Product Monograph Including Patient Medication Information

[□] KEYTRUDA®

pembrolizumab for injection
Produced in Chinese hamster ovary cells by recombinant deoxyribonucleic acid technology

Solution for intravenous infusion, 100 mg/4 mL vial

Antineoplastic agent, monoclonal antibody

KEYTRUDA, indicated for:

- 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 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.

has been issued market 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 web site: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/notice-compliance/conditions.html.

KEYTRUDA, 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.
- 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 and pediatric (12 years and older) patients with Stage IIB, IIC or III melanoma following 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.
- Adjuvant treatment of adult patients with Stage IB (T2a ≥ 4 cm), II, or IIIA NSCLC who
 have undergone complete resection and platinum-based chemotherapy.
- Treatment of adult patients with resectable Stage II, IIIA, or IIIB (T3-4N2) NSCLC in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery.
- First-line treatment of adult patients with unresectable advanced or metastatic malignant pleural mesothelioma (MPM) in combination with pemetrexed and platinum chemotherapy.
- Treatment of adult patients with unresectable locally advanced or metastatic urothelial cancer (mUC) in combination with enfortumab vedotin with no prior systemic therapy for mUC
- Treatment of adult patients with locally advanced unresectable or metastatic urothelial carcinoma, as monotherapy, who are not eligible for any platinum-containing chemotherapy.
- 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.
- Treatment of adult patients with advanced (not amenable to curative surgery or radiation) or metastatic RCC in combination with lenvatinib with no prior systemic therapy for metastatic RCC.
- Adjuvant treatment, as monotherapy, of adult patients with RCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.
- Treatment, as monotherapy, of adult patients with metastatic MSI-H or dMMR colorectal cancer (CRC) as determined by a validated test.
- Treatment, as monotherapy, of adult and pediatric patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumours, as determined by a validated test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.
- Treatment of adult patients with primary advanced or recurrent endometrial carcinoma, in combination with carboplatin and paclitaxel and then continued as monotherapy.
- Treatment of adult patients with advanced endometrial carcinoma, in combination with lenvatinib, 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.

- Treatment of adult patients with resectable locally advanced head and neck squamous cell carcinoma (HNSCC) whose tumours express PD-L1 (Combined Positive Score [CPS] ≥ 1), as determined by a validated test, as neoadjuvant treatment as monotherapy, continued as adjuvant treatment in combination with radiotherapy (RT) with or without cisplatin and then as monotherapy.
- 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.
- First-line treatment, in combination with trastuzumab, fluoropyrimidine- and platinumcontaining chemotherapy, of adult patients with locally advanced unresectable or
 metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma
 whose tumours express PD-L1 (Combined Positive Score [CPS] ≥ 1) as determined by a
 validated test.
- First-line treatment, in combination with fluoropyrimidine- and platinum-containing chemotherapy, of adult patients with locally advanced unresectable or metastatic HER2-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma.
- First-line treatment, in combination with platinum and fluoropyrimidine based chemotherapy, of adult patients with locally advanced unresectable or metastatic, carcinoma of the esophagus.
- Treatment of adult patients with high-risk early-stage triple-negative breast cancer (TNBC) in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery.
- Treatment of adult patients in combination with chemotherapy with locally recurrent unresectable or metastatic triple-negative breast cancer (TNBC), who have not received prior chemotherapy for metastatic disease and whose tumours express PD-L1 (Combined Positive Score [CPS] ≥ 10) as determined by a validated test.
- Treatment of adult patients with FIGO 2014 Stage III-IVA cervical cancer, in combination with chemoradiotherapy (CRT).
- Treatment of adult patients with persistent, recurrent, or metastatic cervical cancer whose tumours express PD-L1 (CPS ≥ 1) as determined by a validated test, in combination with chemotherapy with or without bevacizumab.
- Treatment of adult patients with locally advanced unresectable or metastatic biliary tract carcinoma (BTC), in combination with gemcitabine-based chemotherapy.

has been issued market authorization without conditions.

Merck Canada Inc. 16750 route Transcanadienne Kirkland QC Canada H9H 4M7 www.merck.ca

Control Number: 291851

Date of Authorization: October 9, 2025

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

A NOC/c is a form of market approval 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.

Recent Major Label Changes

1 Indications	08/2025
4 Dosage and Administration	08/2025
7 Warnings and Precautions	01/2025

Table Of Contents

Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

Recent I	Major I	Label Changes	5
Part 1: F	Healtho	care Professional Information	8
1. Indica	ations .		8
	1.1	Pediatrics	11
	1.2	Geriatrics	12
2. Contr	aindica	ations	12
4. Dosag	ge and	Administration	12
	4.1	Dosing Considerations	12
	4.2	Recommended Dose and Dosage Adjustment	13
	4.3	Reconstitution	24
	4.4	Administration	25
	4.5	Missed Dose	25
5. Overd	dose		25
6. Dosag	ge Forn	ns, Strengths, Composition and Packaging	26
7. Warn	ings ar	nd Precautions	26
	Genera	le	26
	Driving	g and Operating Machinery	26
	Hepati	c/Biliary/Pancreatic	26
	Immur	ne	27
	Monito	oring and Laboratory Tests	30
	Renal .		30
	Reprod	ductive Health: Female and Male Potential	30
	7.1	Special Populations	31
	7.1.1	Pregnancy	31
	7.1.2	Breastfeeding	31
	713	Pediatrics	31

	7.1.4	Geriatrics	32
8. Adv	erse Rea	nctions	32
	8.1	Adverse Reaction Overview	32
	8.2	Clinical Trial Adverse Reactions	32
	8.2.1	Clinical Trial Adverse Reactions – Pediatrics	183
	8.3	Less Common Clinical Trial Adverse Reactions	183
	8.4 Data	Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quant	
	8.5	Post-Market Adverse Reactions	219
9. Drug	gInterac	tions	219
	9.2	Drug Interaction Overview	220
	9.3	Drug-Behaviour Interactions	220
	9.4	Drug-Drug Interactions	220
	9.5	Drug-Food Interactions	220
	9.6	Drug-Herb Interactions	220
	9.7	Drug-Laboratory Test Interactions	220
10. Clir	nical Pha	armacology	220
	10.1	Mechanism of Action	220
	10.2	Pharmacodynamics	220
	10.3	Pharmacokinetics	221
	10.4	Immunogenicity	223
11. Sto	rage, St	ability And Disposal	223
12. Spe	ecial Har	ndling Instructions	223
Part 2:	Scientif	ic Information	224
13. Pha	armaceu	itical Information	224
14. Clir	nical Tria	als	224
	14.1	Clinical Trials by Indication	224
	Melan	oma	224
	Adjuva	nt Melanoma	233
	Non-Sr	mall Cell Lung Carcinoma	238
	Malign	ant Pleural Mesothelioma	267
	Classic	al Hodgkin Lymphoma	269
	Primar	v Mediastinal B-cell Lymphoma	271

	Urothelial Carcinoma	272
1	Microsatellite Instability-High Colorectal Cancer	282
	Microsatellite Instability-High Cancer (MSI-H) or Mismatch Repair Deficient (dMMR) Cancer	284
	Endometrial Carcinoma	286
	Renal Cell Carcinoma	294
	Head and Neck Cancer	303
(Gastric or Gastroesophageal junction (GEJ) Adenocarcinoma	310
	Esophageal Cancer	318
-	Triple Negative Breast Cancer (TNBC)	323
	Early-stage Triple-Negative Breast Cancer	327
(Cervical Cancer	332
	Biliary Tract Carcinoma	338
	Alternate Dosing Regimen for Adults	340
15. Micr	obiology	341
16. Non-	-Clinical Toxicology	341
Patient I	Medication Information	345

Part 1: Healthcare Professional Information

1. Indications

KEYTRUDA (pembrolizumab) is indicated for:

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 and pediatric (12 years and older) patients with Stage IIB, IIC or III melanoma following 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) \geq 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 14 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 \geq 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 .

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

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

Malignant Pleural Mesothelioma

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

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.

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, in combination with enfortumab vedotin, is indicated for the treatment of adult patients with unresectable locally advanced or metastatic urothelial cancer (mUC) with no prior systemic therapy for mUC.

KEYTRUDA is indicated for the treatment of adult patients with locally advanced unresectable or metastatic urothelial carcinoma, as monotherapy, who are not eligible for any platinum-containing chemotherapy. An improvement in survival or disease-related symptoms has not been established.

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.

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 <u>14 Clinical Trials</u>).

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 $\underline{14}$ Clinical Trials).

KEYTRUDA, in combination with lenvatinib, is indicated for the treatment of adult patients with advanced (not amenable to curative surgery or radiation) or metastatic RCC with no prior systemic therapy for metastatic RCC (See 14 Clinical Trials).

KEYTRUDA, as monotherapy, is indicated for the adjuvant treatment of adult patients with RCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.

Colorectal Cancer

KEYTRUDA is indicated, as monotherapy, for the treatment of adult patients with metastatic MSI-H or dMMR colorectal cancer (CRC) as determined by a validated test.

Microsatellite Instability-High Cancer (MSI-H) or Mismatch Repair Deficient (dMMR) Cancer KEYTRUDA is indicated as monotherapy for the treatment of adult and pediatric patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumours, as determined by a validated test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.

Endometrial Carcinoma

KEYTRUDA, in combination with carboplatin and paclitaxel is indicated for the treatment of adult patients with primary advanced or recurrent endometrial carcinoma, and then continued as monotherapy.

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.

Head and Neck Cancer

KEYTRUDA is indicated for the treatment of adult patients with resectable locally advanced head and neck squamous cell carcinoma (HNSCC) whose tumours express PD-L1 (Combined Positive Score [CPS] \geq 1), as determined by a validated test, as neoadjuvant treatment as monotherapy, continued as adjuvant treatment in combination with radiotherapy (RT) with or without cisplatin and then as monotherapy.

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 $[CPS] \ge 1$) 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.

Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma

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

KEYTRUDA, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adult patients with locally advanced unresectable or metastatic HER2-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma.

Esophageal Cancer

KEYTRUDA, in combination with platinum and fluoropyrimidine based chemotherapy, is indicated for the first-line treatment of adult patients with locally advanced unresectable or metastatic carcinoma of the esophagus.

Triple-Negative Breast Cancer

KEYTRUDA, in combination with chemotherapy, is indicated for the treatment of adult patients with locally recurrent unresectable or metastatic triple-negative breast cancer (TNBC), who have not received prior chemotherapy for metastatic disease and whose tumours express PD-L1 (Combined Positive Score $[CPS] \ge 10$) as determined by a validated test.

Consult the description of the study for the chemotherapy (paclitaxel, nab-paclitaxel or gemcitabine/carboplatin) and dosing regimens used (See 14 Clinical Trials).

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

Consult the description of the study for the chemotherapy regimen (carboplatin and paclitaxel, followed by doxorubicin or epirubicin and cyclophosphamide) used (See 14 Clinical Trials).

Cervical Cancer

KEYTRUDA, in combination with chemoradiotherapy (CRT), is indicated for the treatment of adult patients with FIGO 2014 Stage III-IVA cervical cancer.

KEYTRUDA, in combination with chemotherapy with or without bevacizumab, is indicated for the treatment of adult patients with persistent, recurrent, or metastatic cervical cancer whose tumours express PD-L1 (CPS \geq 1) as determined by a validated test.

Biliary Tract Carcinoma

KEYTRUDA, in combination with gemcitabine-based chemotherapy, is indicated for the treatment of adult patients with locally advanced unresectable or metastatic biliary tract carcinoma (BTC).

1.1 Pediatrics

Pediatrics: KEYTRUDA as monotherapy is indicated for the treatment of pediatric patients with:

- melanoma, pediatric patients 12 years and older with Stage IIB, IIC or III melanoma who have undergone complete resection
- relapsed or refractory cHL who have failed ASCT, or who are not candidates for multi-agent salvage chemotherapy and ASCT (<18 years of age).
- refractory PMBCL, or pediatric PMBCL patients whose disease has relapsed after 2 or more prior lines of therapy (<18 years of age).
- unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient

(dMMR) solid tumours, as determined by a validated test, that have progressed following prior treatment and who have no satisfactory alternative treatment options (<18 years of age) (See 4 Dosage And Administration, 7 Warnings And Precautions and 8 Adverse Reactions).

The safety and efficacy of KEYTRUDA has not been established for pediatric patients with conditions other than melanoma (Stage IIB, IIC or III), relapsed or refractory cHL, relapsed or refractory PMBCL, or unresectable or metastatic MSI-H or dMMR solid tumours.

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) for pembrolizumab monotherapy.

No overall differences in efficacy were reported between elderly patients (65 years and over) and younger patients (less than 65 years) for pembrolizumab combination therapy.

Limited safety and efficacy information is available for KEYTRUDA in cHL ≥ 65 years of age (n=20) (See 7.1.4 Warnings And Precautions; Geriatrics).

2. Contraindications

KEYTRUDA is contraindicated in patients who have experienced a severe hypersensitivity reaction (See <u>7 Warnings And Precautions</u>) to this drug or to any ingredient in the formulation or component of the container closure system. For a complete listing of ingredients, See <u>6 Dosage Forms, Strengths</u>, Composition And Packaging.

4. Dosage and Administration

4.1 Dosing Considerations

Patient Selection

For treatment of Non-Small Cell Lung Carcinoma, Head and Neck Cancer, Gastric Cancer, Triple-Negative Breast Cancer, and Cervical Cancer

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 <u>14 Clinical Trials, Non-Small Cell Lung Carcinoma</u>); or
- locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma, using the Combined Positive Score (CPS) (See 14 Clinical Trials, Gastric or Gastroesophageal junction (GEJ) Adenocarcinoma); or
- resectable locally advanced, metastatic or unresectable recurrent head and neck squamous cell carcinoma (HNSCC) (See <u>14 Clinical Trials, Head and Neck Cancer</u>); or
- locally recurrent unresectable or metastatic triple-negative breast cancer, 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 14 Clinical Trials, Triple Negative Breast Cancer); or
- persistent, recurrent, or metastatic cervical cancer (See 14 Clinical Trials, Cervical Cancer).

A test authorized by Health Canada which is equivalent to that used in clinical trials should be required (See 14 Clinical Trials).

For treatment of MSI-H or dMMR cancer 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 <u>14 Clinical Trials</u>).

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

For patients with high-risk, early-stage TNBC treated with KEYTRUDA in the neoadjuvant setting, blood cortisol measurement prior to surgery should be included.

4.2 Recommended Dose and Dosage Adjustment

Recommended Dosage for Unresectable or Metastatic Melanoma

KEYTRUDA is administered as an intravenous infusion over 30 minutes.

The recommended dose of KEYTRUDA in adults is either:

- o 200 mg every 3 weeks or
- o 400 mg every 6 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 every 3 weeks.

Recommended Dosage for Adjuvant Treatment of Melanoma

KEYTRUDA is administered as an intravenous infusion over 30 minutes.

The recommended dose of KEYTRUDA:

- in adults is either:
 - o 200 mg every 3 weeks or
 - o 400 mg every 6 weeks

for up to one year or until disease recurrence or unacceptable toxicity or 17 doses for 200 mg or 9 doses for 400 mg, whichever is longer, in patients without disease recurrence.

• in pediatric patients 12 years and older with stage IIB, IIC and III melanoma is 2 mg/kg (up to a maximum of 200 mg) every 3 weeks.

for up to one year or until disease recurrence or, unacceptable toxicity, or for up to 17 doses, whichever is longer, in patients without disease recurrence.

<u>Recommended Dosage for – Previously Untreated NSCLC as Monotherapy or in Combination with</u> <u>Chemotherapy</u>

KEYTRUDA is administered as an intravenous infusion over 30 minutes.

The recommended dose of KEYTRUDA in adults is either:

- o 200 mg every 3 weeks or
- o 400 mg every 6 weeks

until disease progression, unacceptable toxicity or up to 24 months or 35 doses for 200 mg or 18 doses for 400 mg, whichever is longer, 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

KEYTRUDA is administered as an intravenous infusion over 30 minutes.

The recommended dose of KEYTRUDA in adults is either:

- o 200 mg every 3 weeks or
- 400 mg every 6 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 every 3 weeks.

Recommended Dosage for Adjuvant Treatment of NSCLC

KEYTRUDA is administered as an intravenous infusion over 30 minutes.

The recommended dose of KEYTRUDA in adults is either:

- o 200 mg every 3 weeks or
- o 400 mg every 6 weeks

for up to one year or until disease recurrence or unacceptable toxicity.

Recommended Dosage for Neoadjuvant Treatment, in Combination with Chemotherapy, Followed by Adjuvant Treatment for Resectable NSCLC

KEYTRUDA is administered as an intravenous infusion over 30 minutes.

The recommended dose of KEYTRUDA in adults is either:

- o 200 mg every 3 weeks or
- o 400 mg every 6 weeks

For the neoadjuvant and adjuvant treatment of resectable NSCLC, patients should be treated with 4 doses of 200 mg or 2 doses of 400 mg of neoadjuvant KEYTRUDA in combination with chemotherapy until disease progression that precludes definitive surgery or unacceptable toxicity, followed by adjuvant treatment with KEYTRUDA as monotherapy for up to 13 doses of 200 mg or 7 doses of 400 mg or until disease recurrence or unacceptable toxicity.

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 (See <u>14 Clinical Trials</u>).

Recommended Dosage for MPM in Combination with Pemetrexed and Platinum Chemotherapy KEYTRUDA is administered as an intravenous infusion over 30 minutes.

The recommended dose of KEYTRUDA in adults is either:

- o 200 mg every 3 weeks or
- o 400 mg every 6 weeks

until disease progression or unacceptable toxicity, or up to 24 months or 35 doses for 200 mg or 18 doses for 400 mg, whichever is longer, in patients without disease progression.

KEYTRUDA is administered in combination with pemetrexed and platinum chemotherapy for up to 6 cycles followed by KEYTRUDA monotherapy (See 14 Clinical Trials). 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 Hodgkin Lymphoma

KEYTRUDA is administered as an intravenous infusion over 30 minutes.

The recommended dose of KEYTRUDA:

- in adults is either:
 - o 200 mg every 3 weeks or
 - o 400 mg every 6 weeks
- in pediatric patients is 2 mg/kg (up to a maximum of 200 mg) every 3 weeks.

until disease progression or unacceptable toxicity, or up to 24 months in patients without disease progression.

Recommended Dosage for PMBCL

KEYTRUDA is administered as an intravenous infusion over 30 minutes.

The recommended dose of KEYTRUDA:

- in adult patients is either:
 - o 200 mg every 3 weeks or
 - o 400 mg every 6 weeks
- in pediatric patients is 2 mg/kg (up to a maximum of 200 mg) every 3 weeks.

Recommended Dosage for Unresectable Locally Advanced or Metastatic Urothelial Cancer in Combination with Enfortumab vedotin

For adult patients with urothelial cancer, the recommended dosing is:

- KEYTRUDA administered as an intravenous infusion over 30 minutes.
 - o 200 mg every 3 weeks or
 - o 400 mg every 6 weeks

until disease progression or unacceptable toxicity, or up to 24 months or 35 doses for 200 mg or 18 doses for 400 mg, whichever is longer, in patients without disease progression, in combination with;

 enfortumab vedotin 1.25 mg/kg on Days 1 and 8 of each 21-day cycle until unacceptable toxicity or disease progression.

Administer KEYTRUDA after enfortumab vedotin when given on the same day. Provide for an interval of 30 minutes between infusions (for at least Cycle 1, Day 1), which can subsequently be reduced to 15 minutes if well tolerated.

Refer to the enfortumab vedotin Product Monograph for recommended enfortumab vedotin dosing information.

Recommended Dosage for Urothelial Carcinoma – Not Eligible for Platinum-Containing Chemotherapy

KEYTRUDA is administered as an intravenous infusion over 30 minutes.

The recommended dose of KEYTRUDA in adults is either:

- o 200 mg every 3 weeks or
- o 400 mg every 6 weeks

until disease progression or unacceptable toxicity, or up to 24 months or 35 doses for 200 mg or 18 doses for 400 mg, whichever is longer, in patients without disease progression.

Recommended Dosage for Urothelial Carcinoma – Previously Treated

KEYTRUDA is administered as an intravenous infusion over 30 minutes.

The recommended dose of KEYTRUDA in adults is either:

- o 200 mg every 3 weeks or
- o 400 mg every 6 weeks

until disease progression or unacceptable toxicity, or up to 24 months or 35 doses for 200 mg or 18 doses for 400 mg, whichever is longer, in patients without disease progression.

Recommended Dosage for BCG-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) KEYTRUDA is administered as an intravenous infusion over 30 minutes.

The recommended dose of KEYTRUDA in adults is either:

- o 200 mg every 3 weeks or
- o 400 mg every 6 weeks

until disease progression, unacceptable toxicity or up to 24 months or 35 doses for 200 mg or 18 doses for 400 mg, whichever is longer, in patients without disease progression.

Recommended Dosage for MSI-H Colorectal Carcinoma

KEYTRUDA is administered as an intravenous infusion over 30 minutes.

The recommended dose of KEYTRUDA in adults is either:

- o 200 mg every 3 weeks or
- 400 mg every 6 weeks

until disease progression, unacceptable toxicity, or up to 24 months or 35 doses for 200 mg or 18 doses for 400 mg, whichever is longer, in patients without disease progression.

<u>Recommended Dosage for MSI-H or dMMR Cancer – Previously Treated with No Satisfactory</u> Alternative Treatment Options

KEYTRUDA is administered as an intravenous infusion over 30 minutes.

The recommended dose of KEYTRUDA in adults is either:

o 200 mg every 3 weeks or

o 400 mg every 6 weeks

until disease progression or unacceptable toxicity, or up to 24 months or 35 doses for 200 mg or 18 doses for 400 mg, whichever is longer, in patients without disease progression.

• in pediatric patients is 2 mg/kg (up to a maximum of 200 mg) every 3 weeks. until disease progression or unacceptable toxicity, or up to 24 months or 35 doses, whichever is longer, in patients without disease progression.

Recommended Dosage for Endometrial Carcinoma in combination with chemotherapy, and then continued as monotherapy

KEYTRUDA is administered as an intravenous infusion over 30 minutes.

The recommended dose of KEYTRUDA in adults is either:

- o 200 mg every 3 weeks or
- o 400 mg every 6 weeks

until disease progression, unacceptable toxicity or up to 24 months or 35 doses for 200 mg or 18 doses for 400 mg, whichever is longer, in patients without disease progression.

KEYTRUDA is administered in combination with carboplatin and paclitaxel for 6 cycles followed by KEYTRUDA monotherapy (see 14 <u>Clinical Trials</u>). KEYTRUDA should be administered first when carboplatin and paclitaxel are given on the same day. Refer to the Product Monographs for carboplatin and paclitaxel when administered in combination with KEYTRUDA for recommended dosing information, as appropriate.

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 administered as an intravenous infusion over 30 minutes.
 - o 200 mg every 3 weeks or
 - o 400 mg every 6 weeks

until unacceptable toxicity, disease progression, or for up to 24 months or 35 doses for 200 mg or 18 doses for 400 mg, whichever is longer, 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 Advanced or Metastatic RCC with No Prior Systemic Therapy for Metastatic RCC – in Combination with axitinib

For adult patients with RCC, the recommended dosing is:

- KEYTRUDA administered as an intravenous infusion over 30 minutes.
 - 200 mg every 3 weeks or
 - o 400 mg every 6 weeks

until unacceptable toxicity, disease progression, or for up to 24 months or 35 doses for 200 mg or 18 doses for 400 mg, 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 Advanced or Metastatic RCC with No Prior Systemic Therapy for Metastatic RCC - in Combination with lenvatinib

For adult patients with RCC, the recommended dosing is:

- KEYTRUDA administered as an intravenous infusion over 30 minutes.
 - o 200 mg every 3 weeks or
 - o 400 mg every 6 weeks

until unacceptable toxicity, disease progression, or for up to 24 months or 35 doses for 200 mg or 18 doses for 400 mg, whichever is longer, 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 Adjuvant Treatment of RCC

KEYTRUDA is administered as an intravenous infusion over 30 minutes.

The recommended dose of KEYTRUDA in adults is either:

- o 200 mg every 3 weeks or
- o 400 mg every 6 weeks

until disease recurrence, unacceptable toxicity or up to 1 year (12 months) or 17 doses for 200 mg or 9 doses for 400 mg, whichever is longer, in patients without disease recurrence.

Recommended Dosage for Resectable Locally Advanced HNSCC as Neoadjuvant Treatment as Monotherapy, continued as Adjuvant Treatment in Combination with radiotherapy (RT) with or without cisplatin and then as Monotherapy

KEYTRUDA is administered as an intravenous infusion over 30 minutes.

The recommended dose of KEYTRUDA in adults is either:

- o 200 mg every 3 weeks or
- o 400 mg every 6 weeks

For neoadjuvant treatment, administer KEYTRUDA as monotherapy for 2 doses of 200 mg every 3 weeks or 1 dose of 400 mg every 6 weeks or until disease progression that precludes definitive surgery or unacceptable toxicity. For adjuvant treatment, administer KEYTRUDA in combination with RT with or without cisplatin for 3 doses of 200 mg every 3 weeks or 2 doses of 400 mg every 6 weeks followed by 12 doses of KEYTRUDA as monotherapy at 200 mg every 3 weeks or 6 doses of 400 mg every 6 weeks or until disease recurrence or unacceptable toxicity (see 14 Clinical Trials).

Administer KEYTRUDA prior to chemoradiotherapy or prior to RT when given on the same day. Refer to the Product Monograph for cisplatin administered in combination with KEYTRUDA for recommended dosing information, as appropriate.

<u>Recommended Dosage for HNSCC – Previously Untreated as Monotherapy or in Combination with</u> Chemotherapy

KEYTRUDA is administered as an intravenous infusion over 30 minutes.

The recommended dose of KEYTRUDA in adults is either:

- o 200 mg every 3 weeks or
- o 400 mg every 6 weeks

until disease progression, unacceptable toxicity or up to 24 months or 35 doses for 200 mg or 18 doses for 400 mg, whichever is longer, 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.

Recommended Dosage for locally advanced unresectable or metastatic HER2-positive Gastric or gastroesophageal junction (GEJ) adenocarcinoma in combination with trastuzumab, fluoropyrimidine- and platinum-containing Chemotherapy

KEYTRUDA is administered as an intravenous infusion over 30 minutes.

The recommended dose of KEYTRUDA in adults is either:

- o 200 mg every 3 weeks or
- o 400 mg every 6 weeks

until disease progression, unacceptable toxicity or up to 24 months.

Administer KEYTRUDA prior to trastuzumab and 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. Refer to the trastuzumab Product Monograph for recommended trastuzumab dosing information.

Recommended Dosage for locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma – in Combination with fluoropyrimidine- and platinum-containing Chemotherapy KEYTRUDA is administered as an intravenous infusion over 30 minutes.

The recommended dose of KEYTRUDA in adults is either:

- 200 mg every 3 weeks or
- o 400 mg every 6 weeks

until unacceptable toxicity, disease progression or up to 24 months or 35 doses for 200 mg or 18 doses for 400 mg, whichever is longer.

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.

<u>Recommended Dosage for Esophageal Cancer – in Combination with platinum and fluoropyrimidine</u> based Chemotherapy

KEYTRUDA is administered as an intravenous infusion over 30 minutes.

The recommended dose of KEYTRUDA in adults is either:

- o 200 mg every 3 weeks or
- o 400 mg every 6 weeks

until unacceptable toxicity, disease progression or up to 24 months.

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.

Recommended Dosage for locally recurrent unresectable or metastatic Triple-Negative Breast Cancer (TNBC) in Combination with Chemotherapy

KEYTRUDA is administered as an intravenous infusion over 30 minutes.

The recommended dose of KEYTRUDA in adults is either:

- o 200 mg every 3 weeks or
- o 400 mg every 6 weeks

until disease progression, unacceptable toxicity or up to 24 months or 35 doses for 200 mg or 18 doses for 400 mg, whichever is longer, 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.

Recommended Dosage for TNBC – high-risk early-stage in Combination with Chemotherapy as neoadjuvant treatment, then as Monotherapy as adjuvant treatment after surgery

KEYTRUDA is administered as an intravenous infusion over 30 minutes.

The recommended dose of KEYTRUDA in adults is either:

- o 200 mg every 3 weeks or
- o 400 mg every 6 weeks

For the neoadjuvant and adjuvant treatment of early-stage TNBC, patients should be treated with neoadjuvant KEYTRUDA in combination with chemotherapy for 8 doses of 200 mg every 3 weeks or 4 doses of 400 mg every 6 weeks or until disease progression that precludes definitive surgery or unacceptable toxicity, followed by adjuvant treatment with KEYTRUDA as monotherapy for 9 doses of 200 mg every 3 weeks or 5 doses of 400 mg every 6 weeks or until disease recurrence or unacceptable toxicity. Patients who experience disease progression that precludes definitive surgery or unacceptable toxicity related to KEYTRUDA as neoadjuvant treatment in combination with chemotherapy should not receive KEYTRUDA monotherapy as adjuvant treatment.

When administering KEYTRUDA in combination with chemotherapy, administer KEYTRUDA prior to chemotherapy when given on the same day. Consult the description of the study for the chemotherapy

regimen used (containing carboplatin and paclitaxel, followed by doxorubicin or epirubicin and cyclophosphamide; See <u>14 Clinical Trials</u>). Refer to the Product Monographs for the chemotherapy agents administered in combination with KEYTRUDA for recommended dosing information, as appropriate.

Recommended Dosage for Cervical Cancer (FIGO 2014 Stage III-IVA)

KEYTRUDA is administered as an intravenous infusion over 30 minutes.

The recommended dose of KEYTRUDA in adults is either:

- o 200 mg every 3 weeks or
- o 400 mg every 6 weeks

until disease progression or unacceptable toxicity or up to 24 months. (See 14 Clinical Trials).

Administer KEYTRUDA prior to CRT when given on the same day. Refer to the Product Monographs for the chemotherapy administered in combination with KEYTRUDA for further information, as appropriate.

Recommended Dosage for Cervical Cancer (persistent, recurrent or metastatic)

KEYTRUDA is administered as an intravenous infusion over 30 minutes.

The recommended dose of KEYTRUDA in adults is either:

- o 200 mg every 3 weeks or
- o 400 mg every 6 weeks

until disease progression, unacceptable toxicity or up to 24 months or 35 doses for 200 mg or 18 doses for 400 mg, whichever is longer, in patients without disease progression.

Administer KEYTRUDA prior to chemotherapy with or without bevacizumab when given on the same day (See <u>14 Clinical Trials</u>). Refer to the Product Monographs for the chemotherapy or other agents administered in combination with KEYTRUDA for further information, as appropriate.

Recommended Dosage for Biliary Tract Carcinoma

KEYTRUDA is administered as an intravenous infusion over 30 minutes.

The recommended dose of KEYTRUDA in adults is either:

- o 200 mg every 3 weeks or
- 400 mg every 6 weeks

until disease progression, unacceptable toxicity or up to 24 months or 35 doses for 200 mg or 18 doses for 400 mg, whichever is longer, in patients without disease progression.

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.

For all indications:

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		
B	Moderate (Grade 2)	Withhold until adverse reactions recover to Grade 0-1*		
Pneumonitis	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*		
Colitis	Life-threatening (Grade 4) or recurrent severe (Grade 3)	Permanently discontinue		
Nonhvitis	Moderate (Grade 2) with creatinine > 1.5 to ≤ 3 times upper limit of normal (ULN)	Withhold until adverse reactions recover to Grade 0-1*		
Nephritis	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	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*		
combination therapy with axitinib, see	Grade ≥ 3 with AST or ALT > 5 times ULN or total bilirubin > 3 times ULN	Permanently discontinue		

Immune-related adverse reactions	Severity	Treatment modification		
dosing guidelines	For patients with liver metastasis who			
following this table.	begin treatment with moderate			
	(Grade 2) elevation of AST or ALT, if AST	Permanently discontinue		
	or ALT increases ≥ 50% relative to			
	baseline and lasts ≥ 1 week			
Skin reactions or	Severe skin reactions (Grade 3) or	Withhold until adverse reactions		
Stevens-Johnson	suspected SJS or TEN	recover to Grade 0-1*		
syndrome (SJS) or toxic epidermal necrolysis (TEN)	Severe skin reactions (Grade 4) or confirmed SJS or TEN	Permanently discontinue		
	Based on severity and type of reaction	Withhold until adverse reactions		
	(Grade 2 or 3)	recover to Grade 0-1*		
Other immune- related adverse reactions	Severe or life-threatening (Grade 3 or 4) myocarditis, encephalitis, or Guillain- Barré syndrome	Permanently discontinue		
	Life-threatening (Grade 4) or recurrent severe (Grade 3)	Permanently discontinue		
Infusion-related reactions Severe or life-threatening (Grade 3 or 4)		Permanently discontinue		

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

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 \geq 60 mL/min/1.73 m²) or moderate (eGFR < 60 and \geq 30 mL/min/1.73 m²) renal impairment. KEYTRUDA has not been studied in patients with severe (eGFR < 30 and \geq 15 mL/min/1.73 m²) renal impairment.

<u>Hepatic Impairment:</u> No dose adjustment is needed for patients with mild or moderate hepatic impairment. KEYTRUDA has been only studied in a limited number of patients with moderate hepatic impairment (N=20). KEYTRUDA has not been studied in patients with severe hepatic impairment (See <u>10 Clinical Pharmacology</u>).

^{*} 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.

Eastern Cooperative Oncology Group (ECOG) performance status score ≥ 2 : Patients with ECOG performance status score ≥ 2 were excluded from the clinical trials (See <u>14 Clinical Trials</u>).

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, interrupt one or both drugs, dose reduce, or discontinue lenvatinib as appropriate (see Table 1). 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 (see Table 1. No dose reductions are recommended for KEYTRUDA . Withhold, dose reduce, or discontinue axitinib in accordance with the instructions in the axitinib Product Monograph.

Recommended Dose Modification for Chemotherapies used in combination with KEYTRUDA for TNBC: See manufacturer's Product Monograph for the co-administered chemotherapy (ies) for toxicity management, dose adjustment guidelines for special populations, and contraindications. When administering KEYTRUDA in combination with chemotherapy for the treatment of TNBC, interrupt one or both as appropriate. No dose reductions are recommended for KEYTRUDA. Withhold, dose reduce, or discontinue chemotherapies in accordance with the instructions in the respective Product Monograph(s).

Recommended Dose Modification for Enfortumab Vedotin used in combination with KEYTRUDA for mUC:

See manufacturer's Product Monograph for the coadministered product, enfortumab vedotin for toxicity management, dose adjustment guidelines for special populations, and contraindications. When administering KEYTRUDA in combination with enfortumab vedotin, interrupt one or both drugs withhold or discontinue KEYTRUDA as appropriate (see Table 1). No dose reductions are recommended for KEYTRUDA. Withhold, dose reduce, or discontinue enfortumab vedotin in accordance with the instructions in the enfortumab vedotin Product Monograph.

4.3 Reconstitution

Preparation for Intravenous Infusion

- Protect from light. Do not freeze. Do not shake.
- Equilibrate the vial of KEYTRUDA to room temperature.
- Prior to dilution, the vial of liquid can be out of refrigeration (temperatures at or below 25°C) for up to 24 hours.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. KEYTRUDA is a clear to slightly opalescent, colourless to slightly yellow solution. Discard the vial if visible particles are observed. Dilute KEYTRUDA solution prior to intravenous administration.

• Withdraw the required volume up to 4 mL (100 mg) 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 (See 11 Storage, Stability And Disposal).

Storage of Diluted Solution

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

4.4 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 μ m 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.

4.5 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. Overdose

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

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

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6. Dosage Forms, Strengths, Composition and Packaging

To help ensure the traceability of biologic products, health professionals should record both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 2: Dosage Forms, Strengths, Composition.

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

Description

KEYTRUDA is supplied as

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).

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 14 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 or moderate hepatic impairment. KEYTRUDA has been only studied in a limited number of patients with moderate hepatic impairment (N=20). KEYTRUDA has not been studied in patients with severe hepatic impairment (See <u>4 Dosage And Administration</u>).

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 $\frac{4}{2}$ Dosage And Administration and $\frac{8}{2}$ 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 4 Dosage And Administration and 8 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 <u>4 Dosage And Administration</u> and <u>8 Adverse Reactions</u>).

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 4 Dosage And Administration and 8 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 4 Dosage And

Administration and 8 Adverse Reactions).

<u>Immune mediated endocrinopathies</u>

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 4 Dosage And Administration and 8 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 <u>4 Dosage And Administration</u> and <u>8 Adverse Reactions</u>).

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 <u>8 Adverse Reactions</u>). 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 <u>4 Dosage And Administration</u> and Other 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 <u>4 Dosage And Administration</u>).

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 4 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; myelitis; hypoparathyroidism, gastritis and pericarditis.

The following were reported in other clinical studies with KEYTRUDA or in post-marketing use: myocarditis; sclerosing cholangitis; aplastic anemia; and exocrine pancreatic insufficiency.

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 8 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 4 Dosage And Administration and the Product Monograph for axitinib).

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

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.

<u>Complications of allogeneic Hematopoietic Stem Cell Transplant (HSCT)</u>

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 <u>8 Adverse Reactions</u>).

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 4 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 <u>4 Dosage And Administration</u> and <u>7 Warnings And Precautions</u>).

Renal

Renal Impairment

No dose adjustment is needed for patients with mild (estimated Glomerular Filtration Rate (eGFR) <90 and \geq 60 mL/min/1.73 m²) or moderate (eGFR < 60 and \geq 30 mL/min/1.73 m²) renal impairment. KEYTRUDA has not been studied in patients with severe (eGFR < 30 and \geq 15 mL/min/1.73 m²) renal impairment (See 4 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 <u>7.1 Special Populations, Pregnant Women</u>).

7.1 Special Populations

7.1.1 Pregnancy

There are no data on the use of pembrolizumab in pregnant women. Animal reproduction studies have not been conducted with pembrolizumab; however, blockade of 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 16 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: For women of childbearing potential, pregnancy status should be established prior to initiating KEYTRUDA. Women should be advised to use highly effective contraception and take active measures to avoid pregnancy while undergoing KEYTRUDA treatment and for at least 4 months after the last dose (See <u>16 Non-Clinical Toxicology</u>).

7.1.2 Breastfeeding

Nursing Women: 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. Because of the potential for serious adverse reactions in breastfed infants from KEYTRUDA, advise women not to breastfeed during treatment and for at least 4 months after the last dose.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): There is limited experience with KEYTRUDA in pediatric patients compared with 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 trial Phase I/II that enrolled pediatric patients with advanced tumours, immune-mediated adverse reactions were observed. The observed immune-mediated adverse reactions included thyroid disorders (hypothyroidism, hyperthyroidism, and thyroiditis), pneumonitis, colitis, adrenal insufficiency, myelitis, and severe skin reactions. Infusion reactions were also observed (See 8 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 7 Warnings And Precautions and 4 Dosage And Administration sections.

Efficacy for pediatric patients with Stage IIB, IIC or III melanoma (aged 12 years and older), cHL, PMBCL, and MSI-H or dMMR solid tumours is extrapolated from results in the respective adult populations and supported by data from KEYNOTE-051, a Phase I/II study (See 14 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) for pembrolizumab monotherapy. No overall differences in efficacy were reported between elderly patients (65 years and over) and younger patients (less than 65 years) for pembrolizumab combination therapy. No dose adjustment is necessary in this population. Limited safety and efficacy information is available for KEYTRUDA in cHL patients \geq 65 years of age (n=46).

In patients with RCC receiving KEYTRUDA in combination with lenvatinib, the adverse event incidences in patients ≥65 years of age compared to patients <65 years of age are presented in <u>8.2 Clinical Trial</u> Adverse Reactions.

In patients with HER2-negative gastric/GEJ cancer receiving KEYTRUDA in combination with chemotherapy, the adverse event incidences in patients ≥65 years of age compared to patients <65 years of age are presented in 8.2 Clinical Trial Adverse Reactions.

Of the 564 patients treated with KEYTRUDA in combination with enfortumab vedotin in clinical trials, 391 (69%) were 65 years or older and 144 (26%) were 75 years or older. In the KEYTRUDA in combination with enfortumab vedotin arm of the KEYNOTE-A39 study, serious adverse events were reported in 37% of patients < 65 (n=144), 57% of patients \geq 65 and < 75 (n=194), and 56% of patients \geq 75 (n=102). Grade \geq 3 events were reported in 61%, 78% and 79% of patients < 65, \geq 65 and < 75, and \geq 75, respectively. Adverse events leading to discontinuation of KEYTRUDA were reported in 24%, 28% and 28% of patients < 65, \geq 65 and < 75 and \geq 75, respectively.

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 <u>7 Warnings And Precautions</u>). 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

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect frequencies observed in clinical practice and

should not be compared to frequencies reported in clinical trials of another drug.

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.

	KEYTRUDA 2 mg/kg every 3 weeks or 10 mg/kg every 2 or 3 weeks					
Adverse Reaction	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 patients with resected RCC treated with KEYTRUDA as adjuvant monotherapy (n=488) the incidence of hypothyroidism was 21% (all Grades) with 0.2% Grade 3 and the incidence of hyperthyroidism was 12% (all Grades) with 0.2% Grade 3.

In individual studies of patients with NSCLC treated with KEYTRUDA as monotherapy (total n=2602), the incidence of pneumonitis (all Grades) ranged from 3.8% to 8.3%. In cHL patients treated with KEYTRUDA as monotherapy, the incidence of pneumonitis (all Grades) ranged from 5.2% to 10.8% for cHL patients in KEYNOTE-087 (n=210) and KEYNOTE-204 (n=148), respectively. 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. Of the updated results in 342 patients, the incidence of hypothyroidism was 55.3% (all Grades) with 0.6% of cases Grade 3 and 0.3% Grade 4. Hyperthyroidism was reported in 10.8% with 0.9% Grade 3. Hepatitis was reported in 1.8%, all of which were Grade 3. Pancreatitis was reported in 0.9% with 0.3% Grade 3. Severe skin reactions were reported in 3.5% with 2.9% Grade 3.

In patients with high-risk early-stage TNBC treated with KEYTRUDA in combination with chemotherapy as neoadjuvant treatment, then with KEYTRUDA as monotherapy as adjuvant treatment after surgery (n=783), the incidence of adrenal insufficiency was 2.6%, and the incidence of hypophysitis was 1.9%.

In patients with advanced or metastatic RCC treated with KEYTRUDA in combination with lenvatinib (n=352), the incidence of hypothyroidism was 47% (all Grades), with 1.4% Grade 3, and no Grades 4 or 5. The incidence of pneumonitis (all Grades) was 5.4%, with 1.4% Grade 3, 0.3% Grade 4 and 0.3% Grade 5. The incidence of pancreatitis was 2.8% (all Grades) with 1.4% Grade 3 and 0.3% Grade 4. The incidence of hepatitis was 2.0% (all Grades) with 0.9% Grade 3, 0.3% Grade 4 and 0.3% Grade 5. The incidence of nephritis was 1.7% (all Grades) of patients with 0.9% Grade 3 and 0.3% Grade 5.

In patients with locally advanced unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma treated with KEYTRUDA in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy (n=350), the incidence of hypothyroidism was 10.6% (all Grades), with 0.3% Grade 3. The incidence of pneumonitis was 6.0% (all Grades), with 0.9% Grade 3, 0.3% Grade 4 and 0.6% Grade 5. The incidence of colitis was 4.9% (all grades), with 2.6% 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%).

<u>Hyperthyroidism:</u>

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 <u>7 Warnings And Precautions</u> 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 (\geq 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 (\geq 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 (\geq 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.

	KEYTRUDA 10 mg/kg every 2 or 3 weeks			Ipilimumab 3 mg/kg every 3 weeks		
Adverse Reaction	n=555			n=256		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Blood and lymphatic system d	isorders					
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 adminis	tration site co	nditions				
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

Adverse Reaction	5 Grade 4 (%) n (%)		n=256	veeks			
Any Grade n (%) n (%)	le 3 Grade 4 %) n (%)	,		3 mg/kg every 3 weeks n=256			
Blood bilirubin increased 7 (1.3) 0 Blood creatinine increased 7 (1.3) 0 Blood thyroid stimulating hormone decreased 6 (1.1) 0 Weight decreased 6 (1.1) 0 Metabolism and nutrition disorders 0 Decreased appetite 35 (6.3) 0 Hypocalcemia 8 (1.4) 0 Musculoskeletal and connective tissue disorders 4 Arthralgia 58 (10.5) 1 (0 Arthritis 6 (1.1) 0 Back pain 12 (2.2) 0 Muscle spasms 7 (1.3) 0 Myalgia 25 (4.5) 1 (0 Pain in extremity 7 (1.3) 2 (0 Nervous system disorders 9 (1.6) 0 Dysgeusia 15 (2.7) 0 Headache 15 (2.7) 0 Psychiatric disorders 15 (2.7) 0 Insomnia 7 (1.3) 0	0	n (%)	Grade 3	Grade 4			
Blood creatinine increased 7 (1.3) 0 Blood thyroid stimulating hormone decreased 6 (1.1) 0 Weight decreased 6 (1.1) 0 Metabolism and nutrition disorders Decreased appetite 35 (6.3) 0 Hypocalcemia 8 (1.4) 0 Musculoskeletal and connective tissue disorders Arthralgia 58 (10.5) 1 (0 Arthritis 6 (1.1) 0 Back pain 12 (2.2) 0 Muscle spasms 7 (1.3) 0 Myalgia 25 (4.5) 1 (0 Pain in extremity 7 (1.3) 2 (0 Nervous system disorders Dizziness 9 (1.6) 0 Dysgeusia 15 (2.7) 0 Headache 15 (2.7) 0 Psychiatric disorders Insomnia 7 (1.3) 0		(, , ,	n (%)	n (%)			
Blood thyroid stimulating hormone decreased 6 (1.1) 0		0	0	0			
hormone decreased 6 (1.1) 0 Weight decreased 6 (1.1) 0 Metabolism and nutrition disorders Decreased appetite 35 (6.3) 0 Hypocalcemia 8 (1.4) 0 Musculoskeletal and connective tissue disorders Arthralgia 58 (10.5) 1 (0 Arthritis 6 (1.1) 0 Back pain 12 (2.2) 0 Muscle spasms 7 (1.3) 0 Myalgia 25 (4.5) 1 (0 Pain in extremity 7 (1.3) 2 (0 Nervous system disorders 9 (1.6) 0 Dysgeusia 15 (2.7) 0 Headache 15 (2.7) 0 Psychiatric disorders 1 (1.3) 0	0	1 (0.4)	0	0			
Meight decreased 6 (1.1) 0 Metabolism and nutrition disorders Decreased appetite 35 (6.3) 0 Hypocalcemia 8 (1.4) 0 Musculoskeletal and connective tissue disorders Arthralgia 58 (10.5) 1 (0 Arthritis 6 (1.1) 0 Back pain 12 (2.2) 0 Muscle spasms 7 (1.3) 0 Myalgia 25 (4.5) 1 (0 Pain in extremity 7 (1.3) 2 (0 Nervous system disorders Dizziness 9 (1.6) 0 Dysgeusia 15 (2.7) 0 Headache 15 (2.7) 0 Psychiatric disorders Insomnia 7 (1.3) 0	0	2 (0.8)	1 (0.4)	0			
Metabolism and nutrition disorders Decreased appetite 35 (6.3) 0 Hypocalcemia 8 (1.4) 0 Musculoskeletal and connective tissue disorders 4 Arthralgia 58 (10.5) 1 (0 Arthritis 6 (1.1) 0 Back pain 12 (2.2) 0 Muscle spasms 7 (1.3) 0 Myalgia 25 (4.5) 1 (0 Pain in extremity 7 (1.3) 2 (0 Nervous system disorders Dizziness 9 (1.6) 0 Dysgeusia 15 (2.7) 0 Headache 15 (2.7) 0 Psychiatric disorders Insomnia 7 (1.3) 0		2 (0.8)	1 (0.4)				
Decreased appetite 35 (6.3) 0 Hypocalcemia 8 (1.4) 0 Musculoskeletal and connective tissue disorders Arthralgia 58 (10.5) 1 (0 Arthritis 6 (1.1) 0 Back pain 12 (2.2) 0 Muscle spasms 7 (1.3) 0 Myalgia 25 (4.5) 1 (0 Pain in extremity 7 (1.3) 2 (0 Nervous system disorders 9 (1.6) 0 Dysgeusia 15 (2.7) 0 Headache 15 (2.7) 0 Psychiatric disorders 1 (1.3) 0	0	5 (2.0)	1 (0.4)	0			
Hypocalcemia 8 (1.4) 0 Musculoskeletal and connective tissue disorders Arthralgia 58 (10.5) 1 (0 Arthritis 6 (1.1) 0 Back pain 12 (2.2) 0 Muscle spasms 7 (1.3) 0 Myalgia 25 (4.5) 1 (0 Pain in extremity 7 (1.3) 2 (0 Nervous system disorders Dizziness 9 (1.6) 0 Dysgeusia 15 (2.7) 0 Headache 15 (2.7) 0 Psychiatric disorders Insomnia 7 (1.3) 0							
Musculoskeletal and connective tissue disorders Arthralgia 58 (10.5) 1 (0 Arthritis 6 (1.1) 0 Back pain 12 (2.2) 0 Muscle spasms 7 (1.3) 0 Myalgia 25 (4.5) 1 (0 Pain in extremity 7 (1.3) 2 (0 Nervous system disorders Dizziness 9 (1.6) 0 Dysgeusia 15 (2.7) 0 Headache 15 (2.7) 0 Psychiatric disorders Insomnia 7 (1.3) 0	0	20 (7.8)	0	0			
Arthralgia 58 (10.5) 1 (0.5) Arthritis 6 (1.1) 0.0 Back pain 12 (2.2) 0.0 Muscle spasms 7 (1.3) 0.0 Myalgia 25 (4.5) 1 (0.0 Pain in extremity 7 (1.3) 2 (0.0 Nervous system disorders Dizziness 9 (1.6) 0.0 Dysgeusia 15 (2.7) 0.0 Headache 15 (2.7) 0.0 Psychiatric disorders Insomnia 7 (1.3) 0.0	0	0	0	0			
Arthritis 6 (1.1) 0 Back pain 12 (2.2) 0 Muscle spasms 7 (1.3) 0 Myalgia 25 (4.5) 1 (0 Pain in extremity 7 (1.3) 2 (0 Nervous system disorders Dizziness 9 (1.6) 0 Dysgeusia 15 (2.7) 0 Headache 15 (2.7) 0 Psychiatric disorders Insomnia 7 (1.3) 0							
Back pain 12 (2.2) 0 Muscle spasms 7 (1.3) 0 Myalgia 25 (4.5) 1 (0 Pain in extremity 7 (1.3) 2 (0 Nervous system disorders Dizziness 9 (1.6) 0 Dysgeusia 15 (2.7) 0 Headache 15 (2.7) 0 Psychiatric disorders Insomnia 7 (1.3) 0	.2) 0	13 (5.1)	2 (0.8)	0			
Muscle spasms 7 (1.3) 0 Myalgia 25 (4.5) 1 (0 Pain in extremity 7 (1.3) 2 (0 Nervous system disorders Dizziness 9 (1.6) 0 Dysgeusia 15 (2.7) 0 Headache 15 (2.7) 0 Psychiatric disorders Insomnia 7 (1.3) 0	0	0	0	0			
Myalgia 25 (4.5) 1 (0.7) Pain in extremity 7 (1.3) 2 (0.7) Nervous system disorders Dizziness 9 (1.6) 0.7 Dysgeusia 15 (2.7) 0.7 Headache 15 (2.7) 0.7 Psychiatric disorders Insomnia 7 (1.3) 0.7	0	0	0	0			
Pain in extremity 7 (1.3) 2 (0) Nervous system disorders 9 (1.6) 0 Dizziness 9 (1.6) 0 Dysgeusia 15 (2.7) 0 Headache 15 (2.7) 0 Psychiatric disorders Insomnia 7 (1.3) 0	0	1 (0.4)	0	0			
Nervous system disorders Dizziness 9 (1.6) 0 Dysgeusia 15 (2.7) 0 Headache 15 (2.7) 0 Psychiatric disorders Insomnia 7 (1.3) 0	.2) 0	5 (2.0)	1 (0.4)	0			
Dizziness 9 (1.6) 0 Dysgeusia 15 (2.7) 0 Headache 15 (2.7) 0 Psychiatric disorders Insomnia 7 (1.3) 0	.4) 0	1 (0.4)	0	0			
Dysgeusia 15 (2.7) 0 Headache 15 (2.7) 0 Psychiatric disorders 1 7 (1.3) 0							
Dysgeusia 15 (2.7) 0 Headache 15 (2.7) 0 Psychiatric disorders Insomnia 7 (1.3) 0	0	2 (0.8)	0	0			
Headache 15 (2.7) 0 Psychiatric disorders Insomnia 7 (1.3) 0	0	3 (1.2)	0	0			
Insomnia 7 (1.3) 0	0	9 (3.5)	0	0			
Insomnia 7 (1.3) 0	<u>'</u>						
, ,	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	- 1	, ,					
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		O ,	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		37 (14.5)	1 (0.4)	1 (0.4)			
Rash maculo-papular 16 (2.9) 1 (0		7 (2.7)	1 (0.4)	0			
Rash pruritic 7 (1.3) 0		4 (1.6)	0	0			
Skin hypopigmentation 9 (1.6) 0		0	0	0			
Vitiligo 56 (10.1)		4 (1.6)	0	0			
Vascular disorders		1 ()					
Flushing 6 (1.1) 0	0	2 (0.8)	0	0			

Table 5: Treatment-Related Adverse Events (incidence ≥ 1%) KEYTRUDA Treatment Groups

Combined. APaT Population in KEYNOTE-002.

Combined, APaT Population		KEYTRUDA		Chemotherapy			
		g/kg every 3	weeks	,			
Adverse Reaction		n=357			n=171		
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	
Blood and lymphatic syste		(/-/	(/-/	(/-5/	(/-/	(/-/	
Anemia	12 (3.4)	1 (0.3)	0	35 (20.5)	9 (5.3)	0	
Ear and labyrinth disorder		, ,		, ,	. , ,		
Vertigo	5 (1.4)	0	0	2 (1.2)	0	0	
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 adn	ninistration sit	e 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 conn				, ,			
Arthralgia	25 (7.0)	2 (0.6)	0	9 (5.3)	1 (0.6)	0	
	•	•		•	•	•	

		KEYTRUDA	aaka	Chemotherapy						
Adverse Reaction	2 Or 10 M	g/kg every 3 n=357	weeks	n=171						
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)				
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 I	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 tiss	sue 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				
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				

Adjuvant Melanoma

Among the 969 patients with resected Stage IIB or IIC melanoma enrolled in KEYNOTE-716 treated with KEYTRUDA, the median duration of exposure to KEYTRUDA was 11.1 months. For patient with resected Stage IIB or IIC melanoma, the adverse reactions that occurred with KEYTRUDA monotherapy were generally similar to those occurring in the 1019 patients with resected Stage III melanoma enrolled in KEYNOTE-054 and the 2799 patients with unresectable or metastatic melanoma or NSCLC.

Table 6 summarizes the treatment-related adverse events that occurred in at least 1% of patients with resected melanoma treated with KEYTRUDA in KEYNOTE-716. The most common treatment-related adverse events (reported in at least 15% of patients) were pruritis, fatigue, diarrhea, and rash. KEYTRUDA was discontinued for treatment-related adverse events in 15% of patients in KEYNOTE-716. The most common treatment-related adverse event leading to study drug discontinuation were: colitis (n=5, 1.0%) and autoimmune hepatitis (n=5, 1.0%). The median time to discontinuation for treatment-related adverse events was 4.9 months. There were no deaths due to treatment-related adverse events reported in the KEYTRUDA arm or in the placebo group.

Table 7 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 6: Treatment-Related Adverse Events (incidence ≥ 1%) in patients with completely resected Stage IIB or IIC melanoma treated with KEYTRUDA APaT Population in KEYNOTE-716.

		(EYTRUDA	_		Placebo		
	200 mg	g every 3 we	eeks				
Adverse Reaction		n=483		n=486			
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Blood and lymphatic syste	em disorders						
Anemia	6 (1.2)	0	0	2 (0.4)	0	0	
Ear and labyrinth disorder	's						
Vertigo	3 (0.6)	0	0	6 (1.2)	0	0	
Endocrine disorders							
Adrenal insufficiency	11 (2.3)	4 (0.8)	0	0	0	0	
Autoimmune thyroiditis	5 (1.0)	0	0	1 (0.2)	0	0	
Hyperthyroidism	48 (9.9)	1 (0.2)	0	3 (0.6)	0	0	
Hypophysitis	5 (1.0)	1 (0.2)	0	0	0	0	
Hypopituitarism	5 (1.0)	2 (0.4)	0	0	0	0	
Hypothyroidism	70 (14.5)	0	0	12 (2.5)	0	0	
Eye disorders							
Dry eye	6 (1.2)	0	0	5 (1.0)	0	0	
Gastrointestinal disorders	1						
Abdominal pain	11 (2.3)	0	0	12 (2.5)	0	0	
Abdominal pain upper	8 (1.7)	0	0	8 (1.6)	0	0	
Colitis	12 (2.5)	5 (1.0)	0	3 (0.6)	0	0	
Constipation	9 (1.9)	0	0	11 (2.3)	0	0	
Diarrhea	85 (17.6)	5 (1.0)	0	51 (10.5)	1 (0.2)	0	
Dry mouth	22 (4.6)	0	0	8 (1.6)	0	0	
Nausea	38 (7.9)	0	0	31 (6.4)	0	0	
Stomatitis	10 (2.1)	0	0	3 (0.6)	0	0	
Vomiting	14 (2.9)	0	0	5 (1.0)	0	0	
General disorders and adr	ministration sit	te condition	S				
Asthenia	43 (8.9)	1 (0.2)	0	40 (8.2)	0	0	
Chills	7 (1.4)	0	0	2 (0.4)	0	0	
Edema peripheral	5 (1.0)	0	0	5 (1.0)	0	0	
Fatigue	98 (20.3)	1 (0.2)	0	87 (17.9)	0	0	
Influenza like illness	1 (0.2)	0	0	5 (1.0)	0	0	
Pain	5 (1.0)	0	0	0	0	0	

	ŀ	KEYTRUDA		Placebo			
	200 m	g every 3 w	eeks				
Adverse Reaction		n=483	T		n=486	1	
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Pyrexia	5 (1.0)	0	0	5 (1.0)	0	0	
Hepatobiliary disorders	7 (4 4)	C (4.0)		2 (2 1)	2 (2 4)	1 0	
Autoimmune hepatitis	7 (1.4)	6 (1.2)	0	2 (0.4)	2 (0.4)	0	
Investigations	T	ı	T	T		ı	
Alanine							
aminotransferase	34 (7.0)	4 (0.8)	0	18 (3.7)	1 (0.2)	0	
increased							
Amylase increased	10 (2.1)	2 (0.4)	1 (0.2)	8 (1.6)	0	1 (0.2)	
Aspartate							
aminotransferase	28 (5.8)	1 (0.2)	0	8 (1.6)	1 (0.2)	0	
increased							
Blood alkaline	5 (1.0)	1 (0.2)	0	3 (0.6)	0	0	
phosphatase increased			_		_	_	
Blood bilirubin increased	1 (0.2)	0	0	6 (1.2)	0	0	
Blood creatine	- ()	2 (2 1)	. (5.5)	- ()	. ()	_	
phosphokinase	7 (1.4)	2 (0.4)	1 (0.2)	3 (0.6)	1 (0.2)	0	
increased							
Blood creatinine	9 (1.9)	0	0	1 (0.2)	0	0	
increased	` ,			, ,			
Blood thyroid	5 (4.0)			2 (2 1)	•		
stimulating hormone	5 (1.0)	0	0	2 (0.4)	0	0	
decreased							
Blood thyroid	- (4 A)			0 (4.0)			
stimulating hormone	7 (1.4)	0	0	9 (1.9)	0	0	
increased	44 (2.0)		4 (0.0)	44 (2.2)	C (4.2)	2 (0 4)	
Lipase increased	14 (2.9)	0	4 (0.8)	11 (2.3)	6 (1.2)	2 (0.4)	
Metabolism and nutrition		4 (0.2)		4 (0.0)			
Decreased appetite	16 (3.3)	1 (0.2)	0	4 (0.8)	0	0	
Hyperglycemia	4 (0.8)	0	0	5 (1.0)	0	0	
Hypophosphatemia	3 (0.6)	1 (0.2)	0	5 (1.0)	2 (0.4)	0	
Musculoskeletal and conr				25 (5.0)		T .	
Arthralgia	69 (14.3)	1 (0.2)	0	35 (7.2)	0	0	
Arthritis	6 (1.2)	1 (0.2)	0	2 (0.4)	0	0	
Back pain	6 (1.2)	0	0	0	0	0	
Myalgia	27 (5.6)	2 (0.4)	0	14 (2.9)	0	0	
Nervous system disorders				6 (4.6)			
Dizziness	14 (2.9)	0	0	6 (1.2)	0	0	
Headache	19 (3.9)	0	0	13 (2.7)	0	0	
Paraesthesia	9 (1.9)	0	0	7 (1.4)	0	0	
Psychiatric disorders	2 (5 5)	1 6		5 (c. 0)		T 6	
Insomnia	3 (0.6)	0	0	5 (1.0)	0	0	

	KEYTRUDA 200 mg every 3 weeks			Placebo					
Adverse Reaction		n=483			n=486				
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4			
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)			
Respiratory, thoracic and mediastinal disorders									
Cough	12 (2.5)	0	0	8 (1.6)	0	0			
Dyspnea	6 (1.2)	0	0	2 (0.4)	0	0			
Pneumonitis	7 (1.4)	1 (0.2)	0	3 (0.6)	0	0			
Skin and subcutaneous tis	sue disorders								
Dermatitis	4 (0.8)	0	0	5 (1.0)	0	0			
Dermatitis acneiform	5 (1.0)	0	0	1 (0.2)	0	0			
Dry skin	7 (1.4)	0	0	14 (2.9)	0	0			
Eczema	7 (1.4)	0	0	2 (0.4)	0	0			
Erythema	7 (1.4)	0	0	4 (0.8)	0	0			
Pruritus	112 (23.2)	3 (0.6)	0	48 (9.9)	0	0			
Rash	75 (15.5)	7 (1.4)	0	29 (6.0)	1 (0.2)	0			
Rash maculo-papular	34 (7.0)	2 (0.4)	0	8 (1.6)	0	0			
Rash pruritic	6 (1.2)	2 (0.4)	0	3 (0.6)	0	0			
Vitiligo	4 (0.8)	0	0	7 (1.4)	0	0			
Vascular disorders									
Hypertension	7 (1.4)	2 (0.4)	0	1 (0.2)	0	0			

Table 7: Treatment-Related Adverse Events (incidence ≥ 1%) in patients with completely resected of Stage IIIA (>1 mm metastasis), IIIB and IIIC melanoma treated with KEYTRUDA APaT Population in KEYNOTE-054.

	k	(EYTRUDA		Placebo					
	200 mg	g every 3 w	eeks						
Adverse Reaction		n=509			n=502				
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4			
	n (%)	n (%)	n (%)	n (%)	n (%)	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									
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	s								
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			

		EYTRUDA	eeks	Placebo			
Adverse Reaction		n=509			n=502		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
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 adı	ministration sit	te condition	ıs				
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	26 (5.1)	3 (0.6)	0	16 (3.2)	1 (0.2)	0	
increased	, ,	, ,		, ,			
Aspartate							
aminotransferase	19 (3.7)	1 (0.2)	0	14 (2.8)	1 (0.2)	0	
increased							
Blood alkaline	6 (1.2)	0	0	2 (0.4)	0	0	
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	6 (1.2)	1 (0.2)	1 (0.2)	2 (0.4)	0	0	
increased							
Blood creatinine	6 (1.2)	0	0	1 (0.2)	0	0	
increased	0 (1.2)	U	U	1 (0.2)	0	U	
Blood thyroid							
stimulating hormone	7 (1.4)	0	0	1 (0.2)	0	0	
decreased							
Eosinophil count	5 (1.0)	0	0	0	0	0	
increased	3 (1.0)			<u> </u>			
Gamma-	2 (5 -2)	0 (5 3)		. (5 5)	1 (6.5)		
glutamyltransferase	9 (1.8)	2 (0.4)	0	4 (0.8)	1 (0.2)	0	
increased					1		

	K	(EYTRUDA			Placebo	
	200 mg	g every 3 w	eeks			
Adverse Reaction		n=509	T		n=502	T
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Lipase increased	7 (1.4)	3 (0.6)	1 (0.2)	3 (0.6)	3 (0.6)	0
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 conn	ective tissue d	lisorders				
Arthralgia	51 (10.0)	3 (0.6)	0	47 (9.4)	0	0
Arthritis	5 (1.0)	0	0	0	0	0
Musculoskeletal and conn	ective tissue d	lisorders				
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	1					
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 di	sorders				
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 tis	sue 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

NSCLC

Table 8 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 8: Treatment-Related Adverse Events (incidence ≥ 1%) in Patients Treated with KEYTRUDA, APaT Population in KEYNOTE-024.

	К	EYTRUDA		Chemotherapy			
	200 mg	g every 3 w	eeks				
Adverse Reaction		n=154			n=150		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4	
	n (%)	n (%)	n (%)	n (%)	n (%)	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	

	К	EYTRUDA		Che	Chemotherapy			
	200 mg	g every 3 w	eeks					
Adverse Reaction		n=154		n=150				
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4		
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)		
Vomiting	4 (2.6)	1 (0.6)	0	30 (20.0)	1(0.7)	0		
General disorders and administ	ration site cor	nditions				1		
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)	0	0	0	0		
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			0					
hormone increased	5 (3.2)	0	0	0	0	0		
Blood thyroid stimulating	4 (2.6)	0	0	0	0	0		
hormone decreased	4 (2.6)	0	0	0	0	0		
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 disor			1			1		
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		ers						
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		

		EYTRUDA		Chemotherapy			
A.L B	200 mg	every 3 w	eeks	450			
Adverse Reaction		n=154		n=150			
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
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 media	stinal disorde	rs					
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 di	sorders						
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	

Table 9 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 9: Treatment-Related Adverse Events (incidence ≥ 1%) in Patients Treated with KEYTRUDA, APaT Population in KEYNOTE-042.

	20	KEYTR 00 mg eve		s		Chemoth	erapy	
Ad B		n=6	36			n=61	5	
Adverse Reaction	Any	Grade	Grade	Grade	Any	Grade	Grade	Grade
	Grade	3	4	5	Grade	3	4	5
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Blood and lymphatic	system dis	orders						
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 disc	orders			•				
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 ar		ration site	condition	าร		, ,		
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 disord	lers							
Hepatic function	0 (4 3)	1 (0.3)	1 (0.2)	0	4 (0.7)	2 (0.2)	0	0
abnormal	8 (1.3)	1 (0.2)	1 (0.2)	0	4 (0.7)	2 (0.3)	0	0
Investigations	•	•	•				•	
Alanine								
aminotransferase	45 (7.1)	9 (1.4)	0	0	53 (8.6)	5 (0.8)	0	0
increased								
Aspartate								
aminotransferase	41 (6.4)	4 (0.6)	0	0	42 (6.8)	2 (0.3)	0	0
increased								
Blood alkaline								
phosphatase	17 (2.7)	2 (0.3)	0	0	17 (2.8)	2 (0.3)	0	0
increased								
Blood bilirubin	12 (1.9)	0	0	0	8 (1.3)	0	0	0
increased	12 (1.3)	U	U	U	0 (1.3)	U	U	U

	20	KEYTR 00 mg eve		s		Chemoth	erapy	
		n=6	•			n=61	.5	
Adverse Reaction	Any	Grade	Grade	Grade	Any	Grade	Grade	Grade
	Grade	3	4	5	Grade	3	4	5
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Blood thyroid								
stimulating	44 (4 7)	•	•	0	4 (0.2)	0		
hormone	11 (1.7)	0	0	0	1 (0.2)	0	0	0
decreased								
Blood thyroid								
stimulating	14 (2.2)	0	0	0	1 (0.2)	0	0	0
hormone increased								
Gamma-								
glutamyltransferase	8 (1.3)	2 (0.3)	0	0	4 (0.7)	1 (0.2)	0	0
increased								
Tri-iodothyronine	0 (4 4)	0	0	0	2 (0.5)	0	0	0
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 nuti	rition disor	ders						
Decreased appetite	40 (6.3)	5 (0.8)	0	0	109 (17.7)	9 (1.5)	0	0
Musculoskeletal and	connective	tissue dis	orders					
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 diso	rders							
Dysgeusia	7 (1.1)	0	0	0	20 (3.3)	0	0	0
Respiratory, thoracio	and media	stinal disc	orders					
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 subcutaneo	us tissue di	sorders						
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

Table 10 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.

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 in combination with pemetrexed and platinum chemotherapy.

Table 10: Treatment-Related Adverse Events (Incidence ≥ 1%) in Patients Treated with KEYTRUDA in Combination with Pemetrexed and Platinum Chemotherapy, APaT Population in KEYNOTE-189.

		KEYTRI	JDA	• •	•	Place	bo	
		and	-			and	=	
		Pemetr	exed			Pemetr	exed	
Adverse Reaction		and	=			and		
Adverse Reaction	Pla	tinum Che	motherapy	,	Pla		motherapy	,
		n=40	_	1		n=20		1
	Any Grade	Grade 3	Grade 4	Grade 5	Any Grade	Grade 3	Grade 4	Grade 5
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Blood and lymphatics	system disord		1	1	T	1	T	1
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 diso	rders							
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	51 (12.6)	0	0	0	14 (6.9)	0	0	0
increased	51 (12.0)	U	U	U	14 (6.9)	U	U	U
Vision blurred	5 (1.2)	0	0	0	1 (0.5)	0	0	0
Gastrointestinal disor	ders							
Abdominal pain	10 (2.5)	1 (0.2)	0	0	4 (2.0)	1 (0.5)	0	0
Abdominal pain upper	9 (2.2)	0	0	0	0	0	0	0

Adverse Reaction		KEYTRUDA and Pemetrexed and Platinum Chemotherapy n=405				Placebo and Pemetrexed and Platinum Chemotherapy n=202 Any Grade Grade 3 Grade 4 Gra			
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	
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	on site con	ditions					1	
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 infesta			l					1	
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		n=40	d exed d motherapy 05		Placebo and Pemetrexed and 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- glutamyltransferas e 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 nutri	tion disorders	3						
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 o			1	ı	T	I	1	
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 disord					E /2 E\			
Dizziness	10 (2.5)	0 4 (0.2)	0	0	5 (2.5)	0	0	0
Dysgeusia	37 (9.1)	1 (0.2)	0	0	14 (6.9)	0	0	0
Hypoasthesia	9 (2.2)	0	0	0	3 (1.5)	0	0	0
Hypoasthesia	5 (1.2)	U	U	U	U	U	U	0

Adverse Reaction		KEYTRU and Pemetro and tinum Chel n=40	l exed l motherapy 95			n=20	l exed l motherapy	Grade 5 n (%) 0 0 0 0 0 0 0 0 0 0 0 0 0	
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)		
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	
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 disc	orders								
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 mediastin	al disorder	s						
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 subcutaneou	s tissue disor	ders					•	•	
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	

Table 11 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.

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 in combination with carboplatin and paclitaxel or nab-paclitaxel.

Table 11: 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.

			1				
					Place	bo	
	and	t			and	i	
	Carbop	latin			Carbop	latin	
	and	t			and	ł	
Pacl	itaxel or Na	ab-Paclitaxo	el	Pac	litaxel or Na	ab-Paclitaxe	el
	n=27	78				30	
Any Grade	Grade 3	Grade 4	Grade 5	Any Grade	Grade 3	Grade 4	Grade 5
n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
system disord	ers						
123 (44.2)	38 (13.7)	0	0	117 (41.8)	43 (15.4)	0	0
14 (5.0)	12 (4.3)	2 (0.7)	0	10 (3.6)	8 (2.9)	2 (0.7)	0
23 (8.3)	8 (2.9)	4 (1.4)	0	19 (6.8)	12 (4.3)	0	0
5 (1.8)	1 (0.4)	1 (0.4)	0	4 (1.4)	2 (0.7)	0	0
97 (34.9)	35 (12.6)	24 (8.6)	0	86 (30.7)	40 (14.3)	23 (8.2)	0
81 (29.1)	12 (4.3)	6 (2.2)	0	58 (20.7)	12 (4.3)	4 (1.4)	0
17 (6.1)	1 (0.4)	0	0	2 (0.7)	0	0	0
16 (5.8)	0	0	0	3 (1.1)	0	0	0
ders							
4 (1.4)	0	0	0	3 (1.1)	0	0	0
4 (1 4)	0	0	0	2 (0.7)	0	0	0
4 (1.4)	U	U	U	2 (0.7)	U	U	U
6 (2.2)	4 (1.4)	2 (0.7)	0	3 (1.1)	2 (0.7)	0	0
31 (11.2)	1 (0.4)	0	0	25 (8.9)	0	0	0
61 (21.9)	8 (2.9)	0	0	47 (16.8)	4 (1.4)	0	0
4 (1.4)	0	0	0	1 (0.4)	0	0	0
2 (1 1)	0	0	0	1 (0.4)	0	0	0
3 (1.1)	U	U	U	1 (0.4)	U	U	0
85 (30.6)	2 (0.7)	0	0	71 (25.4)	3 (1.1)	0	0
3 (1.1)	0	0	0	0	0	0	0
	Any Grade n (%) system disorde 123 (44.2) 14 (5.0) 23 (8.3) 5 (1.8) 97 (34.9) 81 (29.1) 17 (6.1) 16 (5.8) ders 4 (1.4) 4 (1.4) 6 (2.2) 31 (11.2) 61 (21.9) 4 (1.4) 3 (1.1) 85 (30.6)	Any Grade n (%) system disorders 123 (44.2) 38 (13.7) 14 (5.0) 12 (4.3) 23 (8.3) 8 (2.9) 5 (1.8) 1 (0.4) 97 (34.9) 35 (12.6) 81 (29.1) 12 (4.3) 17 (6.1) 1 (0.4) 16 (5.8) 0 ders 4 (1.4) 0 4 (1.4) 0 6 (2.2) 4 (1.4) 31 (11.2) 1 (0.4) 61 (21.9) 8 (2.9) 4 (1.4) 0 3 (1.1) 0 85 (30.6) 2 (0.7)	n=278 Any Grade n (%) Grade 3 n (%) Grade 4 n (%) system disorders 38 (13.7) 0 123 (44.2) 38 (13.7) 2 (0.7) 23 (8.3) 8 (2.9) 4 (1.4) 5 (1.8) 1 (0.4) 1 (0.4) 97 (34.9) 35 (12.6) 24 (8.6) 81 (29.1) 12 (4.3) 6 (2.2) 17 (6.1) 1 (0.4) 0 16 (5.8) 0 0 ders 4 (1.4) 0 0 4 (1.4) 0 0 6 (2.2) 4 (1.4) 2 (0.7) 31 (11.2) 1 (0.4) 0 61 (21.9) 8 (2.9) 0 4 (1.4) 0 0 3 (1.1) 0 0 85 (30.6) 2 (0.7) 0	Any Grade Grade 3 Grade 4 Grade 5 n (%) n	and Carboplatin and Paclitaxel or Nab-Paclitaxel n=278 Any Grade n(%) n(%) n(%) n(%) n(%) n(%) n(%) Paclitaxel pack n(%) n(%) n(%) Any Grade n(%) n(%) n(%) n(%) n(%) Any Grade 5 n(%) n(%) n(%) n(%) n(%) n(%) n(%) n(%) System disorders 123 (44.2) 38 (13.7) 0 0 10 (3.6) 14 (5.0) 12 (4.3) 2 (0.7) 0 10 (3.6) 23 (8.3) 8 (2.9) 4 (1.4) 0 19 (6.8) 5 (12.6) 35 (12.6) 24 (8.6) 0 86 (30.7) 81 (29.1) 12 (4.3) 6 (2.2) 0 58 (20.7) 17 (6.1) 1 (0.4) 0 0 0 2 (0.7) 16 (5.8) 0 0 0 3 (1.1) ders 4 (1.4) 0 0 0 0 3 (1.1) 31 (11.2) 1 (0.4) 0 0 0 25 (8.9) 61 (21.9) 8 (2.9) 0 0 47 (16.8) 4 (1.4) 0 0 0 1 (0.4) 3 (1.1) 0 0 0 0 1 (0.4) 3 (1.1) 0 0 0 0 1 (0.4) 85 (30.6) 2 (0.7) 0 0 71 (25.4)	and Carboplatin and Paclitaxel or Nab-Paclitaxel or Nab-Paclitaxel n n/%) Grade 3 n (%) Grade 3 n (%) Grade 4 n (%) Any Grade n (%) Grade 3 n (%) Any Grade n (%) Grade 3 n (%) Grade 3 n (%) Any Grade n (%) Grade 3 n (%) Grade 3 n (%) Any Grade n (%) Grade 3 n (%) Grade 3 n (%) Any Grade n (%	and Carboplatin and Paclitaxel or Nab-Paclitaxel or Nab-Paclitaxel or (%) and Carboplatin and Paclitaxel or Nab-Paclitaxel or Nab-Paclitaxel or (%) Paclitaxel or Nab-Paclitaxel or (%) and Carboplatin and Carboplataxel or (%) and Carboplatin and Carboplataxel or (%) paclitaxel or Nab-Paclitaxel or (%) paclitaxel or Nab-Paclitaxel or (%) paclitaxel or (%) and Carboplatin and Carboplataxel or (%) paclitaxel or Nab-Paclitaxel or (%) paclitaxel

Adverse Reaction		n=2	d platin d ab-Paclitax 78		Placebo and Carboplatin and Paclitaxel or Nab-Paclitaxel n=280 5 Any Grade Grade 3 Grade 4 Gra			
	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 an			_		23 (0.3)	3 (1.1)		
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 disorde	ers							
Autoimmune hepatitis	5 (1.8)	4 (1.4)	1 (0.4)	0	0	0	0	0
Infections and infesta	ations							
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 co	mplication	S					
Infusion related reaction	4 (1.4)	2 (0.7)	1 (0.4)	0	3 (1.1)	0	1 (0.4)	0
Investigations	<u> </u>							
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	9 (3.2)	0	0	0	6 (2.1)	1 (0.4)	0	0

Adverse Reaction		n=2	d platin d ab-Paclitax 78	el	Placebo and Carboplatin and Paclitaxel or Nab-Paclitaxel n=280				
	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									
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	
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 nutr	ition disorders	1							
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 tiss	sue disorde	ers						
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 disor	ders								
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	

Adverse Reaction	Pacl Any Grade	KEYTR and Carbop and itaxel or Na n=27 Grade 3	d olatin d ab-Paclitaxo	el Grade 5	Pac Any Grade	Place and Carbop and litaxel or Na n=28 Grade 3	el Grade 5	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	Grade 4 n (%)	n (%)
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 disc	orders							
Acute kidney injury	5 (1.8)	1 (0.4)	0	0	4 (1.4)	2 (0.7)	0	1 (0.4)
Respiratory, thoracic	and mediastin	al disorder	S					
Dyspnea	4 (1.4)	0	0	0	5 (1.8)	0	0	0
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 subcutaneou	ıs tissue disor	ders						
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

Table 12 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 (\geq 1%) were fatigue (1.2%) and decreased appetite (1%).

Table 12: Treatment-Related Adverse Events (incidence ≥ 1%) KEYTRUDA Treatment Groups Combined. APaT Population in KEYNOTE-010.

Combined, APaT Po	pulation in K				r			
Adverse Reaction	2 or :	KEYTR 10 mg/kg e n=68	very 3 wee	eks	75	Docet mg/m² eve n=30	ery 3 week	s
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 disord	ers						
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 disor	ders							
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	on site con	ditions		<u> </u>		l .	
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 infesta	• •	(- /			(/	(/		
Pneumonia	10 (1.5)	4 (0.6)	0	2 (0.3)	5 (1.6)	2 (0.6)	2 (0.6)	0
Investigations	10 (1.5)	1 (0.0)	Ŭ	2 (0.5)	3 (1.0)	2 (0.0)	2 (0.0)	U
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
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	7 (1.0)	0	0	0	0	0	0	0

Adverse Reaction	2 or :	KEYTRI 10 mg/kg e n=68	very 3 wee	eks	75	Doceta mg/m² eve n=30	ery 3 week	s
Auverse Neaction	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
hormone increased								
Weight decreased	15 (2.2)	1 (0.1)	0	0	2 (0.6)	0	0	0
Metabolism and nutri	tion disorders	5						
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 o	connective tis	sue disorde	ers					
Arthralgia	32 (4.7)	2 (0.3)	0	0	18 (5.8)	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 disor								
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 a	and mediastin	al disorder	S					
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 subcutaneou	s tissue disor	ders				•		
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

Adjuvant Therapy for Resected NSCLC

Table 13 summarizes the treatment-related adverse events that occurred in at least 1% of patients with resected NSCLC treated with KEYTRUDA in KEYNOTE-091. The most common treatment-related adverse events (reported in at least 10 % of patients) were hypothyroidism, pruritus, diarrhea, and fatigue.

Serious treatment-related adverse events occurred in 12% of patients receiving KEYTRUDA; the most common (incidence \geq 1%) were pneumonitis (n = 12, 2.1%) and diarrhea (n = 6, 1%). Two fatal adverse reactions of myocarditis occurred.

KEYTRUDA was discontinued for treatment-related adverse events in 16.9 % of patients in KEYNOTE-091. The most common (≥1%) treatment-related adverse events leading to study drug discontinuation were pneumonitis (n=21, 3.6%) and diarrhea (n=7, 1.2%). The median time to discontinuation for treatment-related adverse events was 3.0 months.

Table 13: Treatment-Related Adverse Events (Incidence ≥ 1%) in Patients Treated with KEYTRUDA in APaT Population in KEYNOTE-091.

·	К	EYTRUDA			Placebo	
	200 mg	g every 3 we	eeks			
Adverse Reaction		n=580			n=581	
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Blood and lymphatic sys	stem disorders					
Anemia	12 (2.1)	2 (0.3)	0	2 (0.3)	0	0
Endocrine disorders						
Adrenal Insufficiency	9 (1.6)	4 (0.7)	0	0	0	0
Hyperthyroidism	54 (9.3)	1 (0.2)	0	15 (2.6)	0	0
Hypophysitis	6 (1.0)	3 (0.5)	0	0	0	0
Hypothyroidism	114 (19.7)	1 (0.2)	0	19 (3.3)	0	0
Gastrointestinal disorde	ers					
Colitis	13 (2.2)	3 (0.5)	0	2 (0.3)	1 (0.2)	0
Constipation	7 (1.2)	0	0	8 (1.4)	0	0
Diarrhea	74 (12.8)	6 (1.0)	0	47 (8.1)	1 (0.2)	0
Dry mouth	11 (1.9)	0	0	2 (0.3)	0	0
Nausea	29 (5.0)	1 (0.2)	0	14 (2.4)	0	0
Stomatitis	13 (2.2)	0	0	11 (1.9)	0	0
Vomiting	9 (1.6)	0	0	6 (1.0)	0	0
General disorders and a	dministration	site conditio	ons			
Asthenia	26 (4.5)	2 (0.3)	0	18 (3.1)	0	0
Fatigue	61 (10.5)	1 (0.2)	0	53 (9.1)	3 (0.5)	0
Edema peripheral	6 (1.0)	1 (0.2)	0	5 (0.9)	0	0
Pyrexia	5 (0.9)	0	0	7 (1.2)	0	0
Infections and infestation	ons					
Rash pustular	6 (1.0)	1 (0.2)	0	2 (0.3)	0	0
Investigations						

	K	(EYTRUDA			Placebo	
	200 m	g every 3 w	eeks			
Adverse Reaction		n=580			n=581	
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Alanine						
aminotransferase	33 (5.7)	4 (0.7)	0	24 (4.1)	2 (0.3)	0
increased						
Aspartate		0 (0 0)		10 (0.1)	4 (0.0)	
aminotransferase	24 (4.1)	2 (0.3)	0	18 (3.1)	1 (0.2)	0
increased						
Blood creatinine	13 (2.2)	0	0	10 (1.7)	0	0
increased	, ,			, ,		
Blood thyroid	7 (1 2)	1 (0.2)	_	C (1 0)	0	
stimulating hormone increased	7 (1.2)	1 (0.2)	0	6 (1.0)	0	0
Gamma-						
glutamyltransferase	7 (1.2)	1 (0.2)	1 (0.2)	5 (0.9)	1 (0.2)	0
increased	/ (1.2)	1 (0.2)	1 (0.2)	3 (0.9)	1 (0.2)	
Weight increased	9 (1.6)	0	0	10 (1.7)	1 (0.2)	0
Metabolism and nutrition		0	0	10 (1.7)	1 (0.2)	
Decreased appetite	22 (3.8)	0	0	10 (1.7)	0	0
Musculoskeletal and co		_		10 (117)		
Arthralgia	52 (9.0)	3 (0.5)	0	29 (5.0)	1 (0.2)	0
Arthritis	10 (1.7)	3 (0.5)	0	4 (0.7)	0	0
Back pain	3 (0.5)	0	0	6 (1.0)	0	0
Myalgia	21 (3.6)	2 (0.3)	0	6 (1.0)	0	0
Pain in extremity	4 (0.7)	0	0	8 (1.4)	0	0
Nervous system disorde	ers	•	•		•	•
Headache	12 (2.1)	0	0	7 (1.2)	0	0
Paresthesia	4 (0.7)	0	0	11 (1.9)	0	0
Peripheral sensory	12 (2.2)	0	0	Q /1 /\	0	0
neuropathy	13 (2.2)	U	U	8 (1.4)	U	U
Respiratory, thoracic an	d mediastinal	disorders				
Cough	14 (2.4)	1 (0.2)	0	12 (2.1)	0	0
Dyspnea	18 (3.1)	2 (0.3)	0	8 (1.4)	0	0
Pneumonitis	33 (5.7)	5 (0.9)	2 (0.3)	12 (2.1)	3 (0.5)	0
Skin and subcutaneous	1		r	T	_	T
Dermatitis acneiform	12 (2.1)	1 (0.2)	0	6 (1.0)	0	0
Dry skin	18 (3.1)	0	0	14 (2.4)	0	0
Eczema	7 (1.2)	0	0	1 (0.2)	0	0
Pruritus	104 (17.9)	1 (0.2)	0	60 (10.3)	2 (0.3)	0
Psoriasis	6 (1.0)	2 (0.3)	0	2 (0.3)	0	0
Rash	35 (6.0)	2 (0.3)	0	17 (2.9)	0	0
Rash maculo-papular	38 (6.6)	3 (0.5)	0	13 (2.2)	0	0

Neoadjuvant and Adjuvant Treatment of Resectable NSCLC

Table 14 summarizes the treatment-related adverse events that occurred in at least 1% of patients with resectable NSCLC treated with KEYTRUDA in combination with neoadjuvant platinum-containing chemotherapy followed by surgery and continued as monotherapy adjuvant treatment with KEYTRUDA , in KEYNOTE-671 (See 14 Clinical Trials). The median duration of exposure was 10.9 months (range: 1 day to 18.6 months) in the KEYTRUDA in combination with chemotherapy arm and 10.3 months (range: 1 day to 19.6 months) in the chemotherapy arm.

The most common treatment-related adverse events for patients treated with KEYTRUDA in KEYNOTE-671 (reported in at least 20% of patients) were nausea, neutrophil count decreased, anemia, white blood cell count decreased, fatigue, constipation, and decreased appetite. The most common Grade 3-5 treatment-related adverse events for patients treated with KEYTRUDA in KEYNOTE-671 (reported in at least 5% of patients) were neutrophil count decreased (20.7%), anemia (7.3%), white blood cell count decreased (5.3%), and platelet count decreased (5.1%).

Serious treatment-related adverse events occurred in 17.7% of patients treated with KEYTRUDA in KEYNOTE-671; the most common (incidence ≥ 1%) were anemia, aspartate aminotransferase increase, neutrophil count decrease, pneumonia, alanine aminotransferase increase, immune-mediated lung disease, nausea, and pneumonitis. Fatal treatment-related adverse events occurred in 1.0% of patients receiving KEYTRUDA in KEYNOTE-671 including 1 case each of atrial fibrillation, immune-mediated lung disease, pneumonia, and sudden cardiac death.

KEYTRUDA was discontinued for treatment-related adverse events in 13.9% of patients. The most common treatment-related adverse events resulting in discontinuation of KEYTRUDA (\geq 1%) were diarrhea (1.0%), and pneumonitis (1.0%). The median time to discontinuation for treatment-related adverse events was 6.1 months.

Neoadjuvant Treatment Phase

A total of 396 patients received at least 1 dose of KEYTRUDA in combination with platinum-containing chemotherapy as neoadjuvant treatment and 399 patients received at least 1 dose of placebo in combination with platinum-containing chemotherapy as neoadjuvant treatment.

Serious treatment-related adverse events occurred in 14.1% of patients who received KEYTRUDA in combination with platinum-containing chemotherapy as neoadjuvant treatment; the most frequent (≥ 1%) serious adverse reactions were anemia, neutrophil count decrease, aspartate aminotransferase increase, pneumonia, and nausea.

Permanent discontinuation of any study drug due to a treatment-related adverse event occurred in 12.4% of patients who received KEYTRUDA in combination with platinum-containing chemotherapy as neoadjuvant treatment; the most frequent (≥1%) adverse reactions that led to permanent discontinuation of any study drug were neutrophil count decrease and anemia.

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

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

Of the 325 KEYTRUDA -treated patients who received surgery, 6.8% (n=22) did not receive adjuvant treatment due to adverse events. Of the 317 placebo-treated patients who received surgery, 3.2% (n=10) did not receive adjuvant treatment due to adverse events.

Adjuvant Treatment Phase

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

Of the patients who received single agent KEYTRUDA as adjuvant treatment, 5.5% experienced serious treatment-related adverse events; the most frequent treatment-related adverse event was pneumonitis (0.7%).

Permanent discontinuation of adjuvant KEYTRUDA due to a treatment-related adverse event occurred in 10% of patients; the most frequent (\geq 1%) treatment-related adverse events that led to permanent discontinuation of adjuvant KEYTRUDA were diarrhea and pneumonitis.

Table 14: Treatment-Related Adverse Events (incidence ≥ 1%) in Patients Treated with KEYTRUDA in Combination with Chemotherapy as Neoadjuvant Treatment, and then Continued as Monotherapy Adjuvant Treatment, APaT Population in KEYNOTE-671.

Adverse Reaction	Platinum	KEYTI ar Chemoth n=3	nd erapy / Ki	EYTRUDA	Placebo and Platinum Chemotherapy / Placeb n=399			
	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 di	sorders						
Anemia	143 (36.1)	29 (7.3)	0	0	135 (33.8)	22 (5.5)	0	0
Cardiac disorders		70.2)						•
Atrial fibrillation	5 (1.3)	1 (0.3)	0	1 (0.3)	1 (0.3)	0	0	0
Ear and labyrinth dis	orders							
Tinnitus	24 (6.1)	0	0	0	23 (5.8)	0	0	0
Deafness	4 (1.0)	0	0	0	3 (0.8)	0	0	0
Hypoacusis	4 (1.0)	1 (0.3)	0	0	6 (1.5)	0	0	0
Vertigo	4 (1.0)	0	0	0	4 (1.0)	0	0	0
Endocrine Disorders								
Hypothyroidism	38 (9.6)	0	0	0	6 (1.5)	0	0	0
Hyperthyroidism	15 (3.8)	0	0	0	5 (1.3)	0	0	0

Adverse Reaction	Platinum	ar Chemoth	RUDA nd erapy / KE 396	EYTRUDA	Platinu	Plac ar m Chemot n=3	nd herapy / I	Placebo
	Any Grade	Grade 3	Grade 4	Grade 5	Any Grade	Grade 3	Grade 4	Grade 5
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Eye disorders					•			•
Dry eye	7 (1.8)	0	0	0	2 (0.5)	0	0	0
Lacrimation increased	7 (1.8)	0	0	0	8 (2.0)	0	0	0
Gastrointestinal disc	orders							
Nausea	215 (54.3)	8 (2.0)	0	0	204 (51.1)	6 (1.5)	0	0
Constipation	106 (26.8)	3 (0.8)	0	0	100 (25.1)	0	0	0
Vomiting	75 (18.9)	4 (1.0)	0	0	58 (14.5)	1 (0.3)	0	0
Diarrhea	52 (13.1)	6 (1.5)	0	0	56 (14.0)	3 (0.8)	0	0
Stomatitis	35 (8.8)	0	0	0	27 (6.8)	1 (0.3)	0	0
Dyspepsia	15 (3.8)	0	0	0	12 (3.0)	0	0	0
Abdominal pain upper	10 (2.5)	0	0	0	9 (2.3)	0	0	0
Dry mouth	10 (2.5)	0	0	0	5(1.3)	0	0	0
Abdominal pain	9 (2.3)	0	0	0	7 (1.8)	0	0	0
Gastroesophageal reflux disease	9 (2.3)	0	0	0	6 (1.5)	0	0	0
Abdominal distention	5 (1.3)	0	0	0	3 (0.8)	0	0	0
Colitis	5 (1.3)	3 (0.8)	0	0	0	0	0	0
Flatulence	4 (1.0)	0	0	0	3 (0.8)	0	0	0
General disorders an	d administ	tration site	e conditio	ns				
Fatigue	108 (27.3)	6 (1.5)	0	0	94 (23.6)	3 (0.8)	0	0
Asthenia	45 (11.4)	4 (1.0)	0	0	55 (13.8)	2 (0.5)	0	0
Malaise	29 (7.3)	0	0	0	27 (6.8)	1 (0.3)	0	0
Edema peripheral	15 (3.8)	0	0	0	6 (1.5)	0	0	0
Pyrexia	13 (3.3)	1 (0.3)	0	0	12 (3.0)	0	0	0
Chills	6 (1.5)	0	0	0	3 (0.8)	0	0	0
Chest discomfort	4 (1.0)	0	0	0	0	0	0	0
Face edema	4 (1.0)	1 (0.3)	0	0	2 (0.5)	0	0	0
Infections and infest	ations							

			RUDA nd				ebo nd	
Adverse Reaction	Platinum		erapy / KE 396	YTRUDA	Platinu		herapy / F 399	Placebo
	Any	Grade	Grade	Grade	Any	Grade	Grade	Grade
	Grade	3	4	5	Grade	3	4	5
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Pneumonia	10 (2.5)	3 (0.8)	1 (0.3)	1 (0.3)	8 (2.0)	4 (1.0)	2 (0.5)	1 (0.3)
Conjunctivitis	4 (1.0)	0	0	0	5 (1.3)	0	0	0
Investigations								
Neutrophil count	167	64	10 (4 5)	0	167	63	15 (2.0)	0
decreased	(42.2)	(16.2)	18 (4.5)	0	(41.9)	(15.8)	15 (3.8)	0
White blood cell	111	19 (4.8)	2 (0.5)	0	98	21 (5.3)	1 (0.3)	0
count decreased	(28.0)	13 (4.0)	2 (0.3)	0	(24.6)	21 (3.3)	1 (0.3)	U
Platelet count	74	12 (3.0)	8 (2.0)	0	74	11 (2.8)	13 (3.3)	0
decreased	(18.7)	12 (3.0)	0 (2.0)	0	(18.5)	11 (2.0)	13 (3.3)	0
Blood creatinine	56	3 (0.8)	0	0	48	0	0	0
increased	(14.1)	3 (0.0)			(12.0)	•		
Alanine	51							
aminotransferase	(12.9)	6 (1.5)	1 (0.3)	0	31 (7.8)	3 (0.8)	1 (0.3)	0
increased	(==:0)							
Aspartate			_	_	,_ ,			_
aminotransferase	37 (9.3)	8 (2.0)	0	0	25 (6.3)	1 (0.3)	1 (0.3)	0
increased								
Lymphocyte count	20 (5.1)	3 (0.8)	0	0	19 (4.8)	2 (0.5)	0	0
decreased	, ,				, ,			
Blood urea	14 (3.5)	0	0	0	10 (2.5)	0	0	0
increased								
Weight decreased	13 (3.3)	0	0	0	8 (2.0)	0	0	0
Blood alkaline	- (4.6)	4 (0.0)			. (4.0)			
phosphatase	7 (1.8)	1 (0.3)	0	0	4 (1.0)	0	0	0
increased								
Gamma-	7 (4 0)	1 (0.3)	•	_	2 (0.0)	_	_	
glutamyltransferase	7 (1.8)	1 (0.3)	0	0	3 (0.8)	0	0	0
increased								
Blood lactate	6 (1.5)	0	0	0	7 (1 0)	0	0	0
dehydrogenase increased	0 (1.5)	U	U	U	7 (1.8)	U	U	U
Blood thyroid								
stimulating	6 (1.5)	0	0	0	7 (1.8)	0	0	0
hormone increased	(1.5)		J		, (1.0)			
Lipase increased	4 (1.0)	3 (0.8)	1 (0.3)	0	1 (0.3)	1 (0.3)	0	0
Metabolism and nut		, ,	± (U.J)	<u> </u>	1 (0.3)	± (U.3)		
	1	14613			00			
Decreased appetite	91	6 (1.5)	0	0	88 (22.1)	0	0	0
Hypomagnosomia	(23.0)		2 (0 5)		(22.1)	1 (0.2)	0	
Hypomagnesemia	35 (8.8)	0	2 (0.5)	0	22 (5.5)	1 (0.3)	0	0

Adverse Reaction	Platinum	ar Chemoth	RUDA nd erapy / KE 396	EYTRUDA	Platinu	Plac ar m Chemot n=3	nd herapy / F	Placebo
	Any Grade	Grade 3	Grade 4	Grade 5	Any Grade	Grade 3	Grade 4	Grade 5
Hyponatremia	n (%)	n (%) 3 (0.8)	n (%) 0	n (%) 0	n (%)	n (%)	n (%) 1 (0.3)	n (%) 0
Hypokalemia	24 (6.1) 17 (4.3)	3 (0.8)	0	0	17 (4.3) 20 (5.0)	6 (1.5) 5 (1.3)	0.5)	0
Hyperkalemia	10 (2.5)	0	0	0	9 (2.3)	0	0	0
Hypoalbuminemia	8 (2.0)	0	0	0	5 (2.3)	0	0	0
Dehydration	7 (1.8)	1 (0.3)	1 (0.3)	0	4 (1.0)	1 (0.3)	0	0
Hyperuricemia	7 (1.8)	0	0	0	8 (2.0)	0.5)	0	0
Hypocalcemia	7 (1.8)	0	0	0	5 (1.3)	1 (0.3)	0	0
Hyperglycemia	6 (1.5)	0	0	0	12 (3.0)	2 (0.5)	0	0
Hypophosphatemia	6 (1.5)	1 (0.3)	0	0	9 (2.3)	2 (0.5)	0	0
Hypochloremia	4 (1.0)	0	0	0	2 (0.5)	0	0	0
Musculoskeletal and	. ,				2 (0.0)			
Arthralgia	11 (2.8)	1 (0.3)	0	0	9 (2.3)	1 (0.3)	0	0
Myalgia	8 (2.0)	1 (0.3)	0	0	4 (1.0)	0	0	0
Back pain	5 (1.3)	0	0	0	2 (0.5)	0	0	0
Arthritis	4 (1.0)	1 (0.3)	0	0	0	0	0	0
Nervous system diso		, ,						
Dysgeusia	30 (7.6)	1 (0.3)	0	0	36 (9.0)	0	0	0
Dizziness	24 (6.1)	0	0	0	22 (5.5)	0	0	0
Headache	15 (3.8)	0	0	0	10 (2.5)	0	0	0
Paresthesia	15 (3.8)	0	0	0	8 (2.0)	0	0	0
Neuropathy peripheral	12 (3.0)	2 (0.5)	0	0	13 (3.3)	0	0	0
Hypoesthesia	8 (2.0)	0	0	0	5 (1.3)	0	0	0
Peripheral sensory neuropathy	8 (2.0)	0	0	0	8 (2.0)	0	0	0
Ageusia	4 (1.0)	0	0	0	2 (0.5)	0	0	0
Lethargy	4 (1.0)	0	0	0	2 (0.5)	0	0	0
Renal and urinary dis	orders							
Acute kidney injury	8 (2.0)	3 (0.8)	0	0	9 (2.3)	2 (0.5)	0	0
Renal failure	8 (2.0)	1 (0.3)	0	0	10 (2.5)	2 (0.5)	0	0
Proteinuria	5 (1.3)	0	0	0	2 (0.5)	0	0	0
Renal impairment	4 (1.0)	0	0	0	4 (1.0)	1 (0.3)	0	0
Renal injury	4 (1.0)	1 (0.3)	0	0	2 (0.5)	0	0	0
Respiratory, thoracio	and medi	astinal dis	orders					
Hiccups	22 (5.6)	0	0	0	29 (7.3)	0	0	0

Adverse Reaction	Platinum	ar Chemoth	RUDA nd erapy / KI 396	EYTRUDA	Placebo and Platinum Chemotherapy / Placebo n=399				
	Any Grade	Grade 3	Grade 4	Grade 5	Any Grade	Grade 3	Grade 4	Grade 5	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Dyspnea	17 (4.3)	2 (0.5)	0	0	6 (1.5)	2 (0.5)	0	0	
Cough	10 (2.5)	0	0	0	2 (0.5)	0	0	0	
Pneumonitis	9 (2.3)	4 (1.0)	0	0	2 (0.5)	0	0	0	
Epistaxis	5 (1.3)	0	0	0	4 (1.0)	0	0	0	
Immune-mediated lung disease	4 (1.0)	2 (0.5)	0	1 (0.3)	1 (0.3)	0	0	0	
Oropharyngeal pain	4 (1.0)	0	0	0	1 (0.3)	0	0	0	
Skin and subcutaneo	us tissue c	lisorders							
Rash	45 (11.4)	3 (0.8)	0	0	26 (6.5)	0	0	0	
Alopecia	40 (10.1)	0	0	0	40 (10.0)	1 (0.3)	0	0	
Pruritus	38 (9.6)	2 (0.5)	0	0	25 (6.3)	0	0	0	
Dry skin	15 (3.8)	0	0	0	8 (2.0)	0	0	0	
Rash maculo- papular	11 (2.8)	0	0	0	8 (2.0)	0	0	0	
Dermatitis acneiform	10 (2.5)	0	0	0	3 (0.8)	0	0	0	
Eczema	5 (1.3)	0	0	0	1 (0.3)	0	0	0	
Psoriasis	5 (1.3)	0	0	0	1 (0.3)	0	0	0	
Vascular disorders									
Phlebitis	5 (1.3)	0	0	0	1 (0.3)	0	0	0	
Hypertension	4 (1.0)	3 (0.8)	0	0	5 (1.3)	2 (0.5)	0	0	
Hypotension	4 (1.0)	0	0	0	4 (1.0)	0	0	0	
Superficial vein thrombosis	4 (1.0)	0	0	0	2 (0.5)	0	0	0	

MPM

Table 15 summarizes the treatment-related adverse events that occurred in at least 1% of patients with MPM treated with KEYTRUDA in combination with chemotherapy in KEYNOTE-483. The median duration of exposure was 6.9 months (range: 1 day to 25.2 months) in the KEYTRUDA in combination with chemotherapy arm and 3.5 months (range: 1 day to 6.3 months) in the chemotherapy arm.

The most common treatment-related adverse events (reported in at least 20% of patients) were fatigue, nausea, diarrhea, vomiting and stomatitis. The most common Grade 3-5 treatment-related adverse events for patients treated with KEYTRUDA in combination with chemotherapy in KEYNOTE-483 were fatigue (7.1%), and febrile neutropenia (5.0%).

Fatal treatment-related adverse events occurred in 2.9% of patients receiving KEYTRUDA in combination with chemotherapy, including 3 cases of sepsis and 1 case each of death due to cardiac arrest, dyspnea, febrile neutropenia and sudden death.

Serious treatment-related adverse events occurred in 27.8% of patients receiving KEYTRUDA in combination with chemotherapy; the most common (incidence >2%) were febrile neutropenia, pneumonitis, diarrhea, anemia, nausea, platelet count decreased, sepsis, and vomiting.

KEYTRUDA was discontinued for treatment-related adverse events in 17.8% of patients. The most common treatment-related adverse events resulting in discontinuation of KEYTRUDA (occurring in at least 4 patients) were pneumonitis (n=8), diarrhea (n=4) and sepsis (n=4). The median time to discontinuation of KEYTRUDA for treatment-related adverse events was 3.0 months.

Table 15: Treatment-Related Adverse Events (Incidence ≥ 1%) in Patients Treated with KEYTRUDA in Combination with Pemetrexed and Platinum Chemotherapy, APaT Population in KEYNOTE-483.

Adverse Reaction		KEYTRU and Pemetre and atinum Chen n=24:	xed notherapy	.,,	Pemetrexed and Platinum Chemotherapy n=232				
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3 Grade 4 Grade n (%) n (%)			
Blood and lymphatic	system disord	ders							
Anemia	6 (2.5)	5 (2.1)	1 (0.4)	0	0	0	0	0	
Febrile neutropenia	12 (5.0)	8 (3.3)	3 (1.2)	1 (0.4)	3 (1.3)	3 (1.3)	0	0	
Cardiac disorders									
Palpitations	3 (1.2)	0	0	0	0	0	0	0	
Ear and labyrinth dis	orders								
Hypoacusis	10 (4.1)	0	0	0	13 (5.6)	1 (0.4)	0	0	
Tinnitus	17 (7.1)	0	0	0	16 (6.9)	1 (0.4)	0	0	
Endocrine disorders									
Hyperthyroidism	4 (1.7)	0	0	0	1 (0.4)	0	0	0	
Hypothyroidism	18 (7.5)	0	0	0	3 (1.3)	0	0	0	
Eye disorders									
Dry eye	7 (2.9)	0	0	0	8 (3.4)	0	0	0	
Lacrimation increased	28 (11.6)	0	0	0	17 (7.3)	0	0	0	
Vision blurred	8 (3.3)	0	0	0	3 (1.3)	0	0	0	
Gastrointestinal diso	rders								
Abdominal distention	6 (2.5)	0	0	0	2 (0.9)	0	0	0	
Abdominal pain	9 (3.7)	2 (0.8)	0	0	7 (3.0)	0	0	0	
Colitis	6 (2.5)	3 (1.2)	0	0	0	0	0	0	
Constipation	37 (15.4)	0	0	0	29 (12.5)	0	0	0	
Diarrhea	56 (23.2)	4 (1.7)	0	0	22 (9.5)	4 (1.7)	0	0	

Adverse Reaction	Pla	KEYTRUDA and Pemetrexed and Platinum Chemotherapy n=241				Pemetrexed and Platinum Chemotherapy n=232			
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	
Dry mouth	9 (3.7)	0	0	0	4 (1.7)	0	0	0	
Dyspepsia	14 (5.8)	0	0	0	8 (3.4)	0	0	0	
Gastrooesophageal reflux disease	5 (2.1)	0	0	0	4 (1.7)	0	0	0	
Hemorrhoids	3 (1.2)	1 (0.4)	0	0	0	0	0	0	
Nausea	119 (49.4)	10 (4.1)	0	0	104 (44.8)	2 (0.9)	0	0	
Stomatitis	49 (20.3)	1 (0.4)	0	0	42 (18.1)	2 (0.9)	0	0	
Vomiting	50 (20.7)	4 (1.7)	0	0	32 (13.8)	2 (0.9)	0	0	
General disorders an	d administrat	ion site cond	litions						
Chills	4 (1.7)	0	0	0	2 (0.9)	0	0	0	
Fatigue	120 (49.8)	17 (7.1)	0	0	121 (52.2)	14 (6.0)	0	0	
Influenza like illness	5 (2.1)	0	0	0	0	0	0	0	
Edema peripheral	15 (6.2)	0	0	0	10 (4.3)	0	0	0	
Pyrexia	17 (7.1)	0	0	0	9 (3.9)	0	0	0	
Infections and infest	ations								
Conjunctivitis	11 (4.6)	0	0	0	16 (6.9)	1 (0.4)	0	0	
Mucosal infection	8 (3.3)	1 (0.4)	0	0	3 (1.3)	0	0	0	
Pneumonia	6 (2.5)	3 (1.2)	0	0	3 (1.3)	0	0	0	
Rash pustular	3 (1.2)	0	0	0	0	0	0	0	
Sepsis	5 (2.1)	0	2 (0.8)	3 (1.2)	1 (0.4)	0	0	1 (0.4)	
Urinary tract infection	4 (1.7)	0	0	0	3 (1.3)	0	0	0	
Injury, poisoning and	l procedural co	omplications	;						
Infusion related reaction	9 (3.7)	0	0	0	3 (1.3)	0	0	0	
Investigations									
Alanine aminotransferase increased	4 (1.7)	3 (1.2)	0	0	0	0	0	0	
Aspartate aminotransferase increased	4 (1.7)	2 (0.8)	0	0	0	0	0	0	
Platelet count decreased	5 (2.1)	1 (0.4)	3 (1.2)	0	0	0	0	0	
Metabolism and nuti	rition disorder	s							
Decreased appetite	40 (16.6)	0	0	0	42 (18.1)	2 (0.9)	0	0	
Dehydration	11 (4.6)	2 (0.8)	0	0	9 (3.9)	2 (0.9)	0	0	

Adverse Reaction	Pl	KEYTRU and Pemetre and atinum Chen n=242	xed notherapy			Pemet an Platinum Che n=2	,	
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Musculoskeletal and	connective ti	ssue disorde	rs					
Arthralgia	17 (7.1)	2 (0.8)	0	0	0	0	0	0
Arthritis	3 (1.2)	0	0	0	0	0	0	0
Back pain	4 (1.7)	1 (0.4)	0	0	2 (0.9)	0	0	0
Flank pain	3 (1.2)	0	0	0	0	0	0	0
Muscular weakness	6 (2.5)	0	0	0	4 (1.7)	0	0	0
Myalgia	4 (1.7)	1 (0.4)	0	0	2 (0.9)	0	0	0
Pain in extremity	4 (1.7)	0	0	0	0	0	0	0
Nervous system diso	rders							
Dizziness	11 (4.6)	0	0	0	11 (4.7)	1 (0.4)	0	0
Dysgeusia	27 (11.2)	0	0	0	31 (13.4)	0	0	0
Headache	6 (2.5)	0	0	0	3 (1.3)	0	0	0
Paresthesia	18 (7.5)	0	0	0	8 (3.4)	0	0	0
Peripheral motor neuropathy	3 (1.2)	1 (0.4)	0	0	0	0	0	0
Peripheral sensory neuropathy	29 (12.0)	0	0	0	21 (9.1)	0	0	0
Tremor	3 (1.2)	0	0	0	1 (0.4)	0	0	0
Psychiatric disorders				I.	, ,			
Insomnia	4 (1.7)	0	0	0	2 (0.9)	0	0	0
Renal and urinary dis	, ,			ı	, ,			
Acute kidney injury	5 (2.1)	1 (0.4)	0	0	3 (1.3)	0	0	0
Cystitis noninfective	3 (1.2)	0	0	0	1 (0.4)	0	0	0
Urinary tract pain	3 (1.2)	0	0	0	2 (0.9)	0	0	0
Respiratory, thoracio		nal disorders			_ (0.0)			
Dyspnea	16 (6.6)	0	0	1 (0.4)	6 (2.6)	2 (0.9)	0	0
Epistaxis	7 (2.9)	0	0	0	4 (1.7)	0	0	0
Hiccups	6 (2.5)	0	0	0	5 (2.2)	0	0	0
Pneumonitis	11 (4.6)	3 (1.2)	0	0	0	0	0	0
Rhinitis allergic	7 (2.9)	0	0	0	7 (3.0)	0	0	0
Upper-airway cough syndrome	5 (2.1)	0	0	0	3 (1.3)	0	0	0
Skin and subcutaneo	us tissue diso	rders	1	<u>l</u>	<u> </u>	<u> </u>		
Alopecia	13 (5.4)	0	0	0	7 (3.0)	0	0	0
Dermatitis acneiform	11 (4.6)	0	0	0	6 (2.6)	0	0	0

Adverse Reaction	Pl	KEYTRU and Pemetre and atinum Chen n=24:	exed		Pemetrexed and Platinum Chemotherapy n=232				
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	
Dry skin	12 (5.0)	0	0	0	3 (1.3)	0	0	0	
Erythema	4 (1.7)	0	0	0	2 (0.9)	0	0	0	
Hyperhidrosis	3 (1.2)	0	0	0	0	0	0	0	
Pruritus	35 (14.5)	0	0	0	8 (3.4)	0	0	0	
Rash maculo- papular	34 (14.1)	3 (1.2)	0	0	17 (7.3)	1 (0.4)	0	0	
Skin Hyperpigmentation	3 (1.2)	0	0	0	3 (1.3)	0	0	0	
Vascular disorders									
Embolism	9 (3.7)	3 (1.2)	0	0	5 (2.2)	2 (0.9)	1 (0.4)	0	
Flushing	3 (1.2)	0	0	0	0	0	0	0	
Hypertension	5 (2.1)	0	1 (0.4)	0	2 (0.9)	1 (0.4)	0	0	

Hodgkin Lymphoma

Table 16 summarizes the treatment-related adverse events that occurred in at least 1% of patients with Hodgkin Lymphoma in KEYNOTE-204 (See 14 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 $\geq 1\%$ 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 \geq 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 16: Treatment-Related Adverse Events Occurring in ≥ 1% of Patients with Hodgkin Lymphoma in KEYNOTE-204.

Adverse Event	200	KEYTRUDA mg every 3 w n=148	eeks		ntuximab Vedo ng/kg every 3 w n=152	
Adverse Event	Any Grade n (%)	Grade 3 n (%)	Grade 4 / Grade 5 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Blood and lymphatic	system disorde	rs				
Anemia	1 (0.7)	1 (0.7)	0	7 (4.6)	1 (0.7)	0
Immune thrombocytopenic	3 (2.0)	0	2 (1.4)	0	0	0
purpura						
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		(/	1	- (3.2)	<u> </u>	
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 diso	rders					
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 an	d administration	n site conditio	ns			
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 infest	ations					
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

Advance Front	200	KEYTRUDA mg every 3 w n=148	eeks	Brentuximab Vedotin 1.8 mg/kg every 3 weeks n=152			
Adverse Event	Any Grade n (%)	Grade 3 n (%)	Grade 4 / Grade 5 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	
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 con	nplications					
Infusion related reaction	5 (3.4)	0	0	12 (7.9)	3 (2.0)	0	
Investigations						I	
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 nutr							
Decreased appetite	6 (4.1)	0	0	6 (3.9)	0	0	
Musculoskeletal and		ue 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	4 (2.7)	0	0	2 (1.3)	0	0	

Adverse Event	200	KEYTRUDA mg every 3 wo n=148	eeks	Brentuximab Vedotin 1.8 mg/kg every 3 weeks n=152			
Adverse Event	Any Grade n (%)	Grade 3 n (%)	Grade 4 / Grade 5 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	
pain							
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, m	alignant and ur	nspecified	•				
Tumour flare	2 (1.4)	1 (0.7)	0	0	0	0	
Nervous system disor	. , ,	, ,	1			ı	
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	
Paresthesia	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	
Psychiatric disorders	T		T			T	
Confusional state	2 (1.4)	0	0	0	0	0	
Renal and urinary dis	orders						
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 mediastina	l disorders					
Cough	5 (3.4)	0	0	5 (3.3)	0	0	
Dyspnea exertional	3 (2.0)	0	0	0	0	0	
Interstitial 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 subcutaneou	· · ·			· - /	<u> </u>	<u> </u>	
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	

Ad 5	200	KEYTRUDA 200 mg every 3 weeks n=148			Brentuximab Vedotin 1.8 mg/kg every 3 weeks n=152			
Adverse Event	Any Grade n (%)	Grade 3 n (%)	Grade 4 / Grade 5 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)		
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 3 patients 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.

Primary Mediastinal B-cell Lymphoma (PMBCL)

Table 17 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 17: 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	Grade 3/Grade 4		
	n (%)	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	1			
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 co	onditions			
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	,	1		
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 disor		•		
Myalgia	2 (4.1)	0		
Arthralgia	1 (2.0)	0		
Back pain	1 (2.0)	0		
Muscle spasms	1 (2.0)	0		

Adverse Event	KEYTRUDA 200 mg every 3 weeks n=49			
	Any Grade n (%)	Grade 3/Grade 4 n (%)		
Neoplasm benign, malignant and unspecified	(includes cysts and polyp	os)		
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 disorde	ers			
Pleural effusion	1 (2.0)	0		
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.

There were no new safety signals observed at the final safety analysis (n=53 patients) of KEYNOTE-170 and therefore, with additional follow-up, no meaningful changes occurred in the safety profile of KEYTRUDA .

Urothelial Carcinoma

The safety of KEYTRUDA was evaluated in combination with enfortumab vedotin in an open-label, randomized, multicenter trial (KEYNOTE-A39) in 440 patients with unresectable locally advanced or metastatic urothelial cancer who received at least one dose of KEYTRUDA and enfortumab vedotin compared to 433 patients who received gemcitabine on Days 1 and 8 and investigator's choice of cisplatin or carboplatin on Day 1 of each 21-day cycle. The median duration of overall exposure was 9.4 months (range: 0.3 to 31.9 months). The median duration of exposure to KEYTRUDA in KEYNOTE-A39 was 8.5 months (range: 9 days to 28.5 months).

The safety information reported below are based on all reported adverse events, regardless of the investigator assessment of causality.

Serious adverse events occurred in 50% of patients treated with KEYTRUDA in combination with enfortumab vedotin. The most common serious adverse events (≥2%) were rash (6%), acute kidney injury (5%), pneumonitis/interstitial lung disease (ILD) (4.5%), urinary tract infection (4.3%), diarrhea (3.9%), pneumonia (2.3%), pyrexia (2%) and hyperglycemia (2%).

Seventy three percent of patients had \geq Grade 3 treatment-emergent adverse events. The most common Grade 3 (\geq 5%) were: rash (15%), peripheral neuropathy (8%), hyperglycemia (7%), anemia (7%), diarrhea (6%), fatigue (6%), urinary tract infection (6%), acute kidney injury (5%), hyponatremia (5%), and neutropenia (5%).

Fatal adverse events occurred in 4.3% (19/440) of patients treated with KEYTRUDA in combination with enfortumab vedotin including acute respiratory failure (0.7%), pneumonia (0.5%), and pneumonitis/ILD (0.2%).

Adverse events leading to discontinuation of KEYTRUDA occurred in 27% of patients. The most common adverse events (≥2%) leading to discontinuation of KEYTRUDA were pneumonitis/ILD (4.8%) and rash (3.4%).

Adverse events leading to dose interruption of KEYTRUDA occurred in 61% of patients. The most common adverse events (≥2%) leading to dose interruption of KEYTRUDA were rash (17%), peripheral neuropathy (7%), COVID-19 (5%), diarrhea (4.3%), pneumonitis/ILD (3.6%), neutropenia (3.4%), fatigue (3%), alanine aminotransferase increased (2.7%), hyperglycemia (2.5%), pneumonia (2%), and pruritis (2%).

The combination treatment was discontinued for treatment-emergent adverse events in 40% of patients. The most common adverse events (≥2%) resulting in discontinuation of either KEYTRUDA or enfortumab vedotin were peripheral neuropathy (15%), pneumonitis/ILD (4.8%), and rash (4.5%).

Table 18: Treatment Emergent Adverse Events Reported in ≥ 10% of Patients with Urothelial Cancer Treated with KEYTRUDA in combination with Enfortumab vedotin (KEYNOTE-A39).

	KEYTR an		Chemotherapy		
	Enfortumal	b Vedotin			
	n=4	40	n=	433	
	All Grades*	Grades 3-4	All Grades*	Grades 3-4	
Adverse Event	n (%)	n (%)	n (%)	n (%)	
Blood and lymphatic syste	m disorders				
Anemia	108 (25)	31 (7)	267 (62)	148 (34)	
Endocrine disorders					
Hypothyroidism	46 (10)	2 (0.5)	3 (0.7)	0	
Eye disorders					
Dry eye ¹	107 (24)	0	9 (2)	0	
Gastrointestinal disorders					
Diarrhea ²	168 (38)	25 (6)	69 (16)	6 (1)	
Nausea	116 (26)	7 (2)	178 (41)	12 (3)	
Constipation	116 (26)	0	147 (34)	3 (0.7)	
Abdominal pain ³	68 (15)	6 (1)	48 (11)	3 (0.7)	
Vomiting	51 (12)	6 (1)	69 (16)	7 (2)	
General disorders and adn	ninistration site co	nditions			
Fatigue ⁴	225 (51)	27 (6)	246 (57)	28 (6)	
Pyrexia ⁵	79 (18)	3 (0.7)	67 (15)	5 (1)	
Edema peripheral	60 (14)	0	48 (11)	1 (0.2)	

	KEYTR an Enfortuma	d	Chemo	therapy	
	n=4	40	n=433		
	All Grades*	Grades 3-4	All Grades*	Grades 3-4	
Adverse Event	n (%)	n (%)	n (%)	n (%)	
Infections and infestations					
Urinary tract infection ⁶	98 (22)	25 (6)	93 (21)	40 (9)	
COVID-19 ⁷	69 (16)	9 (2)	24 (6)	6 (1)	
Investigations					
Weight loss	145 (33)	16 (4)	38 (9)	1 (0.2)	
Metabolism and nutrition	disorders				
Decreased appetite	145 (33)	8 (2)	112 (26)	8 (2)	
Hyperglycemia	72 (16)	32 (7)	11 (3)	3 (0.7)	
Musculoskeletal and conne	ctive tissue disor	ders			
Musculoskeletal pain ⁸	151 (34)	9 (2)	109 (25)	10 (2)	
Nervous system disorders					
Peripheral neuropathy ⁹	293 (67)	34 (8)	60 (14)	0	
Dysgeusia ¹⁰	104 (24)	1 (0.2)	40 (9)	0	
Psychiatric disorders					
Insomnia	45 (10)	1 (0.2)	24 (6)	0	
Respiratory, thoracic and n	nediastinal disord	lers			
Pneumonits/ILD ¹¹	45 (10)	17 (4)	2 (0.5)	2 (0.5)	
Dyspnea	58 (13)	6 (1)	51 (12)	5 (1)	
Cough	54 (12)	0	23 (5)	1 (0.2)	
Skin and subcutaneous tiss	ue disorders				
Rash ¹²	297 (68)	64 (15)	64 (15)	0	
Pruritus	182 (41)	5 (1)	29 (7)	0	
Alopecia	152 (35)	2 (0.5)	34 (8)	1 (0.2)	
Dry skin	76 (17)	1 (0.2)	6 (1)	0	
Vascular disorders					
Hemorrhage ¹³	80 (18)	10 (2)	70 (16)	14 (3)	

^{*} Graded per NCI CTCAE v4.03

^{1.} Includes: dry eye, lacrimation increased, conjunctivitis, blepharitis, eye irritation, keratitis, conjunctivitis allergic, meibomian gland dysfunction, punctate keratitis

^{2.} Includes: diarrhea, colitis and enterocolitis

^{3.} Includes: abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, hepatic pain, abdominal tenderness, gastrointestinal pain

^{4.} Includes: fatigue, asthenia

^{5.} Includes: pyrexia, body temperature increased, hyperpyrexia

^{6.} Includes: urinary tract infection, urinary tract infection bacterial, urinary tract infection enterococcal, streptococcal urinary tract infection, escherichia urinary tract infection, pyelonephritis acute, escherichia pyelonephritis, urinary tract infection fungal, cystitis, urinary tract infection staphylococcal, urinary tract infection pseudomonal

^{7.} Includes: COVID-19, COVID-19 pneumonia

^{8.} Includes: myalgia, arthralgia, back pain, bone pain, pain in extremity, musculoskeletal pain, arthritis, neck pain, noncardiac chest pain, musculoskeletal chest pain, spinal pain, musculoskeletal stiffness, musculoskeletal discomfort

- 9. Includes: dysesthesia, hypoesthesia, muscular weakness, neuralgia, neurotoxicity, paresthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, peroneal nerve palsy, gait disturbance, skin burning sensation
- 10. Includes: dysgeusia, ageusia, hypogeusia

hemorrhage.

- 11. Includes: pneumonitis, immune-mediated lung disease, interstitial lung disease, lung opacity, autoimmune lung disease, organizing pneumonia, pulmonary fibrosis, pulmonary toxicity, sarcoidosis, acute respiratory distress syndrome, alveolitis
- 12. Includes: blister, conjunctivitis, dermatitis, dermatitis bullous, dermatitis contact, dermatitis exfoliative generalized, drug eruption, erythema, eczema, erythema multiforme, exfoliative rash, intertrigo, palmar-plantar erythrodysesthesia syndrome, pemphigoid, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rash vesicular, skin irritation, skin exfoliation, stasis dermatitis, stomatitis
 13. Includes: hematuria, rectal hemorrhage, gastrointestinal hemorrhage, epistaxis, upper gastrointestinal hemorrhage, tumour hemorrhage, hemoptysis, vaginal hemorrhage, anal hemorrhage, hemorrhagic stroke, urethral hemorrhage, infusion site hemorrhage, conjunctival hemorrhage, hemorrhagic ascites, hemorrhoidal

Table 19 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 \geq Grade 3 treatment-related adverse events. The most common \geq 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 19: Treatment-Related Adverse Events Occurring in ≥ 1% of Patients with Urothelial Carcinoma Treated with KEYTRUDA (KEYNOTE-052).

	KEYTRUDA						
	200 mg once every three weeks n=370						
Adverse Reaction							
	All Grades	Grade 3	Grade 4				
	n (%)	n (%)	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				
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				

Adverse Reaction	KEYTRUDA 200 mg once every three weeks n=370				
	All Grades	Grade 3	Grade 4		
	n (%)	n (%)	n (%)		
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		1		
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	4 (1.1)	0	0		
increased	4 (1.1)	U	U		
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 dis	sorders				
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 disc			1		
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		

Adverse Reaction	200 m	KEYTRUDA 200 mg once every three weeks n=370					
	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)				
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				
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.

Table 20 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 \geq Grade 3 treatment-related adverse events. The most common \geq 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 20: Treatment-Related Adverse Events Occurring in ≥ 1% of Patients with Urothelial Carcinoma treated with KEYTRUDA in KEYNOTE-045.

Advance Departies	KEYTRUDA 200 mg every 3 weeks n=266				Chemotherapy n=255			
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 lymphati	c system disc	orders						
Anemia	9 (3.4)	2 (0.8)	0	0	63 (24.7)	20 (7.8)	0	0
Endocrine disorders								
Hyperthyroidism	10 (3.8)	0	0	0	0	0	0	0
Hypothyroidism	15 (5.6)	0	0	0	0	0	0	0
Gastrointestinal disorders								

	KEYTRUDA 200 mg every 3 weeks				Chemotherapy				
Adverse Reaction		n=2	66	T	n=255				
Adverse Nedection	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	4 (1.5)	0	0	0	10 (3.9)	0	0	0	
Colitis	5 (1.9)	2 (0.8)	0	0	1 (0.4)	0	0	0	
Constipation	6 (2.3)	0	0	0	52 (20.4)	7 (2.7)	0	0	
Diarrhea	24 (9.0)	3 (1.1)	0	0	33 (12.9)	1 (0.4)	1 (0.4)	0	
Dry mouth	4 (1.5)	0	0	0	2 (0.8)	0	0	0	
Flatulence	3 (1.1)	0	0	0	1 (0.4)	0	0	0	
Nausea	29 (10.9)	1 (0.4)	0	0	62 (24.3)	4 (1.6)	0	0	
Stomatitis	4 (1.5)	1 (0.4)	0	0	21 (8.2)	1 (0.4)	0	0	
Vomiting	12 (4.5)	O ,	0	0	25 (9.8)	1 (0.4)	0	0	
General disorders a		ation site co	nditions		, ,	. ,			
Asthenia	15 (5.6)	1 (0.4)	0	0	36 (14.1)	7 (2.7)	0	0	
Chills	3 (1.1)	0	0	0	4 (1.6)	0	0	0	
Fatigue	37 (13.9)	3 (1.1)	0	0	71 (27.8)	11 (4.3)	0	0	
Influenza like illness	3 (1.1)	0	0	0	3 (1.2)	0	0	0	
Malaise	4 (1.5)	0	0	0	8 (3.1)	0	0	0	
Mucosal	, ,	_			` '				
inflammation	3 (1.1)	1 (0.4)	0	0	17 (6.7)	2 (0.8)	0	0	
Pyrexia	17 (6.4)	0	0	0	8 (3.1)	1 (0.4)	0	0	
Infections and infes	. ,				- ()	_ (** ')			
Urinary Tract Infection	3 (1.1)	0	0	0	8 (3.1)	3 (1.2)	1 (0.4)	0	
Investigations	I.								
Alanine aminotransferase increased	9 (3.4)	2 (0.8)	0	0	3 (1.2)	0	0	0	
Aspartate aminotransferase increased	7 (2.6)	3 (1.1)	0	0	2 (0.8)	0	0	0	
Blood alkaline phosphatase increased	3 (1.1)	1 (0.4)	0	0	1 (0.4)	0	0	0	
Blood thyroid stimulating hormone increased	3 (1.1)	0	0	0	0	0	0	0	
Gamma-glutamyl transferase increased	3 (1.1)	2 (0.8)	0	0	1 (0.4)	0	0	0	
Platelet count	3 (1.1)	1 (0.4)	0	0	7 (2.7)	2 (0.8)	1 (0.4)	0	

		KEYTR 200 mg eve				Chemo	therapy	
Advance Departion		n=2	-			n=	255	
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 (%)
decreased								
Weight decreased	4 (1.5)	0	0	0	8 (3.1)	0	0	0
Metabolism and nu	trition disord	lers						
Decreased appetite	23 (8.6)	0	0	0	41 (16.1)	3 (1.2)	0	0
Hyperglycemia	3 (1.1)	1 (0.4)	0	0	0	0	0	0
Musculoskeletal an	d connective	tissue disor	ders	•	l.		l .	·
Arthralgia	8 (3.0)	0	0	0	17 (6.7)	0	0	0
Back pain	3 (1.1)	0	0	0	2 (0.8)	0	0	0
Muscle spasms	3 (1.1)	0	0	0	1 (0.4)	0	0	0
Musculoskeletal chest pain	3 (1.1)	0	0	0	0	0	0	0
Myalgia	8 (3.0)	1 (0.4)	0	0	12 (4.7)	0	0	0
Pain in extremity	3 (1.1)	0	0	0	13 (5.1)	1 (0.4)	0	0
Nervous system dis					, ,	, ,	I	
Dizziness	6 (2.3)	0	0	0	7 (2.7)	1 (0.4)	0	0
Dysgeusia	3 (1.1)	0	0	0	14 (5.5)	0	0	0
Headache	4 (1.5)	1 (0.4)	0	0	8 (3.1)	0	0	0
Psychiatric disorder	s				, , ,		l.	I.
Insomnia	3 (1.1)	0	0	0	5 (2.0)	0	0	0
Respiratory, thoraci	ic and medias	stinal disord	lers				•	•
Cough	7 (2.6)	0	0	0	2 (0.8)	0	0	0
Dyspnea	7 (2.6)	0	0	0	6 (2.4)	1 (0.4)	0	0
Dyspnea exertional	5 (1.9)	0	0	0	4 (1.6)	0	0	0
Pneumonitis	9 (3.4)	3 (1.1)	0	1 (0.4)	0	0	0	0
Skin and subcutane	ous tissue dis	orders			•		•	•
Dermatitis acneiform	3 (1.1)	0	0	0	2 (0.8)	0	0	0
Dry skin	6 (2.3)	0	0	0	7 (2.7)	0	0	0
Erythema	4 (1.5)	0	0	0	5 (2.0)	0	0	0
Pruritus	52 (19.5)	0	0	0	7 (2.7)	1 (0.4)	0	0
Rash	22 (8.3)	1 (0.4)	0	0	9 (3.5)	0	0	0
Rash maculo- papular	6 (2.3)	0	0	0	2 (0.8)	0	0	0
Urticaria	5 (1.9)	0	0	0	1 (0.4)	0	0	0
Vascular Disorders	- (=.0)	1 -			_ (*)		1 -	1
Hypertension	3 (1.1)	1 (0.4)	0	0	1 (0.4)	0	0	0

Table 21 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 \geq Grade 3 treatment-related adverse events. The most common \geq 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 \geq 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 (\geq 1%) were diarrhea (3.4%), arthralgia (1.4%), alanine aminotransferase increased (1.4%), and hyponatremia (1.4%).

Table 21: Treatment-Related Adverse Events Occurring in ≥ 1% of Patients with High-Risk NMIBC Treated with KEYTRUDA in KEYNOTE-057.

	KEYTRUDA							
	200 mg	g once every three v	weeks					
Adverse Reaction	n=148							
	All Grades	Grade 3	Grade 4					
	n (%)	n (%)	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 of	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					

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

Colorectal Cancer

Table 22 summarizes the treatment-related adverse events that occurred in at least 1% of patients with MSI-H or dMMR colorectal carcinoma treated with KEYTRUDA in KEYNOTE-177. The most common treatment-related adverse events (reported in at least 10% of patients) were diarrhea, fatigue, pruritis, nausea, aspartate aminotransferase increased, rash, hypothyroidism and arthralgia. Twenty two percent of patients had \geq Grade 3 treatment-related adverse events. The most common \geq Grade 3 adverse reactions (occurring in more than 2 patients) were: alanine aminotransferase increase (n=3); colitis (n=3); diarrhea (n=3); and fatigue (n=3).

KEYTRUDA was discontinued for treatment-related adverse events in 9.8% of patients in KEYNOTE-177.

The most common treatment-related adverse events leading to study drug discontinuation (occurring in more than 1 patient) were: alanine aminotransferase increase (n=2); autoimmune colitis (n=2); colitis (n=2); and hepatitis (n=2). The median time to discontinuation for treatment-related adverse events was 6.3 months.

Table 22: Treatment-Related Adverse Events Occurring in ≥ 1% of Patients with MSI-H or dMMR Colorectal Carcinoma treated with KEYTRUDA in KEYNOTE-177.

Colorectal Carcinoma treated with Ke		EYTRUDA		Che	emotherap	у
	200 mg	g every 3 w	veeks			
Adverse Reaction		n=153			n=143	
Adverse Reaction	Any	Grade	Grade	Any	Grade	Grade
	Grade	3	4	Grade	3	4
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Blood and lymphatic system disorder	S					
Anemia	9 (5.9)	2 (1.3)	0	17 (11.9)	7 (4.9)	0
Thrombocytopenia	2 (1.3)	0	1 (0.7)	7 (4.9)	1 (0.7)	0
Endocrine disorders						
Adrenal insufficiency	2 (1.3)	1 (0.7)	0	0	0	0
Hyperthyroidism	4 (2.6)	0	0	0	0	0
Hypophysitis	2 (1.3)	0	0	0	0	0
Hypothyroidism	16 (10.5)	0	0	0	0	0
Eye disorders						
Dry eye	6 (3.9)	0	0	2 (1.4)	0	0
Ocular hyperemia	2 (1.3)	0	0	0	0	0
Gastrointestinal disorders						
Abdominal pain	6 (3.9)	0	0	10 (7.0)	1 (0.7)	0
Abdominal pain upper	4 (2.6)	0	0	3 (2.1)	1 (0.7)	0
Anal Incontinence	2 (1.3)	0	0	1 (0.7)	0	0
Autoimmune Colitis	2 (1.3)	1 (0.7)	1 (0.7)	0	0	0
Colitis	8 (5.2)	2 (1.3)	1 (0.7)	0	0	0
Constipation	2 (1.3)	0	0	10 (7.0)	0	0
Diarrhea	38 (24.8)	3 (2.0)	0	75 (52.4)	13 (9.1)	1 (0.7)
Dry mouth	11 (7.2)	0	0	6 (4.2)	0	0
Dyspepsia	2 (1.3)	0	0	6 (4.2)	0	0
Flatulence	2 (1.3)	0	0	3 (2.1)	0	0
Gastroesophageal reflux disease	2 (1.3)	0	0	1 (0.7)	0	0
Nausea	19 (12.4)	0	0	79 (55.2)	3 (2.1)	0
Stomatitis	8 (5.2)	0	0	43 (30.1)	6 (4.2)	0
Vomiting	5 (3.3)	0	0	40 (28.0)	5 (3.5)	0
General disorders and administration	site conditions					
Asthenia	11 (7.2)	0	0	25 (17.5)	5 (3.5)	0
Chest pain	2 (1.3)	0	0	0	0	0
Chills	3 (2.0)	0	0	2 (1.4)	0	0
Fatigue	32 (20.9)	3 (2.0)	0	63 (44.1)	13 (9.1)	0
Influenza like illness	3 (2.0)	0	0	1 (0.7)	0	0
Malaise	7 (4.6)	0	0	7 (4.9)	0	0
	•					

		EYTRUDA		Chemotherapy			
	200 mg	every 3 w	eeks/				
Adverse Reaction		n=153			n=143	T	
	Any	Grade	Grade	Any	Grade	Grade	
	Grade	3	4	Grade	3	4	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Mucosal Inflammation	4 (2.6)	0	0	25 (17.5)	1 (0.7)	0	
Edema peripheral	7 (4.6)	0	0	3 (2.1)	0	0	
Pyrexia	11 (7.2)	1 (0.7)	0	7 (4.9)	0	0	
Xerosis	4 (2.6)	0	0	1 (0.7)	0	0	
Hepatobiliary Disorder							
Hepatitis	2 (1.3)	2 (1.3)	0	0	0	0	
Injury, poisoning and procedural compli	cations						
Infusion related reaction	2 (1.3)	0	0	7 (4.9)	1 (0.7)	0	
Investigations							
Alanine aminotransferase increased	15 (9.8)	3 (2.0)	0	10 (7.0)	1 (0.7)	0	
Aspartate aminotransferase increased	17 (11.1)	2 (1.3)	0	7 (4.9)	1 (0.7)	0	
Blood alkaline phosphatase increased	12 (7.8)	1 (0.7)	0	3 (2.1)	0	0	
Blood bilirubin increased	3 (2.0)	0	0	0	0	0	
Blood thyroid stimulating hormone				_		_	
increased	2 (1.3)	0	0	0	0	0	
Gamma-glutamyltransferase increased	3 (2.0)	1 (0.7)	1 (0.7)	2 (1.4)	0	0	
Hemoglobin decreased	3 (2.0)	0	0	1 (0.7)	0	0	
Lymphocyte count decreased	3 (2.0)	0	0	3 (2.1)	2 (1.4)	0	
Platelet count decreased	2 (1.3)	0	0	9 (6.3)	1 (0.7)	0	
Weight decreased	3 (2.0)	0	0	8 (5.6)	0	0	
Metabolism and nutrition disorders		I		, , ,		I.	
Decreased appetite	12 (7.8)	0	0	49 (34.3)	3 (2.1)	0	
Dehydration	3 (2.0)	0	0	5 (3.5)	2 (1.4)	0	
Hyperglycemia	3 (2.0)	1 (0.7)	0	2 (1.4)	O ,	0	
Hypokalemia	3 (2.0)	1 (0.7)	0	8 (5.6)	4 (2.8)	0	
Hyponatremia	2 (1.3)	2 (1.3)	0	1 (0.7)	O ,	1 (0.7)	
Musculoskeletal and connective tissue d		. ,		, ,		, ,	
Arthralgia	16 (10.5)	0	0	2 (1.4)	0	0	
Arthritis	3 (2.0)	1 (0.7)	0	0	0	0	
Bursitis	2 (1.3)	0	0	0	0	0	
Muscle spasms	2 (1.3)	0	0	2 (1.4)	0	0	
Musculoskeletal pain	6 (3.9)	0	0	0	0	0	
Myalgia	3 (2.0)	1 (0.7)	0	2 (1.4)	0	0	
Pain in extremity	4 (2.6)	0	0	2 (1.4)	0	0	
Tendon disorder	2 (1.3)	0	0	0	0	0	
Nervous system disorders	\=-01	<u> </u>	<u> </u>	<u> </u>			
Dizziness	4 (2.6)	0	0	15 (10.5)	0	0	
Dysgeusia	2 (1.3)	0	0	13 (9.1)	0	0	
Headache	3 (2.0)	0	0	6 (4.2)	0	0	
Renal and urinary disorders	0 (2.0)			J (11.2)		<u> </u>	
and armary aboracis							

		EYTRUDA		Chemotherapy			
	200 mg	every 3 w	/eeks				
Adverse Reaction		n=153	_	n=143			
	Any	Grade	Grade	Any	Grade	Grade	
	Grade	3	4	Grade	3	4	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Acute kidney injury	2 (1.3)	1 (0.7)	0	2 (1.4)	2 (1.4)	0	
Proteinuria	2 (1.3)	0	0	10 (7.0)	2 (1.4)	0	
Respiratory, thoracic and mediastinal dis	sorders						
Cough	2 (1.3)	0	0	2 (1.4)	0	0	
Dyspnea	4 (2.6)	0	0	6 (4.2)	0	0	
Pneumonitis	5 (3.3)	0	0	0	0	0	
Skin and subcutaneous tissue disorders							
Alopecia	5 (3.3)	0	0	28 (19.6)	0	0	
Dermatitis acneiform	3 (2.0)	0	0	7 (4.9)	0	1 (0.7)	
Dry skin	7 (4.6)	0	0	10 (7.0)	0	0	
Erythema	3 (2.0)	0	0	3 (2.1)	0	0	
Hyperhidrosis	4 (2.6)	0	0	3 (2.1)	0	0	
Nail disorder	2 (1.3)	0	0	1 (0.7)	0	0	
Night sweats	2 (1.3)	0	0	1 (0.7)	0	0	
Pruritus	21 (13.7)	0	0	7 (4.9)	1 (0.7)	0	
Psoriasis	4 (2.6)	2 (1.3)	0	0	0	0	
Rash	17 (11.1)	1 (0.7)	0	11 (7.7)	1 (0.7)	0	
Rash maculo-papular	5 (3.3)	1 (0.7)	0	2 (1.4)	1 (0.7)	0	
Vascular disorders							
Hot flush	2 (1.3)	0	0	1 (0.7)	0	0	
Hypotension	2 (1.3)	0	0	1 (0.7)	0	0	

Microsatellite Instability-High Cancer (MSI-H) or Mismatch Repair Deficient (dMMR) Cancer

Table 23 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, fatigue, diarrhea, and arthralgia. Fourteen percent of patients had \geq Grade 3 adverse events. The most common \geq Grade 3 adverse events (occurring in more than 2 patients) were: alanine aminotransferase increased (n=5, 1.0%), fatigue (n=4, 0.8%), gamma-glutamyltransferase increased (n=4, 0.8%), hyperglycaemia (n=4, 0.8%), pneumonitis (n=4, 0.8%), aspartate aminotransferase increased (n=3, 0.6%), blood alkaline phosphatase increased (n=3, 0.6%), lipase increased (n=3, 0.6%), pancreatitis (n=3, 0.6%).

KEYTRUDA was discontinued for treatment-related adverse events in 7.0% 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=5, 1.0%), alanine aminotransferase increased (n=3, 0.6%), aspartate aminotransferase increased (n=3, 0.6%), hepatitis (n=3, 0.6%), interstitial lung disease (n=3, 0.6%), drug-induced liver injury (n=2, 0.4%), Guillain-Barre syndrome (n=2, 0.4%), transaminases increased (n=2, 0.4%). The median time to discontinuation for treatment-related

adverse events was 8.3 months.

Table 23: Treatment-Related Adverse Events Occurring in ≥ 1% of Patients with MSI-H Cancer treated with KEYTRUDA in KEYNOTE-158 and KEYNOTE-164.

Adverse Event	20	KEYTRUDA 00 mg every 3 weeks n=497	5
Adverse Event	Any Grade	Grade 3	Grade 4*
	n (%)	n (%)	n (%)
Blood and lymphatic system disorders	\ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \	· /	, ,
Anemia	11 (2.2)	0	1 (0.2)
Lymphopenia	7 (1.4)	1 (0.2)	0
Neutropenia	9 (1.8)	0	0
Thrombocytopenia	6 (1.2)	1 (0.2)	0
Endocrine disorders	, , ,	, ,	
Hyperthyroidism	21 (4.2)	1 (0.2)	0
Hypothyroidism	48 (9.7)	0	0
Eye disorders	. , ,		•
Dry eye	7 (1.4)	0	0
Gastrointestinal disorders	· , ,		•
Abdominal pain	10 (2.0)	1 (0.2)	0
Colitis	10 (2.0)	2 (0.4)	0
Constipation	7 (1.4)	0	0
Diarrhea	60 (12.1)	2 (0.4)	0
Dry mouth	12 (2.4)	0	0
Nausea	37 (7.4)	0	0
Stomatitis	9 (1.8)	0	0
Vomiting	15 (3.0)	0	0
General disorders and administration site	conditions		•
Asthenia	46 (9.3)	2 (0.4)	0
Edema peripheral	10 (2.0)	1 (0.2)	0
Fatigue	66 (13.3)	4 (0.8)	0
Pyrexia	15 (3.0)	0	0
Xerosis	7 (1.4)	0	0
Injury, poisoning and procedural complica			•
Infusion related reaction	5 (1.0)	0	0
Investigations			•
Alanine aminotransferase increased	23 (4.6)	4 (0.8)	1 (0.2)
Amylase increased	5 (1.0)	1 (0.2)	Ō
Aspartate aminotransferase increased	20 (4.0)	3 (0.6)	0
Blood alkaline phosphatase increased	6 (1.2)	3 (0.6)	0
Blood creatinine increased	6 (1.2)	0	0
Blood thyroid stimulating hormone increased	6 (1.2)	0	0
Gamma-glutamyltransferase increased	5 (1.0)	4 (0.8)	0
Hemoglobin decreased	5 (1.0)	1 (0.2)	0

Adverse Event	20	KEYTRUDA 200 mg every 3 weeks n=497						
	Any Grade n (%)	Grade 3 n (%)	Grade 4* n (%)					
Lipase increased	5 (1.0)	3 (0.6)	0					
Lymphocyte count decreased	9 (1.8)	2 (0.4)	0					
Metabolism and nutrition disorders			•					
Decreased appetite	19 (3.8)	0	0					
Hyperglycaemia	7 (1.4)	4 (0.8)	0					
Musculoskeletal and connective tissue	disorders							
Arthralgia	57 (11.5)	1 (0.2)	0					
Muscle spasms	8 (1.6)	0	0					
Myalgia	17 (3.4)	0	0					
Pain in extremity	7 (1.4)	0	0					
Nervous system disorders								
Headache	13 (2.6)	0	0					
Respiratory, thoracic and mediastinal	disorders							
Dyspnea	10 (2.0)	0	0					
Interstitial lung disease	5 (1.0)	0	0					
Pneumonitis	11 (2.2)	4 (0.8)	0					
Skin and subcutaneous tissue disorder	S							
Dry skin	17 (3.4)	0	0					
Pruritus	72 (14.5)	0	0					
Psoriasis	6 (1.2)	0	0					
Rash	37 (7.4)	2 (0.4)	0					
Rash maculo-papular	20 (4.0)	0	0					
*No Grade 5 treatment-related adverse even	ents were reported to occu	r in ≥ 1% of patients w	ith MSI-H cancer					

The safety of KEYTRUDA in pediatric patients with advanced melanoma, lymphoma, or PD-L1 positive or MSI-H or dMMR advanced, relapsed, or refractory solid tumours was evaluated in 173 pediatric patients, including 7 pediatric patients with MSI-H or dMMR tumours, in KEYNOTE-051 (See 8.2.1 Clinical Trial Adverse Reactions — Pediatrics).

Endometrial Carcinoma

Table 24 summarizes the treatment-related adverse events that occurred in at least 1% of patients with endometrial carcinoma treated with KEYTRUDA in combination with chemotherapy (paclitaxel and carboplatin) in KEYNOTE-868 (See 14 Clinical Trials). The median duration of exposure was 5.6 months (range: 1 day to 24.0 months) in the KEYTRUDA combination arm and 4.2 months (range: 1 day to 21.4 months) in the chemotherapy arm.

The most common treatment-related adverse events (reported in at least 20% of patients) were fatigue, anemia, alopecia, nausea, peripheral sensory neuropathy, constipation, diarrhea, neuropathy peripheral, white blood cell count decreased, platelet count decreased, neutrophil count decreased, and arthralgia. The most common Grade 3-5 treatment-related adverse events for patients treated with KEYTRUDA in KEYNOTE-868 were anemia (13.9%), neutrophil count decreased (11%), and white

blood cell count decreased (6.8%).

KEYTRUDA was discontinued for adverse events in 13.8% and 15% of patients in the pMMR and dMMR groups, respectively.

Table 24: Treatment-Related Adverse Events Occurring in ≥ 1% of Patients with Endometrial Cancer treated with KEYTRUDA in KEYNOTE-868.

		_						
	and				and			
	Pacli	taxel		Paclitaxel				
	an	d		and				
	Carbo	platin			Carbo	platin		
	n=3	82			n=3	377		
All	Grade	Grade	Grade	All	Grade	Grade	Grade	
Grades	3	4	5	Grades	3	4	5	
n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
em disord	ers							
178 (46.6)	53 (13.9)	0	0	162 (43)	29 (7.7)	0	0	
4 (1.0)	0	0	0	1 (0.3)	0	0	0	
20 (5.2)	9 (2.4)	3 (0.8)	0	19 (5)	5 (1.3)	3 (0.8)	0	
13 (3.4)	1 (0.3)	1 (0.3)	0	7 (1.9)	0	1 (0.3)	0	
6 (1.6)	6 (1.6)	0	0	4 (1.1)	3 (0.8)	0	0	
5 (1.3)	0	0	0	2 (0.5)	0	0	0	
rs								
8 (2.1)	0	0	0	6 (1.6)	0	0	0	
41 (10.7)	0	0	0	11 (2.9)	0	0	0	
23 (6)	0	0	0	9 (2.4)	0	0	0	
6 (1.6)	0	0	0	3 (0.8)	0	0	0	
16 (4.2)	0	0	0	16 (4.2)	0	0	0	
				•			<u> </u>	
s								
4 (1.0)	0	0	0	3 (0.8)	0	0	0	
	All Grades n (%) em disord 178 (46.6) 4 (1.0) 20 (5.2) 13 (3.4) 6 (1.6) 5 (1.3) rs 8 (2.1) 41 (10.7) 23 (6) 6 (1.6) 16 (4.2)	an Paclification of the paclif	KEYTRUDA and Paclitaxel and Carboplatin	KEYTRUDA and Paclitaxel and Carboplatin	KEYTRUDA and Paclitaxel and Carboplatin	REYTRUDA and Place and Paclitaxel and Carboplatin Carbop	REYTRUDA and Paclitaxel and Carboplatin Carbop	

		KEYTR				Plac			
		Pacli			Paclitaxel and				
		an	d						
		Carbo	platin		Carboplatin				
		n=3	82		n=377				
Adverse Reaction	All	Grade	Grade	Grade	All	Grade	Grade	Grade	
Adverse neaction	Grades n (%)	3 n (%)	4 n (%)	5 n (%)	Grades n (%)	3 n (%)	4 n (%)	5 n (%)	
Abdominal pain upper	4 (1.0)	0	0	0	2 (0.5)	0	0	0	
Colitis	6 (1.6)	1 (0.3)	0	0	2 (0.5)	0	0	0	
Constipation	112 (29.3)	2 (0.5)	0	0	90 (23.9)	1 (0.3)	0	0	
Diarrhea	110 (29.8)	5 (1.3)	0	0	103 (27.3)	3 (0.8)	1 (0.3)	0	
Dry mouth	14 (3.7)	0	0	0	6 (1.6)	0	0	0	
Dyspepsia	11 (2.9)	0	0	0	8 (2.1)	0	0	0	
Gastroesophageal reflux disease	5 (1.3)	0	0	0	10 (2.7)	0	0	0	
Hematochezia	4 (1.0)	0	0	0	0	0	0	0	
Nausea	146 (38.2)	4 (1.0)	0	0	129 (34.2)	4 (1.1)	0	0	
Oral pain	4 (1.0)	0	0	0	2 (0.5)	0	0	0	
Stomatitis	31 (8.1)	2 (0.5)	0	0	15 (4.0)	0	0	0	
Vomiting	48 (12.6)	2 (0.5)	0	0	37 (9.8)	4 (1.1)	0	0	
General disorders and ad	ministratio	on site co	nditions						
Asthenia	13 (3.4)	2 (0.5)	0	0	13 (3.4)	1 (0.3)	0	0	
Chest discomfort	4 (1.0)	0	0	0	1 (0.3)	0	0	0	
Chills	8 (2.1)	0	0	0	2 (0.5)	0	0	0	
Edema peripheral	17 (4.5)	0	0	0	7 (1.9)	0	0	0	
Fatigue	225 (58.9)	5 (1.3)	0	0	197 (52.3)	7 (1.9)	0	0	
Localised edema	5 (1.3)	0	0	0	2 (0.5)	0	0	0	
Mucosal inflammation	9 (2.4)	1 (0.3)	0	0	6 (1.6)	0	0	0	
Pain	17 (4.5)	1 (0.3)	0	0	14 (3.7)	1 (0.3)	0	0	
Peripheral swelling	7 (1.8)	0	0	0	2 (0.5)	0	0	0	

	KEYTRUDA and Paclitaxel and Carboplatin n=382				Placebo and Paclitaxel and Carboplatin n=377			
	All	Grade	Grade	Grade	All	Grade	Grade	Grade
Adverse Reaction	Grades n (%)	3 n (%)	4 n (%)	5 n (%)	Grades n (%)	3 n (%)	4 n (%)	5 n (%)
Pyrexia	11 (2.9)	1 (0.3)	0	0	0	0	0	0
Immune system disorders	;							
Drug hypersensitivity	7 (1.8)	0	1 (0.3)	0	5 (1.3)	1 (0.3)	0	0
Hypersensitivity	4 (1.0)	1 (0.3)	0	0	7 (1.9)	1 (0.3)	0	0
Infections and infestation	s							
Candida infection	5 (1.3)	0	0	0	3 (0.8)	0	0	0
Folliculitis	6 (1.6)	0	0	0	5 (1.3)	0	0	0
Rash pustular	6 (1.6)	0	0	0	1 (0.3)	0	0	0
Urinary tract infection	19 (5.0)	7 (1.8)	0	0	3 (0.8)	0	0	0
Injury, poisoning and pro	cedural co	mplicatio	ns					
Contusion	4 (1.0)	0	0	0	3 (0.8)	0	0	0
Infusion related reaction	42 (11.0)	3 (0.8)	0	0	43 (11.4)	5 (1.3)	0	0
Fall	8 (2.1)	1 (0.3)	0	0	6 (1.6)	0	0	0
Investigations						•		•
Alanine aminotransferase increased	42 (11.0)	2 (0.5)	1 (0.3)	0	31 (8.2)	2 (0.5)	0	0
Aspartate aminotransferase increased	40 (10.5)	6 (1.6)	0	0	18 (4.8)	0	0	0
Blood alkaline phosphatase increased	35 (9.2)	1 (0.3)	0	0	33 (8.8)	1 (0.3)	0	0
Blood bilirubin increased	7 (1.8)	0	0	0	3 (0.8)	0	0	0
Blood creatinine increased	39 (10.2)	2 (0.5)	0	0	12 (3.2)	0	0	0
Blood glucose increased	4 (1.0)	1 (0.3)	0	0	1 (0.3)	0	0	0

		KEYTRUDA and Paclitaxel and Carboplatin n=382				Placebo and Paclitaxel and Carboplatin			
					n=377				
Adverse Reaction	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	
Blood magnesium decreased	9 (2.4)	1 (0.3)	0	0	11 (2.9)	0	0	0	
Blood potassium decreased	6 (1.6)	2 (0.5)	0	0	2 (0.5)	0	0	0	
Blood sodium decreased	5 (1.3)	1 (0.3)	1 (0.3)	0	2 (0.5)	0	0	0	
Blood thyroid stimulating hormone increased	18 (4.7)	0	0	0	11 (2.9)	0	0	0	
Blood thyroid stimulating hormone decreased	4 (1.0)	0	0	0	3 (0.8)	0	0	0	
Blood urea increased	8 (2.1)	0	0	0	1 (0.3)	0	0	0	
Hemoglobin decreased	9 (2.4)	3 (0.8)	0	0	9 (2.4)	0	0	0	
Lymphocyte count decreased	62 (16.2)	12 (3.1)	3 (0.8)	0	60 (15.9)	12 (3.2)	1 (0.3)	0	
Neutrophil count decreased	87 (22.8)	24 (6.3)	18 (4.7)	0	81 (21.5)	22 (5.8)	17 (4.5)	0	
Platelet count decreased	93 (24.3)	12 (3.1)	2 (0.5)	0	77 (20.4)	7 (1.9)	0	0	
Weight decreased	25 (6.5)	1 (0.3)	0	0	16 (4.2)	1 (0.3)	0	0	
Weight increased	4 (1.0)	0	0	0	1 (0.3)	0	0	0	
White blood cell count decreased	97 (25.4)	20 (5.2)	6 (1.6)	0	107 (28.4)	17 (4.5)	6 (1.6)	0	
Metabolism and nutrition	disorders	5							
Decreased appetite	66 (17.3)	1 (0.3)	0	0	65 (17.2)	2 (0.5)	0	0	
Dehydration	14 (3.7)	1 (0.3)	0	0	12 (3.2)	4 (1.1)	0	0	
Hypercalcemia	7 (1.8)	0	0	0	4 (1.1)	0	1 (0.3)	0	
Hyperglycemia	24 (6.3)	6 (1.6)	1 (0.3)	0	16 (4.2)	0	0	0	
Hyperkalemia	5 (1.3)	0	0	0	5 (1.3)	0	0	0	
Hypoalbuminemia	22	1 (0.3)	0	0	15	0	0	0	

		KEYTRUDA and Paclitaxel and Carboplatin n=382				Placebo and Paclitaxel and Carboplatin			
					n=377				
Adverse Reaction	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	
	(5.8)				(4.0)				
Hypocalcemia	13 (3.4)	1 (0.3)	0	0	12 (3.2)	1 (0.3)	0	0	
Hypokalemia	31 (8.1)	3 (0.8)	0	0	39 (10.3)	10 (2.7)	1 (0.3)	0	
Hypomagnesemia	41 (10.7)	1 (0.3)	1 (0.3)	0	34 (9.0)	0	0	0	
Hyponatremia	32 (8.4)	3 (0.8)	1 (0.3)	0	14 (3.7)	1 (0.3)	0	0	
Musculoskeletal and connective tissue disorders									
Arthralgia	80 (20.9)	3 (0.8)	0	0	97 (25.7)	1 (0.3)	0	0	
Arthritis	4 (1.0)	0	0	0	0	0	0	0	
Back pain	8 (2.1)	0	0	0	15 (4.0)	1 (0.3)	0	0	
Bone pain	25 (6.5)	1 (0.3)	0	0	26 (6.9)	0	0	0	
Muscle spasms	13 (3.4)	0	0	0	12 (3.2)	0	0	0	
Muscular weakness	25 (6.5)	0	0	0	20 (5.3)	3 (0.8)	0	0	
Myalgia	61 (16.0)	2 (0.5)	0	0	52 (13.8)	4 (1.1)	0	0	
Pain in extremity	37 (9.7)	2 (0.5)	0	0	26 (6.9)	0	0	0	
Nervous system disorders									
Balance disorder	5 (1.3)	0	0	0	0	0	0	0	
Dizziness	30 (7.9)	1 (0.3)	0	0	28 (7.4)	0	0	0	
Dysgeusia	26 (6.8)	0	0	0	29 (7.7)	0	0	0	
Headache	32 (8.4)	1 (0.3)	0	0	22 (5.8)	0	0	0	

	KEYTRUDA and Paclitaxel and Carboplatin n=382				Placebo and Paclitaxel and Carboplatin n=377			
Adverse Reaction	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Hypoesthesia	10 (2.6)	0	0	0	9 (2.4)	0	0	0
Neuralgia	4 (1.0)	1 (0.3)	0	0	0	0	0	0
Neuropathy peripheral	98 (25.7)	3 (0.8)	0	0	86 (22.8)	0	0	0
Paresthesia	27 (7.1)	1 (0.3)	0	0	27 (7.2)	0	0	0
Peripheral motor neuropathy	12 (3.1)	2 (0.5)	0	0	5 (1.3)	0	0	0
Peripheral sensory neuropathy	117 (30.6)	4 (1.0)	0	0	113 (30.0)	2 (0.5)	0	0
Restless legs syndrome	7 (1.8)	0	0	0	3 (0.8)	0	0	0
Taste disorder	10 (2.6)	0	0	0	8 (2.1)	0	0	0
Tremor	5 (1.3)	0	0	0	1 (0.3)	0	0	0
Psychiatric disorders								
Insomnia	16 (4.2)	1 (0.3)	0	0	8 (2.1)	0	0	0
Renal and urinary disorde	ers							
Acute kidney injury	4 (1.0)	3 (0.8)	1 (0.3)	0	2 (0.5)	1 (0.3)	1 (0.3)	0
Pollakiuria	4 (1.0)	0	0	0	2 (0.5)	0	0	0
Respiratory, thoracic and	mediastin	al disorde	ers					
Cough	21 (5.5)	0	0	0	5 (1.3)	0	0	0
Dyspnea	34 (8.9)	2 (0.5)	0	0	28 (7.4)	0	0	0
Epistaxis	5 (1.3)	0	0	0	2 (0.5)	0	0	0
Oropharyngeal pain	6 (1.6)	0	0	0	5 (1.3)	1 (0.3)	0	0
Pneumonitis	4 (1.0)	2 (0.5)	0	0	2 (0.5)	0	0	0
Rhinorrhea	4 (1.0)	0	0	0	3 (0.8)	0	0	0
Skin and subcutaneous tis	sue disor	ders						
Alopecia	163	0	0	0	167	0	0	0

		KEYTRUDA and Paclitaxel and Carboplatin n=382				Placebo and Paclitaxel and Carboplatin n=377			
Adverse Reaction	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	
	(42.7)				(44.3)				
Dermatitis acneiform	7 (1.8)	0	0	0	5 (1.3)	0	0	0	
Dry skin	14 (3.7)	0	0	0	9 (2.4)	0	0	0	
Erythema	5 (1.3)	0	0	0	0	0	0	0	
Nail discoloration	5 (1.3)	0	0	0	0	0	0	0	
Nail disorder	6 (1.6)	0	0	0	2 (0.5)	0	0	0	
Pain of skin	6 (1.6)	0	0	0	5 (1.3)	0	0	0	
Pruritus	47 (12.3)	1 (0.3)	0	0	34 (9.0)	2 (0.5)	0	0	
Rash	44 (11.5)	3 (0.8)	0	0	25 (6.6)	3 (0.8)	0	0	
Rash maculo-papular	43 (11.3)	6 (1.6)	0	0	17 (4.5)	2 (0.5)	0	0	
Skin disorder	4 (1.0)	0	0	0	0	0	0	0	
Vascular disorders									
Embolism	4 (1.0)	1 (0.3)	0	0	2 (0.5)	1 (0.3)	0	0	
Flushing	11 (2.9)	0	0	0	6 (1.6)	0	0	0	
Hot flush	5 (1.3)	0	0	0	5 (1.3)	0	0	0	
Hypertension	13 (3.4)	4 (1.0)	0	0	13 (3.4)	6 (1.6)	0	0	
Hypotension	4 (1.0)	1 (0.3)	0	0	6 (1.6)	0	0	0	

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 14 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 Table 25 and Table 26 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 26 below for the most common serious adverse events.

The most common adverse events (\geq 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 ($\geq 2\%$) 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%); hypomagnesemia (2%); hypomagnesemia (2%); and syncope (2%).

Table 25 summarizes adverse events experienced by patients who received KEYTRUDA in combination with lenvatinib.

Table 25: Adverse Events in ≥ 20% of Patients with Endometrial Carcinoma in KEYNOTE-146.

Adverse Event	KEYTRUDA 200 mg and 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		
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

Table 26: Serious Adverse Events Occurring in ≥ 3% of Endometrial Carcinoma Patients in KEYNOTE-146.

Serious Adverse Event	KEYTRUDA 200 mg and Lenvatinib 20 mg n=94
Endocrine	
Adrenal insufficiency	3.2

^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

¹ Includes dyspnea and exertional dyspnea

^j Includes rash, generalized rash, macular rash, and maculo-papular rash

^k Includes essential hypertension, hypertension, and hypertensive encephalopathy

¹ 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

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

The safety of KEYTRUDA in combination with lenvatinib was investigated in KEYNOTE-775, a multicenter, open-label, randomized (1:1), active-controlled trial in patients with advanced endometrial carcinoma previously treated with at least one prior platinum-based chemotherapy regimen in any setting, including in the neoadjuvant and adjuvant settings (See 14 Clinical Trials). Patients with endometrial carcinoma that is not MSI-H or dMMR received KEYTRUDA 200 mg every 3 weeks in combination with lenvatinib 20mg orally once daily (n=342) or received doxorubicin or paclitaxel (n=325).

For patients with not MSI-H or dMMR tumour status, the median duration of study treatment was 7.2 months (range: 1 day to 26.8 months) and the median duration of exposure to KEYTRUDA was 6.8 months (range: 1 day to 25.8 months). (The conversion is 30.4367 days)

The most common adverse events (reported in at least 30% of patients) among these patients receiving KEYTRUDA and lenvatinib were hypothyroidism, hypertension, fatigue, diarrhea, musculoskeletal disorders, nausea, decreased appetite, vomiting, stomatitis, abdominal pain, weight loss, and urinary tract infection. Eighty-eight percent of patients had \geq Grade 3 adverse events. The most common \geq Grade 3 adverse events (\geq 5%) were hypertension (39%), fatigue (11%), weight loss (10%), decreased appetite (8%), diarrhea (8%), proteinuria (6%), musculoskeletal disorders (5%), and urinary tract infection (5%).

Fatal adverse events among these patients occurred in 4.7% of those treated with KEYTRUDA and lenvatinib, including 2 cases of pneumonia, and 1 case of the following: acute kidney injury, acute

^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

myocardial infarction, colitis, decreased appetite, intestinal perforation, lower gastrointestinal hemorrhage, malignant gastrointestinal obstruction, multiple organ dysfunction syndrome, myelodysplastic syndrome, pulmonary embolism, and right ventricular dysfunction.

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

Discontinuation of KEYTRUDA due to an adverse event occurred in 15% of these patients. The most common adverse event leading to discontinuation of KEYTRUDA (≥1%) was increased ALT (1.2%). Dose interruptions of KEYTRUDA due to an adverse event occurred in 48% of these patients. The most common adverse events leading to interruption of KEYTRUDA (≥3%) were diarrhea (8%), increased ALT (4.4%), increased AST (3.8%), and hypertension (3.5%).

Table 27 Treatment-Related Adverse Events Occurring in ≥ 1% of Patients with Endometrial Carcinoma that is not MSI-H or dMMR treated with KEYTRUDA in Combination with Lenvatinib in KEYNOTE-775.

	KEYTRUDA				Doxorubicin or Paclitaxel			
		an	d					
		Lenva	tinib					
		n=3	42			n=3	25	
Adverse Reaction	All	Grade	Grade	Grade	All	Grade	Grade	Grade
Auverse neaction	Grades	3	4	5	Grades	3	4	5
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Blood and lymphatic system	disorders							
Anemia	50 (14.6)	7 (2.0)	0	0	128 (39.4)	32 (9.8)	2 (0.6)	0
Leukopenia	14 (4.1)	0	0	0	38 (11.7)	18 (5.5)	4 (1.2)	0
Lymphopenia	10 (2.9)	1 (0.3)	0	0	22 (6.8)	7 (2.2)	2 (0.6)	0
Neutropenia	17 (5.0)	4 (1.2)	0	0	108 (33.2)	31 (9.5)	49 (15.1)	0
Thrombocytopenia	22 (6.4)	4 (1.2)	0	0	18 (5.5)	2 (0.6)	1 (0.3)	0
Cardiac disorders								
Palpitations	4 (1.2)	0	0	0	0	0	0	0
Tachycardia	5 (1.5)	0	0	0	2 (0.6)	0	0	0
Endocrine disorders								
Hyperthyroidism	31 (9.1)	3 (0.9)	0	0	1 (0.3)	0	0	0
Hypothyroidism	183 (53.5)	2 (0.6)	0	0	0	0	0	0
Thyroiditis	4 (1.2)	0	0	0	0	0	0	0
Eye disorders								
Dry eye	4 (1.2)	0	0	0	3 (0.9)	0	0	0

		KEYTR and Lenva	d tinib		Dox	Doxorubicin or Paclitaxel			
		n=3	42			n=3	25		
Adverse Reaction	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	
Vision blurred	5 (1.5)	0	0	0	3 (0.9)	0	0	0	
Gastrointestinal disorders	•	•			•			·	
Abdominal distension	5 (1.5)	0	0	0	3 (0.9)	0	0	0	
Abdominal pain	25 (7.3)	2 (0.6)	0	0	9 (2.8)	0	0	0	
Abdominal pain upper	21 (6.1)	0	0	0	12 (3.7)	0	0	0	
Aphthous ulcer	5 (1.5)	0	0	0	3 (0.9)	0	0	0	
Colitis	14 (4.1)	6 (1.8)	0	1 (0.3)	0	0	0	0	
Constipation	34 (9.9)	0	0	0	43 (13.2)	0	0	0	
Diarrhea	146 (42.7)	20 (5.8)	0	0	33 (10.2)	3 (0.9)	0	0	
Dry mouth	29 (8.5)	0	0	0	8 (2.5)	0	0	0	
Dyspepsia	16 (4.7)	1 (0.3)	0	0	6 (1.8)	0	0	0	
Dysphagia	6 (1.8)	0	0	0	0	0	0	0	
Feces soft	4 (1.2)	0	0	0	0	0	0	0	
Flatulence	6 (1.8)	0	0	0	3 (0.9)	0	0	0	
Gastritis	9 (2.6)	0	0	0	0	0	0	0	
Gastroesophageal reflux disease	14 (4.1)	0	0	0	2 (0.6)	0	0	0	
Nausea	128 (37.4)	8 (2.3)	0	0	134 (41.2)	4 (1.2)	0	0	
Oral dysesthesia	6 (1.8)	0	0	0	1 (0.3)	0	0	0	
Oral pain	15 (4.4)	2 (0.6)	0	0	2 (0.6)	0	0	0	
Stomatitis	59 (17.3)	7 (2.0)	0	0	40 (12.3)	1 (0.3)	0	0	
Vomiting	80 (23.4)	7 (2.0)	0	0	49 (15.1)	5 (1.5)	0	0	
General disorders and admir	nistration site	e condition	ns						
Asthenia	64 (18.7)	15 (4.4)	0	0	64 (19.7)	7 (2.2)	0	0	
Chills	6 (1.8)	0	0	0	3 (0.9)	0	0	0	
Fatigue	95 (27.8)	12 (3.5)	0	0	80 (24.6)	9 (2.8)	0	0	
Malaise	14 (4.1)	1 (0.3)	0	0	13 (4.0)	0	0	0	

		KEYTR and Lenva	d		Dox	korubicin or Paclitaxel			
		n=3				n=3	25		
	All	Grade	Grade	Grade	All	Grade	Grade	Grade	
Adverse Reaction	Grades	3	4	5	Grades	3	4	5	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Mucosal inflammation	36 (10.5)	2 (0.6)	0	0	30 (9.2)	3 (0.9)	0	0	
Edema	9 (2.6)	0	0	0	1 (0.3)	0	0	0	
Edema peripheral	16 (4.7)	0	0	0	8 (2.5)	1 (0.3)	0	0	
Pyrexia	25 (7.3)	1 (0.3)	0	0	3 (0.9)	0	0	0	
Hepatobiliary disorders									
Hepatotoxicity	4 (1.2)	3 (0.9)	0	0	0	0	0	0	
Immune-mediated hepatitis	5 (1.5)	5 (1.5)	0	0	0	0	0	0	
Infections and infestations			<u> </u>			<u> </u>			
Urinary tract infection	12 (3.5)	2 (0.6)	0	0	4 (1.2)	0	0	0	
Investigations									
Alanine aminotransferase	56	11 (2.2)	1 (0.2)	0	12 (2.7)	2 (0 6)	0	0	
increased	(16.4)	11 (3.2)	1 (0.3)	0	12 (3.7)	2 (0.6)	0	0	
Amylase increased	17 (5.0)	2 (0.6)	1 (0.3)	0	1 (0.3)	0	0	0	
Aspartate aminotransferase increased	53 (15.5)	11 (3.2)	0	0	9 (2.8)	2 (0.6)	0	0	
Blood alkaline phosphatase increased	22 (6.4)	4 (1.2)	0	0	5 (1.5)	2 (0.6)	0	0	
Blood bilirubin increased	8 (2.3)	2 (0.6)	0	0	2 (0.6)	1 (0.3)	0	0	
Blood cholesterol increased	10 (2.9)	0	0	0	0	0	0	0	
Blood creatine phosphokinase increased	12 (3.5)	3 (0.9)	1 (0.3)	0	1 (0.3)	0	0	0	
Blood creatinine increased	17 (5.0)	1 (0.3)	0	0	2 (0.6)	0	0	0	
Blood lactate dehydrogenase increased	9 (2.6)	0	0	0	4 (1.2)	0	0	0	
Blood thyroid stimulating hormone increased	33 (9.6)	0	0	0	0	0	0	0	
Blood triglycerides increased	6 (1.8)	0	0	0	1 (0.3)	0	0	0	
Electrocardiogram QT prolonged	9 (2.6)	2 (0.6)	0	0	6 (1.8)	0	0	0	
Gamma-glutamyltransferase increased	7 (2.0)	2 (0.6)	1 (0.3)	0	4 (1.2)	0	0	0	
Lipase increased	28 (8.2)	12 (3.5)	5 (1.5)	0	2 (0.6)	1 (0.3)	0	0	
Lymphocyte count	10 (2.9)	3 (0.9)	0	0	19 (5.8)	10	2 (0.6)	0	

		KEYTR			Dox	corubicin or Paclitaxel		
		an Lenva	-					
		n=3				n-2	25	
	All	Grade	All	n=325 All Grade Grade Grade				
Adverse Reaction	Grades	3	Grade 4	Grade 5	Grades	3	Grade 4	Grade 5
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
decreased		. ,			. ,	(3.1)		
Neutrophil count decreased	17 (5.0)	7 (2.0)	0	0	82 (25.2)	24 (7.4)	51 (15.7)	0
Platelet count decreased	39 (11.4)	4 (1.2)	1 (0.3)	0	15 (4.6)	2 (0.6)	0	0
Weight decreased	78 (22.8)	19 (5.6)	0	0	7 (2.2)	0	0	0
White blood cell count decreased	13 (3.8)	3 (0.9)	0	0	56 (17.2)	29 (8.9)	10 (3.1)	0
Metabolism and nutrition disc	orders					I		I.
Decreased appetite	123 (36.0)	19 (5.6)	0	0	54 (16.6)	0	0	0
Dehydration	10 (2.9)	2 (0.6)	1 (0.3)	0	3 (0.9)	1 (0.3)	0	0
Hypercholesterolemia	9 (2.6)	1 (0.3)	0	0	2 (0.6)	0	0	0
Hyperglycemia	11 (3.2)	4 (1.2)	0	0	2 (0.6)	0	0	0
Hypertriglyceridemia	21 (6.1)	3 (0.9)	0	0	1 (0.3)	0	0	0
Hypoalbuminemia	8 (2.3)	1 (0.3)	0	0	3 (0.9)	0	0	0
Hypocalcemia	8 (2.3)	3 (0.9)	0	0	2 (0.6)	1 (0.3)	0	0
Hypokalemia	17 (5.0)	4 (1.2)	1 (0.3)	0	8 (2.5)	1 (0.3)	1 (0.3)	0
Hypomagnesemia	35 (10.2)	3 (0.9)	0	0	11 (3.4)	0	0	0
Hyponatremia	12 (3.5)	5 (1.5)	2 (0.6)	0	4 (1.2)	1 (0.3)	0	0
Musculoskeletal and connecti	ve tissue di	sorders						
Arthralgia	75 (21.9)	3 (0.9)	0	0	15 (4.6)	0	0	0
Back pain	7 (2.0)	0	0	0	6 (1.8)	0	0	0
Muscle spasms	7 (2.0)	0	0	0	4 (1.2)	0	0	0
Muscular weakness	6 (1.8)	1 (0.3)	0	0	4 (1.2)	0	0	0
Musculoskeletal pain	6 (1.8)	0	0	0	0	0	0	0
Musculoskeletal stiffness	4 (1.2)	0	0	0	0	0	0	0
Myalgia	46 (13.5)	3 (0.9)	0	0	11 (3.4)	0	0	0
Pain in extremity	20 (5.8)	4 (1.2)	0	0	8 (2.5)	0	0	0
Nervous system disorders								

Adverse Reaction	des %)	Lenva n=34 Grade 3 n (%)	tinib 42 Grade			n-2			
Dizziness 14 (4 26 7 7 7 7 7 7 7 7 7	des %)	Grade 3	Grade			n-2			
Dizziness 14 (4 26 7 7 7 7 7 7 7 7 7	des %)	3				n=325			
Dizziness 14 (4) Dysgeusia 26 (7) Headache 48 (14) Neuropathy peripheral 7 (2) Taste disorder 4 (1) Tremor 4 (1) Psychiatric disorders Depression 6 (1) Insomnia 4 (1) Renal and urinary disorders Acute kidney injury 8 (2) Hematuria 4 (1) Proteinuria 88 (25)	%)	_	_	Grade	All	Grade	Grade	Grade	
Dizziness 14 (4) Dysgeusia 26 (7) Headache (14. Neuropathy peripheral 7 (2) Taste disorder 4 (1) Tremor 4 (1) Psychiatric disorders Depression 6 (1) Insomnia 4 (1) Renal and urinary disorders Acute kidney injury 8 (2) Hematuria 4 (1) Proteinuria 88 (2) (25. (25.		n (%)	4	5	Grades	3	4	5	
Dysgeusia 26 (7) Headache 48 (14) Neuropathy peripheral 7 (2) Taste disorder 4 (1) Tremor 4 (1) Psychiatric disorders Depression 6 (1) Insomnia 4 (1) Renal and urinary disorders Acute kidney injury 8 (2) Hematuria 4 (1) Proteinuria 88 (25)	1.1)	(/9)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Headache Headache Neuropathy peripheral Taste disorder 4 (1 Tremor Psychiatric disorders Depression Insomnia 4 (1 Renal and urinary disorders Acute kidney injury Hematuria Proteinuria 4 (1 Renal and urinary disorders 8 (25)		0	0	0	4 (1.2)	0	0	0	
Neuropathy peripheral 7 (2 Taste disorder 4 (1 Tremor 4 (1 Psychiatric disorders Depression 6 (1 Insomnia 4 (1 Renal and urinary disorders Acute kidney injury 8 (2 Hematuria 4 (1 Proteinuria 88 (25)	7.6)	0	0	0	22 (6.8)	0	0	0	
Taste disorder 4 (1 Tremor 4 (1 Psychiatric disorders Depression 6 (1 Insomnia 4 (1 Renal and urinary disorders Acute kidney injury 8 (2 Hematuria 4 (1 Proteinuria 88 (25)		1 (0.3)	0	0	13 (4.0)	0	0	0	
Tremor 4 (1 Psychiatric disorders Depression 6 (1 Insomnia 4 (1 Renal and urinary disorders Acute kidney injury 8 (2 Hematuria 4 (1 Proteinuria 88 (25)	.0)	0	0	0	19 (5.8)	1 (0.3)	0	0	
Psychiatric disorders Depression 6 (1 Insomnia 4 (1 Renal and urinary disorders Acute kidney injury 8 (2 Hematuria 4 (1 Proteinuria 88 (25)	.2)	0	0	0	4 (1.2)	0	0	0	
Depression 6 (1 Insomnia 4 (1 Renal and urinary disorders Acute kidney injury 8 (2 Hematuria 4 (1 Proteinuria 88 (25.	.2)	0	0	0	0	0	0	0	
Insomnia 4 (1 Renal and urinary disorders Acute kidney injury 8 (2 Hematuria 4 (1 Proteinuria 88 (25.									
Renal and urinary disorders Acute kidney injury 8 (2 Hematuria 4 (1 Proteinuria 88 (25.	.8)	0	0	0	0	0	0	0	
Acute kidney injury 8 (2 Hematuria 4 (1 Proteinuria 88 (25.	.2)	0	0	0	4 (1.2)	0	0	0	
Hematuria 4 (1 Proteinuria 88 (25.	'								
Proteinuria 88 (25.	.3)	5 (1.5)	0	0	1 (0.3)	1 (0.3)	0	0	
Proteinuria (25.	.2)	0	0	0	6 (1.8)	1 (0.3)	0	0	
Reproductive system and breast disc		15 (4.4)	1 (0.3)	0	3 (0.9)	0	0	0	
	order	rs							
Vaginal hemorrhage 5 (1	.5)	0	0	0	0	0	0	0	
Respiratory, thoracic and mediastina	al disc	orders							
Aphonia 5 (1	.5)	0	0	0	1 (0.3)	0	0	0	
Cough 14 (4	1.1)	0	0	0	5 (1.5)	0	0	0	
Dysphonia 62 (18.		0	0	0	2 (0.6)	0	0	0	
Dyspnea 12 (3	3.5)	1 (0.3)	0	0	11 (3.4)	0	0	0	
Epistaxis 22 (6	5.4)	0	0	0	7 (2.2)	0	0	0	
Nasal dryness 4 (1	.2)	0	0	0	0	0	0	0	
Oropharyngeal pain 4 (1	.2)	0	0	0	1 (0.3)	0	0	0	
Pneumonitis 4 (1	.2)	2 (0.6)	0	0	0	0	0	0	
Pulmonary embolism 5 (1	.5)	4 (1.2)	0	0	3 (0.9)	1 (0.3)	0	1 (0.3)	
Skin and subcutaneous tissue disord	ers								
Alopecia 17 (5	5.0)	0	0	0	103 (31.7)	2 (0.6)	0	0	
Dry skin 14 (4		1 (0.3)	0	0	6 (1.8)	0	0	0	

	KEYTRUDA and Lenvatinib				Doxorubicin or Paclitaxel				
Adverse Reaction		n=342				n=325			
	All Grades	Grade 3	Grade 4	Grade 5	All Grades	Grade 3	Grade 4	Grade 5	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Erythema	5 (1.5)	2 (0.6)	0	0	3 (0.9)	0	0	0	
Pain of skin	4 (1.2)	0	0	0	2 (0.6)	0	0	0	
Palmar-plantar erythrodysesthesia syndrome	74 (21.6)	10 (2.9)	0	0	3 (0.9)	0	0	0	
Pruritus	20 (5.8)	0	0	0	6 (1.8)	0	0	0	
Rash	38 (11.1)	2 (0.6)	0	0	6 (1.8)	0	0	0	
Rash maculo-papular	12 (3.5)	3 (0.9)	0	0	2 (0.6)	0	0	0	
Skin exfoliation	4 (1.2)	0	0	0	0	0	0	0	
Skin lesion	5 (1.5)	1 (0.3)	0	0	0	0	0	0	
Vascular disorders									
Hypertension	213 (62.3)	122 (35.7)	1 (0.3)	0	3 (0.9)	0	0	0	
Hypotension	4 (1.2)	2 (0.6)	0	0	3 (0.9)	0	0	0	

Renal Cell Carcinoma

In Combination with Axitinib (KEYNOTE-426)

Table 28 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 \geq Grade 3 treatment-related adverse events. The most common \geq 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 \geq 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 $\frac{4}{2}$ Dosage And Administration and 7 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 \geq 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 (\geq 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 (\geq 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 ($\geq 2\%$) 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 (\geq 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 (\geq 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 (\geq 2%) were: hypertension (4.0%); diarrhea (3.5%); and palmar-plantar erythrodysesthesia syndrome (2.3%).

Table 28: Treatment-Related Adverse Events Occurring in ≥ 1% of Patients with Renal Cell Carcinoma treated with KEYTRUDA in Combination with Axitinib in KEYNOTE-426.

		KEYTR an Axiti	d			Sunit	inib	
Adverse Reaction		n=4				n=4	25	
	Any	Grade	Grade	Grade	Any	Grade	Grade	Grade
	Grade	3	4	5	Grade	3	4	5
Discolored bounds at a contamp	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Blood and lymphatic system	aisoraers		<u> </u>		<u></u>	12		
Anemia	12 (2.8)	0	1 (0.2)	0	69 (16.2)	13 (3.1)	0	0
Leukopenia	5 (1.2)	0	0	0	37 (8.7)	6 (1.4)	0	0
Neutropenia	6 (1.4)	0	1 (0.2)	0	79 (18.6)	27 (6.4)	1 (0.2)	0
Thrombocytopenia	8 (1.9)	0	0	0	94 (22.1)	20 (4.7)	2 (0.5)	0
Endocrine disorders								
Adrenal insufficiency	9 (2.1)	1 (0.2)	0	0	1 (0.2)	0	0	0
Hyperthyroidism	52 (12.1)	4 (0.9)	0	0	14 (3.3)	0	0	0
Hypophysitis	5 (1.2)	4 (0.9)	0	0	0	0	0	0
Hypothyroidism	135 (31.5)	1 (0.2)	0	0	119 (28.0)	0	0	0
Thyroiditis	10 (2.3)	1 (0.2)	0	0	0	0	0	0
Eye disorders								
Dry eye	5 (1.2)	0	0	0	7 (1.6)	0	0	0
Gastrointestinal disorders		T	ı	T	ı		T	ı
Abdominal discomfort	5 (1.2)	0	0	0	3 (0.7)	0	0	0
Abdominal pain	23 (5.4)	3 (0.7)	0	0	16 (3.8)	0	0	0
Abdominal pain upper	13 (3.0)	1 (0.2)	0	0	20 (4.7)	1 (0.2)	0	0
Colitis	8 (1.9)	5 (1.2)	0	0	1 (0.2)	0	0	0
Constipation	31 (7.2)	0	0	0	29 (6.8)	0	0	0
Diarrhea	210 (49)	31(7.2)	0	0	175 (41.2)	19 (4.5)	0	0
Dry mouth	17 (4.0)	0	0	0	22 (5.2)	0	0	0
Dyspepsia	12 (2.8)	0	0	0	48 (11.3)	1 (0.2)	0	0
Dysphagia	9 (2.1)	1 (0.2)	0	0	4 (0.9)	0	0	0
Esophagitis	6 (1.4)	0	0	0	3 (0.7)	0	0	0
Flatulence	13 (3.0)	0	0	0	9 (2.1)	0	0	0
Gastritis	6 (1.4)	0	0	0	4 (0.9)	0	0	0
Gastroesophageal reflux disease	6 (1.4)	0	0	0	34 (8.0)	3 (0.7)	0	0
Nausea	91 (21.2)	2 (0.5)	0	0	111 (26.1)	4 (0.9)	0	0
Oral pain	17 (4)	0	0	0	13 (3.1)	0	0	0
Stomatitis	61	3 (0.7)	0	0	86	9 (2.1)	0	0

		KEYTR an Axiti	d		Sunitinib				
Adverse Reaction		n=4	-		n=425				
	Any	Grade	Grade	Grade	Any	Grade	Grade	Grade	
	Grade	3	4	5	Grade	3	4	5	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
	(14.2)				(20.2)				
Vomiting	34 (7.9)	1 (0.2)	0	0	56 (13.2)	3 (0.7)	0	0	
General disorders and admin	istration si	te conditio	ns			•	•		
Asthenia	50 (11.7)	6 (1.4)	0	0	54 (12.7)	12 (2.8)	0	0	
Chills	8 (1.9)	0	0	0	11 (2.6)	1 (0.2)	0	0	
Edema peripheral	7 (1.6)	1 (0.2)	0	0	14 (3.3)	0	0	0	
Fatigue	130 (30.3)	10 (2.3)	0	0	142 (33.4)	21 (4.9)	0	0	
Malaise	8 (1.9)	1 (0.2)	0	0	13 (3.1)	0	0	0	
Mucosal inflammation	55 (12.8)	4 (0.9)	0	0	90 (21.2)	7 (1.6)	0	0	
Pyrexia	16 (3.7)	0	0	0	24 (5.6)	0	0	0	
Hepatobiliary disorders		l	I.			I.			
Hepatic function abnormal	13 (3.0)	6 (1.4)	0	0	6 (1.4)	0	0	0	
Hepatitis	6 (1.4)	4 (0.9)	2 (0.5)	0	1 (0.2)	0	0	0	
Hyperbilirubinemia	5 (1.2)	0	0	0	6 (1.4)	0	1 (0.2)	0	
Infections and infestations						•			
Gingivitis	5 (1.2)	0	0	0	4 (0.9)	0	0	0	
Investigations									
Alanine aminotransferase increased	102 (23.8)	48 (11.2)	4 (0.9)	0	54 (12.7)	10 (2.4)	1 (0.2)	0	
Aspartate aminotransferase increased	97 (22.6)	26 (6.1)	3 (0.7)	0	59 (13.9)	7 (1.6)	0	0	
Blood alkaline phosphatase increased	17 (4.0)	5 (1.2)	0	0	15 (3.5)	3 (0.7)	0	0	
Blood bilirubin increased	19 (4.4)	1 (0.2)	1 (0.2)	0	20 (4.7)	1 (0.2)	0	0	
Blood creatinine increased	24 (5.6)	0	0	0	30 (7.1)	1 (0.2)	0	0	
Blood lactate dehydrogenase increased	8 (1.9)	0	0	0	12 (2.8)	0	0	0	
Blood pressure increased	13 (3.0)	6 (1.4)	0	0	6 (1.4)	1 (0.2)	0	0	
Blood thyroid stimulating hormone increased	22 (5.1)	0	0	0	22 (5.2)	0	0	0	
Lymphocyte count decreased	6 (1.4)	1 (0.2)	0	0	13 (3.1)	2 (0.5)	1 (0.2)	0	
Platelet count decreased	14 (3.3)	0	1 (0.2)	0	76 (17.9)	27 (6.4)	4 (0.9)	0	
Weight decreased	41 (9.6)	6 (1.4)	0	0	36 (8.5)	0	0	0	

		KEYTR an Axiti	d nib		Sunitinib n=425				
Adverse Reaction		n=4						Г	
	Any	Grade	Grade	Grade	Any	Grade	Grade	Grade	
	Grade	3	4	5	Grade	3	4	5	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
Metabolism and nutrition dis	1				l		1	1	
Decreased appetite	94 (21.9)	9 (2.1)	0	0	106 (24.9)	2 (0.5)	0	0	
Dehydration	9 (2.1)	4 (0.9)	0	0	8 (1.9)	5 (1.2)	0	0	
Hyperglycemia	13 (3.0)	5 (1.2)	1 (0.2)	0	4 (0.9)	0	0	0	
Hyperkalemia	10 (2.3)	1 (0.2)	0	0	4 (0.9)	1 (0.2)	0	0	
Hypoalbuminemia	6 (1.4)	1 (0.2)	0	0	5 (1.2)	1 (0.2)	0	0	
Hyponatremia	13 (3.0)	5 (1.2)	0	0	13 (3.1)	6 (1.4)	2 (0.5)	0	
Hypophosphatemia	6 (1.4)	2 (0.5)	0	0	26 (6.1)	11 (2.6)	0	0	
Musculoskeletal and connect	ive tissue o	lisorders			•	•	•		
Arthralgia	52 (12.1)	3 (0.7)	0	0	15 (3.5)	2 (0.5)	0	0	
Arthritis	5 (1.2)	2 (0.5)	0	0	0	0	0	0	
Back pain	9 (2.1)	0	0	0	5 (1.2)	0	0	0	
Muscle spasms	8 (1.9)	0	0	0	5 (1.2)	0	0	0	
Muscular weakness	5 (1.2)	0	0	0	1 (0.2)	0	0	0	
Myalgia	23 (5.4)	0	0	0	16 (3.8)	0	0	0	
Pain in extremity	18 (4.2)	0	0	0	20 (4.7)	2 (0.5)	0	0	
Nervous system disorders	, ,				, ,	, ,	I		
Dizziness	10 (2.3)	0	0	0	14 (3.3)	0	0	0	
Dysgeusia	40 (9.3)	1 (0.2)	0	0	129 (30.4)	0	0	0	
Headache	35 (8.2)	3 (0.7)	0	0	33 (7.8)	1 (0.2)	0	0	
Lethargy	9 (2.1)	0	0	0	8 (1.9)	1 (0.2)	0	0	
Paresthesia	6 (1.4)	0	0	0	5 (1.2)	0	0	0	
Psychiatric disorders			•			•		•	
Insomnia	6 (1.4)	0	0	0	8 (1.9)	0	0	0	
Renal and urinary disorders			I.	L		I.		I.	
Acute kidney injury	7 (1.6)	4 (0.9)	0	0	4 (0.9)	1 (0.2)	0	0	
Hematuria	8 (1.9)	2 (0.5)	0	0	8 (1.9)	1 (0.2)	0	0	
Proteinuria	66 (15.4)	11 (2.6)	0	0	39 (9.2)	6 (1.4)	0	0	
Respiratory, thoracic and me	diastinal di	sorders							
Cough	32 (7.5)	1 (0.2)	0	0	12 (2.8)	0	0	0	
Dysphonia	98 (22.8)	1 (0.2)	0	0	12 (2.8)	0	0	0	
Dyspnea	28 (6.5)	2 (0.5)	0	0	16 (3.8)	2 (0.5)	0	0	
Epistaxis	19 (4.4)	0	0	0	32 (7.5)	0	0	0	
•	· · · /	-			/				

		KEYTR	UDA		Sunitinib					
		an								
		Axiti	-							
Adverse Reaction		n=4	29		n=425					
	Any	Grade	Grade	Grade	Any	Grade	Grade	Grade		
	Grade	3	4	5	Grade	3	4	5		
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)		
Oropharyngeal pain	13 (3.0)	1 (0.2)	0	0	5 (1.2)	0	0	0		
Pneumonitis	11 (2.6)	0	0	1 (0.2)	1 (0.2)	0	0	0		
Skin and subcutaneous tissue	disorders									
Alopecia	11 (2.6)	0	0	0	13 (3.1)	0	0	0		
Dermatitis	5 (1.2)	1 (0.2)	0	0	3 (0.7)	0	0	0		
Dermatitis acneiform	5 (1.2)	1 (0.2)	0	0	6 (1.4)	0	0	0		
Dry skin	27 (6.3)	1 (0.2)	0	0	35 (8.2)	0	0	0		
Erythema	7 (1.6)	0	0	0	8 (1.9)	0	0	0		
Palmar-plantar	119		0	0	168	15	0	0		
erythrodysesthesia		22 (5.1)								
syndrome	(27.7)				(39.5)	(3.5)				
Pruritus	53	1 (0.2)	0	0	18 (4.2)	0	0	0		
Trancas	(12.4)	1 (0.2)	Ŭ	Ŭ	10 (1.2)	Ŭ	Ŭ	Ŭ		
Rash	46	1(0.2)	0	0	38 (8.9)	1 (0.2)	0	0		
Tido!!	(10.7)	1(0.2)			30 (0.3)	1 (0.2)				
Rash maculo-papular	17 (4.0)	1 (0.2)	0	0	3 (0.7)	0	0	0		
Skin exfoliation	5 (1.2)	0	0	0	8 (1.9)	0	0	0		
Vascular disorders										
Hypertension	179	91	0	0	184	78	0	0		
пуренензіон	(41.7)	(21.2)	U	<u> </u>	(43.3)	(18.4)	U	U		
Hypotension	5 (1.2)	1 (0.2)	0	0	1 (0.2)	0	0	0		

In Combination with Lenvatinib (KEYNOTE-581)

The safety of KEYTRUDA was evaluated in KEYNOTE-581 (See 14 Clinical Trials). Patients received KEYTRUDA 200 mg intravenously every 3 weeks in combination with lenvatinib 20 mg orally once daily (n=352), or lenvatinib 18 mg orally once daily in combination with everolimus 5 mg orally once daily (n=355), or sunitinib 50 mg orally once daily for 4 weeks then off treatment for 2 weeks (n=340). The median duration of exposure to the combination therapy of KEYTRUDA and lenvatinib was 17.0 months (range: 0.1 to 39.1) and to sunitinib was 7.8 months (range: 0.1 to 37.0). The median duration of exposure to KEYTRUDA was 15.1 months (range: 0.03 to 29.6). KEYTRUDA was continued for a maximum of 24 months; however, treatment with lenvatinib could be continued beyond 24 months.

The most common adverse events (reported in at least 30% of patients) were: fatigue, diarrhea, musculoskeletal pain, hypothyroidism, hypertension, stomatitis, decreased appetite, rash, and nausea. Eighty-two percent of patients had \geq Grade 3 adverse events. The most common \geq Grade 3 adverse events (\geq 5%) were: hypertension (29%); lipase increased (18%); diarrhea (10%); fatigue (9%); amylase increased (9%); hepatotoxicity (9%); proteinuria (8%); weight decreased (8%); and hemorrhagic events (5%).

The frequencies included below and in Table 29 are based on all reported adverse events, regardless of

the investigator assessment of causality.

Fatal adverse events occurred in 4.3% of patients treated with KEYTRUDA in combination with lenvatinib, including cardio-respiratory arrest (0.9%), sepsis (0.9%), and one case (0.3%) each of arrhythmia, autoimmune hepatitis, dyspnea, hypertensive crisis, increased blood creatinine, multiple organ dysfunction syndrome, myasthenic syndrome, myocarditis, nephritis, pneumonitis, ruptured aneurysm, and subarachnoid hemorrhage.

Serious adverse events occurred in 51% of patients receiving KEYTRUDA and lenvatinib. Serious adverse events in \geq 2% of patients were hemorrhagic events (5%), diarrhea (4%), hypertension (3%), myocardial infarction (3%), pneumonitis (3%), vomiting (3%), acute kidney injury (2%), adrenal insufficiency (2%), dyspnea (2%), and pneumonia (2%).

Permanent discontinuation of either of KEYTRUDA, lenvatinib or both due to an adverse event occurred in 37% of patients receiving KEYTRUDA in combination with lenvatinib; 29% KEYTRUDA only, 26% lenvatinib only, and 13% both. The most common adverse events (≥2%) resulting in permanent discontinuation of KEYTRUDA, lenvatinib, or the combination were pneumonitis (3%), myocardial infarction (3%), hepatotoxicity (3%), acute kidney injury (3%), rash (3%), and diarrhea (2%).

Dose interruptions of KEYTRUDA, lenvatinib, or both due to an adverse event occurred in 78% of patients receiving KEYTRUDA in combination with lenvatinib. KEYTRUDA was interrupted in 55% of patients and both drugs were interrupted in 39% of patients. The most common adverse events (≥3%) resulting in interruption of KEYTRUDA were diarrhea (10%), hepatotoxicity (8%), fatigue (7%), lipase increased (5%), amylase increased (4%), musculoskeletal pain (3%), hypertension (3%), rash (3%), acute kidney injury (3%), and decreased appetite (3%).

Of 352 adult patients with advanced or metastatic RCC treated with KEYTRUDA in combination with lenvatinib, 159 (45%) were \geq 65 years of age. In patients \geq 65 years of age the incidence of Grade \geq 3 adverse events was 88.7% compared to patients <65 years of age was 77.2%. Adverse events leading to discontinuation of either KEYTRUDA, or lenvatinib, or both, in patients \geq 65 years of age was 46.5% compared to patients <65 years of age was 29.5%. Adverse events leading to discontinuation of KEYTRUDA in patients \geq 65 years of age was 37.1% compared to patients <65 years of age was 21.8%.

Table 29 summarizes the adverse events that occurred in ≥20% of patients treated with KEYTRUDA and lenvatinib in KEYNOTE-581.

Table 29: Adverse Events Occurring in ≥20% of Patients Receiving KEYTRUDA with Lenvatinib in KEYNOTE-581

ar Lenva	Sunitinib 50 mg n=340		
All Grades	Grades 3-4	All Grades	Grades 3-4
(%)	(%)	(%)	(%)
57	1	32	0
62	10	50	6
43	2	43	2
36	3	33	1
27	2	18	1
26	3	20	1
25	1	19	0
L			
63	9	56	8
25	9	21	5
30	8	9	0.3
41	4	31	1
	l	1	
58	4	41	3
	1		
23	1	16	1
	l		L
30	8	13	3
21	5	16	2
	n= All Grades (%)	n=352 All Grades (%) Grades 3-4 (%) (%) (%) 57 1 62 10 43 2 36 3 27 2 26 3 25 1 63 9 30 8 41 4 58 4 23 1	n=352 n=3 All Grades (%) Grades 3-4 (%) All Grades (%) 57 1 32 62 10 50 43 2 43 36 3 33 27 2 18 26 3 20 25 1 19 63 9 56 25 9 21 30 8 9 41 4 31 58 4 41 23 1 16 30 8 13

Dysphonia	30	0	4	0
Skin and Subcutaneous Tissue	•	<u> </u>		l
Rash ^k	37	5	17	1
Palmar-plantar erythrodysesthesia syndrome ^l	29	4	38	4
Vascular				
Hypertension ^m	56	29	43	20
Hemorrhagic events ⁿ	27	5	26	4

- Includes hypothyroidism, increased blood thyroid stimulating hormone, secondary hypothyroidism
- b Includes diarrhea, gastroenteritis
- Includes aphthous ulcer, gingival pain, glossitis, glossodynia, mouth ulceration, mucosal inflammation, oral discomfort, oral mucosal blistering, oral pain, oropharyngeal pain, pharyngeal inflammation, stomatitis
- discomfort, lower abdominal pain, upper abdominal pain abdominal pain abdominal pain abdominal pain
- e Includes asthenia, fatigue, lethargy, malaise
- f Includes alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, drug-induced liver injury, hepatic enzyme increased, hepatic failure, hepatic function abnormal, hepatocellular injury, hepatotoxicity, hyperbilirubinemia, hypertransaminasemia, immunemediated hepatitis, liver function test increased, liver injury, transaminases increased, gamma-glutamyltransferase increased
- g Includes decreased appetite, early satiety
- Includes arthralgia, arthritis, back pain, bone pain, breast pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, non-cardiac chest pain, pain in extremity, pain in jaw
- ¹ Includes hemoglobinuria, nephrotic syndrome, proteinuria
- Includes acute kidney injury, azotemia, blood creatinine increased, creatinine renal clearance decreased, hypercreatininemia, renal failure, renal impairment, oliguria, glomerular filtration rate decreased, and nephropathy toxic
- Includes genital rash, infusion site rash, penile rash, perineal rash, rash rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular
- Includes palmar erythema, palmar-plantar erythrodysesthesia syndrome, plantar erythema
- Includes essential hypertension, increased blood pressure, increased diastolic blood pressure, hypertension, hypertensive crisis, hypertensive retinopathy, labile blood pressure
- Includes all hemorrhage terms. Hemorrhage terms that occurred in 1 or more subjects in either treatment group include Anal hemorrhage, aneurysm ruptured, blood blister, blood loss anemia, blood urine present, catheter site hematoma, cerebral microhemorrhage, conjunctival hemorrhage, contusion, diarrhea hemorrhagic, disseminated intravascular coagulation, ecchymosis, epistaxis, eye hemorrhage, gastric hemorrhage, gastritis hemorrhagic, gingival bleeding, hemorrhage urinary tract, hemothorax, hematemesis, hematoma, hematochezia, hematuria, hemoptysis, hemorrhoidal hemorrhage, increased tendency to bruise, injection site hematoma, injection site hemorrhage, intra-abdominal hemorrhage, lower gastrointestinal hemorrhage, Mallory-Weiss syndrome, melaena, petechiae, rectal hemorrhage, renal hemorrhage, retroperitoneal hemorrhage, small intestinal hemorrhage, splinter hemorrhages, subcutaneous hematoma, subdural hematoma, subarachnoid hemorrhage, thrombotic thrombocytopenic purpura, tumour hemorrhage, traumatic hematoma, upper gastrointestinal hemorrhage

Adjuvant RCC

Table 30 summarizes the treatment-related adverse events that occurred in at least 1% of patients with resected renal cell cancer treated with KEYTRUDA in KEYNOTE-564. The median duration of exposure to KEYTRUDA was 11.1 months (number of administration ranged 1 to 17). The most common treatment-related adverse events (reported in at least 10 % of patients) were fatigue, pruritus, hypothyroidism, diarrhea, rash, hyperthyroidism.

Serious treatment-related adverse events occurred in 12% of patients receiving KEYTRUDA; the most common (incidence ≥1%) were adrenal insufficiency, colitis, and diabetic ketoacidosis.

Discontinuation of KEYTRUDA due to treatment-related adverse events occurred in 17.6 % of patients; the most common (≥1%) were ALT increase (1.6%), colitis (1.0%), and adrenal insufficiency (1.0%).

Dose interruption of KEYTRUDA due to treatment-related adverse events occurred in 16.4% of patients; the most common (\geq 1%) were arthralgia (1.4%), diarrhea (1.4%), hypothyroidism (1.2%), fatigue (1.0%), ALT increase (1.0%), AST increase (1.2%).

Table 30: Treatment-Related Adverse Events Occurring in ≥ 1% of Patients with RCC treated with KEYTRUDA in KEYNOTE-564.

		EYTRUDA g every 3 we	eeks		Placebo	
Adverse Reaction	200	n= 488			n=496	
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Blood and lymphatic sy	stem disorders					
Anemia	6 (1.2)	0	0	4 (0.8)	0	0
Endocrine disorders						
Adrenal Insufficiency	10 (2.0)	6 (1.2)	0	0	0	0
Hyperthyroidism	50 (10.2)	1 (0.2)	0	0	0	0
Hypothyroidism	86 (17.6)	1 (0.2)	0	13 (2.6)	0	0
Thyroiditis	5 (1.0)	1 (0.2)	0	1 (0.2)	0	0
Gastrointestinal disord	ers					
Colitis	7 (1.4)	4 (0.8)	0	1 (0.2)	0	0
Constipation	8 (1.6)	0	0	6 (1.2)	0	0
Diarrhea	77 (15.8)	8 (1.6)	0	51 (10.3)	0	0
Dry mouth	20 (4.1)	1 (0.2)	0	1 (0.2)	0	0
Dyspepsia	6 (1.2)	0	0	0	0	0
Nausea	39 (8.0)	0	0	23 (4.6)	0	0
Stomatitis	6 (1.2)	0	0	5 (1.0)	0	0
Vomiting	10 (2.0)	1 (1.2)	0	3 (0.6)	0	0
General disorders and	administration	site conditio	ons			
Asthenia	28 (5.7)	1 (0.2)	0	23 (4.6)	0	0
Chills	7 (1.4)	0	0	4 (0.8)	0	0
Fatigue	99 (20.3)	4 (0.8)	0	71 (14.3)	0	0
Edema	6 (1.2)	0	0	1 (0.2)	0	0

		(EYTRUDA	noks		Placebo	
Adverse Reaction	200 m	g every 3 we n= 488	eeks		n=496	
Adverse neaction	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Edema peripheral	8 (1.6)	0	0	8 (1.6)	0	0
Pyrexia	9 (1.8)	1 (0.2)	0	2 (0.4)	0	0
Injury, poisoning and pr	ocedural comp	olications			•	
Infusion related			_			
reaction	5 (1.0)	1 (0.2)	0	4 (0.8)	0	0
Investigations						ı
Alanine						
aminotransferase	22 (4.5)	9 (1.8)	0	9 (1.8)	1 (0.2)	0
increased	, ,			, ,	,	
Amylase increased	6 (1.2)	2 (0.4)	0	4 (0.8)	0	0
Aspartate	-					
aminotransferase	22 (4.5)	6 (1.2)	0	5 (1.0)	0	0
increased						
Blood alkaline	7 (1 4)	1 (0.2)	0	1 (0.2)	0	0
phosphatase increased	7 (1.4)	1 (0.2)	0	1 (0.2)	0	0
Blood creatinine	20 (4.1)	1 (0.2)	0	10 (2.0)	0	0
increased	20 (4.1)	1 (0.2)	U	10 (2.0)	0	0
Blood thyroid						
stimulating hormone	12 (2.5)	0	0	3 (0.6)	0	0
increased						
Gamma-						
glutamyltransferase	6 (1.2)	1 (0.2)	2 (0.4)	0	0	0
increased						
Lipase increased	5 (1.0)	1 (0.2)	1 (0.2)	4 (0.8)	0	0
Transaminase	5 (1.0)	1 (0.2)	0	2 (0.4)	0	0
increased		1 (0.2)		2 (0)		
Metabolism and nutrition		T	T	T		1
Decreased appetite	15 (3.1)	1 (0.2)	0	2 (0.4)	0	0
Diabetic ketoacidosis	5 (1.0)	4 (0.8)	1 (0.2)	0	0	0
Hyperglycemia	5 (1.0)	2 (0.4)	1 (0.2)	4 (0.8)	1 (0.2)	0
Hypophosphatemia	5 (1.0)	1 (0.2)	0	4 (0.8)	0	0
Type 1 diabetes	5 (1.0)	3 (0.6)	1 (0.2)	0	0	0
mellitus		, ,	(,			
Musculoskeletal and co				1 .0 /5 -1	_	1 -
Arthralgia	46 (9.4)	1 (0.2)	0	43 (8.7)	0	0
Arthritis	7 (1.4)	1 (0.2)	0	3 (0.6)	0	0
Muscle spasms	6 (1.2)	0	0	5 (1.0)	0	0
Myalgia	30 (6.1)	1 (0.2)	0	20 (4.0)	0	0
Pain in extremity	7 (1.4)	0	0	1 (0.2)	0	0
Nervous system disorde		_	_		_	1 -
Dizziness	13 (2.7)	0	0	5 (1.0)	0	0

		EYTRUDA		Placebo				
Adverse Reaction	200 mg	g every 3 we n= 488	eeks	n=496				
Adverse Reaction	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4		
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)		
Dysgeusia	8 (1.6)	0	0	4 (0.8)	0	0		
Headache	17 (3.5)	0	0	17 (3.4)	0	0		
Paresthesia	9 (1.8)	0	0	1 (0.2)	0	0		
Psychiatric disorders								
Insomnia	5 (1.0)	0	0	1 (0.2)	0	0		
Renal and urinary disord	ders							
Proteinuria	7 (1.4)	0	0	1 (0.2)	0	0		
Respiratory, thoracic an	d mediastinal	disorders						
Cough	15 (3.1)	0	0	7 (1.4)	0	0		
Dyspnea	12 (2.5)	0	0	9 (1.8)	0	0		
Pneumonitis	8 (1.6)	1 (0.2)	1 (0.2)	3 (0.6)	0	0		
Skin and subcutaneous	tissue disorder	's						
Dermatitis	7 (1.4)	0	0	2 (0.4)	0	0		
Dry skin	14 (2.9)	0	0	11 (2.2)	0	0		
Eczema	5 (1.0)	0	0	1 (0.2)	0	0		
Pruritus	91 (18.6)	1 (0.2)	0	57 (11.5)	0	0		
Psoriasis	6 (1.2)	0	0	0	0	0		
Rash	73 (15.0)	4 (0.8)	0	36 (7.3)	0	0		
Rash maculo-papular	19 (3.9)	2 (0.4)	0	6 (1.2)	0	0		
Rash pruritic	10 (2.0)	0	0	0	0	0		
Urticaria	5 (1.0)	0	0	3 (0.6)	0	0		

HNSCC

Resectable Locally Advanced HNSCC

Table 31 summarizes the treatment-related adverse events that occurred in at least 1% of patients with resectable locally advanced HNSCC treated with KEYTRUDA as neoadjuvant treatment as monotherapy prior to definitive surgery, continued as adjuvant treatment in combination with RT with or without concurrent cisplatin, and then as monotherapy, in KEYNOTE-689 (See 14 Clinical Trials). The median duration of exposure was 9.1 months (range: 1 day to 22.3 months) in the KEYTRUDA in combination with RT with or without cisplatin arm and 2.9 months (range: 1 day to 7.2 months) in the RT with or without cisplatin alone (Standard of Care (SOC)) arm. The median duration of exposure to KEYTRUDA in the neoadjuvant phase was 0.7 months (range: 1 day to 1.1 months) and the median duration of exposure to KEYTRUDA in the adjuvant phase was 9.7 months (range: 1 day to 18.9 months).

The most common treatment-related adverse events for patients treated with KEYTRUDA in KEYNOTE-689 (reported in at least 20% of patients) were radiation skin injury and stomatitis. The most common Grade 3-5 treatment-related adverse events for patients treated with KEYTRUDA in KEYNOTE-689 (reported in at least 5% of patients) were stomatitis (11.6%), lymphocyte count decreased (5.5%), and neutrophil count decreased (5.3%).

Serious treatment-related adverse events occurred in 19.1% of patients treated with KEYTRUDA in KEYNOTE-689. The most common (>1%) included colitis (1.7%), stomatitis (1.7%), immune-mediated hepatitis (1.4%), pneumonitis (1.4%) and adrenal insufficiency (1.1%). Fatal treatment-related adverse events occurred in 1.1% of patients treated with KEYTRUDA in KEYNOTE-689 including 1 case each of the following: covid-19, death (unknown cause), pneumonitis and renal failure.

KEYTRUDA was discontinued for treatment-related adverse events in 13.0% of patients. The most common treatment-related adverse events resulting in discontinuation of KEYTRUDA (\geq 1%) were pneumonitis (1.9%), colitis (1.7%) and immune-mediated hepatitis (1.1%). The median time to discontinuation for treatment-related adverse events was 5.3 months.

Neoadjuvant Treatment Phase

A total of 361 patients received at least 1 dose of KEYTRUDA as neoadjuvant treatment and 1 patient received 1 dose of neoadjuvant treatment in the RT with or without cisplatin (SOC arm) alone.

Serious treatment-related adverse events occurred in 3.0% of patients who received KEYTRUDA as neoadjuvant treatment. The most frequent (at least 2 cases) serious treatment-related adverse event was immune-mediated hepatitis.

Permanent discontinuation of any study drug due to a treatment-related adverse event occurred in 1.9% of patients who received KEYTRUDA as neoadjuvant treatment. The most frequent (at least 2 cases) adverse event that led to permanent discontinuation of any study drug was arthralgia (n=2).

Of the 361 patients in the KEYTRUDA arm and the 351 patients in the SOC arm, 10.5% (n=38) and 12.3% (n=43) respectively did not have surgery. Surgical cancellation in the KEYTRUDA arm was due to disease progression in 4% (n=15), patient decision in 3% (n=10), adverse reactions in 1.4% (n=5), physician's decision in 1.1% (n=4), unresectable tumor in 0.6% (n=2), loss of follow-up in 0.3% (n=1), and use of non-study anti-cancer therapy in 0.3% (n=1). The treatment-related adverse event that led to cancellation of surgery in the KEYTRUDA arm was hyperthyroidism. Surgical cancellation in the SOC arm was due to patient decision in 7% (n=24), physician's decision in 2.3% (n=8), disease progression in 1.7% (n=6), and adverse reactions in 1.4% (n=5).

Of the 323 KEYTRUDA -treated patients who received surgery, there were 38 surgical delays (defined as on-study surgery occurring \geq 6 weeks (\pm 10 days) after randomization, 3.4% (n=11) experienced delay of surgery due to an adverse event. Of the 307 SOC-treated patients who received surgery, there were 10 surgical delays (defined as surgery occurring \geq 4 weeks (\pm 10 days) after randomization), 0.3% (n=1) experienced delay of surgery due to an adverse event.

Of the 323 patients who underwent surgery on the KEYTRUDA arm, 54 patients received surgery but did not receive adjuvant treatment. Of these patients, 16.7% (n=9) did not receive adjuvant treatment due to adverse events. Of the 307 patients who underwent surgery on the SOC arm, 41 patients received surgery but did not receive adjuvant treatment. Of these patients, 26.8% (n=11) did not receive adjuvant treatment due to adverse events.

Adjuvant Treatment Phase

A total of 275 patients started adjuvant treatment in the KEYTRUDA arm and 255 patients received at least 1 dose of KEYTRUDA as adjuvant treatment, and 275 patients received adjuvant treatment in the SOC arm. On the KEYTRUDA arm, 100 patients received KEYTRUDA and cisplatin with concurrent RT, 154 patients received KEYTRUDA alone with concurrent RT, 7 patients received cisplatin alone with concurrent RT, and 13 patients received RT alone. One patient received KEYTRUDA alone. On the SOC arm, 139 patients received cisplatin with concurrent RT while 136 patients received RT alone. For the KEYTRUDA arm, a total of 222 patients received KEYTRUDA as monotherapy following RT.

Of the 255 patients who received KEYTRUDA as adjuvant treatment, 19.6% experienced serious treatment-related adverse events; the most frequent (\geq 1%) treatment-related adverse events were stomatitis (2.4%), colitis (2.0%), pneumonitis (1.6%), and immune-mediated hepatitis (1.2%). During adjuvant treatment, 1.2% of patients experienced fatal treatment-related adverse events, including 1 case each of the following: COVID-19 pneumonia, death (unknown cause), and renal failure.

Permanent discontinuation of adjuvant KEYTRUDA due to a treatment-related adverse event occurred in 13.7% of patients; the most frequent (≥ 1%) treatment-related adverse events that led to permanent discontinuation of adjuvant KEYTRUDA were pneumonitis (2.4%), colitis (2.0%), and immune-mediated hepatitis (1.2%).

Table 31: Treatment-Related Adverse Events (incidence ≥ 1%) in Patients Treated with KEYTRUDA as Neoadjuvant Treatment as Monotherapy, then continued as Adjuvant Treatment in Combination

with RT with or without Cisplatin, and then as Monotherapy, APaT Population in KEYNOTE-689.

with RT with o		•									
		eoadjuvant			Adjuvant radiation with or without cisplatin						
	Mono	therapy/ A	•	YTRUDA							
			ınd								
		tion with o		•							
	K	EYTRUDA	Monothera	ару							
Adverse Reaction		n=	361			n=	315				
	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 lymphat	ic system d	isorders	T		•	T	T	T			
Anemia	32 (8.9)	7 (1.9)	1 (0.3)	0 (0.0)	34 (10.8)	3 (1.0)	0 (0.0)	0 (0.0)			
Febrile neutropenia	2 (0.6)	2 (0.6)	0 (0.0)	0 (0.0)	5 (1.6)	5 (1.6)	0 (0.0)	0 (0.0)			
Ear and labyrinth d	isorders	l .	l .	ı		l	l	l			
Deafness	4 (1.1)	1 (0.3)	0 (0.0)	0 (0.0)	2 (0.6)	1 (0.3)	0 (0.0)	0 (0.0)			
Hypoacusis	8 (2.2)	1 (0.3)	0 (0.0)	0 (0.0)	5 (1.6)	2 (0.6)	0 (0.0)	0 (0.0)			
Tinnitus	13 (3.6)	1 (0.3)	0 (0.0)	0 (0.0)	13 (4.1)	1 (0.3)	0 (0.0)	0 (0.0)			
Endocrine disorders		()	. (5.0)	- ()	- (··-/	()	- ()	- (/			
Adrenal											
insufficiency	5 (1.4)	4 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)			
Hyperthyroidism	27 (7.5)	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)			
Hypothyroidism	70 (19.4)	0 (0.0)	0 (0.0)	0 (0.0)	6 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)			
Gastrointestinal dis	orders										
Colitis	8 (2.2)	6 (1.7)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)			
Constipation	16 (4.4)	0 (0.0)	0 (0.0)	0 (0.0)	14 (4.4)	0 (0.0)	0 (0.0)	0 (0.0)			
Diarrhea	23 (6.4)	3 (0.8)	0 (0.0)	0 (0.0)	7 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)			
Dry mouth	63 (17.5)	3 (0.8)	0 (0.0)	0 (0.0)	68 (21.6)	3 (1.0)	0 (0.0)	0 (0.0)			
Dyspepsia	9 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)			
Dysphagia	37 (10.2)	10 (2.8)	0 (0.0)	0 (0.0)	49 (15.6)	10 (3.2)	0 (0.0)	0 (0.0)			
Nausea	64 (17.7)	5 (1.4)	0 (0.0)	0 (0.0)	67 (21.3)	8 (2.5)	0 (0.0)	0 (0.0)			
Odynophagia	21 (5.8)	2 (0.6)	0 (0.0)	0 (0.0)	25 (7.9)	0 (0.0)	0 (0.0)	0 (0.0)			
Oesophagitis	4 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	6 (1.9)	1 (0.3)	0 (0.0)	0 (0.0)			
Oral mucosal erythema	4 (1.1)	3 (0.8)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)			
Oral pain	19 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)	17 (5.4)	1 (0.3)	0 (0.0)	0 (0.0)			
Salivary duct											
inflammation	5 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)			
Stomatitis	140 (38.8)	42 (11.6)	0 (0.0)	0 (0.0)	164 (52.1)	41 (13.0)	1 (0.3)	0 (0.0)			
Vomiting	39	1 (0.3)	0 (0.0)	0 (0.0)	25 (7.9)	2 (0.6)	0 (0.0)	0 (0.0)			

		eoadjuvant			Adjuvant	radiation w	ith or withou	ut cisplatin		
	iviono	therapy/ A	ajuvant KE nd	TIKUDA						
	Radiat	a ion with or		splatin/						
		EYTRUDA		•						
Adverse Reaction			361	·P)		n=315				
	Any				Any					
	Grade	Grade 3	Grade 4	Grade 5	Grade	Grade 3	Grade 4	Grade 5		
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)		
	(10.8)									
General disorders a	nd adminis	tration site	conditions	5						
Asthenia	19 (5.3)	1 (0.3)	0 (0.0)	0 (0.0)	19 (6.0)	2 (0.6)	0 (0.0)	0 (0.0)		
Face edema	5 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)		
Facial pain	4 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)		
•	65				41					
Fatigue	(18.0)	3 (0.8)	0 (0.0)	0 (0.0)	(13.0)	2 (0.6)	0 (0.0)	0 (0.0)		
Fibrosis	3 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)		
Localized edema	7 (1.9)	1 (0.3)	0 (0.0)	0 (0.0)	4 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)		
Mucosal	4 (1 1)	2 (0.6)	0 (0 0)	0 (0 0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
inflammation	4 (1.1)	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
Pyrexia	8 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)		
Swelling face	9 (2.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)		
Hepatobiliary disor	ders									
Immune-										
mediated	5 (1.4)	4 (1.1)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
hepatitis										
Infections and infe	stations	T			1					
Candida infection	6 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)		
Fungal infection	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.3)	1 (0.3)	0 (0.0)	0 (0.0)		
Oral candidiasis	23 (6.4)	0 (0.0)	0 (0.0)	0 (0.0)	15 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)		
Oral fungal	8 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)		
infection			` ,	0 (0.0)	7 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)		
Injury, poisoning ar	nd procedu	ral complica	ations				T			
Radiation	4 (1.1)	1 (0.3)	0 (0.0)	0 (0.0)	11 (3.5)	1 (0.3)	0 (0.0)	0 (0.0)		
mucositis		_ (0.0)	0 (0.0)	- (0.0)		_ (0.0)	(0.0)	- (0.0)		
Radiation skin	142	15 (4.2)	0 (0.0)	0 (0.0)	148	18 (5.7)	0 (0.0)	0 (0.0)		
injury	(39.3)	(,	- ()	- ()	(47.0)	== (=:: /	- (0.0)	- ()		
Investigations	1									
Alanine	22 (2.5)	F (6.5)	0 (0 0)	0 (0 0)	46 (7.4)	4 (6.0)	0 (0 0)	0 (0 0)		
aminotransferase	23 (6.4)	5 (1.4)	0 (0.0)	0 (0.0)	16 (5.1)	4 (1.3)	0 (0.0)	0 (0.0)		
increased										
Aspartate	20 (5.5)	1 (0.3)	0 (0 0)	0 (0 0)	0 (2.5)	1 (0.3)	0 (0 0)	0 (0 0)		
aminotransferase	20 (5.5)	1 (0.3)	0 (0.0)	0 (0.0)	8 (2.5)	1 (0.3)	0 (0.0)	0 (0.0)		
increased										
Blood alkaline	6 (1.7)	2 (0.6)	0 (0.0)	0 (0.0)	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)		
phosphatase										

	Mono Radiat	therapy/ A a ion with o EYTRUDA	KEYTRUDA djuvant KE and r without ci Monothera	YTRUDA splatin/	Adjuvant radiation with or without cisplat n=315			
Adverse Reaction		n=	361			n=	315	
	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 creatinine increased	16 (4.4)	2 (0.6)	0 (0.0)	0 (0.0)	16 (5.1)	2 (0.6)	0 (0.0)	0 (0.0)
Blood thyroid stimulating hormone increased	8 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Creatinine renal clearance decreased	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)
Gamma- glutamyltransfera se increased	5 (1.4)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Lymphocyte count decreased	41 (11.4)	16 (4.4)	4 (1.1)	0 (0.0)	28 (8.9)	16 (5.1)	5 (1.6)	0 (0.0)
Neutrophil count decreased	42 (11.6)	16 (4.4)	3 (0.8)	0 (0.0)	59 (18.7)	31 (9.8)	6 (1.9)	0 (0.0)
Platelet count decreased	14 (3.9)	3 (0.8)	0 (0.0)	0 (0.0)	24 (7.6)	1 (0.3)	1 (0.3)	0 (0.0)
Weight decreased	35 (9.7)	11 (3.0)	0 (0.0)	0 (0.0)	34 (10.8)	12 (3.8)	0 (0.0)	0 (0.0)
White blood cell count decreased	39 (10.8)	11 (3.0)	2 (0.6)	0 (0.0)	50 (15.9)	26 (8.3)	2 (0.6)	0 (0.0)
White blood cell count increased	4 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Metabolism and nu	trition disc	rders						
Decreased appetite	30 (8.3)	4 (1.1)	0 (0.0)	0 (0.0)	29 (9.2)	4 (1.3)	0 (0.0)	0 (0.0)
Dehydration	11 (3.0)	1 (0.3)	0 (0.0)	0 (0.0)	7 (2.2)	1 (0.3)	0 (0.0)	0 (0.0)
Hyperkalemia	7 (1.9)	3 (0.8)	1 (0.3)	0 (0.0)	5 (1.6)	1 (0.3)	0 (0.0)	0 (0.0)
Hypocalcemia	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.6)	1 (0.3)	0 (0.0)	0 (0.0)
Hypokalemia	9 (2.5)	3 (0.8)	1 (0.3)	0 (0.0)	8 (2.5)	2 (0.6)	1 (0.3)	0 (0.0)
Hypomagnesemia	17 (4.7)	0 (0.0)	0 (0.0)	0 (0.0)	15 (4.8)	1 (0.3)	0 (0.0)	0 (0.0)
Hyponatremia	14 (3.9)	7 (1.9)	2 (0.6)	0 (0.0)	10 (3.2)	4 (1.3)	0 (0.0)	0 (0.0)
Musculoskeletal an		ve tissue di	sorders					
Arthralgia	10 (2.8)	2 (0.6)	0 (0.0)	0 (0.0)	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Neck pain	7 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	7 (2.2)	1 (0.3)	0 (0.0)	0 (0.0)

	N	eoadjuvant	KEYTRUDA	\ as	Adjuvant	radiation w	ith or withou	ut cisplatin			
	Mono	therapy/ A	djuvant KE`	YTRUDA							
		а	ınd								
	Radiat	ion with o	r without ci	splatin/							
	K	EYTRUDA	Monothera	ру		n=315 Any Grade n (%) Grade 3 n (%) Grade 4 n (%) Grade 5 n (%) 8 (2.5) 1 (0.3) 0 (0.0) 0 (0.0) 3 (1.0) 0 (0.0) 0 (0.0) 0 (0.0) 56 (17.8) 2 (0.6) 0 (0.0) 0 (0.0) 4 (1.3) 0 (0.0) 0 (0.0) 0 (0.0) 4 (1.3) 0 (0.0) 0 (0.0) 0 (0.0) 8 (2.5) 5 (1.6) 1 (0.3) 1 (0.3) 1 (0.3) 0 (0.0) 0 (0.0) 0 (0.0) 7 (2.2) 0 (0.0) 0 (0.0) 0 (0.0) 9 (2.9) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0)					
Adverse Reaction			361			n=	315				
	Any				Anv						
	Grade	Grade 3	Grade 4	Grade 5	_						
	n (%)	n (%)	n (%)	n (%)		n (%)	n (%)	n (%)			
Trismus	11 (3.0)	1 (0.3)	0 (0.0)	0 (0.0)		1 (0.3)	0 (0.0)	0 (0.0)			
Nervous system dis				, ,	, ,		. , ,				
Ageusia	4 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)			
Dizziness	5 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	-	· · · · · · · · · · · · · · · · · · ·					
	46										
Dysgeusia	(12.7)	0 (0.0)	0 (0.0)	0 (0.0)		2 (0.6)	U (U.U)	U (U.U)			
Headache	7 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	<u> </u>	0 (0.0)	0 (0.0)	0 (0.0)			
Taste disorder	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)			
Renal and urinary d	lisorders										
Acute kidney	7 (1.9)	2 (0.6)	0 (0.0)	0 (0.0)	0 (2 E)	E /1 6\	1 (0.2)	1 (0.2)			
injury	7 (1.9)	2 (0.6)	0 (0.0)	0 (0.0)	8 (2.5)	5 (1.0)	1 (0.5)	1 (0.5)			
Respiratory, thorac	ic and med	iastinal dis	orders								
Cough	6 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)			
Dysphonia	5 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	7 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)			
Epistaxis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.3)						
Hiccups	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	9 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)			
Increased upper	4 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)			
airway secretion	` '		` '	, ,		. ,	, ,	, ,			
Oropharyngeal pain	9 (2.5)	1 (0.3)	0 (0.0)	0 (0.0)	12 (3.8)	1 (0.3)	0 (0.0)	0 (0.0)			
Pharyngeal		- />	- />	- />		-	- 4>				
inflammation	15 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	19 (6.0)	0 (0.0)	0 (0.0)	0 (0.0)			
Pneumonitis	19 (5.3)	2 (0.6)	2 (0.6)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)			
Pulmonary fibrosis	5 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)			
Skin and subcutane	ous tissue	disorders									
Alopecia	10 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)			
Dermatitis	21 (5.8)	1 (0.3)	0 (0.0)	0 (0.0)	15 (4.8)	5 (1.6)	0 (0.0)	0 (0.0)			
Dry skin	5 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)			
Erythema	11 (3.0)	2 (0.6)	0 (0.0)	0 (0.0)	12 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)			
Pruritus	29 (8.0)	2 (0.6)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)			
Psoriasis	4 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)			
Rash	29 (8.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)			
Rash maculo-	8 (2.2)	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)			
papular	0 (2.2)	2 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)			
Vascular disorders	T	T	T		,		T				
Lymphoedema	12 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.3)	0 (0.0)	0 (0.0)	0 (0.0)			

Metastatic or Unresectable, Recurrent HNSCC

Table 32 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 in combination with chemotherapy.

Table 32: Treatment-Related Adverse Events (incidence ≥ 1%) KEYTRUDA Treatment Groups

Combined, APaT Population in KEYNOTE-048.

		KEYTR	UDA			KEYTF	RUDA			Cetux	imab	
	200	mg ever	y 3 week	(S	20	0 mg eve	ry 3 wee	ks				
						an	ıd			ar	nd	
						Plati	num			Plati	num	
						an	ıd			ar	nd	
Adverse Reaction						FU	J			F	U	
		n=30	00								287	
	Any	Grade	Grade	Grade	Any	Grade	Grade	Grade	Any	Grade	Grade	Grade
	Grade	3	4	5	Grade	3	4	5	Grade	3	4	5
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Blood and lymphatic sys	stem disor	ders										
Anemia	12 (4.0)	2 (0.7)	0	0	134	52 (18.8)	2 (0.7)	0	118	43	0	0
Allellila	12 (4.0)	2 (0.7)			(48.6)	JZ (10.0)	2 (0.7)		(41.1)	(15.0)	U	
Febrile neutropenia	0	0	0	0	22 (8.0)	15 (5.4)	7 (2.5)	0	13 (4.5)	11 (3.8)	2 (0.7)	0
Leukopenia	2 (0.7)	0	0	0	34 (12.3)	8 (2.9)	0	0	38 (13.2)	9 (3.1)	7 (2.4)	0
Lymphopenia	2 (0.7)	1 (0.3)	0	0	7 (2.5)	1 (0.4)	0	0	15 (5.2)	3 (1.0)	1 (0.3)	0
Neutropenia	3 (1.0)	0	0	0	91 (33.0)	35 (12.7)	14 (5.1)	0	89 (31.0)	38 (13.2)	20 (7.0)	0

		KEYTR	IIDA			KEYTF	SIIDV			Cetux	imah	
	200	mg ever		/ C	20	mg eve		ke		Cetux	iiiiab	
	200	ilig evei	y 3 WEEI	13	20	an alii d	•	ins.		ar		
						•						
						Plati	-				num	
						an				ar		
Adverse Reaction						FU	J			F	U	
		n=30	20			n=2	76			n=2	007	
	Any	Grade	Grade	Grade	Any	Grade	Grade	Grade	Any	Grade	Grade	Grade
	Grade	3	4	5	Grade	3	4	5	Grade	3	4	5
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Pancytopenia	0	0	0	0	4 (1.4)	2 (0.7)	0	0	3 (1.0)	1 (0.3)	2 (0.7)	0
	4 (1.3)	0	1 (0.3)	0	75 (27.2)			0	62 (21.6)			0
Thrombocytopenia	. ,	U	1 (0.3)	U	75 (27.2)	16 (5.8)	8 (2.9)	U	02 (21.0)	18 (6.3)	6 (2.1)	U
Ear and labyrinth disord			0		2 /1 1\	0	0		2 /1 0\	0	0	
Deafness	0	0	0	0	3 (1.1)	0	0	0	3 (1.0)	0	0	0
Hypoacusis	0	0	0	0	6 (2.2)	0	0	0	12 (4.2)	1 (0.3)	0	0
Tinnitus	0	0	0	0	15 (5.4)	0	0	0	16 (5.6)	0	0	0
Endocrine disorders	C (2 5)	4 (0.5)			0 (0 =)	_	_		T -		_	_
Hyperthyroidism	6 (2.0)	1 (0.3)	0	0	8 (2.9)	0	0	0	0	0	0	0
Hypothyroidism	39 (13.0)	0	0	0	36 (13.0)	0	0	0	1 (0.3)	0	0	0
Gastrointestinal disorde	_	1		1	,							·
Abdominal pain	0	0	0	0	3 (1.1)	1 (0.4)	0	0	11 (3.8)	4 (1.4)	0	0
Abdominal pain upper	1 (0.3)	0	0	0	4 (1.4)	0	0	0	11 (3.8)	0	0	0
Aphthous ulcer	0	0	0	0	3 (1.1)	0	0	0	5 (1.7)	2 (0.7)	0	0
Colitis	1 (0.3)	0	0	0	6 (2.2)	1 (0.4)	0	0	2 (0.7)	2 (0.7)	0	0
Constipation	9 (3.0)	0	0	0	28 (10.1)	0	0	0	31 (10.8)	0	0	0
Diarrhea	17 (5.7)	1 (0.3)	0	0	50 (18.1)	3 (1.1)	0	0	76 (26.5)	5 (1.7)	0	0
Dry mouth	5 (1.7)	0	0	0	9 (3.3)	0	0	0	5 (1.7)	0	0	0
Dyspepsia	4 (1.3)	0	0	0	7 (2.5)	0	0	0	14 (4.9)	0	0	0
Dysphagia	0	0	0	0	6 (2.2)	1 (0.4)	0	0	3 (1.0)	0	0	0
Nausan	12 (4.0)	0	0	0	125	1	0	0	131	1C /F C)	0	0
Nausea	12 (4.0)				(45.3)	15 (5.4)			(45.6)	16 (5.6)		
Oral pain	0	0	0	0	5 (1.8)	1 (0.4)	0	0	5 (1.7)	1 (0.3)	0	0
Stomatitis	2 (0.7)	0	0	0	69 (25.0)	21 (7.6)	1 (0.4)	0	70 (24.4)	9 (3.1)	1 (0.3)	0
Tongue discomfort	3 (1.0)	0	0	0	0	0	0	0	0	0	0	0
Vomiting	7 (2.3)	0	0	0	75 (27.2)	7 (2.5)	0	0	64 (22.3)	5 (1.7)	0	0
General disorders and a	administrat	ion site	condition	าร								
Asthenia	7 (2.3)	1 (0.3)	0	0	32 (11.6)	7 (2.5)	0	0	30 (10.5)	6 (2.1)	0	0
Chest pain	0	0	0	0	3 (1.1)	0	0	0	3 (1.0)	0	0	0
Chills	4 (1.3)	0	0	0	4 (1.4)	0	0	0	3 (1.0)	0	0	0
Face edema	2 (0.7)	0	0	0	3 (1.1)	0	0	0	1 (0.3)	0	0	0
Fatigue	43 (14.3)	3 (1.0)	0	0	84 (30.4)		0	0	83 (28.9)			0
Malaise	4 (1.3)	0	0	0	18 (6.5)	0	0	0	9 (3.1)	0	0	0
Mucosal inflammation	8 (2.7)	2 (0.7)	0	0	77 (27.9)		1 (0.4)	0	76 (26.5)		0	0
Edema peripheral		0	0	0	3 (1.1)	25 (9.1)	0.4)	0	1 (0.3)	0	0	0
	3 (1.0)	0			· · ·	0					0	
Peripheral swelling	3 (1.0)	U	0	0	1 (0.4)	U	0	0	1 (0.3)	1 (0.3)	U	0

		KEYTR	UDA			KEYTF	RUDA			Cetux	imab	
Adverse Reaction	200	mg ever	y 3 weel	KS	200) mg eve ar Plati ar Fl	num nd	ks				
		n=30	00			n=2	276			n=2	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 (%)
Pyrexia	10 (3.3)	0	0	0	16 (5.8)	0	0	0	12 (4.2)	0	0	0
Infections and infestation	ons											
Bronchitis	0	0	0	0	3 (1.1)	0	0	1 (0.4)	5 (1.7)	0	1 (0.3)	0
Candida infection	1 (0.3)	0	0	0	8 (2.9)	2 (0.7)	0	0	2 (0.7)	0	0	0
Lung infection	0	0	0	0	4 (1.4)	2 (0.7)	0	0	0	0	0	0
Oral candidiasis	0	0	0	0	12 (4.3)	0	0	0	10 (3.5)	0	0	0
Pneumonia	2 (0.7)	1 (0.3)	0	0	8 (2.9)	1 (0.4)	4 (1.4)	0	12 (4.2)	4 (1.4)	0	3 (1.0)
Septic shock	0	0	0	0	6 (2.2)	0	1 (0.4)	5 (1.8)	0	0	0	0
Investigations												
Alanine aminotransferase increased	7 (2.3)	0	0	0	9 (3.3)	1 (0.4)	0	0	15 (5.2)	2 (0.7)	0	0
Aspartate aminotransferase increased	8 (2.7)	1 (0.3)	0	0	11 (4.0)	1 (0.4)	0	0	14 (4.9)	3 (1.0)	0	0
Blood alkaline phosphatase increased	3 (1.0)	1 (0.3)	0	0	5 (1.8)	0	0	0	7 (2.4)	0	0	0
Blood creatinine increased	2 (0.7)	0	0	0	31 (11.2)	1 (0.4)	0	0	16 (5.6)	0	0	0
Blood magnesium decreased	0	0	0	0	8 (2.9)	1 (0.4)	0	0	6 (2.1)	0	0	0
Blood potassium increased	0	0	0	0	4 (1.4)	0	0	0	0	0	0	0
Blood sodium decreased	1 (0.3)	0	0	0	4 (1.4)	2 (0.7)	0	0	2 (0.7)	1 (0.3)	0	0
Blood thyroid stimulating hormone increased	2 (0.7)	0	0	0	5 (1.8)	0	0	0	0	0	0	0
C-reactive protein increased	0	0	0	0	3 (1.1)	0	0	0	1 (0.3)	1 (0.3)	0	0
Gamma- glutamyltransferase increased	2 (0.7)	2 (0.7)	0	0	3 (1.1)	1 (0.4)	0	0	2 (0.7)	1 (0.3)	0	0

KEYTRUDA® (pembrolizumab) Page 127 of 359

		KEYTR	LIDA			KEYTF	DIIDA		1	Cetux	imak	
	200	METIK mg ever		. c	200			.kc		Cetux	imab	
	200	ilig ever	y 5 weer	(5	200	mg eve 0 an	-	:KS			ام	
						an Platii				ar Plati		
							-				-	
						an				ar		
Adverse Reaction						FU	J			F	U	
		n=30	00			n=2	276			n=2	287	
	Any	Grade	Grade	Grade	Any	Grade	Grade	Grade	Any	Grade	Grade	Grade
	Grade	3	4	5	Grade	3	4	5	Grade	3	4	5
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Hemoglobin	0	0	0	0	E (1 0)	2 (0.7)	0	0	2 (1 0)	1 (0.2)	0	0
decreased	U	U	U	U	5 (1.8)	2 (0.7)	U	U	3 (1.0)	1 (0.3)	U	U
Lymphocyte count	4 (1.3)	1 (0.3)	0	0	12 (4.3)	5 (1.8)	4 (1.4)	0	8 (2.8)	4 (1.4)	2 (0.7)	0
decreased	1 (1.5)	1 (0.5)			12 (1.5)	3 (1.0)	1 (±1.1)	Ů	0 (2.0)	1 (2.1)	2 (0.7)	
Neutrophil count	1 (0.3)	0	0	0	45 (16.3)	20 (7.2)	7 (2.5)	0	54 (18.8)	24 (8.4)	11 (3.8)	0
decreased	1 (0.0)				.5 (10.5)	20 (7.2)	, (2.5)		3 . (20.0)	2 . (0)	11 (0.0)	
Platelet count	1 (0.3)	0	0	0	51 (18.5)	9 (3.3)	5 (1.8)	0	46 (16.0)	6 (2.1)	3 (1.0)	0
decreased	_ (0.0)				0= (=0.0)	0 (0.0)	- (=.0)		10 (2010)	(=:=)	(2.0)	
Transaminases	1 (0.3)	0	0	0	3 (1.1)	0	0	0	0	0	0	0
increased												
Weight decreased	9 (3.0)	1 (0.3)	0	0	21 (7.6)	2 (0.7)	0	0	30 (10.5)		0	0
Weight increased	1 (0.3)	1 (0.3)	0	0	3 (1.1)	0	0	0	1 (0.3)	0	0	0
White blood cell	2 (0.7)	0	0	0	36 (13.0)	13 (4.7)	2 (0.7)	0	43 (15.0)	19 (6.6)	3 (1.0)	0
count decreased						- (/	(-)		- (/	- (/	- (- /	
Metabolism and nutriti	1	1	<u> </u>	I -	I / >			I -	I		_	_
Decreased appetite	16 (5.3)	1 (0.3)	0	0	62 (22.5)	, ,	0		62 (21.6)	` '	0	0
Dehydration	2 (0.7)	1 (0.3)	0	0	9 (3.3)	1 (0.4)	0	0	7 (2.4)	3 (1.0)	0	0
Hyperglycemia	5 (1.7)	2 (0.7)	0	0	4 (1.4)	2 (0.7)	1 (0.4)	0	2 (0.7)	0	0	0
Hyperkalemia	1 (0.3)	0	0	0	5 (1.8)	0	0	0	8 (2.8)	3 (1.0)	0	0
Hypoalbuminemia	1 (0.3)	0	0	0	6 (2.2)	0	0	0	3 (1.0)	0	0	0
Hypocalcemia	0	0	0	0	10 (3.6)	2 (0.7)	0	0	12 (4.2)	1 (0.3)	1 (0.3)	0
Hypokalemia	4 (1.3)	1 (0.3)	0	0	16 (5.8)	6 (2.2)	3 (1.1)		36 (12.5)		4 (1.4)	0
Hypomagnesemia	3 (1.0)	0 5 (4.7)	0	0	29 (10.5)	4 (1.4)	0		95 (33.1)		3 (1.0)	0
Hyponatremia	10 (3.3)	5 (1.7)	1 (0.3)	0	23 (8.3)	9 (3.3)	1 (0.4)	0	19 (6.6)	7 (2.4)	1 (0.3)	0
Hypophosphatemia	1 (0.3)	0	0	0	6 (2.2)	2 (0.7)	0	0	19 (6.6)	5 (1.7)	0	0
Musculoskeletal and co	1	1	1		0 (0.0)				0 (4 0)			
Arthralgia	6 (2.0)	1 (0.3)	0	0	9 (3.3)	0	0	0	3 (1.0)	0	0	0
Muscular weakness	3 (1.0)	0	0	0	3 (1.1)	0	0	0	4 (1.4)	0	0	0
Myalgia Norvous system disords	2 (0.7)	0	0	0	4 (1.4)	0	0	0	3 (1.0)	0	0	0
Nervous system disorde		0	0	0	0 (2 0)	0	0	0	0 (2 0)	1 (0.2)	0	0
Dizziness	4 (1.3)	0	0	0	8 (2.9)	0	0	0	8 (2.8)	1 (0.3) 0	0	0
Dysgeusia Headache	6 (2.0)	0	0	0	16 (5.8) 4 (1.4)	0	0	0	15 (5.2) 4 (1.4)	0	0	0
Hypoesthesia	8 (2.7) 0	0	0	0	3 (1.1)	0	0	0	1 (0.3)	0	0	0
Neuropathy	0	0	0	0	9 (3.3)	0	0	0	6 (2.1)	1 (0.3)	0	0
пешораціў	U	U	U	U	9 (3.3)	U	U	U	0 (2.1)	I (U.3)	U	U

		KEVED			1	VEVE	DLID A		1	C-4	l.	
		KEYTR	_	ı		KEYTE	_			Cetux	ımab	
	200	mg ever	y 3 weel	KS	20	0 mg eve	•	:KS				
						ar				ar		
						Plati	num			Plati	num	
						ar	nd			ar	nd	
Adverse Reaction						F	U			F	U	
		n=30		1 -		n=2		T _		n=2		T -
	Any	Grade	Grade	Grade	Any	Grade	Grade	Grade	Any	Grade	Grade	Grade
	Grade	3	4	5	Grade	3	4	5	Grade	3	4	5
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
peripheral												
Neurotoxicity	0	0	0	0	4 (1.4)	0	0	0	3 (1.0)	0	0	0
Paresthesia	1 (0.3)	0	0	0	6 (2.2)	0	0	0	4 (1.4)	0	0	0
Peripheral sensory	1 (0.3)	0	0	0	15 (5.4)	3 (1.1)	0	0	6 (2.1)	2 (0.7)	0	0
neuropathy									0 (2.1)	, ,		
Syncope	0	0	0	0	6 (2.2)	4 (1.4)	0	0	2 (0.7)	2 (0.7)	0	0
Psychiatric disorders												
Insomnia	3 (1.0)	0	0	0	1 (0.4)	0	0	0	4 (1.4)	0	0	0
Renal and urinary disor	ders											
Acute kidney injury	3 (1.0)	1 (0.3)	0	0	15 (5.4)	3 (1.1)	1 (0.4)	0	6 (2.1)	1 (0.3)	0	0
Renal failure	0	0	0	0	6 (2.2)	0	0	0	2 (0.7)	1 (0.3)	0	0
Tubulointerstitial	2 (4 0)	2 (0 7)	0	0	0	0	0	0	0	0	0	0
nephritis	3 (1.0)	2 (0.7)										
Respiratory, thoracic ar	nd mediast	inal diso	rders		•			l .			I.	I.
Cough	5 (1.7)	0	0	0	2 (0.7)	0	0	0	3 (1.0)	0	0	0
Dyspnea	7 (2.3)	2 (0.7)	0	0	4 (1.4)	2 (0.7)	0	0	5 (1.7)	0	0	0
Dyspnea exertional	1 (0.3)	0	0	0	3 (1.1)	0	0	0	1 (0.3)	0	0	0
Epistaxis	1 (0.3)	0	0	0	4 (1.4)	0	0	0	8 (2.8)	0	0	0
Hiccups	0	0	0	0	7 (2.5)	0	0	0	4 (1.4)	0	0	0
Interstitial lung			0	0			0		, ,	0	0	0
disease	2 (0.7)	1 (0.3)			3 (1.1)	1 (0.4)		1 (0.4)	1 (0.3)			
Oropharyngeal pain	1 (0.3)	0	0	0	3 (1.1)	0	0	0	5 (1.7)	1 (0.3)	0	0
Pleural effusion	3 (1.0)	0	0	0	1 (0.4)	1 (0.4)	0	0	1 (0.3)	0	0	0
Pneumonitis	15 (5.0)	3 (1.0)	0	1 (0.3)	11 (4.0)	3 (1.1)	0	0	1 (0.3)	1 (0.3)	0	0
Skin and subcutaneous			_	1	/	/	_		/	/		_
Alopecia	1 (0.3)	0	0	0	13 (4.7)	0	0	0	14 (4.9)	0	0	0
Dermatitis	4 (1.3)	0	0	0	1 (0.4)	0	0	0	6 (2.1)	0	0	0
Dermatitis acneiform	6 (2.0)	0	0	0	1 (0.4)	0	0		82 (28.6)		0	0
Dry skin	6 (2.0)	0	0	0	5 (1.8)	0	0	0	27 (9.4)		0	0
Erythema	3 (1.0)	1 (0.3)	0	0	1 (0.4)	0	0	0	7 (2.4)	0	0	0
Palmar-plantar	- (=.0)	0	0	0	_ (51.1)	0	0	0	. (=: ',		0	0
erythrodysesthesia	1 (0.3)				4 (1.4)				20 (7.0)	2 (0.7)		
syndrome	1 (0.5)				. (±,					_ (0.7)		
Pruritis	22 (7.3)	0	0	0	14 (5.1)	0	0	0	24 (8.4)	1 (0.3)	0	0
Rash	25 (8.3)	2 (0.7)	0	0	23 (8.3)	1 (0.4)	0	0	101	17 (5.9)		0
INUSTI	23 (0.3)	2 (0.7)			23 (0.3)	<u> </u>		J	101	1, (3.3)	U	J

	200	KEYTR mg ever		ks	20	KEYTI 0 mg eve	RUDA ery 3 wee	eks		Cetux	imab		
Adverse Reaction		n=3(00			ar Plati ar F ^l n=2	num nd U			and Platinum and FU n=287			
	Any	Grade	Grade	Grade	Any	Grade	Grade	Grade	Any				
	Grade	3	4	5	Grade	3	4	5	Grade	3	4	5	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
									(35.2)				
Rash maculopapular	6 (2.0)	1 (0.3)	0	0	7 (2.5)	0	0	0	14 (4.9)	1 (0.3)	0	0	
Vascular disorders												•	
Hypotension	0	0	0	0	4 (1.4)	2 (0.7)	1 (0.4)	0	4 (1.4)	0	0	0	
Phlebitis	0	0	0	0	4 (1.4)	0	0	0	2 (0.7)	0	0	0	
Vasculitis	0	0	0	0	5 (1.8)	1 (0.4)	0	0	1 (0.3)	0	0	0	

Gastric or Gastroesophageal Junction (GEJ) adenocarcinoma

Table 33 summarizes the treatment-related adverse events that occurred in at least 1% of patients with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma treated with KEYTRUDA in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy in KEYNOTE-811 (See 14 Clinical Trials). The median duration of exposure for the KEYTRUDA in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy arm was 9.6 months and 7.3 months for the trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy arm.

The most frequently reported treatment-related adverse events (≥20% incidence) for KEYTRUDA in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy group were diarrhea, nausea, anemia, neutrophil count decreased, decreased appetite, platelet count decreased, vomiting, peripheral sensory neuropathy, and palmar-plantar erythrodysesthesia syndrome.

Serious treatment-related adverse events occurred in 25% of patients treated with KEYTRUDA in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy. Serious treatment-related adverse events occurring in ≥2% of patients were diarrhea, infusion-related reaction and pneumonia.

Fatal adverse events considered treatment-related occurred in four patients treated with KEYTRUDA in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy: pneumonitis, hepatitis, sepsis and cerebral infarction.

KEYTRUDA was discontinued for treatment-related adverse events in 8.3% of patients treated with KEYTRUDA in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy. The median time to discontinuation for treatment-related adverse events was 3.9 months. The most common treatment-related adverse event (≥1% incidence) leading to discontinuation of KEYTRUDA was pneumonitis (1.4%). KEYTRUDA was interrupted for treatment-related adverse events in 58% of patients, with the most common treatment-related adverse events (≥5% incidence) leading to interruption of KEYTRUDA being neutrophil count decreased, neutropenia, platelet count decreased and diarrhea.

Table 33: Treatment-Related Adverse Events (Incidence ≥ 1%) in Patients Treated with KEYTRUDA in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, APaT Population in KEYNOTE-811.

Adverse Reaction		KEYTR	UDA			Plac	ebo	
	2	00 mg eve	ry 3 weeks					
		an	d			an	ıd	
		Trastuz	umab			Trastuz	zumab	
		an	d			an	ıd	
		Fluoropyı	rimidine			Fluoropy	rimidine	
		an	d			an	ıd	
	Pla	atinum Che	emotherap	у	Pla	atinum Che	emotherap	у
		n=3	50			n=3	46	
	Any				Any			
	Grade	Grade 3	Grade 4	Grade 5	Grade	Grade 3	Grade 4	Grade 5
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Blood and lymphatic	system disc	orders						
Anemia	109 (31.1)	20 (5.7)	1 (0.3)	0	113 (32.7)	19 (5.5)	1 (0.3)	0
Leukopenia	11 (3.1)	2 (0.6)	0	0	21 (6.1)	3 (0.9)	0	0
Neutropenia	59 (16.9)	19 (5.4)	3 (0.9)	0	54 (15.6)	14 (4.0)	2 (0.6)	0
Thrombocytopenia	40 (11.4)	10 (2.9)	1 (0.3)	0	44 (12.7)	2 (0.6)	4 (1.2)	0
Cardiac disorders								•
Mitral valve	5 (4 A)	0	0	0	4 (0.2)	_	_	
incompetence	5 (1.4)	0	0	0	1 (0.3)	0	0	0
Ear and labyrinth dis	orders					•		
Hypoacusis	5 (1.4)	3 (0.9)	0	0	2 (0.6)	0	0	0
Tinnitus	7 (2.0)	0	0	0	5 (1.4)	0	0	0
Endocrine disorders						•		
Adrenal	4 (4 4)	1 (0.3)	0	0	0			
insufficiency	4 (1.1)	1 (0.3)	0	0	0	0	0	0
Hyperthyroidism	12 (3.4)	0	0	0	7 (2.0)	0	0	0
Hypophysitis	4 (1.1)	2 (0.6)	0	0	0	0	0	0
Hypothyroidism	29 (8.3)	0	0	0	15 (4.3)	0	0	0
Eye disorders	•				•	•	•	•
Dry eye	6 (1.7)	1 (0.3)	0	0	1 (0.3)	0	0	0
Gastrointestinal diso	rders							•
Abdominal	4 (1.1)	0	0	0	3 (0.9)	0	0	0
distension	4 (1.1)	U	U	U	3 (0.3)	U	U	U

Adverse Reaction		KEYTR 00 mg ever an Trastuz an Fluoropyi an atinum Che	ry 3 weeks d umab d rimidine d emotherap		Pla	Placebo and Trastuzumab and Fluoropyrimidine and Platinum Chemotherapy n=346				
	Any Grade	Grade 3	Grade 4	Grade 5	Any Grade	Grade 3	Grade 4	Grade 5		
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)		
Abdominal pain	11 (3.1)	0	0	0	14 (4.0)	0	0	0		
Abdominal pain upper	5 (1.4)	0	0	0	11 (3.2)	0	0	0		
Colitis	12 (3.4)	6 (1.7)	0	0	6 (1.7)	4 (1.2)	0	0		
Constipation	23 (6.6)	0	0	0	28 (8.1)	0	0	0		
Diarrhea	165 (47.1)	28 (8.0)	3 (0.9)	0	145 (41.9)	25 (7.2)	2 (0.6)	0		
Dry mouth	6 (1.7)	0	0	0	8 (2.3)	0	0	0		
Dyspepsia	6 (1.7)	0	0	0	9 (2.6)	0	0	0		
Dysphagia	4 (1.1)	0	0	0	0	0	0	0		
Enteritis	3 (0.9)	3 (0.9)	0	0	5 (1.4)	2 (0.6)	0	0		
Flatulence	3 (0.9)	0	0	0	4 (1.2)	0	0	0		
Gastritis	4 (1.1)	1 (0.3)	0	0	2 (0.6)	0	0	0		
Gastroesophageal reflux disease	6 (1.7)	0	0	0	4 (1.2)	0	0	0		
Nausea	154 (44.0)	14 (4.0)	0	0	152 (43.9)	15 (4.3)	0	0		
Stomatitis	36 (10.3)	4 (1.1)	0	0	31 (9.0)	6 (1.7)	0	0		
Vomiting	88 (25.1)	14 (4.0)	0	0	86 (24.9)	10 (2.9)	0	0		
General disorders ar	nd administi	ration site	conditions							
Asthenia	39 (11.1)	7 (2.0)	0	0	50 (14.5)	9 (2.6)	0	0		
Chills	9 (2.6)	0	0	0	8 (2.3)	0	0	0		
Fatigue	69 (19.7)	12 (3.4)	0	0	57 (16.5)	8 (2.3)	0	0		
Malaise	25 (7.1)	0	0	0	25 (7.2)	3 (0.9)	0	0		
Mucosal inflammation	22 (6.3)	3 (0.9)	0	0	25 (7.2)	2 (0.6)	0	0		
Oedema peripheral	6 (1.7)	0	0	0	4 (1.2)	0	0	0		
Pyrexia	20 (5.7)	0	0	0	19 (5.5)	0	0	0		
Temperature intolerance	6 (1.7)	0	0	0	2 (0.6)	0	0	0		
Hepatobiliary disord	ers		1		1			1		
Hepatic function abnormal	4 (1.1)	2 (0.6)	0	0	5 (1.4)	0	0	0		
Liver injury	4 (1.1)	2 (0.6)	0	0	1 (0.3)	0	0	0		

Adverse Reaction	Pla	KEYTR 00 mg ever an Trastuz an Fluoropyi an atinum Che	ry 3 weeks d umab d rimidine d emotherap 50	у	Any	Placebo and Trastuzumab and Fluoropyrimidine and latinum Chemotherapy n=346				
	Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)		
Immune system diso	rders									
Drug hypersensitivity	4 (1.1)	1 (0.3)	0	0	3 (0.9)	0	0	0		
Hypersensitivity	8 (2.3)	1 (0.3)	0	0	6 (1.7)	0	0	0		
Infections and infest	ations	ı	ı	ı	ı	ı	ı	ı		
Paronychia	5 (1.4)	0	0	0	6 (1.7)	0	0	0		
Pneumonia	12 (3.4)	2 (0.6)	1 (0.3)	0	4 (1.2)	1 (0.3)	0	0		
Injury, poisoning and	l procedural	complicat	ions	T	T	T	T	T		
Infusion related reaction	41 (11.7)	5 (1.4)	1 (0.3)	0	34 (9.8)	2 (0.6)	0	0		
Investigations	1	ı	ı	ı	T	ı	ı	T		
Alanine aminotransferase increased	51 (14.6)	3 (0.9)	0	0	41 (11.8)	1 (0.3)	0	0		
Amylase increased	4 (1.1)	1 (0.3)	0	0	2 (0.6)	0	0	0		
Aspartate aminotransferase increased	66 (18.9)	6 (1.7)	0	0	50 (14.5)	1 (0.3)	0	0		
Bilirubin conjugated increased	3 (0.9)	0	0	0	5 (1.4)	0	0	0		
Blood alkaline phosphatase increased	10 (2.9)	1 (0.3)	0	0	10 (2.9)	0	0	0		
Blood bilirubin increased	39 (11.1)	3 (0.9)	0	0	27 (7.8)	2 (0.6)	0	0		
Blood creatine phosphokinase increased	4 (1.1)	0	0	0	5 (1.4)	0	0	0		
Blood creatinine increased	21 (6.0)	0	0	0	6 (1.7)	1 (0.3)	0	0		
Blood thyroid stimulating hormone increased	2 (0.6)	0	0	0	5 (1.4)	0	0	0		
Blood urea	4 (1.1)	0	0	0	0	0	0	0		

Adverse Reaction	2	KEYTR 00 mg ever an	ry 3 weeks d			Place	d		
		Trastuz				Trastuz			
		an				an			
		Fluoropyı an				Fluoropy an			
	DI	an atinum Che		.,	DI				
	Pic	n=3		y Platinum Chemotherapy n=346					
	Any	11-3	30	Any n=346					
	Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	
increased									
Ejection fraction decreased	13 (3.7)	4 (1.1)	0	0	11 (3.2)	3 (0.9)	0	0	
Gamma- glutamyltransferase increased	10 (2.9)	4 (1.1)	0	0	7 (2.0)	2 (0.6)	1 (0.3)	0	
Lipase increased	2 (0.6)	0	0	0	4 (1.2)	2 (0.6)	0	0	
Lymphocyte count decreased	11 (3.1)	2 (0.6)	0	0	11 (3.2)	4 (1.2)	0	0	
Neutrophil count decreased	92 (26.3)	25 (7.1)	3 (0.9)	0	83 (24.0)	26 (7.5)	4 (1.2)	0	
Platelet count decreased	89 (25.4)	20 (5.7)	2 (0.6)	0	93 (26.9)	19 (5.5)	4 (1.2)	0	
Total bile acids increased	3 (0.9)	0	0	0	4 (1.2)	0	0	0	
Weight decreased	42 (12.0)	5 (1.4)	0	0	24 (6.9)	2 (0.6)	0	0	
White blood cell count decreased	53 (15.1)	3 (0.9)	0	0	41 (11.8)	6 (1.7)	0	0	
Metabolism and nutr	rition disord	lers							
Decreased appetite	91 (26.0)	11 (3.1)	0	0	91 (26.3)	11 (3.2)	0	0	
Dehydration	5 (1.4)	3 (0.9)	0	0	5 (1.4)	4 (1.2)	0	0	
Hyperglycemia	11 (3.1)	2 (0.6)	0	0	7 (2.0)	0	0	0	
Hypoalbuminemia	16 (4.6)	2 (0.6)	0	0	17 (4.9)	0	0	0	
Hypocalcemia	7 (2.0)	0	0	0	6 (1.7)	0	0	0	
Hypochloremia	3 (0.9)	1 (0.3)	0	0	4 (1.2)	0	0	0	
Hypokalemia	21 (6.0)	10 (2.9)	1 (0.3)	0	15 (4.3)	8 (2.3)	2 (0.6)	0	
Hypomagnesemia	13 (3.7)	2 (0.6)	0	0	7 (2.0)	0	1 (0.3)	0	
Hyponatremia	11 (3.1)	2 (0.6)	1 (0.3)	0	13 (3.8)	5 (1.4)	1 (0.3)	0	
Musculoskeletal and			rders		ı	1	1	1	
Arthralgia	8 (2.3)	0	0	0	5 (1.4)	0	0	0	
Myalgia	5 (1.4)	0	0	0	6 (1.7)	0	0	0	
Pain in extremity	4 (1.1)	0	0	0	3 (0.9)	0	0	0	
Nervous system diso			Т		T	1	1	1	
Dizziness	7 (2.0)	0	0	0	4 (1.2)	0	0	0	

Adverse Reaction	2	KEYTR	UDA ry 3 weeks			Place	ebo	
		an	-			an	d	
		Trastuz				Trastuz		
		an				an		
		Fluoropy	rimidine			Fluoropy	rimidine	
		an				an		
	Pla	atinum Che	emotherap	у	Pla	atinum Che	emotherap	у
		n=3	50			n=3	46	
	Any				Any			
	Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Dysesthesia	5 (1.4)	0	0	0	5 (1.4)	1 (0.3)	0	0
Dysgeusia	15 (4.3)	0	0	0	15 (4.3)	0	0	0
Headache	5 (1.4)	0	0	0	5 (1.4)	0	0	0
Hypoesthesia	9 (2.6)	1 (0.3)	0	0	12 (3.5)	0	0	0
Neuropathy peripheral	60 (17.1)	8 (2.3)	0	0	63 (18.2)	9 (2.6)	0	0
Neurotoxicity	7 (2.0)	1 (0.3)	0	0	13 (3.8)	4 (1.2)	0	0
Paraesthesia	25 (7.1)	2 (0.6)	0	0	21 (6.1)	1 (0.3)	0	0
Peripheral motor neuropathy	4 (1.1)	2 (0.6)	0	0	2 (0.6)	1 (0.3)	0	0
Peripheral sensory neuropathy	84 (24.0)	13 (3.7)	0	0	73 (21.1)	7 (2.0)	0	0
Polyneuropathy	2 (0.6)	2 (0.6)	0	0	12 (3.5)	1 (0.3)	0	0
Taste disorder	4 (1.1)	0	0	0	2 (0.6)	0	0	0
Psychiatric disorders			l		. ,	l .		l .
Insomnia	5 (1.4)	0	0	0	0	0	0	0
Renal and urinary dis	sorders				•	•		•
Acute kidney injury	7 (2.0)	2 (0.6)	1 (0.3)	0	2 (0.6)	0	0	0
Respiratory, thoracio	and medias	stinal disor	rders					
Cough	4 (1.1)	0	0	0	1 (0.3)	0	0	0
Dyspnea	4 (1.1)	1 (0.3)	0	0	3 (0.9)	0	1 (0.3)	0
Epistaxis	10 (2.9)	0	0	0	2 (0.6)	1 (0.3)	0	0
Hiccups	10 (2.9)	0	0	0	5 (1.4)	0	0	0
Pneumonitis	16 (4.6)	3 (0.9)	1 (0.3)	1 (0.3)	4 (1.2)	0	0	0
Skin and subcutaneo	us tissue dis	orders						
Alopecia	6 (1.7)	0	0	0	6 (1.7)	0	0	0
Dermatitis	1 (0.3)	0	0	0	4 (1.2)	0	0	0
Dermatitis acneiform	4 (1.1)	0	0	0	0	0	0	0
Dry skin	15 (4.3)	1 (0.3)	0	0	9 (2.6)	0	0	0
Onychomadesis	4 (1.1)	0	0	0	3 (0.9)	0	0	0
Palmar-plantar erythrodysesthesia syndrome	78 (22.3)	5 (1.4)	0	0	72 (20.8)	5 (1.4)	0	0

Adverse Reaction		KEYTR			Placebo					
	2	00 mg eve	-		_					
		an			and					
		Trastuz	umab			Trastuz	umab			
		an	d			an	d			
		Fluoropyı	rimidine			Fluoropy	rimidine			
		an	d			an	d			
	Pla	atinum Che	emotherap	у	Pla	atinum Che	emotherap	у		
		n=3	50			n=3	46			
	Any				Any					
	Grade	Grade 3	Grade 4	Grade 5	Grade	Grade 3	Grade 4	Grade 5		
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)		
Pigmentation disorder	4 (1.1)	0	0	0	3 (0.9)	0	0	0		
Pruritus	25 (7.1)	1 (0.3)	0	0	9 (2.6)	0	0	0		
Rash	20 (5.7)	0	0	0	6 (1.7)	0	0	0		
Rash maculo- papular	8 (2.3)	1 (0.3)	0	0	3 (0.9)	0	0	0		
Skin	7 (2.0)	0	0	0	0 (2 2)	0	0	0		
hyperpigmentation	7 (2.0)	0			8 (2.3)					
Vascular disorders										
Hypotension	4 (1.1)	1 (0.3)	0	0	2 (0.6)	0	1 (0.3)	0		
Vasculitis	4 (1.1)	0	0	0	1 (0.3)	0	0	0		

Table 34 summarizes the treatment-related adverse events that occurred in at least 1% of patients with locally advanced unresectable or metastatic HER2-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma receiving KEYTRUDA plus fluoropyrimidine- and platinum-containing chemotherapy in KEYNOTE-859 (See 14 Clinical Trials). The median duration of exposure was 6.7 months (range: 1 day to 33.7 months) in the KEYTRUDA with chemotherapy arm and 5.6 months (range: 1 day to 29.7 months) in the chemotherapy arm. The most common treatment-related adverse events (≥20% incidence) were nausea, diarrhea, anemia, vomiting, platelet count decreased, neutrophil count decreased, palmar-plantar erythrodysesthesia syndrome, decreased appetite and fatigue. The most common Grade 3-4 treatment-related adverse events for patients treated with KEYTRUDA in KEYNOTE-859 were neutrophil count decreased (9.2%), anemia (8.2%) decreased platelet count (7.0%), and neutropenia (7.0%).

Serious treatment-related adverse events occurred in 23% of patients receiving KEYTRUDA in combination with chemotherapy. Serious treatment-related adverse reactions (≥1% incidence) included diarrhea (3.9%), colitis (2.0%), vomiting (1.8%), and nausea (1.5%). Fatal treatment-related adverse events occurred in 1% of patients who received KEYTRUDA in combination with chemotherapy including 1 case each of death, diarrhea, peripheral embolism, pneumonitis, pulmonary hemorrhage, sepsis, septic shock, and thrombotic thrombocytopenic purpura.

KEYTRUDA was discontinued for treatment-related adverse events in 8.7% of patients receiving KEYTRUDA with chemotherapy. The most common treatment-related adverse events resulting in discontinuation of KEYTRUDA (occurring in more than 3 patients) were diarrhea, colitis and pneumonitis. Treatment-related adverse events leading to interruption of KEYTRUDA occurred in 54% of patients receiving KEYTRUDA with chemotherapy. The most common treatment-related adverse events resulting in interruption of KEYTRUDA (≥3%) were decreased neutrophil count (13%), decreased platelet count

(9.6%), neutropenia (7.6%), diarrhea (5.2%), aspartate aminotransferase increased (3.6%), anemia (3.4%), thrombocytopenia (3.2%), and alanine aminotransferase increased (3.1%).

Of 785 adult patients with locally advanced or metastatic gastric or GEJ cancer treated with KEYTRUDA in combination with chemotherapy, 38% (n=302) were \geq 65 years of age. In patients \geq 65 years of age the incidence of treatment-related Grade \geq 3 adverse and serious adverse events was 65% and 30% compared to patients <65 years of age was 56% and 19%, respectively. In the \geq 75-<85 cohort (n=54) treated with KEYTRUDA in combination with chemotherapy, the incidence of treatment-related Grade \geq 3 adverse and serious adverse events was 65% and 39%, respectively.

Table 34: Treatment-Related Adverse Events (Incidence ≥ 1%) in Patients Treated with KEYTRUDA in Combination with fluoropyrimidine- and platinum-containing Chemotherapy, APaT Population in KEYNOTE-859.

Adverse Reaction	20	KEYTR 00 mg eve		s	Placebo and FP* or CAPOX** n=787				
		an FP* or C/ n=7	APOX**						
	Any	Grade	de Grade Grade	Any	Grade	Grade	Grade		
	Grade [†] n (%)	3 n (%)	4 n (%)	5 n (%)	Grade [†] n (%)	3 n (%)	4 n (%)	5 n (%)	
Blood and lymphatic	system dis	orders			•				
Anemia	243 (31.0)	62 (7.9)	2 (0.3)	0	212 (26.9)	48 (6.1)	3 (0.4)	0	
Leukopenia	44 (5.6)	4 (0.5)	0	0	35 (4.4)	0	1 (0.1)	0	
Lymphopenia	17 (2.2)	5 (0.6)	1 (0.1)	0	9 (1.1)	1 (0.1)	1 (0.1)	0	
Neutropenia	142 (18.1)	50 (6.4)	5 (0.6)	0	135 (17.2)	52 (6.6)	8 (1.0)	0	
Thrombocytopenia	83 (10.6)	10 (1.3)	2 (0.3)	0	77 (9.8)	18 (2.3)	0	0	
Ear and Labyrinth dis	sorders				l				
Tinnitus	14 (1.8)	1 (0.1)	0	0	10 (1.3)	0	0	0	
Endocrine disorders									
Adrenal insufficiency	10 (1.3)	3 (0.4)	1 (0.1)	0	0	0	0	0	
Hyperthyroidism	38 (4.8)	0	0	0	10 (1.3)	0	0	0	
Hypothyroidism	107 (13.6)	1 (0.1)	0	0	32 (4.1)	0	0	0	
Eye disorders	1				ı				
Lacrimation increased	8 (1.0)	0	0	0	1 (0.1)	0	0	0	

Adverse Reaction	20	KEYTF 00 mg eve an FP* or C n=7	ry 3 week d APOX**	s		cebo nd CAPOX** 787	*	
	Any Grade [†] n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade [†] n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Gastrointestinal disc	orders	<u> </u>	<u> </u>					<u> </u>
Abdominal distension	10 (1.3)	0	0	0	15 (1.9)	0	0	0
Abdominal pain	42 (5.4)	4 (0.5)	0	0	31 (3.9)	3 (0.4)	0	0
Abdominal pain upper	17 (2.2)	2 (0.3)	0	0	22 (2.8)	0	0	0
Colitis	18 (2.3)	16 (2.0)	0	0	10 (1.3)	4 (0.5)	0	0
Constipation	62 (7.9)	0	0	0	55 (7)	1 (0.1)	0	0
Diarrhea	252 (32.1)	42 (5.4)	3 (0.4)	1 (0.1)	214 (27.2)	35 (4.4)	1 (0.1)	1 (0.1)
Dry mouth	28 (3.6)	0	0	0	9 (1.1)	0	0	0
Dyspepsia	9 (1.1)	1 (0.1)	0	0	14 (1.8)	0	0	0
Gastroesophageal reflux disease	8 (1.0)	0	0	0	11 (1.4)	1 (0.1)	0	0
Nausea	325 (41.4)	25 (3.2)	1 (0.1)	0	326 (41.4)	29 (3.7)	0	0
Stomatitis	53 (6.8)	6 (0.8)	0	0	42 (5.3)	0	0	0
Vomiting	215 (27.4)	35 (4.5)	0	0	175 (22.2)	32 (4.1)	0	0
General disorders ar	nd administ	ration site	conditio	ns		•		
Asthenia	94 (12.0)	12 (1.5)	1 (0.1)	0	79 (10.0)	16 (2.0)	0	0
Chills	10 (1.3)	0	0	0	3 (0.4)	0	0	0
Edema peripheral	14 (1.8)	0	0	0	8 (1.0)	0	0	0
Fatigue	157 (20.0)	27 (3.4)	0	0	164 (20.8)	32 (4.1)	0	0
Malaise	25 (3.2)	1 (0.1)	0	0	31 (3.9)	0	0	0
Mucosal	49 (6.2)	5 (0.6)	1 (0.1)	0	37 (4.7)	8 (1.0)	0	0

Adverse Reaction	20	KEYTF 00 mg eve an FP* or C n=7	ry 3 week d APOX**	s				
	Any Grade [†] n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade [†] n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
inflammation								
Pyrexia	33 (4.2)	0	0	0	15 (1.9)	3 (0.4)	0	0
Infections and infest	ations			l	1	l		
Oral candidiasis	8 (1.0)	0	0	0	1 (0.1)	0	0	0
Pneumonia	10 (1.3)	4 (0.5)	0	0	5 (0.6)	0	1 (0.1)	0
Injury, poisoning and	d procedura	al complic	ations	l		l		
Infusion related reaction	25 (3.2)	4 (0.5)	1 (0.1)	0	21 (2.7)	2 (0.3)	0	0
Investigations			l	I	l	I		
Alanine aminotransferase increased	101 (12.9)	10 (1.3)	0	0	68 (8.6)	7 (0.9)	0	0
Aspartate aminotransferase increased	139 (17.7)	11 (1.4)	0	0	102 (13.0)	7 (0.9)	1 (0.1)	0
Bilirubin conjugated increased	10 (1.3)	2 (0.3)	0	0	14 (1.8)	0	0	0
Blood alkaline phosphatase increased	36 (4.6)	4 (0.5)	0	0	27 (3.4)	2 (0.3)	0	0
Blood bilirubin increased	78 (9.9)	8 (1)	1 (0.1)	0	51 (6.5)	3 (0.4)	0	0
Blood creatinine increased	28 (3.6)	2 (0.3)	0	0	16 (2.0)	1 (0.1)	0	0
Blood lactate dehydrogenase increased	9 (1.1)	0	0	0	6 (0.8)	0	0	0
Blood thyroid stimulating hormone increased	9 (1.1)	0	0	0	4 (0.5)	0	0	0

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks and FP* or CAPOX** n=785				Placebo and FP* or CAPOX** n=787				
	Any Grade [†] n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade [†] n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	
Gamma- glutamyltransferas e increased	11 (1.4)	3 (0.4)	0	0	12 (1.5)	1 (0.1)	0	0	
Hemoglobin decreased	10 (1.3)	4 (0.5)	0	0	7 (0.9)	0	0	0	
Lymphocyte count decreased	29 (3.7)	8 (1.0)	2 (0.3)	0	15 (1.9)	2 (0.3)	0	0	
Neutrophil count decrease	193 (24.6)	63 (8.0)	9 (1.1)	0	170 (21.6)	54 (6.9)	4 (0.5)	0	
Platelet count decreased	196 (25.0)	47 (6)	8 (1)	0	177 (22.5)	32 (4.1)	4 (0.5)	0	
Weight decreased	67 (8.5)	7 (0.9)	0	0	70 (8.9)	5 (0.6)	0	0	
White blood cell count decreased	101 (12.9)	9 (1.1)	3 (0.4)	0	87 (11.1)	7 (0.9)	2 (0.3)	0	
Metabolism and nuti	rition disor	ders			l				
Decreased appetite	168 (21.4)	15 (1.9)	0	0	168 (21.3)	14 (1.8)	0	0	
Dehydration	18 (2.3)	2 (0.3)	0	0	13 (1.7)	2 (0.3)	0	0	
Hyperglycemia	27 (3.4)	2 (0.3)	0	0	16 (2.0)	2 (0.3)	0	0	
Hypoalbuminemia	52 (6.6)	3 (0.4)	0	0	41 (5.2)	2 (0.3)	0	0	
Hypocalcemia	19 (2.4)	1 (0.1)	2 (0.3)	0	15 (1.9)	2 (0.3)	0	0	
Hypochloremia	8 (1.0)	0	1 (0.1)	0	2 (0.3)	0	0	0	
Hypokalemia	50 (6.4)	22 (2.8)	4 (0.5)	0	44 (5.6)	11 (1.4)	7 (0.9)	0	
Hypomagnesemia	28 (3.6)	0	0	0	21 (2.7)	1 (0.1)	0	0	
Hyponatremia	26 (3.3)	12 (1.5)	1 (0.1)	0	23 (2.9)	9 (1.1)	0	0	
Hypophosphatemia	11 (1.4)	4 (0.5)	0	0	11 (1.4)	3 (0.4)	1 (0.1)	0	
Musculoskeletal and	connective	e tissue di	sorders	1		ı	ı		

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks and FP* or CAPOX** n=785				Placebo and FP* or CAPOX** n=787				
	Any Grade [†] n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade [†] n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	
Arthralgia	8 (1.0)	0	0	0	7 (0.9)	0	0	0	
Muscle spams	9 (1.1)	0	0	0	9 (1.1)	0	0	0	
Nervous system	1				1				
Dizziness	14 (1.8)	1 (0.1)	0	0	11 (1.4)	2 (0.3)	0	0	
Dysesthesia	15 (1.9)	1 (0.1)	0	0	13 (1.7)	0	0	0	
Dysgeusia	44 (5.6)	1 (0.1)	0	0	35 (4.4)	0	0	0	
Headache	8 (1.0)	0	0	0	6 (0.8)	0	0	0	
Hypoesthesia	25 (3.2)	1 (0.1)	0	0	23 (2.9)	1 (0.1)	0	0	
Neuropathy peripheral	150 (19.1)	10 (1.3)	0	0	164 (20.8)	24 (3.0)	1 (0.1)	0	
Neurotoxicity	29 (3.7)	1 (0.1)	0	0	30 (3.8)	3 (0.4)	0	1 (0.1)	
Paresthesia	44 (5.6)	2 (0.3)	0	0	30 (3.8)	3 (0.4)	0	0	
Peripheral sensory neuropathy	137 (17.5)	22 (2.8)	0	0	131 (16.6)	8 (1.0)	0	0	
Respiratory, thoracio	and media	astinal dis	orders	l					
Cough	8 (1.0)	0	0	0	1 (0.1)	0	0	0	
Dyspnea	15 (1.9)	2 (0.3)	0	0	7 (0.9)	1 (0.1)	0	0	
Epistaxis	8 (1.0)	0	0	0	6 (0.8)	0	0	0	
Hiccups	12 (1.5)	0	0	0	15 (1.9)	1 (0.1)	0	0	
Pneumonitis	17 (2.2)	5 (0.6)	1 (0.1)	1 (0.1)	5 (0.6)	1 (0.1)	0	1 (0.1)	
Skin and subcutaneo	us tissue d	isorders			1				
Alopecia	14 (1.8)	0	0	0	14 (1.8)	0	0	0	
Dry skin	28 (3.6)	0	0	0	10 (1.3)	0	0	0	
Palmar-plantar erythrodysesthesia syndrome	189 (24.1)	24 (3.1)	0	0	166 (21.1)	14 (1.8)	0	0	
Pruritus	47 (6.0)	1 (0.1)	0	0	18 (2.3)	0	0	0	

Adverse Reaction	20	KEYTR 00 mg eve an FP* or C/ n=7	Placebo and FP* or CAPOX** n=787					
	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	56 (7.1)	5 (0.6)	0	0	29 (3.7)	1 (0.1)	0	0
Rash maculo- papular	20 (2.5)	5 (0.6)	0	0	6 (0.8)	0	0	0
Skin hyperpigmentation	17 (2.2)	0	0	0	13 (1.7)	0	0	0

^{*5-}FU + cisplatin

Esophageal Cancer

Table 35 summarizes the treatment-related adverse events that occurred in at least 1% of patients with esophageal carcinoma or esophagogastric junction (EGJ) adenocarcinoma treated with KEYTRUDA in combination with cisplatin and 5-fluorouracil (FU) in KEYNOTE-590 (See 14 Clinical Trials). The median duration of exposure was 5.7 months (range: 1 day to 26 months) in the KEYTRUDA combination arm and 5.1 months (range: 3 days to 27 months) in the chemotherapy arm.

The most common treatment-related adverse events (reported in at least 20% of patients) were nausea, decreased appetite, anemia, fatigue, decreased neutrophil count, vomiting, diarrhea, neutropenia, stomatitis, and decreased white blood cells. The most common Grade 3-5 treatment-related adverse events for patients treated with KEYTRUDA in KEYNOTE-590 were decreased neutrophil count (22.7%), neutropenia (14.3%), anemia (12.4%), decreased white blood cell count (8.6%), nausea (7%), fatigue (6.2%), vomiting (6.2%), stomatitis (5.7%), hyponatremia (5.4%). Fatal treatment-related adverse-events occurred in 2.4% of patients receiving KEYTRUDA in combination with chemotherapy including 1 case each of multiple organ dysfunction syndrome, pulmonary embolism, interstitial lung disease, pneumonitis, febrile neutropenia, pneumonia, acute kidney injury, diarrhea, and hepatic failure.

Serious treatment-related adverse events occurred in 32% of patients receiving KEYTRUDA in combination with chemotherapy. Serious adverse events occurring in \geq 2% of patients were pneumonia (3.5%), pneumonitis (3.2%), febrile neutropenia (2.4%), acute kidney injury (2.2%), and vomiting (2.2%).

KEYTRUDA was discontinued for treatment-related adverse events in 7.3% of patients. The most common treatment-related adverse events resulting in discontinuation of KEYTRUDA were pneumonitis/interstitial lung disease (2.2%), transaminase increased (0.6%), blood creatinine increased (0.5%), diarrhea (0.5%), infusion-related reaction (0.5%), hepatitis (0.3%), hepatic failure (0.3%), and acute kidney injury (0.3%). KEYTRUDA was interrupted for treatment-related adverse events in 22.2%

^{**}capecitabine + oxaliplatin

[†]Graded per NCI CTCAE v4.0

APaT: all patients as treated

of patients. The most common treatment-related adverse events leading to interruption of KEYTRUDA were neutropenia/neutrophil count decreased (5.1%), pneumonitis (2.7%), rash/rash maculo-papular (1.6%), malaise (1.6%), fatigue (1.1%), decreased appetite (1.1%), blood creatinine increased (0.8%), transaminase increased (0.6%), hepatic function abnormal (0.5%), acute kidney injury (0.3%), renal failure (0.3%), and liver disorder (0.3%).

Table 35 and Table 71 summarize adverse reactions and laboratory abnormalities, respectively, in patients on KEYTRUDA in KEYNOTE-590.

Table 35: Treatment-Related Adverse Events (Incidence ≥ 1%) in Patients Treated with KEYTRUDA in Combination with Cisplatin and 5-FU, APaT Population in KEYNOTE-590.

Adverse Reaction		KEYTI	_		Placebo				
	200 mg every 3 weeks								
		ar	-		and				
		Cisp					olatin		
		ar					nd		
		F					:U		
		n=3	370	1		n=	370	r	
	Any Grade*	Grade 3	Grade 4	Grade 5	Any Grade*	Grade	Grade 4	Grade 5	
	n (%)	n (%)	n (%)	n (%)	n (%)	3 n (%)	n (%)	n (%)	
Blood and lymphatic sy	stem disor	ders							
Anemia	143	45	1 (0.3)	0	162	54	0	0	
	(38.6)	(12.2)			(43.8)	(14.6)			
Febrile neutropenia	11 (3)	8 (2.2)	2 (0.5)	1 (0.3)	14 (3.8)	8 (2.2)	5 (1.4)	1 (0.3)	
Leukopenia	24 (6.5)	3 (0.8)	3 (0.8)	0	28 (7.6)	10	1 (0.3)	0	
						(2.7)			
Neutropenia	96	41	12 (3.2)	0	88	45	15 (4.1)	0	
	(25.9)	(11.1)			(23.8)	(12.2)			
Thrombocytopenia	25 (6.8)	3 (0.8)	2 (0.5)	0	33 (8.9)	6 (1.6)	4 (1.1)	0	
Ear and labyrinth disord	ders								
Hypoacusis	5 (1.4)	1 (0.3)	0	0	7 (1.9)	0	0	0	
Tinnitus	33 (8.9)	2 (0.5)	0	0	25 (6.8)	0	0	0	
Endocrine disorders									
Adrenal insufficiency	4 (1.1)	2 (0.5)	0	0	2 (0.5)	0	0	0	
Hyperthyroidism	19 (5.1)	0	0	0	2 (0.5)	0	0	0	
Hypothyroidism	38 (10.3)	0	0	0	22 (5.9)	0	0	0	
Gastrointestinal disorde	ers		ı		ı			1	
Abdominal distension	4 (1.1)	0	0	0	6 (1.6)	0	0	0	
	•	•		•				•	

Adverse Reaction	2	KEYTF 200 mg eve an Cispl an FI n=3	ery 3 weeks nd latin nd U	5	Placebo and Cisplatin And FU n=370				
	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	7 (1.9)	1 (0.3)	0	0	2 (0.5)	0	0	0	
Angular cheilitis	4 (1.1)	0	0	0	0	0	0	0	
Aphthous ulcer	5 (1.4)	0	0	0	2 (0.5)	0	0	0	
Colitis	5 (1.4)	3 (0.8)	0	0	3 (0.8)	1 (0.3)	0	0	
Constipation	50 (13.5)	0	0	0	63 (17)	0	0	0	
Diarrhea	97 (26.2)	10 (2.7)	1 (0.3)	1 (0.3)	85 (23)	7 (1.9)	0	0	
Dry mouth	15 (4.1)	0	0	0	7 (1.9)	0	0	0	
Dyspepsia	7 (1.9)	0	0	0	6 (1.6)	0	0	0	
Dysphagia	5 (1.4)	3 (0.8)	0	0	8 (2.2)	2 (0.5)	0	0	
Mouth ulceration	9 (2.4)	1 (0.3)	0	0	5 (1.4)	1 (0.3)	0	0	
Nausea	233 (63)	26 (7)	0	0	220 (59.5)	24 (6.5)	0	0	
Stomatitis	96 (25.9)	21 (5.7)	0	0	93 (25.1)	14 (3.8)	0	0	
Vomiting	110 (29.7)	23 (6.2)	0	0	99 (26.8)	18 (4.9)	0	0	
General disorders and a	administrat	ion site cor	nditions						
Asthenia	45 (12.2)	11 (3)	1 (0.3)	0	35 (9.5)	4 (1.1)	0	0	
Chest pain	5 (1.4)	0	0	0	2 (0.5)	1 (0.3)	0	0	
Edema	11 (3)	0	0	0	8 (2.2)	0	0	0	
Fatigue	135 (36.5)	22 (5.9)	1 (0.3)	0	107 (28.9)	20 (5.4)	0	0	
Infusion site extravasation	7 (1.9)	0	0	0	3 (0.8)	0	0	0	

Adverse Reaction KEYTRUDA 200 mg every 3 weeks and					Placebo and					
		ar Cispl ar FI n=3	latin nd U			Cisp A F	nd blatin nd :U 370			
	Any Grade [*] n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade [*] n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)		
Malaise	43 (11.6)	2 (0.5)	0	0	39 (10.5)	4 (1.1)	0	0		
Mucosal inflammation	59 (15.9)	12 (3.2)	0	0	65 (17.6)	12 (3.2)	1 (0.3)	0		
Pyrexia	14 (3.8)	0	0	0	8 (2.2)	1 (0.3)	0	0		
Infections and infestation	ons									
Pneumonia	17 (4.6)	11 (3)	0	1 (0.3)	7 (1.9)	3 (0.8)	1 (0.3)	0		
Injury, poisoning and procedural complications										
Infusion related reaction	4 (1.1)	1 (0.3)	0	0	0	0	0	0		
Investigations										
Alanine aminotransferase increased	18 (4.9)	1 (0.3)	0	0	15 (4.1)	2 (0.5)	0	0		
Aspartate aminotransferase increased	18 (4.9)	3 (0.8)	0	0	19 (5.1)	1 (0.3)	1 (0.3)	0		
Blood alkaline phosphatase increased	4 (1.1)	0	0	0	7 (1.9)	0	0	0		
Blood bilirubin increased	4 (1.1)	0	0	0	5 (1.4)	0	0	0		
Blood creatinine increased	67 (18.1)	5 (1.4)	0	0	70 (18.9)	1 (0.3)	0	0		
Blood thyroid stimulating hormone decreased	7 (1.9)	0	0	0	2 (0.5)	0	0	0		
Blood thyroid stimulating hormone	8 (2.2)	0	0	0	6 (1.6)	0	0	0		

Adverse Reaction	eaction KEYTRUDA 200 mg every 3 weeks					Placebo				
		ar Cispl ar FI n=3	atin J			Cisp A F	nd blatin nd :U 370			
	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 urea increased	7 (1.9)	0	0	0	5 (1.4)	0	0	0		
Gamma- glutamyltransferase increased	6 (1.6)	1 (0.3)	0	0	3 (0.8)	1 (0.3)	0	0		
Lymphocyte count decreased	21 (5.7)	7 (1.9)	0	0	20 (5.4)	4 (1.1)	1 (0.3)	0		
Neutrophil count decreased	135 (36.5)	60 (16.2)	24 (6.5)	0	109 (29.5)	43 (11.6)	19 (5.1)	0		
Neutrophil percentage decreased	4 (1.1)	1 (0.3)	0	0	5 (1.4)	2 (0.5)	2 (0.5)	0		
Platelet count decreased	61 (16.5)	2 (0.5)	5 (1.4)	0	56 (15.1)	11 (3)	6 (1.6)	0		
Weight decreased	43 (11.6)	4 (1.1)	0	0	47 (12.7)	8 (2.2)	0	0		
White blood cell count decreased	89 (24.1)	27 (7.3)	5 (1.4)	0	69 (18.6)	12 (3.2)	6 (1.6)	0		
Metabolism and nutriti	on disorder	rs								
Decreased appetite	145 (39.2)	13 (3.5)	0	0	119 (32.2)	16 (4.3)	0	0		
Dehydration	20 (5.4)	8 (2.2)	0	0	16 (4.3)	7 (1.9)	1 (0.3)	0		
Hyperglycemia	11 (3)	2 (0.5)	1 (0.3)	0	3 (0.8)	1 (0.3)	0	0		
Hypoalbuminemia	5 (1.4)	0	0	0	12 (3.2)	1 (0.3)	0	0		
Hypocalcemia	10 (2.7)	2 (0.5)	0	0	8 (2.2)	3 (0.8)	0	0		
Hypokalemia	34 (9.2)	12 (3.2)	5 (1.4)	0	41 (11.1)	16 (4.3)	3 (0.8)	0		
Hypomagnesaemia	21 (5.7)	2 (0.5)	0	0	14 (3.8)	2 (0.5)	1 (0.3)	0		
Hyponatremia	32 (8.6)	16 (4.3)	4 (1.1)	0	40	18	2 (0.5)	0		

Adverse Reaction	2	KEYTF 200 mg eve ar Cispl ar FI	ery 3 weeks nd latin nd	5		a Cisp A	cebo nd platin nd :U			
		n=3	_				370			
	Any Grade [*] n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade [*] n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)		
					(10.8)	(4.9)				
Hypophosphatemia	10 (2.7)	3 (0.8)	0	0	13 (3.5)	9 (2.4)	0	0		
Musculoskeletal and co	nnective ti	ssue disorc	lers		I					
Arthralgia	11 (3)	0	0	0	4 (1.1)	0	0	0		
Myalgia	7 (1.9)	0	0	0	6 (1.6)	0	0	0		
Pain in extremity	4 (1.1)	0	0	0	0	0	0	0		
Nervous system disorders										
Dizziness	14 (3.8)	0	0	0	15 (4.1)	0	0	0		
Dysgeusia	34 (9.2)	0	0	0	32 (8.6)	0	0	0		
Headache	9 (2.4)	0	0	0	6 (1.6)	0	0	0		
Hypoesthesia	8 (2.2)	0	0	0	5 (1.4)	1 (0.3)	0	0		
Lethargy	4 (1.1)	0	0	0	6 (1.6)	1 (0.3)	0	0		
Neuropathy peripheral	32 (8.6)	1 (0.3)	0	0	32 (8.6)	0	0	0		
Paresthesia	9 (2.4)	0	0	0	3 (0.8)	0	0	0		
Peripheral sensory neuropathy	34 (9.2)	1 (0.3)	0	0	29 (7.8)	1 (0.3)	0	0		
Psychiatric disorders	ı				I					
Insomnia	12 (3.2)	0	0	0	10 (2.7)	0	0	0		
Renal and urinary disor	ders	I	I	I	ı	1	I			
Acute kidney injury	14 (3.8)	6 (1.6)	1 (0.3)	1 (0.3)	10 (2.7)	5 (1.4)	0	0		
Proteinuria	7 (1.9)	0	0	0	11 (3)	0	0	0		
Renal failure	4 (1.1)	0	0	0	3 (0.8)	3 (0.8)	0	0		
Renal impairment	7 (1.9)	0	0	0	6 (1.6)	0	0	0		
Respiratory, thoracic and mediastinal disorders										

Adverse Reaction		KEYTF 200 mg eve		•		Placebo					
	4	ar Cispl ar Fl	nd atin nd J	•		Cisp A F	nd blatin nd :U				
	Any Grade*	n=3 Grade 3	Grade 4	Grade 5	Any Grade [*]	n= Grade	370 Grade 4	Grade 5			
	n (%)	n (%)	n (%)	n (%)	n (%)	3 n (%)	n (%)	n (%)			
Cough	8 (2.2)	0	0	0	7 (1.9)	0	0	0			
Dyspnea	6 (1.6)	1 (0.3)	0	0	7 (1.9)	1 (0.3)	0	0			
Epistaxis	10 (2.7)	0	0	0	6 (1.6)	0	0	0			
Hiccups	40 (10.8)	0	0	0	33 (8.9)	0	0	0			
Oropharyngeal pain	6 (1.6)	0	0	0	4 (1.1)	0	0	0			
Pneumonitis	20 (5.4)	6 (1.6)	0	1 (0.3)	0	0	0	0			
Pulmonary embolism	4 (1.1)	4 (1.1) 2 (0.5) 1 (0.3) 1 (0.3) 2 (0.5) 1 (0.3) 0									
Skin and subcutaneous tissue disorders											
Alopecia	51 (13.8)	0	0	0	39 (10.5)	0	0	0			
Dermatitis	4 (1.1)	0	0	0	2 (0.5)	0	0	0			
Dry skin	14 (3.8)	0	0	0	6 (1.6)	0	0	0			
Palmar-plantar erythrodysesthesia syndrome	12 (3.2)	2 (0.5)	0	0	14 (3.8)	1 (0.3)	0	0			
Pruritus	23 (6.2)	1 (0.3)	0	0	8 (2.2)	0	0	0			
Rash	29 (7.8)	0	0	0	18 (4.9)	1 (0.3)	0	0			
Rash maculo-papular	10 (2.7)	4 (1.1)	0	0	3 (0.8)	0	0	0			
Skin hyperpigmentation	11 (3)	0	0	0	8 (2.2)	0	0	0			
Vascular disorders											
Hypertension	4 (1.1)	2 (0.5)	0	0	2 (0.5)	1 (0.3)	0	0			
Hypotension	9 (2.4)	0	1 (0.3)	0	7 (1.9)	0	0	0			
Phlebitis	7 (1.9)	0	0	0	4 (1.1)	0	0	0			
Vasculitis	6 (1.6)	0	0	0	7 (1.9)	0	0	0			
* Graded per NC	I CTCAE v4.0	03		1	ı		ı	I			

Adverse Reaction		KEYTI	RUDA			Pla	cebo			
		200 mg every 3 weeks								
		and				and				
	Cisplatin				Cisplatin					
	and				And					
		FU FU								
		n=370 n=370								
	Any				Any					
	Grade *	Grade 3	Grade 4	Grade 5	Grade Grade 4 Grade					
	n (%)	n (%)	n (%)	n (%)	n (%) 3 n (%) n (%) n (%					
APaT: all patients as tr	eated; Grade	d per NCI (TCAE v4.0	3	I	1	l .	I		

Triple Negative Breast Cancer (TNBC)

Table 36 summarizes the treatment-related adverse events that occurred in at least 1% of patients with triple negative breast cancer treated with KEYTRUDA in combination with paclitaxel, nab paclitaxel, or gemcitabine and carboplatin chemotherapy in KEYNOTE-355 (See 14 Clinical Trials). The median duration of exposure was 6.2 months (range: 1 day to 38.3 months) in the KEYTRUDA combination arm and 5.3 months (range: 1 day to 33.6 months) in the chemotherapy arm.

The most common treatment-related adverse events (reported in at least 20% of patients) were anemia, neutropenia, nausea, alopecia, fatigue, and neutrophil count decreased. The most common Grade 3-5 treatment-related adverse events for patients treated with KEYTRUDA in KEYNOTE-355 were neutropenia (29.2%), neutrophil count decreased (17.3%), anemia (16.4%), white blood cell count decreased (10.2%), thrombocytopenia (9.9%), leukopenia (9.7%), platelet count decreased (6.0%), and alanine aminotransferase increased (5.7%).

Fatal treatment-related adverse-events occurred in 0.3% of patients receiving KEYTRUDA in combination with chemotherapy including 1 case each of pneumonia and acute kidney injury. Serious treatment-related adverse events occurred in 17.6% of patients receiving KEYTRUDA in combination with chemotherapy. Serious treatment-related adverse events occurring in \geq 1% of patients were anemia, thrombocytopenia, febrile neutropenia, vomiting, pneumonitis, and pyrexia. KEYTRUDA was discontinued for treatment-related adverse events in 9.1% of patients. The most common treatment-related adverse events resulting in discontinuation of KEYTRUDA (occurring in at least 4 patients) were alanine aminotransferase increased (n=12, 2.0%), aspartate aminotransferase increased (n=9, 1.5%), and pneumonitis (n=7, 1.2%). KEYTRUDA was interrupted for treatment-related adverse events in 43% of patients. The most common treatment-related adverse events leading to interruption of KEYTRUDA (\geq 2%) were neutropenia (13.9%), thrombocytopenia (9.4%), neutrophil count decreased (8.4%), anemia (6.9%), leukopenia (5.2%), alanine aminotransferase increased (4.5%), platelet count decreased (4.2%), aspartate aminotransferase increased (3.9%), and white blood cell count decreased (3.7%).

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 36: Treatment -Related Adverse Events (incidence ≥ 1%) in Patients Treated with KEYTRUDA in Combination with Chemotherapy, APaT Population in KEYNOTE-355.

	KEYTRUDA and Chemotherapy n=596				Placebo and Chemotherapy n=281			
Adverse Reaction	All Grades* n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All Grades* n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Blood and lymphatic sys	stem disord	ers				•	•	
Anemia	291 (48.8)	94 (15.8)	4 (0.7)	0	129 (45.9)	41 (14.6)	0	0
Febrile neutropenia	10 (1.7)	8 (1.3)	2 (0.3)	0	3 (1.1)	3 (1.1)	0	0
Leukopenia	113 (19.0)	48 (8.1)	10 (1.7)	0	49 (17.4)	27 (9.6)	3 (1.1)	0
Lymphopenia	28 (4.7)	10 (1.7)	2 (0.3)	0	4 (1.4)	3 (1.1)	0	0
Neutropenia	241 (40.4)	113 (19.0)	61 (10.2)	0	107 (38.1)	55 (19.6)	29 (10.3)	0
Thrombocytopenia	114 (19.1)	29 (4.9)	30 (5.0)	0	54 (19.2)	19 (6.8)	12 (4.3)	0
Cardiac disorders		l			l	<u>'</u>	I.	
Palpitations	7 (1.2)	0	0	0	0	0	0	0
Ear and labyrinth disord	lers					•	•	
Vertigo	7 (1.2)	0	0	0	2 (0.7)	0	0	0
Endocrine disorders		l			l	·	l .	
Adrenal insufficiency	6 (1.0)	2 (0.3)	0	0	0	0	0	0
Hyperthyroidism	29 (4.9)	1 (0.2)	0	0	1 (0.4)	0	0	0
Hypothyroidism	80 (13.4)	2 (0.3)	0	0	8 (2.8)	0	0	0
Thyroiditis	7 (1.2)	1 (0.2)	0	0	0	0	0	0
Eye disorders		•	•	•		•	•	•
Dry eye	14 (2.3)	0	0	0	7 (2.5)	0	0	0
Lacrimation increased	12 (2.0)	0	0	0	7 (2.5)	0	0	0
Gastrointestinal disorde	ers	ı	1		1	ı		
Abdominal pain	14 (2.3)	0	0	0	10 (3.6)	0	0	0
Abdominal pain upper	22 (3.7)	2 (0.3)	0	0	5 (1.8)	0	0	0
Colitis	9 (1.5)	2 (0.3)	0	0	2 (0.7)	0	0	0

		KEYTRUDA and Chemotherapy n=596				Place and Chemoth n=28	l erapy	
Adverse Reaction	All Grades* n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All Grades* n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Constipation	80 (13.4)	3 (0.5)	0	0	37 (13.2)	0	0	0
Diarrhea	115 (19.3)	8 (1.3)	0	0	45 (16.0)	3 (1.1)	0	0
Dry mouth	18 (3.0)	0	0	0	7 (2.5)	0	0	0
Dyspepsia	22 (3.7)	0	0	0	11 (3.9)	0	0	0
Gastritis	11 (1.8)	0	0	0	3 (1.1)	0	0	0
Gastroesophageal reflux disease	7 (1.2)	0	0	0	5 (1.8)	0	0	0
Nausea	229 (38.4)	9 (1.5)	0	0	115 (40.9)	4 (1.4)	0	0
Stomatitis	47 (7.9)	2 (0.3)	0	0	17 (6.0)	0	0	0
Vomiting	111 (18.6)	13 (2.2)	0	0	42 (14.9)	6 (2.1)	0	0
General disorders and a	dministration	on site co	nditions				•	•
Asthenia	89 (14.9)	6 (1.0)	0	0	37 (13.2)	1 (0.4)	0	0
Chills	7 (1.2)	0	0	0	3 (1.1)	0	0	0
Edema	6 (1.0)	0	0	0	2 (0.7)	1 (0.4)	0	0
Edema peripheral	27 (4.5)	0	0	0	12 (4.3)	0	0	0
Fatigue	164 (27.5)	17 (2.9)	0	0	83 (29.5)	7 (2.5)	0	0
Malaise	26 (4.4)	2 (0.3)	0	0	13 (4.6)	0	0	0
Mucosal inflammation	27 (4.5)	2 (0.3)	0	0	9 (3.2)	1 (0.4)	0	0
Pyrexia	58 (9.7)	3 (0.5)	0	0	23 (8.2)	3 (1.1)	0	0
Immune System Disord	ers	•						
Hypersensitivity	9 (1.5)	1 (0.2)	0	0	6 (2.1)	0	0	0
Infections and infestation	ons	•						
Conjunctivitis	7 (1.2)	0	0	0	1 (0.4)	0	0	0

		KEYTRUDA and Chemotherapy n=596				Placebo and Chemotherapy n=281					
Adverse Reaction	All Grades* n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All Grades* n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)			
Nasopharyngitis	6 (1.0)	0	0	0	2 (0.7)	0	0	0			
Upper respiratory tract infection	7 (1.2)	1 (0.2)	0	0	6 (2.1)	0	0	0			
Urinary tract infection	10 (1.7)	0	0	0	3 (1.1)	0	0	0			
Injury, poisoning and procedural complications											
Infusion related reaction	8 (1.3)	1 (0.2)	0	0	6 (2.1)	0	0	0			
Investigations	l	l			l		I	I			
Alanine aminotransferase increased	118 (19.8)	29 (4.9)	5 (0.8)	0	46 (16.4)	13 (4.6)	0	0			
Aspartate aminotransferase increased	111 (18.6)	23 (3.9)	3 (0.5)	0	42 (14.9)	8 (2.8)	0	0			
Blood alkaline phosphatase increased	35 (5.9)	5 (0.8)	0	0	12 (4.3)	1 (0.4)	0	0			
Blood bilirubin increased	10 (1.7)	2 (0.3)	0	0	2 (0.7)	0	0	0			
Blood creatinine increased	11 (1.8)	0	0	0	6 (2.1)	2 (0.7)	0	0			
Blood lactate dehydrogenase increased	15 (2.5)	1 (0.2)	1 (0.2)	0	11 (3.9)	1 (0.4)	0	0			
Blood thyroid stimulating hormone increased	7 (1.2)	0	0	0	2 (0.7)	0	0	0			
Gamma- glutamyltransferase increased	16 (2.7)	3 (0.5)	0	0	6 (2.1)	3 (1.1)	0	0			
Hemoglobin decreased	11 (1.8)	2 (0.3)	0	0	3 (1.1)	1 (0.4)	0	0			
Lymphocyte count decreased	30 (5.0)	13 (2.2)	1 (0.2)	0	9 (3.2)	4 (1.4)	26 (9.3)	0			

		KEYTRU and Chemoth n=59	l ierapy		Placebo and Chemotherapy n=281			
Adverse Reaction	All Grades* n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All Grades* n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Neutrophil count decreased	132 (22.1)	54 (9.1)	49 (8.2)	0	74 (26.3)	31 (11.0)	0	0
Neutrophil percentage decreased	7 (1.2)	4 (0.7)	3 (0.5)	0	1 (0.4)	1 (0.4)	8 (2.8)	0
Platelet count decreased	90 (15.1)	21 (3.5)	15 (2.5)	0	43 (15.3)	12 (4.3)	0	0
Weight decreased	34 (5.7)	2 (0.3)	0	0	7 (2.5)	1 (0.4)	0	0
White blood cell count decreased	108 (18.1)	57 (9.6)	4 (0.7)	0	54 (19.2)	25 (8.9)	4 (1.4)	0
Metabolism and nutrition	on disorders	5	I.		l	I	I.	
Decreased appetite	97 (16.3)	5 (0.8)	0	0	25 (8.9)	1 (0.4)	0	0
Hypoalbuminemia	11 (1.8)	1 (0.2)	0	0	7 (2.5)	1 (0.4)	0	0
Hypokalemia	9 (1.5)	3 (0.5)	0	0	7 (2.5)	2 (0.7)	2 (0.7)	0
Hypomagnesemia	6 (1.0)	0	0	0	2 (0.7)	0	0	0
Hyponatremia	8 (1.3)	2 (0.3)	0	0	4 (1.4)	0	1 (0.4)	0
Musculoskeletal and co	nnective tis	sue disor	ders		l	I	I.	
Arthralgia	48 (8.1)	4 (0.7)	0	0	23 (8.2)	1 (0.4)	0	0
Arthritis	7 (1.2)	0	0	0	1 (0.4)	0	0	0
Back pain	8 (1.3)	0	0	0	6 (2.1)	0	0	0
Bone pain	9 (1.5)	1 (0.2)	0	0	6 (2.1)	0	0	0
Muscular weakness	6 (1.0)	0	0	0	2 (0.7)	0	0	0
Musculoskeletal pain	6 (1.0)	0	0	0	1 (0.4)	0	0	0
Myalgia	46 (7.7)	1 (0.2)	0	0	21 (7.5)	1 (0.4)	0	0
Pain in extremity	21 (3.5)	3 (0.5)	0	0	8 (2.8)	0	0	0
Nervous system disorde	ers							
Dizziness	14 (2.3)	1 (0.2)	0	0	15 (5.3)	0	0	0
Dysgeusia	47 (7.9)	0	0	0	12 (4.3)	0	0	0
Headache	39 (6.5)	2 (0.3)	0	0	23 (8.2)	0	0	0

		KEYTRUDA and Chemotherapy n=596				Placebo and Chemotherapy n=281				
Adverse Reaction	All Grades* n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All Grades* n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)		
Hypoesthesia	7 (1.2)	0	0	0	5 (1.8)	0	0	0		
Lethargy	12 (2.0)	2 (0.3)	0	0	2 (0.7)	1 (0.4)	0	0		
Neuropathy peripheral	61 (10.2)	6 (1.0)	0	0	32 (11.4)	4 (1.4)	0	0		
Neurotoxicity	7 (1.2)	0	0	0	3 (1.1)	0	0	0		
Paresthesia	20 (3.4)	0	0	0	10 (3.6)	0	0	0		
Peripheral sensory neuropathy	55 (9.2)	8 (1.3)	0	0	20 (7.1)	2 (0.7)	0	0		
Polyneuropathy	12 (2.0)	2 (0.3)	0	0	0	0	0	0		
Taste disorder	8 (1.3)	1 (0.2)	0	0	5 (1.8)	0	0	0		
Psychiatric disorders										
Anxiety	6 (1.0)	0	0	0	1 (0.4)	0	0	0		
Insomnia	10 (1.7)	0	0	0	5 (1.8)	0	0	0		
Respiratory, thoracic an	d mediastin	al disord	ers		l			<u>I</u>		
Cough	22 (3.7)	0	0	0	7 (2.5)	0	0	0		
Dysphonia	21 (3.5)	0	0	0	13 (4.6)	2 (0.7)	0	0		
Epistaxis	14 (2.3)	0	0	0	11 (3.9)	0	0	0		
Oropharyngeal pain	8 (1.3)	0	0	0	4 (1.4)	0	0	0		
Pneumonitis	12 (2.0)	5 (0.8)	1 (0.2)	0	0	0	0	0		
Skin and subcutaneous	tissue disor	ders						•		
Alopecia	197 (33.1)	4 (0.7)	1 (0.2)	0	94 (33.5)	3 (1.1)	0	0		
Dermatitis acneiform	8 (1.3)	0	0	0	4 (1.4)	0	0	0		
Dry skin	15 (2.5)	0	0	0	9 (3.2)	0	0	0		
Eczema	6 (1.0)	1 (0.2)	0	0	4 (1.4)	0	0	0		
Erythema	9 (1.5)	1 (0.2)	0	0	5 (1.8)	0	0	0		
Nail discolouration	8 (1.3)	0	0	0	10 (3.6)	0	0	0		
Nail disorder	12 (2.0)	0	0	0	5 (1.8)	0	0	0		

		KEYTRI and			Placebo and				
		Chemoth							
		n=59				n=28			
Adverse Reaction	All Grades* n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All Grades* n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	
Onycholysis	7 (1.2)	0	0	0	4 (1.4)	0	0	0	
Pruritus	64 (10.7)	1 (0.2)	0	0	26 (9.3)	0	0	0	
Rash	92 (15.4)	4 (0.7)	0	0	26 (9.3)	0	0	0	
Rash maculo-papular	29 (4.9)	7 (1.2)	0	0	9 (3.2)	0	0	0	
Skin hyperpigmentation	7 (1.2)	0	0	0	1 (0.4)	0	0	0	
Urticaria	6 (1.0)	1 (0.2)	0	0	2 (0.7)	0	0	0	
Vascular disorders		l							
Flushing	7 (1.2)	0	0	0	1 (0.4)	0	0	0	
Hot flush	7 (1.2)	0	0	0	8 (2.8)	0	0	0	
Hypertension	9 (1.5)	4 (0.7)	1 (0.2)	0	3 (1.1)	1 (0.4)	0	0	
Hypotension	7 (1.2)	1 (0.2)	0	0	3 (1.1)	0	0	0	

Early-stage Triple-Negative Breast Cancer

Table 37 summarizes the treatment-related adverse events that occurred in at least 1% of patients with high-risk early stage TNBC treated with KEYTRUDA in combination with chemotherapy (carboplatin and paclitaxel followed by doxorubicin or epirubicin and cyclophosphamide) as a neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery in KEYNOTE-522 (See 14 Clinical Trials). The median duration of exposure was 13.3 months (range: 1 day to 21.9 months) in the KEYTRUDA combination arm and 13.6 months (range: 1 day to 19.8 months) in the placebo arm.

The most common treatment-related adverse events for patients treated with KEYTRUDA in KEYNOTE-522 (reported in at least 20% of patients) were nausea, alopecia, anemia, neutropenia, fatigue, diarrhea, alanine aminotransferase increased, vomiting, asthenia, rash, constipation, neutrophil count decreased, aspartate aminotransferase increased, neuropathy peripheral, and decreased appetite. The most common Grade 3-5 treatment related adverse events for patients treated with KEYTRUDA in KEYNOTE-522 (reported in at least 5% of patients) were neutropenia (34.5%), neutrophil count decreased (18.6%), anemia (18%), febrile neutropenia (17.8%), white blood cell count decreased (7.7%), and alanine aminotransferase increased (5.5%).

Serious treatment-related adverse events occurred in 34% of patients receiving KEYTRUDA in KEYNOTE-522. Serious treatment-related adverse events in \geq 2% of patients receiving KEYTRUDA in KEYNOTE-522 included: febrile neutropenia (14.7%), pyrexia (2.6%), and anemia (2.4%). Fatal adverse events regardless of causality to the study treatment occurred in 0.9% of patients receiving KEYTRUDA in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery, including 1 each of autoimmune encephalitis, pneumonia, pneumonitis, pulmonary embolism, sepsis in association with multiple organ dysfunction syndrome and myocardial infarction, shock, and death from unknown cause.

KEYTRUDA was interrupted for treatment-related adverse events in 49% of patients. The most common treatment-related adverse events leading to interruption of KEYTRUDA (\geq 2%) were neutropenia (17.0%), neutrophil count decreased (8.4%), ALT increased (5.2%), anemia (3.3%), thrombocytopenia (3.1%), AST increased (3.1%), febrile neutropenia (2.8%), and platelet count decreased (2.8%). KEYTRUDA was discontinued for treatment-related adverse events in 17.9% of subjects. The most common treatment-related adverse events (\geq 2%) leading to discontinuation of KEYTRUDA were: ALT increased (2.4%).

Of 783 adult patients with high-risk early-stage TNBC treated with KEYTRUDA in combination with chemotherapy as neoadjuvant treatment, then with KEYTRUDA as monotherapy as adjuvant treatment after surgery, 84 (11%) were 65 years or over. Patients \geq 65 years of age had an incidence of serious adverse events (53.6%) compared to younger patients (42.3%). Adverse events leading to the discontinuation of any study drug were more frequent in patients \geq 65 years.

Table 37: Treatment-Related Adverse Events (incidence ≥ 1%) in Patients Treated with KEYTRUDA in Combination with Chemotherapy as Neoadjuvant Treatment, and then Continued as Monotherapy as Adjuvant Treatment After Surgery, APaT Population in KEYNOTE-522

Adverse Reaction KEYTRUDA Placebo 200 mg every 3 weeks and and Chemotherapy*/ Chemotherapy*/ **KEYTRUDA 200 mg every 3 weeks Placebo** n=783 n=389 Any Any Grade 3 Grade Grade 3 Grade 4 Grade 5 Grade Grade 4 Grade 5 n (%)[†] n (%) **Blood and lymphatic system disorders** Anemia 429 137 4 (0.5) 0 215 56 2 (0.5) 0 (54.8)(55.3)(14.4)(17.5)Febrile neutropenia 144 117 22 (2.8) 0 65 52 10 (2.6) 0 (14.9)(16.7)(13.4)(18.4)25 (3.2) 0 49 8 (2.1) 0 Leukopenia 87 8 (1.0) 8 (2.1) (11.1)(12.6)29 2 (0.3) 0 0 0 Lymphopenia 5 (0.6) 17 4 (1.0) (3.7)(4.4)

Adverse Reaction	KEYTF	200 mg evo aı Chemot RUDA 200 ı	nd herapy*/		Placebo and Chemotherapy*/ Placebo n=389 Any					
	Any Grade n (%) [†]	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)		
Neutropenia	367 (46.9)	180 (23.0)	90 (11.5)	0	185 (47.6)	88 (22.6)	42 (10.8)	0		
Pancytopenia	14 (1.8)	11 (1.4)	3 (0.4)	0	5 (1.3)	5 (1.3)	0	0		
Thrombocytopenia	104 (13.3)	16 (2.0)	5 (0.6)	0	65 (16.7)	7 (1.8)	4 (1.0)	0		
Cardiac disorders	1	·		·		·		I		
Palpitations	12 (1.5)	0	0	0	10 (2.6)	0	0	0		
Sinus tachycardia	14 (1.8)	0	0	0	5 (1.3)	0	0	0		
Tachycardia	14 (1.8)	1 (0.1)	0	0	2 (0.5)	0	0	0		
Ear and labyrinth disord	ders	·		·		·		I		
Tinnitus	8 (1.0)	0	0	0	5 (1.3)	0	0	0		
Vertigo	12 (1.5)	0	0	0	8 (2.1)	0	0	0		
Endocrine disorders	-1			•	•					
Adrenal insufficiency	18 (2.3)	7 (0.9)	1 (0.1)	0	0	0	0	0		
Hyperthyroidism	37 (4.7)	2 (0.3)	0	0	5 (1.3)	0	0	0		
Hypophysitis	10 (1.3)	8 (1.0)	0	0	0	0	0	0		
Hypothyroidism	105 (13.4)	4 (0.5)	0	0	19 (4.9)	0	0	0		
Thyroiditis	8 (1.0)	0	0	0	3 (0.8)	0	0	0		
Eye disorders										
Dry eye	35	0	0	0	15	0	0	0		
Dry eye	35	0	0	0	15	0	0			

Adverse Reaction	KEYTR	200 mg eve aı Chemotl UDA 200 ı	nd herapy*/		Placebo and Chemotherapy*/ Placebo n=389			
	Any Grade n (%) [†]	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
	(4.5)				(3.9)			
Lacrimation increased	12 (1.5)	0	0	0	5 (1.3)	0	0	0
Vision blurred	18 (2.3)	0	0	0	3 (0.8)	0	0	0
Gastrointestinal disorde	ers							
Abdominal pain	65 (8.3)	2 (0.3)	0	0	22 (5.7)	1 (0.3)	0	0
Abdominal pain upper	39 (5.0)	0	0	0	22 (5.7)	2 (0.5)	0	0
Colitis	8 (1.0)	4 (0.5)	1 (0.1)	0	1 (0.3)	0	0	0
Constipation	188 (24.0)	0	0	0	85 (21.9)	0	0	0
Diarrhea	238 (30.4)	20 (2.6)	0	0	98 (25.2)	5 (1.3)	0	0
Dry mouth	49 (6.3)	0	0	0	20 (5.1)	0	0	0
Dyspepsia	71 (9.1)	1 (0.1)	0	0	39 (10.0)	0	0	0
Gastritis	15 (1.9)	2 (0.3)	0	0	5 (1.3)	0	0	0
Gastroesophageal reflux disease	41 (5.2)	0	0	0	24 (6.2)	0	0	0
Hemorrhoids	12 (1.5)	0	0	0	3 (0.8)	0	0	0
Mouth ulceration	12 (1.5)	0	0	0	11 (2.8)	0	0	0
Nausea	495 (63.2)	27 (3.4)	0	0	245 (63.0)	6 (1.5)	0	0
Odynophagia	8 (1.0)	0	0	0	2 (0.5)	0	0	0

Adverse Reaction	KEYTR	200 mg eve aı Chemotl UDA 200 ı	nd herapy*/		Placebo and Chemotherapy*/ Placebo n=389			
	Any Grade n (%) [†]	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Oral pain	10 (1.3)	0	0	0	2 (0.5)	0	0	0
Stomatitis	132 (16.9)	11 (1.4)	0	0	55 (14.1)	1 (0.3)	0	0
Vomiting	200 (25.5)	18 (2.3)	1 (0.1)	0	86 (22.1)	6 (1.5)	0	0
General disorders and a	dministra	tion site co	nditions					
Asthenia	198 (25.3)	28 (3.6)	0	0	102 (26.2)	9 (2.3)	0	0
Chest pain	8 (1.0)	0	0	0	5 (1.3)	0	0	0
Chills	26 (3.3)	0	0	0	2 (0.5)	0	0	0
Face edema	10 (1.3)	0	0	0	3 (0.8)	0	0	0
Fatigue	330 (42.1)	28 (3.6)	0	0	151 (38.8)	6 (1.5)	0	0
Influenza like illness	12 (1.5)	1 (0.1)	0	0	3 (0.8)	0	0	0
Malaise	25 (3.2)	0	0	0	12 (3.1)	1 (0.3)	0	0
Mucosal dryness	9 (1.1)	0	0	0	8 (2.1)	0	0	0
Mucosal inflammation	103 (13.2)	8 (1.0)	0	0	45 (11.6)	3 (0.8)	0	0
Edema	12 (1.5)	1 (0.1)	0	0	9 (2.3)	0	0	0
Edema peripheral	35 (4.5)	2 (0.3)	0	0	21 (5.4)	0	0	0
Pain	19 (2.4)	0	0	0	6 (1.5)	0	0	0
Pyrexia	138	8 (1.0)	0	0	41	0	0	0

Adverse Reaction	KEYTR	200 mg eve aı Chemotl UDA 200 ı	nd herapy*/		Placebo and Chemotherapy*/ Placebo n=389			
	Any Grade n (%) [†]	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
	(17.6)				(10.5)			
Immune system disorde	ers							
Drug hypersensitivity	14(1.8)	3(0.4)	0	0	6(1.5)	1(0.3)	0	0
Hypersensitivity	32(4.1)	3(0.4)	0	0	8(2.1)	0	0	0
Infections and infestation	ns	I	·	·		·	ı	I
Conjunctivitis	17(2.2)	0	0	0	4(1.0)	0	0	0
Cystitis	8(1.0)	0	0	0	4(1.0)	0	0	0
Folliculitis	20(2.6)	0	0	0	7(1.8)	1(0.3)	0	0
Gingivitis	8(1.0)	0	0	0	5(1.3)	0	0	0
Herpes zoster	9(1.1)	0	0	0	3(0.8)	0	0	0
Oral candidiasis	14(1.8)	0	0	0	4(1.0)	0	0	0
Oral herpes	10(1.3)	0	0	0	1(0.3)	0	0	0
Paronychia	14(1.8)	0	0	0	5(1.3)	0	0	0
Upper respiratory tract infection	20(2.6)	4(0.5)	0	0	5(1.3)	1(0.3)	0	0
Urinary tract infection	23(2.9)	3(0.4)	0	0	16(4.1)	2(0.5)	0	0
Injury, poisoning and pro	ocedural c	omplicatio	ns		•			
Infusion related reaction	73(9.3)	8(1.0)	0	0	25(6.4)	2(0.5)	0	0
Investigations		I	·	·		·	ı	I
Alanine aminotransferase increased	204 (26.1)	42 (5.4)	1 (0.1)	0	98 (25.2)	9 (2.3)	0	0
Aspartate aminotransferase increased	157 (20.1)	18 (2.3)	2 (0.3)	0	63 (16.2)	1 (0.3)	0	0
Blood alkaline phosphatase increased	29 (3.7)	2 (0.3)	0	0	20 (5.1)	2 (0.5)	0	0

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks and Chemotherapy*/ KEYTRUDA 200 mg every 3 weeks n=783 Any				Placebo and Chemotherapy*/ Placebo n=389			
	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 bicarbonate increased	8 (1.0)	0	0	0	1 (0.3)	0	0	0
Blood bilirubin increased	19 (2.4)	0	0	0	6 (1.5)	0	0	0
Blood chloride increased	8 (1.0)	0	0	0	2 (0.5)	0	0	0
Blood creatinine increased	21 (2.7)	2 (0.3)	1 (0.1)	0	3 (0.8)	0	0	0
Blood lactate dehydrogenase increased	22 (2.8)	0	0	0	14 (3.6)	1 (0.3)	0	0
Blood magnesium decreased	8 (1.0)	1 (0.1)	0	0	2 (0.5)	0	0	0
Blood potassium decreased	8 (1.0)	1 (0.1)	0	0	1 (0.3)	0	0	0
Blood sodium decreased	10 (1.3)	0	0	0	2 (0.5)	0	0	0
Blood thyroid stimulating hormone decreased	8 (1.0)	0	0	0	3 (0.8)	0	0	0
Blood thyroid stimulating hormone increased	14 (1.8)	0	0	0	3 (0.8)	0	0	0
Ejection fraction decreased	9 (1.1)	0	0	0	7 (1.8)	1 (0.3)	0	0
Gamma-glutamyl transferase increased	24 (3.1)	7 (0.9)	1 (0.1)	0	11 (2.8)	1 (0.3)	0	0
Hemoglobin decreased	12 (1.5)	3 (0.4)	0	0	7 (1.8)	2 (0.5)	0	0
Lymphocyte count decreased	26 (3.3)	8 (1.0)	3 (0.4)	0	18 (4.6)	5 (1.3)	0	0

Adverse Reaction		KEYTRUDA 200 mg every 3 weeks and Chemotherapy*/ KEYTRUDA 200 mg every 3 weeks n=783				Placebo and Chemotherapy*/ Placebo n=389			
	Any Grade n (%) [†]	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	
Neutrophil count decreased	185 (23.6)	82 (10.5)	64 (8.2)	0	112 (28.8)	62 (15.9)	28 (7.2)	0	
Platelet count decreased	74 (9.5)	16 (2.0)	5 (0.6)	0	34 (8.7)	3 (0.8)	1 (0.3)	0	
Weight decreased	38 (4.9)	5 (0.6)	0	0	12 (3.1)	0	0	0	
Weight increased	10 (1.3)	0	0	0	3 (0.8)	1 (0.3)	0	0	
White blood cell count decreased	108 (13.8)	39 (5.0)	21 (2.7)	0	52 (13.4)	12 (3.1)	8 (2.1)	0	
Metabolism and nutrition	on disorde	rs	·	·		ı	·		
Decreased appetite	153 (19.5)	6 (0.8)	0	0	57 (14.7)	1 (0.3)	0	0	
Dehydration	28 (3.6)	2 (0.3)	0	0	7 (1.8)	1 (0.3)	0	0	
Hyperglycemia	17 (2.2)	2 (0.3)	0	0	10 (2.6)	2 (0.5)	0	0	
Hypoalbuminemia	21 (2.7)	1 (0.1)	0	0	6 (1.5)	0	0	0	
Hypocalcemia	19 (2.4)	1 (0.1)	0	0	6 (1.5)	1 (0.3)	0	0	
Hypokalemia	37 (4.7)	4 (0.5)	1 (0.1)	0	12 (3.1)	1 (0.3)	0	0	
Hypomagnesaemia	26 (3.3)	1 (0.1)	0	0	9 (2.3)	0	0	0	
Hyponatremia	20 (2.6)	7 (0.9)	1 (0.1)	0	9 (2.3)	0	1 (0.3)	0	
Hypophosphatemia	11 (1.4)	2 (0.3)	0	0	2 (0.5)	0	0	0	
Hypoproteinemia	11	0	0	0	2 (0.5)	0	0	0	

Adverse Reaction	KEYTR	200 mg eve a Chemot RUDA 200 i	nd herapy*/		Placebo and Chemotherapy*/ Placebo n=389				
	Any Grade n (%) [†]	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	
	(1.4)								
Musculoskeletal and co	nnective t	issue disor	ders						
Arthralgia	121 (15.5)	4 (0.5)	0	0	59 (15.2)	0	0	0	
Back pain	14 (1.8)	0	0	0	10 (2.6)	0	0	0	
Bone pain	29 (3.7)	1 (0.1)	0	0	8 (2.1)	0	0	0	
Muscle spasms	18 (2.3)	0	0	0	6 (1.5)	0	0	0	
Muscular weakness	15 (1.9)	1 (0.1)	0	0	2 (0.5)	0	0	0	
Musculoskeletal pain	20 (2.6)	1 (0.1)	0	0	12 (3.1)	0	0	0	
Myalgia	112 (14.3)	3 (0.4)	0	0	49 (12.6)	0	0	0	
Pain in extremity	30 (3.8)	2 (0.3)	0	0	13 (3.3)	0	0	0	
Nervous system disord	ers								
Cognitive disorder	10 (1.3)	1 (0.1)	0	0	6 (1.5)	0	0	0	
Dizziness	61 (7.8)	1 (0.1)	0	0	29 (7.5)	0	0	0	
Dysesthesia	10 (1.3)	0	0	0	4 (1.0)	1 (0.3)	0	0	
Dysgeusia	124 (15.8)	0	0	0	49 (12.6)	0	0	0	
Headache	100 (12.8)	2 (0.3)	0	0	42 (10.8)	1 (0.3)	0	0	
Hypoesthesia	28	1 (0.1)	0	0	11	1 (0.3)	0	0	

Adverse Reaction		KEYTRUDA 200 mg every 3 weeks and Chemotherapy*/ KEYTRUDA 200 mg every 3 weeks n=783 Any			Placebo and Chemotherapy*/ Placebo n=389			
	Any Grade n (%) [†]	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
	(3.6)				(2.8)			
Lethargy	8 (1.0)	0	0	0	4 (1.0)	0	0	0
Memory impairment	10 (1.3)	0	0	0	1 (0.3)	0	0	0
Neuralgia	8 (1.0)	0	0	0	4 (1.0)	0	0	0
Neuropathy peripheral	154 (19.7)	15 (1.9)	0	0	84 (21.6)	4 (1.0)	0	0
Neurotoxicity	17 (2.2)	0	0	0	9 (2.3)	0	0	0
Paresthesia	45 (5.7)	0	0	0	28 (7.2)	0	0	0
Peripheral sensory neuropathy	148 (18.9)	11 (1.4)	0	0	72 (18.5)	5 (1.3)	0	0
Polyneuropathy	21 (2.7)	2 (0.3)	0	0	15 (3.9)	4 (1.0)	0	0
Taste disorder	24 (3.1)	0	0	0	16 (4.1)	0	0	0
Psychiatric disorders		•						
Anxiety	9 (1.1)	0	0	0	3 (0.8)	0	0	0
Insomnia	42 (5.4)	3 (0.4)	0	0	13 (3.3)	0	0	0
Renal and urinary disord	ders							
Acute kidney injury	10 (1.3)	7 (0.9)	1 (0.1)	0	1 (0.3)	0	0	0
Dysuria	11 (1.4)	0	0	0	3 (0.8)	0	0	0
Reproductive system an	d breast o	lisorders	•	•		•	•	
Amenorrhea	10 (1.3)	1 (0.1)	0	0	1 (0.3)	1 (0.3)	0	0

Adverse Reaction	KEYTR	200 mg eve aı Chemotl UDA 200 ı	nd herapy*/		Placebo and Chemotherapy*/ Placebo n=389				
	Any Grade n (%) [†]	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	
Menstruation irregular	9 (1.1)	4 (0.5)	0	0	3 (0.8)	1 (0.3)	0	0	
Respiratory, thoracic an	d mediast	inal disord	ers	•	•	•			
Cough	52 (6.6)	1 (0.1)	0	0	13 (3.3)	0	0	0	
Dysphonia	14 (1.8)	0	0	0	3 (0.8)	0	0	0	
Dyspnea	46 (5.9)	2 (0.3)	0	0	23 (5.9)	1 (0.3)	0	0	
Dyspnea exertional	8 (1.0)	0	0	0	2 (0.5)	0	0	0	
Epistaxis	76 (9.7)	0	0	0	41 (10.5)	0	0	0	
Nasal dryness	12 (1.5)	0	0	0	4 (1.0)	0	0	0	
Oropharyngeal pain	17 (2.2)	0	0	0	10 (2.6)	0	0	0	
Pneumonitis	13 (1.7)	6 (0.8)	0	1 (0.1)	6 (1.5)	2 (0.5)	0	0	
Pulmonary embolism	10 (1.3)	8 (1.0)	1 (0.1)	1 (0.1)	2 (0.5)	1 (0.3)	1 (0.3)	0	
Rhinorrhea	10 (1.3)	0	0	0	2 (0.5)	0	0	0	
Skin and subcutaneous	tissue disc	rders							
Acne	8 (1.0)	0	0	0	4 (1.0)	0	0	0	
Alopecia	471 (60.2)	0	0	0	220 (56.6)	0	0	0	
Dermatitis	8 (1.0)	1 (0.1)	0	0	4 (1.0)	0	0	0	
Dermatitis acneiform	45 (5.7)	2 (0.3)	0	0	10 (2.6)	0	0	0	
Dermatitis allergic	8 (1.0)	2 (0.3)	0	0	0	0	0	0	

Adverse Reaction	KEYTR	KEYTRUDA 200 mg every 3 weeks and Chemotherapy*/ KEYTRUDA 200 mg every 3 weeks n=783 Any Grado 6 Grado 3 Grado 4 Grado 5				Placebo and Chemotherapy*/ Placebo n=389				
	Any Grade n (%) [†]	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)		
Dry skin	47 (6.0)	1 (0.1)	0	0	20 (5.1)	0	0	0		
Eczema	11 (1.4)	0	0	0	8 (2.1)	0	0	0		
Erythema	31 (4.0)	0	0	0	14 (3.6)	0	0	0		
Hyperhidrosis	8 (1.0)	0	0	0	3 (0.8)	0	0	0		
Nail discoloration	48 (6.1)	0	0	0	31 (8.0)	0	0	0		
Nail disorder	22 (2.8)	1 (0.1)	0	0	15 (3.9)	0	0	0		
Onycholysis	25 (3.2)	2 (0.3)	0	0	12 (3.1)	0	0	0		
Onychomadesis	12 (1.5)	0	0	0	3 (0.8)	0	0	0		
Palmar-plantar erythrodysesthesia syndrome	8 (1.0)	0	0	0	3 (0.8)	0	0	0		
Pruritus	116 (14.8)	2 (0.3)	0	0	38 (9.8)	0	0	0		
Rash	196 (25.0)	12 (1.5)	0	0	66 (17.0)	1 (0.3)	0	0		
Rash maculo-papular	50 (6.4)	12 (1.5)	0	0	23 (5.9)	0	0	0		
Rash pruritic	9 (1.1)	0	0	0	2 (0.5)	0	0	0		
Skin hyperpigmentation	13 (1.7)	0	0	0	9 (2.3)	0	0	0		
Skin toxicity	8 (1.0)	2 (0.3)	0	0	4 (1.0)	0	0	0		
Urticaria	8 (1.0)	0	0	0	6 (1.5)	0	0	0		

Adverse Reaction		200 mg eve aı Chemotl RUDA 200 ı	nd herapy*/	Placebo and Chemotherapy*/ Placebo n=389				
	Any Grade n (%) [†]	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Flushing	21 (2.7)	0	0	0	7 (1.8)	0	0	0
Hot flush	55 (7.0)	3 (0.4)	0	0	45 (11.6)	0	0	0
Hypotension	17 (2.2)	3 (0.4)	0	0	5 (1.3)	0	1 (0.3)	0

^{*} Chemotherapy: carboplatin and paclitaxel followed by epirubicin and cyclophosphamide

Cervical Cancer

Table 38 summarizes the treatment-related adverse events that occurred in at least 1% of patients with FIGO 2014 Stage III-IVA cervical cancer treated with KEYTRUDA in combination with CRT (cisplatin plus external beam radiation therapy [EBRT] followed by brachytherapy [BT]) in KEYNOTE-A18 (See 14 Clinical Trials). The median duration of exposure was 20.0 months (range: 1 day to 31.7 months) in the KEYTRUDA combination arm and 16.0 months (range: 1 day to 31.9 months) in the CRT arm.

For the FIGO 2014 Stage III-IVA population, the most common treatment-related adverse events (reported in at least 20% of patients) were anemia, nausea, diarrhea, white blood cell count decreased, neutrophil count decreased, vomiting, platelet count decreased, and hypothyroidism. The most common Grade 3-5 treatment-related adverse events were anemia (23.8%), white blood cell count decreased (23.1%), neutrophil count decreased (16.3%), lymphocyte count decreased (12.9%), lymphopenia (8.5%), neutropenia (8.2%), leukopenia (7.8%), hypokalemia (5.8%), platelet count decreased (4.8%), and diarrhea (4.1%).

Fatal adverse events occurred in 4 (1.4%) patients receiving KEYTRUDA in combination with CRT in the FIGO 2014 Stage III-IVA population, including 1 case each of large intestine perforation, sepsis, urosepsis, and vaginal hemorrhage.

KEYTRUDA was discontinued for treatment-related adverse events in 8.1% of patients. The most common treatment-related adverse events resulting in discontinuation of KEYTRUDA (occurring in at least 2 patients) were diarrhea (n=3, 1.0%), anemia (n=2, 0.7%), alanine aminotransferase increased (n=2, 0.7%), and pneumonitis (n=2, 0.7%).

Table 38: Treatment-Related Adverse Events (Incidence ≥ 1%) in Patients Treated with KEYTRUDA in Combination with Chemoradiotherapy, FIGO 2014 Stage III-IVA Population in KEYNOTE-A18.

[†] Graded per NCI CTCAE v4.0

Adverse Reaction		YTRUDA		Placebo with CRT				
	_	ery 3 week			with CRT			
	400 mg ever	=	vith CRT					
		n=295	1	_	n=304	I		
	Amy Crada	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4		
	Any Grade n (%)	n (%)	n (%)	n (%)	n (%)	n (%)		
Blood and lymphatic system disorde		11 (70)	11 (70)	11 (70)	11 (70)	11 (70)		
Anemia	182 (61.7)	68	2 (0.7)	172	45	0 (0.0)		
	, ,	(23.1)	` ′	(56.6)	(14.8)	, ,		
Febrile neutropenia	4 (1.4)	3 (1.0)	1 (0.3)	2 (0.7)	1 (0.3)	1 (0.3)		
Leukopenia	51 (17.3)	20 (6.8)	3 (1.0)	39	17 (5.6)	2 (0.7)		
				(12.8)				
Lymphopenia	28 (9.5)	18 (6.1)	7 (2.4)	26 (8.6)	15 (4.9)	7 (2.3)		
Neutropenia	51 (17.3)	21 (7.1)	3 (1.0)	42	15 (4.9)	5 (1.6)		
				(13.8)				
Thrombocytopenia	33 (11.2)	5 (1.7)	0 (0.0)	29 (9.5)	3 (1.0)	1 (0.3)		
Ear and labyrinth disorders	1							
Tinnitus	12 (4.1)	1 (0.3)	0 (0.0)	14 (4.6)	0 (0.0)	0 (0.0)		
Endocrine disorders								
Autoimmune thyroiditis	3 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
Hyperthyroidism	33 (11.2)	1 (0.3)	0 (0.0)	10 (3.3)	0 (0.0)	0 (0.0)		
Hypothyroidism	65 (22.0)	2 (0.7)	0 (0.0)	20 (6.6)	0 (0.0)	0 (0.0)		
Thyroid mass	3 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
Gastrointestinal disorders	1		T	T	Т	1		
Abdominal distension	5 (1.7)	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)	0 (0.0)		
Abdominal pain	14 (4.7)	0 (0.0)	0 (0.0)	21 (6.9)	2 (0.7)	0 (0.0)		
Abdominal pain upper	10 (3.4)	0 (0.0)	0 (0.0)	7 (2.3)	0 (0.0)	0 (0.0)		
Colitis	3 (1.0)	1 (0.3)	0 (0.0)	3 (1.0)	0 (0.0)	0 (0.0)		
Constipation	37 (12.5)	0 (0.0)	0 (0.0)	31 (10.2)	1 (0.3)	0 (0.0)		
Diarrhoea	139 (47.1)	12 (4.1)	0 (0.0)	140	12 (3.9)	0 (0.0)		
	- ()	- ()	- />	(46.1)	- ()	- />		
Dry mouth	4 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
Dyspepsia	7 (2.4)	0 (0.0)	0 (0.0)	7 (2.3)	0 (0.0)	0 (0.0)		
Enteritis	3 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		
Flatulence	3 (1.0)	0 (0.0)	0 (0.0)	3 (1.0)	0 (0.0)	0 (0.0)		
Gastritis	5 (1.7)	0 (0.0)	0 (0.0)	6 (2.0)	0 (0.0)	0 (0.0)		
Hamatochezia	4 (4.1)	1 (0.3)	0 (0.0)	4 (1.3)	0 (0.0)	0 (0.0)		
Hemorrhoids	3 (1.0)	0 (0.0)	0 (0.0)	7 (2.3)	0 (0.0)	0 (0.0)		
Nausea	157 (53.2)	0 (0.0)	0 (0.0)	179 (58.9)	7 (2.3)	0 (0.0)		
Proctalgia	3 (1.0)	0 (0.0)	0 (0.0)	5 (1.6)	0 (0.0)	0 (0.0)		
Proctitis	8 (2.7)	1 (0.3)	0 (0.0)	7 (2.3)	0 (0.0)	0 (0.0)		
Rectal hemorrhage	5 (1.7)	0 (0.0)	0 (0.0)	4 (1.3)	1 (0.3)	0 (0.0)		
Stomatitis	4 (1.4)	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)	0 (0.0)		

Adverse Reaction	KE	YTRUDA	Placebo			
	200 mg ev	ery 3 week	s and		with CRT	
	400 mg ever	y 6 weeks v	vith CRT			
		n=295			n=304	
				Any		
	Any Grade	Grade 3	Grade 4	Grade	Grade 3	Grade 4
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Vomiting	88 (29.8)	2 (0.7)	0 (0.0)	92	5 (1.6)	0 (0.0)
				(30.3)		
General disorders and administration						
Asthenia	24 (8.1)	1 (0.3)	0 (0.0)	26 (8.6)	2 (0.7)	0 (0.0)
Fatigue	45 (15.3)	2 (0.7)	0 (0.0)	50 (16.4)	2 (0.7)	0 (0.0)
Illness	6 (2.0)	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)	0 (0.0)
Malaise	15 (5.1)	2 (0.7)	0 (0.0)	15 (4.9)	0 (0.0)	0 (0.0)
Oedema peripheral	6 (2.0)	0 (0.0)	0 (0.0)	5 (1.6)	1 (0.3)	0 (0.0)
Pyrexia	16 (5.4)	1 (0.3)	0 (0.0)	11 (3.6)	0 (0.0)	0 (0.0)
Hepatobiliary disorders	, ,	1 , ,	. , ,	. , ,	. , ,	. , ,
Hypertransaminasemia	3 (1.0)	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)	0 (0.0)
Infections and infestations			•			
Cystitis	10 (3.4)	1 (0.2)	0 (0.0)	5 (1.6)	0 (0.0)	0 (0.0)
Pneumonia	3 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Urinary tract infection	28 (9.5)	3 (1.0)	0 (0.0)	28 (9.2)	2 (0.7)	0 (0.0)
Vaginal infection	5 (1.7)	0 (0.0)	0 (0.0)	4 (1.3)	1 (0.3)	0 (0.0)
Vulvitis	6 (2.0)	2 (0.7)	0 (0.0)	2 (0.7)	0 (0.0)	0 (0.0)
Injury, poisoning and procedural co	mplications					
Cystitis radiation	13 (4.4)	0 (0.0)	0 (0.0)	10 (3.3)	0 (0.0)	0 (0.0)
Fractured sacrum	3 (1.0)	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)	0 (0.0)
Gastroenteritis radiation	12 (4.1)	2 (0.7)	0 (0.0)	2 (0.7)	0 (0.0)	0 (0.0)
Radiation proctitis	17 (5.8)	2 (0.7)	1 (0.3)	18 (5.9)	1 (0.3)	0 (0.0)
Radiation skin injury	25 (8.5)	0 (0.0)	0 (0.0)	23 (7.6)	0 (0.0)	0 (0.0)
Investigations		•		•	•	•
Alanine aminotransferase increased	47 (15.9)	5 (1.7)	0 (0.0)	30 (9.9)	1 (0.3)	0 (0.0)
Aspartate aminotransferase	46 (15.6)	2 (0.7)	0 (0.0)	31	1 (0.3)	0 (0.0)
increased				(10.2)		
Blood alkaline phosphatase increased	15 (5.1)	0 (0.0)	0 (0.0)	6 (2.0)	0 (0.0)	0 (0.0)
Blood bilirubin increased	6 (2.0)	0 (0.0)	0 (0.0)	3 (1.0)	1 (0.3)	0 (0.0)
Blood calcium decreased	3 (1.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Blood chloride decreased	3 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Blood creatinine increased	30 (10.2)	0 (0.0)	0 (0.0)	27 (8.9)	0 (0.0)	0 (0.0)
Blood lactate dehydrogenase	7 (2.4)	0 (0.0)	0 (0.0)	4 (1.3)	0 (0.0)	0 (0.0)
increased						
Blood magnesium decreased	4 (1.4)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Blood thyroid stimulating hormone	4 (1.4)	0 (0.0)	0 (0.0)	6 (2.0)	0 (0.0)	0 (0.0)
decreased						
Blood thyroid stimulating hormone increased	11 (3.7)	0 (0.0)	0 (0.0)	16 (5.3)	0 (0.0)	0 (0.0)
Blood urea increased	4 (1.4)	0 (0.0)	0 (0.0)	7 (2.3)	0 (0.0)	0 (0.0)
-					• • • • • • • • • • • • • • • • • • • •	·

Adverse Reaction	KE	YTRUDA	Placebo			
	200 mg ev	ery 3 week		with CRT		
	400 mg ever	y 6 weeks v	vith CRT			
		n=295			n=304	
				Any		
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Gamma-glutamyltransferase	7 (2.4)	2 (0.7)	0 (0.0)	2 (0.7)	1 (0.3)	0 (0.0)
increased	7 (2.4)	2 (0.7)	0 (0.0)	2 (0.7)	1 (0.5)	0 (0.0)
Lymphocyte count decreased	40 (13.6)	23 (7.8)	15 (5.1)	47 (15.5)	21 (6.9)	20 (6.6)
Neutrophil count decreased	102 (34.6)	41	7 (2.4)	97	40	5 (1.6)
	1	(13.9)		(31.9)	(13.2)	
Platelet count decreased	72 (24.4)	11 (3.7)	3 (1.0)	69 (22.7)	6 (2.0)	1 (0.3)
Thyroxine increased	3 (1.0)	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)	0 (0.0)
Tri-iodothyronine decreased	3 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Urinary occult blood positive	11 (3.7)	0 (0.0)	0 (0.0)	3 (1.0)	0 (0.0)	0 (0.0)
Weight decreased	38 (12.9)	4 (1.4)	0 (0.0)	39 (12.8)	3 (1.0)	0 (0.0)
White blood cell count decreased	111 (37.6)	61	7 (2.4)	125	64	10 (3.3)
		(20.7)		(41.1)	(21.1)	
White blood cells urine positive	3 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders			I	Π	T	I
Decreased appetite	49 (16.6)	2 (0.7)	0 (0.0)	39 (12.8)	1 (0.3)	0 (0.0)
Dehydration	3 (1.0)	0 (0.0)	0 (0.0)	4 (1.3)	1 (0.3)	0 (0.0)
Hyperglycemia	9 (3.1)	0 (0.0)	0 (0.0)	6 (2.0)	0 (0.0)	0 (0.0)
Hyperkalemia	4 (1.4)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Hyperuricemia	6 (2.0)	0 (0.0)	0 (0.0)	4 (1.3)	0 (0.0)	0 (0.0)
Hypoalbuminemia	12 (4.1)	1 (0.3)	0 (0.0)	15 (4.9)	0 (0.0)	0 (0.0)
Hypocalcaemia	17 (5.8)	2 (0.7)	2 (0.7)	15 (4.9)	1 (0.3)	0 (0.0)
Hypochloremia	5 (1.7)	0 (0.0)	0 (0.0)	4 (1.3)	0 (0.0)	0 (0.0)
Hypokalemia	47 (15.9)	13 (4.4)	4 (1.4)	37 (12.2)	4 (1.3)	4 (1.3)
Hypomagnesemia	52 (17.6)	5 (1.7)	1 (0.3)	52 (17.1)	2 (0.7)	3 (1.0)
Hyponatremia	30 (10.2)	3 (1.0)	0 (0.0)	26 (8.6)	6 (2.0)	0 (0.0)
Hypoproteinemia	5 (1.7)	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tis						
Arthralgia	12 (4.1)	0 (0.0)	0 (0.0)	16 (5.3)	0 (0.0)	0 (0.0)
Back pain	3 (1.0)	0 (0.0)	0 (0.0)	4 (1.3)	0 (0.0)	0 (0.0)
Myalgia	8 (2.7)	0 (0.0)	0 (0.0)	5 (1.6)	0 (0.0)	0 (0.0)
Pain in extremity	5 (1.7)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Nervous system disorders	1	1 .	T .	T .	T .	T .
Dizziness	5 (1.7)	0 (0.0)	0 (0.0)	6 (2.0)	0 (0.0)	0 (0.0)
Dysgeusia	10 (3.4)	0 (0.0)	0 (0.0)	15 (4.9)	0 (0.0)	0 (0.0)
Headache	10 (3.4)	0 (0.0)	0 (0.0)	11 (3.6)	0 (0.0)	0 (0.0)
Neuropathy peripheral	7 (2.4)	0 (0.0)	0 (0.0)	7 (2.3)	1 (0.2)	0 (0.0)
Paresthesia	3 (1.0)	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)	0 (0.0)
Peripheral sensory neuropathy	6 (2.0)	0 (0.0)	0 (0.0)	6 (2.0)	0 (0.0)	0 (0.0)

Adverse Reaction	KE 200 mg every 400 mg every	Placebo with CRT					
	I	n=295	ı	_	n=304	I	
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	
Psychiatric disorders	• •						
Insomnia	6 (2.0)	0 (0.0)	0 (0.0)	6 (2.0)	0 (0.0)	0 (0.0)	
Renal and urinary disorders		•					
Acute kidney injury	4 (1.4)	2 (0.7)	0 (0.0)	4 (1.3)	3 (1.0)	1 (0.3)	
Dysuria	29 (9.8)	1 (0.3)	0 (0.0)	25 (8.2)	0 (0.0)	0 (0.0)	
Hematuria	9 (3.1)	1 (0.3)	0 (0.0)	7 (2.3)	1 (0.3)	0 (0.0)	
Micturition urgency	3 (1.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	
Pollakiuria	5 (1.7)	0 (0.0)	0 (0.0)	4 (1.3)	0 (0.0)	0 (0.0)	
Proteinuria	8 (2.7)	0 (0.0)	0 (0.0)	7 (2.3)	0 (0.0)	0 (0.0)	
Renal failure	4 (1.4)	0 (0.0)	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)	
Renal impairment	4 (1.4)	1 (0.3)	0 (0.0)	2 (0.7)	0 (0.0)	0 (0.0)	
Urinary incontinence	3 (1.0)	1 (0.3)	0 (0.0)	6 (2.0)	0 (0.0)	0 (0.0)	
Urinary retention	3 (1.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	
Urogenital fistula	3 (1.0)	2 (0.7)	1 (0.3)	3 (1.0)	1 (0.3)	0 (0.0)	
Reproductive system and breast dis	orders						
Pelvic pain	19 (6.4)	2 (0.7)	0 (0.0)	20 (6.6)	0 (0.0)	0 (0.0)	
Vaginal discharge	3 (1.0)	0 (0.0)	0 (0.0)	9 (3.0)	0 (0.0)	0 (0.0)	
Vaginal haemorrhage	9 (3.1)	1 (0.3)	0 (0.0)	6 (2.0)	2 (0.7)	0 (0.0)	
Vulvovaginal pain	6 (2.0)	0 (0.0)	0 (0.0)	8 (2.6)	0 (0.0)	0 (0.0)	
Respiratory, thoracic and mediastin	al disorders						
Cough	3 (1.0)	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)	0 (0.0)	
Dyspnea	3 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Pneumonitis	3 (1.0)	0 (0.0)	1 (0.3)	2 (0.7)	0 (0.0)	0 (0.0)	
Skin and subcutaneous tissue disorc	lers						
Alopecia	3 (1.0)	0 (0.0)	0 (0.0)	5 (1.6)	0 (0.0)	0 (0.0)	
Dermatitis	4 (1.4)	1 (0.3)	0 (0.0)	3 (1.0)	0 (0.0)	0 (0.0)	
Dry skin	7 (2.4)	0 (0.0)	0 (0.0)	3 (1.0)	0 (0.0)	0 (0.0)	
Pruritus	16 (5.4)	0 (0.0)	0 (0.0)	8 (2.6)	0 (0.0)	0 (0.0)	
Rash	12 (4.1)	0 (0.0)	0 (0.0)	8 (2.6)	0 (0.0)	0 (0.0)	
Rash maculo-papular	3 (1.0)	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)	0 (0.0)	
Vascular disorders							
Hot flush	3 (1.0)	0 (0.0)	0 (0.0)	9 (3.0)	0 (0.0)	0 (0.0)	
Hypertension	7 (2.4)	2 (0.7)	0 (0.0)	2 (0.7)	2 (0.7)	0 (0.0)	
Every participant is counted a single	-						
Only the highest reported grade of a	given event is co	ounted for t	the individu	ual participa	ant.		

Table 39 summarizes the treatment-related adverse events that occurred in at least 1% of patients with persistent, recurrent or metastatic cervical cancer treated with KEYTRUDA in combination with chemotherapy (paclitaxel and cisplatin or paclitaxel and carboplatin) with or without bevacizumab in KEYNOTE-826. A total of 616 patients, regardless of tumour PD-L1 expression, received KEYTRUDA 200 mg and chemotherapy with or without bevacizumab (n=307) every 3 weeks or placebo and chemotherapy with or without bevacizumab (n=309) every 3 weeks. The median duration of exposure to KEYTRUDA was 9.9 months (range: 1 day to 26 months).

For patients treated with KEYTRUDA in combination with chemotherapy with or without bevacizumab, the most common treatment-related adverse events (reported in at least 20% of patients) were nausea, anemia, fatigue, vomiting, diarrhea, neutropenia, neuropathy peripheral, peripheral sensory neuropathy and alopecia. The most common Grade 3-5 adverse events were: anemia (30.3%), neutrophil count decreased (13.0%), neutropenia (12.4%), hypertension (9.4%), urinary tract infection (8.8%), thrombocytopenia (7.5%), febrile neutropenia (7.2%), platelet count decreased (6.8%); and white blood cell count decreased (6.8%).

For patients treated with KEYTRUDA, chemotherapy, and bevacizumab (n=196), the most common (≥20%) adverse reactions were peripheral neuropathy (62%), alopecia (58%), anemia (55%), fatigue/asthenia (53%), nausea (41%), neutropenia (41%), diarrhea (39%), hypertension (35%), thrombocytopenia (35%), constipation (31%), arthralgia (31%), vomiting (30%), urinary tract infection (27%), rash (26%), leukopenia (24%), hypothyroidism (22%), and decreased appetite (21%). The most common Grade 3-5 adverse events were: anemia (26.5%), neutrophil count decreased (14.8%), neutropenia (13.3%), hypertension (13.3%), urinary tract infection (10.2%), platelet count decreased (8.2%), febrile neutropenia (7.7%), thrombocytopenia (6.1%), white blood cell count decreased (6.1%) and sepsis (5.1%).

Fatal adverse events occurred in 4.6% of patients receiving KEYTRUDA in combination with chemotherapy with or without bevacizumab, including 3 cases of hemorrhage, 2 cases of sepsis, 2 cases due to unknown causes, and 1 case each of acute myocardial infarction, autoimmune encephalitis, cardiac arrest, cerebrovascular accident, femur fracture with perioperative pulmonary embolus, intestinal perforation, and pelvic infection.

Serious adverse events occurred in 50% of patients receiving KEYTRUDA in combination with chemotherapy with or without bevacizumab. Serious adverse events in at least 3% of patients included febrile neutropenia (6.8%), urinary tract infection (5.2%), anemia (4.6%), acute kidney injury (3.3%), and sepsis (3.3%).

KEYTRUDA was discontinued for adverse events in 15% of patients. The most common adverse events resulting in discontinuation of KEYTRUDA (occurring in 2 or more patients) were colitis (1%), immune-mediated enterocolitis (0.7%), immune-mediated hepatitis (0.7%), pyelonephritis (0.7%), increased alanine aminotransferase (0.7%), increased aspartate aminotransferase (0.7%), maculopapular rash (0.7%) and shock hemorrhagic (0.7%). The median time to discontinuation for adverse events was 4.6 months for patients treated with KEYTRUDA.

There were no new safety signals identified at the final analysis for KEYNOTE-826, and with additional follow-up, no meaningful changes were observed in the safety profile of pembrolizumab in combination with chemotherapy with or without bevacizumab.

Table 39: Treatment-Related Adverse Events (Incidence ≥ 1%) in Patients Treated with KEYTRUDA in

Combination with Chemotherapy, APaT Population in KEYNOTE-826.

Adverse Reaction		KEYTI	RUDA			Pla	cebo			
		200 mg eve	ry 3 weeks							
		ar	ıd		and					
	Chemotherapy*					Chemotherapy*				
	with	with	or withou		umah					
		n=3					309	amas		
	Any	11-5			Any		30 5			
	Grade	Grade 3	Grade 4	Grade 5	Grade	Grade 3	Grade 4	Grade 5		
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)		
			11 (70)	11 (70)	11 (70)	11 (70)	11 (70)	11 (70)		
Blood and lymphatic	system diso	rders								
Anemia	149	74 (24.1)	2 (0.7)	0	132	63	2 (0.6)	0		
	(48.5)	, ,	` ,		(42.7)	(20.4)				
Eosinophilia	10 (3.3)	0	0	0	0	0	0	0		
·										
Febrile neutropenia	21 (6.8)	20 (6.5)	1 (0.3)	0	13	10 (3.2)	3 (1.0)	0		
					(4.2)					
Leukopenia	38 (12.4)	11 (3.6)	3 (1.0)	0	31	6 (1.9)	1 (0.3)	0		
	, ,	, ,			(10.0)	, ,	, ,			
Lymphopenia	9 (2.9)	2 (0.7)	0	0	6 (1.9)	5 (1.6)	0	0		
,										
Neutropenia	68 (22.1)	18 (5.9)	19 (6.2)	0	57	18 (5.8)	11 (3.6)	0		
					(18.4)					
Thrombocytopenia	55 (17.9)	13 (4.2)	8 (2.6)	0	58	11 (3.6)	1 (0.3)	0		
					(18.8)					
Cardiac disorders										
	T			T	1	1	1	1		
Palpitations	2 (0.7)	0	0	0	5 (1.6)	0	0	0		
Ear and labyrinth dis	orders			·I			l .	ı		
Tinnitus	5 (1.6)	0	0	0	4 (1.3)	0	0	0		
	3 (1.0)				7 (1.5)		Ŭ			
Endocrine disorders										
Adrenal	4 (1.3)	3 (1.0)	0	0	0	0	0	0		
insufficiency										
Hyperthyroidism	19 (6.2)	0	0	0	7 (2.3)	1 (0.3)	0	0		
						` ′				
Hypothyroidism	52 (16.9)	3 (1.0)	0	0	25	1 (0.3)	0	0		
					(8.1)					
Thyroiditis	9 (2.9)	2 (0.7)	0	0	1 (0.3)	0	0	0		
Eye disorders	I	I		1	<u>I</u>	ı	I	<u>I</u>		
Vision blurred	2 (0.7)	0	0	0	5 (1.6)	0	0	0		
Gastrointestinal diso	rders			1	<u> </u>	1	l	<u> </u>		
Abdominal pain	15 (4.9)	0	0	0	19	1 (0.3)	0	0		
	== ,,		-	1	(6.1)	= (5.5)	-	1		

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks and Chemotherapy* with or without bevacizumab n=307					Placebo and Chemotherapy* with or without bevacizumab n=309				
	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	8 (2.6)	0	0	0	7 (2.3)	0	0	0		
Colitis	10 (3.3)	3 (1.0)	0	0	2 (0.6)	2 (0.6)	0	0		
Constipation	49 (16.0)	1 (0.3)	0	0	49 (15.9)	1 (0.3)	0	0		
Diarrhea	76 (24.8)	5 (1.6)	0	0	58 (18.8)	5 (1.6)	0	0		
Dry mouth	2 (0.7)	0	0	0	7 (2.3)	0	0	0		
Dyspepsia	4 (1.3)	0	0	0	9 (2.9)	0	0	0		
Gastroesophageal reflux disease	3 (1.0)	0	0	0	8 (2.6)	0	0	0		
Gingival bleeding	9 (2.9)	0	0	0	3 (1.0)	0	0	0		
Nausea	104 (33.9)	3 (1.0)	0	0	120 (38.8)	4 (1.3)	0	0		
Rectal haemorrhage	7 (2.3)	2 (0.7)	0	0	4 (1.3)	1 (0.3)	0	0		
Stomatitis	20 (6.5)	1 (0.3)	0	0	15 (4.9)	0	0	0		
Vomiting	63 (20.5)	5 (1.6)	0	0	66 (21.4)	3 (1.0)	0	0		
General disorders ar	nd administra	tion site cor	nditions							
Asthenia	51 (16.6)	5 (1.6)	0	0	56 (18.1)	4 (1.3)	0	0		
Chest pain	4 (1.3)	0	0	0	2 (0.6)	0	0	0		
Chills	4 (1.3)	0	0	0	0	0	0	0		
Fatigue	70 (22.8)	8 (2.6)	0	0	77 (24.9)	13 (4.2)	0	0		
Illness	5 (1.6)	0	0	0	3 (1.0)	0	0	0		
Malaise	7 (2.3)	0	0	0	4 (1.3)	0	0	0		
Mucosal inflammation	20 (6.5)	2 (0.7)	0	0	9 (2.9)	1 (0.3)	0	0		

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks and Chemotherapy* with or without bevacizumab n=307					Placebo and Chemotherapy* with or without bevacizumab n=309				
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)		
Oedema peripheral	4 (1.3)	0	0	0	4 (1.3)	0	0	0		
Pain	4 (1.3)	0	0	0	3 (1.0)	1 (0.3)	0	0		
Pyrexia	16 (5.2)	0	0	0	9 (2.9)	0	0	0		
Immune system diso	rders				L	ı		l		
Drug hypersensitivity	9 (2.9)	0	0	0	11 (3.6)	3 (1.0)	0	0		
Hypersensitivity	11 (3.6)	4 (1.3)	0	0	12 (3.9)	2 (0.6)	0	0		
Infections and infest	ations			•	l .					
Cystitis	1 (0.3)	0	0	0	4 (1.3)	0	0	0		
Pneumonia	0	0	0	0	4 (1.3)	2 (0.6)	0	0		
Urinary tract infection	16 (5.2)	5 (1.6)	0	0	12 (3.9)	6 (1.9)	0	0		
Injury, poisoning and	procedural	complicatio	ns							
Infusion related reaction	16 (5.2)	1 (0.3)	1 (0.3)	0	13 (4.2)	2 (0.6)	0	0		
Investigations	•			•	<u> </u>					
Alanine aminotransferase increased	31 (10.1)	9 (2.9)	1 (0.3)	0	23 (7.4)	5 (1.6)	0	0		
Aspartate aminotransferase increased	22 (7.2)	6 (2.0)	2 (0.7)	0	16 (5.2)	1 (0.3)	0	0		
Blood alkaline phosphatase increased	14 (4.6)	1 (0.3)	0	0	9 (2.9)	2 (0.6)	0	0		
Blood bilirubin increased	3 (1.0)	1 (0.3)	1 (0.3)	0	4 (1.3)	0	0	0		
Blood creatinine increased	16 (5.2)	0	0	0	13 (4.2)	0	0	0		
Blood thyroid stimulating	8 (2.6)	0	0	0	3 (1.0)	0	0	0		

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks and Chemotherapy* with or without bevacizumab n=307					Placebo and Chemotherapy* with or without bevacizumab n=309				
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)		
hormone increased										
Gamma- glutamyltransferase increased	8 (2.6)	2 (0.7)	1 (0.3)	0	10 (3.2)	7 (2.3)	0	0		
Hemoglobin decreased	1 (0.3)	1 (0.3)	0	0	5 (1.6)	4 (1.3)	1 (0.3)	0		
Lymphocyte count decreased	4 (1.3)	2 (0.7)	0	0	5 (1.6)	2 (0.6)	0	0		
Neutrophil count decreased	56 (18.2)	23 (7.5)	17 (5.5)	0	47 (15.2)	17 (5.5)	9 (2.9)	0		
Platelet count decreased	49 (16.0)	17 (5.5)	4 (1.3)	0	40 (12.9)	11 (3.6)	3 (1.0)	0		
Reticulocyte count increased	4 (1.3)	0	0	0	1 (0.3)	0	0	0		
Weight decreased	17 (5.5)	6 (2.0)	0	0	15 (4.9)	2 (0.6)	0	0		
White blood cell count decreased	37 (12.1)	17 (5.5)	4 (1.3)	0	21 (6.8)	11 (3.6)	1 (0.3)	0		
Metabolism and nutr	rition disorde	ers			L	I		l		
Decreased appetite	45 (14.7)	4 (1.3)	0	0	33 (10.7)	1 (0.3)	0	0		
Dehydration	3 (1.0)	1 (0.3)	0	0	5 (1.6)	1 (0.3)	0	0		
Hyperglycemia	5 (1.6)	0	0	0	2 (0.6)	0	0	0		
Hypoalbuminemia	5 (1.6)	0	0	0	0	0	0	0		
Hypokalemia	13 (4.2)	2 (0.7)	1 (0.3)	0	7 (2.3)	3 (1.0)	0	0		
Hypomagnesemia	15 (4.9)	1 (0.3)	1 (0.3)	0	9 (2.9)	0	0	0		
Hyponatremia	7 (2.3)	3 (1.0)	0	0	5 (1.6)	0	0	0		
Musculoskeletal and	connective t	issue disord	ers							
Arthralgia	53 (17.3)	1 (0.3)	0	0	57 (18.4)	3 (1.0)	0	0		
Back pain	7 (2.3)	1 (0.3)	0	0	6 (1.9)	1 (0.3)	0	0		

Adverse Reaction		KEYTI 200 mg eve	RUDA ery 3 weeks			Pla	cebo	
	with	and Chemotherapy* with or without bevacizumab 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 (%)
Bone pain	11 (3.6)	0	0	0	10 (3.2)	2 (0.6)	0	0
Muscle spasms	2 (0.7)	0	0	0	4 (1.3)	0	0	0
Muscular weakness	5 (1.6)	1 (0.3)	0	0	3 (1.0)	1 (0.3)	0	0
Musculoskeletal pain	2 (0.7)	0	0	0	6 (1.9)	0	0	0
Myalgia	53 (17.3)	2 (0.7)	0	0	53 (17.2)	3 (1.0)	0	0
Pain in extremity	17 (5.5)	1 (0.3)	0	0	11 (3.6)	0	0	0
Nervous system diso	rders			l				l .
Dizziness	8 (2.6)	0	0	0	5 (1.6)	0	0	0
Dysgeusia	12 (3.9)	0	0	0	19 (6.1)	0	0	0
Headache	15 (4.9)	1 (0.3)	0	0	19 (6.1)	0	0	0
Hypoesthesia	8 (2.6)	1 (0.3)	0	0	2 (0.6)	0	0	0
Neuralgia	4 (1.3)	0	0	0	1 (0.3)	1 (0.3)	0	0
Neuropathy peripheral	75 (24.4)	8 (2.6)	0	0	76 (24.6)	9 (2.9)	0	0
Paresthesia	26 (8.5)	0	0	0	24 (7.8)	2 (0.6)	0	0
Peripheral motor neuropathy	12 (3.9)	2 (0.7)	0	0	5 (1.6)	0	0	0
Peripheral sensory neuropathy	69 (22.5)	3 (1.0)	0	0	78 (25.2)	5 (1.6)	1 (0.3)	0
Polyneuropathy	2 (0.7)	0	0	0	4 (1.3)	0	0	0
Syncope	4 (1.3)	2 (0.7)	0	0	1 (0.3)	1 (0.3)	0	0
Taste disorder	5 (1.6)	0	0	0	0	0	0	0

Adverse Reaction	KEYTRUDA 200 mg every 3 weeks and Chemotherapy* with or without bevacizumab n=307 Any				Placebo and Chemotherapy* with or without bevacizumab n=309 Any				
	Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	
Renal and urinary dis	orders			•			•	•	
Acute kidney injury	10 (3.3)	5 (1.6)	0	0	2 (0.6)	0	0	0	
Hematuria	4 (1.3)	1 (0.3)	0	0	5 (1.6)	2 (0.6)	0	0	
Proteinuria	38 (12.4)	6 (2.0)	0	0	22 (7.1)	2 (0.6)	1 (0.3)	0	
Reproductive system	and breast	disorders		•	l .		l		
Female genital tract fistula	8 (2.6)	6 (2.0)	0	0	7 (2.3)	6 (1.9)	0	1 (0.3)	
Pelvic pain	0	0	0	0	5 (1.6)	0	0	0	
Vaginal haemorrhage	4 (1.3)	0	2 (0.7)	0	10 (3.2)	1 (0.3)	1 (0.3)	0	
Respiratory, thoracic	and medias	tinal disorde	ers	•	l .		l		
Cough	8 (2.6)	0	0	0	5 (1.6)	0	0	0	
Dysphonia	13 (4.2)	0	0	0	4 (1.3)	0	0	0	
Dyspnea	11 (3.6)	0	0	0	9 (2.9)	0	0	0	
Dyspnea exertional	2 (0.7)	0	0	0	4 (1.3)	0	0	0	
Epistaxis	26 (8.5)	1 (0.3)	0	0	36 (11.7)	1 (0.3)	0	0	
Rhinorrhea	1 (0.3)	0	0	0	6 (1.9)	0	0	0	
Skin and subcutaneo	us tissue dis	orders							
Alopecia	171 (55.7)	0	0	0	172 (55.7)	0	0	0	
Dry skin	11 (3.6)	0	0	0	4 (1.3)	0	0	0	
Erythema	4 (1.3)	0	0	0	5 (1.6)	0	0	0	
Palmar-plantar erythrodysesthesia syndrome	4 (1.3)	0	0	0	1 (0.3)	0	0	0	
Pruritus	29 (9.4)	2 (0.7)	0	0	17 (5.5)	0	0	0	
Rash	33 (10.7)	3 (1.0)	0	0	27	1 (0.3)	0	0	

Adverse Reaction			RUDA ery 3 weeks	Placebo				
		and				а	nd	
		Chemot	herapy*			Chemot	therapy*	
	with		t bevacizum	nab	with	or withou		umab
		n=3					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 (%)
					(8.7)			
Rash maculo- papular	17 (5.5)	6 (2.0)	0	0	8 (2.6)	0	0	0
Vascular disorders						I	I	
Deep vein thrombosis	4 (1.3)	1 (0.3)	0	0	0	0	0	0
Hot flush	9 (2.9)	0	0	0	6 (1.9)	0	0	0
Hypertension	54 (17.6)	20 (6.5)	0	0	55 (17.8)	23 (7.4)	0	0
Phlebitis	2 (0.7)	0	0	0	4 (1.3)	1 (0.3)	0	0

Biliary Tract Carcinoma

Table 40 summarizes the treatment-related adverse events that occurred in at least 1% of patients with biliary tract carcinoma treated with KEYTRUDA in combination with gemcitabine and cisplatin chemotherapy in KEYNOTE-966 (See 14 Clinical Trials). The median duration of exposure was 6.37 months (range: 1 day to 36.4 months) in the KEYTRUDA combination arm and 5.54 months (range: 1 day to 30.6 months) in the chemotherapy arm.

The most common treatment-related adverse events (reported in at least 20% of patients) were neutrophil count decreased, anemia, platelet count decreased, nausea, fatigue, and white blood cell count decreased. The most common Grade 3-5 treatment-related adverse events for patients treated with KEYTRUDA in KEYNOTE-966 (reported in at least 5% of patients) were neutrophil count decreased (46.7%), anemia (23.3%), platelet count decreased (16.1%) and white blood cell count decreased (11.5%).

KEYTRUDA was discontinued for treatment-related adverse events in 8.9% of patients. The most common treatment-related adverse events resulting in discontinuation of KEYTRUDA (occurring in at least 2 patients) were pneumonitis (n=7, 1.3%), platelet count decreased (n=5, 0.9%), immune-mediated hepatitis (n=3, 0.6%), autoimmune hepatitis (n=2, 0.4%), enterocolitis (n=2, 0.4%), and pulmonary embolism (n=2, 0.4%).

There were 8 participants (1.5%) with drug-related AEs resulting in death in the pembrolizumab plus chemotherapy arm, as assessed by the investigator. Of the 8 deaths, 5 were considered related to chemotherapy: cholangitis (n=1), lower respiratory tract infection (n=1), myocardial infarction (n=1),

pneumonia viral (n=1), septic shock (n=1); 2 were considered related to pembrolizumab: abdominal abscess (n=1) and malignant neoplasm progression (n=1), and 1 was related to both chemotherapy (gemcitabine) and pembrolizumab (pneumonitis).

Serious treatment-related adverse events occurred in 22.9% of patients receiving KEYTRUDA in combination with chemotherapy. Serious treatment-related adverse events occurring in \geq 1% of patients were platelet count decreased (3%), neutrophil count decreased (2.1%), pyrexia (1.7%), anemia (1.3%), febrile neutropenia (1.3%), and pneumonitis (1.3%).

Table 40: Treatment-Related Adverse Events (Incidence ≥ 1%) in Patients Treated with KEYTRUDA in Combination with Chemotherapy, APaT Population in KEYNOTE-966.

Adverse reaction		KEYTR				Plac	cebo			
		200 mg eve	-	;						
		an	_				nd			
		Chemot				Chemotherapy				
		n=5				1	534			
	All Grades	Grade 3	Grade 4	Grade 5	All Grades	Grade 3	Grade 4	Grade 5		
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)		
Blood and lymphatic sy	stem disord	lers								
Anemia	278 (52.6)	122 (23.1)	1 (0.2)	0	269 (50.4)	127 (23.8)	4 (0.7)	0		
Febrile neutropenia	9 (1.7)	7 (1.3)	2 (0.4)	0	9 (1.7)	8 (1.5)	1 (0.2)	0		
Leukopenia	25 (4.7)	9 (1.7)	2 (0.4)	0	12 (2.2)	5 (0.9)	1 (0.2)	0		
Lymphopenia	9 (1.7)	2 (0.4)	1 (0.2)	0	5 (0.9)	3 (0.6)	1 (0.2)	0		
Ear and labyrinth disor	ders									
Tinnitus	16 (3.0)	0	0	0	14 (2.6)	0	0	0		
Endocrine disorders										
Hyperthyroidism	14 (2.6)	1 (0.2)	0	0	10 (1.9)	0	0	0		
Hypothyroidism	41 (7.8)	1 (0.2)	0	0	11 (2.1)	0	0	0		
Gastrointestinal disord	ers									
Abdominal distension	14 (2.6)	0	0	0	13 (2.4)	0	0	0		
Abdominal pain	14 (2.6)	0	0	0	23 (4.3)	2 (0.4)	0	0		
Abdominal pain upper	11 (2.1)	0	0	0	10 (1.9)	0	0	0		
Constipation	85 (16.1)	1 (0.2)	0	0	74 (13.9)	1 (0.2)	0	0		
Diarrhea	53 (10.0)	5 (0.9)	0	0	55 (10.3)	3 (0.6)	0	0		
Dry mouth	7 (1.3)	0	0	0	5 (0.9)	0	0	0		
Dyspepsia	12 (2.3)	0	0	0	24 (4.5)	0	0	0		
Gastritis	6 (1.1)	0	0	0	5 (0.9)	1 (0.2)	0	0		
Gastroesophageal reflux disease	6 (1.1)	0	0	0	7 (1.3)	0	0	0		
Nausea	195 (36.9)	7 (1.3)	0	0	219 (41.0)	9 (1.7)	0	0		
Stomatitis	19 (3.6)	3 (0.6)	0	0	27 (5.1)	2 (0.4)	0	0		
Vomiting	86 (16.3)	7 (1.3)	0	0	101 (18.9)	4 (0.7)	0	0		

Adverse reaction		KEYTF	RUDA		Placebo			
		200 mg eve	ry 3 weeks	;				
		an	ıd			а	nd	
		Chemot	herapy		Chemotherapy			
		n=5	29			n=	534	
	All Grades	Grade 3	Grade 4	Grade 5	All Grades	Grade 3	Grade 4	Grade 5
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
General disorders and	administrati	on site con	ditions					
Asthenia	51 (9.6)	7 (1.3)	0	0	81 (15.2)	15 (2.8)	0	0
Fatigue	154 (29.1)	20 (3.8)	1 (0.2)	0	147 (27.5)	18 (3.4)	0	0
Malaise	30 (5.7)	1 (0.2)	0	0	27 (5.1)	0	0	0
Mucosal inflammation	24 (4.5)	2 (0.4)	0	0	23 (4.3)	1 (0.2)	0	0
Edema peripheral	31 (5.9)	0	0	0	32 (6.0)	4 (0.7)	0	0
Pyrexia	55 (10.4)	2 (0.4)	0	0	35 (6.6)	0	0	0
Infections and infestati	ons							
Urinary tract infection	6 (1.1)	1 (0.2)	0	0	4 (0.7)	1 (0.2)	0	0
Investigations	•				•	•		
Alanine	56 (10.6)	6 (1.1)	0	0	71 (13.3)	3 (0.6)	0	0
aminotransferase								
increased								
Aspartate	45 (8.5)	4 (0.8)	0	0	60 (11.2)	8 (1.5)	1 (0.2)	0
aminotransferase								
increased		- ()	_	_	()	- 4	_	
Blood alkaline	17 (3.2)	3 (0.6)	0	0	24 (4.5)	6 (1.1)	0	0
phosphatase increased	22 (4.2)	C (4.4)	4 (0.2)	0	40 (2.4)	2 (0 4)	4 (0.2)	
Blood bilirubin increased	22 (4.2)	6 (1.1)	1 (0.2)	0	18 (3.4)	2 (0.4)	1 (0.2)	0
Blood creatinine	39 (7.4)	1 (0.2)	0	0	39 (7.3)	0	0	0
increased	39 (7.4)	1 (0.2)	U	U	39 (7.3)			U
Gamma-	14 (2.6)	2 (0.4)	2 (0.4)	0	17 (3.2)	6 (1.1)	2 (0.4)	0
glutamyltransferase	1 (2.0)	2 (0.1)	2 (0.1)	Ŭ	17 (3.2)	0 (1.1)	2 (0.1)	Ü
increased								
Lymphocyte count	20 (3.8)	5 (0.9)	1 (0.2)	0	27 (5.1)	9 (1.7)	1 (0.2)	0
decreased								
Neutrophil count	321 (60.7)	158 (29.9)	89 (16.8)	0	320 (59.9)	167	79 (14.8)	0
decreased						(31.3)		
Platelet count	199 (37.6)	55 (10.4)	30 (5.7)	0	197 (36.9)	66	33 (6.2)	0
decreased						(12.4)		
Transaminases	6 (1.1)	3 (0.6)	0	0	2 (0.4)	1 (0.2)	0	0
increased			_	_		>	-	
Weight decreased	16 (3.0)	1 (0.2)	0	0	24 (4.5)	2 (0.4)	0	0
White blood cell count	139 (26.3)	57 (10.8)	4 (0.8)	0	124 (23.2)	43 (8.1)	3 (0.6)	0
decreased	 				<u> </u>			
Metabolism and nutriti			1 (0.2)		104 (10 5)	C (1 1)		
Decreased appetite	103 (19.5)	6 (1.1)	1 (0.2)	0	104 (19.5)	6 (1.1)	0	0
Hyperglycemia	12 (2.3)	0	0	0	10 (1.9)	2 (0.4)	0	0
Hyperkalemia	12 (2.3)	2 (0.4)	0	0	4 (0.7)	1 (0.2)	0	0

Adverse reaction		KEYTI	RUDA			Plac	cebo	
	2	200 mg eve	ry 3 weeks	;				
		ar	nd			а	nd	
		Chemot	therapy		Chemotherapy			
	n=529				n=	534		
	All Grades	Grade 3	Grade 4	Grade 5	All Grades	Grade 3	Grade 4	Grade 5
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Hyperuricemia	7 (1.3)	0	0	0	5 (0.9)	0	0	0
Hypoalbuminemia	8 (1.5)	1 (0.2)	0	0	11 (2.1)	3 (0.6)	0	0
Hypokalemia	19 (3.6)	4 (0.8)	0	0	17 (3.2)	2 (0.4)	0	0
Hypomagnesemia	49 (9.3)	4 (0.8)	0	0	61 (11.4)	5 (0.9)	0	0
Hyponatremia	20 (3.8)	2 (0.4)	0	0	20 (3.7)	4 (0.7)	1 (0.2)	0
Musculoskeletal and co	nnective tis	sue disord	ers					
Arthralgia	9 (1.7)	0	0	0	11 (2.1)	0	0	0
Muscular weakness	7 (1.3)	1 (0.2)	0	0	4 (0.7)	0	0	0
Myalgia	15 (2.8)	1 (0.2)	0	0	12 (2.2)	1 (0.2)	0	0
Pain in extremity	9 (1.7)	0	0	0	3 (0.6)	0	0	0
Nervous system disord	ers							
Dizziness	14 (2.6)	0	0	0	20 (3.7)	2 (0.4)	0	0
Dysgeusia	29 (5.5)	0	0	0	27 (5.1)	1 (0.2)	0	0
Headache	21 (4.0)	1 (0.2)	0	0	16 (3.0)	0	0	0
Neuropathy peripheral	16 (3.0)	0	0	0	23 (4.3)	0	0	0
Paresthesia	15 (2.8)	1 (0.2)	0	0	14 (2.6)	0	0	0
Peripheral sensory neuropathy	24 (4.5)	2 (0.4)	0	0	21 (3.9)	0	0	0
Polyneuropathy	8 (1.5)	0	0	0	6 (1.1)	0	0	0
Taste disorder	6 (1.1)	0	0	0	4 (0.7)	0	0	0
Psychiatric disorders	o (=:=)				. (0.7)			
Insomnia	8 (1.5)	1 (0.2)	0	0	9 (1.7)	0	0	0
Renal and urinary	0 (1.5)	1 (0.2)			3 (2.7)			
disorders								
Acute kidney injury	9 (1.7)	1 (0.2)	0	0	9 (1.7)	3 (0.6)	2 (0.4)	0
Renal impairment	17 (3.2)	0	0	0	8 (1.5)	2 (0.4)	0	0
Respiratory, thoracic a	nd mediastir	nal disorde	rs			I.		
Dyspnea	14 (2.6)	1 (0.2)	0	0	15 (2.8)	2 (0.4)	0	0
Epistaxis	11 (2.1)	0	0	0	8 (1.5)	0	0	0
Hiccups	8 (1.5)	1 (0.2)	0	0	8 (1.5)	0	0	0
Pneumonitis	22 (4.2)	4 (0.8)	0	1 (0.2)	7 (1.3)	0	0	0
Pulmonary embolism	6 (1.1)	5 (0.9)	1 (0.2)	0	0	0	0	0
Skin and subcutaneous	tissue disor	ders	•		•	•		
Alopecia	53 (10.0)	0	0	0	65 (12.2)	0	0	0
Dry skin	11 (2.1)	0	0	0	12 (2.2)	0	0	0
Pruritus	52 (9.8)	0	0	0	31 (5.8)	0	0	0
Rash	73 (13.8)	3 (0.6)	0	0	37 (6.9)	2 (0.4)	0	0
Rash maculo-papular	11 (2.1)	2 (0.4)	0	0	9 (1.7)	0	0	0

Adverse reaction	KEYTRUDA 200 mg every 3 weeks			Placebo				
		and Chemotherapy n=529			and Chemotherapy n=534			
	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Skin hyperpigmentation	8 (1.5)	0	0	0	3 (0.6)	0	0	0
Urticaria	6 (1.1)	1 (0.2)	0	0	1 (0.2)	1 (0.2)	0	0

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

In a Phase I/II study (KEYNOTE-051), 173 pediatric patients (65 children ages 6 months to less than 12 years and 108 adolescents ages 12 years to 17 years) with advanced melanoma, lymphoma, or PD-L1 positive or MSI-H advanced, relapsed, or refractory solid tumours were administered KEYTRUDA 2 mg/kg every 3 weeks. Patients received KEYTRUDA for a median of 4 doses (range 1-52 doses), with 147 patients (85%) receiving KEYTRUDA for 2 doses or more. The concentrations of pembrolizumab in 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; nausea; diarrhea; fatigue; arthralgia; aspartate aminotransferase increased; decreased appetite; lymphocyte count decreased; pain in extremity; alanine aminotransferase increased; pruritus; asthenia; back pain; white blood cell count decreased. 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 (29%); headache (25%); abdominal pain (23%); lymphocyte count decreased (13%) and white blood cell count decreased (11%). Laboratory abnormalities that occurred at a ≥10% higher rate in pediatric patients when compared to adults were leukopenia (31%), neutropenia (28%), and thrombocytopenia (22%).

8.3 Less Common Clinical Trial Adverse Reactions

Melanoma

Treatment-related adverse events reported in <1% patients with melanoma treated with KEYTRUDA 10 mg/kg every 2 or 3 weeks (n=555) in KEYNOTE-006 by system organ class (SOC) are shown below:

Endocrine disorders: adrenal insufficiency, hypophysitis, hypopituitarism

Eve 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

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) in KEYNOTE-002 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.

Adjuvant Melanoma

Treatment-related adverse events reported in <1% of patients with complete resection of Stage IIB or IIC melanoma treated with KEYTRUDA (n=483) in KEYNOTE-716 by SOC are shown below:

Eye disorders: uveitis

Gastrointestinal disorders: pancreatitis **Immune system disorders:** sarcoidosis

Injury, poisoning and procedural complications: infusion related reaction

Metabolism and nutrition disorders: type 1 diabetes mellitus Musculoskeletal and connective tissue disorder: myositis Nervous system disorders: myasthenic syndrome, myelitis

Renal and urinary disorders: nephritis

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) in KEYNOTE-054 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

NSCLC

Treatment-related adverse events reported in <1% patients with NSCLC treated with KEYTRUDA 200 mg every 3 weeks (n=154) in KEYNOTE-024 by SOC are shown below:

Endocrine disorders: hypophysitis
Gastrointestinal disorders: pancreatitis

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

Treatment-related adverse events reported in <1% patients with NSCLC treated with KEYTRUDA

200 mg every 3 weeks (n=636) in KEYNOTE-042 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

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) in KEYNOTE-189 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

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 nabpaclitaxel (n=278) in KEYNOTE-407 by SOC are shown below:

Endocrine disorders: hypophysitis, hypopituitarism

Renal and urinary disorders: nephritis

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) in KEYNOTE-010 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

Adjuvant NSCLC

Treatment-related adverse events reported in <1% of patients with resected NSCLC treated with KEYTRUDA 200 mg every 3 weeks (n=580) in KEYNOTE-091 by SOC are shown below:

Cardiac disorders: myocarditis

Endocrine disorders: hypopituitarism; thyroiditis

Gastrointestinal disorders: pancreatitis

Hepatobiliary disorders: immune-mediated hepatitis **Immune system disorders:** hypersensitivity; sarcoidosis

Injury, poisoning and procedural complications: infusion related reaction

Metabolism and nutrition disorders: type 1 diabetes mellitus

Renal and urinary disorders: nephritis

Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome

Neoadjuvant and Adjuvant Treatment of Resectable NSCLC

Treatment-related adverse events reported in <1% patients with resectable NSCLC treated with

KEYTRUDA in combination with platinum-containing chemotherapy, given as neoadjuvant treatment and continued as monotherapy adjuvant treatment in KEYNOTE-671 (n=396) by SOC are shown below:

Cardiac disorders: myocarditis

Endocrine disorders: adrenal insufficiency, hypophysitis, thyroiditis

Hepatobiliary disorders: immune-mediated hepatitis

Injury, poisoning and procedural complications: infusion-related reaction

Musculoskeletal and connective tissue disorders: myositis

Nervous system disorders: myasthenic syndrome

MPM

Treatment-related adverse events reported in <1% of patients with unresectable advanced or metastatic MPM with KEYTRUDA 200 mg every 3 weeks in combination with pemetrexed and platinum chemotherapy (n=241) in KEYNOTE-483 by SOC are shown below:

Endocrine disorders: adrenal insufficiency, hypophysitis

Eye disorders: uveitis

Gastrointestinal disorders: gastritis, pancreatitis **Immune system disorders:** hypersensitivity

Infections and infestations: myelitis **Renal and urinary disorders:** nephritis

Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome

Vascular disorders: vasculitis

Hodgkin Lymphoma

Treatment related adverse events reported in <1% patients with HL treated with KEYTRUDA 200 mg every 3 weeks (n=148) in KEYNOTE-204 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

Urothelial Carcinoma

Other clinically important adverse events, regardless of relationship to KEYTRUDA, that occurred in < 10% of recipients of KEYTRUDA in combination with enfortumab vedotin in KEYNOTE-A39 by SOC are shown below:

Blood and lymphatic disorders: neutropenia, febrile neutropenia

Cardiac disorders: myocarditis, tachycardia

Endocrine disorder: hyperthyroidism, adrenal insufficiency, hypophysitis, type 1 diabetes mellitus,

thyroiditis

Eye disorder: uveitis

Gastrointestinal disorder: pancreatitis

General disorders and administrative site conditions: infusion site extravasation **Hepatobiliary disorders:** hepatitis, immune-mediated hepatitis, sclerosing cholangitis

Immune system disorder: hypersensitivity, sarcoidosis Infections and infestations: sepsis and septic shock

Musculoskeletal and connective tissue disorders: myositis

Nervous system disorder: immune-mediated encephalitis, myasthenia gravis

Renal and urinary disorders: immune-mediated nephritis

Skin and subcutaneous tissue disorders: toxic epidermal necrolysis, skin hyperpigmentation, skin

discolouration

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

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

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

Colorectal Cancer

Treatment-related adverse events reported in <1% patients with MSI-H or dMMR colorectal carcinoma treated with KEYTRUDA 200 mg every 3 weeks (n=153) in KEYNOTE-177 by SOC are shown below:

Endocrine disorders: thyroiditis, autoimmune thyroiditis **Musculoskeletal and connective tissue disorders:** myositis

Renal and urinary disorders: nephritis

Microsatellite Instability-High Cancer (MSI-H) or Mismatch Repair Deficient (dMMR) Cancer

Treatment-related adverse events reported in <1% patients with MSI-H cancer treated with KEYTRUDA 200 mg every 3 weeks (n=497) in KEYNOTE-158 and KEYNOTE-164 by SOC are shown below:

Cardiac disorders: myocarditis

Endocrine disorders: adrenal insufficiency

Eye disorders: uveitis

Gastrointestinal disorders: pancreatitis

Hepatobiliary disorders: hepatitis **Immune system disorders:** sarcoidosis

Metabolism and nutrition disorders: type 1 diabetes mellitus, diabetic ketoacidosis

Musculoskeletal and connective tissue disorders: myositis

Nervous system disorders: Guillain-Barré syndrome

Renal and urinary disorders: nephritis

Vascular disorders: vasculitis

Endometrial Carcinoma

Treatment-related adverse events attributable to KEYTRUDA and reported in <1% patients with endometrial cancer treated with KEYTRUDA in combination with chemotherapy (n=382) in KEYNOTE-

868 by SOC are shown below: **Cardiac disorders:** myocarditis

Endocrine disorders: adrenal insufficiency, hypophysitis

Eye disorders: uveitis

Gastrointestinal disorders: pancreatitis

Immune system disorders: anaphylactic reaction

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

Nervous system disorders: encephalitis, Guillain-Barré syndrome, myasthenia gravis

Renal and urinary disorders: nephritis

Vascular disorders: vasculitis

Endometrial Carcinoma (Not MSI-H or not dMMR)

Serious adverse events reported in <3% patients with endometrial cancer treated with KEYTRUDA in combination with lenvatinib (n=94) in KEYNOTE-146 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

Treatment-related adverse events attributable to KEYTRUDA and reported in <1% patients with endometrial carcinoma treated with KEYTRUDA in combination with lenvatinib (n=342) in KEYNOTE-775 by SOC are shown below:

Cardiac disorders: myocarditis

Endocrine disorders: adrenal insufficiency, hypophysitis

Eye disorders: uveitis

Gastrointestinal disorders: pancreatitis **Hepatobiliary disorders:** hepatitis

Immune system disorders: hypersensitivity, anaphylactic reaction

Metabolism and nutrition disorders: Type 1 diabetes mellitus, diabetic ketoacidosis

Musculoskeletal and connective tissue disorders: myositis, arthritis

Nervous system disorders: encephalitis, myasthenia gravis

Renal and urinary disorders: nephritis

Skin and subcutaneous tissue disorders: Steven's Johnson syndrome

Vascular disorders: vasculitis

Renal Cell Carcinoma

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

Serious adverse events reported in <2% patients with renal cell carcinoma treated with KEYTRUDA in combination with lenvatinib (n=352) in KEYNOTE-581 by SOC are shown below:

Blood and lymphatic system disorders: Eosinophilia myalgia syndrome, thrombocytopenia, thrombotic thrombocytopenic purpura

Cardiac disorders: Acute coronary syndrome, cardio-respiratory arrest, myocarditis, arrhythmia, atrial fibrillation, cardiac arrest, cardiac failure acute, cardiac failure congestive, cardiomyopathy, pericardial effusion, stress cardiomyopathy, tachycardia

Endocrine disorders: Hypothyroidism, hypophysitis, hypopituitarism, steroid withdrawal syndrome

Eye disorders: Cataract, retinal vascular occlusion, Vogt-Koyanagi-Harada syndrome

Gastrointestinal disorder: Pancreatitis, abdominal pain, nausea, constipation, colitis, hematemesis, abdominal pain upper, duodenal ulcer perforation, enterocolitis, eosinophilic gastritis, food poisoning, gastric hemorrhage, gastritis, immune-mediated enterocolitis, immune-mediated pancreatitis, inguinal hernia, intestinal obstruction, lower gastrointestinal hemorrhage, odynophagia, pancreatitis acute, retroperitoneal hemorrhage, small intestinal hemorrhage, upper gastrointestinal hemorrhage

General disorders and administrative site conditions: Pyrexia, asthenia, non-cardiac chest pain, pain, death, general physical health deterioration, multiple organ dysfunction syndrome, oedema

Hepatobiliary disorders: Immune-mediated hepatitis, cholecystitis, cholecystitis acute, autoimmune hepatitis, cholangitis, cholelithiasis, drug-induced liver injury, hepatic function abnormal Infections and infestations: Urinary tract infection, sepsis, appendicitis, gastroenteritis, peritonsillar abscess, respiratory tract infection, urosepsis, acute sinusitis, anal abscess, bronchitis, cellulitis, clostridium difficile infection, colonic abscess, encephalitis, encephalitis viral, enteritis infectious, enterocolitis infectious, influenza, klebsiella sepsis, localised infection, osteomyelitis, peritonitis, pneumocystis jirovecii pneumonia, prostatic abscess, pyelonephritis, septic arthritis staphylococcal, sinusitis, skin infection, staphylococcal bacteremia

Injury, poisoning, and procedural complications: Accidental overdose, incisional hernia, infusion related reaction, radiation injury, radiation proctitis, rib fracture, subdural hematoma, upper limb fracture, wound dehiscence

Investigations: Lipase increased, amylase increased, weight decreased, alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, blood creatinine increased, Hemoglobin increased, neutrophil count decreased, platelet count decreased, transaminases increased, troponin increased, white blood cell count decreased

Metabolism and nutrition disorders: Decreased appetite, hyponatremia, dehydration, diabetic ketoacidosis, electrolyte imbalance, hyperglycemia, hyperglycemic hyperosmolar nonketotic syndrome, hyperkalemia, hypocalcemia, hypoglycemia, hypophosphatemia

Musculoskeletal and connective tissue disorders: Pathological fracture, arthralgia, back pain, flank pain, myalgia, myositis, osteoarthritis

Neoplasms benign, malignant and unspecified (incl cysts and polyps): Cancer pain, tumour hemorrhage, external ear neoplasm malignant, metastases to central nervous system, metastases to chest wall, metastases to lung, metastases to spine

Nervous system disorders: Cerebrovascular accident, dizziness, encephalopathy, headache, posterior reversible encephalopathy syndrome, syncope, transient ischemic attack, ataxia, carotid artery stenosis, cerebral ischemia, dementia, depressed level of consciousness, dysgeusia, myasthenic syndrome, noninfective encephalitis, peripheral sensory neuropathy, spinal cord compression, subarachnoid hemorrhage

Product issues: Device deposit issue

Psychiatric disorders: Mental status changes, delirium

Renal and urinary disorders: Renal failure, nephritis, urinary retention, hemorrhage urinary tract, proteinuria, renal hemorrhage, urinary tract obstruction

Respiratory, thoracic and mediastinal disorders: Pulmonary embolism, pleural effusion, bronchial obstruction, hemoptysis, Hemothorax, hypoxia, lung disorder, pneumonia aspiration, pneumothorax, pulmonary mass, respiratory failure

Skin and subcutaneous disorders: Rash, erythema multiforme, pyoderma gangrenosum, rash maculo-papular, skin ulcer, toxic epidermal necrolysis

Vascular disorders: Deep vein thrombosis, aortic dissection, aortic stenosis, hypertensive crisis, peripheral ischemia

Adjuvant RCC

Treatment-related adverse events reported in <1% patients with RCC treated with KEYTRUDA 200 mg every 3 weeks (n=488) in KEYNOTE-564 by SOC are shown below:

Cardiac disorders: myocarditis **Endocrine disorders:** hypophysitis

Hepatobiliary disorders: hepatitis, immune-mediated hepatitis

Immune system disorders: hypersensitivity, sarcoidosis

Musculoskeletal and connective tissue disorders: myositis, myasthenia gravis, myasthenia syndrome

Nervous system disorders: encephalitis **Renal and urinary disorders:** nephritis

Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome

Vascular Disorders: vasculitis

HNSCC

Resectable Locally Advanced HNSCC

Treatment-related adverse events attributable to KEYTRUDA and reported in <1% patients with resectable locally advanced HNSCC treated with KEYTRUDA as neoadjuvant treatment, continued as adjuvant treatment in combination with RT with or without cisplatin, and then as monotherapy in KEYNOTE-689 (n=361) by SOC are shown below:

Cardiac disorders: myocarditis

Endocrine disorders: hypoparathyroidism, hypophysitis, thyroiditis

Gastrointestinal disorders: pancreatitis **Hepatobiliary disorders:** hepatitis

Immune system disorders: hypersensitivity

Injury, poisoning, and procedural complications: infusion-related reaction **Musculoskeletal and connective tissue disorders:** arthritis, myositis

Metastatic or Unresectable, Recurrent HNSCC

Treatment-related adverse events reported in <1% patients with HNSCC treated with KEYTRUDA 200 mg every 3 weeks (n=300) in KEYNOTE-048 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 KEYNOTE-048 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

Gastric or Gastroesophageal junction (GEJ) Adenocarcinoma

Treatment-related adverse events reported in <1% of patients with locally advanced unresectable or metastatic HER2-positive gastric or GEJ adenocarcinoma receiving KEYTRUDA in combination with trastuzumab and fluoropyrimidine- and platinum-containing chemotherapy (n=350) are shown below:

Blood and lymphatic system disorders: autoimmune hemolytic anemia

Endocrine disorders: autoimmune thyroiditis, thyroiditis

Eye disorders: uveitis

Gastrointestinal disorders: enterocolitis, gastritis, immune-mediated enterocolitis

Hepatobiliary disorders: hepatitis

Immune system disorders: anaphylactic reaction

Injury, poisoning, and procedural complications: infusion-related reaction

Metabolism and nutrition disorders: type 1 diabetes mellitus

Musculoskeletal and connective tissue disorders: immune mediated arthritis, rhabdomyolysis

Renal and urinary disorders: nephritis

Treatment-related adverse events attributable to KEYTRUDA and reported in <1% patients with locally advanced or metastatic HER2-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma treated with KEYTRUDA in combination with fluoropyrimidine- and platinum-containing chemotherapy (n=785) by SOC are shown below:

Blood and lymphatic system disorders: aplastic anemia, hemolytic anemia, thrombotic

thrombocytopenic purpura

Cardiac disorders: cardiac failure, sinus tachycardia

Endocrine disorders: hypoparathyroidism, hypopituitarism, thyroiditis

Eye disorders: uveitis

Gastrointestinal disorders: enterocolitis, immune-mediated enterocolitis, gastrointestinal

haemorrhage, intestinal obstruction, pancreatitis

Hepatobiliary disorders: hepatitis

Infections and infestations: sepsis, septic shock

Injury, poisoning, and procedural complications: anaphylactic reaction

Metabolism and nutrition disorders: diabetic ketoacidosis, type 1 diabetes mellitus

Musculoskeletal and connective tissue disorders: arthritis, myositis Nervous system disorders: myasthenia gravis, septic encephalopathy

Renal and urinary disorders: haematuria, immune-mediated nephritis, nephritis

Respiratory, thoracic and mediastinal disorders: immune-mediated lung disease, pulmonary

haemorrhage

Vascular disorders: peripheral embolism, vasculitis

Esophageal Cancer

Treatment-related adverse events attributable to KEYTRUDA and reported in <1% patients with esophageal carcinoma treated with KEYTRUDA in combination with cisplatin and FU (n=370) by SOC are shown below:

Endocrine disorders: Basedow's disease, hypophysitis, hypopituitarism, thyroiditis

Gastrointestinal disorders: autoimmune colitis, enterocolitis, pancreatitis

Hepatobiliary disorders: hepatitis, autoimmune hepatitis

Immune system disorders: hypersensitivity

Metabolism and nutrition disorders: Type 1 diabetes mellitus Musculoskeletal and connective tissue disorders: myopathy

Renal and urinary disorders: tubulointerstitial nephritis

Respiratory, thoracic and mediastinal disorders: interstitial lung disease

Skin and subcutaneous tissue disorders: pruritus

Triple Negative Breast Cancer (TNBC)

Treatment-related adverse events attributable to KEYTRUDA and reported in <1% patients with TNBC treated with KEYTRUDA in combination with chemotherapy (n=596) by SOC are shown below:

Cardiac disorders: myocarditis

Endocrine disorders: hypophysitis, thyroiditis acute

Eye disorders: uveitis

Gastrointestinal disorders: enterocolitis, pancreatitis

Hepatobiliary disorders: autoimmune hepatitis, hepatitis, immune-mediated hepatitis

Metabolism and nutrition disorders: type 1 diabetes mellitus **Musculoskeletal and connective tissue disorders**: myositis

Nervous system disorders: Guillain-Barre syndrome

Renal and urinary disorders: nephritis

Respiratory, thoracic and mediastinal disorders: organising pneumonia

Skin and subcutaneous tissue disorders: dermatomyositis

Vascular disorders: vasculitis

Early-stage Triple-Negative Breast Cancer

Treatment-related adverse events attributable to KEYTRUDA and reported in <1% patients with early-stage TNBC treated with KEYTRUDA in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery (n=783) in KEYNOTE-522 by SOC are shown below:

Blood and lymphatic system disorders: hemolytic anemia

Cardiac disorders: myocarditis

Endocrine disorders: autoimmune thyroiditis, hypopituitarism

Eye disorders: iridocyclitis, uveitis

Gastrointestinal disorders: autoimmune colitis, enterocolitis, pancreatitis, pancreatitis acute **Hepatobiliary disorders:** autoimmune hepatitis, hepatitis, immune-mediated hepatitis **Immune system disorders:** cytokine release syndrome, drug hypersensitivity, hypersensitivity,

sarcoidosis, serum sickness

Injury, poisoning and procedural complications: infusion-related reaction

Metabolism and nutrition disorders: diabetic ketoacidosis, type 1 diabetes mellitus

Musculoskeletal and connective tissue disorders: arthritis, myositis

Nervous system disorders: encephalitis autoimmune, myasthenia gravis

Renal and urinary disorders: autoimmune nephritis, nephritis, tubulointerstitial nephritis, **Skin and subcutaneous tissue disorders:** dermatitis bullous, dermatitis exfoliative generalized, erythema multiforme, pemphigoid, pruritus, Stevens-Johnson syndrome, toxic skin eruption

Vascular disorders: vasculitis

Cervical Cancer

Treatment-related adverse events attributable to KEYTRUDA and reported in <1% patients with FIGO 2014 Stage III-IVA cervical cancer treated with KEYTRUDA 200 mg every 3 weeks with chemoradiotherapy and 400 mg every 6 weeks as monotherapy (n= 295) in KEYNOTE-A18 in combination with chemoradiotherapy are shown below.

Endocrine disorders: thyroiditis

Gastrointestinal disorders: pancreatitis

Hepatobiliary disorders: autoimmune hepatitis Infections and infestations: encephalitis Immune system disorders: sarcoidosis

Injury, poisoning and procedural complications: Infusion related reaction

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

Nervous system disorders: Guillain-Barre syndrome **Renal and urinary disorders:** autoimmune nephritis

Vascular disorders: vasculitis

Treatment-related adverse events attributable to KEYTRUDA and reported in <1% patients with persistent, recurrent or metastatic cervical cancer treated with KEYTRUDA 200 mg every 3 weeks (n= 307) in KEYNOTE-826 in combination with chemotherapy with or without bevacizumab by SOC are shown below:

Cardiac disorders: myocarditis

Endocrine disorders: hypophysitis, immune-mediated hypothyroidism, autoimmune thyroiditis

Gastrointestinal disorders: pancreatitis, pancreatitis acute

Hepatobiliary disorders: hepatitis, autoimmune hepatitis, immune-mediated cholangitis

Injury, poisoning, and procedural complications: anaphylactic reaction

Metabolism and nutrition disorders: diabetic ketoacidosis

Musculoskeletal and connective tissue disorders: myositis, autoimmune myositis

Nervous system disorders: encephalitis autoimmune

Skin and subcutaneous tissue disorders: pruritus, rash erythematous

Vascular disorders: vasculitis

Biliary Tract Carcinoma

Treatment-related adverse events attributable to KEYTRUDA and reported in <1% patients with biliary tract carcinoma treated with KEYTRUDA 200 mg every 3 weeks (n= 529) in KEYNOTE-966 in combination with chemotherapy by SOC are shown below:

Cardiac disorders: myocarditis

Endocrine disorders: adrenal insufficiency, hypophysitis, thyroiditis

Gastrointestinal disorders: pancreatitis **Hepatobiliary disorders:** hepatitis

Immune system disorders: infusion-related reaction

Musculoskeletal and connective tissue disorders: arthritis

Nervous system disorders: encephalitis **Renal and urinary disorders:** nephritis

Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome

Vascular disorders: vasculitis

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Melanoma

Laboratory abnormalities (worsened from baseline in \geq 10% of patients), reported in KEYNOTE-006 in patients with advanced melanoma are presented in Table 41.

Table 41: Laboratory Abnormalities Worsened from Baseline in \geq 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 \geq 5% [All Grades] or \geq 2% [Grades 3-4]) (KEYNOTE-006).

		RUDA	Ipilimumab	
		y 2 or 3 weeks		
Laboratory Test	n=!	555	n=	256
	All Grades	Grades 3-4	All Grades	Grades 3-4
	%	%	%	%
Hematology	·			
Lymphopenia	33	6	25	6
Leukopenia	12	0.4	4.7	0
Thrombocytopenia	11	1.1	6	0.8
Chemistry				
Hypertriglyceridemia	42	2.7	33	1.2
Hypercholesterolemia	22	1.1	17	0

Laboratory abnormalities (worsened from baseline in \geq 10% of patients), reported in KEYNOTE-002 in patients with advanced melanoma are presented in Table 42.

Table 42: 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).

		RUDA every 3 weeks	Chemotherapy	
Laboratory Test	n=	357	n=	171
	All Grades	Grades 3-4	All Grades	Grades 3-4
	%	%	%	%
Chemistry				
Hyperglycemia	48	6	42	6
Hyponatremia	36	7	24	4.1
Increased Alkaline Phosphatase	26	3.1	17	1.8
Increased Aspartate	22	2.2	16	0.6
Aminotransferase	23	2.2	16	0.6
Hypercholesterolemia	20	0.6	11	0
Increased Alanine Aminotransferase	20	2.0	15	0.6
Bicarbonate decreased	18	0.3	10	0
Hyperkalemia	15	0.8	8	0.6
Creatinine increased	14	0.6	9	1.2

Adjuvant Melanoma

Laboratory abnormalities (worsened from baseline in ≥ 10% of patients), reported in KEYNOTE-716 in patients who have undergone complete resection of Stage IIB or IIC melanoma are presented in Table 43.

Table 43: Laboratory Abnormalities Worsened from Baseline in \geq 10% of Patients Treated with KEYTRUDA and at a Higher Incidence than in Control Arm (Between Arm Difference of \geq 5% [All Grades] or \geq 2% [Grades 3-4]) APaT Population (KEYNOTE-716).

Labourton, Tost	KEYTF 200 mg eve	ry 3 weeks	Placebo		
Laboratory Test	n=4	1	n=486		
	All Grades	Grades 3-4	All Grades	Grades 3-4	
	%	%	%	%	
Alanine Aminotransferase Increased	28	2.5	14	0.4	
Aspartate Aminotransferase Increased	24	1.4	12	0.8	
Hemoglobin Decreased	21	0.2	14	0	
Creatinine Increased	15	0.8	10	0.2	

Laboratory abnormalities (worsened from baseline in \geq 10% of patients), reported in KEYNOTE-054 in patients with lymph node involvement who have undergone complete resection of Stage IIIA (>1 mm metastasis), IIIB and IIIC melanoma are presented in Table 44.

Table 44: Laboratory Abnormalities Worsened from Baseline in ≥ 10% of Patients 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 (KEYNOTE-054).

	KEYTF	RUDA	Placebo		
	200 mg eve	ry 3 weeks			
Laboratory Test	n=5	609	n=502		
	All Grades	Grades 3-4	All Grades	Grades 3-4	
	%	%	%	%	
Alanine Aminotransferase Increased	24	2.4	15	0.2	
Aspartate Aminotransferase Increased	22	1.8	14	0.4	
Lymphocyte Count Decreased	22	1.0	15	1.2	
Hypocalcemia	12	0	7	0.2	
Hypoalbuminemia	12	0	3.8	0.2	
Alkaline Phosphatase Increased	11	0.2	5	0.2	

NSCLC

Laboratory abnormalities (worsened from baseline in \geq 10% of patients), reported in KEYNOTE-024 in patients with NSCLC, are presented in Table 45.

Table 45: Laboratory Abnormalities Worsened from Baseline in \geq 10% of Patients with NSCLC Treated with KEYTRUDA and at a Higher Incidence than in the Chemotherapy Arm (Between Arm Difference of \geq 5% [All Grades] or \geq 2% [Grades 3-4]), APaT population in KEYNOTE-024.

	KEYTF	RUDA	Chemotherapy	
	200 mg eve	ry 3 weeks		
Laboratory Test	n=1	.54	n=150	
	All Grades	Grades 3-4	All Grades	Grades 3-4
	%	%	%	%
Chemistry				
Glucose Increased	52	8	46	6

Laboratory Test	KEYTR 200 mg ever n=1	ry 3 weeks	Chemotherapy n=150		
,	All Grades	Grades 3-4	All Grades	Grades 3-4	
	%	%	%	%	
Alanine Aminotransferase Increased	31	4.5	31	0	
Calcium Decreased	25	0	20	0	
Aspartate Aminotransferase Increased	25	3.9	33	0	
Alkaline Phosphatase Increased	22	2.6	24	0	

Laboratory abnormalities (worsened from baseline in ≥ 10% of patients), reported in KEYNOTE-042 in patients with NSCLC, are presented in Table 46.

Table 46: Laboratory Abnormalities Worsened from Baseline in \geq 10% of Patients with NSCLC Treated with KEYTRUDA and at a Higher Incidence than in the Chemotherapy Arm (Between Arm Difference of \geq 5% [All Grades] or \geq 2% [Grades 3-4]), APaT population in KEYNOTE-042

		RUDA ery 3 weeks	Chemotherapy		
Laboratory Test	_	636	n=615		
	All Grades	Grades 3-4	All Grades	Grades 3-4	
	%	%	%	%	
Chemistry					
Calcium Decreased	24	2.4	18	0.8	

Laboratory abnormalities (worsened from baseline in \geq 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 47.

Table 47: Laboratory Abnormalities Worsened from Baseline in \geq 10% of Patients with Nonsquamous 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 \geq 5% [All Grades] or \geq 2% [Grades 3-4]) (KEYNOTE-189).

Laboratory Test	KEYTF an Pemet an Platinum Che	d rexed d emotherapy	Placebo and Pemetrexed and Platinum Chemotherapy		
	n=4	Grades 3-4	n= All Grades	202 Grades 3-4	
	%	%	%	%	
Hematology	l	1			
Neutropenia	49	21	40	18	
Platelet Count Decreased	29	11	28	7	
Chemistry					
Hyperglycemia	62	8	57	7	
Alanine Aminotransferase	46	3.7	40	2.5	
Increased					
Aspartate Aminotransferase	46	2.7	38	1.0	
Increased					
Creatinine Increased	36	4.2	24	1.0	
Hyponatremia	32	7	22	5	
Hyperkalemia	24	2.7	18	3.0	
Hypocalcemia	23	2.7	16	0.5	

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 48.

Table 48: 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).

actitates Arm (Detween Arm Difference of 2.5% [An diades] of 2.2% [diades 3-4] (KETWOTE-407).							
	KEYTF	RUDA	Placebo				
	an	d	and				
	Carbo	platin	Carbo	oplatin			
Laboratory Test*	and and		nd				
	Paclitaxel or N	lab-Paclitaxel	Paclitaxel or Nab-Paclitaxel				
	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			
Hyperglycemia	57	7	51	8			

	KEYTR	UDA	Pla	cebo	
	an	d	а	and	
	Carbo	olatin	Carboplatin		
Laboratory Test*	an	d	а	nd	
	Paclitaxel or N	ab-Paclitaxel	Paclitaxel or	Nab-Paclitaxel	
	All Grades	Grades 3-4	All Grades	Grades 3-4	
	%	% %		%	
Lymphocyte Count Decreased	50	19	46	12	
Hypoalbuminemia	36	3.0	32	0.8	
Chemistry					
Aspartate Aminotransferase	30	4.1	19	1.9	
Increased	30	4.1	19	1.9	
Alanine Aminotransferase	27	3.3	20	1.9	
Increased		3.3	20	1.5	

Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA + carboplatin + paclitaxel or nab-paclitaxel (range: 266 to 273 patients) and placebo + carboplatin + paclitaxel or nab-paclitaxel (range: 263 to 270 patients)

Laboratory abnormalities (worsened from baseline in \geq 10% of patients), reported in KEYNOTE-010, in patients with NSCLC, are presented in Table 49. Patients were treated with pembrolizumab at 2 mg/kg or 10 mg/kg every 3 weeks.

Table 49: 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).

<u> </u>	KEYTRUDA 2 or 10 mg/kg every 3 weeks n=682		Docetaxel 75 mg/m² every 3 weeks n=309	
Laboratory Test				
	All Grades	Grades 3-4	All Grades	Grades 3-4
	%	%	%	%
Chemistry				
Hyponatremia	31	8	25	2.6
Increased Alkaline Phosphatase	28	2.8	16	0.6
Increased Aspartate Aminotransferase	25	1.6	12	0.6
Alanine Aminotransferase Increased	21	2.5	9	0.3
Creatinine Increased	18	0.9	9	0.6

Adjuvant NSCLC

Laboratory abnormalities (worsened from baseline in \geq 20% of patients), reported in KEYNOTE-091 in patients with resected NSCLC, are presented in Table 50.

Table 50: Laboratory abnormalities Worsened from baseline in ≥ 20% of patients, reported in KEYNOTE-091 in patients with NSCLC Treated with KEYTRUDA.

	KEYTRUDA	Placebo
Laboratory Test*	200 mg every 3 weeks	

	All Grades [†]	Grades 3-4	All Grades [†]	Grades 3-4
	%	%	%	%
Chemistry				
Alanine Aminotransferase	29	3.1	20	0.5
Increased				
Aspartate Aminotransferase	28	2.8	19	0.9
Increased				
Hyperkalemia	28	1.4	28	1.9
Creatinine Increased	27	0.3	26	0.2
Hyponatremia	21	3.3	19	1.9
Hematology				
Lymphocytes Decreased	21	1.7	12	1.0

Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (range: 577 to 578 patients) and placebo (range: 577 to 579 patients).

Neoadjuvant and Adjuvant Treatment of Resectable NSCLC

Laboratory abnormalities (worsened from baseline in \geq 20% of patients), reported in KEYNOTE-671 in patients with resectable NSCLC are presented in Table 51.

Table 51: Laboratory Abnormalities Worsened from Baseline in ≥20% of Patients with Resectable NSCLC Treated with KEYTRUDA in Combination with Chemotherapy as Neoadjuvant Treatment, and then Continued as Monotherapy Adjuvant Treatment in KEYNOTE-671

Laboratory Test	a Platinum Ch	KEYTRUDA and Platinum Chemotherapy / KEYTRUDA		Placebo and Platinum Chemotherapy / Placebo	
	All Grades	Grades 3-4	All Grades	Grades 3-4	
	%	%	%	%	
Hematology			1	1	
Anemia	81	9	77	8	
White Blood Cell Decreased	67	11	58	9	
Neutrophil Count Decreased	65	29	65	29	
Lymphocyte Count Decreased	48	16	42	13	
Platelet Count Decreased	44	9	39	8	
Hypoalbuminemia	28	1.8	24	1.5	
Chemistry					
Hyperglycemia	57	7	56	7	
Hyponatremia	53	11	49	11	
Creatinine Increased	50	2.8	40	2.8	
Alanine Aminotransferase Increased	44	3.3	37	2.3	
Aspartate Aminotransferase Increased	32	3.0	24	2.0	
Hyperkalemia	32	5	31	3.0	
Hypocalcemia	29	3.6	26	4.6	

[†] Graded per NCI CTCAE v4.03

Alkaline Phosphatase Increased	27	1.0	23	0.5
Hypophosphatemia	25	6	26	7
Hypokalemia	21	6	18	3.3

^{*} Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (range: 385 to 395 patients) and placebo (range: 392 to 399 patients).

MPM

Laboratory abnormalities (worsened from baseline in \geq 20% of patients), reported in KEYNOTE-483 in patients with MPM are presented in Table 52.

Table 52: Laboratory Abnormalities Worsened from Baseline in ≥ 20% of Patients Receiving KEYTRUDA with Pemetrexed and Platinum Chemotherapy, in KEYNOTE-483.

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks and Pemetrexed and Platinum Chemotherapy		Pemetrexed and Platinum Chemotherapy	
	All Grades [†]	Grades 3-4	All Grades	Grades 3-4
	%	%	%	%
Hematology		T		.
Hemoglobin Decreased	80	22	73	12
Leukocytes Decreased	73	16	60	7
Lymphocytes Decreased	67	26	62	15
Neutrophils Decreased	53	27	51	19
Platelets Decreased	38	11	24	4.1
Prothrombin INR Increased	20	1.1	11	0
Chemistry				
Glucose Increased	47	6	41	4.9
Magnesium Decreased	47	0.9	41	4.7
Creatinine Increased	36	0.9	20	0
Albumin Decreased	35	1.3	26	0.9
Aspartate Aminotransferase Increased	30	0	13	1.0
Alanine Aminotransferase Increased	27	0.9	16	0
Amylase Increased	24	3.0	18	1.6
Potassium Increased	24	2.4	24	1.8
Potassium Decreased	23	8	5	0
Triacylglycerol Lipase Increased	22	7	14	1.9
Alkaline Phosphatase Increased	21	0.8	15	0.5

Laboratory abnormality percentage is based on the number of patients who had both baseline and at least one post-baseline laboratory measurement for each parameter: KEYTRUDA /Pemetrexed/Platinum chemotherapy (range 109 patients to 241 patients) and Pemetrexed/Platinum chemotherapy (range: 93 patients to 228 patients).
 Graded per NCI CTCAE v4.03

Hodgkin Lymphoma

Laboratory abnormalities (worsened from baseline in \geq 20% of patients), reported in KEYNOTE-204 in patients with Hodgkin Lymphoma are presented in Table 53.

Table 53: Laboratory Abnormalities Increased from Baseline in ≥ 20% of Patients with Hodgkin

Lymphoma Treated with KEYTRUDA.

	KEYTR	UDA	Brentuximab Vedotin		
	200 mg every 3 weeks		1.8 mg/kg every 3 weeks		
Laboratory Test	n=1	48	n=1	.52	
	All Grades	Grades 3-4	All Grades	Grades 3-4	
	%	%	%	%	
Alanine Aminotransferase Increased	31	5	43	2.6	
Aspartate Aminotransferase	38	4.7	38	2.0	
Increased				_	
Calcium Decreased	21	2.0	15	0	
Creatinine Increased	26	3.4	13	2.6	
Glucose Increased	45	4.1	36	2.0	
Hemoglobin Decreased	22	4.1	32	7	
Leukocytes Decreased	30	4.7	43	11	
Lymphocytes Decreased	33	7	32	13	
Neutrophils Decreased	27	8	41	16	
Phosphate Decreased	32	5	18	3.3	
Platelet Decreased	32	9	24	3.9	
Sodium Decreased	24	4.1	20	3.3	

Primary Mediastinal B-cell Lymphoma (PMBCL)

Laboratory abnormalities (worsened from baseline in \geq 20% of patients), reported in KEYNOTE-170 in patients with PMBCL are presented in Table 54.

Table 54: Laboratory Abnormalities Increased from Baseline in ≥ 20% of Patients with PMBCL.

Laboratory Test	200 mg eve	KEYTRUDA 00 mg every 3 weeks n=49
	All Grades	Grades 3-4
	%	%
Glucose Increased	29	2.0
Hemoglobin Decreased	20	0
Leukocytes Decreased	39	8
Lymphocytes Decreased	24	10
Neutrophils Decreased	31	8
Phosphate Decreased	20	8

Urothelial Carcinoma

Laboratory abnormalities (worsened from baseline in ≥ 20% of patients), reported in KEYNOTE-A39 in

patients with urothelial cancer are presented in Table 55.

Table 55: Select Laboratory Abnormalities Occurring in ≥ 15% of Patients with Metastatic Urothelial Cancer Receiving KEYTRUDA with enfortumab vedotin in KEYNOTE-A39

	KEYT	RUDA	Chemo	therapy
	200 mg ev	ery 3 weeks		
	and			
Laboratory Test*		ab Vedotin		
	All Grades [†]	Grades 3-4	All Grades [†]	Grades 3-4
	%	%	%	%
Chemistry			•	
Hypercalcemia	21	1.2	14	0.2
Hyperglycemia	66	14	54	4.7
Hyperkalemia	24	1.4	36	4.0
Hypoalbuminemia	39	1.8	35	0.5
Hypocalcemia	18	0.2	19	1.2
Hypokalemia	26	5	16	3.1
Hyponatremia	46	13	47	13
Hypophosphatemia	44	9	36	9
Increased Alanine Aminotransferase	59	5	49	3.3
Increased Aspartate Aminotransferase	75	4.6	39	3.3
Increased Creatinine	71	3.2	68	2.6
Hematology				
Anemia	53	7	89	33
Lymphopenia	58	15	59	17
Neutropenia	30	9	80	50
Platelets Decreased	20	2.3	86	33

^{*} Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available (range: 407 to 439 patients).

Laboratory abnormalities (worsened from baseline in \geq 10% of patients), reported in KEYNOTE-052 in patients with urothelial carcinoma not eligible for cisplatin –containing chemotherapy are presented in Table 56.

Table 56: Laboratory Abnormalities Increased from Baseline in ≥ 10% of Patients with Urothelial Carcinoma Not Fligible to Cisplatin-Containing Chemotherapy (KEYNOTE-052).

Laboratory Test	KEYTRUDA 200 mg every 3 weeks n=370				
	All Grades %	Grades 3-4 %			
Chemistry					
Alanine Aminotransferase Increased	28	3.2			
Albumin Decreased	43	3.0			
Alkaline Phosphatase Increased	34	7			

[†] Graded per NCI CTCAE v4.03

Laboratory Test	KEYTRUDA 200 mg every 3 weeks n=370		
	All Grades	Grades 3-4	
	%	%	
Aspartate Aminotransferase Increased	30	4.9	
Calcium Decreased	28	2.2	
Calcium Increased	13	2.4	
Creatinine Increased	44	4.6	
Glucose Decreased	10	1.4	
Glucose Increased	54	8	
Phosphate Decreased	21	5	
Potassium Decreased	11	1.1	
Potassium Increased	28	4.9	
Sodium Decreased	41	14	
Hematology			
Hemoglobin Decreased	54	10	
Leukocytes Decreased	11	1.1	
Lymphocytes Decreased	43	15	
Neutrophil Decreased	11	4.9	
Platelet Decreased	15	1.6	

Laboratory abnormalities (worsened from baseline in ≥ 10% of patients), reported in KEYNOTE-045 in patients with urothelial carcinoma are presented in Table 57.

Table 57: 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).

	KEYTRUDA 200 mg every 3 weeks		Chemotherapy	
Laboratory Test	n=	n=266 All Grades Grades 3-4		255
	All Grades			Grades 3-4
	%	%	%	%
Chemistry				
Alkaline Phosphatase Increased	35	7	32	4.7
Aspartate Aminotransferase Increased	26	3.8	20	2.4
Creatinine Increased	35	4.1	27	3.1

The most frequently (\geq 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-057 in patients with high-risk NMIBC are presented in Table 58.

Table 58: Laboratory Abnormalities Increased from Baseline in ≥ 10% of Patients with High Risk NMIBC (KEYNOTE-057).

	200 mg evei				
	200 mg every 3 weeks n=148				
Laboratory Test					
	All Grades	Grades 3-4			
	%	%			
Chemistry					
Alanine Aminotransferase Increased	25	2.7			
Albumin Decreased	24	1.4			
Aspartate Aminotransferase Increased	20	2.7			
Bilirubin Increased	14	0.7			
Calcium Decreased	22	0.7			
Creatinine Increased	20	0.7			
Glucose Increased	59	7			
Phosphate Decreased	24	6			
Potassium Decreased	10	1.4			
Potassium Increased	22	1.4			
Sodium Decreased	24	7			
Hematology					
Hemoglobin Decreased	34	1.4			
Leukocytes Decreased	10	0.7			
Lymphocytes Decreased	26	1.4			
Platelet Decreased	12	0.7			

Colorectal Cancer

Laboratory abnormalities (worsened from baseline in \geq 10% of patients), reported in KEYNOTE-177 in patients with MSI-H or dMMR colorectal carcinoma are presented in Table 59.

Table 59: Laboratory Abnormalities Worsened from Baseline in \geq 10% of Patients with MSI-H or dMMR Colorectal Carcinoma treated with KEYTRUDA and at a Higher Incidence than in the Chemotherapy Arm (Between Arm Difference of \geq 5% [All Grades] or \geq 2% [Grades 3-4]) (KEYNOTE-177).

		KEYTRUDA 200 mg every 3 weeks n=153		therapy
Laboratory Test	n=			143
	All Grades Grade		All Grades	Grades 3-4
	%	%	%	%
Chemistry				
Blood Bilirubin Increased	21	3.3	10	3.5
Glucose Increased	48	9	52	4.9
Potassium Increased	25	6	19	1.4

Sodium Decreased	33	12	33	10
------------------	----	----	----	----

Microsatellite Instability-High-Cancer (MSI-H) or Mismatch Repair Deficient (dMMR) Cancer 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 60.

Table 60: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients Receiving KEYTRUDA in KEYNOTE-158 and KEYNOTE-164.

I ala austaus T aut*	KEYTRUDA 200 mg every 3 weeks			
Laboratory Test*	All Grades % [†]	Grades 3-4 % [†]		
Chemistry	1	1		
Alanine Aminotransferase Increased	33	6		
Albumin Decreased	36	3.0		
Alkaline Phosphatase Increased	38	8		
Aspartate Aminotransferase Increased	38	7		
Calcium Decreased	27	1.5		
Creatinine Increased	22	1.3		
Glucose Increased	49	7		
Phosphate Decreased	24	10		
Potassium Increased	23	2.4		
Sodium Decreased	28	8		
Hematology				
Hemoglobin Decreased	47	9		
Leukocytes Decreased	21	2.2		
Lymphocytes Decreased	42	15		

^{*} Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available (range: 404 to 464 patients)

Endometrial Carcinoma

Laboratory abnormalities (worsened from baseline in ≥ 20% of patients), reported in KEYNOTE-868 in endometrial cancer patients receiving KEYTRUDA with chemotherapy are presented in Table 61.

Table 61: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients Receiving

[†] Graded per NCI CTCAE v4.03

KEYTRUDA with Chemotherapy in KEYNOTE-868

		KEYTRUDA and Chemotherapy 200 mg every 3 weeks n=382 All Grades %† Grades 3-4 %†		cebo nd		
	_			therapy		
Laboratory Test*				377		
	All Grades % [†]			Grades 3-4 % [†]		
Chemistry						
Alanine Aminotransferase Increased	85 (23.7)	3 (0.8)	52 (14.5)	1 (0.3)		
Hematology						
Hemoglobin Decreased	275 (76.8)	49 (13.7)	232 (64.4)	28 (7.8)		
Leucocytes Decreased	195 (54.3)	26 (7.2)	182 (50.6)	25 (6.9)		
Lymphocytes Decreased	144 (40.7)	44 (12.4)	113 (31.8)	32 (9.0)		
Neutrophils Decreased	125 (35.1)	42 (11.8)	140 (39.2)	37 (10.4)		
Platelets Decreased	155 (43.2)	10 (2.8)	121 (33.6)	8 (2.2)		

^{*} Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available (range: 354 to 359 patients)

Endometrial Carcinoma (Not MSI-H or not dMMR)

Table 62 summarizes laboratory abnormalities in patients on KEYTRUDA in combination with lenvatinib.

Table 62 : 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 and Lenvatinib 20 mg				
Laboratory Abnormality ^a					
	All Grades	Grade 3-4			
	% ^b	% ^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			
ncreased Alkaline Phosphatase	32	1			
Hypokalemia	27	5			
ncreased Amylase	19	6			
Hypocalcemia	14	3			

[†] Graded per NCI CTCAE version 5.0

Laboratory Abnormality ^a	KEYTRUDA 200 mg and Lenvatinib 20 mg			
	All Grades % ^b	Grade 3-4 % ^b		
Hypermagnesemia	4	3		
Hematology				
Thrombocytopenia	48	0		
Leukopenia	38	2		
Lymphopenia	36	7		
Anemia	35	1		
ncreased INR	21	3		
Neutropenia	12	3		

^a With at least 1 grade increase from baseline

Laboratory abnormalities (worsened from baseline in \geq 20% (All Grades) or \geq 3% (Grades 3-4) of patients), reported in KEYNOTE-775 in patients with endometrial carcinoma are presented in Table 63.

Table 63 : Laboratory Abnormalities Worsened from Baseline* Occurring in ≥20% (All Grades) or ≥3% (Grades 3-4) of Patients with Endometrial Carcinoma in KEYNOTE-775

	Endometrial Carcinoma (not MSI-H or dMMR)			
	KEYTRUDA		Doxoru	bicin or
	200 mg eve	ry 3 weeks	Paclitaxel	
+	ar	nd		
Laboratory Test [†]	Lenva	itinib		
	All Grades [‡]	Grades 3-4	All Grades [‡]	Grades 3-4
	%	%	%	%
Chemistry			1	
Hypertriglyceridemia	70	6	45	1.7
Hypoalbuminemia	60	2.7	42	1.6
Increased Aspartate	58	9	23	1.6
Aminotransferase				
Hyperglycemia	58	8	45	4.4
Hypomagnesemia	46	0	27	1.3
Increased Alanine Aminotransferase	55	9	21	1.2
Hypercholesteremia	53	3.2	23	0.7
Hyponatremia	46	15	28	7
Increased Alkaline Phosphatase	43	4.7	18	0.9
Hypocalcemia	40	4.7	21	1.9
Increased Lipase	36	14	13	3.9
Increased Creatinine	35	4.7	18	1.9
Hypokalemia	34	10	24	5
Hypophosphatemia	26	8	17	3.2
Increased Amylase	25	7	8	1

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)

	Endometrial Carcinoma (not MSI-H or dMMR)				
	KEYT	RUDA	Doxorubicin or		
	200 mg eve	ery 3 weeks	Paclitaxel		
+	aı	nd			
Laboratory Test [†]	Lenva	atinib			
	All Grades [‡]	Grades 3-4	All Grades [‡]	Grades 3-4	
	%	%	%	%	
Hyperkalemia	23	2.4	12	1.2	
Increased Creatine Kinase	19	3.7	7	0	
Increased Bilirubin	18	3.6	6	1.6	
Hematology					
Lymphopenia	51	18	66	23	
Thrombocytopenia	50	8	30	4.7	
Anemia	49	8	84	14	
Leukopenia	43	3.5	83	43	
Neutropenia	34	8	80	60	

^{*} With at least one grade increase from baseline

Renal Cell Carcinoma

Laboratory abnormalities (worsened from baseline in \geq 10% of patients), reported in KEYNOTE-426 in patients with renal cell carcinoma are presented in Table 64.

Table 64: Laboratory Abnormalities Worsened from Baseline in \geq 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 \geq 5% [All Grades] or \geq 2% [Grades 3-4]) (KEYNOTE-426).

Laboratory Test	KEYTRUDA and Axitinib n=429		Sunitinib n=425	
	All Grades	Grades 3-4	All Grades	Grades 3-4
	%	%	%	%
Activated Partial Thromboplastin Time Increased	19	0.9	12	0
Alanine Aminotransferase Increased	59	20	44	5
Aspartate Aminotransferase Increased	56	13	55	4.5
Calcium Increased	26	0.7	15	1.9
Glucose Decreased	12	0.2	7	0.2
Glucose Increased	61	9	52	3.1
Lymphocytes Decreased	33	11	47	8
Potassium Decreased	17	3.5	12	2.4
Potassium Increased	34	6	22	1.6
Sodium Decreased	35	8	29	8

[†] Laboratory abnormality percentage is based on the number of patients who had both baseline and at least one post-baseline laboratory measurement for each parameter: KEYTRUDA /lenvatinib (range: 263 to 340 patients) and doxorubicin or paclitaxel (range: 240 to 322 patients).

[‡] Graded per NCI CTCAE v4.03

Laboratory abnormalities (worsened from baseline in ≥ 20% (All Grades) or ≥2% (Grade 3-4) of patients), reported in KEYNOTE-581 in patients with renal cell carcinoma are presented in Table 65.

Table 65: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% (All Grades) or ≥2% (Grade 3-4) of Patients Receiving KEYTRUDA with Lenvatinib in KEYNOTE-581

Laboratory Test*	200 mg eve	RUDA ery 3 weeks and ivatinib	Sunitinib 50 mg	
	All Grades % [†]	Grade 3-4 % [†]	All Grades % [†]	Grade 3-4 % [†]
Chemistry				
Hypertriglyceridemia	80	15	71	15
Hypercholesterolemia	64	5	43	1
Lipase Increased	61	34	59	28
Creatinine Increased	61	5	61	2
Amylase Increased	59	17	41	9
Aspartate Aminotransferase Increased	58	7	57	3
Hyperglycemia	55	7	48	3
Alanine Aminotransferase Increased	52	7	49	4
Hyperkalemia	44	9	28	6
Hypoglycemia	44	2	27	1
Hyponatremia	41	12	28	9
Albumin Decreased	34	0.3	22	0
Alkaline Phosphatase Increased	32	4	32	1
Hypocalcemia	30	2	22	1
Hypophosphatemia	29	7	50	8
Hypomagnesemia	25	2	15	3
Creatine Phosphokinase Increased	24	6	36	5
Hypermagnesemia	23	2	22	3
Hypercalcemia	21	1	11	1
Hypokalemia	13	4	7	1
Hematology				
Lymphopenia	54	9	66	15
Thrombocytopenia	39	2	73	13
Anemia	38	3	66	8
Leukopenia	34	1	77	8
Neutropenia	31	4	72	16
INR Increased	17	3	9	1

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks and Lenvatinib		Sunitinib 50 mg	
	All Grades	Grade 3-4	All Grades	Grade 3-4
	% [†]	% [†]	% [†]	% [†]

With at least one Grade increase from baseline

Grade 3 and 4 increased ALT or AST was seen in 9% of patients. Grade \geq 2 increased ALT or AST was reported in 64 (18%) patients, of whom 20 (31%) received \geq 40 mg daily oral prednisone equivalent. Recurrence of Grade \geq 2 increased ALT or AST was observed on rechallenge in 10 patients receiving both KEYTRUDA and lenvatinib (n=38) and was not observed on rechallenge with KEYTRUDA alone (n=3).

Adjuvant RCC

Laboratory abnormalities (worsened from baseline in ≥ 10% of patients), reported in KEYNOTE-564 in patients with RCC are presented in Table 66.

Table 66: Laboratory Abnormalities Worsened from Baseline in \geq 10% of Patients Treated with KEYTRUDA and at a Higher Incidence than in Control Arm (Between Arm Difference of \geq 5% [All Grades] or \geq 2% [Grades 3-4]). (KEYNOTE-564).

Laboratory Test	200 mg eve	RUDA ery 3 weeks 488	Placebo n=496		
•	All Grades	Grades 3-4	All Grades	Grades 3-4	
	%	%	%	%	
Hematology					
Hemoglobin Decreased	30	0.4	21	0.4	
Lymphocytes Decreased	17	2.3	10	0.6	
Sodium Decreased	22	3.3	13	1.8	
Chemistry					
Alanine Aminotransferase Increased	19	3.9	11	0.2	
Alkaline Phosphate Increased	14	0.6	6	0	
Aspartate Aminotransferase Increased	15	2.3	7	0.4	
Creatinine Increased	39	1.0	29	0.2	
Glucose Increased	47	8	46	4.4	

HNSCC

Resectable Locally Advanced HNSCC

Laboratory abnormalities (worsened from baseline in \geq 20% of patients), reported in KEYNOTE-689 are presented in Table 67.

Laboratory abnormality percentage is based on the number of patients who had both baseline and at least one post-baseline laboratory measurement for each parameter: KEYTRUDA with lenvatinib (range: 343 to 349 patients) and sunitinib (range: 329 to 335 patients).

Table 67: Laboratory Abnormalities Worsened from Baseline in ≥ 20% of Patients Receiving KEYTRUDA in KEYNOTE-689.

Laboratory Test*	Mond Adjuvan Radiation v	at KEYTRUDA as otherapy/ t KEYTRUDA and with or without platin/ monotherapy	-	diation with or it cisplatin
	All Grades [†]	Grades 3-4	All Grades [†]	Grades 3-4
	%	%	%	%
Hematology				
Lymphopenia	76	50	86	55
Anemia	75	12	74	12
Leukopenia	44	11	52	18
Neutropenia	32	13	35	19
Thrombocytopenia	22	1.7	29	1.9
Chemistry				
Hyperglycemia	57	5.7	47	2.7
Hyponatremia	47	16	36	11
Increased ALT	42	6.2	37	2.0
Hypoalbuminemia	40	1.4	38	1.0
Increased AST	38	4.8	23	2.0
Hypomagnesemia	34	1.2	22	1.3
Hypokalemia	29	6.8	20	7.4
Hyperkalemia	29	3.4	24	2.3
Increased Alkaline Phosphatase	27	2.5	19	0.0
Hypocalcemia	27	2.6	26	3.3
Hypophosphatemia	23	6.1	15	7.0
Increased Creatinine	22	2.0	27	2.9
Hypercalcemia	21	2.0	14	1.3

^{*} Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA + radiation with or without cisplatin (range: 240 to 267 patients); radiation with or without cisplatin (range: 245 to 292 patients).

Metastatic or Unresectable, Recurrent HNSCC

Laboratory abnormalities (worsened from baseline in \geq 10% of patients), reported in KEYNOTE-048 are presented in Table 68.

[†] Graded per NCI CTCAE v4.0

Table 68: Laboratory Abnormalities Worsened from Baseline in ≥ 10% of Patients 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.

		KEYTRUDA 200 mg every 3 weeks		KEYTRUDA 200 mg every 3 weeks		rimab
	200 mg every 3 weeks		and		_	nd
_				Platinum		num
Laboratory Test				nd	_	nd
			F	FU		U
	n=3	n=300		n=276		287
	All Grades	Grades 3-4	All Grades Grades 3-4		All Grades	Grades 3-4
	%	%	%	%	%	%
Chemistry						
Albumin Decreased	43	3.3	43	3.6	48	1.0
Calcium Increased	21	4.7	16	4.0	12	2.4
Creatinine Increased	17	1.0	34 2.2		27	2.1
Hematology						
Hemoglobin Decreased	51	7	86	28	77	19

Gastric or Gastroesophageal junction (GEJ) Adenocarcinoma

Laboratory abnormalities (worsened from baseline in \geq 20% of patients), reported in KEYNOTE-811 are presented in Table 69.

Table 69: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients Receiving KEYTRUDA in KEYNOTE-811.

	KEYTI	RUDA	Plac	ebo
	200 mg eve	ry 3 weeks		
	ar	nd	and	
	Trastu	zumab	Trastu	zumab
Laboratory Test [¥]	ar	nd	ar	ıd
Laboratory rest	Fluoropy	rimidine	Fluoropy	rimidine
	ar	nd	and	
	Platinum Chemotherapy		Platinum Ch	emotherapy
	All Grades [†]	Grades 3-4	All Grades [†]	Grades 3-4
	% %		%	%
Hematology				
Anemia	71	17	66	14
Thrombocytopenia	65	14	63	12
Neutropenia	64	20	59	18
Leukopenia	59	7	54	7
Lymphopenia	58	19	51	16
Chemistry				
Hypoalbuminemia	56	2.9	52	3.9
Hypocalcemia	55	3.5	45	2.4
Increased AST	52	4.9	51	3.0
Hyperglycemia	51	7	56	6.0
Hypokalemia	40	13	35	12

Increased ALT	40	3.5	36	1.8
Increased Alkaline Phosphatase	39	2.9	39	4.2
Hypophosphatemia	33	10	34	10
Hyponatremia	32	8	32	10
Bilirubin Increased	31	4.1	25	2.7
Hypomagnesemia	29	2.3	29	1.2
Increased Creatinine	26	3.2	17	2.1

Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA /Trastuzumab/FP or CAPOX (range: 340 to 347 patients) and placebo/ Trastuzumab/FP or CAPOX (range: 333 to 340 patients)

Laboratory abnormalities (worsened from baseline in ≥ 20% of patients), reported in KEYNOTE-859 in patients with locally advanced unresectable or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma treated with KEYTRUDA in combination with fluoropyrimidine-and platinum-containing chemotherapy, are presented in Table 70.

Table 70: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients Receiving KEYTRUDA in KEYNOTE-859

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks and FP or CAPOX		Placebo and FP or CAPOX	
	All Grades [†]	Grades 3-4	All Grades [†]	Grades 3-4
	%	%	%	%
Hematology	1	1		1
Anemia	65	15	69	13
Thrombocytopenia	64	12	62	10
Neutropenia	62	24	57	20
Leukopenia	59	7	56	6
Lymphopenia	57	20	51	16
Chemistry	•			
Increased AST	57	4.7	48	3.6
Hypoalbuminemia	55	4.1	52	2.9
Hyperglycemia	53	6	52	4.6
Hypocalcemia	49	3.6	45	3.3
Increased Alkaline Phosphatase	48	6	41	5
Hyponatremia	40	13	40	12
Increased ALT	40	4.2	29	2.9
Hypokalemia	35	10	27	9
Bilirubin Increased	32	5	30	5
Hypophosphatemia	30	10	27	8
Hypomagnesemia	29	0.3	22	0.7
Increased Creatinine	21	3.5	18	1.7
Hyperkalemia	20	3.7	18	2.9

[†] Graded per NCI CTCAE v4.03

Laboratory Test*	KEYTRUDA 200 mg every 3 weeks and FP or CAPOX		Placebo and FP or CAPOX	
	All Grades [†]	Grades 3-4	All Grades [†]	Grades 3-4
	%	%	%	%
Increased INR	20	1.4	22	0

^{*} Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA /FP or CAPOX (range: 210 to 766 patients) and placebo/ FP or CAPOX (range: 190 to 762 patients)

Esophageal Cancer

Laboratory abnormalities (worsened from baseline in ≥ 10% of patients), reported in KEYNOTE-590 in patients with esophageal carcinoma and gastroesophageal junction adenocarcinoma treated with KEYTRUDA in combination with cisplatin and FU, are presented in Table 71.

Table 71: Laboratory Abnormalities Worsened from Baseline in ≥ 10% of Esophageal Cancer Patients Receiving KEYTRUDA in Combination with Cisplatin and FU and at a Higher Incidence than in the Placebo, Cisplatin, and FU Chemotherapy Arm (Between Arm Difference of ≥ 5% [All Grades] or ≥ 2% [Grades 3-4]) (KEYNOTE-590).

	KEYT	RUDA	Pla	cebo
	200 mg eve	ery 3 weeks		
	aı	nd	а	nd
	Cisp	latin	Cisp	olatin
Laboratory Test	ar	nd	а	nd
	F	U	F	·υ
	n=3	370	n=	370
	All Grades*	Grades 3-4	All Grades*	Grades 3-4
	%	%	%	%
Hematology				
Neutrophils Decreased	76	43	70	39
Leukocytes Decreased	71	21	70	16
Lymphocytes Decreased	56	22	51	18
Chemistry				
Calcium Decreased	43	3.8	36	1.9
Phosphate Decreased	36	9	29	10
Alanine Aminotransferase	23	3.5	17	1.6
Increased				
* Graded per NCI CTCAE v4.03		•		

Triple Negative Breast Cancer (TNBC)

Table 72: Laboratory Abnormalities Worsened from Baseline Occurring in ≥ 20% of Patients Receiving KEYTRUDA with Chemotherapy in KEYNOTE-355.

[†] Graded per NCI CTCAE v4.03

Laboratory Test*	KEYTRUDA 200 mg every 3 week and Chemotherapy		Placebo every 3 weeks and Chemotherapy		
	All Grades [†]	Grades 3-4	All Grades [†]	Grades 3-4	
	%	%	%	%	
Hematology	<u>. </u>				
Anemia	90	20	85	19	
Leukopenia	85	39	86	39	
Neutropenia	78	50	79	53	
Lymphopenia	73	28	71	19	
Thrombocytopenia	54	19	53	21	
Chemistry					
Increased ALT	60	11	58	8	
Increased AST	57	9	55	6	
Hyperglycemia	52	4.4	51	2.2	
Hypoalbuminemia	36	2.0	32	2.2	
Increased Alkaline	35	3.9	39	2.2	
Phosphatase					
Hypocalcemia	29	3.3	27	1.8	
Hyponatremia	28	5	26	6	
Hypophosphatemia	21	7	18	4.8	
Hypokalemia	20	4.4	18	4.0	

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

Early-stage Triple-Negative Breast Cancer

Laboratory abnormalities (worsened from baseline in \geq 10% of patients), reported in KEYNOTE-522 in patients with TNBC are presented in Table 73.

Table 73: Laboratory Abnormalities Worsened from Baseline in \geq 10% of patients with TNBC Treated with KEYTRUDA in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery (Between Arm Difference of \geq 5% [All Grades] or \geq 2% [Grades 3-4]) (KEYNOTE-522).

Laboratory Test	Chemo KEYTRUDA W	200 mg every 3 veeks and otherapy*/ 200 mg every 3 veeks =783	Chemo	acebo and otherapy*/ acebo =389
	All Grades % [†]	Grades 3-4 %	All Grades %	Grades 3-4 %
Hematology			I	ı

[†] Graded per NCI CTCAE v4.03

Laboratory Test	KEYTRUDA 200 mg every 3 weeks and Chemotherapy*/ KEYTRUDA 200 mg every 3 weeks n=783		Chemo Pl	acebo and otherapy*/ acebo n=389
	All Grades % [†]	Grades 3-4 %	All Grades %	Grades 3-4 %
Hemoglobin Decreased	96	21	96	19
Leukocytes Decreased	92	40	92	32
Lymphocytes Decreased	78	28	74	22
Platelet Decreased	57	10	56	8
Chemistry	•			
Alanine Aminotransferase Increased	69	9	67	3.9
Aspartate Aminotransferase Increased	64	6	56	1.5
Sodium Decreased	35	9	25	4.6
Potassium Decreased	31	6	22	2.8
* Chemotherapy: carboplatin and paclitaxel foll † Graded per NCI CTCAE v4.0	owed by doxorubici	n or epirubicin and cyclo	phosphamide	

Cervical Cancer

Laboratory abnormalities (worsened from baseline in \geq 20% of patients), reported in KEYNOTE-A18 are presented in Table 74.

Table 74: Laboratory Abnormalities Worsened from Baseline Occurring in ≥ 20% of Patients Receiving KEYTRUDA in KEYNOTE-A18

Laboratory Test*	200 mg eve and 400 n	KEYTRUDA 200 mg every 3 weeks and 400 mg every 6 weeks with CRT		cebo ı CRT
	All Grades [†]	Grades 3-4	All Grades [†]	Grades 3-4
	%	%	%	%
Hematology				
Lymphopenia	99	97	99	94
Leukopenia	96	51	95	51
Anemia	86	26	84	25
Neutropenia	79	35	78	36
Thrombocytopenia	65	8	64	7
Chemistry				
Hypomagnesemia	61	3.5	64	3.3
Increased ALT	54	3.8	50	1.5
Hyponatremia	52	4.2	50	3.4
Increased AST	52	2.7	43	1.5

Hypokalemia	44	13	40	12
Hypocalcemia	41	4.6	41	5
Increased Creatinine	40	4.9	41	4.4
Hypoalbuminemia	34	1.7	34	1.5
Increased Alkaline Phosphatase	34	0.6	32	0.2

^{*}Laboratory abnormality percentage is based on the number of patients who had both baseline and at least one post-baseline laboratory measurement for each parameter: KEYTRUDA + chemoradiotherapy (range: 512 to 527 patients) and placebo + chemoradiotherapy (range: 520 to 527 patients)

†Graded per NCI CTCAE v5.0

Laboratory abnormalities (worsened from baseline in \geq 20% of patients), reported in KEYNOTE-826 are presented in Table 75.

Table 75: Laboratory Abnormalities Worsened from Baseline Occurring in ≥ 20% of Patients Receiving KEYTRUDA in KEYNOTE-826

	KEY	TRUDA	Placebo		
	200 mg every 3 weeks				
		and		and	
Laboratory Test*		therapy†		notherapy†	
Laboratory rest		ut bevacizumab		nout bevacizumab	
	All Grades [‡]	Grades 3-4	All	Grades 3-4	
	%	%	Grades [‡]	%	
			%		
Hematology					
Anemia	80	35	77	33	
Leukopenia	76	27	69	19	
Neutropenia	73	43	62	32	
Lymphopenia	64	35	59	35	
Thrombocytopenia	57	19	53	15	
Chemistry					
Hyperglycemia	51	4.7	46	2.3	
Hypoalbuminemia	46	1.4	37	5	
Hyponatremia	39	14	38	11	
Increased ALT	40	7	38	6	
Increased AST	40	6	36	3.0	
Increased Alkaline Phosphatase	38	3.4	40	2.3	
Hypocalcemia	37	4.1	31	5	
Increased Creatinine	34	5	32	6	
Hypokalemia	29	7	26	7	
Hyperkalemia	23	3.7	27	4.7	
Hypercalcemia	21	1.0	20	1.3	

^{*} Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA plus chemotherapy (range: 296 to 301 patients) and placebo plus chemotherapy (range: 299 to 302 patients)

Biliary Tract Carcinoma

[†] Chemotherapy (paclitaxel and cisplatin or paclitaxel and carboplatin)

[#] Graded per NCI CTCAE v4.0

There was a difference of ≥5% incidence in laboratory abnormalities between patients treated with KEYTRUDA plus chemotherapy versus placebo plus chemotherapy for decreased lymphocytes (69% vs 61%). There were no clinically meaningful differences in incidence of Grade 3-4 toxicity between arms.

Table 76: Laboratory Abnormalities Worsened from Baseline Occurring in ≥20% of Patients with BTC Receiving KEYTRUDA in KEYNOTE-966

		KEYTRUDA and		ebo nd
Laboratory Test*	Chemo	therapy	Chemotherapy	
	All Grades†	Grades 3-4	All Grades†	Grades 3-4
	%	%	%	%
Chemistry				
Increased AST	57	6	58	9
Increased ALT	55	5	63	7
Hyponatremia	55	4.2	56	4.9
Hypoalbuminemia	51	3.2	51	6
Hypomagnesemia	49	2.7	50	2.7
Hypocalcemia	47	4.6	43	4.2
Increased Creatinine	41	5	39	7
Hyperkalemia	36	4.0	35	6
Increased Alkaline	35	3.5	36	4.3
Phosphatase				
Increased Bilirubin	33	12	36	15
Hypokalemia	27	7	26	9
Hematology				
Anemia	91	32	89	32
Leukopenia	81	32	79	27
Neutropenia	77	55	77	52
Decreased Lymphocytes	69	32	61	24
Decreased Platelets	68	24	69	25

Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: KEYTRUDA (range: 517 to 525 patients) and placebo (range: 522 to 532 patients).

8.5 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

Endocrine disorders: hypoparathyroidism **Nervous system disorders:** optic neuritis

9. Drug Interactions

[†] Graded per NCI CTCAE v5.0

9.2 Drug Interaction 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.

9.3 Drug-Behaviour Interactions

The interaction of KEYTRUDA with individual behavioural risks (e.g. cigarette smoking, cannabis use, and/or alcohol consumption) has not been studied.

9.4 Drug-Drug Interactions

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 <u>7 Warnings And Precautions</u>). 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.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10. 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 KEYNOTE-555, 44 patients with advanced melanoma received KEYTRUDA monotherapy (See 14 Clinical Trials, Alternate Dosing Regimen for Adults (KEYNOTE-555)) at a dose of 400 mg every 6 weeks. Based on observed preliminary pharmacokinetic and clinical data from an interim analysis of KEYNOTE-555, no clinically significant differences in efficacy and safety are expected between KEYTRUDA doses of 200 mg or 2 mg/kg every 3 weeks or 400 mg every 6 weeks.

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

10.3 Pharmacokinetics

The pharmacokinetics (PK) 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 (Q3W). There are neither statistically nor clinically meaningful differences in the PK parameters in the model of pembrolizumab across indications. The pharmacokinetics of pembrolizumab in patients for the dosage of 200 mg Q3W is described below.

Table 77: Summary of Pembrolizumab Pharmacokinetic Parameters.

Para	meters	Mean*	%CV [†]
C (mag/ml)	First dose ¹	59.1	37%
C _{max} (mcg/mL)	Steady state ²	93.3	41%
T _{max} [‡]		0.02	N/A
Half life (days)	First dose	17	27%
Half-life (days)	Steady state	22	32%
AUC	First dose ³	490	29%
(mcg*day/mL)	Steady state ⁴	1060	46%
	Vc	3.2	23%
Vdss (L) §	Vp	2.7	19%
	Vss	6.0	20%
CL (ml /day)	First dose	252	37%
CL (mL/day)	Steady state	195	40%
Time to steady st	ate (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%.

Absorption:

KEYTRUDA is dosed via the IV route and therefore is immediately and completely bioavailable. T_{max} is the end of infusion after IV administration, at 0.02 day or 30 min.

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%:

^{* %}CV: coefficient of variation

 $^{^{\}ddagger}$ T_{max} for pembrolizumab occurs at the end of infusion, at 0.02 day or 30 min

[§] Volume of distribution at steady state

¹30 min post-dose on Day 1

² 30 min post-dose on Day 169

³ Cycle 1; week 1 to week 3

⁴ Cycle 10; week 27 to week 30

37%]); this decrease in clearance with time is not considered clinically important. The geometric mean value (CV%) for the terminal half-life (t%) 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 Time-dependent Pharmacokinetics (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.

- Age: Population PK analysis suggested no clinically important effect on the clearance parameter
 of pembrolizumab based on age (15 to 94 years). Also 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.
- **Sex:** Population PK analysis suggested no clinically important effect on the clearance parameter of pembrolizumab based on gender.
- **Ethnic Origin:** Population PK analysis suggested no clinically important effect on the clearance parameter of pembrolizumab based on race.
- Hepatic Insufficiency: The effect of hepatic impairment on the clearance parameter in the pembrolizumab population pharmacokinetic model was evaluated in patients with Hepatocellular Carcinoma (HCC) and non-HCC (i.e., melanoma and NSCLC) with mild and moderate hepatic impairment (total bilirubin (TB) 1.0 to 1.5 x ULN or AST > ULN and TB >1.5 to 3 x ULN and any AST, respectively, as defined using the National Cancer Institute criteria of hepatic dysfunction) compared to patients with normal hepatic function (TB and AST ≤ ULN). No clinically important differences in the clearance parameter in the pembrolizumab population pharmacokinetic model were found between patients with mild or moderate hepatic impairment and normal hepatic function. KEYTRUDA has been only studied in a limited number of patients with moderate hepatic impairment (N=20). KEYTRUDA has not been studied in patients with severe (TB > 3 x ULN and any AST) hepatic impairment (See 7 Warnings And Precautions, and 4 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 m²) or moderate (eGFR < 60 and ≥ 30 mL/min/1.73 m²) renal impairment compared to patients with normal (eGFR ≥ 90 mL/min/1.73 m²) 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 m²) renal impairment (See 7 Warnings And

Precautions and 4 Dosage And Administration).

 Body Weight: Population PK analysis suggested that 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.

10.4 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 antipembrolizumab 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.

11. Storage, Stability And Disposal

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 dilution of the medicinal product, See 4 Dosage And Administration.

12. Special Handling Instructions

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

Part 2: Scientific Information

13. Pharmaceutical Information

Drug Substance

Non-proprietary name of drug substance: pembrolizumab

Chemical name: humanized X PD-1 mAb (H409A11) IgG4

Molecular formula and molecular mass: the intact protein has a molecular formula of C6504H10004N1716O2036S46. The observed molecular weight of the most abundant form of the intact antibody is 148.9 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: 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.

Pharmaceutical standard: professed.

Product Characteristics:

KEYTRUDA is an IgG4 monoclonal antibody subtype and is produced in Chinese hamster ovary cells by recombinant DNA technology.

Viral Inactivation:

Not applicable

14. Clinical Trials

14.1 Clinical Trials by Indication

Melanoma

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

The efficacy of KEYTRUDA was 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 78: Baseline Characteristics in KEYNOTE-006.

	KEYTRUDA	KEYTRUDA	Ipilimumab	
	10 mg/kg every	10 mg/kg every		
	3 weeks	2 weeks		
	n=277	n=279	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 \geq 6 months. No patients in either arm received treatment for more than one year.

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 79 summarizes key efficacy measures, and the Kaplan-Meier curves for OS and PFS are shown in Figure 1 and Figure 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 79: Response to KEYTRUDA 10 mg/kg every 2 or 3 weeks in Patients with Ipilimumab Naïve

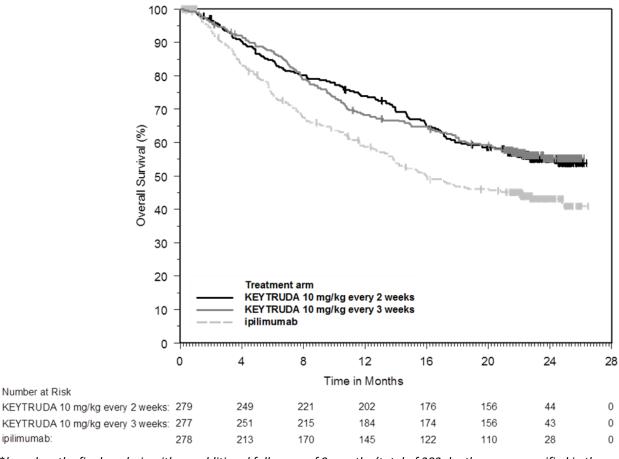
Advanced Melanoma in KEYNOTE-006 (Intent-to-Treat Analysis).

Endpoint	KEYTRUDA 10 mg/kg every 3 weeks	KEYTRUDA 10 mg/kg every 2 weeks	Ipilimumab
	n=277	n=279	n=278
Primary Efficacy Outcome M	easure 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 M	easure 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 [‡]	<0.0001	<0.0001	
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 Re	sponse by IRO*	

Endpoint	KEYTRUDA 10 mg/kg every 3 weeks n=277	KEYTRUDA 10 mg/kg every 2 weeks n=279	Ipilimumab n=278	
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	8.3	Not reached	
iviedian in months (range)	(1.4+, 8.1+)	(1.4+, 8.3)	(1.1+, 7.9+)	

^{*}IRO = Independent radiology plus oncologist review using RECIST 1.1

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



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

[†]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

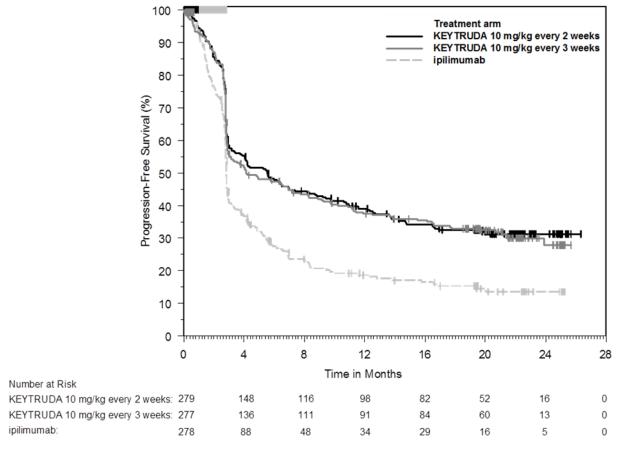


Figure 2: Kaplan-Meier Curve for Progression-Free Survival (Based on IRO) by Treatment Arm in KEYNOTE-006 (Intent to Treat Population) *

Sub-population analysis by PD-L1 status

In a subgroup analysis of KEYNOTE-006, the association between PD-L1 expression status using predefined 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)

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

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

The efficacy of KEYTRUDA was 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/m² intravenously every 3 weeks (26%); temozolomide 200 mg/m² orally once daily for 5 days every 28 days (25%); carboplatin AUC 6 intravenously plus paclitaxel 225 mg/m² intravenously every 3 weeks for four cycles then carboplatin AUC of 5 plus paclitaxel 175 mg/m² every 3 weeks (25%); paclitaxel 175 mg/m² 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 80: Baseline Characteristics in KEYNOTE-002.

	KEYTRUDA	KEYTRUDA	Chemotherapy*
	2 mg/kg every	10 mg/kg every	
	3 weeks	3 weeks	
	n=180	n=181	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	<u> </u>		
Normal	56%	59%	61%
Elevated	43%	40%	39%
BRAF status	<u>.</u>		
wild type	76%	78%	77%
V600 mutant	24%	22%	24%
* Chemotherapy: dacarbazine,	temozolomide, carboplatin pl	us 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 \geq 6 months and in 22% of patients exposed for \geq 12 months. In the KEYTRUDA 10 mg/kg arm, 41% of patients were exposed to KEYTRUDA for \geq 6 months and 28% of patients were exposed to KEYTRUDA for \geq 12 months.

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 81 summarizes key efficacy measures in patients previously treated with ipilimumab. 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 81: 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

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.

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

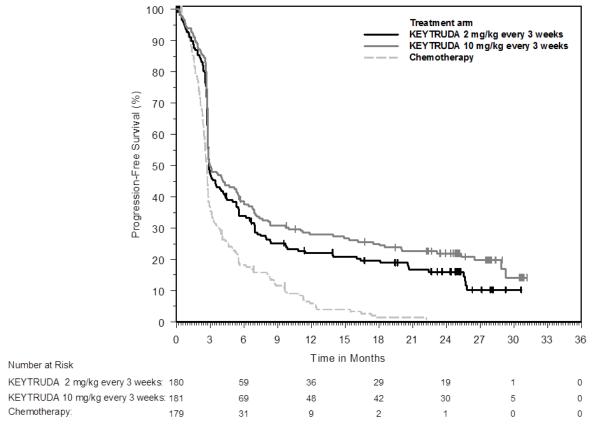
[‡]Based on stratified Log rank test

[§]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

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



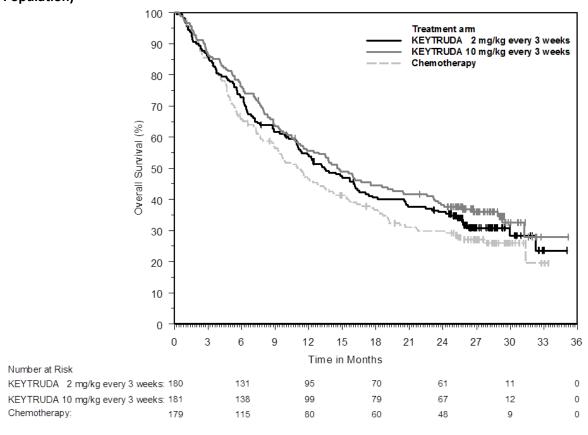


Figure 4: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-002 (Intent to Treat Population)

Adjuvant Melanoma

<u>KEYNOTE-716: Placebo-controlled trial for the adjuvant treatment of patients with completely resected</u> Stage IIB or IIC melanoma

The efficacy of KEYTRUDA was investigated in KEYNOTE-716, a multicenter, randomized, double-blind, placebo-controlled trial in patients with completely resected stage IIB or IIC melanoma. A total of 976 patients were randomized (1:1) to receive KEYTRUDA 200 mg or the pediatric (≥12 years old) dose of KEYTRUDA 2 mg/kg intravenously (up to a maximum of 200 mg) every three weeks (n=487) or placebo (n=489) for up to one year, until disease recurrence, or until unacceptable toxicity. Randomization was stratified by American Joint Committee on Cancer 8th edition (AJCC) T stage (T3b, T4a, and T4b). Patients must not have been previously treated for melanoma beyond complete surgical resection for their melanoma prior to study entry. Patients with active autoimmune disease or a medical condition that required immunosuppression or mucosal or ocular melanoma were ineligible. Patients underwent imaging every 6 months for 1 year from randomization, every 6 months from years 2 to 4, and then once in year 5 from randomization or until recurrence, whichever came first.

Among the 976 patients, the baseline characteristics were: median age of 61 years (range: 16 to 87; 2 adolescent patients [one per treatment arm, 16 and 17 years of age]), 39% age 65 or older; 60% male; and 93% ECOG PS of 0 and 7% ECOG PS of 1. Sixty-four percent had stage IIB and 35% had stage IIC.

The primary efficacy outcome measure was investigator-assessed recurrence free survival (RFS) in the whole population, where RFS was defined as the time between the date of randomization and the date

of first recurrence (local, regional, or distant metastasis) or death, whichever occurred first. New primary melanomas were not included in the definition of RFS. The secondary outcome measures were distant metastasis-free survival (DMFS) and overall survival (OS) in the whole population. OS was not assessed at the time of these analyses.

The trial demonstrated a statistically significant improvement in RFS at the first pre-specified interim analysis with a median follow-up of 14.3 months and, for DMFS at the third pre-specified interim analysis with a median follow up of 26.9 months, as summarized in Table 82.

Table 82: Efficacy Results in KEYNOTE-716

Endpoint	KEYTRUDA	Placebo	
	200 mg every 3 weeks		
	n=487	n=489	
RFS			
Number (%) of patients with event	54 (11%)	82 (17%)	
Median in months (95% CI)	NR (22.6, NR)	NR (NR, NR)	
Hazard ratio* (95% CI)	0.65 (0.46, 0.92)	
p-Value (stratified log-rank) †	0.0	00658‡	
DMFS			
Number (%) of patients with event	63 (13%)	95 (19%)	
Median in months (95% CI)	NR (49.6, NR)	NR (NR, NR)	
Hazard ratio [*] (95% CI)	0.64 (0.47, 0.88)		
p-Value (stratified log-rank)	0.00292 ^ξ		

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

[†] One-sided p-value based on log-rank test stratified by melanoma T Stage (T3b vs. T4a vs. T4b)

[‡] p-Value is compared with 0.0101 of the allocated alpha for this interim analysis.

ξ p-Value is compared with 0.0128 of the allocated alpha for this interim analysis.

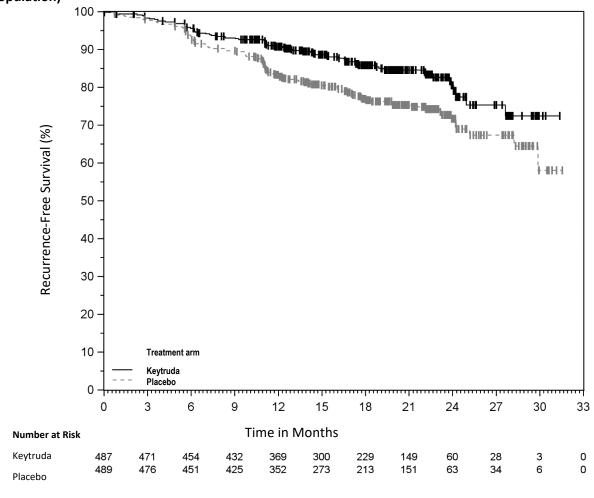


Figure 5: Kaplan-Meier Curve for Recurrence-Free Survival in KEYNOTE-716 (Intent to Treat Population)

An updated pre-specified final RFS analysis was performed with a median follow-up time of 20.5 months (range: 4.6 to 32.7 months). At the time of this updated RFS analysis, the hazard ratio was 0.61 (95% CI: 0.45, 0.82) (Figure 5). At final analysis for RFS and DMFS with a median follow-up time of 20.5 months and 38.5 months, respectively, the RFS and DMFS results remained consistent with the interim analysis.

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

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 \geq 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 83: Baseline Characteristics in KEYNOTE-054.

	KEYTRUDA	Placebo
	200 mg every 3 weeks	
	n=514	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).

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 secondary outcome measures were distant metastasis-free survival (DMFS) and OS in the ITT population and in the subgroup of patients with PD-L1 positive tumours. The trial demonstrated statistically significant improvement in RFS at the prespecified interim analysis for patients randomized to the KEYTRUDA arm compared with placebo with

a median follow-up of 16.0 months. A pre-specified DMFS analysis was conducted with a median follow-up time of 45.5 months. At the time of the DMFS analysis, OS was not formally assessed. Efficacy results are summarized in Table 84 and Figure 6.

Table 84: Efficacy Results in KEYNOTE-054.

KEYTRUDA	Placebo	
200 mg every 3 weeks		
n=514	n=505	
135 (26%)	216 (43%)	
NR (NR, NR)	20.4 (16.2, NR)	
0.57 (0.43, 0.74)		
<0.0001 [‡]		
82%	73%	
75%	61%	
173 (34%)	245 (49%)	
65%	49%	
NR (49.6, NR)	40.0 (27.7, NR)	
0.60 (0.49, 0.73)		
< 0.0001 [¶]		
	200 mg every 3 weeks n=514 135 (26%) NR (NR, NR) 0.57 (0.43, <0.000) 82% 75% 173 (34%) 65% NR (49.6, NR) 0.60 (0.49,	

^{*} At pre-specified 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.

For patients with PD-L1 positive tumours, the DMFS HR (KEYTRUDA versus placebo) was 0.61 (95% CI: 0.49, 0.76). The DMFS benefit for KEYTRUDA compared to placebo was observed regardless of tumour PD-L1 expression or BRAF mutation status.

[†] Based on the stratified Cox proportional hazard model

[‡] p-Value (based on stratified log rank test) is compared with 0.014 of the allocated alpha for this interim analysis.

[§] At DMFS analysis

[¶] p-value (based on stratified log-rank test) is compared with 0.014 of the allocated alpha for this interim analysis

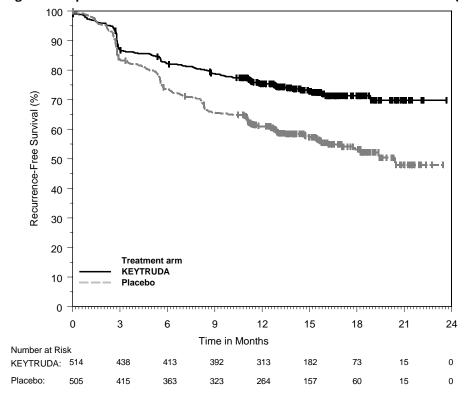


Figure 6: Kaplan-Meier Curve for Recurrence-Free Survival in KEYNOTE-054 (Intent to Treat Population)

Non-Small Cell Lung Carcinoma

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

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/m² 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/m² every 3 weeks for patients with non-squamous histologies;
- Pemetrexed 500 mg/m² every 3 weeks and cisplatin 75 mg/m² every 3 weeks on Day 1 for 4 to 6 cycles followed by optional pemetrexed 500 mg/m² every 3 weeks for patients with non-squamous histologies;
- Gemcitabine 1250 mg/m² on days 1 and 8 and cisplatin 75 mg/m² every 3 weeks on Day 1 for 4 to 6 cycles;
- Gemcitabine 1250 mg/m² 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/m² 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 85: Baseline Characteristics in KEYNOTE-024.

	KEYTRUDA	Chemotherapy
	200 mg every 3 weeks	
	n=154	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.

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 86 summarizes key efficacy measures for the entire ITT population.

Table 86: Efficacy Results in KEYNOTE-024.

	Chemotherapy
200 mg every 3 weeks	
n=154	n=151
73 (47%)	116 (77%)
0.50 (0.37, 0.68)	
<0.001	
10.3 (6.7, NA)	6.0 (4.2, 6.2)
44 (29%)	64 (42%)
0.60 (0.41, 0.89)	
0.005	
Not reached (NA, NA)	Not reached (9.4, NA)
Response Rate*	
45% (37, 53)	28% (21, 36)
4%	1%
41%	27%
	n=154 73 (47%) 0.50 (0.37, 0.68) <0.001 10.3 (6.7, NA) 44 (29%) 0.60 (0.41, 0.89) 0.005 Not reached (NA, NA) Response Rate* 45% (37, 53) 4%

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

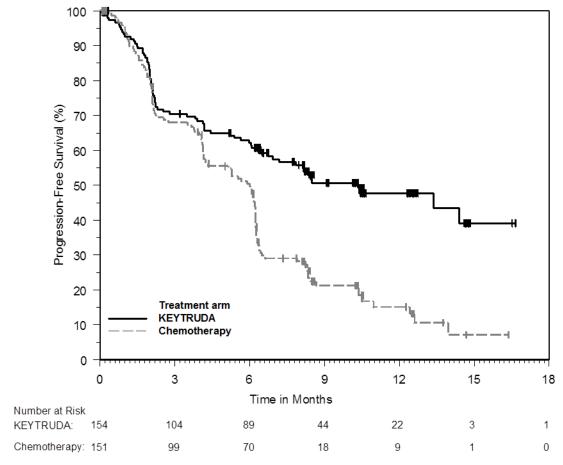
In exploratory subgroup analyses, a reduced survival benefit of KEYTRUDA compared to chemotherapy was observed in females as well as in never-smokers. In females, the HR for PFS was 0.75 (95% CI: 0.46, 1.21) and the HR for OS was 0.95 (95% CI: 0.50, 1.83). In never-smokers, the HR for PFS was 0.90 (95% 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 8.

[‡] Based on stratified Log rank test

NA = not available

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



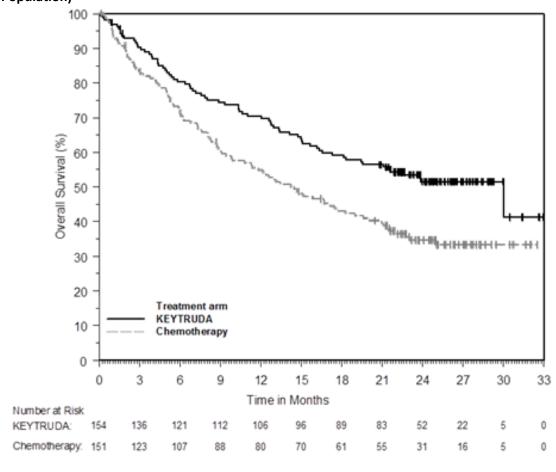


Figure 8: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-024 (Intent to Treat Population)

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

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 nonsquamous 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 \geq 50%, and 53% had TPS 1 to 49%.

The primary efficacy outcome measure was OS. Secondary efficacy outcome measures were PFS and ORR as assessed by blinded independent central review (BICR) using RECIST 1.1. Table 87 summarizes key efficacy measures for the entire ITT population (TPS \geq 1%).

Table 87: Efficacy results (PD-L1 TPS \geq 1%) in KEYNOTE-042.

KEYTRUDA	Chemotherapy
200 mg every 3 weeks	
n=637	n=637
422 (66%)	481 (76%)
0.82 (0.71, 0.93)
0	0.0013
16.4 (14.0, 19.7)	12.1 (11.3, 13.3)
PFS [‡]	
532 (84%)	541 (85%)
1.06 (0.93, 1.19)	
5.4 (4.3, 6.2)	6.6 (6.3, 7.3)
Overall response rate [‡]	
27% (24, 31)	27% (23, 30)
0.5%	0.5%
27%	26%
	200 mg every 3 weeks n=637 422 (66%) 0.82 (16.4 (14.0, 19.7) PFS [‡] 532 (84%) 1.06 (5.4 (4.3, 6.2) Overall response rate [‡] 27% (24, 31) 0.5%

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

The findings of an analysis based on PD-L1 TPS ≥ 50% and TPS 1 to 49% are shown in Table 88.

[†] 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.

Table 88: Efficacy results by PD-L1 Expression in KEYNOTE-042.

Endpoint	KEYTRUDA	Chemotherapy	KEYTRUDA	Chemotherapy
	200 mg every 3 weeks		200 mg every 3 weeks	
	n=299	n=300	n=338	n=337
OS	TPS ≥ 50%		TPS 1 to 4	19%
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 9: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-042 (TPS ≥ 1%, Intent-to-Treat Population)

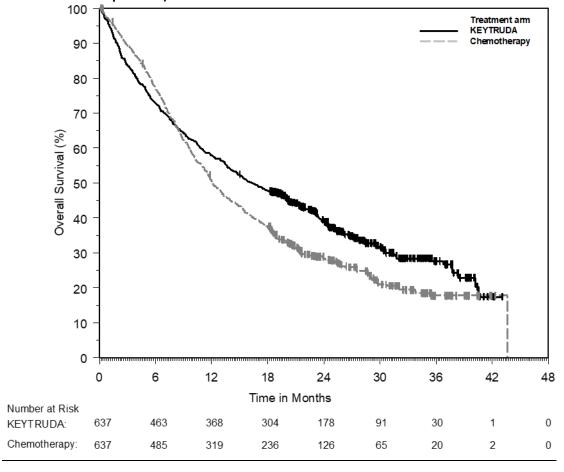


Figure 10: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-042 (TPS ≥ 50%, Intent-to-Treat Population)

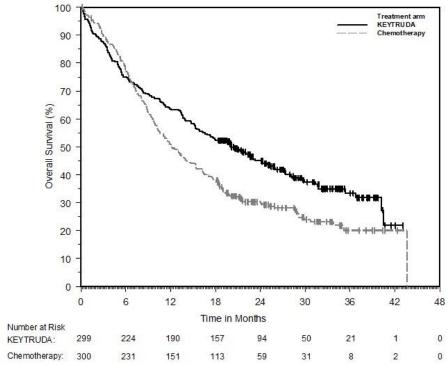
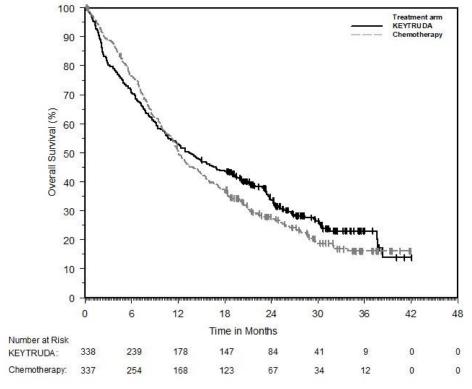


Figure 11: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-042 (TPS 1-49%, Intent-to-Treat Population)



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

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/m² and investigator's choice of cisplatin 75 mg/m² or carboplatin AUC 5 mg/mL/min intravenously every 3 weeks for 4 cycles followed by KEYTRUDA 200 mg and pemetrexed 500 mg/m² intravenously every 3 weeks. KEYTRUDA was administered prior to chemotherapy; or
- Placebo with pemetrexed 500 mg/m² and investigator's choice of cisplatin 75 mg/m² or carboplatin AUC 5 mg/mL/min intravenously every 3 weeks for 4 cycles followed by placebo and pemetrexed 500 mg/m² 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 89: Baseline Characteristics in KEYNOTE-189.

	KEYTRUDA	Placebo
	and	and
	Pemetrexed	Pemetrexed
	and	and
	Platinum Chemotherapy	Platinum Chemotherapy
	n=410	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		

	KEYTRUDA and	Placebo and
	Pemetrexed	Pemetrexed
	and	and
	Platinum Chemotherapy	Platinum Chemotherapy
	n=410	n=206
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%

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 90 summarizes key efficacy measures of the interim analysis.

Table 90: Response to KEYTRUDA, Pemetrexed, and Platinum Chemotherapy in Patients with Non-Squamous NSCLC in KEYNOTE-189.

Endpoint	KEYTRUDA and Pemetrexed and Platinum Chemotherapy n=410	Placebo and Pemetrexed and 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†	<0.0001			
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 I	Primary Efficacy Outcome Measure PFS			
Number (%) of patients with event	245 (60%)	166 (81%)		
Hazard ratio* (95% CI)	0.52 (0.43, 0.64)			
p-Value†	<0.0001			
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%		

	KEYTRUDA	Placebo	
	and	and	
Endnoint	Pemetrexed	Pemetrexed	
Endpoint	and	and	
	Platinum Chemotherapy	Platinum Chemotherapy	
	n=410	n=206	
Secondary Efficacy Outcome Measur	re 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¶	59%	44%	

^{*} Based on the stratified Cox proportional hazard model

NA = not available

The final descriptive analysis of OS was performed at a median duration of follow-up of 18.8 months after 421 patient events (258 for KEYTRUDA combination arm and 163 for the placebo plus chemotherapy arm). Median OS was 22.0 months for the KEYTRUDA combination arm and 10.6 months for the placebo plus chemotherapy arm. The OS HR was 0.56 (95% CI: 0.46, 0.69; see Figure 12). At final analysis, the results for PFS and ORR remained consistent with the interim analysis (see Table 90).

[†] 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

Overall Survival (%) Treatment arm KEYTRUDA Control Time in Months Number at Risk KEYTRUDA: 410 Control:

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

^{*}based on the final analysis

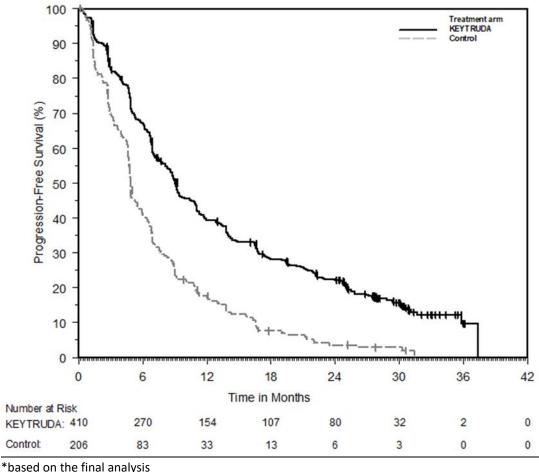


Figure 13: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-189 (Intent to Treat Population)*

KEYNOTE-407: Controlled trial of combination therapy in squamous NSCLC patients naïve to treatment 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/m² on Day 1 of each 21-day cycle for 4 cycles or nab-paclitaxel 100 mg/m² 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/m² on Day 1 of each 21-day cycle for 4 cycles or nab-paclitaxel 100 mg/m² 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 91: Baseline Characteristics in KEYNOTE-407.

	KEYTRUDA	Placebo
	and	and
	Carboplatin	Carboplatin
	and	and
	Paclitaxel or Nab-Paclitaxel	Paclitaxel or Nab-Paclitaxel
	n=278	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%

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, Table 92 summarizes key efficacy measures of the interim analysis.

Table 92: Efficacy Results in KEYNOTE-407.

	KEYTRUDA	Placebo	
	and	and	
Endpoint	Carboplatin	Carboplatin	
Lilapoint	and	and	
	Paclitaxel or Nab-Paclitaxel	Paclitaxel or Nab-Paclitaxel	
	n=278	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 (0.4	9, 0.85)	
p-Value (stratified log rank)	0.00	008	
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 (4.2, 5.7)	
Hazard ratio* (95% CI)	0.56 (0.4	5, 0.70)	
p-Value(stratified log rank)	<0.0001		
Secondary Efficacy Outcome Measure Object	ctive Response Rate [†]		
ORR [‡]	58%	38%	
(95% CI)	(52, 64)	(33, 44)	
Secondary Efficacy Outcome Measure Duration of Response [†]			
Median duration of response in months	7.7 (1.1+, 14.7+)	4.8 (1.3+, 15.8+)	
(range)§	/./ (1.1+, 14./+)	4.0 (1.3+, 13.0+)	
% with duration ≥ 6 months¶	62%	40%	
* D + + + + + + + + +			

^{*} Based on the stratified Cox proportional hazard model

The final descriptive analysis of OS was performed at a median duration of follow-up of 14.3 months after 365 patient events (168 for KEYTRUDA combination arm and 197 for placebo plus chemotherapy arm). Median OS was 17.1 months for the KEYTRUDA combination arm and 11.6 months for the placebo plus chemotherapy arm. The OS HR was 0.71 (95% CI: 0.58, 0.88; see Figure 14). At final analysis, the results for PFS and ORR remained consistent with the interim analysis (see Table 92).

[†] 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

^{§ &#}x27;+' indicates there is no progressive disease by the time of last disease assessment

[¶] Based on Kaplan-Meier estimation

NA = not available

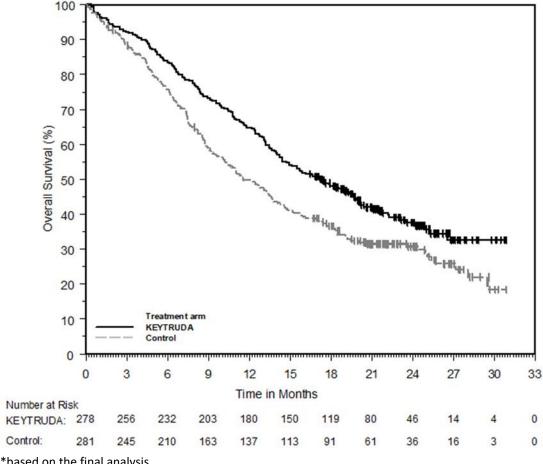


Figure 14: Kaplan-Meier Curve for Overall Survival in KEYNOTE-407*

^{*}based on the final analysis

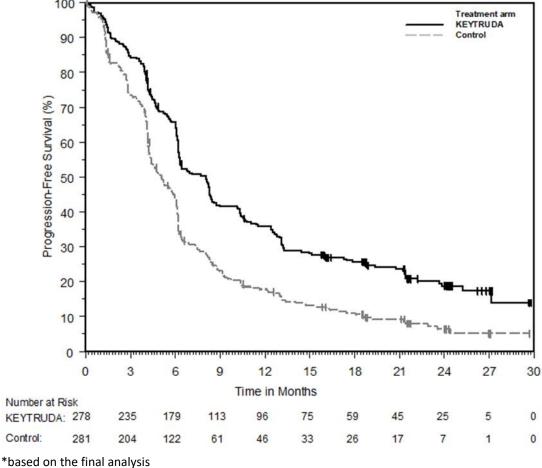


Figure 15: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-407*

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

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 platinumcontaining 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/m² 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 93: Baseline Characteristics in KEYNOTE-010.

	KEYTRUDA	KEYTRUDA KEYTRUDA		
	2 mg/kg every	10 mg/kg every	75 mg/m ² every	
	3 weeks	3 weeks	3 weeks	
	n=344	n=346	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 75 mg/m² every 3 weeks was 2.0 months (range: 1 day to 13.7 months).

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 \geq 50% and the overall population with TPS \geq 1%. Assessment of tumour status was performed every 9 weeks. A secondary efficacy outcome measure was ORR in the subgroup of patients with TPS \geq 50% and the overall population with TPS \geq 1%. Table 94 and Table 95 summarize key efficacy measures for the entire ITT population (TPS \geq 1%) and for the subgroup of patients with TPS \geq 50%. Kaplan-Meier curves for OS (TPS \geq 1% and TPS \geq 50%) are shown in Figure 16 and Figure 18. Kaplan-Meier curves for PFS (TPS \geq 1% and TPS \geq 50%) are shown in Figure 17 and Figure 19.

Table 94: 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

 $^{^{\}ddagger}$ Statistically significant based on a pre-specified α level of 0.00825 for the two pairwise comparisons versus docetaxel using a Hochberg procedure

 $[\]S$ Assessed by BICR using RECIST 1.1

[¶] All responses were partial responses.

Figure 16: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-010 (TPS \geq 1%, Intent to Treat Population)

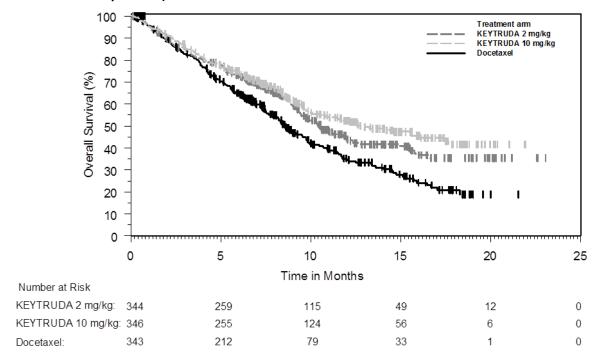


Figure 17: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-010 (TPS ≥ 1%, Intent to Treat Population)

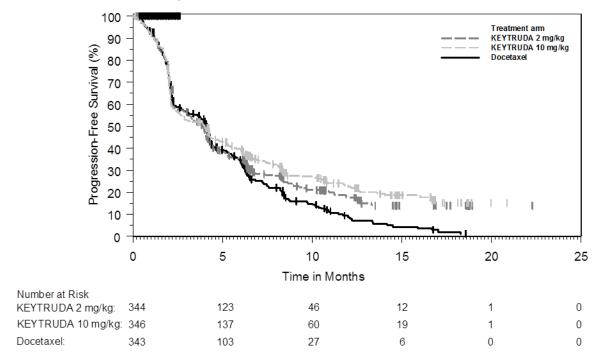


Table 95: Response to KEYTRUDA 2 or 10 mg/kg every 3 Weeks in Previously Treated Patients with NSCLC in KEYNOTE-010, with TPS ≥ 50%.

Endpoint	KEYTRUDA 2 mg/kg every	KEYTRUDA 10 mg/kg every	Docetaxel 75 mg/m ² every	
	3 weeks	3 weeks	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

 $^{^{\}ddagger}$ 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

 $^{^{\}P}$ 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 18: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-010 (TPS ≥ 50%, Intent to Treat Population)

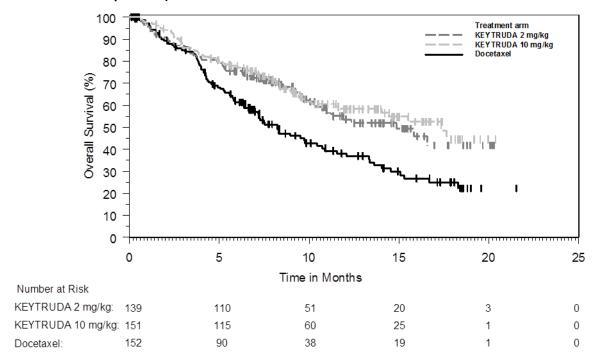
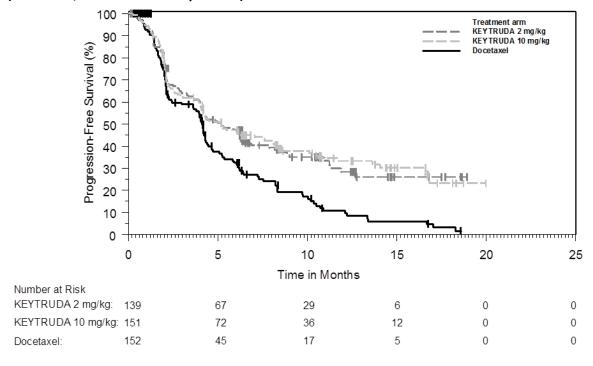


Figure 19: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-010 (TPS ≥ 50%, Intent to Treat Population)



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 \geq 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).

Adjuvant NSCLC

KEYNOTE-091: Controlled trial for the adjuvant treatment of patients with resected NSCLC

The efficacy of KEYTRUDA was investigated in KEYNOTE-091, a multicenter, randomized, triple-blind, placebo-controlled trial. Key eligibility criteria were completely resected stage IB (T2a ≥ 4 cm), II, or IIIA NSCLC by AJCC 7th edition, regardless of tumour PD-L1 expression status. Patients had not received neoadjuvant or adjuvant radiotherapy and/or neoadjuvant chemotherapy. Adjuvant chemotherapy up to 4 cycles was optional. Patients were ineligible if they had autoimmune disease that required systemic therapy within 2 years of treatment; a medical condition that required immunosuppression; a history of interstitial lung disease or pneumonitis, or received more than 4 cycles of adjuvant chemotherapy. Randomization was stratified by stage (IB vs. II vs. IIIA), adjuvant chemotherapy (yes vs. no), PD-L1 status (TPS <1% [negative] vs. TPS 1-49% vs. TPS ≥50%), and geographic region (Western Europe vs. Eastern Europe vs. Asia vs. Rest of World). Patients were randomized (1:1) to receive KEYTRUDA 200 mg or placebo intravenously every 3 weeks.

Treatment continued until RECIST 1.1-defined disease recurrence as determined by the investigator, unacceptable toxicity, or approximately one year (18 doses). Patients underwent imaging to assess tumour recurrence every 12 weeks for the first year, then every 6 months for years 2 to 3, and then annually up to the end of year 5. After year 5, imaging is performed as per local standard of care.

Among the 1177 patients in KEYNOTE-091, 1010 (86%) received adjuvant platinum-based chemotherapy following complete resection. Among these 1010 patients, the median age was 64 years (range: 35 to 84), 49% age 65 or older; 68% male; 77% White, 18% Asian; 86% current or former smokers; and 39% with ECOG PS of 1. Eleven percent had stage IB, 57% had stage II, and 31% had stage IIIA disease. Thirty-nine percent had PD-L1 TPS <1% [negative], 33% had TPS 1-49%, and 28% had TPS ≥50%. Fifty-two percent were from Western Europe, 20% from Eastern Europe, 17% from Asia, and 11% from Rest of World.

The primary efficacy outcome measures were investigator-assessed disease-free survival (DFS) in the overall population and in the population with tumour PD-L1 expression TPS \geq 50%, where DFS was defined as the time between the date of randomization and the date of first recurrence (local/regional recurrence, distant metastasis), a second malignancy, or death, whichever occurred first. Secondary efficacy outcome measures were investigator-assessed DFS in the population with tumour PD-L1 expression TPS \geq 1%, and OS in the overall population and in the populations with tumour PD-L1 expression TPS \geq 50% and TPS \geq 1%.

The trial demonstrated a statistically significant improvement in DFS in the overall population at a prespecified interim analysis for patients randomized to the KEYTRUDA arm compared to patients randomized to the placebo arm. In an exploratory subgroup analysis of the 167 patients (14%) who did not receive adjuvant chemotherapy, the DFS HR was 1.25 (95% CI: 0.76, 2.05). At the time of analysis, OS results were not mature (18% with events in the overall population). The median follow-up time was 32.4 months (range: 0.6 to 68 months). Efficacy results for KEYNOTE-091 in patients who received adjuvant chemotherapy are summarized in Table 96 and Figure 20.

Table 96: Efficacy Results in KEYNOTE-091 for Patients Who Received Adjuvant Chemotherapy

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

^{*} Based on the unstratified univariate Cox regression model

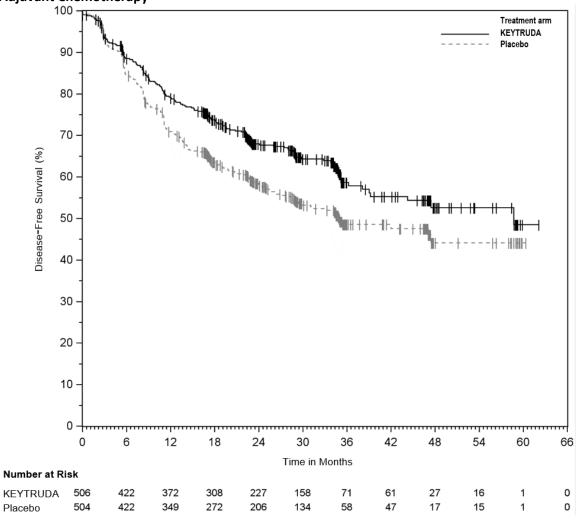


Figure 20: Kaplan-Meier Curve for Disease-Free Survival in KEYNOTE-091 for Patients Who Received Adjuvant Chemotherapy

Neoadjuvant and Adjuvant Treatment of Resectable NSCLC

<u>KEYNOTE 671: Controlled trial for the neoadjuvant and adjuvant treatment of patients with resectable NSCLC</u>

The efficacy of KEYTRUDA in combination with platinum-containing chemotherapy given as neoadjuvant treatment and continued as monotherapy adjuvant treatment was investigated in KEYNOTE-671, a multicenter, randomized, double-blind, placebo-controlled trial. Patients with previously untreated and resectable Stage II, IIIA, or IIIB (N2) NSCLC as assessed by the AJCC 8th edition were eligible for the trial. Patients were enrolled regardless of tumor PD-L1 expression. Patients with active autoimmune disease that required systemic therapy within 2 years of treatment, a medical condition that required immunosuppression, a history of interstitial lung disease (ILD)/pneumonitis that required steroid treatment were ineligible. Randomization was stratified by stage (II vs. III), tumor PD-L1 expression (TPS ≥50% or <50%), histology (squamous vs. non squamous), and geographic region (East Asia vs. non-East Asia).

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

Treatment Arm A: neoadjuvant KEYTRUDA 200 mg on Day 1 in combination with cisplatin 75

- mg/m² and either pemetrexed 500 mg/m² on Day 1 or gemcitabine 1000 mg/m² on Days 1 and 8 of each 21 day cycle for up to 4 cycles. Following surgery, KEYTRUDA 200 mg was administered every 3 weeks for up to 13 cycles.
- Treatment Arm B: neoadjuvant placebo on Day 1 in combination with cisplatin 75 mg/m² and either pemetrexed 500 mg/m² on Day 1 or gemcitabine 1000 mg/m² on Days 1 and 8 of each 21 day cycle for up to 4 cycles. Following surgery, placebo was administered every 3 weeks for up to 13 cycles.

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

The dual primary efficacy outcome measures were investigator-assessed event-free survival (EFS) and overall survival (OS). Secondary efficacy outcome measures included pathological complete response (pCR) rate and major pathological response (mPR) rate as assessed by blinded independent pathology review (BIPR). The trial was not designed to isolate the efficacy of KEYTRUDA in each phase (neoadjuvant or adjuvant) of treatment.

A total of 797 patients in KEYNOTE-671 were randomized: 397 patients to the KEYTRUDA arm and 400 to the placebo arm. Baseline characteristics were: median age of 64 years (range: 26 to 83), 45% age 65 or older; 71% male; 61% White, 31% Asian, and 2% Black. Sixty-three percent and 37% had ECOG performance status of 0 or 1, respectively; 30% had Stage II and 70% had Stage III disease; 33% had TPS ≥50% and 67% had TPS <50%; 43% had tumors with squamous histology and 57% had tumors with non-squamous histology; 31% were from the East Asian region. Four percent of patients had EGFR mutations and in 66% EGFR mutation status was unknown. Three percent of patients had ALK translocations and in 68% ALK translocation status was unknown.

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

The trial demonstrated statistically significant improvements in EFS and OS for patients randomized to KEYTRUDA in combination with platinum-containing chemotherapy followed by KEYTRUDA monotherapy compared with patients randomized to placebo in combination with platinum-containing chemotherapy followed by placebo alone. At the first interim analysis, EFS efficacy results achieved statistical significance with a median follow-up time of 21.4 months (range: 0.4 to 50.6 months) and are summarized in Table 97 and Figure 21. At the second interim analysis, OS efficacy results achieved statistical significance with a median follow-up time of 29.8 months (range: 0.4 to 62.0 months) and are summarized in Table 97 and Figure 22.

Table 97: Efficacy Results in KEYNOTE-671

Endpoint	KEYTRUDA with chemotherapy/ KEYTRUDA n=397	Placebo with chemotherapy/Placebo n=400	
EFS*			
Number of patients with event (%)	139 (35%)	205 (51%)	
Median in months ⁺ (95% CI)	NR (34.1, NR)	17.0 (14.3, 22.0)	
Hazard ratio [‡] (95% CI)	0.58 (0.4	6, 0.72)	
p-Value [§]	< 0.00	001	
OS*			
Number of patients with event (%)	110 (28%)	144 (36%)	
Median in months† (95% CI)	NR (NR, NR)	52.4 (45.7, NR)	
Hazard ratio [‡] (95% CI)	0.72 (0.5	6, 0.93)	
p-Value [§]	0.00	0.0052	

^{*} EFS result based on the first interim analysis; OS result based on the second interim analysis

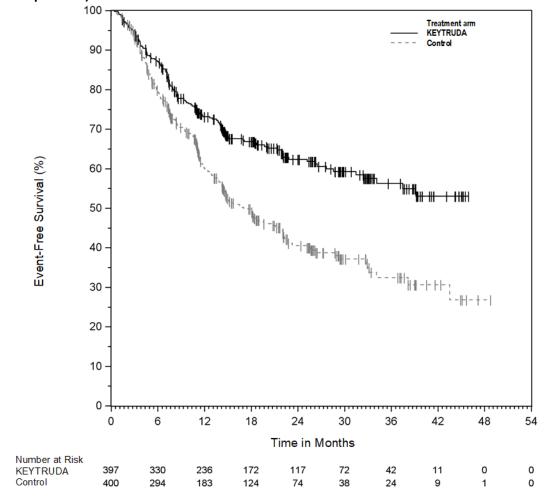
[†] Based on Kaplan-Meier estimates

[‡] Based on Cox regression model with treatment as a covariate stratified by stage, tumor PD-L1 expression, histology, and geographic region

 $[\]S$ Based on stratified log-rank test

NR = not reached

Figure 21: Kaplan-Meier Curve for Event-Free Survival by Treatment Arm in KEYNOTE-671 (Intent to Treat Population)



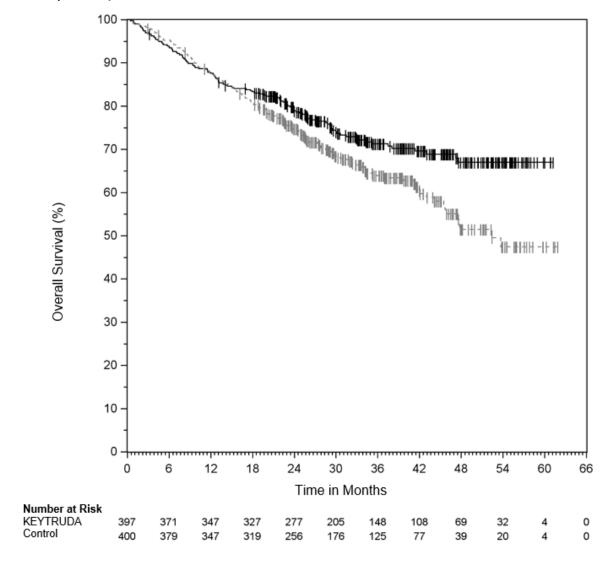


Figure 22: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-671 (Intent to Treat Population)

The trial demonstrated a statistically significant difference in pCR rate (18.1% vs. 4.0%; p<0.0001) and mPR rate (30.2% vs. 11.0%; p<0.0001).

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

Malignant Pleural Mesothelioma

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

The efficacy of KEYTRUDA in combination with pemetrexed and platinum chemotherapy was investigated in KEYNOTE-483, a multicenter, randomized, open-label, active-controlled trial that enrolled 440 patients with unresectable advanced or metastatic MPM with no prior systemic therapy for advanced/metastatic disease. Patients were enrolled regardless of tumour PD-L1 expression. Patients with autoimmune disease that required systemic therapy within 3 years of treatment or a medical condition that required immunosuppression were ineligible. Randomization was stratified by histological subtype (epithelioid vs. non-epithelioid). Patients were randomized (1:1) to one of the following treatment arms; all study medications were administered via intravenous infusion:

- KEYTRUDA 200 mg with pemetrexed 500 mg/m² and cisplatin 75 mg/m² or carboplatin AUC 5-6 mg/mL/min on Day 1 of each 21-day cycle for up to 6 cycles, followed by KEYTRUDA 200 mg every 3 weeks. KEYTRUDA was administered prior to chemotherapy on Day 1.
- Pemetrexed 500 mg/m² and cisplatin 75 mg/m² or carboplatin AUC 5-6 mg/mL/min on Day 1 of each 21-day cycle for up to 6 cycles.

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

Among the 440 patients in KEYNOTE-483, baseline characteristics were: median age of 70 years (77% age 65 or older); 76% male; 79% White, 21% race not reported or unknown; 2% Hispanic or Latino; and 47% and 53% ECOG performance status of 0 or 1, respectively. Seventy-eight percent had epithelioid and 22% had non-epithelioid histology; 60% had tumours with PD-L1 CPS \geq 1 and 30% had tumours with PD-L1 CPS <1.

The primary efficacy outcome measure was OS. Additional efficacy outcome measures were PFS, ORR, and DoR, as assessed by BICR using mRECIST. The trial demonstrated a statistically significant improvement in OS, PFS, and ORR in patients randomized to KEYTRUDA in combination with chemotherapy compared with patients randomized to chemotherapy alone. The median follow-up time was 17 months (range: 0.8 - 60.3 months). Table 98 and Figure 23 summarizes the key efficacy measures for KEYNOTE-483.

Table 98: Efficacy Results in KEYNOTE-483

Endpoint	KEYTRUDA 200 mg every 3 weeks and Pemetrexed and Platinum Chemotherapy	Pemetrexed and Platinum Chemotherapy
	(n=222)	(n=218)
OS*		
Number (%) of patients with event	167 (75%)	175 (80%)
Hazard ratio [†] (95% CI)	0.79 (0.6	64, 0.98)
p-Value [‡]	0.0	162
Median in months (95% CI)	17.3 (14.4, 21.3)	16.1 (13.1, 18.2)
PFS* ^{,§}		
Number (%) of patients with event	190 (86%)	166 (76%)
Hazard ratio [†] (95% CI)	0.80 (0.6	65, 0.99)
p-Value [‡]	0.0	194
Median in months (95% CI)	7.1 (6.9, 8.1)	7.1 (6.8, 7.7)
Objective Response Rate ^{§,¶}		
ORR % (95% CI)	52% (45.5, 59.0)	29% (23.0, 35.4)
Number (%) of complete responses	1 (0.5%)	0 (0%)
Number (%) of partial responses	115 (52%)	63 (29%)
p-Value [#]	<0.0001	
Duration of Response*,§,Þ		
Median in months (range)	6.9 (1.2+, 38.9+)	6.8 (1.4+, 25.1+)

^{*} Based on the final analysis

[†] Based on stratified Cox proportional hazard model

[‡] One sided p-value based on stratified log-rank test

[§] Assessed by BICR using mRECIST

Based on an interim analysis

Based on Miettinen & Nurminen method stratified by histological subtype at randomization (epithelioid vs non-epithelioid)

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

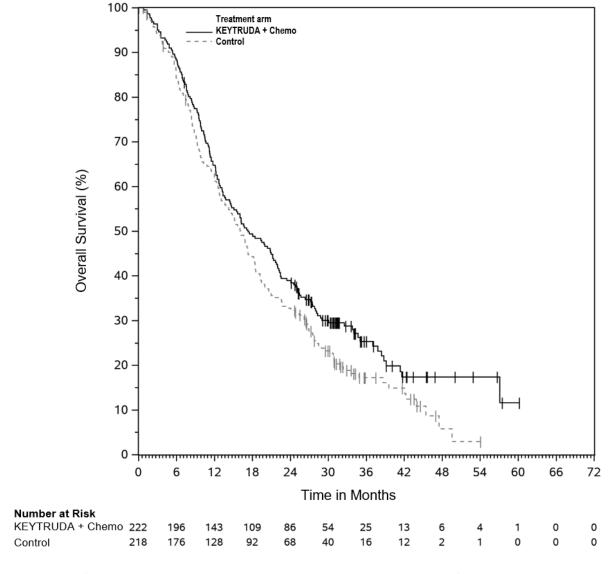


Figure 23: Kaplan-Meier Curve for Overall Survival in KEYNOTE-483

In a pre-specified exploratory analysis based on histology, in the subgroup of patients with epithelioid histology (n=345), the hazard ratio (HR) for OS was 0.89 (95% CI: 0.70, 1.13), with median OS of 19.8 months in KEYTRUDA in combination with chemotherapy and 18.2 months in chemotherapy alone. In the subgroup of patients with non-epithelioid histology (n=95), the HR for OS was 0.57 (95% CI: 0.36, 0.89), with median OS of 12.3 months in KEYTRUDA in combination with chemotherapy and 8.2 months in chemotherapy alone.

Classical Hodgkin Lymphoma

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

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 \geq 1000/ μ L, platelet count \geq 75,000/ μ L, hepatic transaminases \leq 2.5 times the upper limit of normal (ULN), bilirubin \leq 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.

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 99 and Figure 24.

Table 99: 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 BV.

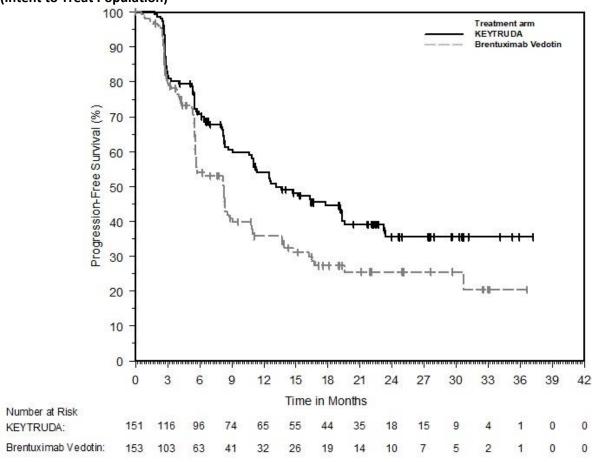


Figure 24: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-204 (Intent to Treat Population)

Primary Mediastinal B-cell Lymphoma

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

The efficacy of KEYTRUDA was investigated in KEYNOTE-170, a multicenter, open-label, single-arm trial in 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.

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 100. For the 12 responders, the median time to first objective response was 2.9 months (range 2.4 to 8.5 months).

Table 100: 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		

The final efficacy analysis of KEYNOTE-170 included 53 patients. The ORR was 45% (95% CI: 32, 60) with a median follow-up time of 22.3 months. Ten (19%) patients achieved a best overall response of complete remission and 14 (26%) patients achieved a best overall response of partial remission. The median response duration was not reached (range: 1.1+ to 46.9+ months).

Urothelial Carcinoma

<u>KEYNOTE-A39: Controlled trial of combination therapy with enfortumab vedotin in urothelial cancer</u> patients

The efficacy of KEYTRUDA in combination with enfortumab vedotin was investigated in KEYNOTE-A39, an open-label, multicenter, randomized, active-controlled trial that enrolled 886 adult patients with unresectable locally advanced or metastatic urothelial cancer who received no prior systemic therapy for unresectable locally advanced or metastatic disease. The trial excluded patients with autoimmune disease or a medical condition that required immunosuppression, active CNS metastases, cardiac symptoms (including congestive heart failure) consistent with New York Heart Association Class III-IV, severe renal impairment, ongoing sensory or motor neuropathy Grade \geq 2, or uncontrolled diabetes defined as hemoglobin A1C (HbA1c) \geq 8% or HbA1c \geq 7% with associated diabetes symptoms. Randomization was stratified by cisplatin eligibility, PD-L1 expression, and liver metastases . Patients were randomized (1:1) to one of the following treatment arms:

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

- until RECIST v1.1-defined progression of disease, unacceptable toxicity or, for KEYTRUDA maximum of 35 cycles (up to approximately 2 years).
- Gemcitabine 1000 mg/m² on Days 1 and 8 and investigator's choice of cisplatin 70 mg/m² or carboplatin (AUC 4.5 or 5 mg/mL/min according to local guidelines) on Day 1 of each 21-day cycle. Treatment was permitted until disease progression or unacceptable toxicity for up to 6 cycles.

Table 101: Baseline characteristics in KEYNOTE-A39

	KEYTRUDA	Gemcitabine
	200 mg every 3 weeks	and
	and	Platinum Chemotherapy
	Enfortumab Vedotin	with or without maintenance
		immunotherapy
	n=442	n=444
	% (n)	% (n)
Men	78% (344)	76% (336)
Women	22% (98)	24% (108)
Age (median - years)	69	69
Age (range - years)	37-87	22-91
Race		
White	70% (308)	65% (290)
Asian	22% (99)	21% (92)
Black or African American	0.7% (3)	2% (7)
Other	7% (30)	12% (52)
ECOG PS		·
0	50% (223)	48% (215)
1	46% (204)	49% (216)
2	3% (15)	2% (11)
Disease status		•
metastatic	95% (421)	95% (420)
locally advanced	5% (21)	5% (24)
Metastasis category		
visceral metastasis	72% (318)	72% (318)
lymph nodes only disease	23% (103)	23% (104)
locally advanced without	50/ (24)	
metastasis	5% (21)	5% (22)
Cisplatin eligibility		·
eligible	54% (240)	55% (242)
ineligible	46% (202)	45% (202)
Liver metastasis		•
present	22% (98)	22% (98)
absent	78% (344)	78% (346)
Renal function	· ,	· ·

	KEYTRUDA	Gemcitabine	
	200 mg every 3 weeks	and	
	and	Platinum Chemotherapy	
	Enfortumab Vedotin	with or without maintenance	
		immunotherapy	
	n=442	n=444	
	% (n)	% (n)	
normal	19% (84)	21% (95)	
mild impairment	37% (165)	36% (162)	
moderate impairment	42% (186)	40% (179)	
severe impairment	2% (7)	2% (8)	
Documented baseline HbA1c			
<5.7%	46% (205)	47% (208)	
Histology		•	
Urothelial cancer (UC)	86% (379)	84% (373)	
UC mixed squamous	F0/ /24\	60/ (20)	
differentiation	5% (24)	6% (28)	
UC mixed other	20/ (7)	20/ (7)	
histological varients	2% (7)	2% (7)	

The major efficacy outcome measures were overall survival (OS) and progression-free survival (PFS) as assessed by BICR according to RECIST v1.1. Additional outcome measures were overall response rate (ORR) as assessed by BICR according to RECIST v1.1. The median follow-up time for KEYNOTE-A39 was 17.2 months.

Efficacy results were consistent across all stratified patient subgroups. Results are summarized in Table 102 and

Figure 25 and Figure 26.

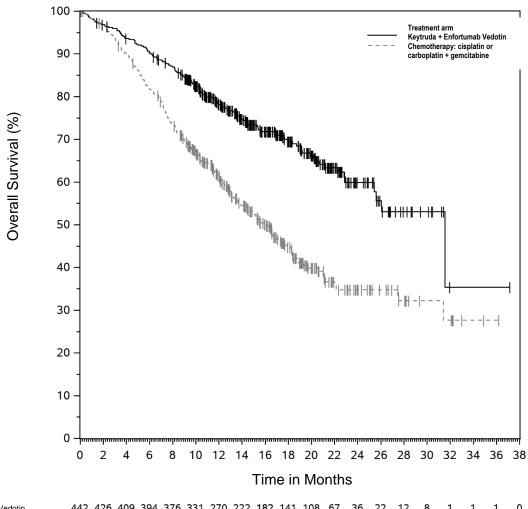
Table 102: Efficacy Results in KEYNOTE-A39

	KEYTRUDA	Gemcitabine
	200 mg every 3 weeks	and
	and	Platinum Chemotherapy
Endpoint	Enfortumab Vedotin	with or without
		maintenance
		immunotherapy
	n=442	n=444
OS		
Number (%) of patients with event	133 (30%)	226 (51%)
Median in months (95% CI)	31.5 (25.4, NR)	16.1 (13.9, 18.3)
Hazard ratio* (95% CI)	0.47 (0.38, 0.58)	
p-Value [†]	<0.0001	
PFS		
Number (%) of patients with event	223 (50%)	307 (69%)
Median in months (95% CI)	12.5 (10.4, 16.6)	6.3 (6.2, 6.5)
Hazard ratio* (95% CI)	0.45 ((0.38, 0.54)
p-Value [†]	<	0.0001
Objective Response Rate [‡]		
ORR§ % (95% CI)	68% (63.1, 72.1)	44% (39.7, 49.2)
p-Value [¶]	<0.0001	
Complete response	29%	12%
Partial response	39%	32%

NR = not reached

- * Based on the stratified Cox proportional hazard regression model
- [†] Two-sided p-Value based on stratified log-rank test
- [‡] Includes only patients with measurable disease at baseline
- § Based on patients with a best overall response as confirmed complete or partial response
- Two-sided p-Value based on Cochran-Mantel-Haenszel test stratified by PD-L1 expression, cisplatin eligibility and liver metastases

Figure 25: Kaplan-Meier Curve for Overall Survival in KEYNOTE-A39



Number at Risk

Keytruda + Enfortumab Vedotin

Chemotherapy: cisplatin or carboplatin + gemcitabine

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

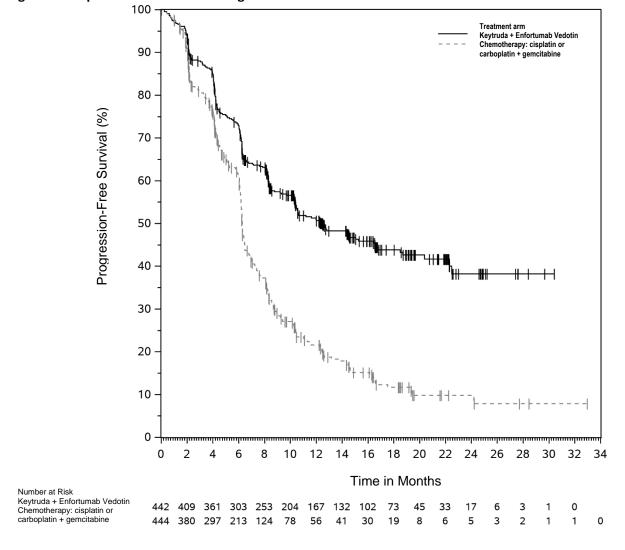


Figure 26: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-A39

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

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 including patients who were not considered eligible for any platinum-containing chemotherapy. Participants were required to have a creatinine clearance ≥30ml/min and an ECOG performance status ≤ 2. 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 [one subject], 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 4 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.

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 103.

Table 103: 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 pa	tients with responses of 6 months or longer	

In a long-term follow-up analysis performed 33.9 months after the interim analysis with 107 ORR events for all patients [median follow-up of 11.4 months (range: 0.1, 63.8 months)], the ORR was 29% with the complete and partial response rates of 10% and 20%, respectively. Among the responding patients, the median response duration was 33.4 months (range 1.4+ to 60.7+ months).

KEYNOTE-361: Platinum-Eligible Patients with Previously Untreated Urothelial Carcinoma
The efficacy of KEYTRUDA for the first-line treatment of platinum-eligible patients with locally advanced or metastatic urothelial carcinoma was investigated in KEYNOTE-361, a multicenter, randomized, open-label, active-controlled study in 1010 previously untreated patients. The safety and efficacy of KEYTRUDA in combination with platinum-based chemotherapy for previously untreated patients with locally advanced or metastatic urothelial carcinoma has not been established. The study compared KEYTRUDA with or without platinum-based chemotherapy (i.e., cisplatin or

carboplatin with gemcitabine) to platinum-based chemotherapy alone. Among the patients receiving KEYTRUDA plus platinum-based chemotherapy, 44% received cisplatin and 56% received carboplatin. The study did not meet its major efficacy outcome measures of improved PFS or OS in the KEYTRUDA plus chemotherapy arm compared to the chemotherapy-alone arm. Additional efficacy endpoints, including improvement of OS in the KEYTRUDA monotherapy arm, could not be formally tested.

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

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/m² (n=84); docetaxel 75 mg/m² (n=84); or vinflunine 320 mg/m² (n=87). Patients received KEYTRUDA until unacceptable toxicity or disease progression. Clinically stable patients with initial evidence of disease progression were permitted to remain on treatment until disease progression was confirmed. Patients without disease progression were treated for up to 24 months. 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 \geq 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.

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 104 summarizes the key efficacy measures and Figure 27 shows the Kaplan-Meier survival curve for OS.

Table 104: Efficacy Results in Patients with Urothelial Carcinoma Previously Treated with Chemotherapy.

	KEYTRUDA	Chemotherapy		
Endpoint	200 mg every 3 weeks			
	n=270	n=272		
OS				
Number (%) of patients with event	155 (57%)	179 (66%)		
Hazard ratio* (95% CI)	0.73 (0.5	0.73 (0.59, 0.91)		
p-Value [†]	0.0	02 [£]		
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 (0.8	0.98 (0.81, 1.19)		
p-Value [†]	0.4	0.416€		
Median in months (95% CI)	2.1 (2.0, 2.2)	3.3 (2.3, 3.5)		
Objective Response Rate [‡]	Objective Response Rate [‡]			
ORR % (95% CI)	21% (16, 27)	11% (8, 16)		
Complete Response Rate (%)	7%	3%		
Partial Response Rate (%)	14%	8%		
p-Value ^{§,}	0.0	0.001 [¥]		
Duration of Response				
Modian in months (range)	Not reached	4 2 /1 4 . 15 4 .)		
Median in months (range)	(1.6+, 15.6+)	4.3 (1.4+, 15.4+)		

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

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

[†] 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

 $^{^{\}varepsilon}$ 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

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 27 for OS curve. In the final analysis of PFS there was no statistically significant difference between KEYTRUDA and chemotherapy.

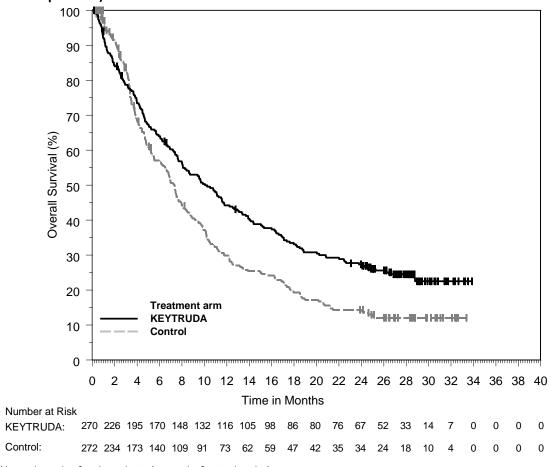


Figure 27: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-045 (Intent to Treat Population)*

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

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

carcinoma of the urothelium, autoimmune disease or a medical condition that required immunosuppression.

Patients received KEYTRUDA 200 mg every 3 weeks until unacceptable toxicity, persistent or recurrent high-risk NMIBC, or progressive disease. Assessment of tumour status was performed every 12 weeks, and patients without disease progression could be treated for up to 24 months 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.

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 105. 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 105: 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).

Microsatellite Instability-High Colorectal Cancer

<u>KEYNOTE-177: Controlled trial in colorectal carcinoma patients previously untreated for metastatic MSI-H or dMMR CRC</u>

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

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

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

⁺Denotes ongoing response

- mFOLFOX6 (oxaliplatin, leucovorin, and FU) or mFOLFOX6 in combination with either bevacizumab or cetuximab: Oxaliplatin 85 mg/m², leucovorin 400 mg/m² (or levoleucovorin 200 mg/m²), and FU 400 mg/m² bolus on Day 1, then FU 2400 mg/m² over 46-48 hours. Bevacizumab 5 mg/kg on Day 1 or cetuximab 400 mg/m² on first infusion, then 250 mg/m² weekly.
- FOLFIRI (irinotecan, leucovorin, and FU) or FOLFIRI in combination with either bevacizumab or cetuximab: Irinotecan 180 mg/m², leucovorin 400 mg/m² (or levoleucovorin 200 mg/m²), and FU 400 mg/m² bolus on Day 1, then FU 2400 mg/m² over 46-48 hours. Bevacizumab 5 mg/kg on Day 1 or cetuximab 400 mg/m² on first infusion, then 250 mg/m² weekly.

Treatment with KEYTRUDA or chemotherapy continued until RECIST v1.1-defined progression of disease as determined by the investigator or unacceptable toxicity. Patients treated with KEYTRUDA without disease progression could be treated for up to 24 months or 35 administrations, whichever was longer. Treatment with pembrolizumab could be reinitiated for subsequent disease progression and administered for up to one additional year. Assessment of tumour status was performed every 9 weeks. Patients randomized to chemotherapy were offered KEYTRUDA at the time of disease progression. The primary efficacy outcome measures were PFS (as assessed by BICR according to RECIST v1.1) and OS. The secondary outcome measure was ORR.

The trial demonstrated a statistically significant improvement in PFS for patients randomized to KEYTRUDA compared with chemotherapy. The median follow-up at the time of the PFS analysis was 27.6 months (range: 0.2 to 48.3 months). At the time of the PFS analysis, the overall survival data were not mature (66% of the required number of events for the OS final analysis). Table 106 and Figure 28 summarize the key efficacy measures for KEYNOTE-177 assessed at the time of the PFS analysis.

Table 106: Efficacy Results in Patients with MSI-H or dMMR CRC in KEYNOTE-177.

Endpoint	KEYTRUDA	Chemotherapy	
	200 mg every 3 weeks		
	n=153	n=154	
PFS			
Number (%) of patients with event	82 (54%)	113 (73%)	
Median in months (95% CI)	16.5 (5.4, 32.4)	8.2 (6.1, 10.2)	
Hazard ratio* (95% CI)	0.60 (0.45, 0.80)		
p-Value [†]	0.0002		
Objective Response Rate			
ORR (95% CI)	44% (35.8, 52.0)	33% (25.8, 41.1)	
Complete response rate	11%	4%	
Partial response rate	33%	29%	
* Based on Cox regression model			
Based on log-rank test (compared to a significance level of 0.0117)			

The protocol-specified final analysis for OS was performed 12 months after the PFS analysis, with 140 patient events (62 for KEYTRUDA and 78 for chemotherapy). There was no statistically significant difference between KEYTRUDA and chemotherapy. The HR for OS was 0.74 (95% CI: 0.53, 1.03), with a p-value of 0.0359 (based on log-rank test compared to a significance level of 0.0246). Median OS was not reached (95% CI: 49.2 months, NR) for KEYTRUDA and was 36.7 months (95% CI: 27.6 months, NR)

for chemotherapy. Sixty percent of patients who had been randomized to receive chemotherapy had crossed over to receive subsequent anti-PD-1/PD-L1 therapies including KEYTRUDA.

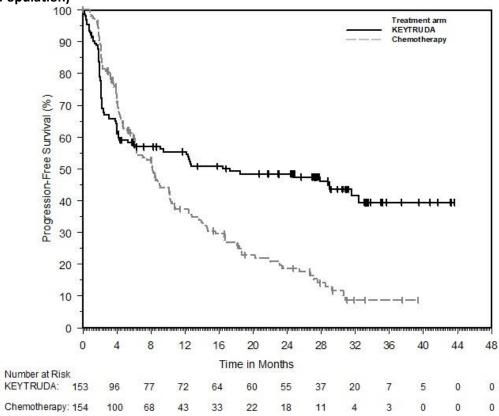


Figure 28: Kaplan-Meier Curve for PFS by Treatment Arm in KEYNOTE-177 (Intent to Treat Population)

In an exploratory subgroup analysis, the estimated PFS HRs for KEYTRUDA versus chemotherapy for the KRAS/NRAS/BRAF all wild type (N=69) subgroup and mutant KRAS or NRAS (N=74) subgroup were 0.28 (95% CI 0.14, 0.55) and 1.19 (95% CI 0.68, 2.07), respectively.

At the time of the PFS analysis corresponding to a median follow up duration of 27.6 months, the median duration of response was not reached in patients treated with KEYTRUDA versus 10.6 months in patients treated with chemotherapy.

Microsatellite Instability-High Cancer (MSI-H) or Mismatch Repair Deficient (dMMR) Cancer <u>KEYNOTE-164</u>, <u>KEYNOTE-158</u>, and <u>KEYNOTE-051</u>: Open-label studies in patients with MSI-H or dMMR, cancer

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

 KEYNOTE-164 enrolled 124 patients with advanced MSI-H or dMMR colorectal cancer (CRC) that progressed following treatment with a fluoropyrimidine and either oxaliplatin or

- irinotecan +/- anti-VEGF/EGFR mAb-based therapy.
- KEYNOTE-158 enrolled 373 patients with advanced MSI-H or dMMR non-colorectal cancer (non-CRC) who had disease progression following prior therapy.
- KEYNOTE-051 enrolled 7 pediatric patients with MSI H or dMMR cancers.

Adult patients received KEYTRUDA 200 mg every 3 weeks (pediatric patients received 2 mg/kg every 3 weeks) until unacceptable toxicity or disease progression. Clinically stable patients with initial evidence of disease progression were permitted to remain on treatment until disease progression was confirmed. Patients without disease progression were treated for up to 24 months. Treatment with pembrolizumab could be reinitiated for subsequent disease progression and administered for up to one additional year. In KEYNOTE-164 and KEYNOTE-158, assessment of tumour status was performed every 9 weeks through the first year, then every 12 weeks thereafter. In KEYNOTE-051, assessment of tumour status was performed every 8 weeks for 24 weeks, and then every 12 weeks thereafter. The major efficacy outcome measures were ORR and DoR as assessed by BICR according to RECIST 1.1 and as assessed by the investigator according to RECIST 1.1 in KEYNOTE-051.

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

Among the 7 pediatric patients, in KEYNOTE-051, the baseline characteristics were: median age of 11 years (range: 3 to 16); 71% female; 86% White and 14% Asian; and 57% had a Lansky/Karnofsky Score of 100. Seventy one percent of patients had Stage IV and 14% had Stage III disease. Fifty seven percent of patients received one prior line of therapy and 29% received two prior lines of therapy.

The median follow-up time for 497 adult and 7 pediatric patients (KEYNOTE-051) treated with KEYTRUDA was 20.5 months and 5.2 months, respectively. Efficacy results are summarized in Table 107 and Table 108.

Table 107: Efficacy Results for Adult Patients with MSI-H/dMMR Cancer

Endpoint	n=497			
Objective Response Rate*				
ORR%, (95% CI)	34% (30, 38)			
Complete Response	11%			
Partial Response	23%			
Stable Disease	18%			
Disease Control Rate [†]	52%			
Response Duration*	•			
Median in months (range)	63.2 (1.9+, 63.9+)			
% with duration ≥ 36-months	75% [‡]			
Time to Response				
Median in months (range)	2.2 (1.3, 49.3)			
* A	•			

- * Assessed by BICR using RECIST 1.1
- † Based on best response of stable disease or better
- Based on Kaplan-Meier estimates; includes 65 patients with response of 36 months or longer
- Denotes ongoing response

Among the 7 pediatric patients from KEYNOTE-051 (6 with brain cancer [anaplastic astrocytoma (1), glioblastoma multiforme (5)], 1 with abdominal adenocarcinoma), there were no responders per RECIST 1.1. One patient with a GBM had a radiographic complete response per irRECIST that lasted 15 months after initial pseudo-progression; however, given the limited data, interpretation of the results should be made with caution.

Table 108: Response by Tumour Type

Table 100. Response by Fulliour Ty	•	Objective Response Rate		Duration of Response range
	n	n (%)	95% CI	(months)
CRC	124	42 (34%)	(26%, 43%)	(4.4, 58.5+)
Non-CRC	373	126 (34%)	(29%, 39%)	(1.9+, 63.9+)
Endometrial cancer	94	47 (50%)	(40%, 61%)	(2.9, 63.2)
Gastric or GE junction cancer	51	20 (39%)	(26%, 54%)	(1.9+, 63.0+)
Small intestinal cancer	27	16 (59%)	(39%, 78%)	(3.7+, 57.3+)
Ovarian cancer	25	8 (32%)	(15%, 54%)	(4.2, 56.6+)
Biliary cancer	22	9 (41%)	(21%, 64%)	(6.2, 49.0+)
Pancreatic cancer	22	4 (18%)	(5%, 40%)	(8.1, 24.3+)
Brain cancer	21	1 (5%)	(0%, 24%)	18.9
Sarcoma	14	3 (21%)	(5%, 51%)	(35.4+, 57.2+)
Breast cancer	13	1 (8%)	(0%,36%)	24.3+
Other*	12	4 (33%)	(10%, 65%)	(6.2+, 32.3+)
Cervical cancer	11	1 (9%)	(0%, 41%)	63.9+
Neuroendocrine cancer	11	1 (9%)	(0%, 41%)	13.3
Prostate cancer	8	1 (13%)	(0%, 53%)	24.5+
Adrenocortical cancer	7	1 (14%)	(0%, 58%)	4.2
Mesothelioma	7	0 (0%)	(0%, 41%)	
Thyroid cancer	7	1 (14%)	(0%, 58%)	8.2
Small cell lung cancer	6	2 (33%)	(4%, 78%)	(20.0, 47.5)
Bladder cancer	6	3 (50%)	(12%, 88%)	(35.6+, 57.5+)
Salivary cancer	5	2 (40%)	(5%, 85%)	(42.6+, 57.8+)
Renal cell cancer	4	1 (25%)	(0%, 81%)	22.0

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

Endometrial Carcinoma

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

The efficacy of KEYTRUDA in combination with paclitaxel and carboplatin was investigated in KEYNOTE-868, a multicenter, randomized, double blind, placebo-controlled trial in 810 patients with advanced or recurrent endometrial carcinoma including those with dMMR and pMMR tumors. Patients had not received prior systemic therapy or had received prior chemotherapy in the adjuvant setting. Patients who had received prior adjuvant chemotherapy were eligible if their chemotherapy-free interval was at least 12 months. Patients with endometrial sarcoma, including carcinosarcoma, or patients with active

⁺ Denotes ongoing response

autoimmune disease or a medical condition that required immunosuppression were ineligible. Randomization was stratified according to MMR status, ECOG PS (0 or 1 vs. 2), and prior adjuvant chemotherapy. Patients were randomized (1:1) to one of the following treatment arms:

- KEYTRUDA 200 mg every 3 weeks, paclitaxel 175 mg/m² and carboplatin AUC 5 mg/mL/min for 6 cycles, followed by KEYTRUDA 400 mg every 6 weeks for up to 14 cycles.
- Placebo every 3 weeks, paclitaxel 175 mg/m² and carboplatin AUC 5 mg/mL/min for 6 cycles, followed by placebo every 6 weeks for up to 14 cycles.

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

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

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

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

The primary efficacy outcome measure was PFS as assessed by the investigator according to RECIST 1.1. Secondary efficacy outcome measures included OS. The trial demonstrated statistically significant improvements in PFS for patients randomized to KEYTRUDA in combination with chemotherapy compared to placebo in combination with chemotherapy in both the dMMR and pMMR populations. The median follow-up time was 13.6 months (range: 0.6 to 39.4 months) and 8.7 months (range: 0.1 to 37.2 months) in the dMMR and pMMR populations, respectively. At the time of PFS analysis, OS data were not mature with 12% deaths in the dMMR population and 17% of deaths in the pMMR population. Among the patients who had been randomized to receive placebo in combination with chemotherapy and discontinued from the study, 55% from the dMMR population and 45% from the pMMR population subsequently received post-study therapies that incorporated anti-PD-1/PD-L1 therapy. Table 109, Figure 29 and Figure 30 summarize the efficacy results for KEYNOTE-868 by MMR status.

Table 109: Efficacy Results in KEYNOTE-868

Endpoint	dMMR Po	opulation	pMMR Population		
	KEYTRUDA	Placebo	KEYTRUDA	Placebo	
	and	and	and	and	
	chemotherapy*	chemotherapy*	chemotherapy*	chemotherapy*	
	n=110	n=112	n=294	n=294	
PFS					
Number (%) of patients with event	29 (26%)	60 (54%)	95 (32%)	138 (47%)	
Median in months (95% CI)	NR (30.7, NR)	8.3 (6.5, 12.3)	13.1 (10.6, 19.5)	8.7 (8.4, 11.0)	
Hazard ratio [†] (95% CI)	0.34 (0.22, 0.53)		0.57 (0.44, 0.74)		
p-Value [‡]	<0.0001		<0.0001		

^{*} Chemotherapy (paclitaxel and carboplatin)

[†] Based on the stratified Cox proportional hazard model

[‡] Based on stratified log-rank test (compared to an alpha boundary of 0.00207 for dMMR and 0.00116 for pMMR) NR=not reached

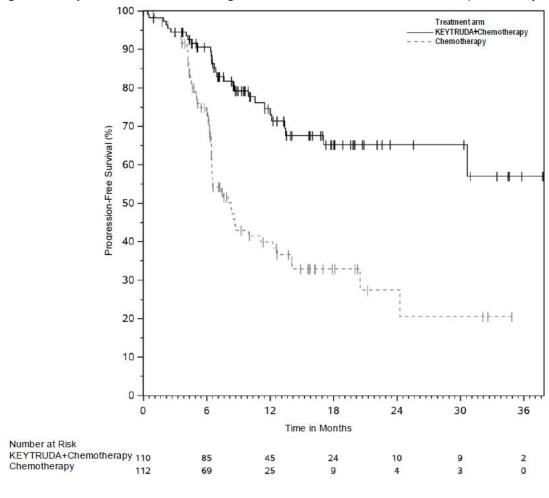


Figure 29: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-868 (dMMR Population)

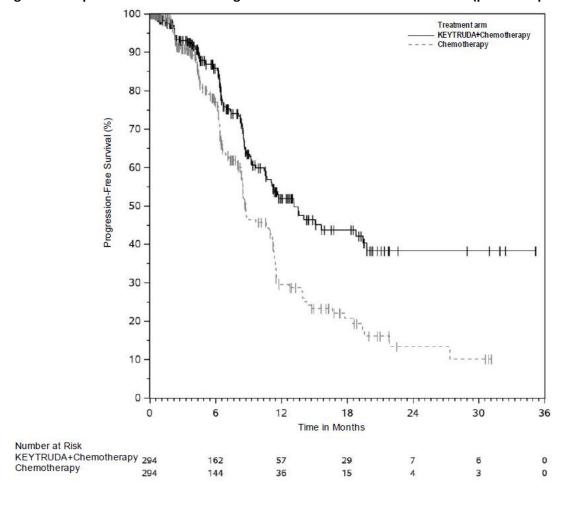


Figure 30: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-868 (pMMR Population)

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

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.

Efficacy results are summarized in Table 110.

Table 110: Efficacy Results for Patients with Endometrial Carcinoma that is not MSI-H or dMMR in KEYNOTE-146.

	KEYTRUDA and 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

<u>KEYNOTE-775: Controlled trial of combination therapy in patients with advanced endometrial</u> carcinoma, who have received prior systemic therapy

The efficacy of KEYTRUDA in combination with lenvatinib was investigated in KEYNOTE-775, a multicenter, open-label, randomized, active-controlled trial that enrolled 827 patients with advanced endometrial carcinoma who had been previously treated with at least one prior platinum-based chemotherapy regimen in any setting, including in the neoadjuvant and adjuvant settings.

Patients with endometrial sarcoma, including carcinosarcoma, or patients who had active autoimmune disease or a medical condition that required immunosuppression were ineligible. Patients with endometrial carcinoma that were not MSI-H or dMMR were stratified by ECOG performance status, geographic region, and history of pelvic radiation. Patients were randomized (1:1) to one of the following treatment arms:

 KEYTRUDA 200 mg intravenously every 3 weeks in combination with lenvatinib 20 mg orally once daily.

[†] Based on patients (n=36) with a response by independent review

⁺ Censored at Data cutoff

CI = confidence interval; NR= Not reached.

• Investigator's choice, consisting of either doxorubicin 60 mg/m² every 3 weeks or paclitaxel 80 mg/m² given weekly, 3 weeks on/1 week off.

Treatment with KEYTRUDA and lenvatinib continued until RECIST v1.1-defined progression of disease as verified by BICR, unacceptable toxicity, or for KEYTRUDA, a maximum of 24 months or up to 35 administrations which ever was longer; however, treatment with lenvatinib could be continued beyond 24 months.

Treatment was permitted beyond RECIST v1.1-defined disease progression if the treating investigator considered the patient to be deriving clinical benefit, and the treatment was tolerated. Assessment of tumour status was performed every 8 weeks. The primary efficacy outcome measures were OS and PFS as assessed by BICR according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Additional efficacy outcome measures included ORR and DoR, as assessed by BICR.

Among the 697 not dMMR patients, 346 patients were randomized to KEYTRUDA in combination with lenvatinib, and 351 patients were randomized to investigator's choice of doxorubicin (n=254) or paclitaxel (n=97). The not dMMR population characteristics were: median age of 65 years (range: 30 to 86), 52% age 65 or older; 62% White, 22% Asian, and 3% Black; 60% ECOG PS of 0 and 40% ECOG PS of 1. The histologic subtypes were endometrioid carcinoma (55%), serous (30%), clear cell carcinoma (7%), mixed (4%), and other (3%). All 697 of these patients received prior systemic therapy for endometrial carcinoma: 67% had one, 30% had two, and 3% had three or more prior systemic therapies. Thirty-seven percent of patients received only prior neoadjuvant or adjuvant therapy.

Efficacy results for the not MSI-H or dMMR patients are summarized in Table 111 and Figure 31 and Figure 32.

Table 111 : Efficacy Results for Patients with Advanced Endometrial Carcinoma that is not MSI-H or dMMR in KEYNOTE-775

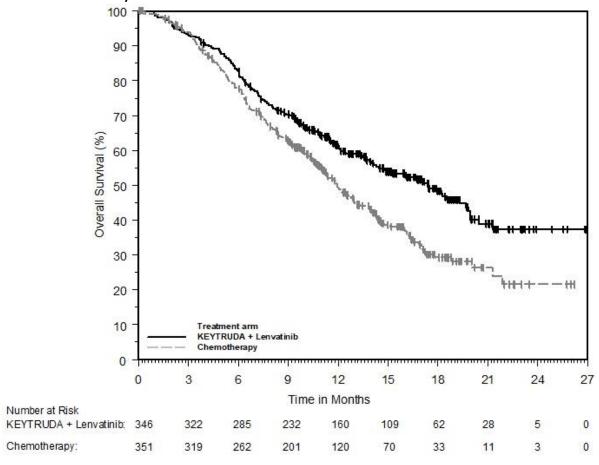
	Endometrial Carcinoma (not MSI-H or dMMR)		
Endpoint	KEYTRUDA	Doxorubicin or Paclitaxel	
	200 mg every 3 weeks		
	and		
	Lenvatinib		
	n=346	n=351	
os			
Number (%) of patients with event	165 (48%)	203 (58%)	
Median in months (95% CI)	17.4 (14.2, 19.9)	12.0 (10.8, 13.3)	
Hazard ratio* (95% CI)	0.68 (0.56, 0.84)		
p-Value [†]	0.	0001	
PFS			
Number (%) of patients with event	247 (71%)	238 (68%)	
Median in months (95% CI)	6.6 (5.6, 7.4)	3.8 (3.6, 5.0)	
Hazard ratio* (95% CI)	0.60 (0.50, 0.72)		
p-Value [†]	<0.0001		
Objective Response Rate			
ORR [‡] (95% CI)	30% (26, 36)	15% (12, 19)	
Complete response rate	5%	3%	

Partial response rate	25%	13%
p-Value [¶]	<0	0.0001

Based on the stratified Cox regression model

The exploratory analyses in responders suggested the median duration of response of 9.2 months (range from 1.6+ to 23.7+) for KEYTRUDA in combination with lenvatinib treated patients (n=105) and 5.7 months (0+ to 24.2+ months) for patients treated with doxorubicin or paclitaxel (n=53).

Figure 31: Kaplan-Meier Curve for Overall Survival in KEYNOTE-775 (Not MSI-H or dMMR)



Based on stratified log-rank test

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

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

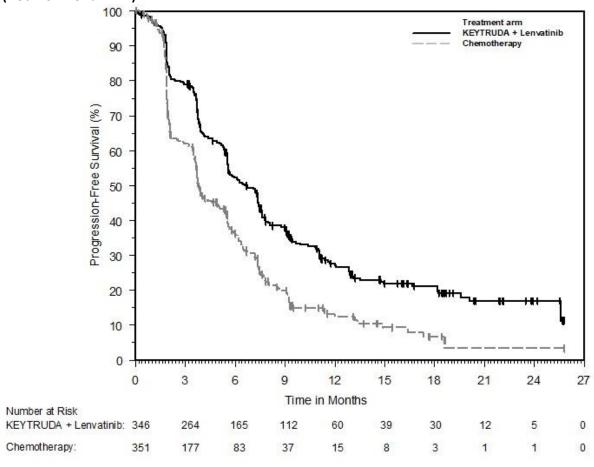


Figure 32: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-775 (Not MSI-H or dMMR)

Renal Cell Carcinoma

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

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.

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 112 summarizes key efficacy measures at the prespecified first interim analysis. OS and PFS benefits were observed in the Intent To Treat population and regardless of PD-L1 expression level.

Table 112: Efficacy Results for Patients with Advanced and Metastatic RCC in KEYNOTE-426, Interim Analysis 1 (Intent To Treat Population).

	KEYTRUDA	Sunitinib	
Fuduciut	and		
Endpoint	Axitinib		
	n=432	n=429	
Primary Efficacy Outcome Measur	e OS ^a		
Number of patients with event	59 (14%)	97 (23%)	
(%)	39 (14%)	97 (23%)	
Median in months (95% CI)	Not reached (NA, NA)	Not reached (NA, NA)	
Hazard ratio* (95% CI)	0.5	3 (0.38, 0.74)	
p-Value [†]	0.00005		
Primary Efficacy Outcome Measur	e PFS ^a		
Number of patients with event	183 (42%)	213 (50%)	
(%)	183 (42%)	213 (30%)	
Median in months (95% CI)	15.1 (12.6, 17.7)	11.1 (8.7, 12.5)	
Hazard ratio* (95% CI)	0.6	9 (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.

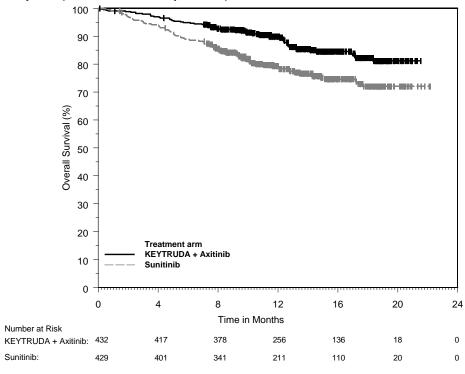
	KEYTRUDA	Sunitinib
Findingint	and	
Endpoint	Axitinib	
	n=432	n=429

[‡] Based on patients with a best overall response as confirmed complete or partial response

The final OS analysis was performed at a median follow-up of 37.7 months after 418 patient events (193 in the KEYTRUDA and axitinib arm and 225 in the sunitinib arm). Median OS was 45.7 months (95% CI: 43.6, NA) in the KEYTRUDA and axitinib arm and 40.1 months (95% CI: 34.3, 44.2) in the sunitinib arm. Approximately 47.2% of participants in the KEYTRUDA and axitinib arm and 65.5% of participants in the sunitinib arm received a new subsequent anticancer therapy. The OS HR was 0.73 (95% CI: 0.60, 0.88).

In an exploratory analysis, the updated analysis of OS in patients with IMDC favourable, intermediate, and poor risk demonstrated a HR of 1.17 (95% CI: 0.76, 1.80), 0.67 (95% CI: 0.52, 0.86) and 0.51 (95% CI: 0.32, 0.81), respectively.

Figure 33: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-426, Interim Analysis 1 (Intent to Treat Population)



The OS Kaplan-Meier curves separated in favour of pembrolizumab + axitinib at the first Interim Analysis and remained separated at the time of the final analysis of 51-month follow-up.

[§] Based on Miettinen and Nurminen method stratified by IMDC risk group and geographic region NA = not available

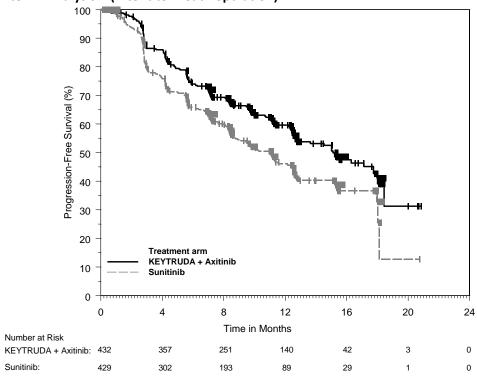


Figure 34: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-426, Interim Analysis 1 (Intent to Treat Population)

<u>KEYNOTE-581: Controlled trial of combination therapy with lenvatinib in patients with advanced or metastatic RCC with no prior systemic therapy</u>

The efficacy of KEYTRUDA in combination with lenvatinib was investigated in KEYNOTE-581, a multicenter, open-label, randomized trial conducted in 1069 patients with advanced or metastatic RCC, with clear cell component, who have not received prior systemic therapy for metastatic RCC. Patients were enrolled regardless of PD-L1 tumour expression status. Patients were stratified by geographic region (North America versus Western Europe versus "Rest of the World") and Memorial Sloan Kettering Cancer Center (MSKCC) prognostic groups (favorable versus intermediate versus poor risk). The study excluded patients with active autoimmune disease or a medical condition that required immunosuppression, active brain metastasis, poorly controlled hypertension, uncontrolled adrenal insufficiency, gastrointestinal malabsorption, bleeding or thrombotic disorders.

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

- KEYTRUDA 200 mg intravenously every 3 weeks up to 24 months in combination with lenvatinib 20 mg orally once daily (n=355).
- Lenvatinib 18 mg orally once daily in combination with everolimus 5 mg orally once daily (n=357).
- Sunitinib 50 mg orally once daily for 4 weeks then off treatment for 2 weeks (n=357).

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

or 35 administrations which ever was longer; however, treatment with lenvatinib could be continued beyond 24 months. Assessment of tumour status was performed at baseline and then every 8 weeks.

The study population baseline characteristics were in general comparable between the treatment arms with a median age of 62 years (range: 29 to 88 years); 42% were age 65 or older and 11% age 75 or older; 75% male; 74% White, 21% Asian, 1% Black, and 2% other races; 18% and 82% of patients had a baseline KPS of 70% to 80% and 90% to 100%, respectively; MSKCC risk categories was 27% favorable, 64% intermediate and 9% poor. Common sites of metastases in patients were lung (68%), lymph node (45%), and bone (25%). In addition, 6.8% of patients had tumours with sarcomatoid features. Metastatic disease was present in 99% of the patients and locally advanced disease was present in 1%.

The primary efficacy outcome measure was PFS based on BICR using RECIST 1.1. Key secondary efficacy outcome measures included OS and ORR. The trial demonstrated statistically significant improvements in PFS, OS, and ORR in patients randomized to KEYTRUDA in combination with lenvatinib compared with sunitinib. The median overall survival follow-up time was 26.6 months (range: 0.03+, 46.13+ months). Pre-specified interim analysis efficacy results for KEYNOTE-581 are summarized in Table 113 and Figure 35.

Table 113: Efficacy Results for Patients with Advanced and Metastatic RCC in KEYNOTE-581, Interim Analysis 3

Endpoint	KEYTRUDA	Sunitinib
	200 mg every 3 weeks	
	and	
	Lenvatinib	
	n=355	n=357
PFS	·	
Number of patients with event (%)	160 (45%)	205 (57%)
Median in months (95% CI)	23.9 (20.8, 27.7)	9.2 (6.0, 11.0)
Hazard ratio* (95% CI)	0.39 (0.32, 0.49)	
p-Value [†]	<0.0001	
OS		
Number of patients with event (%)	80 (23%)	101 (28%)
Median in months (95% CI)	NR (33.6, NR)	NR (NR, NR)
Hazard ratio* (95% CI)	0.66 (0.49, 0.	88)
p-Value [†]	0.0049	
Objective Response Rate		
ORR [‡] (95% CI)	71% (66, 76)	36% (31, 41)
Complete response rate	16%	4%
Partial response rate	55%	32%
p-Value [‡]	<0.0001	

^{*} Based on the stratified Cox proportional hazard model stratified by geographic region and MSKCC prognostic groups.

NR = not reached

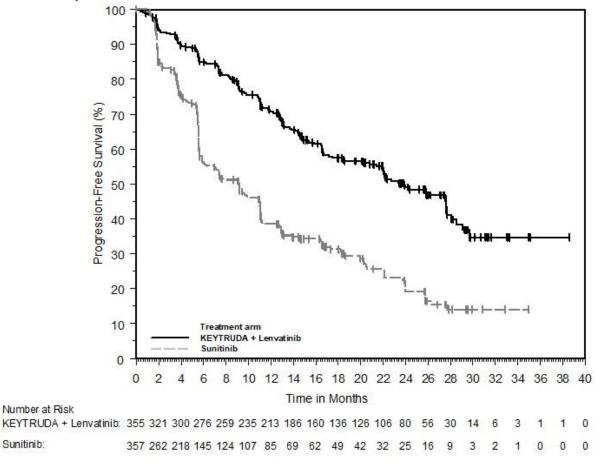
Two-sided p-Value based on stratified log-rank test, compared with a boundary of 0.0411 for PFS, and 0.0161 for OS, respectively.

[‡] Two-sided p-Value based on Cochran-Mantel-Haenszel test

The exploratory analyses in responders suggested the median duration of response of 25.8 months (range: 1.64+, 36.76+) for KEYTRUDA in combination with lenvatinib treated patients and 14.6 months (range: 1.64+, 33.15+) for sunitinib treated patients. Additional exploratory analyses indicated a consistent treatment benefit in PFS across all three pre-specified MSKCC risk groups.

The final descriptive OS analysis was performed at median follow-up of 49.4 months after 149 patient events for KEYTRUDA in combination with lenvatinib and 159 patient events for sunitinib. Median OS was 53.7 months (95% CI: 48.7, NE) for KEYTRUDA in combination with lenvatinib and 54.3 months (95% CI: 40.9, NE) for sunitinib. The OS HR was 0.79 (95% CI: 0.63, 0.99). A total of 195/357 (54.6%) patients in the sunitinib arm and 56/355 (15.8%) patients in the KEYTRUDA plus lenvatinib arm received subsequent systemic anti-PD-1/PD-L1 therapy. See Figure 36. At final analysis, the results for PFS and ORR remained consistent with the interim analysis (see Table 113).

Figure 35: Kaplan-Meier Curve for Progression-Free Survival by Treatment Arm in KEYNOTE-581, Interim Analysis 3



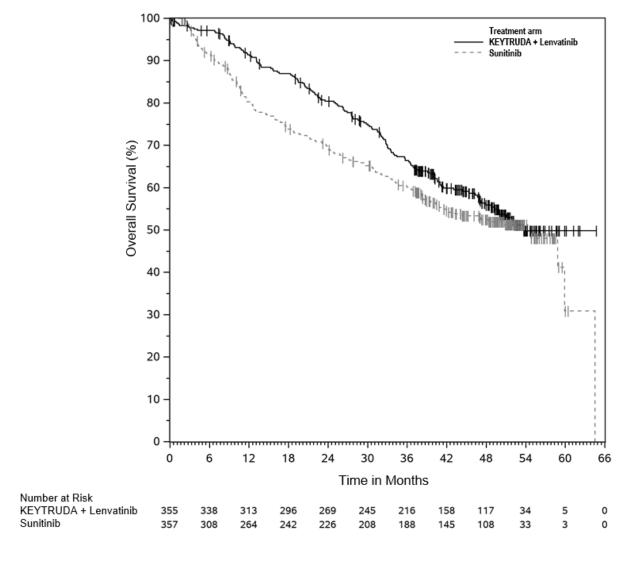


Figure 36: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-581, Final Analysis

Adjuvant RCC

KEYNOTE-564: Placebo-controlled study for the adjuvant treatment of adult patients with resected RCC The efficacy of KEYTRUDA was investigated as adjuvant therapy for RCC in KEYNOTE-564, a multicenter, randomized, double-blind, placebo-controlled study in 994 patients with intermediate-high or high risk of recurrence of RCC, or M1 no evidence of disease (NED). The intermediate high-risk category included: pT2 with Grade 4 or sarcomatoid features; pT3, any Grade without nodal involvement (N0) or distant metastases (M0). The high-risk category included: pT4, any Grade N0 and M0; any pT, any Grade with nodal involvement and M0. The M1 NED category included patients with metastatic disease who had undergone complete resection of primary and metastatic lesions. Patients must have undergone a partial nephroprotective or radical complete nephrectomy (and complete resection of solid, isolated, soft tissue metastatic lesion(s) in M1 NED participants) with negative surgical margins ≥4 weeks prior to the time of screening. Patients with active autoimmune disease or a medical condition that required immunosuppression were ineligible. Patients who had received prior systemic therapy for advanced RCC were excluded from the trial. Patients were randomized (1:1) to

receive KEYTRUDA 200 mg every 3 weeks (n=496) or placebo (n=498) for up to 1 year, until disease recurrence, or until unacceptable toxicity. Randomization was stratified by metastasis status (M0, M1 NED), within M0 group, further stratified by ECOG PS (0,1), and geographic region (US, non-US). Patients underwent imaging every 12 weeks for the first 2 years from randomization, then every 16 weeks from year 3 to 5, and then every 24 weeks annually.

Baseline characteristics and demographics were generally comparable between the KEYTRUDA and placebo arms. Overall, 86% were intermediate-high risk, 8% were high risk, and 6% were M1 NED. Ninety-two percent of patients had a radical nephrectomy, 8% had a partial nephrectomy. Among the 994 patients, the baseline characteristics were: median age of 60 years (range: 25 to 84), 33% age 65 or older; 71% male; and 85% ECOG PS of 0 and 15% ECOG PS of 1. Ninety-four percent were N0; 84% had no sarcomatoid features; 86% were pT2 with Grade 4 or sarcomatoid features or pT3; 8% were pT4 or with nodal involvement; and 6% were M1 NED.

The primary efficacy outcome measure was investigator-assessed disease-free survival (DFS) defined as time to recurrence, metastasis, or death. The key secondary outcome measure was OS. At pre-specified interim analyses, statistically significant improvements in DFS (at the first interim analysis; median follow-up time was 23.9 months (range: 2.5 to 41.5 months)) and OS (at the third interim analysis; median follow-up time was 55.8 months (range: 2.5 to 74.5 months)) were demonstrated for patients randomized to the KEYTRUDA arm compared with placebo. Efficacy results are summarized in Table 114, Figure 37, and Figure 38.

Table 114: Efficacy Results in KEYNOTE-564

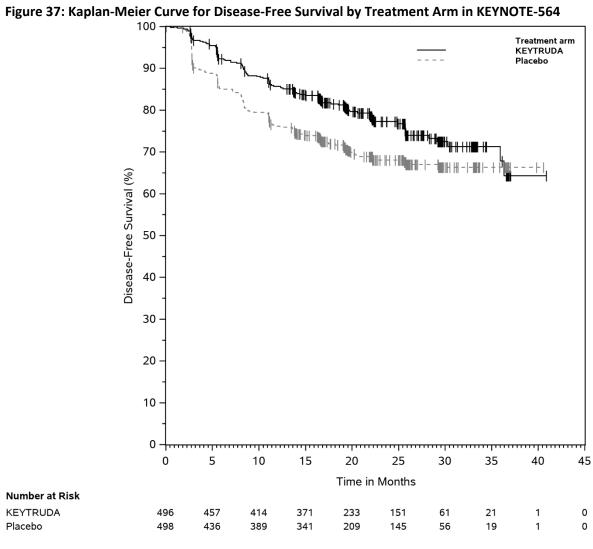
Endpoint	KEYTRUDA 200 mg every 3 weeks n=496	Placebo n=498
DFS	11-450	11-456
Number (%) of patients with event	109 (22%)	151 (30%)
Median in months (95% CI)	NR	NR
Hazard ratio* (95% CI)	0.68 (0.53, 0.87)	
p-Value	0.0010 [†]	
OS		
Number (%) of patients with event	55 (11%)	86 (17%)
Median in months (95% CI)	NR	NR
Hazard ratio* (95% CI)	0.62 (0.44, 0.87)	
p-Value	0.0024 [‡]	

^{*} Based on the stratified Cox proportional hazard model.

At the pre-specified third interim analysis, the updated DFS HR was 0.72 (95% CI: 0.59, 0.87).

[†] Based on stratified log-rank test. p-Value is one-sided comparison with a boundary of 0.00114.

[‡] Based on stratified log-rank test. p-Value is one-sided comparison with a boundary of 0.0072. NR = not reached



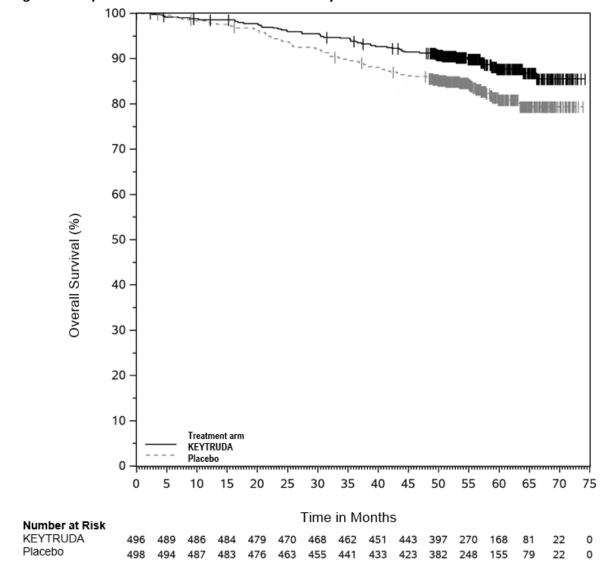


Figure 38: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-564

Head and Neck Cancer

<u>KEYNOTE-689: Controlled trial for the neoadjuvant and adjuvant treatment of patients with resectable locally advanced HNSCC</u>

The efficacy of KEYTRUDA was investigated in KEYNOTE-689, a randomized, multicenter, open label, active controlled trial conducted in 714 patients with resectable locally advanced (Stage III-IVA) HNSCC. Patients with active autoimmune disease that required systemic therapy within two years of treatment or a medical condition that required immunosuppression were ineligible.

Randomization was stratified by primary tumour site (oropharynx/oral cavity vs. larynx vs. hypopharynx), tumour stage (III vs. IVA) and PD-L1 status (TPS ≥ 50% vs. TPS < 50%).

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

Neoadjuvant KEYTRUDA 200 mg for 2 cycles every 3 weeks prior to surgical resection. Within 6 weeks following surgery, KEYTRUDA 200 mg for 3 cycles in combination with either radiation +

- 3 cycles of cisplatin 100 mg/m2 every 3 weeks for patients with high-risk pathological features after surgery or radiation alone for patients without high-risk pathological features after surgery. This was followed by KEYTRUDA 200 mg every 3 weeks for up to 12 cycles.
- No neoadjuvant treatment prior to surgery. Within 6 weeks following surgery, either radiation
 + 3 cycles of cisplatin 100 mg/m2 every 3 weeks for patients with high-risk pathological
 features after surgery or radiation alone for patients without high-risk pathological features
 after surgery.

High risk pathological features included the presence of positive margins or extranodal extension following surgical resection.

Treatment with KEYTRUDA continued until completion of the treatment (17 cycles), disease progression that precluded definitive surgery, disease recurrence in the adjuvant phase, disease progression for those who did not undergo surgery or had incomplete resection and entered the adjuvant phase, or unacceptable toxicity.

Assessment of tumour status was performed prior to surgery at Week 6 in the neoadjuvant phase. Following the start of the adjuvant phase, assessment of tumour status was performed 12 weeks after the end of RT \pm cisplatin treatment and then every 3 months until the end of Year 3; then every 6 months thereafter up to the end of Year 5.

The primary efficacy outcome measure was event free survival (EFS) by Blinded Independent Central Review (BICR) defined as the time from randomization to the first occurrence of any of the following events: progression of disease that precludes definitive surgery, local or distant disease progression or recurrence, or death due to any cause. Secondary primary malignancy was not considered an event. An additional efficacy outcome measure was overall survival (OS).

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

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

Eighty-eight percent of patients completed definitive surgery in both the KEYTRUDA and in the SOC arm. Seventy-six percent of patients in the KEYTRUDA arm and 78% of patients in the SOC arm started the radiation phase of treatment. In the KEYTRUDA arm, 35% of patients received KEYTRUDA and cisplatin with concurrent radiation and 57% received KEYTRUDA alone with concurrent radiation, 3% of patients received cisplatin alone with concurrent RT, 5% of patients received RT alone and one patient (0.4%) received KEYTRUDA alone without concurrent RT. In the SOC arm, 52% of patients received cisplatin with concurrent radiation, and 48% received radiation alone.

Table 115 and Figure 39 describe efficacy results in KEYNOTE-689.

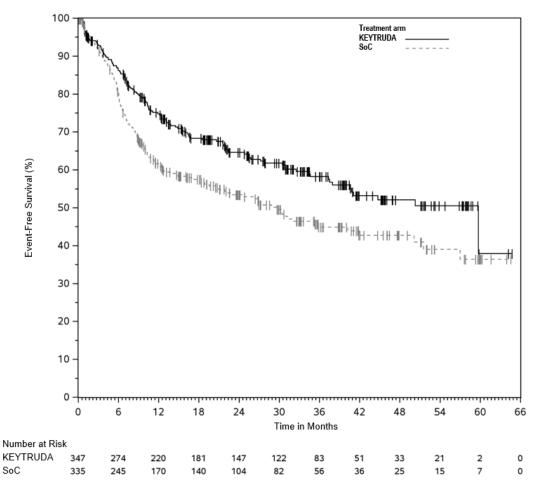
Table 115: Efficacy Results for Perioperative KEYTRUDA with adjuvant RT with or without cisplatin in patients with HNSCC CPS ≥ 1 in KEYNOTE-689

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

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

NR = not reached

Figure 39: Kaplan-Meier Curve for Event-Free Survival for KEYTRUDA in patients with HNSCC CPS ≥ 1 in KEYNOTE-689



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

[‡]One-sided p-value based on log-rank test stratified by primary tumour site and tumour stage. Compared to a one-sided p value boundary of 0.0120

Hypopharyngeal Tumours

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

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

The efficacy of KEYTRUDA was investigated in Study KEYNOTE-048, a 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 tumour PD-L1 expression (TPS \geq 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/m² every 3 weeks, and FU 1000 mg/m²/d 4 days continuous every 3 weeks (maximum of 6 cycles of platinum and FU)
- Cetuximab 400 mg/m² load then 250 mg/m² once weekly, carboplatin AUC 5 mg/ml/min every 3 weeks or cisplatin 100 mg/m² every 3 weeks, and FU 1000 mg/m²/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 tumour status was performed at Week 9 and then every 6 weeks for the first year, followed by every 9 weeks through 24 months.

Table 116: Baseline Characteristics in KEYNOTE-048.

	KEYTRUDA	KEYTRUDA	Standard
	and		Treatment*
	Platinum Chemotherapy		
	and		
	FU		
	n=281	n=301	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%

	KEYTRUDA and	KEYTRUDA	Standard Treatment*
	Platinum Chemotherapy		
	and		
	FU		
	n=281	n=301	n=300
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%
* Cetuximab, platinum, and FU			

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 \geq 1 randomized to pembrolizumab monotherapy compared to standard treatment. Table 117 and Table 118 and Figure 40 and Figure 41 describe key efficacy results for KEYTRUDA in KEYNOTE-048.

Table 117: Efficacy Results for KEYTRUDA plus Chemotherapy in KEYNOTE-048 at Final Analysis.

Endpoint	KEYTRUDA and Platinum Chemotherapy and 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, 0.87)	
p-Value [‡]	0.000	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 haz	ard model		

	KEYTRUDA	Standard
	and	Treatment*
Fordering	Platinum Chemotherapy	
Endpoint	and	
	FU	
	n=281	n=278
[‡] Based on stratified log-rank test		

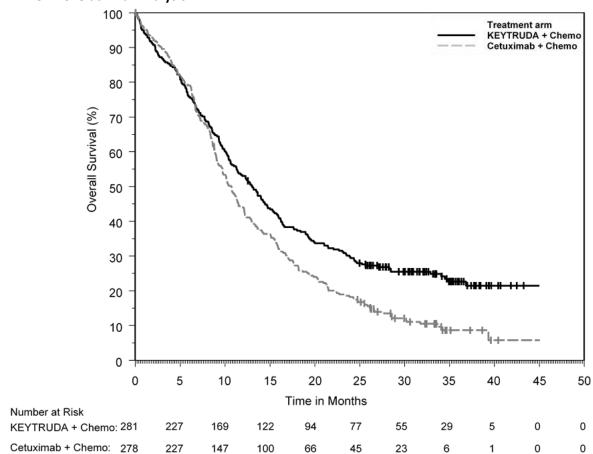


Figure 40: Kaplan-Meier Curve for Overall Survival for KEYTRUDA plus Chemotherapy in KEYNOTE-048 at Final Analysis

Table 118: Efficacy Results for KEYTRUDA as Monotherapy in KEYNOTE-048, with CPS ≥ 1 at Final Analysis.

Endpoint	KEYTRUDA	Standard Treatment*
	n=257	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

[‡] Based on stratified log-rank test

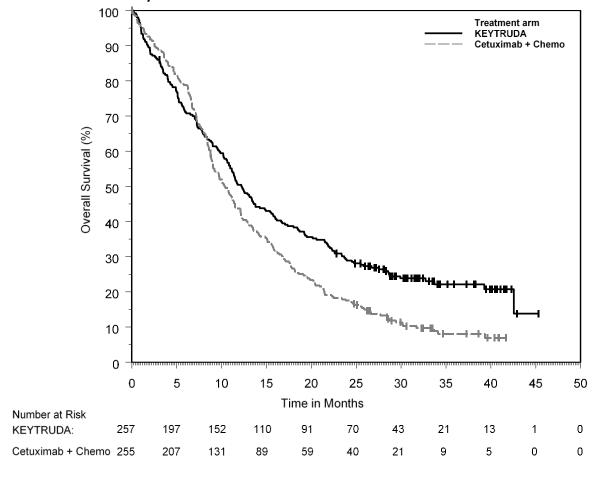


Figure 41: Kaplan-Meier Curve for Overall Survival for KEYTRUDA as Monotherapy in KEYNOTE-048, with CPS ≥ 1 at Final Analysis

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 \geq 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.

Gastric or Gastroesophageal junction (GEJ) Adenocarcinoma

<u>KEYNOTE-811: First-line treatment of locally advanced unresectable or metastatic HER2-positive gastric</u> or gastroesophageal junction (GEJ) adenocarcinoma

The efficacy of KEYTRUDA in combination with trastuzumab plus fluoropyrimidine and platinum chemotherapy was investigated in KEYNOTE-811, a multicenter, randomized, double-blind, placebo-controlled trial that enrolled 698 patients with HER2-positive advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma regardless of PD-L1 expression status, who had not previously received systemic therapy for metastatic disease. Patients with an autoimmune disease that required systemic

therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Randomization was stratified by PD-L1 expression (CPS ≥1 or <1), chemotherapy regimen (5-FU plus cisplatin [FP] or capecitabine plus oxaliplatin [CAPOX]), and geographic region (Europe/ Israel/ North America/ Australia, Asia or Rest of the World). Patients were randomized (1:1) to one of the following treatment arms; all study medications, except oral capecitabine, were administered as an intravenous infusion for every 3-week cycle:

- KEYTRUDA 200 mg, trastuzumab 8 mg/kg on first infusion and 6 mg/kg in subsequent cycles, followed by investigator's choice of combination chemotherapy of cisplatin 80 mg/m² for up to 6 cycles and 5-FU 800 mg/m²/day for 5 days (FP) or oxaliplatin 130 mg/m² up to 6-8 cycles and capecitabine 1000 mg/m² bid for 14 days (CAPOX). KEYTRUDA was administered prior to trastuzumab and chemotherapy on Day 1 of each cycle.
- Placebo, trastuzumab 8 mg/kg on first infusion and 6 mg/kg in subsequent cycles, followed by investigator's choice of combination chemotherapy of cisplatin 80 mg/m² for up to 6 cycles and 5-FU 800 mg/m²/day for 5 days (FP) or oxaliplatin 130 mg/m² up to 6-8 cycles and capecitabine 1000 mg/m² bid for 14 days (CAPOX). Placebo was administered prior to trastuzumab and chemotherapy on Day 1 of each cycle.

Treatment with KEYTRUDA, trastuzumab and chemotherapy or placebo, trastuzumab and chemotherapy continued until RECIST v1.1-defined progression of disease as determined by BICR, unacceptable toxicity, or a maximum of 24 months. Treatment was permitted beyond RECIST defined disease progression if the patient was clinically stable and deriving clinical benefit as determined by the investigator. Assessment of tumour status was performed every 6 weeks.

Among the 698 patients randomized in KEYNOTE-811, the study population characteristics were: median age of 63 years (range: 19 to 85), 43% age 65 or older; 81% male; 61% White, 34% Asian, and 0.6% Black; 42% ECOG PS of 0 and 58% ECOG PS of 1. Ninety-eight percent of patients had metastatic disease (stage IV) and 2% had locally advanced unresectable disease. Ninety-four percent had tumours that were not MSI-H, 1% had tumours that were MSI-H, and in 5% the status was not known. Eighty-five percent of patients had tumours that expressed PD-L1 with a CPS ≥1 based on the PD-L1 IHC pharmDx* kit. Eighty-five percent of patients received CAPOX.

The primary efficacy outcome measures were PFS, based on BICR using RECIST 1.1, and OS. Secondary efficacy outcome measures included ORR and DoR, based on BICR using RECIST 1.1.

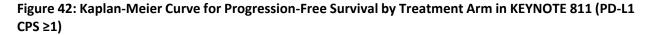
At the second interim analysis in the overall population, a statistically significant improvement in PFS (HR 0.72; 95% CI 0.60, 0.87; p-Value 0.0002) was demonstrated in patients randomized to KEYTRUDA in combination with trastuzumab and chemotherapy compared with placebo in combination with trastuzumab and chemotherapy. At the time of this analysis in the overall population, there was no statistically significant difference with respect to OS. At the first interim analysis conducted on the first 264 patients randomized in the overall population, a statistically significant improvement in ORR was demonstrated in patients randomized to KEYTRUDA in combination with trastuzumab and chemotherapy.

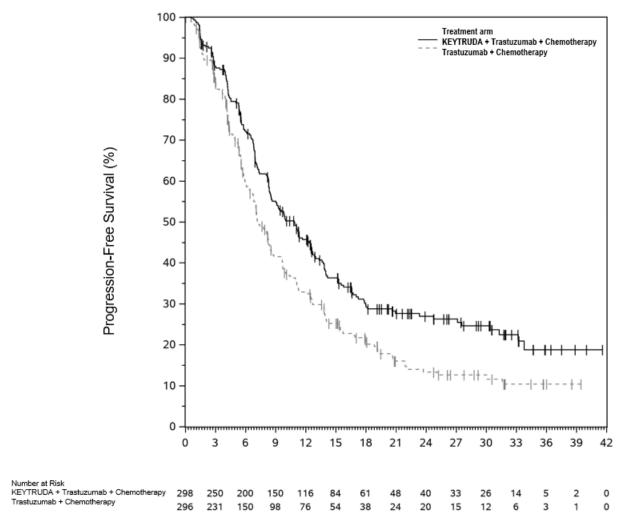
At the second interim analysis, assessment of pre-specified subgroups based on PD-L1 status showed the HR for PFS and OS in patients with PD-L1 CPS <1 (n=104) was 1.17 (95% CI 0.73, 1.89) and 1.61 (95% CI 0.98, 2.64), respectively. Efficacy results at the second interim analysis for the pre-specified subgroup of patients whose tumours expressed PD-L1 with a CPS ≥1 are summarized in Table 119 and Figure 42.

Table 119: Efficacy Results for KEYNOTE-811 with PD-L1 Expression CPS ≥1

Endpoint	KEYTRUDA	Placebo
	200 mg every 3 weeks	
	and	and
	Trastuzumab	Trastuzumab
	and	and
	Fluoropyrimidine	Fluoropyrimidine
	and	and
	Platinum Chemotherapy	Platinum Chemotherapy
	n=298	n=296
PFS		
Number (%) of patients with event	199 (67%)	215 (73%)
Median in months (95% CI)	10.8 (8.5, 12.5)	7.2 (6.8, 8.4)
Hazard ratio [*] (95% CI)	0.7 (0.58, 0.85)	
os		
Number (%) of patients with event	167 (56%)	183 (61.8%)
Median in months (95% CI)	20.5 (18.2, 24.3)	15.6 (13.5, 18.6)
Hazard ratio [∗] (95% CI)	0.79	9 (0.64, 0.98)
Objective Response Rate		
ORR [‡] (95% CI)	73% (67.7, 78.1)	58% (52.6, 64.1)
Complete response rate	14%	10%
Partial response rate	59%	49%
Duration of Response	n=218	n=173
Median in months (range)	11.3 (1.1+, 40.1+)	9.5 (1.4+, 38.3+)

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





In the overall population, a statistically significant improvement in OS (HR 0.80; 95% CI 0.67, 0.94; p-Value=0.004), was demonstrated at final analysis. Updated OS results (HR 0.79; 95% CI 0.66, 0.95) from the final analysis for the pre-specified subgroup of patients whose tumours expressed PD-L1 with a CPS ≥1 are consistent with those observed in the second interim analysis and are summarized in Figure 43.

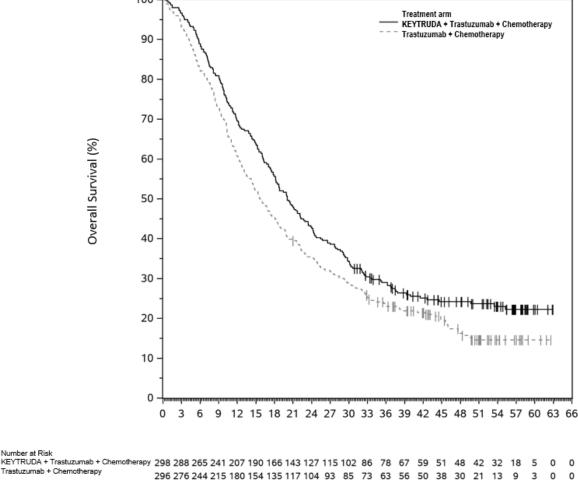


Figure 43: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE 811 (PD-L1 CPS ≥1)*

*Based on the pre-specified final analysis

<u>KEYNOTE-859: Controlled trial of combination therapy in HER2-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma cancer patients naïve to treatment</u>

The efficacy of KEYTRUDA in combination with fluoropyrimidine and platinum based chemotherapy was investigated in KEYNOTE-859, a multicenter, randomized, double-blind, placebo-controlled trial that enrolled 1579 patients with HER2-negative advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma, who had not previously received systemic therapy for metastatic disease. Patients with an autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible. Randomization was stratified by PD-L1 expression (CPS \geq 1 vs. < 1), chemotherapy regimen (5-FU plus cisplatin [FP] vs. capecitabine plus oxaliplatin [CAPOX]), and geographic region (Europe/ Israel/ North America/ Australia vs. Asia vs. Rest of the World). Patients were randomized (1:1) to one of the following treatment arms; treatment was administered prior to chemotherapy on Day 1 of each cycle:

 KEYTRUDA 200 mg, investigator's choice of combination chemotherapy of cisplatin 80 mg/m² and 5-FU 800 mg/m²/day for 5 days (FP) or oxaliplatin 130 mg/m² and capecitabine 1000 mg/m² bid for 14 days (CAPOX) Placebo, investigator's choice of combination chemotherapy of cisplatin 80 mg/m² and 5-FU 800 mg/m²/day for 5 days (FP) or oxaliplatin 130 mg/m² and capecitabine 1000 mg/m² bid for 14 days (CAPOX)

All study medications, except oral capecitabine, were administered as an intravenous infusion for every 3-week cycle. Platinum agents could be administered for 6 or more cycles following local guidelines. Treatment continued until RECIST v1.1-defined progression of disease as determined by BICR, unacceptable toxicity, or a maximum of 24 months. Treatment was permitted beyond RECIST-defined disease progression if the patient was clinically stable and deriving clinical benefit as determined by the investigator. Assessment of tumour status was performed every 6 weeks.

The population characteristics were: median age 62 years (range: 21 to 86), 39% age 65 or older; 68% male; 55% White, 34% Asian, 4.6% Multiple, 4.2% American Indian or Alaskan Native, 1.3% Black and 0.2% Native Hawaiian or other Pacific Islander; 76% Not Hispanic or Latino and 21% Hispanic or Latino; 37% ECOG PS of 0 and 63% ECOG PS of 1; 97% had metastatic disease (Stage IV) and 3% had locally advanced unresectable disease; 78% had tumours that expressed PD-L1 with a CPS ≥1 and 5% (n=74) had tumours that were MSI-H. Eighty-six percent of patients received CAPOX.

The primary efficacy outcome measure was OS. Additional secondary efficacy outcome measures included PFS and ORR as assessed by BICR using RECIST v1.1 modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ.

A statistically significant improvement in OS, PFS and ORR was demonstrated in patients randomized to KEYTRUDA in combination with chemotherapy compared with placebo in combination with chemotherapy.

Efficacy results from the pre-specified interim analysis are summarized in Table 120 and Figure 44.

Table 120: Efficacy Results* in KEYNOTE-859

Endpoint	KEYTRUDA and FP or CAPOX n=790	Placebo and FP or CAPOX n=789	KEYTRUDA and FP or CAPOX n=618	Placebo and FP or CAPOX n=617
	All Pa	tients	PD-L1 (CPS ≥ 1
OS				
Number (%) of patients with event	603 (76)	666 (84)	464 (75)	526 (85)
Median in months	12.9	11.5	13.0	11.4
(95% CI)	(11.9, 14.0)	(10.6, 12.1)	(11.6, 14.2)	(10.5, 12.0)
Hazard ratio [†] (95% CI)	0.78 (0.7	70, 0.87)	0.74 (0.6	55, 0.84)
p-value [‡]	<0.0	0001	<0.0	0001

Endpoint	KEYTRUDA and FP or CAPOX n=790	Placebo and FP or CAPOX n=789	KEYTRUDA and FP or CAPOX n=618	Placebo and FP or CAPOX n=617
	All Pa	tients	PD-L1 (CPS ≥ 1
PFS				
Number (%) of patients with event	572 (72)	608 (77)	443 (72)	483 (78)
Median in months	6.9	5.6	6.9	5.6
(95% CI)	(6.3, 7.2)	(5.5, 5.7)	(6.0, 7.2)	(5.4, 5.7)
Hazard ratio [†] (95% CI)	0.76 (0.6	57, 0.85)	0.72 (0.6	3, 0.82)
p-value [‡]	<0.0	001	<0.0	001
Objective Response Rate				
ORR§ (95% CI)	51% (48%, 55%)	42% (38%, 45%)	52% (48% <i>,</i> 56%)	43% (39%, 47%)
Complete response rate	9%	6%	10%	6%
Partial response rate	42%	36%	42%	37%
p-value [¶]	<0.0	001	0.00	004

 $[\]ensuremath{^*}$ Based on the pre-specified interim analysis

[†] Based on a stratified Cox proportional hazards model

[‡] One-sided p-value based on stratified log-rank test

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

[¶]One-sided p-value based on stratified Miettinen & Nurminen method

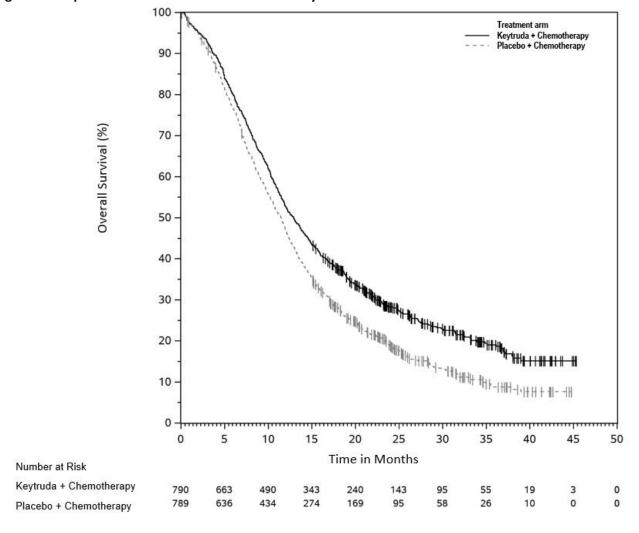


Figure 44: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-859

The duration of response (DOR) was analyzed as a secondary efficacy outcome. In all randomized patients, the median DOR was 8.0 months (range: 1.2+, 41.5+) in the KEYTRUDA with chemotherapy arm compared to 5.7 months (range: 1.3+, 34.7+) in the placebo with chemotherapy arm. In patients with PD-L1 CPS \geqslant 1, the median DOR was 8.3 months (range: 1.2+, 41.5+) in the KEYTRUDA with chemotherapy arm compared to 5.6 months (range: 1.3+, 34.2+) in the placebo with chemotherapy arm.

A positive association was observed between PD-L1 CPS score and the magnitude of the treatment benefit. The hazard ratios (HR) for OS were 0.78, 0.74, 0.65 for all randomized patients (N=1579), PD-L1 CPS \geq 1 patients (n=1235), and PD-L1 CPS \geq 10 patients (n=551), respectively. In an exploratory OS analysis in patients with PD-L1 CPS < 1 (n=344), the HR was 0.92 (95% CI: 0.73, 1.17).

Esophageal Cancer

<u>KEYNOTE-590: Controlled trial of combination therapy in esophageal carcinoma patients naïve to treatment</u>

The efficacy of KEYTRUDA was investigated in KEYNOTE-590, a multicenter, randomized, placebo-controlled trial that enrolled 749 patients as a first-line treatment in patients with locally advanced (not resectable or curable with radiation therapy) or metastatic esophageal carcinoma or esophagogastric junction (EGJ) adenocarcinoma (Siewert Type 1). Eligible patients should have adequate organ function and tumour specimens (newly obtained or archival sample) for PD-L1 testing at a central laboratory at baseline. PD-L1 status was determined using the PD-L1 IHC 22C3 pharmDx kit. Patients with active autoimmune disease, a medical condition that required immunosuppression, known HER2 positive EGJ adenocarcinoma, or a history of prior treatment with an immune checkpoint inhibitor were ineligible.

Randomization was stratified by tumour histology (squamous cell carcinoma vs. adenocarcinoma), geographic region (Asia vs. ex-Asia), and ECOG performance status (0 vs. 1). Patients were randomized (1:1) to one of the following treatment arms; all study medications were administered via intravenous infusion:

- KEYTRUDA 200 mg on Day 1 of each three-week cycle in combination with cisplatin 80 mg/m²
 IV on Day 1 of each three-week cycle for up to six cycles and fluorouracil (FU) 800 mg/m² IV per
 day on Day 1 to Day 5 of each three-week cycle, or per local standard for FU administration, for
 up to24 months.
- Placebo on Day 1 of each three-week cycle in combination with cisplatin 80 mg/m² IV on Day 1 of each three-week cycle for up to six cycles and FU 800 mg/m² IV per day on Day 1 to Day 5 of each three-week cycle, or per local standard for FU administration, for up to24 months.

Treatment with KEYTRUDA or chemotherapy continued until unacceptable toxicity or disease progression. Patients randomized to KEYTRUDA were permitted to continue beyond the first RECIST v1.1-defined disease progression if clinically stable until the first radiographic evidence of disease progression was confirmed at least 4 weeks later with repeat imaging. Patients treated with KEYTRUDA without disease progression could be treated for up to 24 months.

Table 121: Baseline Characteristics in KEYNOTE-590.

	KEYTRUDA	Placebo
	200 mg every 3 weeks	
	and	and
	Cisplatin	Cisplatin
	and	and
	FU	FU
	n=373	n=376
Men	82%	85%
Women	18%	15%
Age (median)	64	62
Age (range)	28-94 years	27-89 years
Race		
White	37%	37%
Asian	54%	53%

	KEYTRUDA 200 mg every 3 weeks	Placebo
	and	and
	Cisplatin and	Cisplatin and
	FU	FU
	n=373	n=376
ECOG PS		
0	40%	40%
1	60%	60%
Metastatic Staging		
M0	8%	10%
M1	92%	90%
Histology		
Adenocarcinoma	27%	27%
Squamous Cell Carcinoma	74%	73%

The major efficacy outcome measures were OS and PFS as assessed by the investigator according to RECIST v1.1. The study pre-specified analyses of OS and PFS based on squamous cell histology, PD-L1 CPS \geq 10, and in all patients. Secondary efficacy outcome measures were ORR and DoR, according to RECIST v1.1, as assessed by the investigator.

The study demonstrated a statistically significant improvement in OS and PFS for patients randomized to KEYTRUDA in combination with cisplatin and FU, compared to cisplatin and FU.

Table 122, Figure 45 and Figure 46 summarize the key efficacy measures for KEYNOTE-590 in all randomized patients (ITT population).

Table 122: Efficacy Results in Patients with Locally Advanced or Metastatic Esophageal and EGJ carcinoma in KEYNOTE-590 (ITT Population).

Endpoint	KEYTRUDA 200 mg every 3 weeks	Placebo
	and	and
	Cisplatin	Cisplatin
	and	and
	FU	FU
	n=373	n=376
OSª		
Number (%) of patients with event	262 (70%)	309 (82%)
Median in months* (95% CI)	12.4 (10.5, 14.0)	9.8 (8.8, 10.8)
Hazard ratio [†] (95% CI)	0.73 (0.62, 0.86)	
p-Value (stratified log-rank)	<0.0001	
PFS ^{‡a}		
Number (%) of patients with event	297 (79.6%)	333 (88.6%)
Median in months* (95% CI)	6.3 (6.2, 6.9)	5.8 (5.0, 6.0)
Hazard ratio [†] (95% CI)	0.65 (0.55, 0.76)	
p-Value (stratified log-rank)	<0.0001	

Endpoint	KEYTRUDA 200 mg every 3 weeks and Cisplatin and FU n=373	Placebo and Cisplatin and FU n=376
Objective Response Rate ^{‡a}		
ORR % (95% CI)	45% (39.9 <i>,</i> 50.2)	29.3% (24.7,34.1)
Complete response rate	6.4%	2.4%
Partial response rate	38.6%	26.9%
p-Value (Miettinen-Nurminen)	<0.0	0001

The corresponding p-value bounds at the interim analysis for OS, PFS and ORR were 0.01421, 0.02477 and 0.025, respectively, following pre-specified multiplicity adjustment.

The duration of response (DOR) was analysed as a secondary efficacy outcome. The median duration of response in patients receiving KEYTRUDA in combination with chemotherapy was 8.3 months (range: 1.2+, 31.0+) compared to 6.0 months (range: 1.5+, 25.0+) for patients receiving standard treatment.

^{*} Based on Kaplan-Meier estimation

[†] Based on the stratified Cox proportional hazard model

[‡] Assessed by investigator using RECIST 1.1

[§] Based on patients with a best overall response as confirmed complete or partial response

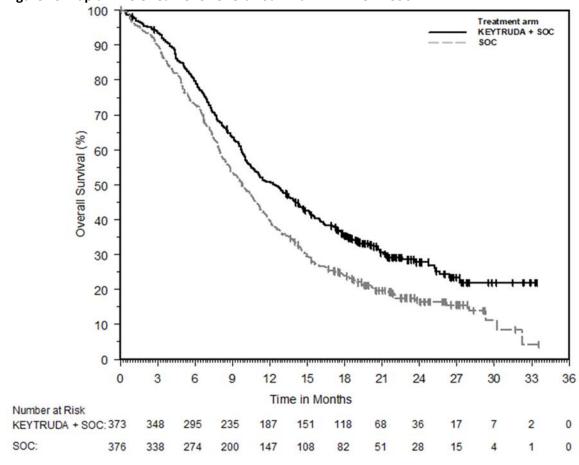


Figure 45: Kaplan-Meier Curve for Overall Survival in KEYNOTE-590

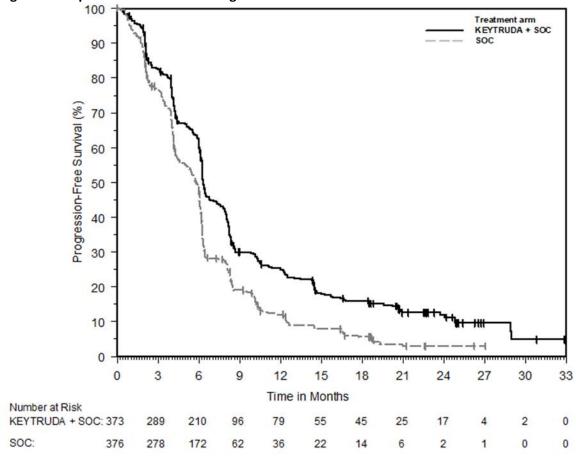


Figure 46: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-590

Table 123: Efficacy Results for Overall Survival in Patients with ESCC PD-L1 CPS ≥ 10, ESCC, and PD-L1 CPS ≥ 10 in KEYNOTE-590.

Endpoint	KEYTRUDA 200 mg every 3 weeks and Cisplatin and FU	Placebo and Cisplatin and FU	
ESCC with PD-L1 CPS ≥ 10 ^a			
	n=143	n=143	
Number (%) of patients with event	94 (65.7)	121 (84.6)	
Median in months* (95% CI)	13.9 (11.1, 17.7)	8.8 (7.8, 10.5)	
Hazard ratio [†] (95% CI)	0.57 (0.43, 0.75)		
p-Value (stratified log-rank)	<0.0001		
ESCC ^a			
	n=274	n=274	
Number (%) of patients with event	190 (69.3)	222 (81.0)	
Median in months* (95% CI)	12.6 (10.2, 14.3)	9.8 (8.6, 11.1)	
Hazard ratio [†] (95% CI)	0.72 (0.60, 0.88)		
p-Value (stratified log-rank)	0.0006		

Endpoint	KEYTRUDA 200 mg every 3 weeks	Placebo
	and Cisplatin and	and Cisplatin and
	FU	FU
PD-L1 CPS ≥ 10 ^a		
	n=186	n=197
Number (%) of patients with event	124 (66.7)	165 (83.8)
Median in months* (95% CI)	13.5 (11.1; 15.6)	9.4 (8.0, 10.7)
Hazard ratio [†] (95% CI)	0.62 (0.49, 0.78)	
p-Value (stratified log-rank)	<0.0001	

- The corresponding p-value bounds at the interim analysis for OS in ESCC PD-L1 CPS \geq 10, ESCC and PD-L1 CPS \geq 10 was 0.0067, 0.01003 and 0.01414, respectively, following prespecified multiplicity adjustment.
- * Based on Kaplan-Meier
- [†] Based on the stratified Cox proportional hazard model
- * Assessed by investigator using RECIST 1.1

ESCC: esophageal squamous cell carcinoma

Exploratory Analysis

In patients with esophageal adenocarcinoma (n=201), the median OS was 11.6 months (95% CI: 9.7, 15.2) for the KEYTRUDA arm and 9.9 months (95% CI: 7.8, 12.3) for the placebo arm, with an HR of 0.74 (95% CI: 0.52, 1.02). In patients with PD-L1 CPS<10 (n=347), the median OS was 10.5 months (95% CI: 9.7, 13.5) for the KEYTRUDA arm and 10.6 months (95% CI: 8.8, 12.0) for the placebo arm, with an HR of 0.86 (95% CI: 0.68, 1.10). In patients with squamous cell carcinoma and PD-L1 CPS < 10 (n=247), the median OS was 10.5 months (95% CI: 9.2, 13.5) for the KEYTRUDA arm and 11.1 months (95% CI: 9.1, 12.4) for the placebo arm, with an HR of 0.99 (95% CI: 0.74, 1.32).

Triple Negative Breast Cancer (TNBC)

KEYNOTE 355: Controlled study of combination therapy in locally recurrent unresectable or metastatic TNBC patients naïve to treatment

The efficacy of KEYTRUDA in combination with paclitaxel, nab paclitaxel, or gemcitabine and carboplatin was investigated in Study KEYNOTE 355, a randomized, double blind, multicenter, placebocontrolled study. The key eligibility criteria for this study were locally recurrent unresectable or metastatic TNBC, regardless of tumour PD L1 expression, and which had not been previously treated with chemotherapy in the metastatic setting. Patients with active autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible for the study. Randomization was stratified by chemotherapy treatment (paclitaxel or nab paclitaxel vs. gemcitabine and carboplatin), tumour PD L1 expression (CPS ≥ 1 vs. CPS <1) based on the PD L1 IHC 22C3 pharmDx* kit, and prior treatment with the same class of chemotherapy in the neoadjuvant setting (yes vs. no).

A total of 847 patients were randomized (2:1) to one of the following treatment arms; all study medications were administered via intravenous infusion.

• KEYTRUDA 200 mg on Day 1 every 3 weeks in combination with nab-paclitaxel 100 mg/m² on Days 1, 8 and 15 every 28 days, or paclitaxel 90 mg/m² on Days 1, 8, and 15 every 28

- days, or gemcitabine 1000 mg/m² and carboplatin AUC 2 mg/mL/min on Days 1 and 8 every 21 days (n=566).
- Placebo on Day 1 every 3 weeks in combination with nab-paclitaxel 100 mg/m² on Days 1, 8 and 15 every 28 days, or paclitaxel 90 mg/m² on Days 1, 8, and 15 every 28 days, or gemcitabine 1000 mg/m² and carboplatin AUC 2 mg/mL/min on Days 1 and 8 every 21 days (n=281).

Assessment of tumour status was performed at Weeks 8, 16, and 24, then every 9 weeks for the first year, and every 12 weeks thereafter. Treatment with KEYTRUDA or placebo continued until RECIST 1.1 defined progression of disease as determined by the investigator, unacceptable toxicity, or a maximum of 24 months. Administration of KEYTRUDA was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered to be deriving clinical benefit by the investigator.

The study population characteristics were: median age of 53 years (range: 22 to 85), 21% age 65 or older; 100% female; 68% White, 21% Asian, and 4% Black; 60% ECOG PS of 0 and 40% ECOG PS of 1; and 68% were post-menopausal status. Seventy five percent of the patients had tumour PD-L1 expression defined as $CPS \ge 1$ and 38% had tumour PD-L1 expression $CPS \ge 10$.

The major efficacy outcome measures were PFS as assessed by blinded independent central review (BICR) using RECIST 1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, and OS in patients with tumour PD-L1 expression CPS ≥10. Final PFS was assessed in the second interim analysis (IA2). Additional efficacy outcome measures were ORR and DOR in patients with tumour PD-L1 expression CPS ≥10 as assessed by BICR using RECIST 1.1. Findings are shown in Table 124 and Figure 47 and Figure 48 below.

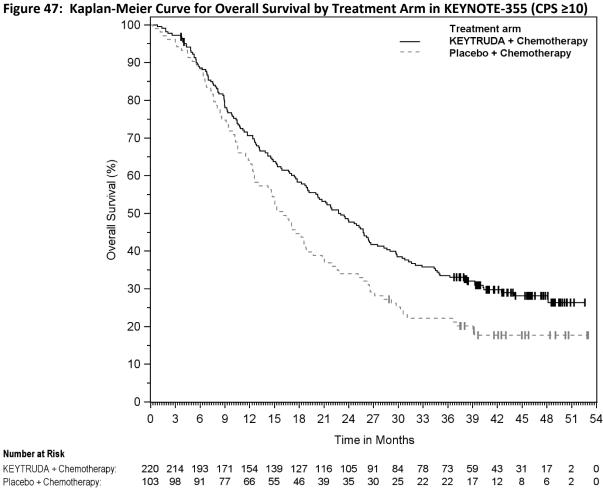
Table 124: Efficacy Results for Patients with locally recurrent unresectable or metastatic TNBC with PD-L1 Expression CPS ≥ 10 in KEYNOTE-355

Endpoint	KEYTRUDA	Placebo
	and	and
	Chemotherapy*	Chemotherapy*
	n=220	n=103
OS [†]		
Number of patients with event	155 (70%)	84 (82%)
(%)		
Median in months (95% CI)	23.0 (19.0, 26.3)	16.1 (12.6, 18.8)
Hazard ratio [‡] (95% CI)	0.73 (0.55, 0.95)	
p-Value [§]	0.0	093
PFS ^{1,#}		
Number of patients with	136 (62%)	79 (77%)
event (%)		
Median in months (95% CI)	9.7 (7.6, 11.3)	5.6 (5.3, 7.5)
Hazard ratio [‡] (95% CI)	0.65 (0.49, 0.86)	
p-Value Þ §	0.0012	

Endpoint	KEYTRUDA and Chemotherapy* n=220	Placebo and Chemotherapy* n=103
Objective Response Rate ^{¶,#†}		
ORR, (95% CI)	53% (46, 59)	41% (31, 51)

- * Chemotherapy: paclitaxel, nab-paclitaxel, or gemcitabine and carboplatin
- [†] Based on the pre-specified final analysis (data cutoff 15 June 2021)
- [‡] Based on stratified Cox regression model
- One-sided p-Value based on stratified log-rank test (compared to a significance level of 0.0113)
- Assessed by BICR using RECIST 1.1
- Based on a pre-specified interim analysis (data cutoff 11 December 2019)
- One-sided p-Value based on stratified log-rank test (compared to a significance level of 0.00411)

The duration of response (DOR) was analysed as a secondary efficacy outcome. At final analysis, the median duration of response was 12.8 months in the KEYTRUDA with chemotherapy arm and 7.3 months in the placebo with chemotherapy arm.



Treatment arm KEYTRUDA + Chemo Placebo + Chemo Progression-Free Survival (%) Time in Months Number at Risk KEYTRUDA + Chemo: 220 Placebo + Chemo:

Figure 48: Kaplan-Meier Curve for Progression Free Survival by Treatment Arm in KEYNOTE-355 (CPS ≥ 10)

Early-stage Triple-Negative Breast Cancer

KEYNOTE-522: Controlled study of neoadjuvant and adjuvant treatment of patients with early-stage TNBC The efficacy of KEYTRUDA in combination with carboplatin and paclitaxel followed by doxorubicin or epirubicin and cyclophosphamide, given as a neoadjuvant treatment and continued as monotherapy adjuvant treatment was investigated in Study KEYNOTE-522, a randomized, double-blind, multicenter, placebo-controlled study. The key eligibility criteria for this study were newly diagnosed previously untreated high-risk early-stage TNBC (tumour size >1 cm but ≤2 cm in diameter with nodal involvement or tumour size >2 cm in diameter regardless of nodal involvement), regardless of tumour PD-L1 expression. Patients with active autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression were ineligible for the study. Randomization was stratified by nodal status (positive vs. negative), tumour size (T1/T2 vs. T3/T4), and choice of carboplatin (dosed every 3 weeks vs. weekly).

Patients were randomized (2:1) to one of the following treatment arms; all study medications were administered via intravenous infusion.

Arm 1:

- Four cycles of preoperative KEYTRUDA 200 mg every 3 weeks on Day 1 of cycles 1-4 of treatment regimen in combination with:
 - Carboplatin
 - AUC 5 mg/mL/min every 3 weeks on Day 1 of cycles 1-4 of treatment regimen
 or AUC 1.5 mg/mL/min every week on Day 1, 8, and 15 of cycles 1-4 of treatment regimen and
 - Paclitaxel 80 mg/m² every week on Day 1, 8, and 15 of cycles 1-4 of treatment regimen
- Followed by four additional cycles of preoperative KEYTRUDA 200 mg every 3 weeks on Day 1 of cycles 5-8 of treatment regimen in combination with:
 - Doxorubicin 60 mg/m² or epirubicin 90 mg/m² every 3 weeks on Day 1 of cycles 5-8 of treatment regimen and
 - Cyclophosphamide 600 mg/m² every 3 weeks on Day 1 of cycles 5-8 of treatment regimen
- Following surgery, 9 cycles of KEYTRUDA 200 mg every 3 weeks were administered.

Arm 2:

- Four cycles of preoperative placebo every 3 weeks on Day 1 of cycles 1-4 of treatment regimen in combination with:
 - Carboplatin
 - AUC 5 mg/mL/min every 3 weeks on Day 1 of cycles 1-4 of treatment regimen
 or AUC 1.5 mg/mL/min every week on Day 1, 8, and 15 of cycles 1-4 of treatment regimen and
 - Paclitaxel 80 mg/m² every week on Day 1, 8, and 15 of cycles 1-4 of treatment regimen
- Followed by four additional cycles of preoperative placebo every 3 weeks on Day 1 of cycles 5-8 of treatment regimen in combination with:
 - Doxorubicin 60 mg/m² or epirubicin 90 mg/m² every 3 weeks on Day 1 of cycles 5-8 of treatment regimen and
 - Cyclophosphamide 600 mg/m² every 3 weeks on Day 1 of cycles 5-8 of treatment regimen
- o Following surgery, 9 cycles of placebo every 3 weeks were administered.

Treatment with KEYTRUDA or placebo continued until completion of the treatment (17 cycles), disease progression that precludes definitive surgery, disease recurrence in the adjuvant phase, or unacceptable toxicity.

The major efficacy outcome measures were pathological complete response (pCR) rate and event-free survival (EFS). pCR was defined as absence of invasive cancer in the breast and lymph nodes (ypT0/Tis ypN0) and was assessed by the blinded local pathologist at the time of definitive surgery. EFS was defined as the time from randomization to the first occurrence of any of the following events: progression of disease that precludes definitive surgery, local or distant recurrence, second primary malignancy, or death due to any cause. An additional efficacy outcome measure was OS.

A total of 1174 patients were randomized: 784 patients to the KEYTRUDA arm and 390 patients to the placebo arm. The study population characteristics were: median age of 49 years (range: 22 to 80), 11% age 65 or older; 99.9% female; 64% White, 20% Asian, and 5% Black; 87% ECOG PS of 0 and 13% ECOG PS of 1; 56% were pre-menopausal status and 44% were post-menopausal status; 7% were primary Tumour 1 (T1), 68% T2, 19% T3, and 7% T4; 49% were nodal involvement 0 (N0), 40% N1, 11% N2, and 0.2% N3; 75% of patients were overall stage II and 25% were stage III; 98.0% of patients received surgery in the KEYTRUDA arm and 97.7% of patients received surgery in the placebo arm.

The trial demonstrated a statistically significant improvement in pCR, EFS, and OS at pre-specified analyses for patients randomized to KEYTRUDA in combination with chemotherapy followed by KEYTRUDA monotherapy compared with patients randomized to placebo in combination with chemotherapy followed by placebo alone. Efficacy results are summarized in Table 125 and Figure 49 and Figure 50.

Table 125: Efficacy Results in Patients with Early-Stage TNBC in KEYNOTE-522

Endpoint	KEYTRUDA	Placebo	
	and	and	
	Chemotherapy/	Chemotherapy/	
	KEYTRUDA	Placebo	
pCR (ypT0/Tis ypN0)*	n=401	n=201	
Number of patients with pCR	260	103	
pCR Rate (%), (95% CI)	64.8 (59.9, 69.5)	51.2 (44.1, 58.3)	
Treatment difference (%) estimate (95% CI) ^{†,‡}	13.6 (5.4, 21.8)		
p-Value	0.000	55	
EFS §	n=784	n=390	
Number of patients with event (%)	123 (16%)	93 (24%)	
Hazard ratio (95% CI) ¶	0.63 (0.48	3, 0.82)	
p-Value [#]	0.000	31	
OSÞ	n=784	n=390	
Number of patients with event (%)	115 (15%)	85 (22%)	
Hazard ratio (95% CI)§	0.66 (0.50, 0.87)		
p-Value [¶]	0.00150		

- * Based on a pre-specified pCR interim analysis (compared to a significance level of 0.003) in 602 patients
- [†] Based on a follow-up analysis in the entire intention-to-treat population (n=1174), the pCR rate difference was 7.5 (95% CI: 1.6, 13.4).
- ‡ Based on Miettinen and Nurminen method stratified by nodal status, tumour size, and choice of carboplatin
- § Based on a pre-specified EFS interim analysis (compared to a significance level of 0.0052) with a median follow-up time of 37.8 months (range: 2.7 to 48 months)
- ¶ Based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by nodal status, tumour size, and choice of carboplatin
- # Based on log-rank test stratified by nodal status, tumour size, and choice of carboplatin
- Based on a pre-specified OS interim analysis (compared to a significance level of 0.0050) with a median follow-up time was 73.1 months (range: 2.7 to 83.9 months)

Figure 49: Kaplan-Meier Curve for Event-Free Survival by Treatment Arm in KEYNOTE-522 (Intent to Treat Population)

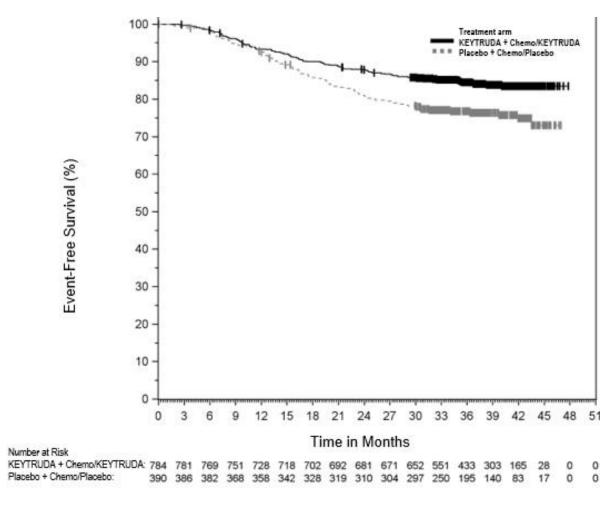
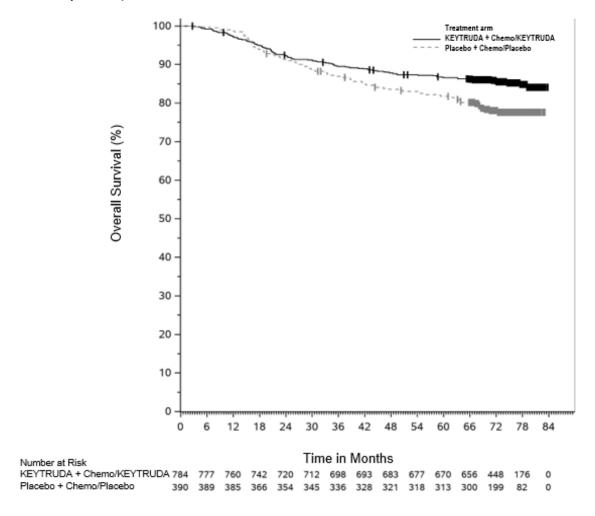


Figure 50: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-522 (Intent to Treat Population)



Cervical Cancer

<u>KEYNOTE-A18: Controlled trial of combination therapy with chemoradiotherapy in patients with FIGO</u> 2014 Stage III-IVA Cervical Cancer

The efficacy of KEYTRUDA in combination with CRT (cisplatin and external beam radiation therapy [EBRT] followed by brachytherapy [BT]) was investigated in KEYNOTE-A18, a multicenter, randomized, double-blind, placebo-controlled trial that enrolled 1060 patients with cervical cancer who had not previously received any definitive surgery, radiation, or systemic therapy for cervical cancer. There were 599 patients with FIGO 2014 Stage III-IVA (tumor involvement of the lower vagina with or without extension onto pelvic sidewall or hydronephrosis/non-functioning kidney or has spread to adjacent pelvic organs) with either node-positive or node-negative disease, and 459 patients with FIGO 2014 Stage IB2-IIB (tumor lesions >4 cm or clinically visible lesions that have spread beyond the uterus but have not extended onto the pelvic wall or to the lower third of vagina) with node-positive disease; two patients had FIGO 2014 Stage IVB disease. Randomization was stratified by planned type of EBRT (Intensity-modulated radiation therapy [IMRT] or volumetric modulated arc therapy [VMAT] vs. non-IMRT and non-VMAT), stage at screening of cervical cancer (FIGO 2014 Stage IB2-IIB vs. FIGO 2014 Stage III-IVA), and planned total radiotherapy dose (EBRT + brachytherapy dose of <70 Gy vs. ≥70 Gy as per equivalent dose [EQD2]).

Patients were randomized (1:1) to one of two treatment arms:

- KEYTRUDA 200 mg IV every 3 weeks (5 cycles) concurrent with cisplatin 40 mg/m² IV weekly (5 cycles, an optional sixth infusion could be administered per local practice) and radiotherapy (EBRT followed by BT), followed by KEYTRUDA 400 mg IV every 6 weeks (15 cycles)
- Placebo IV every 3 weeks (5 cycles) concurrent with cisplatin 40 mg/m² IV weekly (5 cycles, an optional sixth infusion could be administered per local practice), and radiotherapy (EBRT followed by BT), followed by placebo IV every 6 weeks (15 cycles)

Treatment continued until RECIST v1.1-defined progression of disease as determined by investigator or unacceptable toxicity.

Assessment of tumor status was performed every 12 weeks from completion of CRT for the first two years, followed by every 24 weeks in year 3, and then annually. The major efficacy outcome measures were PFS as assessed by investigator according to RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, or histopathologic confirmation, and OS.

Among the 599 patients with FIGO 2014 Stage III-IVA disease, the baseline characteristics were: median age of 52 years (range: 22 to 87), 17% age 65 or older; 36% White, 34% Asian, 2% Black; 38% Hispanic or Latino; 68% ECOG PS 0 and 32% ECOG PS 1; 93% with CPS ≥1; 71% had positive pelvic and/or positive para-aortic lymph node(s) and 29% had neither positive pelvic nor para-aortic lymph node; 83% had squamous cell carcinoma and 17% had non-squamous histology. Regarding radiation, 86% of patients received IMRT or VMAT EBRT, and the median EQD2 dose was 87 Gy (range: 7 to 114).

The trial demonstrated statistically significant improvements in both PFS (HR 0.70; 95% CI: 0.55-0.89; p = 0.002) and OS (HR 0.67; 95% CI: 0.50-0.90; p = 0.004) in the overall population. In an exploratory subgroup analysis for the 459 patients (43%) with FIGO 2014 Stage IB2–IIB disease, the PFS and OS HR estimates were 0.91 (95% CI: 0.63-1.32) and 0.89 (95% CI: 0.55-1.44), respectively, suggesting that the improvements in PFS and OS observed in the overall population were primarily driven by the later-stage subgroup of patients with FIGO 2014 Stage III–IVA disease.

The efficacy results in the exploratory subgroup analysis of 599 patients with FIGO 2014 Stage III-IVA disease are summarized in Table 126, Figure 50 and Figure 51.

Table 126: Efficacy Results in KEYNOTE-A18 (Patients with FIGO 2014 Stage III-IVA Cervical Cancer)

Endpoint	KEYTRUDA 200 mg every 3 weeks and 400 mg every 6 weeks with CRT n=295	Placebo with CRT n=304		
PFS by Investigator*				
Number of patients with event (%)	61 (21)	94 (31)		
Median in months (95% CI)	NR (NR, NR)	NR (18.8, NR)		
Hazard ratio† (95% CI)	0.59 (0.4	43, 0.81)		
OS [‡]				
Number of patients with event (%)	43 (14.5)	73 (23.9)		
Median in months (95% CI)	NR (NR, NR)	NR (NR, NR)		
Hazard ratio [†] (95%CI)	0.58 (0.	0.58 (0.40,0.85)		
* Based on a pre-specified interim PFS analysis with a r	nedian follow-up of 17 month	s (range: 0.9 to 31		

^{*} Based on a pre-specified interim PFS analysis with a median follow-up of 17 months (range: 0.9 to 31 months)

CRT = Chemoradiotherapy

NR = Not reached

At the second interim analysis, the OS rate at 36 months was 82% in patients receiving KEYTRUDA with CRT versus 71% in patients receiving placebo with CRT.

[†]Based on the unstratified Cox proportional hazard model

[‡] Based on a pre-specified interim OS analysis with a median follow-up of 28 months (range 0.9 to 43 months)

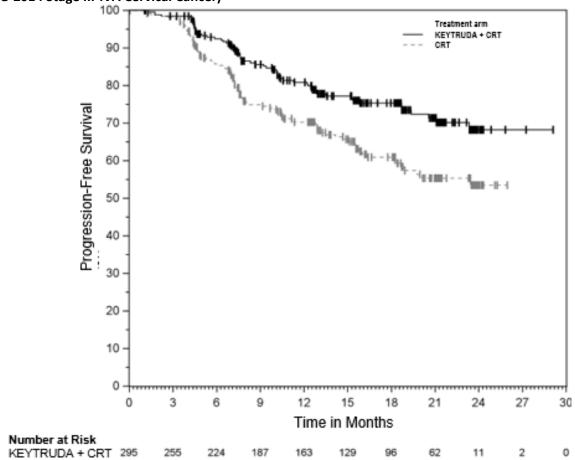


Figure 50: Kaplan-Meier Curve for Progression-Free Survival in KEYNOTE-A18 (Patients with FIGO 2014 Stage III-IVA Cervical Cancer)*

CRT

^{*}Results at the time of first pre-specified interim analysis for PFS.

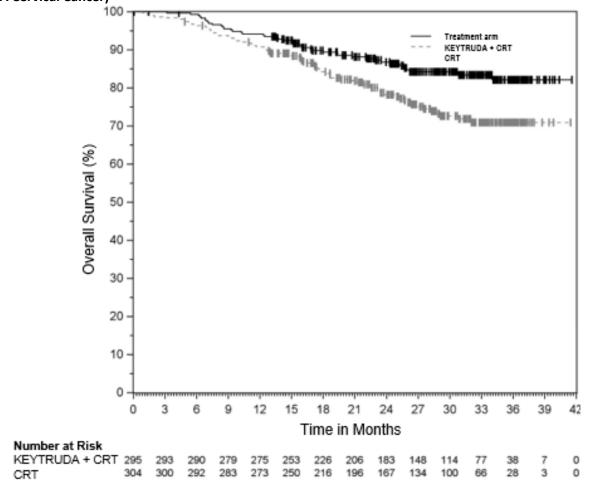


Figure 51: Kaplan-Meier Curve for Overall Survival in KEYNOTE-A18 (Patients with FIGO 2014 Stage III-IVA Cervical Cancer)

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

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

Treatment Group 1: KEYTRUDA 200 mg plus chemotherapy

^{*}Results at the time of second pre-specified interim analysis for OS.

• Treatment Group 2: Placebo plus chemotherapy

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

- 1. Paclitaxel 175 mg/m² + cisplatin 50 mg/m²
- 2. Paclitaxel 175 mg/m² + cisplatin 50 mg/m² + bevacizumab 15 mg/kg
- 3. Paclitaxel 175 mg/m² + carboplatin AUC 5 mg/mL/min
- 4. Paclitaxel 175 mg/m² + carboplatin AUC 5 mg/mL/min + bevacizumab 15 mg/kg

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

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

The primary efficacy outcome measures were OS and PFS as assessed by investigator according to RECIST v1.1. Secondary efficacy outcome measures were ORR and DoR, according to RECIST v1.1, as assessed by investigator. The median follow-up time was 17.2 months (range: 0.3 to 29.4 months). Efficacy results are summarized in Table 127.

Table 127: Efficacy Results* for Patients with Persistent, Recurrent or Metastatic Cervical Cancer (CPS ≥ 1) in KEYNOTE-826

Endpoint	KEYTRUDA 200 mg every 3 weeks and Chemotherapy [†] with or without bevacizumab	Placebo and Chemotherapy [†] with or without bevacizumab		
	n=273	n=275		
OS				
Number (%) of patients with event	118 (43.2)	154 (56.0)		
Median in months (95% CI)	NR (19.8, NR)	16.3 (14.5, 19.4)		
Hazard ratio [‡] (95% CI)	0.64 (0.50	0, 0.81)		
p-Value [§]	0.00	01		
PFS				
Number of patients with event (%)	157 (57.5)	198 (72.0)		
Median in months (95% CI)	10.4 (9.7, 12.3)	8.2 (6.3, 8.5)		
Hazard ratio [‡] (95% CI)	0.62 (0.50	0, 0.77)		
p-Value [¶]	< 0.00	001		
Objective Response Rate				
ORR# (95% CI)	68% (62, 74)	50% (44, 56)		
Complete response rate	23%	13%		
Partial response rate	45%	37%		
Duration of Response				
Median in months (range)	18.0 (1.3+, 24.2+)	10.4 (1.5+, 22.0+)		

^{*} Based on pre-specified interim analysis

NR = not reached

An updated OS analysis was performed at the time of the final analysis with a median follow-up time of 21.3 months (range: 0.3-46.5 months). At the time of this analysis, the median OS for patients treated with KEYTRUDA in combination with chemotherapy with or without bevacizumab was 28.6 months (95% CI: 22.1, 38.0), compared to 16.5 months (95% CI: 14.5, 20.0) for placebo in combination with chemotherapy with or without bevacizumab, with a hazard ratio of 0.60 (95% CI: 0.49, 0.74). The Kaplan-Meier curve for the updated OS analysis is presented in Figure 52. The results for PFS and ORR remained consistent with the interim analysis (see Table 127).

[†] Chemotherapy (paclitaxel and cisplatin or paclitaxel and carboplatin)

[‡] Based on the stratified Cox proportional hazard model

[§] p-Value (one-sided) is compared with the allocated alpha of 0.0055 for this interim analysis (with 72% of the planned number of events for final analysis)

p-Value (one-sided) is compared with the allocated alpha of 0.0014 for this interim analysis (with 82% of the planned number of events for final analysis)

[#] Response: Best objective response as confirmed complete response or partial response

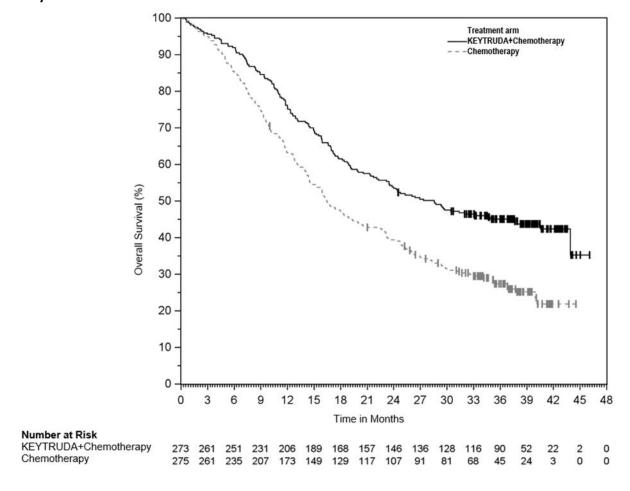


Figure 52: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-826 (CPS ≥ 1), Final Analysis*[†]

Biliary Tract Carcinoma

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

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

^{*}Treatment arms include KEYTRUDA plus chemotherapy (paclitaxel and cisplatin or paclitaxel and carboplatin) with or without bevacizumab versus placebo plus chemotherapy with or without bevacizumab.

†Based on the protocol-specified final OS analysis.

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

- KEYTRUDA 200 mg on Day 1 plus gemcitabine 1000 mg/m² and cisplatin 25 mg/m² on Day 1 and Day 8 every 3 weeks.
- Placebo on Day 1 plus gemcitabine 1000 mg/m² and cisplatin 25 mg/m² on Day 1 and Day 8 every 3 weeks

All study medications were administered via intravenous infusion. Treatment continued until unacceptable toxicity or disease progression. For pembrolizumab, treatment continued for a maximum of 35 cycles, or approximately 24 months. For cisplatin, treatment could be administered for a maximum of 8 cycles and for gemcitabine, treatment could be continued beyond 8 cycles.

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

Treatment with pembrolizumab could be reinitiated for subsequent disease progression and administered for up to one additional year.

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

The primary efficacy outcome measure was OS and the secondary efficacy measures were PFS and ORR as assessed by BICR according to RECIST v1.1. The KEYTRUDA with gemcitabine/cisplatin arm demonstrated a clinically meaningful and statistically significant improvement vs. the placebo with gemcitabine/cisplatin arm in OS. The results are summarized in Table 128 and Figure 53.

Table 128: Efficacy Results in Patients with BTC in KEYNOTE-966

Endpoint	KEYTRUDA	Placebo	
	200 mg every 3 weeks		
	and	and	
	gemcitabine	gemcitabine	
	and	and	
	cisplatin	cisplatin	
	n=533	n=536	
OS*			
Number (%) of patients with event	414 (78%)	443 (83%)	
Median in months (95% CI)	12.7 (11.5, 13.6)	10.9 (9.9, 11.6)	
Hazard ratio [†] (95% CI)	0.83 (0.72, 0.95)		
p-Value [‡]	0.0034		
* December at the same and affined fined OC	and the set of	<u> </u>	

^{*} Results at the pre-specified final OS analysis

[†] Based on the stratified Cox proportional hazard model

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

The PFS hazard ratio at the pre-specified interim analysis in patients randomized to the pembrolizumab plus chemotherapy arm versus patients randomized to the placebo plus chemotherapy arm was 0.86 (95% CI 0.75, 1.00). The median PFS was 6.5 months (95% CI: 5.7, 6.9) versus 5.6 months (95% CI: 5.1, 6.6) for the pembrolizumab plus chemotherapy arm versus the placebo plus chemotherapy arm. The objective response rate at the pre-specified interim analysis was 28.7% (24.9, 32.8) for the pembrolizumab plus chemotherapy arm vs 28.5% (24.8, 32.6) for the placebo plus chemotherapy arm.

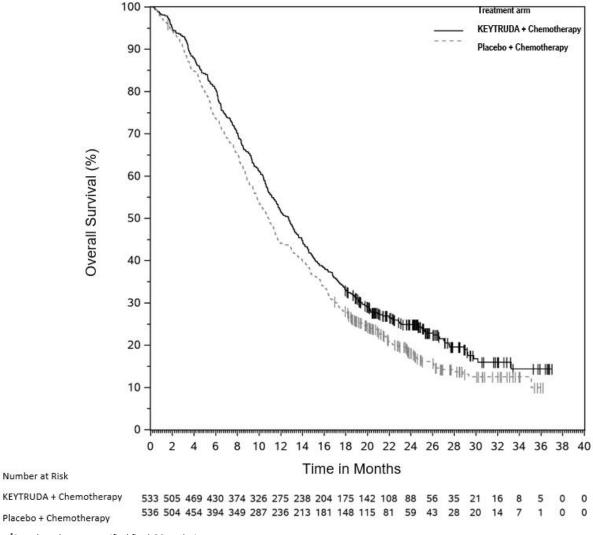


Figure 53: Kaplan-Meier Curve for Overall Survival in KEYNOTE-966*

*Based on the pre-specified final OS analysis

Alternate Dosing Regimen for Adults

KEYNOTE-555: Additional dosing regimen of 400 mg every 6 weeks for adults

The safety and efficacy of KEYTRUDA 400 mg every 6 weeks was evaluated in Cohort B of KEYNOTE-555, a Phase 1 clinical trial in adult patients with advanced (unresectable or metastatic) melanoma (at least 1 measurable lesion) who were naïve to prior immuno-oncology therapy, and had an ECOG

performance status of 0 or 1. The interim data of 44 patients support that the safety and efficacy of 400 mg every 6 weeks are consistent with the safety and efficacy of 200 mg every 3 weeks of KEYTRUDA.

15. Microbiology

No microbiological information is required for this drug product.

16. Non-Clinical Toxicology

General toxicology: 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 administered 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.

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

Genotoxicity: The genotoxic potential of pembrolizumab has not been evaluated.

Reproductive and developmental toxicology: 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.

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 on1month 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.

Table 129: 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 30 mg/kg was observed. Antidrug 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	1	1	T	T			
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.		

Study Type	Treatment Duration and Dosing Schedule	Species / Test system	Gender and No. per Group	Doses (mg/kg) ^a	Findings/Conclusions
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	 		T	I	
Tissue Cross- reactivity in vitro	N/A	Cryosections of normal human tissues	n = 3 donors per tissue (~ 32 tissues / donor)	1, 10 µg/mL MK-3475 pre- complexe d with biotinylat ed 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 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 <i>in vitro</i> tissue cross-reactivity studies with no <i>in vivo</i> 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- complexe d with biotinylat ed 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 <i>in vitro</i> tissue cross-reactivity studies with no <i>in vivo</i> toxicological significance.
Cytokine Release Studies In vitro	^{b, c, d, e} 4 days culture for cytokine release after	^{b, f} Human, normal donors ^c Human,	^b n = 3 ^c n = 8	b, c, d, e 25, 2.5, 0.25, 0.025, 0.0025,	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

Study Type	Treatment Duration and Dosing Schedule	Species / Test system	Gender and No. per Group	Doses (mg/kg) ^a	Findings/Conclusions
	Staphylococcus	advanced	^d n = 8	0.00025	(less than 2-fold). In the absence of SEB
	enterotoxin B	metastatic		μg/mL	stimulation, MK-3475 did not induce
	(SEB) stimulation	melanoma	^e n = 6		cytokine production.
		patients		^b 25	
	^f 48 hr for	d	^f n = 7	μg/mL	^e MK-3475 enhances SEB-induced IL-2
	cytokine release,	dHuman,			production.
	dry coat assay	prostate		^f 25, 2.5,	
		cancer		0.25,	^f MK-3475 did not induce cytokine
		patients		0.025,	release. Superagonist anti-CD28 induced
		eCynomolgus		0.0025,	robust cytokine release.
		monkey		0.00025	
		monkey		μg/mL for	
				dry coat	
Other Ctudies				assay	
Other Studies		Lluman	1	25.25	<u> </u>
		Human donors,		25, 2.5, 0.25,	
T-cell recall for		recently		0.23,	MK-3475 enhanced tetanus toxoid-
Tetanus toxoid	g 7 days	revaccinated	n = 2	0.025,	induced production of IFNγ in a dose-
Tetanas toxola		with tetanus		0.0025	dependent manner.
		toxoid		μg/mL	
				All doses	
				IV. First	
				dose =	
				1 mg/kg,	
	Once per week, 5			second	No shanges in viral load were observed
	dose, rising dose			dose =	No changes in viral load were observed. ALT/AST/GGT flares were observed in 2
HBV infection	escalation.	HBV-infected	n = 4	2 mg/kg,	animals following the fifth dose (10
nbv iiilection	Postdose (last	chimpanzees	11 – 4	third dose	mg/kg); ALT/AST/GGT levels remained
	dose) period of 1			=	elevated for at least one month.
	month			5 mg/kg,	cievated for at least one month.
				fourth	
				and fifth	
				dose =	
				10 mg/kg	

^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.

 $^{^{\}rm g}$ Peripheral blood mononuclear cells from donors recently revaccinated with tetanus toxoid (TT) were stimulated *in vitro* for 7 days with 1 μ g/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; IFNy = interferon gamma; IL-6 = interleukin 6; IL-17 = interleukin 17

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

™ KEYTRUDA

Pembrolizumab

This Patient Medication Information is written for the person who will be taking **KEYTRUDA**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **KEYTRUDA**, talk to a healthcare professional.

What KEYTRUDA is used for:

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:
 - o 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
 - o that was not responsive to other treatments, or
 - o 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 tumour 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

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
 - o 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
- o 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 skin cancer called melanoma in children (12 years of age or older)
 - 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.

- KEYTRUDA may be used alone after surgery and platinum-based chemotherapy to help prevent your lung cancer from coming back, and
 - you have stage IB and your tumour(s) is 4 cm or greater in size, stage II, or stage IIIA lung cancer.
- KEYTRUDA may be used in combination with chemotherapy that contains platinum and another chemotherapy medicine before surgery when you have Stage II, IIIA, or IIIB NSCLC and then continued alone after surgery to help prevent your lung cancer from coming back.
- a kind of cancer in adults called malignant pleural mesothelioma (MPM) that affects the lining of the lungs and chest wall.
 - KEYTRUDA may be used with the chemotherapy medicines pemetrexed and a platinum as your first treatment when your MPM has spread or cannot be removed by surgery (advanced MPM).
- a kind of bladder and urinary tract cancer called urothelial carcinoma in adults
 - KEYTRUDA may be used with the medicine enfortumab vedotin when your bladder or urinary tract cancer has spread or cannot be removed by surgery (advanced urothelial cancer).
 - KEYTRUDA may be used alone when your bladder or urinary cancer 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;
 - you are not able to receive a medicine called cisplatin or carboplatin.
- a kind of kidney cancer in adults called renal cell carcinoma
 - KEYTRUDA may be used with the medicine axitinib as your first treatment when your kidney cancer has spread or cannot be removed by surgery (advanced RCC).
 - KEYTRUDA may be used with the medicine lenvatinib as your first treatment when your kidney cancer has spread or cannot be removed by surgery (advanced RCC).
 - KEYTRUDA may be used alone to help prevent kidney cancer from coming back after surgery.
- a kind of cancer called colon or rectal cancer. KEYTRUDA may be used when your cancer:
 - has spread (advanced colon or rectal cancer), and
 - has been shown by a laboratory test to be microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR).
- a kind of cancer in adults and children that is shown by a laboratory test to be microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)
 - after 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 may be used with chemotherapy medicines, and then KEYTRUDA may

be used alone:

- if your cancer has spread outside the uterus, or
- if your cancer has returned.
- 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).
- a kind of head and neck cancer called head and neck squamous cell carcinoma (HNSCC) in adults:
 - KEYTRUDA may be used alone as treatment before surgery when you have newly diagnosed head and neck cancer that has not spread and
 - then continued in combination with radiation with or without platinum chemotherapy after surgery

and

- then continued alone to help prevent your head and neck cancer from coming back
- KEYTRUDA 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"
- o KEYTRUDA may be used with the chemotherapy medicines platinum and fluorouracil (FU) as your first treatment when your head and neck cancer:
 - has spread
 - has come back after previous therapy
- a kind of stomach cancer called gastric or gastroesophageal junction (GEJ) adenocarcinoma.
 - KEYTRUDA may be used in combination with the medicine trastuzumab along with fluoropyrimidine and platinum chemotherapy as your first treatment when your stomach cancer:
 - is HER2-positive, and
 - has spread or cannot be removed by surgery (advanced gastric cancer or GEJ), and
 - tests positive for "PD-L1"
 - KEYTRUDA may be used in combination with chemotherapy medicines containing fluoropyrimidine and platinum as your first treatment when your stomach cancer:
 - is HER2-negative, and
 - has spread or
 - your tumour cannot be removed by surgery (advanced gastric cancer or GEJ).
- a kind of cancer called esophageal carcinoma
 - o may be used with the chemotheapy medicines platinum and fluorouracil (FU) as your first treatment when your esophageal cancer:
 - has spread (advanced esophageal cancer), or

- your tumour cannot be removed by surgery.
- a kind of cancer called triple-negative breast cancer in adults
 - o may be used with chemotherapy medicines as treatment before surgery and then continued alone after surgery when you:
 - have early-stage breast cancer, and
 - are at high risk of your breast cancer coming back.
- a kind of cancer called triple negative breast cancer in adults:
 - tests positive for "PD-L1", and
 - has returned and cannot be removed by surgery or has spread
- a kind of cancer called cervical cancer in adult women
 - o may be used with the chemotheapy medicines, with or without the medicine bevacizumab, when your cervical cancer:
 - does not go away, has returned, or has spread, and
 - tests positive for "PD-L1"
 - o may be used with chemotherapy and radiation therapy, when your cervical cancer:
 - has spread to nearby tissue or organs or has affected your kidneys (Stage III to IVA cervical cancer based on FIGO 2014 classification).
- a kind of bile duct or gallbladder cancer called biliary tract carcinoma in adults
 - o may be used with chemotherapy medicines when your biliary tract cancer has spread or cannot be removed by surgery.

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

A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.

Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug's performance after it has been sold, and to report their findings to Health Canada.

KEYTRUDA may be given in combination with other anti-cancer medicines with or without radiation therapy. 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 less than 18 years of age with classical Hodgkin lymphoma, primary mediastinal B-cell lymphoma, or MSI-H or dMMR cancer, or in children 12 years and older with melanoma. 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.

People get KEYTRUDA before surgery to treat head and neck cancer or triple-negative breast cancer and then continued after surgery to help prevent their cancer from coming back.

How KEYTRUDA works:

KEYTRUDA works by helping your immune system fight your cancer.

The ingredients in KEYTRUDA are:

Medicinal ingredients: pembrolizumab

Non-medicinal ingredients: L-histidine; L-histidine monohydrochloride monohydrate; polysorbate-80; sucrose; and water for infusion.

KEYTRUDA comes in the following dosage forms:

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.

Other warnings you should know about:

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. Your healthcare provider should do a pregnancy test before you start treatment with KEYTRUDA.
- Tell your healthcare provider right away if you become pregnant during treatment with KEYTRUDA.
- 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. You and your doctor should decide whether you will breast-feed or take KEYTRUDA . You should not do both.
- KEYTRUDA may pass into your breast milk. You should not breast-feed for at least 4 months after the last dose.
- **Females of Childbearing Potential:** KEYTRUDA may cause fertility problems, which may affect the ability to have children. Talk to your healthcare provider if you have concerns about fertility.

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 or every 6 weeks, depending on the dose you are given.
- Your doctor will decide how many treatments you need.

Usual dose:

The recommended dose is 200 mg or 400 mg in adults, depending on how often you are given a dose.

The recommended dose is 2 mg/kg (up to a maximum of 200 mg) in children treated for melanoma (12 years of age and older), classical Hodgkin lymphoma or primary mediastinal B-cell lymphoma or MSI-H or dMMR cancer.

Overdose:

If you think you, or a person you are caring for, have taken too much KEYTRUDA, contact a healthcare professional, hospital emergency department regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or 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.

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;
- low levels of thyroid hormone;
- high levels of thyroid hormone;
- fever;
- feeling less hungry;
- shortness of breath;
- patches of skin which have lost colour (vitiligo);
- increase in liver enzyme levels.

Common (may affect more than 2 in 100 people and up to 1 in 10 people)

- flu-like illness;
- dry mouth;
- dry eyes;
- headache;
- change in your sense of taste;
- cough;
- dehydration;
- feeling dizzy;
- excessive sweating;
- joint disorder;
- hair loss;
- lack of white blood cells;
- rapid heartbeat;
- cold sores;
- upper respiratory tract infection;
- stuffy nose;
- loss of appetite;
- stomach pain, constipation, vomiting, inflammation of the mucous membrane in the mouth;
- dry skin, redness of the skin, red raised skin rash; itchy patches of thick red skin with silvery scales (psoriasis); skin conditions resembling acne;
- back pain, muscle aches; pain in the upper and lower extremities;
- 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
- decrease in hemoglobin
- abnormal liver enzyme levels in the blood
- decreased in bilirubin levels in the blood
- decreased sodium levels in the blood
- abnormal levels of thyroid stimulating hormone in the blood
- increased level of sugar in the blood
- decreased level of potassium in the blood
- increased creatinine levels in the blood
- weight loss
- weight gain.

The most common (may affect more than 1 in 10 children) side effects when KEYTRUDA is given to children are:

- fever;
- vomiting;
- headache;
- abdominal pain;
- decrease in number of red blood cells;
- cough;
- constipation;
- nausea;
- diarrhea;
- feeling tired;
- joint pain;
- abnormal liver enzyme levels in the blood;
- decreased appetite;
- decrease in white blood cell count;
- pain in arms or legs;
- rash;
- feeling unusually tired or weak;
- back pain.

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

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

- decrease in red blood cell count;
- nausea;
- hair loss;
- decrease in neutrophils (a type of white blood cell);
- decrease in lymphocytes (a type of white blood cell);
- decrease in white blood cell count;
- fatigue;
- decrease in platelet count;

- swelling of the lining of the mouth, nose, eyes, throat, intestines, or vagina;
- vomiting;
- mouth sores;
- diarrhea;
- decreased appetite;
- increased liver enzyme levels in the blood;
- inflammation of the nerves causing numbness, weakness, tingling or burning pain of the arms and legs;
- constipation;
- weakness;
- rash;
- low levels of thyroid hormone;
- high levels of thyroid hormone;
- joint pain;
- eye tearing;
- weight loss;
- muscle pain;
- hiccups;
- increased creatinine levels in the blood;
- fever;
- change in your sense of taste;
- itching;
- decreased magnesium levels in the blood;
- decreased potassium levels in the blood;
- high blood pressure;
- protein in urine;
- pain or burning on urination;
- blisters or rash on the palms of your hands and soles of your feet;
- reaction related to infusion;
- decrease in lymphocytes (a type of white blood cell);
- difficulty to swallow;
- skin irritation in the radiation area;
- dry mouth.

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

- rash
- protein in your urine
- voice change
- high level of amylase or lipase in your blood
- itching
- abnormal levels of thyroid stimulating hormone in the blood
- change in your sense of taste
- liver problems
- kidney problems
- indigestion
- dry mouth
- trouble sleeping
- low level of platelets (cells that help blood clot)
- anemia, a low number of red blood cells (that carry oxygen)
- increase in liver enzyme levels
- inflammation of the mucous membranes including in the mouth

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.

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

The most common side effects when KEYTRUDA is given in combination with enfortumab vedotin are (may affect more than 1 in 10 people):

- anemia, a low number of red blood cells (that carry oxygen);
- dry eye;
- diarrhea;
- nausea;
- feeling unusually tired or weak;
- weight decreased;
- constipation;
- decreased appetite;
- inflammation of the nerves causing numbness, weakness, tingling or burning pain of the arms and legs;
- change of taste;
- urinary tract infection
- itching;
- hair loss;
- dry skin;
- rash;
- low levels of thyroid hormones;
- increase in liver enzyme levels;
- increased level of sugar in the blood;
- stomach pain;
- vomiting;
- swelling of legs or arms;
- COVID-19 infection;
- pain in joints or muscles;
- trouble sleeping;
- blood in your urine;
- shortness of breath;
- cough;
- have pneumonia or inflammation of your lungs (called pneumonitis);
- skin discoloration;
- bleeding from a damaged blood vessel that may be severe.

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

Frequency/Side Effects/Symptom	Talk to your healthcare professional		
Frequency/side Effects/symptom	Only if severe	In all cases	
Common			
Inflammation of the lungs (pneumonitis) which can cause		٦	
shortness of breath, chest pain, or coughing		Y	
Inflammation of the intestines (colitis) which can cause		V	

	Talk to your healthcare professional			
Frequency/Side Effects/Symptom	Only if severe	In all cases		
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		.1		
sweating, weight gain, hair loss, feeling cold, constipation,		٧		
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		.1		
side of stomach, yellowing of skin or whites of eyes, dark		٧		
urine, bleeding or bruising more easily than normal				
Inflammation of the kidneys (nephritis) which can cause		V		
changes in the amount or colour of your urine		٧		
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		٧		
legs (myasthenia gravis or Guillain-Barré syndrome)		.1		
Low red blood cell count (anemia/hemolytic anemia)		1		
Eye problems, which can cause changes in eyesight Shortness of breath, irregular heartbeat, feeling tired, or		ν		
chest pain (myocarditis, pericarditis)		\checkmark		
Blood sugar problems (type 1 diabetes mellitus) which can				
cause hunger or thirst, a need to urinate more often, or		\checkmark		
weight loss		,		
Confusion, fever, memory problems, or seizures		.1		
(encephalitis)		\checkmark		
Swollen lymph nodes, rash or tender lumps on skin, cough,		21		
or eye pain (sarcoidosis)		٧		
Inflammation of the pancreas (pancreatitis), which can		V		
cause abdominal pain, nausea, and vomiting		٧		
Reactions related to the infusion such as shortness of		,		
breath, itching or rash, dizziness, or fever, wheezing,		√		
flushing, feeling like passing out		1		
Pain, numbness, tingling, or weakness in the arms or legs;		٧		

Francisco (Sido Efforto (Sumento m	Talk to your healthcare professional		
Frequency/Side Effects/Symptom	Only if severe	In all cases	
bladder or bowel problems including needing to urinate			
more frequently, urinary incontinence, difficulty urinating			
and constipation (myelitis)			
Inflammation of blood vessels (vasculitis), symptoms		V	
include red skin lesions, numbness and weakness		,	
Decreased function of the parathyroid gland, which may			
include muscle cramps or spasms, fatigue and weakness		\checkmark	
(hypoparathyroidism)			
Inflammation of the stomach lining, which may include		_	
severe stomach pain or tenderness, nausea or vomiting		$\sqrt{}$	
(gastritis)			
Pain in the upper right part of the stomach, swelling of the			
liver or spleen, fatigue, itching, or yellowing of the skin or		$\sqrt{}$	
the whites of eyes (sclerosing cholangitis)			
Decreased ability of the pancreas to make digestive			
enzymes, which may include diarrhea with loose and oily			
stools associated with bloating and abdominal discomfort,		\checkmark	
weight loss, metabolic bone disease, and vitamin or			
mineral deficiencies (exocrine pancreatic insufficiency)			
Unknown			
Insufficient production of new blood cells (aplastic		J	
anemia)		٧	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell 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 (<u>canada.ca/drug-device-reporting</u>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

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.

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 the
 Patient Medication Information by visiting the Health Canada Drug Product Database website (<u>Drug
 Product Database</u>: Access the database); the manufacturer's website <u>www.merck.ca</u> or by calling
 1-800-567-2594.

This leaflet was prepared by Merck Canada Inc.

Date of Authorization: October 9, 2025

[®] Merck Sharp & Dohme LLC. Used under license.

^{*} All other trademarks are the property of their respective owner(s). © 2015, 2025 Merck & Co., Inc., Rahway, NJ, USA and its affiliates. All rights reserved.