.4)	0 (0)	0 (0)	21 (8.2)	1 (0.4)	0 (0)	0 (0)
Vomiting	12 (4.5)	0 (0)	0 (0)	0 (0)	25 (9.8)	1 (0.4)	0 (0)	0 (0)
General disorders and administration site conditions								
Asthenia	15 (5.6)	1 (0.4)	0 (0)	0 (0)	36 (14.1)	7 (2.7)	0 (0)	0 (0)
Chills	3 (1.1)	0 (0)	0 (0)	0 (0)	4 (1.6)	0 (0)	0 (0)	0 (0)
Fatigue	37 (13.9)	3 (1.1)	0 (0)	0 (0)	71 (27.8)	11 (4.3)	0 (0)	0 (0)
Influenza like illness	3 (1.1)	0 (0)	0 (0)	0 (0)	3 (1.2)	0 (0)	0 (0)	0 (0)
Malaise	4 (1.5)	0 (0)	0 (0)	0 (0)	8 (3.1)	0 (0)	0 (0)	0 (0)
Mucosal inflammation	3 (1.1)	1 (0.4)	0 (0)	0 (0)	17 (6.7)	2 (0.8)	0 (0)	0 (0)
Pyrexia	17 (6.4)	0 (0)	0 (0)	0 (0)	8 (3.1)	1 (0.4)	0 (0)	0 (0)
Infections and infestations								
Urinary Tract Infection	3 (1.1)	0 (0)	0 (0)	0 (0)	8 (3.1)	3 (1.2)	1 (0.4)	0 (0)
Investigations								
Alanine aminotransferase increased	9 (3.4)	2 (0.8)	0 (0)	0 (0)	3 (1.2)	0 (0)	0 (0)	0 (0)
Aspartate aminotransferase increased	7 (2.6)	3 (1.1)	0 (0)	0 (0)	2 (0.8)	0 (0)	0 (0)	0 (0)
Blood alkaline phosphatase	3 (1.1)	1 (0.4)	0 (0)	0 (0)	1 (0.4)	0 (0)	0 (0)	0 (0)

Adverse Reaction	KEYTRUDA® 200 mg every 3 weeks n=266				Chemotherapy n=255			
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
increased								
Blood thyroid stimulating hormone increased	3 (1.1)	0 (0)	0 (0)	0 (0)	0 (0.0)	0 (0.0)	0 (0)	0 (0)
Gamma-glutamyl transferase increased	3 (1.1)	2 (0.8)	0 (0)	0 (0)	1 (0.4)	0 (0)	0 (0)	0 (0)
Platelet count decreased	3 (1.1)	1 (0.4)	0 (0)	0 (0)	7 (2.7)	2 (0.8)	1 (0.4)	0 (0)
Weight decreased	4 (1.5)	0 (0)	0 (0)	0 (0)	8 (3.1)	0 (0)	0 (0)	0 (0)
Metabolism and nutrition disorders								
Decreased appetite	23 (8.6)	0 (0)	0 (0)	0 (0)	41 (16.1)	3 (1.2)	0 (0)	0 (0)
Hyperglycemia	3 (1.1)	1 (0.4)	0 (0)	0 (0)	0 (0.0)	0 (0.0)	0 (0)	0 (0)
Musculoskeletal and connective tissue disorders								
Arthralgia	8 (3.0)	0 (0)	0 (0)	0 (0)	17 (6.7)	0 (0)	0 (0)	0 (0)
Back pain	3 (1.1)	0 (0)	0 (0)	0 (0)	2 (0.8)	0 (0)	0 (0)	0 (0)
Muscle spasms	3 (1.1)	0 (0)	0 (0)	0 (0)	1 (0.4)	0 (0)	0 (0)	0 (0)
Musculoskeletal chest pain	3 (1.1)	0 (0)	0 (0)	0 (0)	0 (0.0)	0 (0.0)	0 (0)	0 (0)
Myalgia	8 (3.0)	1 (0.4)	0 (0)	0 (0)	12 (4.7)	0 (0)	0 (0)	0 (0)
Pain in extremity	3 (1.1)	0 (0)	0 (0)	0 (0)	13 (5.1)	1 (0.4)	0 (0)	0 (0)
Nervous system disorders								
Dizziness	6 (2.3)	0 (0)	0 (0)	0 (0)	7 (2.7)	1 (0.4)	0 (0)	0 (0)
Dysgeusia	3 (1.1)	0 (0)	0 (0)	0 (0)	14 (5.5)	0 (0)	0 (0)	0 (0)
Headache	4 (1.5)	1 (0.4)	0 (0)	0 (0)	8 (3.1)	0 (0)	0 (0)	0 (0)
Psychiatric disorders								
Insomnia	3 (1.1)	0 (0)	0 (0)	0 (0)	5 (2.0)	0 (0)	0 (0)	0 (0)
Respiratory, thoracic and mediastinal disorders								
Cough	7 (2.6)	0 (0)	0 (0)	0 (0)	2 (0.8)	0 (0)	0 (0)	0 (0)
Dyspnea	7 (2.6)	0 (0)	0 (0)	0 (0)	6 (2.4)	1 (0.4)	0 (0)	0 (0)
Dyspnea exertional	5 (1.9)	0 (0)	0 (0)	0 (0)	4 (1.6)	0 (0)	0 (0)	0 (0)
Pneumonitis	9 (3.4)	3 (1.1)	0 (0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0)	0 (0)
Skin and subcutaneous tissue disorders								
Dermatitis acneiform	3 (1.1)	0 (0)	0 (0)	0 (0)	2 (0.8)	0 (0)	0 (0)	0 (0)
Dry skin	6 (2.3)	0 (0)	0 (0)	0 (0)	7 (2.7)	0 (0)	0 (0)	0 (0)
Erythema	4 (1.5)	0 (0)	0 (0)	0 (0)	5 (2.0)	0 (0)	0 (0)	0 (0)
Pruritus	52 (19.5)	0 (0)	0 (0)	0 (0)	7 (2.7)	1 (0.4)	0 (0)	0 (0)

Adverse Reaction	KEYTRUDA® 200 mg every 3 weeks n=266				Chemotherapy n=255			
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Rash	22 (8.3)	1 (0.4)	0 (0)	0 (0)	9 (3.5)	0 (0)	0 (0)	0 (0)
Rash maculo-papular	6 (2.3)	0 (0)	0 (0)	0 (0)	2 (0.8)	0 (0)	0 (0)	0 (0)
Urticaria	5 (1.9)	0 (0)	0 (0)	0 (0)	1 (0.4)	0 (0)	0 (0)	0 (0)
Vascular Disorders								
Hypertension	3 (1.1)	1 (0.4)	0 (0)	0 (0)	1 (0.4)	0 (0)	0 (0)	0 (0)

Treatment related adverse events reported in <1% patients with urothelial carcinoma treated with KEYTRUDA® 200 mg every 3 weeks (n=266) in KEYNOTE-045 by SOC are shown below:

Injury, poisoning and procedural complications: infusion related reaction
Musculoskeletal and connective tissue disorders: arthritis
Renal and urinary disorders: nephritis, acute renal injury
Blood and lymphatic system disorders: thrombocytopenia, eosinophilia
Endocrine disorders: adrenal insufficiency, thyroiditis

Table 25 summarizes the treatment-related adverse events that occurred in at least 1% of patients with urothelial carcinoma treated with KEYTRUDA® in KEYNOTE-052. The most common adverse events (reported in at least 10% of patients) were fatigue, pruritus, rash, decreased appetite and hypothyroidism. Twenty percent of patients had ≥ Grade 3 treatment-related adverse events. The most common ≥ Grade 3 treatment related adverse events (occurring in more than 1% of patients) were: fatigue (n=8; 2.2%); colitis (n=6; 1.6%); blood alkaline phosphatase increased (n=5; 1.4%); muscular weakness (n=5; 1.4%); pneumonitis (n=4; 1.1%); diarrhea (n=4; 1.1%); and aspartate aminotransferase increased (n=4; 1.1%).

KEYTRUDA® was discontinued for treatment-related adverse events in 9.7% of patients in KEYNOTE 052. The most common treatment-related adverse events leading to study drug discontinuation (occurring in more than 2 patients) were: pneumonitis (n=5, 1.4%); colitis (n=3, 0.8%); and diarrhea (n=3, 0.8%). The median time to discontinuation for treatment-related adverse events was 4.2 months.

Table 25: Treatment-Related Adverse Events Occurring in ≥ 1% of Patients with Urothelial Carcinoma Treated with KEYTRUDA® (KEYNOTE-052).

Adverse Reaction	KEYTRUDA® 200 mg once every three weeks N=370		
	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Blood and lymphatic system disorders			
Anemia	9 (2.4)	1 (0.3)	0
Thrombocytopenia	4 (1.1)	0	0
Endocrine disorders			
Hyperthyroidism	9 (2.4)	0	0
Hypothyroidism	37 (10.0)	0	0
Gastrointestinal disorders			
Abdominal pain	5 (1.4)	0	0

Adverse Reaction	KEYTRUDA® 200 mg once every three weeks N=370		
	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Colitis	9 (2.4)	5 (1.4)	1 (0.3)
Constipation	11 (3.0)	1 (0.3)	0
Diarrhea	34 (9.2)	4 (1.1)	0
Dry mouth	11 (3.0)	0	0
Nausea	32 (8.6)	1 (0.3)	0
Vomiting	13 (3.5)	0	0
General disorders and administration site conditions			
Asthenia	15 (4.1)	2 (0.5)	1 (0.3)
Chills	10 (2.7)	0	0
Fatigue	67 (18.1)	8 (2.2)	0
Influenza like illness	11 (3.0)	0	0
Edema peripheral	11 (3.0)	0	0
Pyrexia	14 (3.8)	1 (0.3)	0
Investigations			
Alanine aminotransferase increased	14 (3.8)	3 (0.8)	0
Aspartate aminotransferase increased	15 (4.1)	4 (1.1)	0
Blood alkaline phosphatase increased	8 (2.2)	5 (1.4)	0
Blood bilirubin increased	6 (1.6)	1 (0.3)	0
Blood creatinine increased	9 (2.4)	1 (0.3)	0
Blood thyroid stimulating hormone increased	4 (1.1)	0	0
Weight decreased	10 (2.7)	1 (0.3)	0
Metabolism and nutrition disorders			
Decreased appetite	39 (10.5)	1 (0.3)	1 (0.3)
Dehydration	4 (1.1)	2 (0.5)	0
Hyperglycemia	5 (1.4)	3 (0.8)	0
Hyponatremia	8 (2.2)	2 (0.5)	0
Musculoskeletal and connective tissue disorders			
Arthralgia	10 (2.7)	1 (0.3)	0
Arthritis	8 (2.2)	2 (0.5)	0
Muscular weakness	6 (1.6)	5 (1.4)	0
Myalgia	7 (1.9)	0	0
Nervous system disorders			
Dizziness	6 (1.6)	1 (0.3)	0
Dysgeusia	13 (3.5)	0	0
Lethargy	6 (1.6)	0	0
Respiratory, thoracic and mediastinal disorders			
Cough	12 (3.2)	0	0
Dyspnea	8 (2.2)	0	0
Pneumonitis	13 (3.5)	4 (1.1)	0
Skin and subcutaneous tissue disorders			
Dermatitis acneiform	4 (1.1)	0	0
Dry skin	6 (1.6)	0	0
Erythema	4 (1.1)	0	0
Pruritus	66 (17.8)	2 (0.5)	0
Pruritus generalized	5 (1.4)	1 (0.3)	0
Psoriasis	5 (1.4)	0	0
Rash	44 (11.9)	2 (0.5)	0

Adverse Reaction	KEYTRUDA® 200 mg once every three weeks N=370		
	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Rash macular	4 (1.1)	0	0
Rash maculo-papular	15 (4.1)	1 (0.3)	0
Rash pruritic	6 (1.6)	0	0

Grade 5 adverse events (adverse events leading to death) occurred in 24 (6.5%) patients. The fatal events were urosepsis (n=4, 1.1%), pneumonia (n=3, 0.8%), sepsis (n=2, 0.5%), death (unknown cause, n=2, 0.5%) and others which were reported in 1 subject each: septic shock; clostridium difficile infection; ischemic cardiomyopathy; cerebrovascular accident; embolism; duodenal obstruction; large intestine perforation; colonic fistula; multiple organ dysfunction syndrome; type 2 diabetes mellitus; myositis; acute kidney injury; chronic kidney disease; renal failure; aspiration; and respiratory failure. One of the deaths (myositis) was considered to be related to the treatment by the investigator.

Treatment related adverse events reported in <1% patients with urothelial carcinoma treated with KEYTRUDA® 200 mg every 3 weeks (n=370) in KEYNOTE 052 by SOC are shown below:

Endocrine disorder: adrenal insufficiency, hypophysitis, thyroiditis
Hepatobiliary disorder: hepatitis
Metabolism and nutrition disorders: type 1 diabetes mellitus, diabetic ketoacidosis
Musculoskeletal and connective tissue disorder: myositis

Table 26 summarizes the treatment-related adverse events that occurred in at least 1% of patients with BCG-unresponsive high-risk NMIBC treated with KEYTRUDA® in KEYNOTE-057, 96 of whom had BCG-unresponsive carcinoma in situ (CIS) with or without papillary tumours. The most common adverse events (reported in at least 10% of patients) were fatigue, pruritus and diarrhea. Fourteen percent of patients had ≥ Grade 3 treatment-related adverse events. The most common ≥ Grade 3 treatment related adverse events (occurring in more than 1% of patients) were: hyponatremia (n=3; 2.0%), adrenocorticotropic hormone deficiency (n=2; 1.4%), colitis (n=2; 1.4%), and arthralgia (n=2; 1.4%).

Serious treatment-related adverse events occurred in 11% of patients receiving KEYTRUDA®. Serious treatment-related adverse events in ≥1% of patients receiving KEYTRUDA® included colitis (2.0%), and adrenocorticotropic hormone deficiency (1.4%).

KEYTRUDA® was discontinued for treatment-related adverse events in 9.5 % of patients in KEYNOTE-057. The most common treatment-related adverse event leading to study drug discontinuation (occurring in 2 patients or more) was: pneumonitis (n=2; 1.4%). The median time to discontinuation for treatment-related adverse events was 3.76 months.

Treatment-related adverse events leading to interruption of KEYTRUDA® occurred in 12% of patients; the most common (≥1%) were diarrhea (3.4%), arthralgia (1.4%), alanine aminotransferase increased (1.4%), and hyponatraemia (1.4%).

Table 26: Treatment-Related Adverse Events Occurring in ≥ 1% of Patients with High-Risk NMIBC Treated with KEYTRUDA® in KEYNOTE-057.

Adverse Reaction	KEYTRUDA® 200 mg once every three weeks N=148		
	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Endocrine disorders			
Adrenocorticotropic hormone deficiency	2 (1.4)	2 (1.4)	0
Hyperthyroidism	9 (6.1)	0	0
Hypothyroidism	14 (9.5)	0	0
Gastrointestinal disorders			
Abdominal pain	2 (1.4)	0	0
Colitis	3 (2.0)	2 (1.4)	0
Constipation	4 (2.7)	0	0
Diarrhea	16 (10.8)	1 (0.7)	0
Dry mouth	4 (2.7)	0	0
Nausea	6 (4.1)	0	0
Vomiting	2 (1.4)	0	0
General disorders and administration site conditions			
Asthenia	5 (3.4)	0	0
Fatigue	20 (13.5)	0	0
Influenza like illness	2 (1.4)	0	0
Malaise	3 (2.0)	1 (0.7)	0
Pyrexia	4 (2.7)	0	0
Hepatobiliary disorders			
Hepatic function abnormal	2 (1.4)	1 (0.7)	0
Investigations			
Alanine aminotransferase increased	6 (4.1)	0	0
Aspartate aminotransferase increased	5 (3.4)	0	0
Blood alkaline phosphatase increased	2 (1.4)	0	0
Blood thyroid stimulating hormone decreased	3 (2.0)	0	0
Lymphocyte count decreased	2 (1.4)	1 (0.7)	0
Weight decreased	2 (1.4)	0	0
Metabolism and nutrition disorders			
Hyponatremia	3 (2.0)	2 (1.4)	1 (0.7)
Hypophosphatemia	2 (1.4)	1 (0.7)	0
Musculoskeletal and connective tissue disorders			
Arthralgia	8 (5.4)	2 (1.4)	0
Myalgia	3 (2.0)	0	0
Nervous system disorders			
Neuropathy peripheral	3 (2.0)	0	0
Renal and urinary disorders			
Hematuria	2 (1.4)	0	0
Respiratory, thoracic and mediastinal disorders			
Cough	2 (1.4)	0	0
Pneumonitis	3 (2.0)	0	0
Skin and subcutaneous tissue disorders			
Dermatitis	2 (1.4)	1 (0.7)	0
Dry skin	2 (1.4)	0	0
Erythema	2 (1.4)	0	0
Pruritus	18 (12.2)	1 (0.7)	0
Rash	7 (4.7)	0	0

Adverse Reaction	KEYTRUDA® 200 mg once every three weeks N=148		
	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Rash erythematous	2 (1.4)	0	0
Rash maculo-papular	8 (5.4)	0	0
Rash pruritic	3 (2.0)	0	0

Treatment related adverse events reported in <1% patients with high-risk NMIBC treated with KEYTRUDA® 200 mg every 3 weeks (n=148) in KEYNOTE-057 by SOC are shown below:

Endocrine disorder: adrenal insufficiency, hypophysitis
Eye disorders: uveitis
Hepatobiliary disorder: hepatitis
Infections and Infestations: septic shock
Injury, poisoning and procedural complications: infusion related reaction
Metabolism and nutrition disorders: type 1 diabetes mellitus
Renal and urinary disorders: nephritis

Abnormal Hematologic and Clinical Chemistry Findings
Laboratory abnormalities (worsened from baseline in ≥ 10% of patients), reported in KEYNOTE-045 in patients with urothelial carcinoma are presented in Table 27.

Table 27: Laboratory Abnormalities Worsened from Baseline in ≥ 10% of Patients with Urothelial Carcinoma 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-045).

Laboratory Test	KEYTRUDA® 200 mg every 3 weeks n=266		Chemotherapy n=255	
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
Chemistry				
Alkaline Phosphatase Increased	35.4	7.2	32.2	4.7
Aspartate Aminotransferase Increased	26	3.8	19.6	2.4
Creatinine Increased	34.9	4.1	27.4	3.1

The most frequently (≥ 20%) reported laboratory values that showed clinically meaningful worsening in CTCAE grade from baseline on the pembrolizumab arm were lymphocytes decreased and phosphate decreased. The incidence in the pembrolizumab arm was lower than in the control arm (lymphocytes decreased: 25.6% with pembrolizumab vs 34.9% with chemotherapy; phosphate decreased: 23.7% with pembrolizumab vs 27.5% with chemotherapy). The most frequent liver function test elevation by predetermined normal limit cutoffs was alkaline phosphatase (31.6%), a rate only slightly higher than the chemotherapy control group (28.5%).

Laboratory abnormalities (worsened from baseline in ≥ 10% of patients), reported in KEYNOTE-052 in patients with urothelial carcinoma not eligible for cisplatin –containing chemotherapy are presented in Table 28.

Table 28: Laboratory Abnormalities Increased from Baseline in ≥ 10% of Patients with Urothelial Carcinoma Not Eligible to Cisplatin-Containing Chemotherapy (KEYNOTE-052).

Laboratory Test	KEYTRUDA® 200 mg every 3 weeks N=370	
	All Grades n (%)	Grades 3-4 n (%)
Chemistry		
Alanine Aminotransferase Increased	104 (28)	12 (3.2)
Albumin Decreased	159 (43)	11 (3.0)
Alkaline Phosphatase Increased	125 (32)	26 (7)
Aspartate Aminotransferase Increased	113 (31)	18 (5)
Calcium Decreased	105 (28)	8 (2.2)
Calcium Increased	49 (13)	9 (2.4)
Creatinine Increased	161 (44)	17 (4.6)
Glucose Decreased	38 (10)	5 (1.4)
Glucose Increased	201 (54)	31 (8)
Phosphate Decreased	79 (21)	20 (5)
Potassium Decreased	39 (11)	4 (1.1)
Potassium Increased	104 (28)	18 (4.9)
Sodium Decreased	152 (41)	50 (14)
Hematology		
Hemoglobin Decreased	198 (54)	36 (10)
Leukocytes Decreased	41 (11)	4 (1.1)
Lymphocytes Decreased	161 (44)	56 (15)
Neutrophil Decreased	38 (10)	18 (4.9)
Platelet Decreased	55 (15)	6 (1.6)

Laboratory abnormalities (worsened from baseline in ≥ 10% of patients), reported in KEYNOTE-057 in patients with high-risk NMIBC are presented in Table 29.

Table 29: Laboratory Abnormalities Increased from Baseline in ≥ 10% of Patients with High Risk NMIBC (KEYNOTE-057).

Laboratory Test	KEYTRUDA® 200 mg every 3 weeks n=148	
	All Grades n (%)	Grades 3-4 n (%)
Chemistry		
Alanine Aminotransferase Increased	37 (25.0)	5 (3.4)
Albumin Decreased	35 (23.6)	3 (2.0)
Alkaline Phosphatase Increased	15 (10.1)	3 (2.0)
Aspartate Aminotransferase Increased	30 (20.3)	5 (3.4)
Bilirubin Increased	21 (14.2)	1 (0.7)
Calcium Decreased	33 (22.3)	1 (0.7)
Creatinine Increased	30 (20.3)	1 (0.7)
Glucose Increased	86 (58.1)	11 (7.4)
Phosphate Decreased	34 (23.0)	9 (6.1)
Potassium Decreased	16 (10.8)	2 (1.4)
Potassium Increased	33 (22.3)	2 (1.4)
Sodium Decreased	35 (23.6)	10 (6.8)
Hematology		
Hemoglobin Decreased	51 (34.5)	2 (1.4)
Leukocytes Decreased	15 (10.1)	1 (0.7)
Lymphocytes Decreased	36 (24.3)	2 (1.4)
Platelet Decreased	18 (12.2)	1 (0.7)

Microsatellite Instability-High Cancer (MSI-H)

Table 30 summarizes the treatment-related adverse events that occurred in at least 1% of patients with MSI-H cancers treated with KEYTRUDA® in KEYNOTE-158 (adult patients with various types of solid tumours previously treated and who had progressed with no satisfactory alternative treatment options) and KEYNOTE-164 (adult patients with previously treated unresectable or metastatic colorectal cancer). The most common adverse events (reported in at least 10% of patients) were pruritus, diarrhea, fatigue and nausea. Fourteen percent of patients had ≥ Grade 3 adverse events. The most common ≥ Grade 3 adverse events (occurring in more than 2 patients) were: pancreatitis (n=3, 1.9%); blood alkaline phosphatase increased (n=3, 1.9%); and gamma-glutamyltransferase increased (n=3, 1.9%).

KEYTRUDA® was discontinued for treatment-related adverse events in 4.5% of patients with MSI-H cancers. The most common treatment-related adverse events leading to study drug discontinuation (occurring in 2 or more patients) were: pneumonitis (n=2, 1.3%); and blood alkaline phosphatase increased (n=2, 1.3%). The median time to discontinuation for treatment-related adverse events was 0.7 months.

Table 30: Treatment-Related Adverse Events Occurring in ≥ 1% of Patients with MSI-H Cancer treated with KEYTRUDA® in KEYNOTE-158 and KEYNOTE-164.

Adverse Event	KEYTRUDA® 200 mg every 3 weeks N=155	
	Any Grade n (%)	Grade 3* n (%)
Blood and lymphatic system disorders		
Anemia	3 (1.9)	0

Adverse Event	KEYTRUDA® 200 mg every 3 weeks N=155	
	Any Grade n (%)	Grade 3* n (%)
Endocrine disorders		
Hyperthyroidism	6 (3.9)	1 (0.6)
Hypothyroidism	6 (3.9)	0
Gastrointestinal disorders		
Diarrhea	17 (11.0)	1 (0.6)
Nausea	17 (11.0)	0
Vomiting	10 (6.5)	0
Dry mouth	4 (2.6)	0
Abdominal pain	3 (1.9)	0
Colitis	3 (1.9)	0
Constipation	3 (1.9)	0
Pancreatitis	3 (1.9)	3 (1.9)
Stomatitis	2 (1.3)	0
General disorders and administration site conditions		
Fatigue	17 (11.0)	2 (1.3)
Asthenia	15 (9.7)	2 (1.3)
Peripheral Edema	4 (2.6)	1 (0.6)
Pyrexia	3 (1.9)	0
Pain	2 (1.3)	0
Infections and infestations		
Conjunctivitis	2 (1.3)	0
Sinusitis	2 (1.3)	0
Investigations		
Aspartate aminotransferase increased	5 (3.2)	1 (0.6)
Alanine aminotransferase increased	4 (2.6)	1 (0.6)
Blood alkaline phosphatase increased	4 (2.6)	3 (1.9)
Gamma-glutamyltransferase increased	3 (1.9)	3 (1.9)
Blood Creatinine increased	2 (1.3)	0
Blood thyroid stimulating hormone decreased	2 (1.3)	0
Blood thyroid stimulating hormone increased	2 (1.3)	0
Hemoglobin decreased	2 (1.3)	1 (0.6)
Lipase increased	2 (1.3)	2 (1.3)
Metabolism and nutrition disorders		
Decreased appetite	7 (4.5)	0
Hypercalcemia	2 (1.3)	0
Musculoskeletal and connective tissue disorders		
Arthralgia	13 (8.4)	0
Muscle spasms	3 (1.9)	0
Myalgia	3 (1.9)	0
Nervous system disorders		
Headache	4 (2.6)	0
Dysgeusia	2 (1.3)	0
Psychiatric disorders		
Insomnia	2 (1.3)	0
Respiratory, thoracic and mediastinal disorders		
Pneumonitis	5 (3.2)	1 (0.6)
Skin and subcutaneous tissue disorders		
Pruritus	18 (11.6)	0

Adverse Event	KEYTRUDA® 200 mg every 3 weeks N=155	
	Any Grade n (%)	Grade 3* n (%)
Rash	7 (4.5)	0
Rash maculo-papular	6 (3.9)	0
Dry skin	3 (1.9)	0
Eczema	2 (1.3)	0
Rash-generalised	2 (1.3)	1 (0.6)

*No Grade 4 or Grade 5 treatment-related adverse events were reported to occur in ≥ 1% of patients with MSI-H cancer

Treatment related adverse events reported in <1% patients with MSI-H cancer treated with KEYTRUDA® 200 mg every 3 weeks (n=155) by SOC are shown below:

Injury, poisoning and procedural complications: infusion related reaction
Nervous system disorders: Guillain-Barré syndrome

Abnormal Hematologic and Clinical Chemistry Findings
Laboratory abnormalities (worsened from baseline in ≥ 20% of patients), reported in KEYNOTE-158 and KEYNOTE-164 in patients with MSI-H cancer are presented in Table 31.

Table 31: Laboratory Abnormalities Increased from Baseline in ≥ 20% of Patients with MSI-H.

Laboratory Test	KEYTRUDA® 200 mg every 3 weeks n=155	
	All Grades n (%)	Grades 3-4 n (%)
Alanine Aminotransferase Increased	40 (25.8)	10 (6.5)
Albumin Decreased	54 (34.8)	5 (3.2)
Alkaline Phosphatase Increased	54 (34.8)	11 (7.1)
Aspartate Aminotransferase Increased	44 (28.3)	7 (4.5)
Calcium Decreased	43 (27.7)	0
Glucose Increased	80 (51.6)	12 (7.7)
Hemoglobin Decreased	73 (47.1)	12 (7.7)
Lymphocytes Decreased	53 (34.2)	12 (7.7)
Potassium Increased	32 (20.6)	3 (1.9)
Sodium Decreased	43 (27.7)	10 (6.5)

Endometrial Carcinoma (Not MSI-H or not dMMR)
The safety of KEYTRUDA® administered in combination with lenvatinib was evaluated in KEYNOTE-146, a single-arm, multicenter, open-label trial in 94 patients with endometrial carcinoma whose tumours had progressed following at least one line of platinum-based chemotherapy in any setting, and were not MSI-H or dMMR (See CLINICAL TRIALS). Patients were required to have adequately controlled blood pressure, and adequate renal, bone marrow, blood coagulation, cardiac and liver function. The median duration of study treatment was 7.4 months (range: 1 day to 37.8 months). The median duration of exposure to KEYTRUDA® was 6.4 months (range: 1 day to 23.8 months). KEYTRUDA® was continued for a maximum of 24 months; however, treatment with lenvatinib could be continued beyond 24 months.

The frequencies included below and in Tables 32 and 33 are based on all reported adverse events, regardless of the investigator assessment of causality.

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

Serious adverse events occurred in 52% of patients receiving KEYTRUDA® and lenvatinib. See Table 33 below for the most common serious adverse events.

The most common adverse events (≥ 40%) in patients treated with KEYTRUDA® and lenvatinib were musculoskeletal pain (65%), fatigue (65%), hypertension (65%), diarrhea (64%), decreased appetite (52%), hypothyroidism (51%), nausea (48%), and stomatitis (43%).

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

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

Table 32 summarizes adverse events experienced by patients who received KEYTRUDA® in combination with lenvatinib.

Table 32: Adverse Events in ≥ 20% of Patients with Endometrial Carcinoma in KEYNOTE-146.

Adverse Event	**KEYTRUDA® 200 mg in Combination with Lenvatinib 20 mg N=94**	
	All Grades (%)	Grade 3-4 (%)
Endocrine		
Hypothyroidism[a]	51	1
Gastrointestinal		
Diarrhea[b]	64	4
Nausea	48	5
Stomatitis[c]	43	0
Vomiting	39	0
Abdominal pain[d]	33	6
Constipation	32	0
General		
Fatigue[e]	65	17
Infections		

Adverse Event	KEYTRUDA® 200 mg in Combination with Lenvatinib 20 mg N=94	
	All Grades (%)	Grade 3-4 (%)
Urinary tract infection[f]	31	4
Investigations		
Decreased weight	36	3
Metabolism		
Decreased appetite[g]	52	0
Hypomagnesemia	27	3
Musculoskeletal and Connective Tissue		
Musculoskeletal pain[h]	65	3
Nervous System		
Headache	33	1
Respiratory, Thoracic and Mediastinal		
Dysphonia	29	0
Dyspnea[i]	24	2
Cough	21	0
Skin and Subcutaneous Tissue		
Palmar-plantar erythrodysesthesia	26	3
Rash[j]	21	3
Vascular		
Hypertension[k]	65	38
Hemorrhagic events[l]	28	4

[a] Includes increased blood thyroid stimulating hormone and hypothyroidism
[b] Includes diarrhea, gastroenteritis, gastrointestinal viral infection, and viral diarrhea
[c] Includes glossitis, mouth ulceration, oral discomfort, oral mucosal blistering, oropharyngeal pain, and stomatitis
[d] Includes abdominal discomfort, abdominal pain, lower abdominal pain, and upper abdominal pain
[e] Includes asthenia, fatigue, and malaise
[f] Includes cystitis and urinary tract infection
[g] Includes decreased appetite and early satiety
[h] Includes arthralgia, arthritis, back pain, breast pain, musculoskeletal chest pain, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, non-cardiac chest pain and pain in extremity
[i] Includes dyspnea and exertional dyspnea
[j] Includes rash, generalized rash, macular rash, and maculo-papular rash
[k] Includes essential hypertension, hypertension, and hypertensive encephalopathy
[l] Includes catheter site bruise, contusion, epistaxis, gastrointestinal hemorrhage, hematemesis, hematuria, injection site hemorrhage, intracranial hemorrhage, intraventricular hemorrhage, large intestinal hemorrhage, metrorrhagia, mouth hemorrhage, uterine hemorrhage, and vaginal hemorrhage

Table 33: Serious Adverse Events Occurring in ≥3% of Endometrial Carcinoma Patients in KEYNOTE-146.

Serious Adverse Event	KEYTRUDA® 200 mg in Combination with Lenvatinib 20 mg N=94
Endocrine	
Adrenal insufficiency	3.2
Gastrointestinal	
Abdominal pain[a]	6.4
Nausea	4.3
Colitis[b]	3.2
General	
Fatigue[c]	4.3
Pyrexia	3.2
Musculoskeletal and Connective Tissue	
Musculoskeletal pain[d]	5.3
Psychiatric	
Confusional state	4.3
Respiratory, Thoracic and Mediastinal	
Pleural effusion	4.3
Dyspnea	3.2
Vascular	
Hypertension[e]	8.5
Hemorrhage[f]	4.3

[a] Includes abdominal pain and upper abdominal pain
[b] Includes colitis and ischemic colitis
[c] Includes asthenia and fatigue
[d] Includes back pain, breast pain, musculoskeletal pain, and non-cardiac chest pain
[e] Includes hypertensive encephalopathy and hypertension
[f] Includes gastrointestinal hemorrhage, intracranial hemorrhage, and intraventricular hemorrhage

Serious adverse events reported in <3% patients with endometrial cancer treated with KEYTRUDA® in combination with lenvatinib (n=94) by SOC are shown below.

Cardiac disorders: angina pectoris, cardiac failure
Endocrine disorders: hypothyroidism
Eye disorders: retinal vein occlusion
Gastrointestinal disorders: pancreatitis, small intestinal obstruction, diarrhea, gastrointestinal perforation, pneumoperitoneum, vomiting
General disorders and administration site conditions: decreased appetite
Hepatobiliary disorders: autoimmune hepatitis, blood bilirubin increased, cholecystitis acute
Infections and infestations: urinary tract infection, appendicitis, Escherichia sepsis, influenza, pelvic abscess, pneumonia, respiratory tract infection
Investigations: amylase increased, lipase increased
Metabolism and nutrition disorders: failure to thrive, dehydration, hyperkalemia, hypocalcemia, hypomagnesemia, hyponatremia
Musculoskeletal and connective tissue disorders: muscular weakness, flank pain
Nervous system disorders: encephalopathy, seizure, syncope, transient ischemic attack, cerebral ischemia, dysarthria, headache, nervous system disorder, peripheral sensory neuropathy, posterior reversible encephalopathy syndrome
Renal and urinary disorders: hydronephrosis, acute kidney injury, autoimmune nephritis

Reproductive system and breast disorders: female genital tract fistula
Respiratory, thoracic and mediastinal disorders: pleuritic pain, pneumothorax, pulmonary embolism
Skin and subcutaneous tissue disorders: rash maculo-papular, skin ulcer, swelling face
Vascular disorders: hypotension

Abnormal Hematologic and Clinical Chemistry Findings
Table 34 summarizes laboratory abnormalities in patients on KEYTRUDA® in combination with lenvatinib.

Table 34: Laboratory Abnormalities Worsened from Baseline in ≥ 20% (All Grades) or ≥ 3% (Grades 3-4) of Patients on KEYTRUDA® plus Lenvatinib in KEYNOTE-146

	KEYTRUDA® 200 mg in Combination with Lenvatinib 20 mg	
Laboratory Abnormality[a]	**All Grades %[b]**	**Grade 3-4 %[b]**
Chemistry		
Increased creatinine	80	7
Hypertriglyceridemia	58	4
Hyperglycemia	53	1
Hypercholesteremia	49	6
Hypoalbuminemia	48	0
Hypomagnesemia	47	2
Increased aspartate aminotransferase	43	4
Hyponatremia	42	13
Increased lipase	42	18
Increased alanine aminotransferase	35	3
Increased alkaline phosphatase	32	1
Hypokalemia	27	5
Increased amylase	19	6
Hypocalcemia	14	3
Hypermagnesemia	4	3
Hematology		
Thrombocytopenia	48	0
Leukopenia	38	2
Lymphopenia	36	7
Anemia	35	1
Increased INR	21	3
Neutropenia	12	3

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

Renal Cell Carcinoma
Table 35 summarizes the treatment-related adverse events that occurred in at least 1% of patients with renal cell carcinoma treated with KEYTRUDA® in combination with axitinib in KEYNOTE-426. The most common treatment-related adverse events (reported in at least 10% of patients) were: hyperthyroidism; hypothyroidism; diarrhea; nausea; stomatitis; asthenia; fatigue; mucosal inflammation; ALT increased; AST increased; decreased appetite; arthralgia; proteinuria; dysphonia; palmar-plantar erythrodysesthesia syndrome; pruritus; rash; and hypertension. Sixty three percent of patients had ≥ Grade 3 treatment-related adverse events. The most common ≥ Grade 3 adverse reactions were: hypertension (21.2%); ALT increased

(12,1%); diarrhea (7.2%); AST increased (6.8%); and palmar-plantar erythrodysesthesia syndrome (5.1%).

In KEYNOTE-426, a higher than expected incidence of Grades 3 and 4 ALT increased (20%) and AST increased (13%), as measured by laboratory tests, were observed in previously untreated patients with RCC receiving KEYTRUDA® in combination with axitinib. The median time to onset of ALT increased was 2.3 months (range: 7 days to 19.8 months). In patients with ALT ≥ 3 times ULN (Grades 2-4, n=116), ALT resolved to Grades 0-1 in 94%. Fifty-nine percent of the patients with increased ALT received systemic corticosteroids. Of the patients who recovered, 92 (84%) were rechallenged with either KEYTRUDA® (3%) or axitinib (31%) monotherapy or with both (50%). Of these patients, 55% had no recurrence of ALT >3 times ULN, and of those patients with recurrence of ALT >3 times ULN, all recovered (See DOSAGE AND ADMINISTRATION and WARNINGS AND PRECAUTIONS).

Fatal treatment-related adverse events occurred in 0.9% of patients receiving KEYTRUDA® in combination with axitinib. These included 1 case each of myasthenia gravis, myocarditis, necrotising fasciitis, and pneumonitis.

Serious treatment-related adverse events occurred in 24% of patients receiving KEYTRUDA® in combination with axitinib. Serious treatment-related adverse events in ≥ 1% of patients receiving KEYTRUDA® in combination with axitinib included: diarrhea (1.9%); ALT increased (1.4%); AST increased (1.2%); and pneumonitis (1.2%).

KEYTRUDA® and axitinib were simultaneously discontinued for treatment-related adverse events (Grades 1-4) in 6.3% of patients in KEYNOTE 426. The most common treatment-related adverse event leading to discontinuation of both study drugs was ALT increased (1.2%). The median time to discontinuation of both drugs for treatment-related adverse events was 63 days. In KEYNOTE 426, KEYTRUDA® was discontinued for treatment-related adverse events in 18.6% of subjects, regardless of action taken with axitinib; the most common treatment-related adverse events (≥ 2%) leading to discontinuation of KEYTRUDA® were: ALT increased (4.7%); and AST increased (3.7%). Axitinib was discontinued for treatment-related adverse events in 15.4% of subjects, regardless of action taken with pembrolizumab; the most common treatment-related adverse event (≥ 2%) leading to discontinuation of axitinib was ALT increased (3.7%).

Treatment-related adverse events leading to simultaneous interruption of both KEYTRUDA® and axitinib occurred in 28% of patients; the most common treatment-related adverse events leading to interruption of both study drugs (≥ 2%) were: ALT increased (7.0%); AST increased (6.5%); and diarrhea (6.1%).

Treatment-related adverse events leading to interruption of KEYTRUDA® occurred in 41% of patients, regardless of action taken with axitinib. The most common treatment-related adverse events leading to interruption of KEYTRUDA® (≥ 2%) were: ALT increased (9.1%); AST increased (8.4%); diarrhea (8.4%); and hyperthyroidism (2.1%).

Axitinib was interrupted due to treatment-related adverse events in 57.6% of patients, regardless of action taken with pembrolizumab. The most common treatment-related adverse events leading to interruption of axitinib (≥ 2%) were: diarrhea (12.8%); hypertension (12.6%); ALT increased (11.9%); AST increased (11.4%); palmar-plantar erythrodysesthesia syndrome (6.8%); decreased appetite (4.4%); proteinuria (3.5%); fatigue (3.0%); mucosal inflammation (2.6%); stomatitis (2.6%); and nausea (2.3%). Axitinib was dose reduced in 21% of patients, regardless of action taken with pembrolizumab. The most common treatment-related adverse

events leading to dose reduction (≥ 2%) were: hypertension (4.0%); diarrhea (3.5%); and palmar-plantar erythrodysesthesia syndrome (2.3%).

Table 35: Treatment-Related Adverse Events Occurring in ≥ 1% of Patients with Renal Cell Carcinoma treated with KEYTRUDA® in Combination with Axitinib in KEYNOTE-426

	KEYTRUDA® + axitinib n=429				Sunitinib n=425			
Adverse Reaction	**Any Grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**	**Any Grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**
Blood and lymphatic system disorders								
Anemia	12 (2.8)	0 (0)	1 (0.2)	0 (0)	69 (16.2)	13 (3.1)	0 (0)	0 (0)
Leukopenia	5 (1.2)	0 (0)	0 (0)	0 (0)	37 (8.7)	6 (1.4)	0 (0)	0 (0)
Neutropenia	6 (1.4)	0 (0)	1 (0.2)	0 (0)	79 (18.6)	27 (6.4)	1 (0.2)	0 (0)
Thrombocytopenia	8 (1.9)	0 (0)	0 (0)	0 (0)	94 (22.1)	20 (4.7)	2 (0.5)	0 (0)
Endocrine disorders								
Adrenal insufficiency	9 (2.1)	1 (0.2)	0 (0)	0 (0)	1 (0.2)	0 (0)	0 (0)	0 (0)
Hyperthyroidism	52 (12.1)	4 (0.9)	0 (0)	0 (0)	14 (3.3)	0 (0)	0 (0)	0 (0)
Hypophysitis	5 (1.2)	4 (0.9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Hypothyroidism	135 (31.5)	1 (0.2)	0 (0)	0 (0)	119 (28.0)	0 (0)	0 (0)	0 (0)
Thyroiditis	10 (2.3)	1 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Eye disorders								
Dry eye	5 (1.2)	0 (0)	0 (0)	0 (0)	7 (1.6)	0 (0)	0 (0)	0 (0)
Gastrointestinal disorders								
Abdominal discomfort	5 (1.2)	0 (0)	0 (0)	0 (0)	3 (0.7)	0 (0)	0 (0)	0 (0)
Abdominal pain	23 (5.4)	3 (0.7)	0 (0)	0 (0)	16 (3.8)	0 (0)	0 (0)	0 (0)
Abdominal pain upper	13 (3.0)	1 (0.2)	0 (0)	0 (0)	20 (4.7)	1 (0.2)	0 (0)	0 (0)
Colitis	8 (1.9)	5 (1.2)	0 (0)	0 (0)	1 (0.2)	0 (0)	0 (0)	0 (0)
Constipation	31 (7.2)	0 (0)	0 (0)	0 (0)	29 (6.8)	0 (0)	0 (0)	0 (0)
Diarrhea	210 (49)	31(7.2)	0 (0)	0 (0)	175 (41.2)	19 (4.5)	0 (0)	0 (0)
Dry mouth	17 (4.0)	0 (0)	0 (0)	0 (0)	22 (5.2)	0 (0)	0 (0)	0 (0)
Dyspepsia	12 (2.8)	0 (0)	0 (0)	0 (0)	48 (11.3)	1 (0.2)	0 (0)	0 (0)
Dysphagia	9 (2.1)	1 (0.2)	0 (0)	0 (0)	4 (0.9)	0 (0)	0 (0)	0 (0)
Esophagitis	6 (1.4)	0 (0)	0 (0)	0 (0)	3 (0.7)	0 (0)	0 (0)	0 (0)
Flatulence	13 (3.0)	0 (0)	0 (0)	0 (0)	9 (2.1)	0 (0)	0 (0)	0 (0)
Gastritis	6 (1.4)	0 (0)	0 (0)	0 (0)	4 (0.9)	0 (0)	0 (0)	0 (0)
Gastroesophageal reflux disease	6 (1.4)	0 (0)	0 (0)	0 (0)	34 (8.0)	3 (0.7)	0 (0)	0 (0)

	KEYTRUDA® + axitinib n=429				Sunitinib n=425			
Adverse Reaction	**Any Grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**	**Any Grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**
Nausea	91 (21.2)	2 (0.5)	0 (0)	0 (0)	111 (26.1)	4 (0.9)	0 (0)	0 (0)
Oral pain	17 (4)	0 (0)	0 (0)	0 (0)	13 (3.1)	0 (0)	0 (0)	0 (0)
Stomatitis	61 (14.2)	3 (0.7)	0 (0)	0 (0)	86 (20.2)	9 (2.1)	0 (0)	0 (0)
Vomiting	34 (7.9)	1 (0.2)	0 (0)	0 (0)	56 (13.2)	3 (0.7)	0 (0)	0 (0)
General disorders and administration site conditions								
Asthenia	50 (11.7)	6 (1.4)	0 (0)	0 (0)	54 (12.7)	12 (2.8)	0 (0)	0 (0)
Chills	8 (1.9)	0 (0)	0 (0)	0 (0)	11 (2.6)	1 (0.2)	0 (0)	0 (0)
Edema peripheral	7 (1.6)	1 (0.2)	0 (0)	0 (0)	14 (3.3)	0 (0)	0 (0)	0 (0)
Fatigue	130 (30.3)	10 (2.3)	0 (0)	0 (0)	142 (33.4)	21 (4.9)	0 (0)	0 (0)
Malaise	8 (1.9)	1 (0.2)	0 (0)	0 (0)	13 (3.1)	0 (0)	0 (0)	0 (0)
Mucosal inflammation	55 (12.8)	4 (0.9)	0 (0)	0 (0)	90 (21.2)	7 (1.6)	0 (0)	0 (0)
Pyrexia	16 (3.7)	0 (0)	0 (0)	0 (0)	24 (5.6)	0 (0)	0 (0)	0 (0)
Hepatobiliary disorders								
Hepatic function abnormal	13 (3.0)	6 (1.4)	0 (0)	0 (0)	6 (1.4)	0 (0)	0 (0)	0 (0)
Hepatitis	6 (1.4)	4 (0.9)	2 (0.5)	0 (0)	1 (0.2)	0 (0)	0 (0)	0 (0)
Hyperbilirubinemia	5 (1.2)	0 (0)	0 (0)	0 (0)	6 (1.4)	0 (0)	1 (0.2)	0 (0)
Infections and infestations								
Gingivitis	5 (1.2)	0 (0)	0 (0)	0 (0)	4 (0.9)	0 (0)	0 (0)	0 (0)
Investigations								
Alanine aminotransferase increased	102 (23.8)	48 (11.2)	4 (0.9)	0 (0)	54 (12.7)	10 (2.4)	1 (0.2)	0 (0)
Aspartate aminotransferase increased	97 (22.6)	26 (6.1)	3 (0.7)	0 (0)	59 (13.9)	7 (1.6)	0 (0)	0 (0)
Blood alkaline phosphatase increased	17 (4.0)	5 (1.2)	0 (0)	0 (0)	15 (3.5)	3 (0.7)	0 (0)	0 (0)
Blood bilirubin increased	19 (4.4)	1 (0.2)	1 (0.2)	0 (0)	20 (4.7)	1 (0.2)	0 (0)	0 (0)
Blood creatinine increased	24 (5.6)	0 (0)	0 (0)	0 (0)	30 (7.1)	1 (0.2)	0 (0)	0 (0)
Blood lactate dehydrogenase increased	8 (1.9)	0 (0)	0 (0)	0 (0)	12 (2.8)	0 (0)	0 (0)	0 (0)
Blood pressure increased	13 (3.0)	6 (1.4)	0 (0)	0 (0)	6 (1.4)	1 (0.2)	0 (0)	0 (0)

	KEYTRUDA® + axitinib n=429				Sunitinib n=425			
Adverse Reaction	**Any Grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**	**Any Grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**
Blood thyroid stimulating hormone increased	22 (5.1)	0 (0)	0 (0)	0 (0)	22 (5.2)	0 (0)	0 (0)	0 (0)
Lymphocyte count decreased	6 (1.4)	1 (0.2)	0 (0)	0 (0)	13 (3.1)	2 (0.5)	1 (0.2)	0 (0)
Platelet count decreased	14 (3.3)	0 (0)	1 (0.2)	0 (0)	76 (17.9)	27 (6.4)	4 (0.9)	0 (0)
Weight decreased	41 (9.6)	6 (1.4)	0 (0)	0 (0)	36 (8.5)	0 (0)	0 (0)	0 (0)
Metabolism and nutrition disorders								
Decreased appetite	94 (21.9)	9 (2.1)	0 (0)	0 (0)	106 (24.9)	2 (0.5)	0 (0)	0 (0)
Dehydration	9 (2.1)	4 (0.9)	0 (0)	0 (0)	8 (1.9)	5 (1.2)	0 (0)	0 (0)
Hyperglycemia	13 (3.0)	5 (1.2)	1 (0.2)	0 (0)	4 (0.9)	0 (0)	0 (0)	0 (0)
Hyperkalemia	10 (2.3)	1 (0.2)	0 (0)	0 (0)	4 (0.9)	1 (0.2)	0 (0)	0 (0)
Hypoalbuminemia	6 (1.4)	1 (0.2)	0 (0)	0 (0)	5 (1.2)	1 (0.2)	0 (0)	0 (0)
Hyponatremia	13 (3.0)	5 (1.2)	0 (0)	0 (0)	13 (3.1)	6 (1.4)	2 (0.5)	0 (0)
Hypophosphatemia	6 (1.4)	2 (0.5)	0 (0)	0 (0)	26 (6.1)	11 (2.6)	0 (0)	0 (0)
Musculoskeletal and connective tissue disorders								
Arthralgia	52 (12.1)	3 (0.7)	0 (0)	0 (0)	15 (3.5)	2 (0.5)	0 (0)	0 (0)
Arthritis	5 (1.2)	2 (0.5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Back pain	9 (2.1)	0 (0)	0 (0)	0 (0)	5 (1.2)	0 (0)	0 (0)	0 (0)
Muscle spasms	8 (1.9)	0 (0)	0 (0)	0 (0)	5 (1.2)	0 (0)	0 (0)	0 (0)
Muscular weakness	5 (1.2)	0 (0)	0 (0)	0 (0)	1 (0.2)	0 (0)	0 (0)	0 (0)
Myalgia	23 (5.4)	0 (0)	0 (0)	0 (0)	16 (3.8)	0 (0)	0 (0)	0 (0)
Pain in extremity	18 (4.2)	0 (0)	0 (0)	0 (0)	20 (4.7)	2 (0.5)	0 (0)	0 (0)
Nervous system disorders								
Dizziness	10 (2.3)	0 (0)	0 (0)	0 (0)	14 (3.3)	0 (0)	0 (0)	0 (0)
Dysgeusia	40 (9.3)	1 (0.2)	0 (0)	0 (0)	129 (30.4)	0 (0)	0 (0)	0 (0)
Headache	35 (8.2)	3 (0.7)	0 (0)	0 (0)	33 (7.8)	1 (0.2)	0 (0)	0 (0)
Lethargy	9 (2.1)	0 (0)	0 (0)	0 (0)	8 (1.9)	1 (0.2)	0 (0)	0 (0)
Paresthesia	6 (1.4)	0 (0)	0 (0)	0 (0)	5 (1.2)	0 (0)	0 (0)	0 (0)
Psychiatric disorders								
Insomnia	6 (1.4)	0 (0)	0 (0)	0 (0)	8 (1.9)	0 (0)	0 (0)	0 (0)
Renal and urinary disorders								
Acute kidney injury	7 (1.6)	4 (0.9)	0 (0)	0 (0)	4 (0.9)	1 (0.2)	0 (0)	0 (0)
Hematuria	8 (1.9)	2 (0.5)	0 (0)	0 (0)	8 (1.9)	1 (0.2)	0 (0)	0 (0)
Proteinuria	66	11 (2.6)	0 (0)	0 (0)	39	6 (1.4)	0 (0)	0 (0)

	KEYTRUDA® + axitinib n=429				Sunitinib n=425			
Adverse Reaction	**Any Grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**	**Any Grade n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**	**Grade 5 n (%)**
	(15.4)				(9.2)			
Respiratory, thoracic and mediastinal disorders								
Cough	32 (7.5)	1 (0.2)	0 (0)	0 (0)	12 (2.8)	0 (0)	0 (0)	0 (0)
Dysphonia	98 (22.8)	1 (0.2)	0 (0)	0 (0)	12 (2.8)	0 (0)	0 (0)	0 (0)
Dyspnea	28 (6.5)	2 (0.5)	0 (0)	0 (0)	16 (3.8)	2 (0.5)	0 (0)	0 (0)
Epistaxis	19 (4.4)	0 (0)	0 (0)	0 (0)	32 (7.5)	0 (0)	0 (0)	0 (0)
Oropharyngeal pain	13 (3.0)	1 (0.2)	0 (0)	0 (0)	5 (1.2)	0 (0)	0 (0)	0 (0)
Pneumonitis	11 (2.6)	0 (0)	0 (0)	1 (0.2)	1 (0.2)	0 (0)	0 (0)	0 (0)
Skin and subcutaneous tissue disorders								
Alopecia	11 (2.6)	0 (0)	0 (0)	0 (0)	13 (3.1)	0 (0)	0 (0)	0 (0)
Dermatitis	5 (1.2)	1 (0.2)	0 (0)	0 (0)	3 (0.7)	0 (0)	0 (0)	0 (0)
Dermatitis acneiform	5 (1.2)	1 (0.2)	0 (0)	0 (0)	6 (1.4)	0 (0)	0 (0)	0 (0)
Dry skin	27 (6.3)	1 (0.2)	0 (0)	0 (0)	35 (8.2)	0 (0)	0 (0)	0 (0)
Erythema	7 (1.6)	0 (0)	0 (0)	0 (0)	8 (1.9)	0 (0)	0 (0)	0 (0)
Palmar-plantar erythrodysesthesia syndrome	119 (27.7)	22 (5.1)	0 (0)	0 (0)	168 (39.5)	15 (3.5)	0 (0)	0 (0)
Pruritus	53 (12.4)	1 (0.2)	0 (0)	0 (0)	18 (4.2)	0 (0)	0 (0)	0 (0)
Rash	46 (10.7)	1(0.2)	0 (0)	0 (0)	38 (8.9)	1 (0.2)	0 (0)	0 (0)
Rash maculo-papular	17 (4.0)	1 (0.2)	0 (0)	0 (0)	3 (0.7)	0 (0)	0 (0)	0 (0)
Skin exfoliation	5 (1.2)	0 (0)	0 (0)	0 (0)	8 (1.9)	0 (0)	0 (0)	0 (0)
Vascular disorders								
Hypertension	179 (41.7)	91 (21.2)	0 (0)	0 (0)	184 (43.3)	78 (18.4)	0 (0)	0 (0)
Hypotension	5 (1.2)	1 (0.2)	0 (0)	0 (0)	1 (0.2)	0 (0)	0 (0)	0 (0)

Treatment related adverse events attributable to KEYTRUDA® and reported in <1% patients with renal cell carcinoma treated with KEYTRUDA® in combination with axitinib (n=429) in KEYNOTE-426 by SOC are shown below:

Blood and lymphatic system: lymphopenia
Eye disorders: uveitis
Cardiac disorders: myocarditis
Gastrointestinal disorders: pancreatitis
Metabolism and nutrition disorders: diabetic ketoacidosis, diabetes mellitus
Musculoskeletal and connective tissue disorders: myositis
Nervous system disorders: myasthenic syndrome

Injury, poisoning and procedural complications: infusion related reaction
Renal and urinary disorders: nephritis

Abnormal Hematologic and Clinical Chemistry Findings
Laboratory abnormalities (worsened from baseline in ≥ 10% of patients), reported in KEYNOTE-426 in patients with renal cell carcinoma are presented in Table 36.

Table 36: Laboratory Abnormalities Worsened from Baseline in ≥ 10% of Patients with Renal Cell Carcinoma treated with KEYTRUDA® and Axitinib at a Higher Incidence than in the Sunitinib Arm (Between Arm Difference of ≥ 5% [All Grades] or ≥ 2% [Grades 3-4]) (KEYNOTE-426)

	KEYTRUDA® + axitinib n=429		Sunitinib n=425	
Laboratory Test	**All Grades n (%)**	**Grades 3-4 n (%)**	**All Grades n (%)**	**Grades 3-4 n (%)**
Activated Partial Thromboplastin Time Increased	80 (18.6)	4 (0.9)	51 (12.0)	0 (0)
Alanine Aminotransferase Increased	253 (59.0)	85 (19.8)	186 (43.8)	23 (5.4)
Aspartate Aminotransferase Increased	241 (56.2)	57 (13.3)	234 (55.1)	19 (4.5)
Calcium Increased	112 (26.1)	3 (0.7)	64 (15.1)	8 (1.9)
Glucose Decreased	52 (12.1)	1 (0.2)	29 (6.8)	1 (0.2)
Glucose Increased	262 (61.1)	38 (8.9)	224 (52.7)	13 (3.1)
Lymphocytes Decreased	142 (33.1)	46 (10.7)	195 (45.9)	33 (7.8)
Potassium Decreased	71 (16.6)	15 (3.5)	49 (11.5)	10 (2.4)
Potassium Increased	145 (33.8)	26 (6.1)	92 (21.6)	7 (1.6)
Sodium Decreased	149 (34.7)	33 (7.7)	124 (29.2)	33 (7.8)

HNSCC

Table 37 summarizes the treatment-related adverse events that occurred in at least 1% of patients with HNSCC treated with KEYTRUDA® in KEYNOTE-048. The most common treatment-related adverse events (reported in at least 10% of patients) in either the KEYTRUDA® monotherapy arm or KEYTRUDA® in combination with chemotherapy arm were anemia, nausea, neutropenia, fatigue, mucosal inflammation, thrombocytopenia, vomiting, stomatitis, decreased appetite, platelet count decreased, diarrhea, neutrophil count decreased, white blood cell count decreased, hypothyroidism, leukopenia, asthenia, blood creatinine increased, hypomagnesemia, and constipation. The most common Grade 3-5 treatment-related adverse events for patients treated with KEYTRUDA® as monotherapy in KEYNOTE-048 were hyponatremia (n=6, 2%), pneumonitis (n=4, 1.3%), and fatigue (n=3, 1%). The most common Grade 3-5 treatment-related adverse events for patients treated with KEYTRUDA® in combination with chemotherapy in KEYNOTE-048 were anemia (n=54, 19.6%), neutropenia (n=49, 17.8%), neutrophil count decreased (n=27, 9.8%), mucosal inflammation (n=26, 9.4%), thrombocytopenia (n=24, 8.7%), febrile neutropenia (n=22, 8.0%), stomatitis (n-22, 8.0%), fatigue (n=19, 6.9%), nausea (n=15, 5.4%), white blood cell decreased (n=15, 5.4%), and platelet count decreased (n=14, 5.1%).

Treatment was discontinued for treatment-related adverse events in 5.0% of the 300 patients receiving KEYTRUDA® as monotherapy and in 25.0% of the 276 patients receiving KEYTRUDA® in combination with chemotherapy. The most common treatment-related adverse events leading to study drug discontinuation for KEYTRUDA® as monotherapy (occurring in at least 2 patients) were adrenal insufficiency (n=2), autoimmune hepatitis (n=2), and pneumonitis (n=2) and for KEYTRUDA® in combination with chemotherapy (occurring in at least 4 patients) were blood creatinine increased (n=6), mucosal inflammation (n=5), febrile neutropenia (n=4), neutropenia (n=4) and septic shock (n=4). The median time to discontinuation for treatment-related adverse events was 7.0 months for patients treated with KEYTRUDA® as monotherapy and 0.2 months for patients treated with KEYTRUDA® in combination with chemotherapy.

Table 37: Treatment-Related Adverse Events (incidence ≥ 1%) KEYTRUDA® Treatment Groups Combined, APaT Population in KEYNOTE 048

Adverse Reaction	KEYTRUDA® 200 mg every 3 weeks n=300				KEYTRUDA® 200 mg every 3 weeks Platinum FU n=276				Cetuximab Platinum FU n=287			
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Blood and lymphatic system disorders												
Anemia	12 (4.0)	2 (0.7)	0 (0.0)	0 (0.0)	134 (48.6)	52 (18.8)	2 (0.7)	0 (0.0)	118 (41.1)	43 (15.0)	0 (0.0)	0 (0.0)
Febrile neutropenia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	22 (8.0)	15 (5.4)	7 (2.5)	0 (0.0)	13 (4.5)	11 (3.8)	2 (0.7)	0 (0.0)
Leukopenia	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	34 (12.3)	8 (2.9)	0 (0.0)	0 (0.0)	38 (13.2)	9 (3.1)	7 (2.4)	0 (0.0)
Lymphopenia	2 (0.7)	1 (0.3)	0 (0.0)	0 (0.0)	7 (2.5)	1 (0.4)	0 (0.0)	0 (0.0)	15 (5.2)	3 (1.0)	1 (0.3)	0 (0.0)
Neutropenia	3 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	91 (33.0)	35 (12.7)	14 (5.1)	0 (0.0)	89 (31.0)	38 (13.2)	20 (7.0)	0 (0.0)
Pancytopenia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.4)	2 (0.7)	0 (0.0)	0 (0.0)	3 (1.0)	1 (0.3)	2 (0.7)	0 (0.0)
Thrombocytopenia	4 (1.3)	0 (0.0)	1 (0.3)	0 (0.0)	75 (27.2)	16 (5.8)	8 (2.9)	0 (0.0)	62 (21.6)	18 (6.3)	6 (2.1)	0 (0.0)
Ear and labyrinth disorders												
Deafness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypoacusis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	12 (4.2)	1 (0.3)	0 (0.0)	0 (0.0)
Tinnitus	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	15 (5.4)	0 (0.0)	0 (0.0)	0 (0.0)	16 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)
Endocrine disorders												
Hyperthyroidism	6 (2.0)	1 (0.3)	0 (0.0)	0 (0.0)	8 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypothyroidism	39 (13.0)	0 (0.0)	0 (0.0)	0 (0.0)	36 (13.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders												
Abdominal pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.1)	1 (0.4)	0 (0.0)	0 (0.0)	11 (3.8)	4 (1.4)	0 (0.0)	0 (0.0)
Abdominal pain upper	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	11 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)
Aphthous ulcer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.7)	2 (0.7)	0 (0.0)	0 (0.0)
Colitis	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	6 (2.2)	1 (0.4)	0 (0.0)	0 (0.0)	2 (0.7)	2 (0.7)	0 (0.0)	0 (0.0)

Adverse Reaction	KEYTRUDA® 200 mg every 3 weeks n=300				KEYTRUDA® 200 mg every 3 weeks Platinum FU n=276				Cetuximab Platinum FU n=287			
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Constipation	9 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)	28 (10.1)	0 (0.0)	0 (0.0)	0 (0.0)	31 (10.8)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhea	17 (5.7)	1 (0.3)	0 (0.0)	0 (0.0)	50 (18.1)	3 (1.1)	0 (0.0)	0 (0.0)	76 (26.5)	5 (1.7)	0 (0.0)	0 (0.0)
Dry mouth	5 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	9 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)
Dyspepsia	4 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	7 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	14 (4.9)	0 (0.0)	0 (0.0)	0 (0.0)
Dysphagia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (2.2)	1 (0.4)	0 (0.0)	0 (0.0)	3 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	12 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)	125 (45.3)	15 (5.4)	0 (0.0)	0 (0.0)	131 (45.6)	16 (5.6)	0 (0.0)	0 (0.0)
Oral pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.8)	1 (0.4)	0 (0.0)	0 (0.0)	5 (1.7)	1 (0.3)	0 (0.0)	0 (0.0)
Stomatitis	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	69 (25.0)	21 (7.6)	1 (0.4)	0 (0.0)	70 (24.4)	9 (3.1)	1 (0.3)	0 (0.0)
Tongue discomfort	3 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vomiting	7 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)	75 (27.2)	7 (2.5)	0 (0.0)	0 (0.0)	64 (22.3)	5 (1.7)	0 (0.0)	0 (0.0)
General disorders and administration site conditions												
Asthenia	7 (2.3)	1 (0.3)	0 (0.0)	0 (0.0)	32 (11.6)	7 (2.5)	0 (0.0)	0 (0.0)	30 (10.5)	6 (2.1)	0 (0.0)	0 (0.0)
Chest pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Chills	4 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Face edema	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue	43 (14.3)	3 (1.0)	0 (0.0)	0 (0.0)	84 (30.4)	19 (6.9)	0 (0.0)	0 (0.0)	83 (28.9)	11 (3.8)	0 (0.0)	0 (0.0)
Malaise	4 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	18 (6.5)	0 (0.0)	0 (0.0)	0 (0.0)	9 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)
Mucosal inflammation	8 (2.7)	2 (0.7)	0 (0.0)	0 (0.0)	77 (27.9)	25 (9.1)	1 (0.4)	0 (0.0)	76 (26.5)	14 (4.9)	0 (0.0)	0 (0.0)
Edema peripheral	3 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Peripheral swelling	3 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)
Pyrexia	10 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	16 (5.8)	0 (0.0)	0 (0.0)	0 (0.0)	12 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations												
Bronchitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.1)	0 (0.0)	0 (0.0)	1 (0.4)	5 (1.7)	0 (0.0)	1 (0.3)	0 (0.0)
Candida infection	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	8 (2.9)	2 (0.7)	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Lung infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.4)	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Oral candidiasis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	12 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	10 (3.5)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumonia	2 (0.7)	1 (0.3)	0 (0.0)	0 (0.0)	8 (2.9)	1 (0.4)	4 (1.4)	0 (0.0)	12 (4.2)	4 (1.4)	0 (0.0)	3 (1.0)
Septic shock	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (2.2)	0 (0.0)	1 (0.4)	5 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Investigations												

Adverse Reaction	KEYTRUDA® 200 mg every 3 weeks n=300				KEYTRUDA® 200 mg every 3 weeks Platinum FU n=276				Cetuximab Platinum FU n=287			
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Alanine aminotransferase increased	7 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)	9 (3.3)	1 (0.4)	0 (0.0)	0 (0.0)	15 (5.2)	2 (0.7)	0 (0.0)	0 (0.0)
Aspartate aminotransferase increased	8 (2.7)	1 (0.3)	0 (0.0)	0 (0.0)	11 (4.0)	1 (0.4)	0 (0.0)	0 (0.0)	14 (4.9)	3 (1.0)	0 (0.0)	0 (0.0)
Blood alkaline phosphatase increased	3 (1.0)	1 (0.3)	0 (0.0)	0 (0.0)	5 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	7 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)
Blood creatinine increased	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	31 (11.2)	1 (0.4)	0 (0.0)	0 (0.0)	16 (5.6)	0 (0.0)	0 (0.0)	0 (0.0)
Blood magnesium decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (2.9)	1 (0.4)	0 (0.0)	0 (0.0)	6 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Blood potassium increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Blood sodium decreased	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.4)	2 (0.7)	0 (0.0)	0 (0.0)	2 (0.7)	1 (0.3)	0 (0.0)	0 (0.0)
Blood thyroid stimulating hormone increased	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
C-reactive protein increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)
Gamma-glutamyltransferase increased	2 (0.7)	2 (0.7)	0 (0.0)	0 (0.0)	3 (1.1)	1 (0.4)	0 (0.0)	0 (0.0)	2 (0.7)	1 (0.3)	0 (0.0)	0 (0.0)
Hemoglobin decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.8)	2 (0.7)	0 (0.0)	0 (0.0)	3 (1.0)	1 (0.3)	0 (0.0)	0 (0.0)
Lymphocyte count decreased	4 (1.3)	1 (0.3)	0 (0.0)	0 (0.0)	12 (4.3)	5 (1.8)	4 (1.4)	0 (0.0)	8 (2.8)	4 (1.4)	2 (0.7)	0 (0.0)
Neutrophil count decreased	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	45 (16.3)	20 (7.2)	7 (2.5)	0 (0.0)	54 (18.8)	24 (8.4)	11 (3.8)	0 (0.0)
Platelet count decreased	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	51 (18.5)	9 (3.3)	5 (1.8)	0 (0.0)	46 (16.0)	6 (2.1)	3 (1.0)	0 (0.0)
Transaminases increased	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Weight decreased	9 (3.0)	1 (0.3)	0 (0.0)	0 (0.0)	21 (7.6)	2 (0.7)	0 (0.0)	0 (0.0)	30 (10.5)	1 (0.3)	0 (0.0)	0 (0.0)
Weight increased	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	3 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
White blood cell count decreased	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	36 (13.0)	13 (4.7)	2 (0.7)	0 (0.0)	43 (15.0)	19 (6.6)	3 (1.0)	0 (0.0)
Metabolism and nutrition disorders												
Decreased appetite	16 (5.3)	1 (0.3)	0 (0.0)	0 (0.0)	62 (22.5)	12 (4.3)	0 (0.0)	0 (0.0)	62 (21.6)	8 (2.8)	0 (0.0)	0 (0.0)
Dehydration	2 (0.7)	1 (0.3)	0 (0.0)	0 (0.0)	9 (3.3)	1 (0.4)	0 (0.0)	0 (0.0)	7 (2.4)	3 (1.0)	0 (0.0)	0 (0.0)
Hyperglycemia	5 (1.7)	2 (0.7)	0 (0.0)	0 (0.0)	4 (1.4)	2 (0.7)	1 (0.4)	0 (0.0)	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Hyperkalemia	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	8 (2.8)	3 (1.0)	0 (0.0)	0 (0.0)

Adverse Reaction	KEYTRUDA® 200 mg every 3 weeks n=300				KEYTRUDA® 200 mg every 3 weeks Platinum FU n=276				Cetuximab Platinum FU n=287			
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Hypoalbuminemia	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	6 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypocalcemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	10 (3.6)	2 (0.7)	0 (0.0)	0 (0.0)	12 (4.2)	1 (0.3)	1 (0.3)	0 (0.0)
Hypokalemia	4 (1.3)	1 (0.3)	0 (0.0)	0 (0.0)	16 (5.8)	6 (2.2)	3 (1.1)	0 (0.0)	36 (12.5)	7 (2.4)	4 (1.4)	0 (0.0)
Hypomagnesemia	3 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	29 (10.5)	4 (1.4)	0 (0.0)	0 (0.0)	95 (33.1)	8 (2.8)	3 (1.0)	0 (0.0)
Hyponatremia	10 (3.3)	5 (1.7)	1 (0.3)	0 (0.0)	23 (8.3)	9 (3.3)	1 (0.4)	0 (0.0)	19 (6.6)	7 (2.4)	1 (0.3)	0 (0.0)
Hypophosphatemia	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	6 (2.2)	2 (0.7)	0 (0.0)	0 (0.0)	19 (6.6)	5 (1.7)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders												
Arthralgia	6 (2.0)	1 (0.3)	0 (0.0)	0 (0.0)	9 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Muscular weakness	3 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)
Myalgia	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous system disorders												
Dizziness	4 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	8 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	8 (2.8)	1 (0.3)	0 (0.0)	0 (0.0)
Dysgeusia	6 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	16 (5.8)	0 (0.0)	0 (0.0)	0 (0.0)	15 (5.2)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	8 (2.7)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)
Hypoesthesia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Neuropathy peripheral	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	6 (2.1)	1 (0.3)	0 (0.0)	0 (0.0)
Neurotoxicity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Paresthesia	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	6 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)
Peripheral sensory neuropathy	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	15 (5.4)	3 (1.1)	0 (0.0)	0 (0.0)	6 (2.1)	2 (0.7)	0 (0.0)	0 (0.0)
Syncope	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (2.2)	4 (1.4)	0 (0.0)	0 (0.0)	2 (0.7)	2 (0.7)	0 (0.0)	0 (0.0)
Psychiatric disorders												
Insomnia	3 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)
Renal and urinary disorders												
Acute kidney injury	3 (1.0)	1 (0.3)	0 (0.0)	0 (0.0)	15 (5.4)	3 (1.1)	1 (0.4)	0 (0.0)	6 (2.1)	1 (0.3)	0 (0.0)	0 (0.0)
Renal failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.7)	1 (0.3)	0 (0.0)	0 (0.0)
Tubulointerstitial nephritis	3 (1.0)	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders												
Cough	5 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dyspnea	7 (2.3)	2 (0.7)	0 (0.0)	0 (0.0)	4 (1.4)	2 (0.7)	0 (0.0)	0 (0.0)	5 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)
Dyspnea exertional	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Epistaxis	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	8 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)
Hiccups	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)
Interstitial lung disease	2 (0.7)	1 (0.3)	0 (0.0)	0 (0.0)	3 (1.1)	1 (0.4)	0 (0.0)	1 (0.4)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)

Adverse Reaction	KEYTRUDA® 200 mg every 3 weeks n=300				KEYTRUDA® 200 mg every 3 weeks Platinum FU n=276				Cetuximab Platinum FU n=287			
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Oropharyngeal pain	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.7)	1 (0.3)	0 (0.0)	0 (0.0)
Pleural effusion	3 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumonitis	15 (5.0)	3 (1.0)	0 (0.0)	1 (0.3)	11 (4.0)	3 (1.1)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders												
Alopecia	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	13 (4.7)	0 (0.0)	0 (0.0)	0 (0.0)	14 (4.9)	0 (0.0)	0 (0.0)	0 (0.0)
Dermatitis	4 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	6 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Dermatitis acneiform	6 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	82 (28.6)	6 (2.1)	0 (0.0)	0 (0.0)
Dry skin	6 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	27 (9.4)	2 (0.7)	0 (0.0)	0 (0.0)
Erythema	3 (1.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	7 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)
Palmar-plantar erythrodysesthesia syndrome	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	20 (7.0)	2 (0.7)	0 (0.0)	0 (0.0)
Pruritis	22 (7.3)	0 (0.0)	0 (0.0)	0 (0.0)	14 (5.1)	0 (0.0)	0 (0.0)	0 (0.0)	24 (8.4)	1 (0.3)	0 (0.0)	0 (0.0)
Rash	25 (8.3)	2 (0.7)	0 (0.0)	0 (0.0)	23 (8.3)	1 (0.4)	0 (0.0)	0 (0.0)	101 (35.2)	17 (5.9)	0 (0.0)	0 (0.0)
Rash maculopapular	6 (2.0)	1 (0.3)	0 (0.0)	0 (0.0)	7 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	14 (4.9)	1 (0.3)	0 (0.0)	0 (0.0)
Vascular disorders												
Hypotension	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.4)	2 (0.7)	1 (0.4)	0 (0.0)	4 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)
Phlebitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Vasculitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.8)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)

Treatment-related adverse events reported in <1% patients with HNSCC treated with KEYTRUDA® 200 mg every 3 weeks (n=300) by SOC are shown below.

Endocrine disorders: adrenal insufficiency, hypopituitarism
Eye disorders: uveitis
Gastrointestinal disorders: enterocolitis, colitis, pancreatitis, pancreatitis acute
Hepatobiliary disorders: autoimmune hepatitis
Infections and infestations: encephalitis
Injury, poisoning, and procedural complications: infusion-related reaction
Renal and urinary disorders: tubulointerstitial nephritis
Respiratory, thoracic, and mediastinal disorders: interstitial lung disease, organizing pneumonia
Skin and subcutaneous disorders: rash, dermatitis exfoliative, erythema multiforme, rash generalized, rash maculopapular

Treatment-related adverse events attributable to KEYTRUDA® and reported in <1% patients with HNSCC treated with KEYTRUDA® 200 mg every 3 weeks (n=276) in combination with chemotherapy by SOC are shown below.

Cardiac disorders: autoimmune myocarditis
Endocrine disorders: hypophysitis, thyroiditis
Gastrointestinal disorders: colitis microscopic
Hepatobiliary disorders: autoimmune hepatitis
Immune system disorders: hypersensitivity
Injury, poisoning, and procedural complications: infusion-related reaction
Renal and urinary disorders: nephritis
Skin and subcutaneous disorders: rash, rash generalized

Laboratory abnormalities (worsened from baseline in ≥ 10% of patients), reported in KEYNOTE-048 are presented in Table 38.

Table 38 Laboratory Abnormalities Worsened from Baseline in ≥10% Treated with KEYTRUDA® and at a Higher Incidence than in Control Arm (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-4]) APaT Population

Laboratory Test	KEYTRUDA® 200 mg every 3 weeks n=300		KEYTRUDA® 200 mg every 3 weeks Platinum FU n=276		Cetuximab Platinum FU n=287	
	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %	All Grades %	Grades 3-4 %
Chemistry						
Calcium increased	21	5	16	4	12	2
Creatinine increased	16	1	34	2	27	2
Hematology						
Hemoglobin decreased	50	7	85	27	77	19

8.3 Clinical Trial Adverse Reactions (Pediatrics)

In a Phase I/II study (KEYNOTE-051), 161 pediatric patients (62 children ages 6 months to less than 12 years and 199 adolescents ages 12 years to 17 years) with advanced melanoma, lymphoma, or PD-L1 positive advanced, relapsed, or refractory solid tumours were administered KEYTRUDA® 2 mg/kg every 3 weeks. Patients received KEYTRUDA® for a median of 4 doses (range 1-35 doses), with 138 patients (86%) receiving KEYTRUDA® for 2 doses or more. The concentrations of pembrolizumab in pediatric patients were similar to those observed in adult patients at the same dose regimen of 2 mg/kg every 3 weeks.

The most common adverse reactions (reported in at least 10% of pediatric patients) were: pyrexia; vomiting; headache; abdominal pain; anemia, cough: constipation; fatigue; nausea; diarrhea; decreased appetite; aspartate aminotransferase increased; alanine aminotransferase increased; arthralgia; lymphocyte count decreased; asthenia; back pain; pain in extremity; pruritus; white blood cell count decreased and dyspnea. Adverse reactions that occurred more frequently among pediatric patients (>10% increased) in comparison to a reference dataset of 2799 adult patients were: pyrexia (33%); vomiting (30%); headache (25%); abdominal pain (22%); lymphocyte count decreased (12%) and white blood cell count decreased (11%).

8.4 Post-Market Adverse Reactions

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.

Eye disorders: Vogt-Koyanagi-Harada syndrome

Immune system disorders: hemophagocytic lymphohistiocytosis

Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. Trough levels of pembrolizumab interfere with the electrochemiluminescent (ECL) assay results, therefore, a subset analysis was performed in the patients with a concentration of pembrolizumab below the drug tolerance level of the anti-product antibody assay. In clinical studies in patients treated with pembrolizumab at a dose of 2 mg/kg every three weeks, 200 mg every three weeks, or 10 mg/kg every two or three 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 or neutralizing antibody development.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including: assay methodology; sample handling; timing of sample collection; concomitant medications; and underlying disease. For these reasons, comparison of incidence of antibodies to KEYTRUDA® with the incidences of antibodies to other products may be misleading.

NOC/c

9 DRUG INTERACTIONS

9.1 Overview

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 WARNINGS AND PRECAUTIONS). 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.

NOC/c

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 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 dual 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.

10.2 Pharmacodynamics

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.

10.3 Pharmacokinetics

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 neither statistically nor clinically meaningful differences in the pharmacokinetic (PK) parameters in the model of pembrolizumab across indications.

Table 39 - Summary of KEYTRUDA® Pharmacokinetic Parameters

Parameters		Mean*	%CV†
Half-life (days)	First dose	17	27%
	Steady state	22	32%
Vdss (L)‡	Vc	3.2	23%
	Vp	2.7	19%
	Vss	6.0	20%
CL (mL/day)	First dose	252	37%
	Steady state	195	40%
Time to steady state (weeks)		16	N/A

* Mean values are based on a population pharmacokinetics model. In this model, the parameters were estimated with good precision with the shrinkage estimates for CL at 15% and for Vc or Vp at 27%.

† %CV: coefficient of variation

‡ Volume of distribution at steady state

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

Distribution: The volume of distribution of pembrolizumab at steady state is small (approximately 6.0 L; Coefficient of Variation (CV): 20%).

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

Elimination: Pembrolizumab clearance parameter (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 17 days (27%) after the first dose and 22 days (32%) at steady state.

Based on analyses of post-hoc PK parameters from the final TDPK model, steady-state concentrations of pembrolizumab were reached by 16 weeks of repeated dosing with an every 3-week regimen and the systemic accumulation was 2.1-fold. The peak concentration (C_{max}), trough concentration (C_{min}), and area under the plasma concentration versus time curve at

steady state (AUC_{ss}) of pembrolizumab increased dose proportionally in the dose range of 2 to 10 mg/kg every 3 weeks.

Special Populations and Conditions
The effects of various covariates on the pharmacokinetic parameters of the pembrolizumab model were assessed in population pharmacokinetic analyses using a two-compartment model with linear clearance from the central compartment. The clearance parameter in the current population pharmacokinetic model for pembrolizumab increases in a less than proportional manner with increasing body weight. Therefore, both body weight-based dose and fixed-dose options provide similar control of variability in systemic pharmacokinetic exposures. Also, the analysis suggested that the following factors had no clinically important effect on the clearance parameter in the population pharmacokinetic model of pembrolizumab: age (range 15-94 years); gender; race; mild or moderate renal impairment; mild hepatic impairment; and tumour burden. Based on population pharmacokinetic (PK) analysis, pembrolizumab exposures with weight-based dosing at 2 mg/kg every 3 weeks in patients aged 6-17 years are comparable to those of adults that receive the same dose. For patients aged 2-6 years, exposure is approximately 1.3 fold higher than in adults. For patients aged <2 years, exposure is predicted to be approximately 2.2 fold higher than in adults; this should be interpreted with caution as it is based on PK extrapolation.

Hepatic Insufficiency: The effect of hepatic impairment on the clearance parameter in the pembrolizumab population pharmacokinetic model was evaluated in patients with melanoma and NSCLC 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 or statistically important differences in the clearance parameter in the pembrolizumab population pharmacokinetic model 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 WARNINGS AND PRECAUTIONS, and DOSAGE AND ADMINISTRATION).

Renal Insufficiency: The effect of renal impairment on the clearance parameter in the pembrolizumab population pharmacokinetic model was evaluated in patients with melanoma and NSCLC with mild (estimated Glomerular Filtration Rate (eGFR) < 90 and ≥ 60 mL/min/1.73 m^2) or moderate (eGFR < 60 and ≥ 30 mL/min/1.73 m^2) renal impairment compared to patients with normal (eGFR ≥ 90 mL/min/1.73 m^2) renal function. No clinically or statistically important differences in the clearance parameter in the pembrolizumab population pharmacokinetic model 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 (eGFR < 30 and ≥ 15 mL/min/1.73 m^2) renal impairment (See WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION).

11 STORAGE, STABILITY AND DISPOSAL
KEYTRUDA® Powder for Solution for Infusion: Store under refrigeration at 2°C to 8°C.

KEYTRUDA® Solution for Infusion: Store under refrigeration at 2°C to 8°C. Protect from light. Do not freeze. Do not shake.

For storage conditions after reconstitution or dilution of the medicinal product, See DOSAGE AND ADMINISTRATION.

12 SPECIAL HANDLING INSTRUCTIONS

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

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

KEYTRUDA® has been issued marketing authorization **with conditions**, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for KEYTRUDA®, please refer to Health Canada's Notice of Compliance with conditions – drug products website: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/index-eng.php

KEYTRUDA® is indicated for the treatment of:

- Adult and pediatric patients with refractory or relapsed classical Hodgkin Lymphoma (cHL), as monotherapy, who have failed autologous stem cell transplant (ASCT) or who are not candidates for multi-agent salvage chemotherapy and ASCT.

- Adult and pediatric patients with refractory Primary Mediastinal B-cell Lymphoma (PMBCL) or who have relapsed after 2 or more lines of therapy, as monotherapy.

- Adult patients with locally advanced unresectable or metastatic urothelial carcinoma, as monotherapy, who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by a validated test, or in adults who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.

- Adult 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.

- Adult patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)
    - colorectal cancer whose tumours have progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, as monotherapy, or
    - endometrial cancer whose tumours have progressed following prior therapy and who have no satisfactory alternative treatment options, as monotherapy.

- In combination with lenvatinib, adult patients with advanced endometrial carcinoma that is not microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior

platinum-based systemic therapy, and are not candidates for curative surgery or radiation.

KEYTRUDA® has been issued marketing authorization **without conditions** for:

- Treatment of adult patients with unresectable or metastatic melanoma who have not received prior treatment with ipilimumab. Subjects with BRAF V600 mutant melanoma may have received prior BRAF inhibitor therapy.

- Treatment of adult patients with unresectable or metastatic melanoma and disease progression following ipilimumab therapy and, if BRAF V600 mutation positive, following a BRAF or MEK inhibitor.

- Adjuvant treatment of adult patients with Stage III melanoma with lymph node involvement who have undergone complete resection.

- First-line treatment, as monotherapy, of adult patients with metastatic non-small cell lung carcinoma (NSCLC) or stage III disease where patients are not candidates for surgical resection or definitive chemoradiation, expressing PD-L1 [Tumour Proportion Score (TPS ≥1%)] as determined by a validated test, with no EGFR or ALK genomic tumour aberrations.

- Treatment of adult patients with metastatic non-squamous NSCLC in combination with pemetrexed and platinum chemotherapy with no EGFR or ALK genomic tumour aberrations, and no prior systemic chemotherapy treatment for metastatic NSCLC.

- Treatment of adult patients with metastatic squamous NSCLC in combination with carboplatin and either paclitaxel or nab-paclitaxel with no prior systemic chemotherapy treatment for metastatic NSCLC.

- Treatment of adult patients with metastatic NSCLC as monotherapy whose tumours express PD-L1 [(Tumour Proportion Score (TPS) ≥ 1%)] as determined by a validated test and who have disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have received authorized therapy for these aberrations prior to receiving KEYTRUDA®.

- Treatment of adult patients with locally advanced or metastatic urothelial carcinoma, as monotherapy who have disease progression during or following platinum-containing chemotherapy or within 12 months of completing neoadjuvant or adjuvant platinum-containing chemotherapy.

- Treatment of adult patients with advanced or metastatic renal cell carcinoma (RCC) in combination with axitinib with no prior systemic therapy for metastatic RCC.

- First-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) as monotherapy, in adult patients whose tumours have PD-L1 expression (Combined Positive Score [CPS] ≥ 1) as determined by a validated test.

- First-line treatment of metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) in combination with platinum and fluorouracil (FU) chemotherapy, in adult patients.

Drug Substance

Proper name: pembrolizumab

Molecular mass: The observed molecular weight of the most abundant form of the intact antibody is 149 kDa.

Structural formula: pembrolizumab is an IgG4 monoclonal antibody subtype and contains 32 cysteine residues. A correctly folded antibody molecule includes 4 disulfide linkages as interchain bonds and 12 intrachain bonds.

Physicochemical properties: is an aqueous solution stored frozen at –40 °C at a concentration of 22.5–27.5 mg/mL in 10 mM histidine buffer, pH 5.2–5.8, containing 7% sucrose and 0.02% polysorbate 80.

The pembrolizumab drug substance solution is colorless to slightly yellow. The solution clarity is clear to opalescent. It is essentially free of extraneous particulates and may contain some proteinaceous particulates.

The pH of pembrolizumab drug substance is 5.2–5.8.
The theoretical extinction coefficient of pembrolizumab at 280 nm is 1.42 $L \cdot g^{-1} \cdot cm^{-1}$

The pI of pembrolizumab is 6.8–6.9 as determined by capillary isoelectric focusing (cIEF).

14 CLINICAL TRIALS

14.1 Trial Design, Study Demographics and Study Results

Melanoma

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

Study demographics and trial design
The safety and efficacy of KEYTRUDA® were investigated in KEYNOTE-006, a multicenter, controlled, Phase III study for the treatment of unresectable or metastatic melanoma in patients who were naïve to ipilimumab and who received no or one prior systemic therapy. Patients were randomized (1:1:1) to receive KEYTRUDA® at a dose of 10 mg/kg every 2 (n=279) or 3 weeks (n=277) or ipilimumab at a dose of 3 mg/kg every 3 weeks (n=278). Randomization was stratified by line of therapy, ECOG performance status, and PD-L1 expression status. The study

excluded patients with autoimmune disease or those receiving immunosuppression; previous severe hypersensitivity to other monoclonal antibodies; and HIV, hepatitis B or hepatitis C infection. Patients with BRAF V600E mutant melanoma were not required to have received prior BRAF inhibitor therapy.

Patients were treated with KEYTRUDA® until disease progression, unacceptable toxicity, 24 months of therapy, or in the case of complete response, 6 months of therapy plus at least two doses beyond complete response. 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.

Table 40: Baseline Characteristics in KEYNOTE-006.

	KEYTRUDA® 10 mg/kg every 3 weeks n=277	**KEYTRUDA® 10 mg/kg every 2 weeks n=279**	**Ipilimumab n=278**
Men	63%	58%	58%
Women	37%	42%	42%
Age (median)	63	61	62
Age (range)	22-89 years	18-89 years	18-88 years
Prior systemic therapies			
0	67%	66%	65%
1	33%	34%	35%
ECOG PS			
0	68%	70%	68%
1	32%	30%	32%
PD-L1 status*			
Positive	80%	81%	81%
Negative	19%	18%	17%
M-stage at study entry			
M0	3%	3%	5%
M1	1%	2%	2%
M1a	12%	8%	11%
M1b	15%	23%	19%
M1c	68%	64%	64%
Baseline LDH			
Normal	63%	69%	64%
Elevated	35%	29%	33%
BRAF status			
wild type	64%	63%	61%
V600 mutant	35%	35%	38%
History of Brain Metastases			
No	89%	91%	90%
Yes	10%	8%	10%

*Based on an immunohistochemistry research assay with the 22C3 anti-PD-L1 antibody. PD-L1 positive = membrane expression in ≥1% of cells within tumour nests as assessed prospectively

The median duration of exposure was 5.6 months (range: 1 day to 11.0 months) for KEYTRUDA® and similar in both treatment arms. Fifty-one and 46% of patients received KEYTRUDA® 10 mg/kg every 2 or 3 weeks, respectively, for ≥ 6 months. No patients in either arm received treatment for more than one year.

Study Results
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 41 summarizes key efficacy measures, and the Kaplan-Meier curves for OS and PFS are shown in Figures 1 and 2.

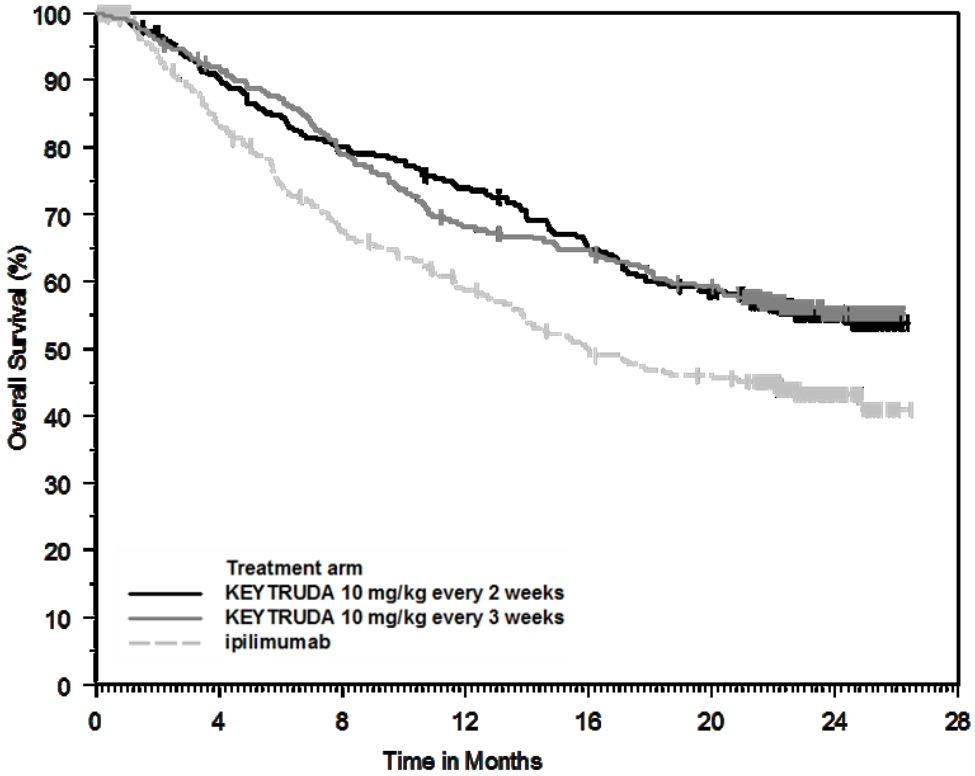
Based on a formal interim analysis for OS that occurred at a minimum of 12 months follow up in which 289 deaths were observed, pembrolizumab demonstrated clinically meaningful and statistically significant improvement in OS compared in patients with unresectable or metastatic melanoma previously untreated with ipilimumab. The OS HRs vs. ipilimumab were 0.69 (95% CI: 0.52, 0.90; p 0.00358) for patients treated with KEYTRUDA® 10 mg/kg every 3 weeks and 0.63 (95% CI: 0.47, 0.83; p=0.00052) for patients treated with KEYTRUDA® 10 mg/kg every 2 weeks. The OS rate at 12 months was 68.4% (95% CI: 62.5, 73.6) for patients treated with KEYTRUDA® 10 mg/kg every 3 weeks, 74.1% (95% CI: 68.5, 78.9) for patients treated with KEYTRUDA® 10 mg/kg every 2 weeks, and 58.2% (95% CI: 51.8, 64.0) for patients treated with ipilimumab. Median OS was not reached for any of the three treatment arms. The PFS HRs vs. ipilimumab were 0.58 (95% CI: 0.47, 0.72; p<0.00001) for patients treated with KEYTRUDA® 10 mg/kg every 3 weeks and 0.58 (95% CI: 0.46, 0.72; p<0.00001) for patients treated with KEYTRUDA® 10 mg/kg every 2 weeks. The median PFS in months was 4.1 (95% CI: 2.9, 6.9) for patients treated with KEYTRUDA® 10 mg/kg every 3 weeks, 5.5 (95% CI: 3.4, 6.9) for patients treated with KEYTRUDA® 10 mg/kg every 2 weeks, and 2.8 (95% CI: 2.8, 2.9) for patients treated with ipilimumab.

Table 41: Response to KEYTRUDA® 10 mg/kg every 2 or 3 weeks in Patients with Ipilimumab Naïve Advanced Melanoma in KEYNOTE-006 (Intent-to-Treat Analysis).

Endpoint	KEYTRUDA® 10 mg/kg every 3 weeks n=277	KEYTRUDA® 10 mg/kg every 2 weeks n=279	Ipilimumab n=278
Primary Efficacy Outcome Measure 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)
Primary Efficacy Outcome Measure 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)
Secondary Efficacy Outcome Measure Best Overall Response by IRO*			
ORR % (95% CI)	33% (27, 39)	34% (28, 40)	12% (8, 16)
Complete response n (%)	17 (6%)	14 (5%)	4 (1%)
Partial response n (%)	74 (27%)	80 (29%)	29 (10%)
Secondary Efficacy Outcome Measure Response Duration§ by IRO*			
Median in months (range)	Not reached (1.4+, 8.1+)	8.3 (1.4+, 8.3)	Not reached (1.1+, 7.9+)

*IRO = Independent radiology plus oncologist review using RECIST 1.1
†Hazard ratio (KEYTRUDA® compared to ipilimumab) based on the Cox proportional hazard model stratified by line of therapy, ECOG performance status, and PD-L1 expression status
‡Based on stratified Log rank test
§Based on patients with a best overall response as confirmed complete or partial response
NA = not available

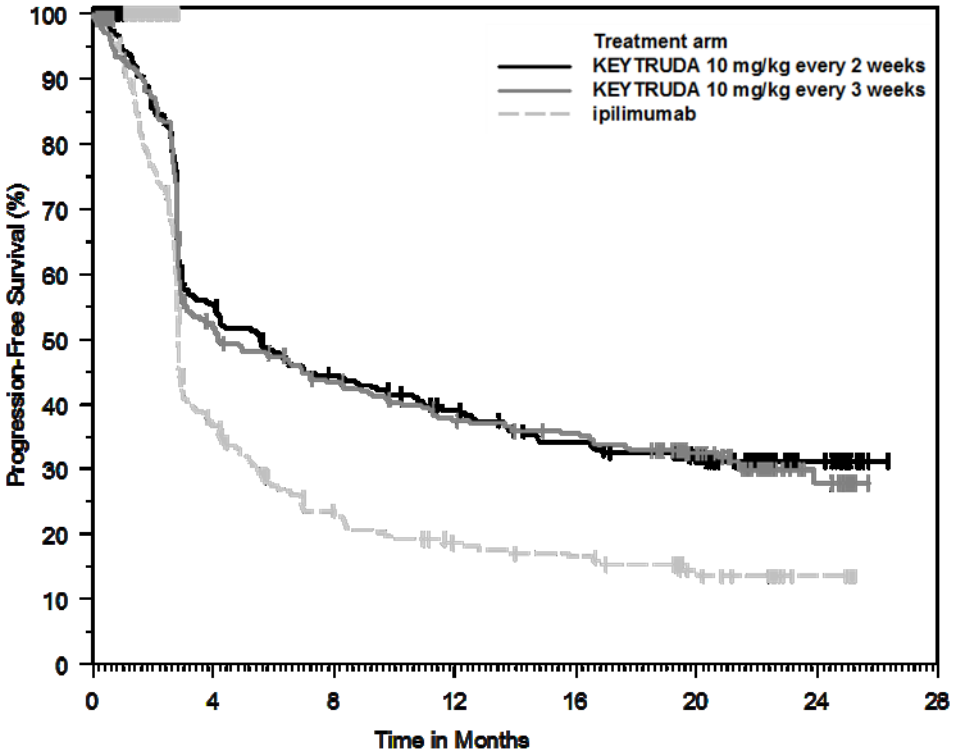
Figure 1: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-006 (Intent to Treat Population) *



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

**based on the final analysis with an additional follow-up of 9 months (total of 383 deaths as pre-specified in the protocol)*

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

**based on the final analysis with an additional follow-up of 9 months (total of 566 events)*

Sub-population analysis by PD-L1 status

In a subgroup analysis of KEYNOTE-006, the association between PD-L1 expression status using pre-defined 1% expression levels and efficacy measures suggested a clinically important signal predictive of the treatment effect in PFS and OS. In PD-L1 positive patients, pembrolizumab demonstrated improved efficacy vs ipilimumab in ipilimumab-naïve subjects with advanced melanoma across all efficacy endpoints. In contrast, no meaningful difference was detected in efficacy between the treatment groups in the PD-L1 negative patients. Among patients who were evaluable for PD-L1 expression (98%), 82% were PD-L1 positive and 18% were PD-L1 negative. The PFS HRs (pooled pembrolizumab [10 mg/kg every 2 or 3 weeks] vs. ipilimumab) were 0.53 (95% CI: 0.43, 0.65) for PD-L1 positive patients and 0.73 (95% CI: 0.47, 1.11) for PD-L1 negative patients. The OS HRs for pooled pembrolizumab vs. ipilimumab were 0.56 (95% CI: 0.43, 0.73) for PD-L1 positive patients and 0.95 (95% CI: 0.56, 1.62) for PD-L1 negative patients.

Sub-population analysis by BRAF mutation status

A subgroup analysis of KEYNOTE-006 in patients who were BRAF wild type, BRAF mutant without prior BRAF treatment and BRAF mutant with prior BRAF treatment was performed. The PFS hazard ratios (HRs) (pooled KEYTRUDA® [10 mg/kg every 2 or 3 weeks] vs. ipilimumab) were 0.57 (95% CI: 0.45, 0.73) for BRAF wild type, 0.50 (95% CI: 0.32, 0.77) for BRAF mutant without prior BRAF treatment, and 0.73 (95% CI: 0.48, 1.11) for BRAF mutant with prior BRAF

treatment. The OS HRs for pooled KEYTRUDA® vs. ipilimumab were 0.61 (95% CI: 0.46, 0.82) for BRAF wild type, 0.69 (95% CI: 0.33, 1.45) for BRAF mutant without prior BRAF treatment, and 0.75 (95% CI: 0.45, 1.26) for BRAF mutant with prior BRAF treatment. ORR for pooled KEYTRUDA® vs. ipilimumab was 34% vs. 13% for BRAF wild type, 41% vs. 13% for BRAF mutant without prior BRAF treatment, and 21% vs. 6% for BRAF mutant with prior BRAF treatment.

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

Study demographics and trial design

The safety and efficacy of KEYTRUDA® were investigated in KEYNOTE-002, a Phase II multicenter, randomized (1:1:1) 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. The treatment arms consisted of KEYTRUDA® 2 mg/kg or 10 mg/kg intravenously every 3 weeks or investigator's choice of any of the following chemotherapy regimens: dacarbazine 1000 mg/m^2 intravenously every 3 weeks (26%); temozolomide 200 mg/m^2 orally once daily for 5 days every 28 days (25%); carboplatin AUC 6 intravenously plus paclitaxel 225 mg/m^2 intravenously every 3 weeks for four cycles then carboplatin AUC of 5 plus paclitaxel 175 mg/m^2 every 3 weeks (25%); paclitaxel 175 mg/m^2 intravenously every 3 weeks (16%); or carboplatin AUC 5 or 6 intravenously every 3 weeks (8%). Randomization was stratified by ECOG performance status (0 vs. 1), LDH levels (normal vs. elevated [≥ 110% ULN]) and BRAF V600 mutation status (wild-type [WT] or V600E). The trial included patients with unresectable or metastatic melanoma with progression of disease; refractory to two or more doses of ipilimumab (3 mg/kg or higher) and, if BRAF V600 mutation-positive, a BRAF or MEK inhibitor; and disease progression within 24 weeks following the last dose of ipilimumab. The study excluded patients with: uveal melanoma and active brain metastasis; 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 received KEYTRUDA® until: unacceptable toxicity; disease progression that was symptomatic; was rapidly progressive; required urgent intervention; occurred with a decline in performance status, or was confirmed at 4 to 6 weeks with repeat imaging; withdrawal of consent; or physician's decision to stop therapy for the patient. Assessment of tumour status was performed at 12 weeks after randomization, 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.

Table 42: Baseline Characteristics in KEYNOTE-002.

	KEYTRUDA® 2 mg/kg every 3 weeks n=180	KEYTRUDA® 10 mg/kg every 3 weeks n=181	Chemotherapy* n=179
Men	58%	60%	64%
Women	42%	40%	36%
Age (median)	62	60	63
Age (range)	15-87 years	27-89 years	27-87 years
Prior systemic therapies			
At least 2	77%	70%	74%
3 or more	33%	34%	30%
ECOG PS			
0	54%	55%	55%
1	44%	45%	45%
M-stage at study entry			
M0	1%	1%	1%
M1a	5%	7%	8%
M1b	12%	9%	8%
M1c	82%	82%	82%
Baseline LDH			
Normal	56%	59%	61%
Elevated	43%	40%	39%
BRAF status			
wild type	76%	78%	77%
V600 mutant	24%	22%	24%

* Chemotherapy: dacarbazine, temozolomide, carboplatin plus paclitaxel, paclitaxel, or carboplatin

The median duration of exposure to KEYTRUDA® 2 mg/kg every 3 weeks was 3.7 months (range: 1 day to 32.5 months) and to KEYTRUDA® 10 mg/kg every 3 weeks was 4.8 months (range: 1 day to 31.8 months). The data described below reflect exposure to KEYTRUDA® 2 mg/kg in 37% of patients exposed to KEYTRUDA® for ≥ 6 months and in 22% of patients exposed for ≥ 12 months. In the KEYTRUDA® 10 mg/kg arm, 41% of patients were exposed to KEYTRUDA® for ≥ 6 months and 28% of patients were exposed to KEYTRUDA® for ≥ 12 months.

Study Results

The co-primary efficacy outcome measures were PFS (as assessed by IRO review using RECIST 1.1), and OS. Secondary efficacy outcome measures were, ORR and response duration. Table 43 summarizes key efficacy measures in patients previously treated with ipilimumab, and the Kaplan-Meier curves for PFS and OS are shown in Figures 3 and 4. Both pembrolizumab arms were superior to chemotherapy for PFS. There was no statistically significant difference between pembrolizumab and chemotherapy in the final OS analysis that was not adjusted for the potentially confounding effects of crossover. Of the patients randomized to the chemotherapy arm, 55% crossed over and subsequently received treatment with KEYTRUDA®.

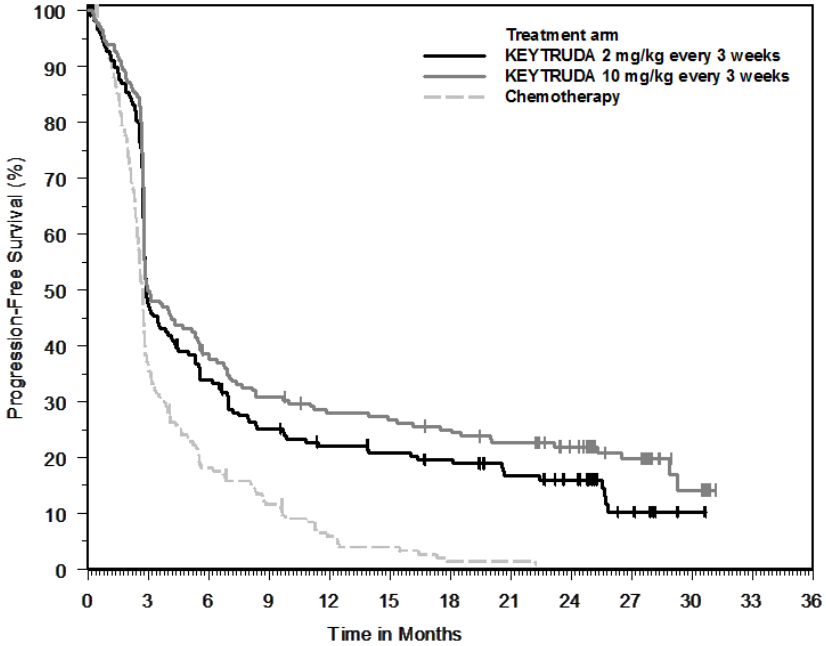
Table 43: Response to KEYTRUDA® 2 mg/kg or 10 mg/kg every 3 weeks in Patients with Unresectable or Metastatic Melanoma in KEYNOTE-002.

Endpoint	KEYTRUDA®. 2 mg/kg every 3 weeks n=180	KEYTRUDA®. 10 mg/kg every 3 weeks n=181	Chemotherapy n=179
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)
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	0.011 #	--
Median in months (95% CI)	13.4 (11.0, 16.4)	14.7 (11.3, 19.5)	11.0 (8.9, 13.8)

*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
#Not statistically significant compared to multiplicity adjusted significance level of 0.01

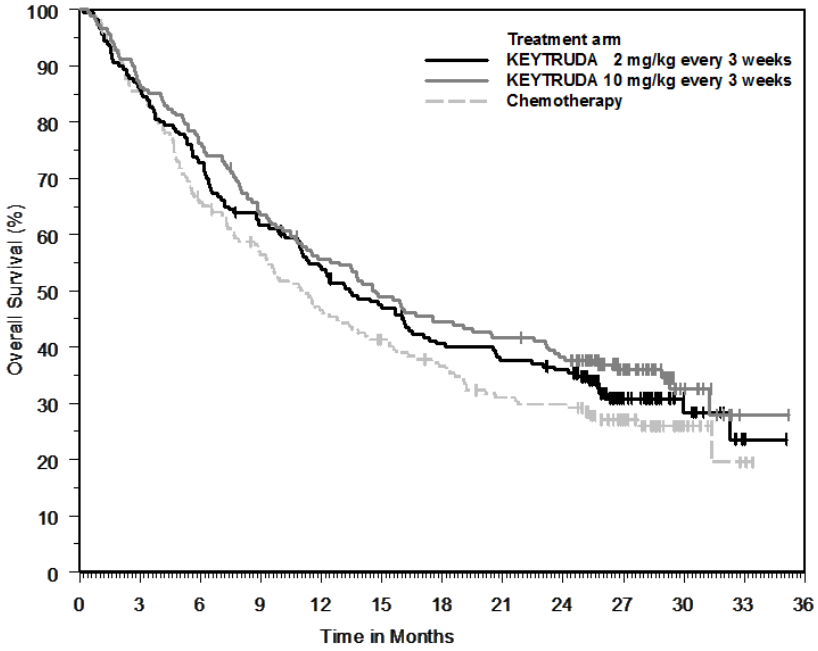
Based on the second interim analysis the ORR was 21% (95% CI: 15, 28), 25% (95% CI: 19, 32) and 4% (95%: CI 2, 9) for the KEYTRUDA® 2 mg/kg every 3 weeks, KEYTRUDA® 10 mg/kg every 3 weeks, and chemotherapy arms, respectively. ORR consisted of 4 (2%) complete responses and 34 (19%) partial responses for the KEYTRUDA® 2 mg/kg treatment arm, 5 (3%) complete responses and 41 (23%) partial responses for the KEYTRUDA® 10mg/kg treatment arm, and 0 (0%) complete responses and 8 (4%) partial responses for the chemotherapy arm.

Figure 3: Kaplan-Meier Curve for Progression-Free Survival (Based on IRO) by Treatment Arm in KEYNOTE-002 (Intent to Treat Population)



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

Figure 4: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-002 (Intent to Treat Population)



Number at Risk							
KEYTRUDA 2 mg/kg every 3 weeks:	180	131	95	70	61	11	0
KEYTRUDA 10 mg/kg every 3 weeks:	181	138	99	79	67	12	0
Chemotherapy:	179	115	80	60	48	9	0

Adjuvant Melanoma

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

Study demographics and trial design

The efficacy of KEYTRUDA® was evaluated in KEYNOTE-054, a multicenter, randomized 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 randomized (1:1) to receive KEYTRUDA® 200 mg every 3 weeks (n=514) or placebo (n=505), for up to one year until disease recurrence or unacceptable toxicity. The study design included reinitiation with KEYTRUDA® for subsequent disease recurrence that occurs >6 months after completion of one year of adjuvant treatment. Randomization was stratified by American Joint Committee on Cancer 7th edition (AJCC) stage (IIIA vs. IIIB vs. IIIC 1-3 positive lymph nodes vs. IIIC ≥ 4 positive lymph nodes) and geographic region (North America, European countries, Australia, and other countries as designated). Patients must have undergone lymph node dissection and if indicated, radiotherapy within 13 weeks prior to starting treatment. Patients with active autoimmune disease or a medical condition that required immunosuppression or mucosal or ocular melanoma were ineligible.

Patients 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.

Table 44: Baseline Characteristics in KEYNOTE-054.

	KEYTRUDA® 200 mg every 3 weeks n=514	**Placebo n=505**
Men	63%	60%
Women	37%	40%
Age (median)	54 years	54 years
Age (range)	19 to 88 years	19 to 83 years
Age (≥ 65)	24%	25%
ECOG PS		
0	94%	94%
1	6%	6%
Stage		
IIIA (> 1 mm)	16%	16%
IIIB	46%	46%
IIIC (1-3 positive lymph nodes)	18%	18%
IIIC (≥ 4 positive lymph nodes)	20%	20%
BRAF Status		
Mutation Detected	48%	52%
Mutation Not Detected	45%	42%
Unknown	7%	6%
PD-L1 Status*		
Positive	83%	84%
Negative	11%	11%
Unknown	5%	5%

* Tumour PD-L1 expression was assessed by an immunohistochemistry research assay. Results were recorded as positive (≥ 1% PD-L1), negative (<1% PD-L1) or unknown level of expression (indeterminate PD-L1).

The median duration of exposure to KEYTRUDA® was 11.7 months (range: 1 day to 21 months).

Study Results

The primary efficacy outcome measures were investigator-assessed recurrence free survival (RFS) in the ITT population and in the subgroup of patients with PD-L1 positive tumours. RFS was defined as the time between the date of randomization and the date of first recurrence (local, regional, or distant metastasis) or death, whichever occurs first. The trial demonstrated statistically significant improvement in RFS for patients randomized to the KEYTRUDA® arm compared with placebo. Efficacy results are summarized in Table 45 and Figure 5.

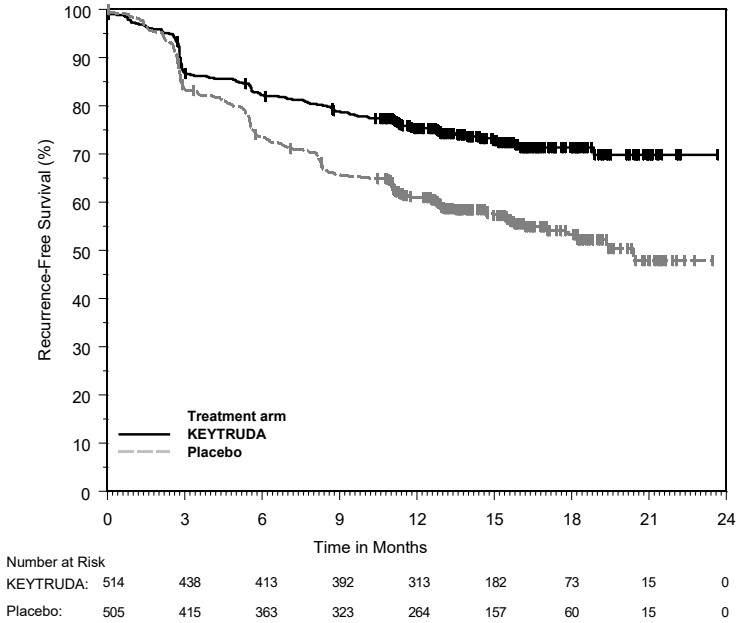
Table 45: Efficacy Results in KEYNOTE-054

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

*Based on the stratified Cox proportional hazard model
†p-Value (based on stratified log rank test) is compared with 0.008 of the allocated alpha for this interim analysis.
NR = not reached

For patients with PD-L1 positive tumours, the RFS HR (KEYTRUDA® versus placebo) was 0.54 (95% CI: 0.42, 0.69). The RFS benefit for KEYTRUDA® compared to placebo was observed regardless of tumour PD-L1 expression or BRAF mutation status.

Figure 5: Kaplan-Meier Curve for Recurrence-Free Survival in KEYNOTE-054 (Intent to Treat Population)



Non-Small Cell Lung Carcinoma

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

Study demographics and trial design

The efficacy of KEYTRUDA® was investigated in KEYNOTE-024, a multicenter, open-label randomized, controlled trial. Key eligibility criteria were metastatic NSCLC, PD-L1 expression tumour proportion score (TPS) of 50% or greater by an immunohistochemistry assay using the PD-L1 IHC 22C3 pharmDx* Kit, and no prior systemic treatment for metastatic NSCLC. 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. Randomization was stratified by ECOG performance status (0 vs 1), histology (squamous vs non-squamous), and geographic region (East Asia vs. non East-Asia). Patients were randomized (1:1) to receive KEYTRUDA® 200 mg intravenously every 3 weeks (n = 154) or investigator's choice of any of the following platinum-containing chemotherapy regimens (n = 151):

- Pemetrexed 500 mg/m^2 every 3 weeks and carboplatin AUC 5 to 6 mg/mL/min every three weeks on Day 1 for 4 to 6 cycles followed by optional pemetrexed 500 mg/m^2 every 3 weeks for patients with non-squamous histologies;
- Pemetrexed 500 mg/m^2 every 3 weeks and cisplatin 75 mg/m^2 every 3 weeks on Day 1 for 4 to 6 cycles followed by optional pemetrexed 500 mg/m^2 every 3 weeks for patients with non-squamous histologies;
- Gemcitabine 1250 mg/m^2 on days 1 and 8 and cisplatin 75 mg/m^2 every 3 weeks on Day 1 for 4 to 6 cycles;
- Gemcitabine 1250 mg/m^2 on Days 1 and 8 and carboplatin AUC 5 to 6 mg/mL/min every 3 weeks on day 1 for 4 to 6 cycles; or
- Paclitaxel 200 mg/m^2 every 3 weeks and carboplatin AUC 5 to 6 mg/mL/min every 3 weeks on Day 1 for 4 to 6 cycles followed by optional pemetrexed maintenance (for non-squamous histologies).

Treatment with KEYTRUDA® continued until RECIST 1.1-defined progression of disease as determined by an independent radiology committee or unacceptable toxicity. 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 were treated for up to 24 months or 35 administrations, whichever was longer. Subsequent disease progression could be retreated for up to one additional year. Patients on chemotherapy who experienced independently-verified progression of disease were able to crossover and receive KEYTRUDA®.

Table 46: Baseline Characteristics in KEYNOTE-024.

	KEYTRUDA® 200 mg every 3 weeks n=154	Chemotherapy n=151
Men	60%	63%
Women	40%	37%
Age (median)	65	66
Age (range)	33-90 years	38-85 years
ECOG PS		
0	35%	35%
1	64%	65%
2	1%	0%
Geographic region		
East Asia	14%	13%
Non-East Asia	86%	87%
Histology		
Squamous	19%	18%
Non-squamous	81%	82%
Cancer stage at study entry		
IIIB	1%	1%
IV	99%	99%

The median duration of exposure was 7.0 months (range 1 day to 18.7 months) in the KEYTRUDA® arm and 3.5 months (range 1 day to 16.8 months) in the chemotherapy arm.

Study Results

The primary efficacy outcome measure was PFS as assessed by blinded independent central review (BICR) using RECIST 1.1. Assessment of tumour status was performed every 9 weeks. Secondary efficacy outcome measures were OS and ORR (as assessed by BICR using RECIST 1.1). Table 47 summarizes key efficacy measures for the entire ITT population.

Table 47: Efficacy Results in KEYNOTE-024.

Endpoint	KEYTRUDA® 200 mg every 3 weeks n=154	Chemotherapy n=151
Primary Efficacy Outcome Measure 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)
Key Secondary Efficacy Outcome Measure 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)
Secondary Efficacy Outcome Measure Objective Response Rate*		
ORR % (95% CI)	45% (37, 53)	28% (21, 36)
Complete response %	4%	1%
Partial response %	41%	27%

*Assessed by BICR using RECIST 1.1

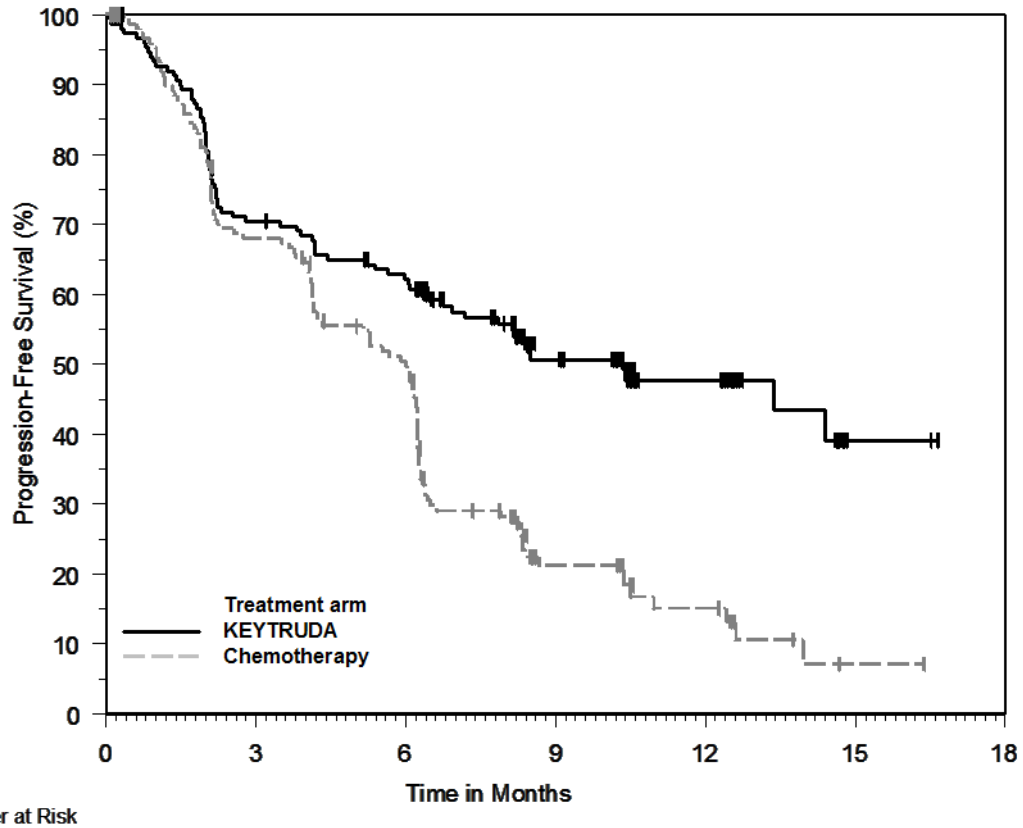
†Hazard ratio (KEYTRUDA® compared to chemotherapy) based on the stratified Cox proportional hazard model

‡Based on stratified Log rank test
NA = not available

In exploratory subgroup analyses, a reduced survival benefit of KEYTRUDA® compared to chemotherapy was observed in females as well as in never-smokers. In females, the HR for PFS was 0.75 (95% CI: 0.46, 1.21) and the HR for OS was 0.95 (95% CI: 0.50, 1.83). In never-smokers, the HR for PFS was 0.90 (95% CI: 0.11, 7.59) and the HR for OS was 1.69 (95% CI: 0.19, 15.25).

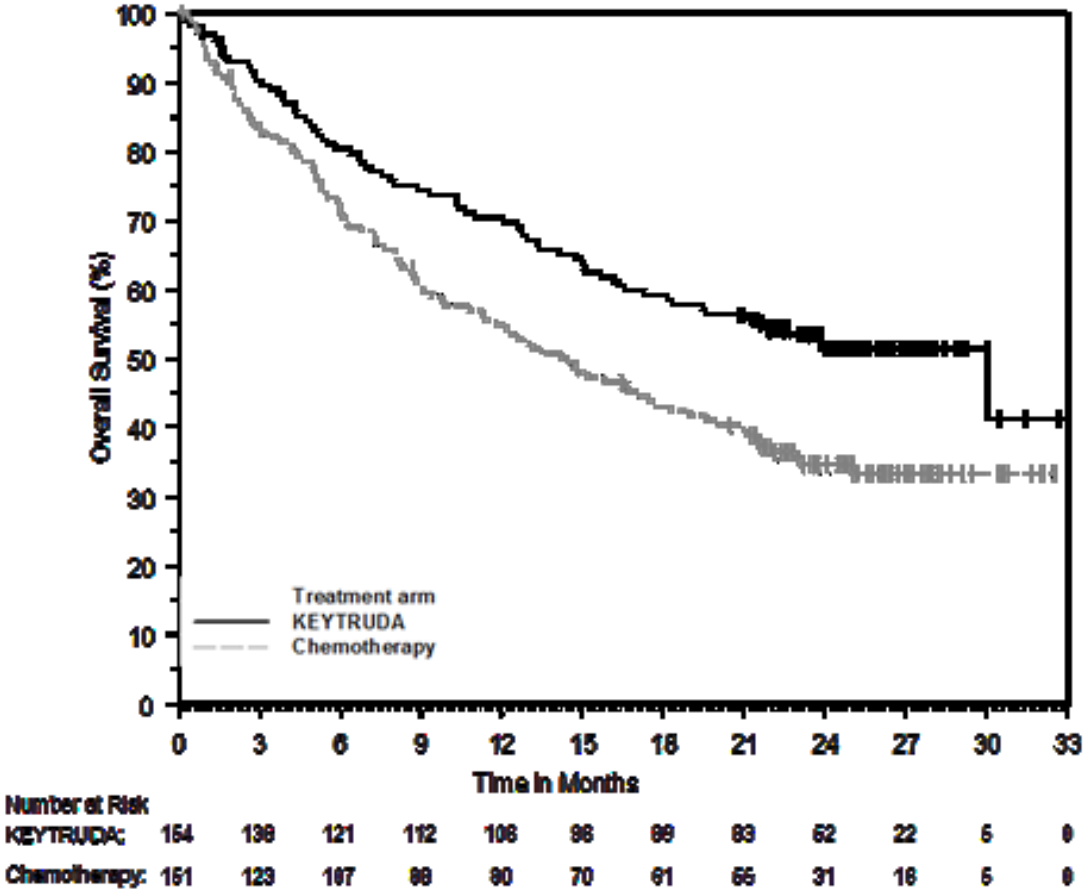
The final OS analysis was performed at a median follow-up of 25 months after 169 patient events (73 for KEYTRUDA® and 96 for chemotherapy). Median OS was 30.0 months (95% CI: 18.3, NA) for KEYTRUDA® and 14.2 months (95% CI: 9.8, 19.0) for chemotherapy. The OS HR was 0.63 (95% CI: 0.47, 0.86). See Figure 7.

Figure 6: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-024 (Intent to Treat Population)



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

Figure 7: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-024 (Intent to Treat Population)



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

Study demographics and trial design

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

Study Results

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 48 summarizes key efficacy measures for the entire ITT population (TPS ≥ 1%).

Table 48: Efficacy results (PD-L1 TPS ≥ 1%) in KEYNOTE-042

Endpoint	KEYTRUDA® 200 mg every 3 weeks (n=637)	Chemotherapy (n=637)
Primary Efficacy Outcome Measure OS		
Number (%) of patients with event	422 (66%)	481 (76%)
Hazard ratio* (95% CI)	0.82 (0.71, 0.93)	
p-Value†	0.0013	
Median in months (95% CI)	16.4 (14.0, 19.7)	12.1 (11.3, 13.3)
Secondary Efficacy Outcome Measure PFS‡		
Number (%) of patients with event	532 (84%)	541 (85%)
Hazard ratio*,§ (95% CI)	1.06 (0.93, 1.19)	
Median in months (95% CI)	5.4 (4.3, 6.2)	6.6 (6.3, 7.3)
Secondary Efficacy Outcome Measure Overall response rate‡		
ORR %§ (95% CI)	27% (24, 31)	27% (23, 30)
Complete response %	0.5%	0.5%
Partial response %	27%	26%

*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.

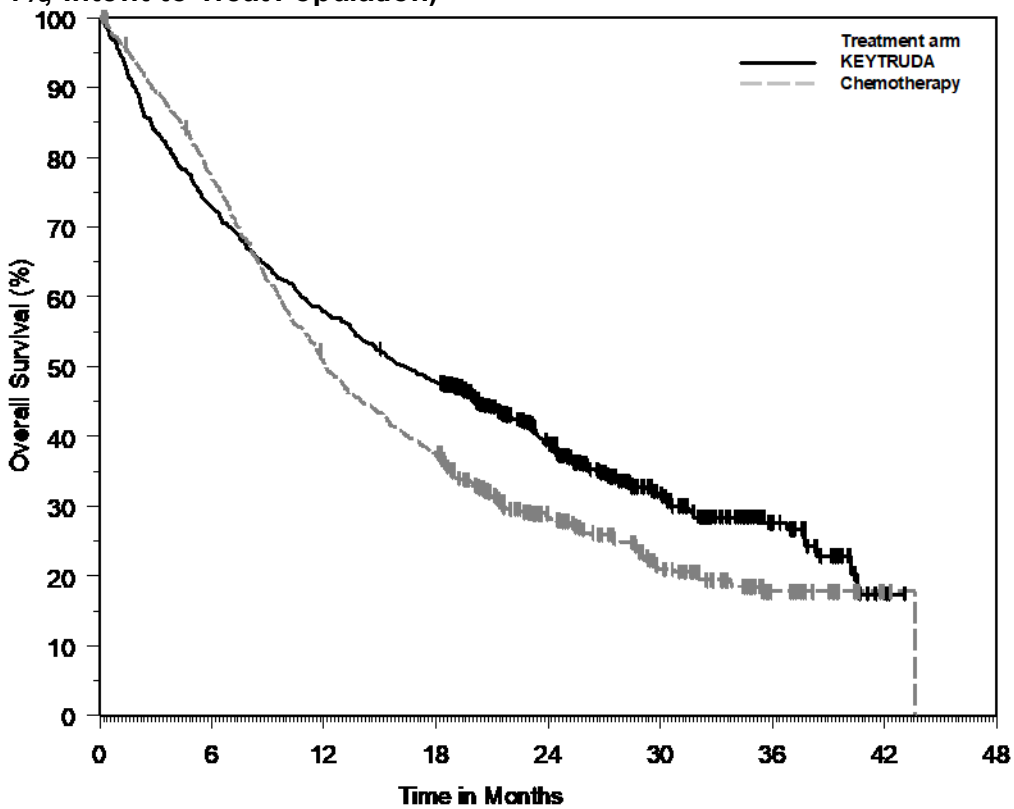
The findings of an analysis based on PD-L1 TPS ≥ 50% and TPS 1 to 49% are shown in Table 49.

Table 49: Efficacy results by PD-L1 Expression in KEYNOTE-042

Endpoint	KEYTRUDA® 200 mg every 3 weeks (n=299)	Chemotherapy (n=300)	KEYTRUDA® 200 mg every 3 weeks (n=338)	Chemotherapy (n=337)
OS	**TPS ≥50%**		**TPS 1 to 49%**	
Number (%) of patients with event	180 (60%)	220 (73%)	242 (72%)	261 (77%)
Hazard ratio* (95% CI)	0.70 (0.58, 0.86)		0.91 (0.77, 1.09)	
Median in months (95% CI)	20.0 (15.9, 24.2)	12.2 (10.4, 14.6)	13.4 (10.7, 16.9)	12.1 (11.0, 14.0)

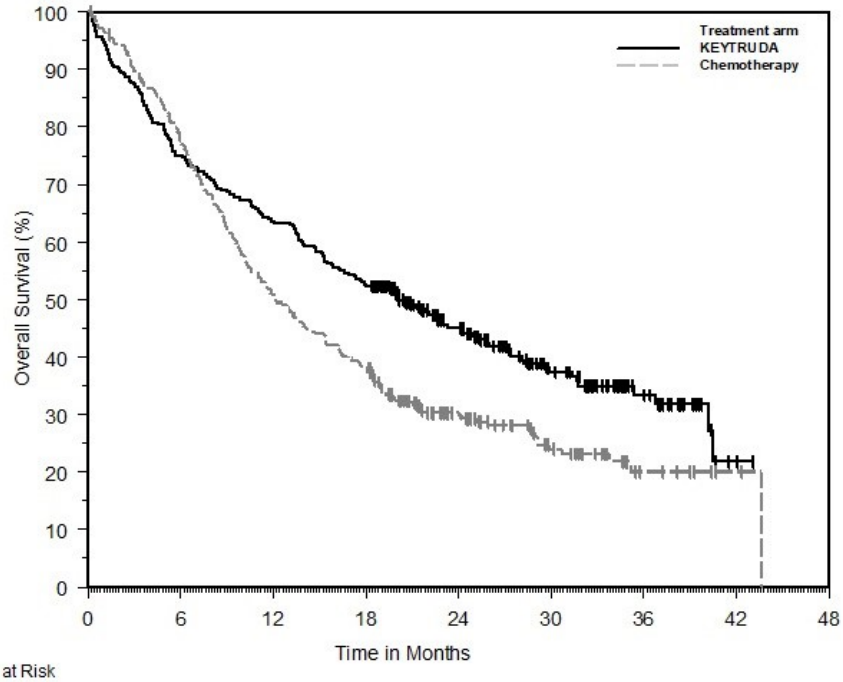
*Hazard ratio (KEYTRUDA® compared to chemotherapy) based on the stratified Cox proportional hazard model

Figure 8: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-042 (TPS ≥ 1%, Intent-to-Treat Population)



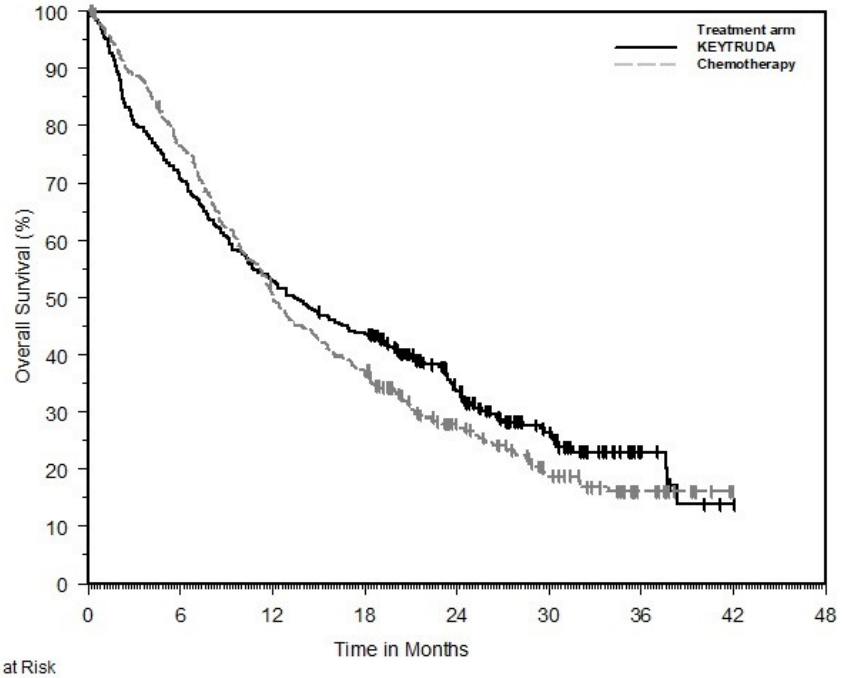
Number at Risk									
KEYTRUDA:	637	463	368	304	178	91	30	1	0
Chemotherapy:	637	485	319	236	126	65	20	2	0

Figure 9: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-042 (TPS ≥ 50%, Intent-to-Treat Population)



Number at Risk									
KEYTRUDA:	299	224	190	157	94	50	21	1	0
Chemotherapy:	300	231	151	113	59	31	8	2	0

Figure 10: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-042 (TPS 1-49%, Intent-to-Treat Population)



Number at Risk									
KEYTRUDA:	338	239	178	147	84	41	9	0	0
Chemotherapy:	337	254	168	123	67	34	12	0	0

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

Study demographics and trial design

The efficacy of KEYTRUDA® in combination with pemetrexed and platinum chemotherapy was investigated in a multicenter, randomized, 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 randomized (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. KEYTRUDA® was administered prior to chemotherapy; or
- 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 one 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.

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.

Table 50: Baseline Characteristics in KEYNOTE-189.

	KEYTRUDA® + Pemetrexed + Platinum Chemotherapy n=410	Placebo + Pemetrexed + Platinum Chemotherapy n=206
Men	62%	53%
Women	38%	47%
Age (median)	65	63.5
Age (range)	34-84 years	34-84 years
ECOG PS		
0	45%	39%
1	54%	61%
2	<1%	0%
Geographic region		
East Asia	1%	3%
Non-East Asia	99%	97%
PD-L1 status		
< 1%	31%	31%
≥ 1%	63%	62%
Not evaluable	6%	7%
Brain metastases (treated or untreated) at baseline		
Yes	18%	17%
No	82%	83%
Platinum chemotherapy		
Cisplatin	28%	28%
Carboplatin	72%	72%

Study Results
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 51 summarizes key efficacy measures.

Table 51: 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
Primary Efficacy Outcome Measure 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)
OS rate at 6 months (%)	85%	72%
OS rate at 9 months (%)	78%	56%
Primary Efficacy Outcome Measure PFS		
Number (%) of patients with event	244 (60%)	166 (81%)
Hazard ratio* (95% CI)	0.52 (0.43, 0.64)	
p-Value†	<0.00001	
Median in months (95% CI)	8.8 (7.6, 9.2)	4.9 (4.7, 5.5)
PFS rate at 6 months (%)	66%	40%
PFS rate at 9 months (%)	48%	25%
Secondary Efficacy Outcome Measure 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	
Secondary Efficacy Outcome Measure 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¶	60%	44%

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

Figure 11: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-189 (Intent to Treat Population)

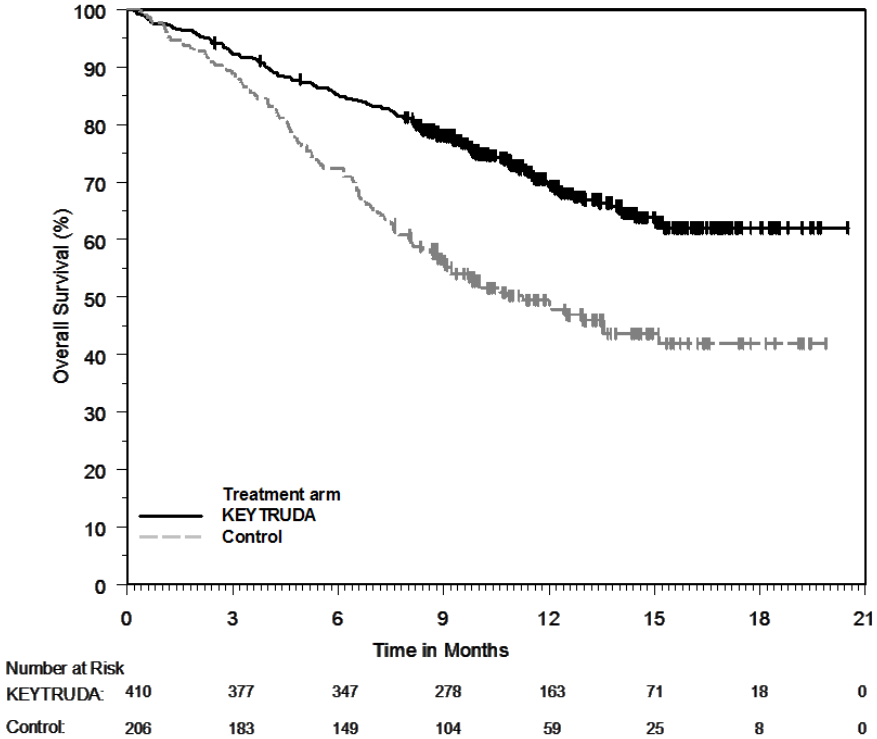
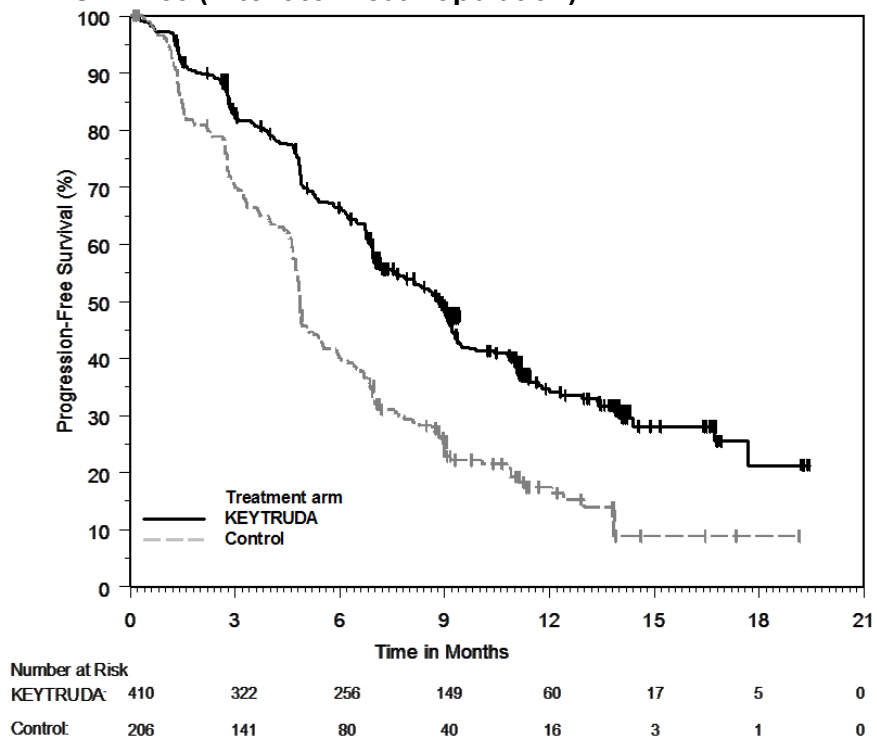


Figure 12: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-189 (Intent to Treat Population)



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

Study demographics and trial design

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

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

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

Table 52: Baseline Characteristics in KEYNOTE-407.

	KEYTRUDA® + Carboplatin + Paclitaxel or Nab-Paclitaxel n=278	Placebo + Carboplatin + Paclitaxel or Nab-Paclitaxel n=281
Men	79%	84%
Women	21%	16%
Age (median)	65	65
Age (range)	29-87 years	36-88 years
ECOG PS		
0	26%	32%
1	74%	68%
Geographic region		
East Asia	19%	19%
Non-East Asia	81%	81%
PD-L1 status		
< 1%	34%	35%
≥ 1%	63%	63%
Not evaluable	3%	2%
Brain metastases (treated or untreated) at baseline		
Yes	7%	9%
No	93%	91%
Taxane chemotherapy		
Paclitaxel	61%	59%
Nab-Paclitaxel	39%	41%

Study Results

In KEYNOTE-407, there was a statistically significant improvement in OS, PFS and ORR in patients randomized to KEYTRUDA® in combination with carboplatin and either paclitaxel or nab-paclitaxel compared with patients randomized to placebo with carboplatin and either paclitaxel or nab-paclitaxel (See Table 53 and Figures 13 and 14).

Table 53: Efficacy Results in KEYNOTE-407.

Endpoint	KEYTRUDA® Carboplatin Paclitaxel/Nab-Paclitaxel n=278	Placebo Carboplatin Paclitaxel/Nab-Paclitaxel n=281
Primary Efficacy Outcome Measure 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	
Primary Efficacy Outcome Measure PFS†		
Number of events (%)	152 (55%)	197 (70%)
Median in months (95% CI)	6.4 (6.2, 8.3)	4.8 (4.3, 5.7)
Hazard ratio* (95% CI)	0.56 (0.45, 0.70)	
p-Value(stratified log rank)	<0.0001	
Secondary Efficacy Outcome Measure Objective Response Rate†		
Objective response rate ‡	58%	38%
(95% CI)	(52, 64)	(33, 44)
Secondary Efficacy Outcome Measure 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
†Assessed by BICR using RECIST 1.1
‡ 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, 68)] and 35% [95% CI (26, 45)] for placebo, p=0.0004
§ '+' indicates there is no progressive disease by the time of last disease assessment
¶Based on Kaplan-Meier estimation
NA = not available

Figure 13: Kaplan-Meier Curve for Overall Survival in KEYNOTE-407

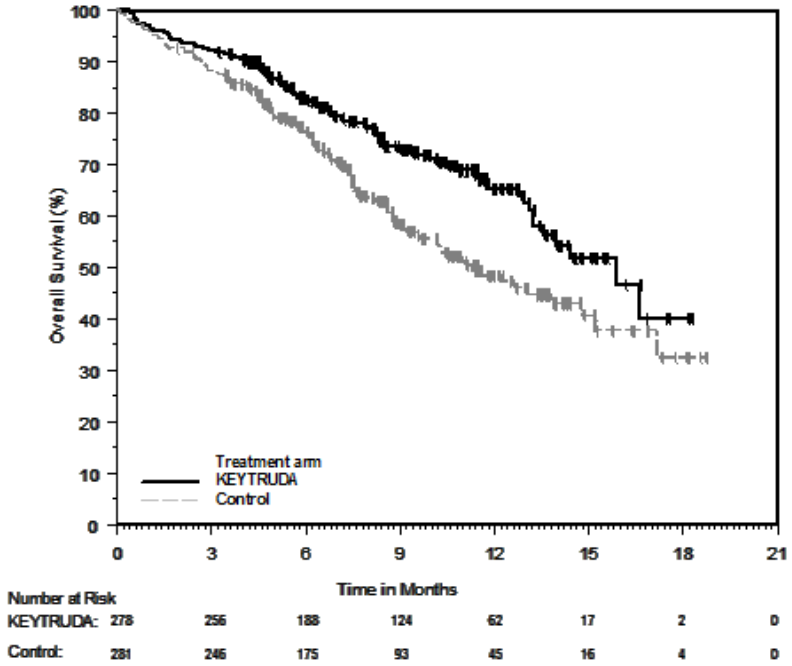
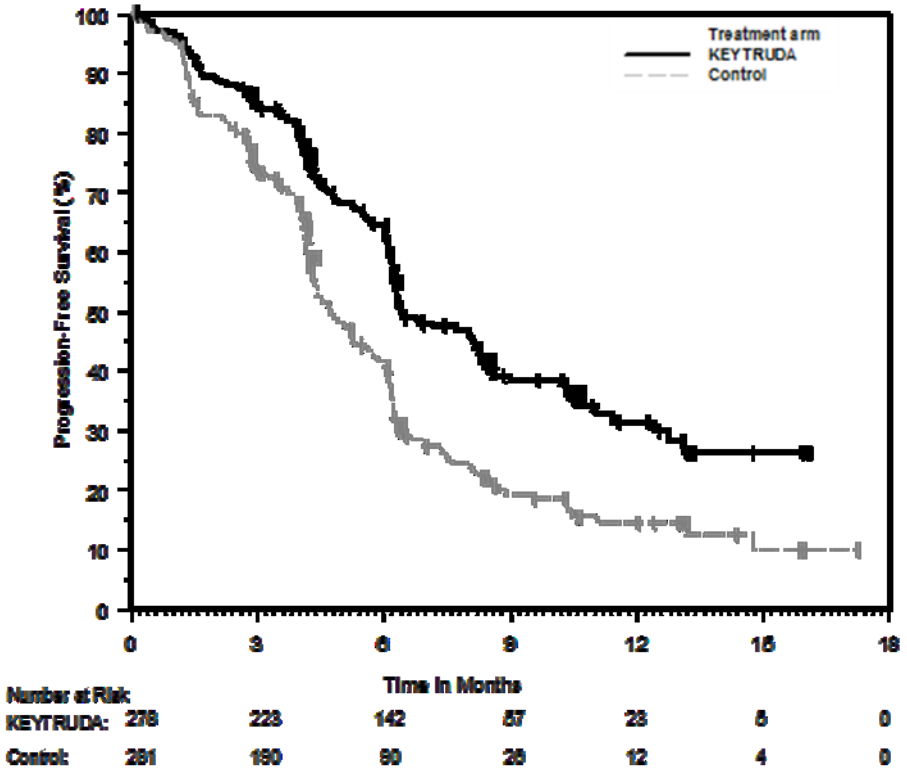


Figure 14: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-407



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

Study demographics and trial design

The efficacy of KEYTRUDA® was investigated in KEYNOTE-010, a multicenter, randomized, open-label controlled trial. Key eligibility criteria were metastatic NSCLC that had progressed following platinum-containing chemotherapy, and if appropriate, targeted therapy for ALK or EGFR mutations, and PD-L1 expression tumour proportion score (TPS) of 1% or greater by a clinical trial assay version of the PD-L1 IHC 22C3 pharmDx* kit. Patients with autoimmune disease; a medical condition that required immunosuppression; or who had received more than 30 Gy of thoracic radiation within the prior 26 weeks were ineligible. Randomization was stratified by tumour PD-L1 expression (PD-L1 expression TPS ≥50% vs. PD-L1 expression TPS=1-49%), ECOG performance scale (0 vs. 1), and geographic region (East Asia vs. non-East Asia). Patients were randomized (1:1:1) to receive KEYTRUDA® 2 mg/kg intravenously every 3 weeks (n=344), KEYTRUDA® 10 mg/kg intravenously every 3 weeks (n=346) or docetaxel 75 mg/m^2 intravenously every 3 weeks (n=343). Patients randomized to KEYTRUDA® were permitted to continue until disease progression that was symptomatic, rapidly progressive, required urgent intervention, occurred with a decline in performance status, or confirmation of progression at 4 to 6 weeks with repeat imaging or for up to 24 months without disease progression.

Table 54: Baseline Characteristics in KEYNOTE-010.

	KEYTRUDA® 2 mg/kg every 3 weeks n=344	KEYTRUDA® 10 mg/kg every 3 weeks n=346	Docetaxel 75 mg/m^2 every 3 weeks n=343
Men	62%	62%	61%
Women	38%	38%	39%
Age (median)	63 years	63 years	62 years
Age (range)	29-82 years	20-88 years	33-82 years
ECOG PS			
0	33%	35%	34%
1	67%	65%	65%
2	1%	0%	0%
Geographic region			
East Asia	19%	19%	18%
Non-East Asia	81%	82%	82%
Histology			
Squamous	22%	23%	19%
Non-squamous	70%	71%	70%
Cancer stage at study entry			
IIIB	6%	8%	6%
IV	92%	91%	91%
Brain Metastasis	16%	14%	14%
EGFR Mutant	8%	9%	8%
ALK Translocation Mutant	1%	1%	1%
Prior Lines of Systemic Therapy			
One	71%	68%	69%
Two or more	27%	30%	30%

The median duration of exposure to treatment to KEYTRUDA® 2 mg/kg every 3 weeks was 3.5 months (range: 1 day to 22.4 months) and to KEYTRUDA® 10 mg/kg every 3 weeks was 3.5 months (range 1 day to 20.8 months). The median duration of exposure to docetaxel 7 5 mg/m^2 every 3 weeks was 2.0 months (range: 1 day to 13.7 months).

Study Results

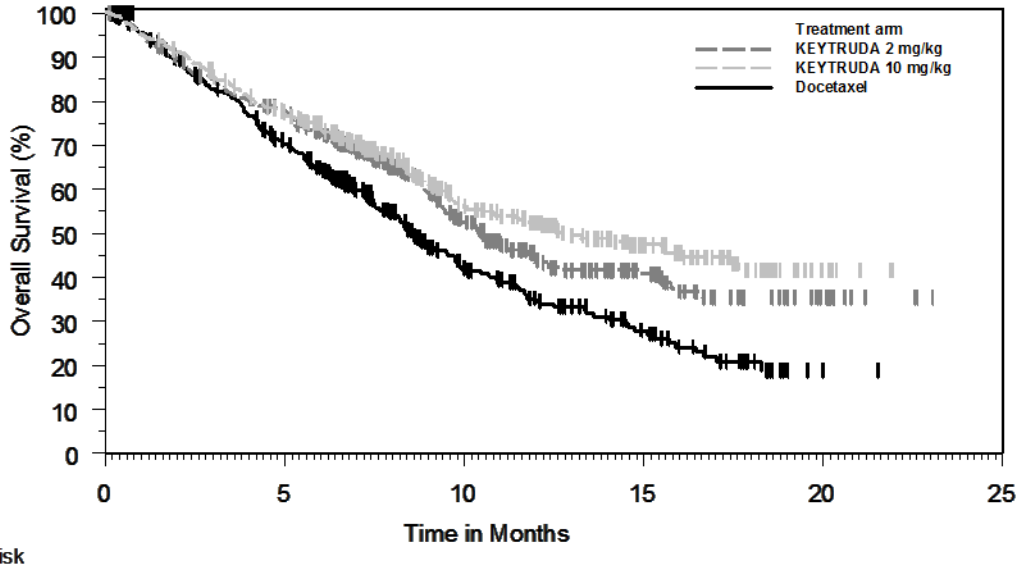
The primary efficacy outcome measures were OS and PFS as assessed by a Blinded Independent Central Review (BICR) according to RECIST 1.1 in the subgroup of patients with TPS ≥ 50% and the overall population with TPS ≥ 1%. Assessment of tumour status was performed every 9 weeks. A secondary efficacy outcome measure was ORR in the subgroup of patients with TPS ≥ 50% and the overall population with TPS ≥ 1%. Tables 55 and 56 summarize 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 17. Kaplan-Meier curves for PFS (TPS ≥ 1% and TPS ≥ 50%) are shown in Figures 16 and 18.

Table 55: Response to KEYTRUDA® 2 or 10 mg/kg every 3 Weeks in Previously Treated Patients with NSCLC in KEYNOTE-010, with TPS ≥ 1%

Endpoint	KEYTRUDA® 2 mg/kg every 3 weeks	KEYTRUDA® 10 mg/kg every 3 weeks	Docetaxel 75 mg/m² every 3 weeks
TPS ≥1%			
Number of patients	344	346	343
Primary Efficacy Outcome Measure OS			
Number (%) of patients with event	172 (50%)	156 (45%)	193 (56%)
Hazard ratio (98.35% CI)*	0.71 (0.55, 0.92)	0.61 (0.47, 0.79)	---
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)
Primary Efficacy Outcome Measure PFS‡,§			
Number (%) of patients with event	266 (77%)	255 (74%)	257 (75%)
Hazard ratio (99.80% CI)*	0.88 (0.66, 1.15)	0.79 (0.60, 1.05)	---
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)
Secondary Efficacy Outcome Measure Overall Response Rate§			
ORR %¶ (95% CI)	18% (14, 23)	18% (15, 23)	9% (7, 13)

*Hazard ratio (KEYTRUDA® compared to docetaxel) based on the stratified Cox proportional hazard model. The confidence levels correspond to the allocated Type I error of 0.00825 and 0.001 for the OS and PFS endpoints, respectively.
†Based on one-sided stratified Log rank test
‡Statistically significant based on a pre-specified α level of 0.00825 for the two pairwise comparisons versus docetaxel using a Hochberg procedure
§Assessed by BICR using RECIST 1.1
¶All responses were partial responses.

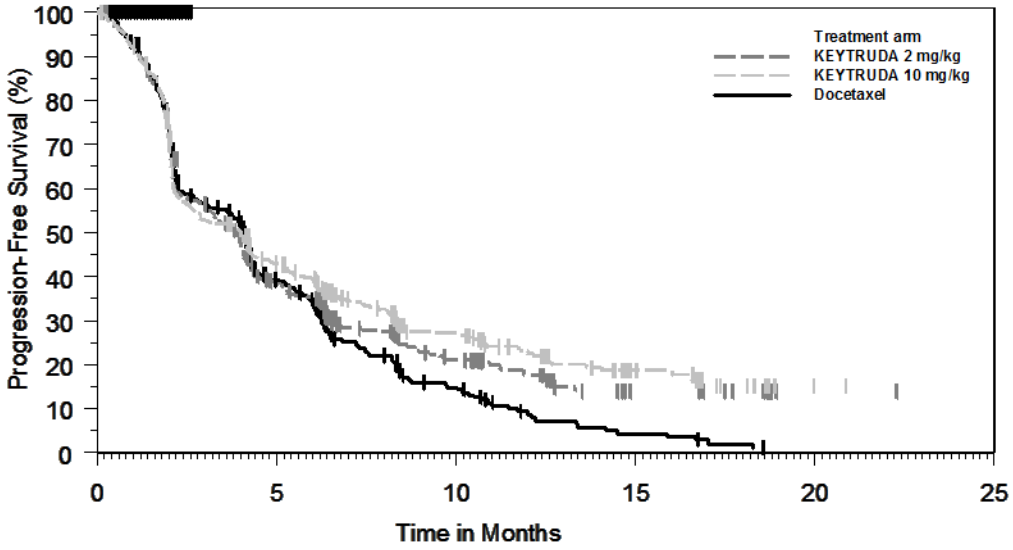
Figure 15: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-010 (TPS ≥ 1%, Intent to Treat Population)



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 Progression-Free Survival by Treatment Arm in KEYNOTE-010 (TPS ≥ 1%, Intent to Treat Population)



Number at Risk						
KEYTRUDA 2 mg/kg:	344	123	46	12	1	0
KEYTRUDA 10 mg/kg:	346	137	60	19	1	0
Docetaxel:	343	103	27	6	0	0

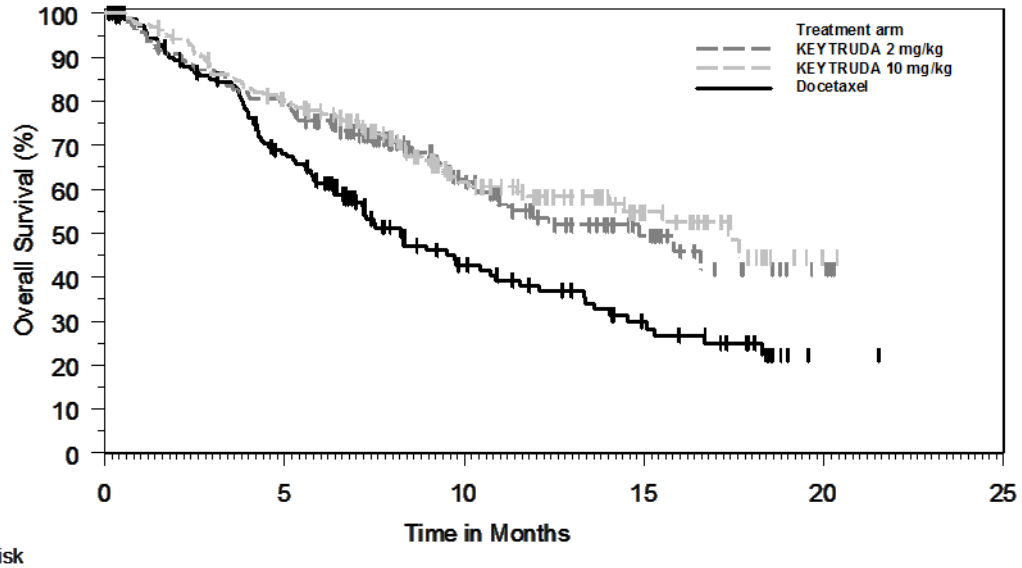
Table 56: Response to KEYTRUDA® 2 or 10 mg/kg every 3 Weeks in Previously Treated Patients with NSCLC in KEYNOTE-010, with TPS ≥ 50%

Endpoint	KEYTRUDA® 2 mg/kg every 3 weeks	KEYTRUDA® 10 mg/kg every 3 weeks	Docetaxel 75 mg/m² every 3 weeks
TPS ≥50%			
Number of patients	139	151	152
Primary Efficacy Outcome Measure OS			
Number (%) of patients with event	58 (42%)	60 (40%)	86 (57%)
Hazard ratio (98.35% CI)*	0.54 (0.35, 0.83)	0.50 (0.33, 0.75)	---
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)
Primary Efficacy Outcome Measure PFS‡, §			
Number (%) of patients with event	89 (64%)	97 (64%)	118 (78%)
Hazard ratio (99.80% CI)*	0.58 (0.37, 0.92)	0.59 (0.38, 0.91)	---
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)
Secondary Efficacy Outcome Measure Overall Response Rate§			
ORR %# (95% CI)	30% (23, 39)	29% (22, 37)	8% (4, 13)

*Hazard ratio (KEYTRUDA® compared to docetaxel) based on the stratified Cox proportional hazard model. The confidence levels correspond to the allocated Type I error of 0.00825 and 0.001 for the OS and PFS endpoints, respectively.
†Based on one-sided stratified Log rank test
‡Statistically significant based on a pre-specified α level of 0.00825 for the two pairwise comparisons versus docetaxel using a Hochberg procedure
§Assessed by BICR using RECIST 1.1
¶Statistically significant based on a pre-specified α level of 0.001 for the two pairwise comparisons versus docetaxel using a Hochberg procedure

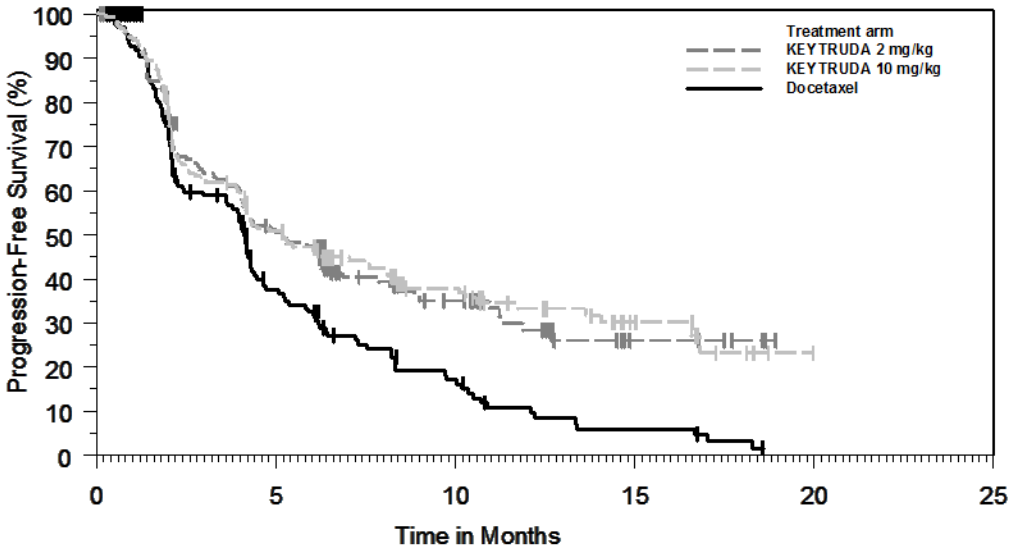
[#]All responses were partial responses.

Figure 17: 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

Figure 18: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-010 (TPS ≥ 50%, Intent to Treat Population)



Number at Risk						
KEYTRUDA 2 mg/kg:	139	67	29	6	0	0
KEYTRUDA 10 mg/kg:	151	72	36	12	0	0
Docetaxel:	152	45	17	5	0	0

In exploratory subgroup analyses, a reduced survival benefit of KEYTRUDA® compared to chemotherapy was observed in patients with tumours harbouring EGFR activating mutations (n=54), never-smokers (n=130) and patients of East Asian Ethnicity (n=126). In patients with tumours expressing PD-L1 with a TPS ≥ 1% that received KEYTRUDA® at 2 mg/kg every three weeks, with EGFR activating mutations, the HR for PFS was 1.78 (95% CI: 0.82, 3.85) and the HR for OS was 1.07 (95% CI: 0.49, 2.37). In never smokers, the HR for PFS was 1.33 (95% CI: 0.86, 2.04) and the HR for OS was 0.84 (95% CI: 0.48, 1.49). In patients of East Asian Ethnicity the HR for PFS was 1.38 (95% CI: 0.87, 2.21) and the HR for OS was 1.39 (95% CI: 0.72, 2.68). The efficacy and safety of pembrolizumab in patients with tumours that do not express PD-L1 (TPS <1%) have not been established.

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).

NOC/c Classical Hodgkin Lymphoma

KEYNOTE-204: *Controlled study in patients with relapsed or refractory cHL*

Study demographics and trial design

The efficacy of KEYTRUDA® was investigated in KEYNOTE-204, a randomized, open-label, active-controlled study in 304 patients with relapsed or refractory cHL after at least one multi-agent chemotherapy regimen. Patients eligible for allo- or auto-SCT per investigator assessment were excluded. The trial required an ANC ≥ 1000/µL, platelet count ≥75,000/µL, hepatic transaminases ≤ 2.5 times the upper limit of normal (ULN), bilirubin ≤ 1.5 times ULN, and ECOG performance status of 0 or 1. Patients with active, non-infectious pneumonitis, an allogeneic hematopoietic stem cell transplant within the past 5 years (or greater than 5 years but with GVHD), active autoimmune disease, a medical condition that required immunosuppression or an active infection requiring systemic therapy were ineligible for the trial. Randomization 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 randomized (1:1) to one of the following treatment arms:

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

Patients received KEYTRUDA® 200 mg intravenously every 3 weeks (n=151) until unacceptable toxicity or documented disease progression, or for up to approximately 24 months or 35 administrations, whichever was longer. Disease assessment was performed every 12 weeks. The primary efficacy outcome measures was PFS as assessed by BICR according to the 2007 revised International Working Group (IWG) criteria, including clinical and imaging data following ASCT or allogeneic stem cell transplant. The additional primary efficacy outcome measure, OS, was not formally assessed at the time of the analysis.

The study population characteristics were: median age of 35 years (range: 18 to 84 ; 16% age 65 or older), 57% male, 77% White, 9% Asian, 3.9% Black and 61% with ECOG PS of 0 and 38% ECOG PS of 1. The median number of prior therapies was 2 (range: 1 to 10) in the KEYTRUDA® arm and 3 (range: 1 to 11) in the BV arm, with 18% in both arms having 1 prior line. Forty-two percent of patients were refractory to the last prior therapy, 29% had primary refractory disease, 37% had prior autologous HSCT, 5% had received prior BV, and 39% had prior radiation therapy.

Study Results
The median follow-up time for 151 patients treated with KEYTRUDA® was 24.9 months (range: 1.8 - 42.0 months). The primary PFS results are summarized in Table 57 and Figure 19.

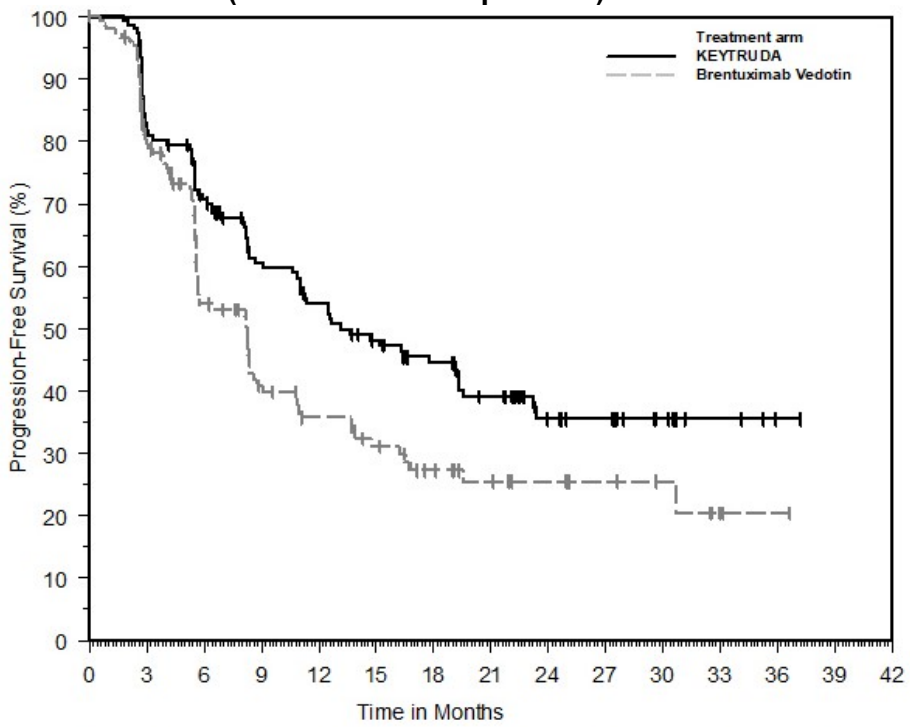
Table 57: Efficacy Results in Patients with Refractory or Relapsed Classical Hodgkin Lymphoma.

Endpoint	KEYTRUDA® 200 mg/kg every 3 weeks n=151	Brentuximab vedotin 1.8 mg/kg every 3 weeks n=153
PFS		
Number of patients with event (%)	81 (54%)	88 (58%)
Median in months (95% CI)	13.2 (10.9, 19.4)	8.3 (5.7, 8.8)
Hazard ratio* (95% CI)	0.65 (0.48, 0.88)	
p-Value†	0.0027	

* Based on the stratified Cox proportional hazard model
† Based on stratified log-rank test. One-sided p-value, with a prespecified boundary of 0.0043.

ORR was 66% (95% CI: 57.4, 73.1) in patients treated with pembrolizumab versus 54% (95% CI: 46.0, 62.3) in patients treated with BV. The difference in ORR was 11.3% (95% CI: 0.2, 22.1; stratified Miettinen-Nurminen method). The complete response rate was 25% in patients treated with pembrolizumab versus 24% in patients treated with BV. The response duration, assessed by BICR using IWG 2007, was based on patients with a best objective response as complete or partial response. The median response duration was 20.7 months (range: 0.0+, 33.2+) in patients treated with pembrolizumab versus 13.8 months (range: 0.0+, 33.9+) in patients treated with BV.

Figure 19: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-204 (Intent to Treat Population)



Number at Risk															
KEYTRUDA:	151	116	96	74	65	55	44	35	18	15	9	4	1	0	0
Brentuximab Vedotin:	153	103	63	41	32	26	19	14	10	7	5	2	1	0	0

NOC/c Primary Mediastinal B-cell Lymphoma

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

Study demographics and trial design
The efficacy of KEYTRUDA® was investigated in KEYNOTE-170, a multicenter, open-label, single-arm trial in 29 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 29 patients, the baseline characteristics were: median age of 33 years (range: 20 to 58), 0% age 65 or older; 45% male; 93% White; 38% had an ECOG performance status (PS) of 0 and 62% 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). Sixty-nine percent were refractory to the last prior therapy, including 38% with primary refractory disease and 79% whose disease was chemo-refractory to any prior regimen. Thirty-four percent of patients had undergone prior auto-HSCT, 66% did not receive prior transplant; and 38% of patients had prior radiation therapy.

Study Results
Efficacy from interim analysis was based on overall response rate (ORR) with the median follow-up duration of 6.6 months. The median duration of response was not reached. The efficacy results for KEYNOTE-170 are summarized in Table 58. For the 12 responders, the median time to first objective response was 2.9 months (range 2.4 to 8.5 months).

Table 58: Efficacy Results in Patients with Refractory or Relapsed PMBCL.

Endpoint	KEYNOTE-170* n=29
Objective Response Rate*	
ORR %, (95% CI)	41% (24, 61)
Complete Remission	14%
Partial Remission	28%
Response Duration*	
Median in months (range)	Not reached (1.1+,8.2+)†

*Assessed by blinded independent central review according to the 2007 revised IWG criteria
†Based on patients (n=12) with a response by independent review

Urothelial Carcinoma

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

Study demographics and trial design
The efficacy of KEYTRUDA® was evaluated in KEYNOTE-045, a multicenter, randomized (1:1), active-controlled trial in patients with locally advanced or metastatic urothelial carcinoma with

disease progression on or after platinum-containing chemotherapy. The trial excluded patients with autoimmune disease or a medical condition that required immunosuppression.

Patients were randomized 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/m^2 (n=84); docetaxel 75 mg/m^2 (n=84); or vinflunine 320 mg/m^2 (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. Treatment with pembrolizumab could be reinitiated for subsequent disease progression and administered for up to one additional year. Assessment of tumour status was performed at 9 weeks after randomization, then every 6 weeks through the first year, followed by every 12 weeks thereafter.

The major efficacy outcomes were OS and PFS as assessed by BICR per RECIST v1.1 at the time of the second interim analysis using the intent-to-treat (ITT) population. These outcomes were also assessed for the subgroup defined by PD-L1 CPS cutoff of ≥ 10 (PD-L1 positive). Additional efficacy outcome measures were ORR as assessed by BICR per RECIST v1.1 and duration of response.

Among the 542 randomized 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; 57% ECOG performance status of 1 or greater; and 96% M1 disease and 4% M0 disease. Eight-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.

Study Results

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 in the ITT population randomized to KEYTRUDA® as compared to chemotherapy. No statistically significant difference was demonstrated between KEYTRUDA® and chemotherapy with respect to PFS. Table 59 summarizes the key efficacy measures and Figure 19 shows the Kaplan-Meier survival curve for OS.

Table 59: 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 Rate (%)	7%	3%
Partial Response Rate (%)	14%	8%
p-Value§,	0.001¥	
Duration of Response		
Median in months (range)	Not reached (1.6+, 15.6+)	4.3 (1.4+, 15.4+)

* 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
£ p-value is compared with 0.0123 of the allocated alpha for the interim analysis
€ p-value is compared with 0.0151 of the allocated alpha for the interim analysis
¥ p-value is compared with 0.0170 of the allocated alpha for the interim analysis

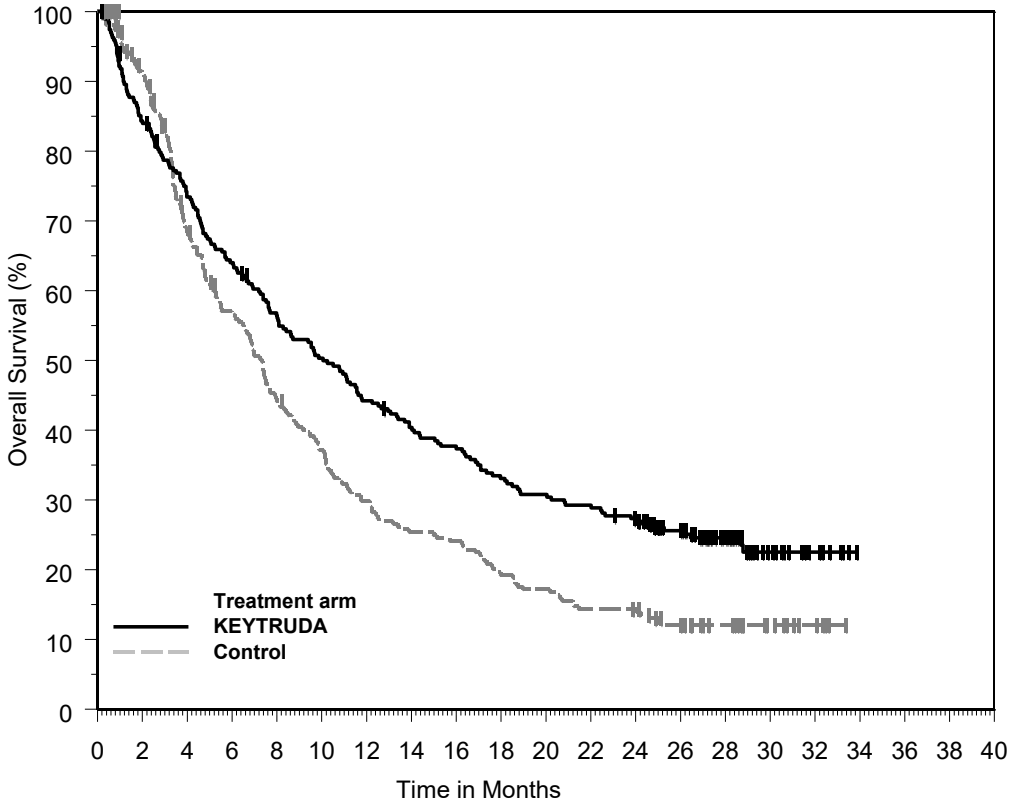
The interim analysis also demonstrated a statistically significant improvement in OS favouring KEYTRUDA® for patients whose tumours tested positive for PD-L1 CPS ≥ 10% [Hazard Ratio (HR) 0.57 (95% CI 0.37, 0.88)]. As with the ITT population, there was no statistically significant difference between KEYTRUDA® and chemotherapy with respect to PFS among patients whose tumours tested positive for PD-L1.

In exploratory subgroup analyses, a reduced survival benefit of KEYTRUDA® monotherapy compared to chemotherapy was observed in patients who were never smokers (n =187), who were classified as Non-White (n=133) (92% of whom identified with Asian ethnicity), or who lived in the East-Asia geographic region (n=106). In never smokers, the HR for OS was 1.06 (95% CI: 0.72, 1.55) and the HR for PFS was 1.13 (95% CI: 0.80, 1.60). In Non-White subjects, the HR for OS was 1.12 (95% CI 0.70, 1.79) and the HR for PFS was 1.48 (95% CI 0.99, 2.23). In subjects from the East-Asia geographic region, the HR for OS was 1.25 (95% CI: 0.72, 2.18) while the HR for PFS was 1.68 (95% CI: 1.05, 2.67).

The final descriptive analysis for OS 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). See Figure 19 for OS curve. In the

final analysis of PFS there was no statistically significant difference between KEYTRUDA® and chemotherapy.

Figure 19: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-045 (Intent to Treat Population) *



Number at Risk																					
KEYTRUDA:	270	226	195	170	148	132	116	105	98	86	80	76	67	52	33	14	7	0	0	0	0
Control:	272	234	173	140	109	91	73	62	59	47	42	35	34	24	18	10	4	0	0	0	0

**based on the final analysis (a total of 419 deaths)*

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

Study demographics and trial design

The efficacy of KEYTRUDA® was investigated in KEYNOTE-052, a multicenter, open-label, single arm trial of patients with locally advanced unresectable or metastatic urothelial carcinoma who were not eligible for cisplatin-containing chemotherapy. The trial excluded patients with autoimmune disease or a medical condition that required immunosuppression.

Patients received KEYTRUDA® 200 mg every 3 weeks until unacceptable toxicity or disease progression. If benefits were deemed to outweigh the risks based on clinical judgement, clinically stable patients with initial radiographic disease progression could continue treatment until disease progression was confirmed. Patients without disease progression could be treated for up to 24 months. Assessment of tumour status was performed at 9 weeks after the first dose, then every 6 weeks through the first year, followed by every 12 weeks thereafter.

Among the 370 treated patients, baseline characteristics were: median age 74 years (82% age 65 or older); 77% male; and 89% White and 7% Asian. Eighty-one percent had a primary tumour in the lower tract, and 19% of patients had a primary tumour in the upper tract. Eighty-eight percent had M1 disease, 12% had M0 disease. Eighty-five percent of patients had visceral metastases, including 21% with liver metastases. Ninety percent of patients were treatment naïve, and 10% received prior adjuvant or neoadjuvant platinum-based chemotherapy. Reasons for cisplatin ineligibility included: 50% with baseline creatinine clearance of <60 mL/min; 32% with ECOG performance status of 2; 9% with ECOG performance status of 2 and baseline creatinine clearance of <60 mL/min; and 9% with other reasons (Class III heart failure, Grade 2 or greater peripheral neuropathy, and Grade 2 or greater hearing loss). In the study, PD-L1 status by the combined positive score (CPS) was determined using the PD-L1 IHC 22C3 pharmDx* Kit (See DOSAGE AND ADMINISTRATION: Patient Selection). Among the 370 patients, 30% (n = 110) had tumours that expressed PD-L1 CPS ≥ 10 and 68% (n = 251) had tumours that expressed PD-L1 CPS <10.

The primary efficacy outcome measure was Objective Response Rate (ORR) according to RECIST 1.1 as assessed by the blinded independent central radiology review. The key secondary efficacy outcome measure was duration of response. A confirmation of response by repeat radiographic assessment was required 4 to 6 weeks after the initial assessment.

Study Results

The median follow-up time for the 370 patients treated with KEYTRUDA® was 11.5 months (range 0.1 – 31.3 months). Efficacy results are summarized in Table 60.

Table 60: Efficacy Results in Patients with Urothelial Carcinoma Ineligible for Cisplatin-Containing Chemotherapy in KEYNOTE-052.

Endpoint	All Subjects n=370
Objective Response Rate*	
ORR %, (95% CI)	29% (25, 34)
Complete Response	8%
Partial Response	21%
Response Duration	
Median in months (range)	Not reached (1.4+, 27.9+)
% with duration ≥ 6-months	82% †

* Assessed by BICR using RECIST 1.1

† Based on Kaplan-Meier estimates; includes 85 patients with responses of 6 months or longer

In an exploratory subgroup analysis, the ORRs were 47% and 21% among subjects with PD-L1 CPS ≥ 10 and subjects with PD-L1 CPS <10 respectively.

KEYNOTE-361 is an ongoing phase III, randomized trial of pembrolizumab with or without platinum-based combination chemotherapy versus chemotherapy in subjects with previously untreated metastatic urothelial carcinoma. The independent Data Monitoring Committee (iDMC) for the study conducted a review of early data and a decreased survival with pembrolizumab monotherapy was revealed as compared to chemotherapy among subjects with PD-L1 CPS <10 expressing tumours. Following the iDMC's recommendation, further accrual was stopped for subjects with PD-L1 CPS <10 expression to the pembrolizumab monotherapy arm. However, no other changes were recommended, including any change of therapy for patients who had already been randomized to and were receiving treatment in the pembrolizumab monotherapy arm.

NOC/c *KEYNOTE-057: Open label trial in BCG-unresponsive High-Risk Non-Muscle Invasive Bladder Cancer*

Study demographics and trial design

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

Patients received KEYTRUDA® 200 mg every 3 weeks until unacceptable toxicity, persistent or recurrent high-risk NMIBC, or progressive disease. Assessment of tumour status was performed every 12 weeks, and patients without disease progression could be treated for up to 24 months or 35 administrations, whichever was longer. The major efficacy outcome measure was complete response (as defined by negative results for cystoscopy [with TURBT/biopsies as applicable], urine cytology, and computed tomography urography [CTU] imaging) at the first assessment (12 weeks). Duration of response was a key supportive endpoint.

Study Results

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 summarized in Table 61. A total of 36 patients went on to receive radical cystectomy. Upon review of pathology, 2 patients who underwent cystectomy within 90 days after treatment discontinuation were found to have T2 disease, and one patient who underwent cystectomy greater than 1 year after treatment discontinuation had T3 disease. No patients progressed to muscle invasive or metastatic bladder cancer while on study therapy, based on protocol specified disease assessments.

Table 61: Efficacy Results for Patients with BCG-unresponsive, High-Risk NMIBC in KEYNOTE-057

Endpoint	n=96
Complete Response Rate % (95% CI)*	41% (30.7, 51.1)
Response Duration†	
Median in months (range)	16.2 (0.0+, 30.4+)
% (n) with duration ≥ 6 months	69% (27)
% (n) with duration ≥ 12 months	46% (18)

* Based on negative cystoscopy (with TURBT/biopsies as applicable), urine cytology, and computed tomography urography (CTU imaging) at the first assessment (12 weeks).

† Based on patients who achieved a complete response (n=39). Duration reflects period from the time complete response was achieved.

\+ Denotes ongoing response

NOC/c Microsatellite Instability-High Cancer (MSI-H)

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

Study demographics and trial design

The efficacy of KEYTRUDA® was investigated in 85 patients with MSI-H or dMMR cancer enrolled in two single-arm multicenter, nonrandomized, open-label, multi-cohort Phase II studies. Regardless of histology, MSI or MMR tumour status was determined using polymerase chain reaction (PCR) or immunohistochemistry (IHC), respectively. Efficacy was evaluated in 61 patients enrolled in KEYNOTE-164 with advanced MSI-H or dMMR colorectal cancer (CRC) that progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. Efficacy was also evaluated in 24 patients enrolled in KEYNOTE-158, cohorts D and K, with advanced MSI-H or dMMR endometrial cancer who had disease progression following prior therapy and had no satisfactory alternative treatment options. Patients with autoimmune disease or a medical condition that required immunosuppression were ineligible for either trial.

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 one additional year. Assessment of tumour status in KEYNOTE-164 was performed every 9 weeks and in KEYNOTE-158 every 9 weeks through the first year, then every 12 weeks thereafter. The major efficacy outcome measures were ORR and duration of response according to RECIST 1.1.

Among the 61 patients with MSI H colorectal cancer (CRC) and the 24 patients with endometrial cancer, the baseline characteristics were (for CRC and endometrial cancer, respectively): median age 53 years vs 66 years (31% vs 58% age 65 or older); 59% of patients with CRC were male; 69% vs 92% White, 31% vs 4% Asian; and ECOG PS 0 (48% vs 50%) and 1 (52% vs 50%); 100% of patients with CRC and 83% of patients with endometrial cancer had M1 disease; and 17% of patients with endometrial cancer had M0 disease. Ninety percent of patients with CRC and 54% of patients with endometrial cancer received two or more prior lines of therapy.

Study Results
The median follow-up times for 61 CRC patients and 24 endometrial cancer patients treated with KEYTRUDA® were 13.2 months and 8.4 months, respectively. Efficacy results are summarized in Table 62.

Table 62: Efficacy Results for Patients with MSI-H or dMMR CRC or Endometrial Cancer.

Endpoint	CRC n=61	Endometrial Cancer n=24
Objective Response Rate*		
ORR %, (95% CI)	28% (17.1, 40.8)	54% (32.8, 74.4)
Complete Response	0	4%
Partial Response	28%	50%
Stable Disease	23%	25%
Disease Control Rate†	51%	79%
Response Duration*		
Median in months (range)	Not reached (2.9+, 12.5+)	Not reached (2.1+, 8.4+)
% with duration ≥ 6-months	82%‡	100%§
Time to Response		
Median in months (range)	4.0 (1.8, 10.4)	2.2 (1.3, 10.2)

* Assessed by BICR using RECIST 1.1
† Based on best response of stable disease or better
‡ Based on Kaplan-Meier estimates; includes 14 patients with response of 6 months or longer
§ Based on Kaplan-Meier estimates; includes 5 patients with response of 6 months or longer

NOC/c Endometrial Carcinoma

KEYNOTE-146: Open label trial in patients with endometrial carcinoma that is not MSI-H or dMMR

Study demographics and trial design
The efficacy of KEYTRUDA® in combination with lenvatinib was investigated in a multicenter, single-arm, open-label, multi-cohort trial that enrolled 108 patients with metastatic endometrial carcinoma that had progressed following at least one prior platinum-based systemic therapy in any setting. Eligible patients were 18 years of age or older with pathologically confirmed endometrial carcinoma and had an ECOG performance status of 0 or 1. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible.

Patients were treated with KEYTRUDA® 200 mg intravenously every 3 weeks in combination with lenvatinib 20 mg orally once daily until unacceptable toxicity or disease progression as determined by the investigator. The major efficacy outcome measures were ORR and DOR by independent radiologic review committee (IRC) using RECIST v1.1.

Administration of KEYTRUDA® and lenvatinib was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered by the investigator to be deriving clinical benefit. KEYTRUDA® dosing was continued for a maximum of 24 months; however, treatment with lenvatinib could be continued beyond 24 months. Assessment of tumour status was performed at baseline and then every 6 weeks until week 24, followed by every 9 weeks thereafter.

Among the 108 patients, 87% (n=94) had tumours that were not MSI-H or dMMR, 10% (n=11) had tumours that were MSI-H or dMMR, and in 3% (n=3) the status was not known. Tumour MSI status was determined using a polymerase chain reaction (PCR) test. Tumour MMR status

was determined using an immunohistochemistry (IHC) test. The baseline characteristics of the 94 patients with tumours that were not MSI-H or dMMR were: median age of 66 years with 62% age 65 or older; 86% White, 6% Black, 4% Asian, 3% other races; and ECOG PS of 0 (52%) or 1 (48%). The majority of patients had endometrioid (48.9%) or serous (35.1%) histology. All 94 patients received prior platinum-based systemic therapy for endometrial carcinoma: 51% received one; 38% received two; and 11% received three or more prior systemic therapies.

Study Results
Efficacy results are summarized in Table 63.

Table 63: Efficacy Results for Patients with Endometrial Carcinoma that is not MSI-H or dMMR in KEYNOTE-146.

	KEYTRUDA® with lenvatinib N=94
Objective Response Rate (ORR)	
ORR (95% CI)	38.3% (29%, 49%)
Complete response, n (%)	10 (10.6%)
Partial response, n (%)	26 (27.7%)
Duration of Response	
Median in months (range)	NR (1.2+, 33.1+)[†]
Duration of response ≥ 6 months, n (%)	25 (69%)
Tumour assessments were based on RECIST 1.1 per independent radiologic review committee (IRC). All responses were confirmed. Median follow-up time of 18.7 months [†] Based on patients (n=36) with a response by independent review [+] Censored at Data cutoff CI = confidence interval; NR= Not reached.	

Renal Cell Carcinoma

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

Study demographics and trial design
The efficacy of KEYTRUDA® in combination with axitinib was investigated in a randomized, multicenter, open-label, active-controlled trial KEYNOTE-426, conducted in patients with advanced or metastatic RCC with clear cell component, regardless of PD-L1 tumour status and International Metastatic RCC Database Consortium (IMDC) risk group categories. The trial excluded patients with autoimmune disease or a medical condition that required systemic immunosuppression within the last 2 years. Patients were randomized (1:1) to receive either KEYTRUDA® 200 mg once every 3 weeks in combination with axitinib 5 mg twice daily or sunitinib 50 mg once daily for 4 weeks and then off treatment for 2 weeks. Randomization was stratified by risk categories (favorable versus intermediate versus poor) and geographic region (North America versus Western Europe versus “Rest of the World”).

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®, for up to 24 months or 35 administrations, whichever was longer. Administration of KEYTRUDA® and axitinib was permitted beyond RECIST 1.1-defined disease progression if the patient was clinically stable and considered to be deriving clinical benefit by the investigator. Treatment with pembrolizumab could be reinitiated for subsequent disease progression and

administered for up to one additional year. Assessment of tumour status was performed at baseline, after randomization at Week 12, then every 6 weeks thereafter until Week 54, and then every 12 weeks thereafter.

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%; and patient distribution by IMDC risk categories was 31% favorable, 56% intermediate and 13% poor.

Study Results

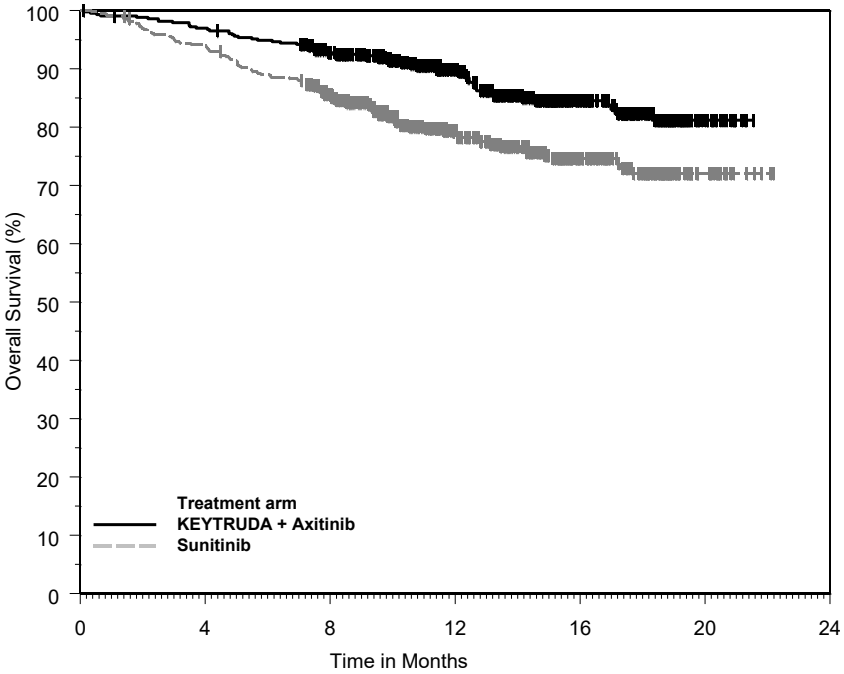
The primary efficacy outcome measures were OS and PFS (as assessed by BICR according to RECIST 1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ). Secondary efficacy outcome measures were objective response rate (ORR) and response duration, as assessed by BICR using RECIST 1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. The median follow-up time for the KEYTRUDA® combination arm was 13.2 months (range: 0.1 – 21.5 months). Table 64 summarizes key efficacy measures at the pre-specified first interim analysis. OS and PFS benefits were observed in the Intent To Treat population and regardless of PD-L1 expression level.

Table 64: Efficacy Results for Patients with Advanced and Metastatic RCC in KEYNOTE-426

Endpoint	KEYTRUDA® with axitinib n=432	Sunitinib n=429
Primary Efficacy Outcome Measure OS[a]		
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	
Primary Efficacy Outcome Measure PFS[a]		
Number of patients with event (%)	183 (42%)	213 (50%)
Median in months (95% CI)	15.1 (12.6, 17.7)	11.1 (8.7, 12.5)
Hazard ratio* (95% CI)	0.69 (0.56, 0.84)	
p-Value[†]	0.00012	
Secondary Efficacy Outcome Measure ORR[a]		
Overall response rate[‡] (95% CI)	59% (54, 64)	36% (31, 40)
Complete response	6%	2%
Partial response	53%	34%
p-Value[§]	<0.0001	

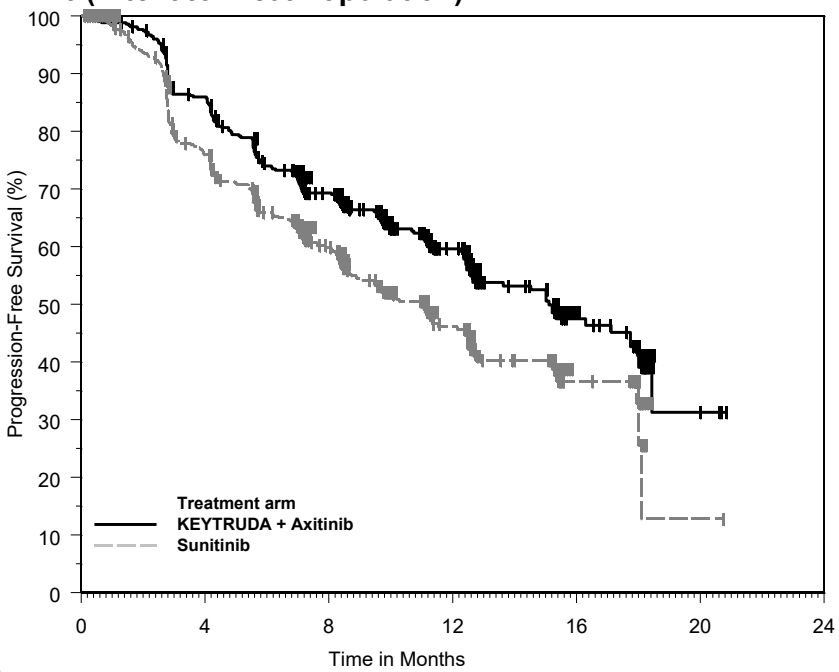
[a] The initial one-sided type 1 error rate level for OS, PFS, ORR were 0.023, 0.002, and 0.025 respectively. The corresponding p-value bounds at the interim analysis for OS and PFS were 0.0001 and 0.0013, respectively. For ORR, the corresponding p-value bound after alpha reallocation from PFS and OS following pre-specified multiplicity adjustment was 0.025.
* 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
NA = not available

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



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

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



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

Head and Neck Cancer

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

Study demographics and trial design

The efficacy of KEYTRUDA® was investigated in Study KEYNOTE-048, a multicenter, randomized, 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. Randomization was stratified by tumor PD-L1 expression (TPS≥50% or <50%), HPV status (positive or negative), and ECOG PS (0 vs. 1).

Patients were randomized 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 FU 1000 mg/m^2/d 4 days continuous every 3 weeks (maximum of 6 cycles of platinum and 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 FU 1000 mg/m^2/d 4 days continuous every 3 weeks (maximum of 6 cycles of platinum and 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. Subjects on the pembrolizumab arm who stop pembrolizumab with stable disease or better were eligible for up to one year of additional pembrolizumab therapy if they progressed after stopping study treatment. 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 tumor status was performed at Week 9 and then every 6 weeks for the first year, followed by every 9 weeks through 24 months.

Table 65: Baseline Characteristics in KEYNOTE-048

	KEYTRUDA® Platinum Chemotherapy FU n=281	KEYTRUDA® n=301	Standard Treatment* n=300
Men	80%	83%	87%
Women	20%	17%	13%
Age (median)	61 years	62 years	61 years
Age (range)	20-85 years	22-94 years	22-84 years
ECOG PS			
0	39%	40%	40%
1	61%	60%	60%
Former/current smokers	80%	79%	78%
HPV positive	21%	21%	22%
CPS ≥1	86%	85%	85%
CPS ≥20	45%	44%	41%
TPS ≥50%	24%	22%	22%
Ethnicity			
White	72%	73%	75%
Asian	21%	19%	18%
Cancer stage at study entry			
Iva	18%	20%	20%
IVb	5%	4%	7%
IVc	72%	72%	68%

Study Results

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 randomized to KEYTRUDA® in combination with chemotherapy compared to standard treatment. The trial demonstrated a statistically significant improvement in OS in patients whose tumours expressed PD L1 CPS ≥ 1 randomized to pembrolizumab monotherapy compared to standard treatment. Tables 66 and 67 and Figures 22 and 23 describe key efficacy results for KEYTRUDA® in KEYNOTE-048.

Table 66: Efficacy Results for KEYTRUDA® plus Chemotherapy in KEYNOTE-048 at Final Analysis

Endpoint	KEYTRUDA® Platinum Chemotherapy FU n=281	Standard Treatment* n=278
Primary Efficacy Outcome Measure OS		
Number (%) of patients with event	213 (76%)	247 (89%)
Median in months (95% CI)	13.0 (10.9, 14.7)	10.7 (9.3, 11.7)
Hazard ratio† (95% CI)	0.72 (0.60, 0.87)	
p-Value‡	0.00025	
Primary Efficacy Outcome Measure PFS		
Number of patients with event (%)	250 (89%)	260 (94%)
Median in months (95% CI)	4.9 (4.7, 6.1)	5.2 (4.9, 6.1)
Hazard ratio† (95% CI)	0.93 (0.78, 1.11)	
p-Value‡	0.2121	

* Cetuximab, platinum, and FU

† Based on the stratified Cox proportional hazard model
‡ Based on stratified log-rank test

Figure 22: Kaplan-Meier Curve for Overall Survival for KEYTRUDA® plus Chemotherapy in KEYNOTE-048 at Final Analysis

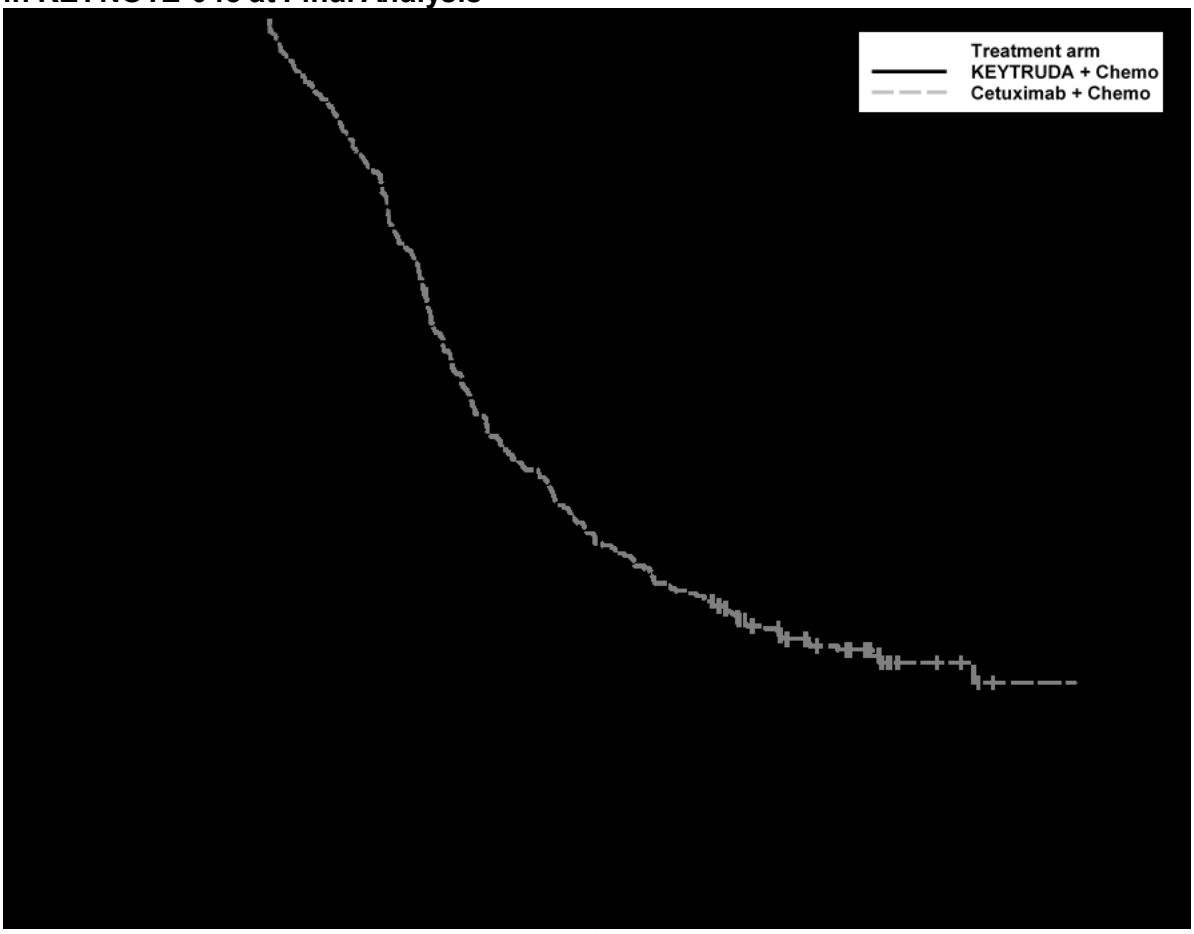
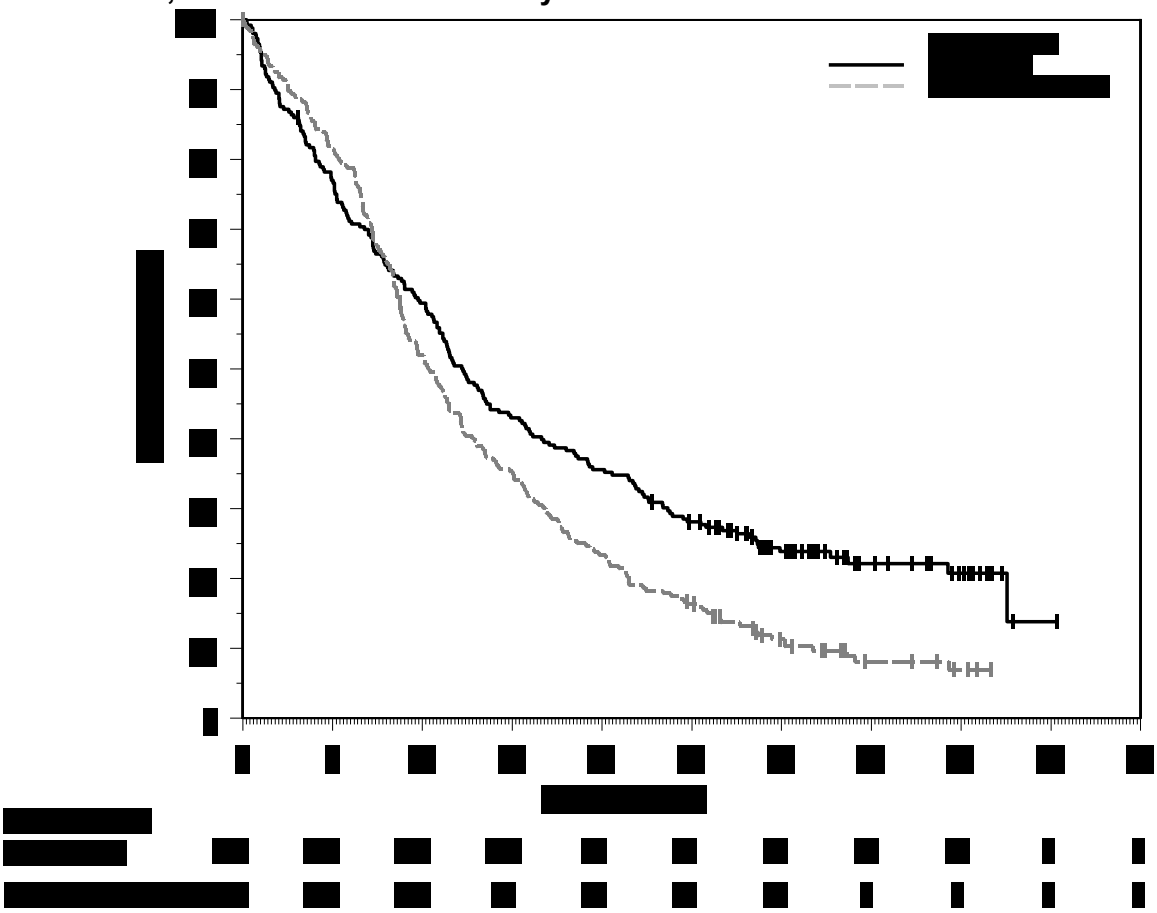


Table 67: Efficacy Results for KEYTRUDA® as Monotherapy in KEYNOTE-048, with CPS ≥ 1 at Final Analysis

Endpoint	KEYTRUDA® n=257	Standard Treatment* n=255
Primary Efficacy Outcome Measure 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	
Primary Efficacy Outcome Measure 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	

* Cetuximab, platinum, and FU
† Based on the stratified Cox proportional hazard model
‡ Non-inferiority p-Value
§ Based on stratified log-rank test

Figure 23: Kaplan-Meier Curve for Overall Survival for KEYTRUDA® as Monotherapy in KEYNOTE-048, with CPS ≥ 1 at Final Analysis



The duration of response (DOR) was analysed as an exploratory efficacy outcome. A longer median DOR in months (range) was observed for KEYTRUDA® as monotherapy [20.9 (1.5+, 34.8+)] compared to the standard treatment [4.5 (1.2+, 30.6)] in patients with PD-L1 CPS ≥1, or for KEYTRUDA® in combination with chemotherapy [6.7 (1.6+, 30.4+)] compared to the standard treatment [4.3 (1.2+, 27.9+)].

In exploratory analyses, a positive association was observed between CPS expression and treatment benefit.

15 NON-CLINICAL TOXICOLOGY

Repeat-dose toxicity

Repeat-dose toxicology studies were carried out in monkeys. In a 1-month study, monkeys received 0, 6, 40, or 200 mg/kg IV pembrolizumab administered weekly for a total of 5 doses followed by a 4 month recovery period. In the 6 month study, monkeys received 0, 6, 40, or 200 mg/kg IV pembrolizumab administered biweekly for a total of 12 doses, followed by a 4-month recovery period. In both studies, all dose levels administered exceeded the recommended human dose and resulted in exposures and peak serum concentrations that were greater than those observed in humans receiving the recommended dose. Pembrolizumab was not associated with any adverse test article-related findings at doses up to 200 mg/kg

administered weekly for 1-month (NOAEL (No Observed Adverse Effect Level) > 200 mg/kg) or at doses up to 200 mg/kg adminstered biweekly for 6 months (NOAEL > 200 mg/kg).

In an exploratory study, 4 chimpanzees with naturally occuring chronic hepatitis B virus (HBV) infection received rising doses of IV pembrolizumab over 5 weeks. Chimpanzees were administered pembrolizumab (IV) doses of 1, 2, 5, 10, and 10 mg/kg on Day 0, 7, 14, 21, and 28, respectively. Two (2) of the four HBV infected chimpanzees had significantly increased levels of serum ALT, AST, and GGT beginning on day 21 and persisting for at least 1 month after the discontinuation of pembrolizumab.

Reproduction
Animal reproduction studies have not been conducted with KEYTRUDA®. The central function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining immune tolerance to the fetus. Blockade of PD-L1 signaling has been shown in murine models of pregnancy to disrupt tolerance to the fetus and to result in an increase in fetal loss. These results indicate a potential risk that administration of KEYTRUDA® during pregnancy could cause fetal harm, including increased rates of abortion or stillbirth.

Development
Fertility studies have not been conducted with pembrolizumab. There were no notable effects in the male and female reproductive organs in a limited number of sexually mature monkeys based on1-month and 6-month repeat dose toxicity studies.

Special Toxicology Studies
PD-1 deficiency was associated with enhanced inflammatory responses, increased severity of infections and reduced survival in some animal models. Compared to wild-type mice, PD-1 knockout mice infected with *M. tuberculosis* had enhanced inflammatory responses, increased bacterial proliferation and decreased survival. Decreased survival has also been observed in PD-1 knockout mice infected with LCMV.

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

Mutagenesis
The genotoxic potential of pembrolizumab has not been evaluated.

Table 68: Summary of Toxicology Studies

Study Type	Treatment Duration and Dosing Schedule	Species/Test system	Gender and No. per Group	Doses (mg/kg)[a]	Findings/Conclusions
Pharmacokinetic Studies					
Non-GLP Pharmacokinetic study IV	Single dose	Monkey/ Cynomolgus	3F per group	0.3, 3 and 30	The decline of serum concentration followed multiphasic kinetics. Slightly greater than dose proportional exposure between 0.3 and 3.0 mg/kg and approximately linear exposure between 3.0 and

Study Type	Treatment Duration and Dosing Schedule	Species/Test system	Gender and No. per Group	Doses (mg/kg)[a]	Findings/Conclusions
					30 mg/kg was observed. Anti-drug antibodies (ADA) were detected in most of the treated animals. Clearance (CL) and terminal half-life (t1/2) appeared to be dose dependent in the dose range tested with CL ranging from 3.7 to 5.7 mL/day/kg and t1/2 ranging from 4 to 10 days
General Toxicity					
Repeat-Dose Toxicity IV	1-month Dosing Period with 4-month treatment-free Postdose Period, dosing once weekly (total of 5 doses)	Monkey/ Cynomolgus	4F, 4M per group (dosing period); 2 F, 2M per group (treatment-free postdose period)	0, 6, 40, 200	There was no test article-related mortality. Test article-related changes were limited to an increased incidence of inguinal swelling, and increased splenic weights in males receiving 200 mg/kg at end of the Dosing Period. Both of these findings were not considered adverse and there was no histopathologic correlate. Splenic weights were normal at the necropsy performed after the treatment-free period. Based on the lack of adverse test article-related findings, the NOAEL was > 200 mg/kg
Repeat-Dose Toxicity IV	6-month Dosing Period with 4-month treatment-free Postdose Period, dosing once every other week (total of 12 doses)	Monkey/ Cynomolgus	3F, 3M per group (dosing period); 2F, 2M per group (treatment-free postdose period)	0, 6, 40, 200	There were no test article-related antemortem, electrocardiographic or ophthalmic findings. There were no test article-related changes at injection sites. Following the interim and final necropsies, there were no identified test article-related postmortem findings. The NOAEL was > 200 mg/kg
Other Studies					
Tissue Cross-reactivity *in vitro*	N/A	Cryosections of normal human	n = 3 donors per	1, 10 µg/mL MK-3475 pre-	Positive staining of mononuclear leukocyte membranes was considered

Study Type	Treatment Duration and Dosing Schedule	Species/Test system	Gender and No. per Group	Doses (mg/kg)[a]	Findings/Conclusions
		tissues	tissue (~ 32 tissues/donor)	complexed with biotinylated secondary antibody	on-target binding consistent with the known biology and expression of PD-1. Off-target cross-reactivity staining was noted in the cytoplasm of various cell types/tissues and the stroma (extracellular connective tissue matrix) of many tissues. These off-target findings were interpreted as spurious binding inherent to the experimental conditions of the *in vitro* tissue cross-reactivity studies with no *in vivo* toxicological significance.
Tissue Cross-reactivity *in vitro*	N/A	Cryosections of normal Cynomolgus monkey tissues	n = 3 donors per tissue (~ 32 tissues/donor)	1, 10 µg/mL MK-3475 pre-complexed with biotinylated secondary antibody	Positive staining of mononuclear leukocyte membranes was considered on-target binding consistent with the known biology and expression of PD-1. Off-target cross-reactivity staining was noted in the cytoplasm of various cell types/tissues, the extracellular material in the neurohypophysis and the stroma (extracellular connective tissue matrix) of many tissues. These off-target findings were interpreted as spurious binding inherent to the experimental conditions of the *in vitro* tissue cross-reactivity studies with no *in vivo* toxicological significance.

Study Type	Treatment Duration and Dosing Schedule	Species/Test system	Gender and No. per Group	Doses (mg/kg)[a]	Findings/Conclusions
Cytokine Release Studies *In vitro*	[b, c, d, e] 4 days culture for cytokine release after Staphylococcus enterotoxin B (SEB) stimulation [f] 48 hr for cytokine release, dry coat assay	[b, f] Human, normal donors [c]Human, advanced metastatic melanoma patients [d]Human, prostate cancer patients [e]Cynomolgus monkey	[b]n = 3 [c]n = 8 [d]n = 8 [e]n = 6 [f]n = 7	[b, c, d, e] 25, 2.5, 0.25, 0.025, 0.0025, 0.00025 µg/mL [b]25 µg/mL [f] 25, 2.5, 0.25, 0.025, 0.0025, 0.00025 µg/mL for dry coat assay	[b, c, d] MK-3475 enhances SEB-induced IL-2 production from approximately 2- to 4-fold; MK-3475 modestly enhances production TNF-α, IFNγ, IL-6, and IL-17 (less than 2-fold). In the absence of SEB stimulation, MK-3475 did not induce cytokine production. [e] MK-3475 enhances SEB-induced IL-2 production. [f] MK-3475 did not induce cytokine release. Superagonist anti-CD28 induced robust cytokine release.
Other Studies					
T-cell recall for Tetanus toxoid	[g] 7 days	Human donors, recently revaccinated with tetanus toxoid	n = 2	25, 2.5, 0.25, 0.025, 0.0025, 0.00025 µg/mL	MK-3475 enhanced tetanus toxoid-induced production of IFNγ in a dose-dependent manner.
HBV infection	Once per week, 5 dose, rising dose escalation. Postdose (last dose) period of 1 month	HBV-infected chimpanzees	n = 4	All doses IV. First dose = 1 mg/kg, second dose = 2 mg/kg, third dose = 5 mg/kg, fourth and fifth dose = 10 mg/kg	No changes in viral load were observed. ALT/AST/GGT flares were observed in 2 animals following the fifth dose (10 mg/kg); ALT/AST/GGT levels remained elevated for at least one month.

[a] For Repeat-Dose Toxicity, the highest NOAEL (No Observed Adverse Effect Level) is underlined.
[b, c, d, e] MK-3475 or control human IgG4 antibody was pre-incubated with heparinized whole blood for 30-60 minutes, and then cultured for 4 days after stimulation with 0.1 µg/mL Staphylococcus enterotoxin B (SEB). Cytokine levels were assessed by immunoassay.
[f] MK-3475 or superagonistic anti-human CD28 antibody were immobilized by air drying directly onto microtiter plates. Human peripheral blood mononuclear cells (PBMC) were cultured in the wells for 48 hr; cytokine levels were assessed by immunoassay.
[g] Peripheral blood mononuclear cells from donors recently revaccinated with tetanus toxoid (TT) were stimulated *in vitro* for 7 days with 1 µg/mL TT in the presence or absence of MK-3475 or a human IgG4 isotype control antibody. Cytokine levels were assessed by immunoassay.
IL-2 = interleukin 2; TNF-α = tumour necrosis factor-alpha; IFNγ = interferon gamma; IL-6 = interleukin 6; IL-17 = interleukin 17

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

℞ KEYTRUDA®
Pembrolizumab

Read this carefully before you start taking **KEYTRUDA®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **KEYTRUDA®**.

What is KEYTRUDA® (key-true-duh) **used for?**

- **See the following boxed text**

For the following indication(s) KEYTRUDA® has been approved ***with conditions* (NOC/c)**. This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to make sure the drug works the way it should. For more information, talk to your healthcare professional.

KEYTRUDA® is a prescription medicine used to treat:

- a kind of cancer called classical Hodgkin lymphoma (cHL) in adults and children:
  - that has come back after an autologous stem cell transplant (ASCT), or
  - that was not suitable for ASCT

- a kind of cancer called primary mediastinal B-cell lymphoma in adults and children
  - that was not responsive to other treatments, or
  - that has come back after you have tried at least 2 other treatments

- a kind of bladder and urinary tract cancer called urothelial carcinoma, in adults
  - KEYTRUDA® may be used when your cancer has not spread to nearby tissue in the bladder, but is at high-risk for spreading (high-risk non-muscle-invasive bladder cancer [NMIBC]) when:
    - your tumor is a type called "carcinoma in situ" (CIS), and
    - you have tried treatment with Bacillus Calmette-Guerin (BCG) and it did not work, and
    - you are not able to or have decided not to have surgery to remove your bladder

  - KEYTRUDA® may be used when your bladder or urinary tract cancer:
    - has spread or cannot be removed by surgery (advanced urothelial cancer), and
      - you are not able to receive chemotherapy that contains a medicine called cisplatin, and your tumour tests positive for PD-L1, or
      - you are not able to receive a medicine called cisplatin or carboplatin

- a kind of colon, rectal, or endometrial cancer in adults that is shown by a laboratory test to be microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)
    - when you have received prior anti-cancer medicine and it did not work or is no longer working

- a kind of uterine cancer in adults called endometrial carcinoma. KEYTRUDA® is used with the medicine lenvatinib when your endometrial carcinoma:
    - has worsened after anti-cancer treatment that contained platinum;
    - cannot be cured by surgery or radiation;
    - is not microsatellite instability high (MSI-H); or
    - is not mismatch repair deficient (dMMR).

For the following indications KEYTRUDA® has been approved ***without conditions***. This means it has passed Health Canada's review and can be bought and sold in Canada.

KEYTRUDA® is a prescription medicine used to treat:

- a kind of skin cancer called melanoma in adults
    - KEYTRUDA® may be used alone as your first treatment when your skin cancer:
        - has spread or cannot be removed by surgery (advanced melanoma)

    - KEYTRUDA® may be used alone when your skin cancer:
        - has spread or cannot be removed by surgery (advanced melanoma), and
        - after you have tried a medicine called ipilimumab and it did not work or is no longer working, and
        - if your tumour has an abnormal "BRAF" gene, and you also have tried a different medicine called a BRAF or MEK inhibitor, and it did not work or is no longer working

    - KEYTRUDA® may be used alone when your skin cancer:
        - has been removed by surgery to help prevent the cancer from coming back

- a kind of lung cancer called non-small cell lung cancer in adults
    - KEYTRUDA® may be used alone as your first treatment when your lung cancer:
        - has spread (advanced lung cancer), or
        - has not spread outside your chest (stage III) and you cannot have surgery or chemotherapy with radiation, and
        - tests positive for "PD-L1", and
        - if your tumour does not have an abnormal "EGFR" or "ALK" gene

    - KEYTRUDA® may be used with the medicine pemetrexed and chemotherapy that contains platinum as your first treatment when your lung cancer:
        - has spread (advanced lung cancer), and
        - is a type called "non-squamous", and
        - if your tumour does not have an abnormal "EGFR" or "ALK" gene

- KEYTRUDA® may be used with the chemotherapy medicines carboplatin and either paclitaxel or nab-paclitaxel as your first treatment when your lung cancer:
  - has spread (advanced lung cancer), and
  - is a type called "squamous"

- KEYTRUDA® may be used alone when your lung cancer:
  - has worsened on or after chemotherapy that contains platinum, and
  - has spread (advanced lung cancer), and
  - tests positive for "PD-L1", and
  - if your tumour has an abnormal "EGFR" or "ALK" gene, you have tried an EGFR or ALK inhibitor medicine.

- a kind of bladder and urinary tract cancer called urothelial carcinoma, in adults when
  - it has spread or cannot be removed by surgery (advanced urothelial cancer); and
  - you have received chemotherapy that contains platinum, and it did not work or is no longer working

- a kind of kidney cancer in adults called renal cell carcinoma

- a kind of head and neck cancer called head and neck squamous cell carcinoma in adults:
  - may be used alone as your first treatment when your head and neck cancer:
    - has spread
    - has come back after previous therapy
      and
    - test positive for "PD-L1"
- a kind of head and neck cancer called head and neck squamous cell carcinoma in adults:
  - may be used with the chemotheapy medicines platinum and fluorouracil (FU) as your first treatment when your head and neck cancer:
    - has spread
    - has come back after previous therapy

KEYTRUDA® may be given in combination with other anti-cancer medicines. It is important that you also read the package leaflets for these other medicines. If you have any questions about these medicines, please ask your doctor.

KEYTRUDA® can be used only in children with classical Hodgkin lymphoma or primary mediastinal B-cell lymphoma. It is not known if KEYTRUDA® is safe and effective in children less than 18 years of age for other pediatric diseases.

People get KEYTRUDA® when their cancer has spread or cannot be taken out by surgery.

How does KEYTRUDA® work?
KEYTRUDA® works by helping your immune system fight your cancer.

What are the ingredients in KEYTRUDA®?
The active substance is pembrolizumab.
The other ingredients are: L-histidine; polysorbate-80; L-histidine monohydrochloride monohydrate; sucrose; and water for infusion.

KEYTRUDA® comes in the following dosage forms:
Powder for solution for infusion, 50 mg per vial
Solution for infusion 100 mg/4 mL vial

Do not use KEYTRUDA® if:
- you have had a severe allergic reaction to pembrolizumab or any other ingredients in KEYTRUDA®

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take KEYTRUDA®. Talk about any health conditions or problems you may have, including if you:
- have an autoimmune disease (a condition where the body attacks its own cells), such as Crohn's disease, Ulcerative Colitis or Lupus;
- have pneumonia or inflammation of your lungs (called pneumonitis);
- were previously given ipilimumab, another medicine for treating melanoma, and experienced serious side effects because of that medicine;
- had an allergic reaction to other monoclonal antibody therapies;
- have or have had chronic viral infection of the liver, including hepatitis B (HBV) or hepatitis C (HCV);
- have human immunodeficiency virus (HIV) infection or acquired immune deficiency syndrome (AIDS);
- have liver damage or have had a liver transplant;
- have kidney damage or have had a kidney transplant;
- have had a solid organ transplant or a bone marrow (stem cell) transplant that used donor stem cells (allogeneic); or
- take other medicines that make your immune system weak. Examples of these may include steroids, such as prednisone.

There are possible side effects of KEYTRUDA® treatment in people who have received a transplant.
- **Rejection of a transplanted organ.** People who have had an organ transplant may have an increased risk of organ transplant rejection. Your doctor should tell you what signs and symptoms you should report and monitor you, depending on the type of organ transplant that you have had.
- **Complications, including graft-versus-host-disease (GVHD) in people with bone marrow (stem cell) transplant that uses donor stem cells (allogeneic).** These complications can be severe and can lead to death. They may occur if you had this kind of transplant in the past or if you get it in the future. Your doctor will monitor you for the following signs and symptoms: skin rash; liver inflammation; abdominal pain; and diarrhea.

Pregnancy
- If you are pregnant, think you may be pregnant or are planning to have a baby, tell your doctor.
- KEYTRUDA® can cause harm or death to your unborn baby.
- You must use effective contraception while you are being treated with KEYTRUDA® and for

at least 4 months after the last dose of KEYTRUDA® if you are a woman who could become pregnant.

Breast-feeding
- If you are breast-feeding, tell your doctor.
- Do not breast-feed while taking KEYTRUDA®.

Driving and using machines
If you experience side effects affecting your ability to concentrate or react, do not drive or use machines until you feel better.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How you are given KEYTRUDA®:
- Your doctor will give you KEYTRUDA® through an infusion into your vein (IV) for about 30 minutes.
- Most people get KEYTRUDA® every 3 weeks.
- Your doctor will decide how many treatments you need.

Usual dose:
The recommended dose is 200 mg in adults.

The recommended dose is 2 mg/kg (up to a maximum of 200 mg) in children treated for classical Hodgkin lymphoma or primary mediastinal B-cell lymphoma.

Overdose:

If you think you have taken too much KEYTRUDA®, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

If you miss an appointment to get KEYTRUDA®
- Call your doctor right away to reschedule your appointment.
- It is very important that you do not miss a dose of this medicine.

What are possible side effects from using KEYTRUDA®?

When you get KEYTRUDA®, you can have some serious side effects. These side effects can sometimes become life-threatening and can lead to death. These side effects may happen anytime during treatment or even after your treatment has ended. You may experience more than one side effect at the same time. The following lists do not include all the possible side effects you may feel when taking KEYTRUDA®. If you experience any side effects not listed here, contact your healthcare professional.

The following side effects have been reported in clinical trials when KEYTRUDA® is given alone:

Very common (may affect more than 1 in 10 people)
- diarrhea, nausea;
- itching, rash;

- joint pain;
- feeling unusually tired or weak;
- fever;
- feeling less hungry;
- shortness of breath;
- patches of skin which have lost colour (vitiligo).

Common (may affect more than 2 in 100 people and up to 1 in 10 people)
- flu-like illness;
- dry mouth;
- headache;
- change in your sense of taste;
- cough;
- lack of white blood cells;
- rapid heartbeat;
- cold sores;
- upper respiratory tract infection;
- stuffy nose;
- stomach pain, constipation, vomiting, inflammation of the mucous membrane in the mouth dry skin, redness of the skin, red raised skin rash;
- back pain, muscle aches;
- chills;
- swelling of the face, legs or arms;
- numbness, prickling, tingling or pain in the feet or hands;
- changes in test results:
    - decrease in the number of red blood cells
    - decrease in the number of white blood cells
    - abnormal liver enzyme levels in the blood
    - decreased sodium levels in the blood
    - abnormal levels of thyroid stimulating hormone in the blood
    - increased creatinine levels in the blood
    - weight loss
    - weight gain.

The most common side effects when KEYTRUDA® is given to children are:
- fever;
- vomiting;
- headache;
- abdominal pain;
- decrease in number of red blood cells;
- cough;
- constipation
- feeling tired
- nausea;
- diarrhea;
- decreased appetite
- abnormal liver enzyme levels in the blood
- joint pain
- feeling unusually tired or weak

- back pain
- pain in arms or legs
- rash
- decrease in white blood cell count
- shortness of breath

The following side effects have been reported in clinical trials when KEYTRUDA® is given in combination with chemotherapy. Ask your doctor for more information regarding side effects of your chemotherapy.

Very common (may affect more than 1 in 10 people)
- nausea;
- decrease in red blood cell count;
- fatigue;
- decrease in white blood cell count;
- decreased appetite;
- diarrhea;
- vomiting;
- decrease in platelet count;
- constipation;
- weakness;
- rash;
- eye tearing.

The following side effects of KEYTRUDA® have been reported in clinical trials when given with lenvatinib. If you are taking KEYTRUDA® in combination with lenvatinib, then you should also read the Patient Medication Information for lenvatinib. It contains more information on the side-effects of lenvatinib.

Very common (may affect more than 1 in 10 people)

• feeling tired • high blood pressure • diarrhea • joint and muscle pain • decreased appetite • low levels of thyroid hormone • nausea • vomiting • mouth sores • weight loss • stomach-area (abdominal) pain	• headache • constipation • hoarseness • urinary tract infection • bleeding • low magnesium level • blisters or rash on the palms of your hands and soles of your feet • shortness of breath • cough • rash.

The most common side effects when KEYTRUDA® is given in combination with axitinib are:
- low or high levels of thyroid hormone;
- diarrhea;
- nausea;
- inflammation of the mucous membranes including in the mouth;
- feeling unusually tired or weak;

- fatigue;
- increase in liver enzyme levels;
- decreased appetite;
- joint pain;
- protein in urine;
- voice change;
- blisters or rash on the palms of your hands and soles of your feet;
- itching;
- rash;
- high blood pressure.

If you are being treated with KEYTRUDA® either alone or in combination with chemotherapy and have any of the following conditions, call or see your doctor right away. Your doctor may give you other medicines in order to prevent more severe complications and reduce your symptoms. Your doctor may withhold the next dose of KEYTRUDA® or stop your treatment with KEYTRUDA®.

Serious side effects and what to do about them		
Symptom / effect	Talk to your healthcare professional	
	Only if severe	In all cases
COMMON Inflammation of the lungs (pneumonitis) which can cause shortness of breath, chest pain, or coughing		√
Inflammation of the intestines (colitis) which can cause diarrhea or more bowel movements than usual, black, tarry, sticky stools or stools with blood or mucus, severe stomach pain or tenderness, nausea, vomiting		√
Inflammation of the pituitary or thyroid gland (hypophysitis, hypopituitarism, including secondary adrenal insufficiency; hyperthyroidism, hypothyroidism) which can cause rapid heartbeat, weight loss, increased sweating, weight gain, hair loss, feeling cold, constipation, voice getting deeper, muscle aches, dizziness or fainting, headaches that will not go away or unusual headache, feeling more hungry or thirsty, urinating more often than usual.		√
Skin problems which can cause rash, itching; skin blistering, peeling, or sores; ulcers in mouth or in lining of nose, throat, or genital area		√
UNCOMMON Inflammation of the liver (hepatitis) which can cause nausea or vomiting, feeling less hungry, pain on the right side of stomach, yellowing of skin or whites of eyes, dark urine, bleeding or bruising more easily than normal		√
Inflammation of the kidneys (nephritis) which can cause changes in the amount or colour of your urine		√

Serious side effects and what to do about them		
Symptom / effect	Talk to your healthcare professional	
	Only if severe	In all cases
Muscle problems, which can cause muscle pain or weakness, severe or persistent muscle or joint pains(myositis).		√
Muscle problems, which can cause weakness and rapid fatigue of muscles or weakness and tingling in arms and legs (myasthenia gravis or Guillain-Barre syndrome)		√
low red blood cell count (anemia/hemolytic anemia).		√
Eye problems, which can cause changes in eyesight		√
Shortness of breath, irregular heartbeat, feeling tired, or chest pain (myocarditis).		√
Blood sugar problems (type 1 diabetes mellitus) which can cause hunger or thirst, a need to urinate more often, or weight loss		√
Confusion, fever, memory problems, or seizures (encephalitis)		√
Swollen lymph nodes, rash or tender lumps on skin, cough, or eye pain (sarcoidosis)		√
Inflammation of the pancreas (pancreatitis), which can cause abdominal pain, nausea, and vomiting		√
Reactions related to the infusion such as shortness of breath, itching or rash, dizziness, or fever, wheezing, flushing, feeling like passing out.		√
Pain, numbness, tingling, or weakness in the arms or legs; bladder or bowel problems including needing to urinate more frequently, urinary incontinence, difficulty urinating and constipation (myelitis)		√
Inflammation of blood vessels (vasculitis), symptoms include red skin lesions, numbness and weakness		√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Also, to report an adverse event related to KEYTRUDA®, please contact Merck Canada at 1-800-567-2594.

Storage:
It is unlikely that you will be asked to store KEYTRUDA® yourself. It will be stored in the hospital or clinic where it is given to you.

Keep out of reach and sight of children.

Powder for Solution for Infusion: Store in a refrigerator (2°C to 8°C).
Solution for Infusion: Store in a refrigerator (2°C to 8°C). Protect from light.

If you want more information about KEYTRUDA®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website http://hc-sc.gc.ca/index-eng.php or the Merck Canada website www.merck.ca or by calling Merck Canada at 1-800-567-2594.

This leaflet was prepared by Merck Canada Inc.

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