
Pr KEYTRUDA®
(pembrolizumab)

Indicated in 8 different tumour types[1]

MILESTONES

2015

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

2016

Indicated for the treatment of adult patients with metastatic NSCLC, as monotherapy, whose tumours express PD-L1 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®.

- 2016 Patients were initially selected for treatment based on the presence of positive PD-L1 expression defined as a TPS ≥50%.
- 2017 The indication was amended to include adults with metastatic NSCLC whose tumours expressed PD-L1 (TPS ≥1%).

Indicated for the treatment of 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.

2017

Indicated for the treatment of patients with metastatic NSCLC as monotherapy, in adults whose tumours have high PD-L1 expression (TPS ≥50%) as determined by a validated test, with no EGFR or ALK genomic tumour aberrations, and no prior systemic chemotherapy treatment for metastatic NSCLC.

Indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma, as monotherapy, in adults who have disease progression during or following platinum-containing chemotherapy or within 12 months of completing neoadjuvant or adjuvant platinum-containing chemotherapy.

Indicated for the treatment of adult patients with refractory or relapsed cHL, as monotherapy, who have failed ASCT and BV or who are not ASCT candidates and have failed BV. KEYTRUDA® has been issued marketing authorization **with conditions**, pending the results of studies to verify its clinical benefit. Patients should be advised of the nature of the authorization.

2018

Indicated for the treatment of adult and pediatric patients with refractory PMBCL or who have relapsed after two or more lines of therapy, as monotherapy. KEYTRUDA® has been issued marketing authorization **with conditions**, pending the results of studies to verify its clinical benefit. Patients should be advised of the nature of the authorization.

MILESTONES

2019

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

Indicated for the adjuvant treatment of patients with Stage III melanoma with lymph node involvement who have undergone complete resection.

Indicated for the treatment of adult patients with locally advanced unresectable or metastatic urothelial carcinoma, as monotherapy, who are not eligible for cisplatin-containing chemotherapy and whose tumours express PD-L1 (CPS ≥10) as determined by a validated test, or in adults who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status. KEYTRUDA® has been issued marketing authorization **with conditions**, pending the results of studies to verify its clinical benefit. Patients should be advised of the nature of the authorization.

Indicated for the treatment of adult patients with unresectable or metastatic MSI-H or dMMR

- colorectal cancer whose tumours have progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, as monotherapy, or
- endometrial cancer whose tumours have progressed following prior therapy and who have no satisfactory alternative treatment options, as monotherapy.

KEYTRUDA® has been issued marketing authorization **with conditions**, pending the results of studies to verify its clinical benefit. Patients should be advised of the nature of the authorization.

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

2020

Indicated for the treatment of patients with advanced or metastatic RCC in combination with axitinib, in adults with no prior systemic therapy for metastatic RCC.

ALK=anaplastic lymphoma kinase; ASCT=autologous stem cell transplant; BV=brentuximab vedotin; cHL=classical Hodgkin Lymphoma; CPS=combined positive score; dMMR=mismatch repair deficient; EGFR=epidermal growth factor receptor; MSI-H=microsatellite instability-high; NSCLC=non-small cell lung carcinoma; PD-L1=programmed cell death ligand 1; PMBCL=primary mediastinal B-cell lymphoma; RCC=renal cell carcinoma; TPS=tumour proportion score

Pr KEYTRUDA® (pembrolizumab)

Efficacy data across multiple clinical trials

Patients in some of the KEYNOTE trials were administered a dose of 2 mg/kg or 10 mg/kg every 3 weeks or 10 mg/kg every 2 weeks. These doses differ from the recommended dosing in the KEYTRUDA® Product Monograph. The recommended dosing schedule for KEYTRUDA® is 200 mg every 3 weeks.

MELANOMA

KN-002[1a]

Unresectable or metastatic melanoma – prior treatment with ipilimumab

PFS† (co-primary endpoint)	KEYTRUDA® 2 mg/kg every 3 weeks (n=180)		Chemotherapy (n=179)
% of patients with event	**72%**	vs.	87%
	HR‡ 0.57 (95% CI: 0.45, 0.73); $p<0.0001$§		

There was no statistically significant difference between KEYTRUDA® and chemotherapy in the final OS analysis (co-primary endpoint) that was not adjusted for the potentially confounding effects of crossover.

KN-006[1b]

Unresectable or metastatic melanoma – no prior treatment

OS (primary endpoint)	KEYTRUDA® 10 mg/kg every 3 weeks (n=277)		Ipilimumab (n=278)
% of patients with event	**33%**	vs.	40%
	HR‡ 0.69 (95% CI: 0.52, 0.90); $p=0.0036$§		
OS at 1 year	**68%** (95% CI: 62.5, 73.6)	vs.	58% (95% CI: 51.8, 64.0)

KN-054[1,2c]

Adjuvant treatment in Stage III melanoma

RFS (primary endpoint)	KEYTRUDA® 200 mg every 3 weeks (n=514)		Placebo (n=505)
% of patients with event	**26%**	vs.	43%
	HR‡ 0.57 (98% CI: 0.43, 0.74); $p<0.0001$¶		
RFS at 1 year	**75%**	vs.	61%

RFS was defined as the time between the date of randomization and the date of first recurrence (local, regional or distant metastasis) or death.

The study parameters relating to the data presented can be found on pages 8 and 9.

BICR=blinded independent central review; CI=confidence interval; CR=complete response; HR=hazard ratio; IC=investigator's choice; IRO=independent radiology plus oncology; IWG=International Working Group; ORR=objective response rate; OS=overall survival; PR=partial response; PFS=progression-free survival; RCC=renal cell carcinoma; RECIST=Response Evaluation Criteria in Solid Tumors; RFS=recurrence-free survival

† Based on second interim analysis. IRO review using RECIST 1.1.
‡ Based on the stratified Cox proportional hazard model.
§ Based on stratified log rank test.
¶ *p*-value (based on stratified log rank test) is compared with 0.008 of the allocated alpha for this interim analysis.
†† Assessed by BICR according to the 2007 revised IWG criteria.
‡‡ Assessed by BICR using RECIST 1.1.

PMBCL

KN-170[1e]

Relapsed or refractory PMBCL

Single-arm trial

ORR†† (primary endpoint)	KEYTRUDA® 200 mg every 3 weeks (n=29)
	41% (95% CI: 24, 61)
CR	14%
PR	28%

RCC

KN-426[1m]

Combination with axitinib in patients with advanced RCC naive to treatment

Open-label trial
Results are from the prespecified first interim analysis

OS††† (co-primary endpoint)	KEYTRUDA® 200 mg every 3 weeks (n=432)		Sunitinib (n=429)
% of patients with event	**14%**	vs.	23%
	HR‡ 0.53 (95% CI: 0.38, 0.74); $p<0.00005$§		

MSI-H/dMMR

Advanced MSI-H or dMMR colorectal and endometrial cancer

Single-arm, open-label trials

	KN-164[1l] Colorectal cancer	**KN-158[1l]** Endometrial cancer
	KEYTRUDA® 200 mg every 3 weeks (n=61)	KEYTRUDA® 200 mg every 3 weeks (n=24)
ORR‡‡ (primary endpoint)	**28%** (95% CI: 17.1, 40.8)	**54%** (95% CI: 32.8, 74.4)
CR	0%	4%
PR	28%	50%

§§ Based on the stratified Cox proportional hazard model. The confidence levels correspond to the allocated type 1 error of 0.00825 and 0.001 for the OS and PFS endpoints, respectively.
¶¶ Statistically significant based on a prespecified alpha level of 0.00825 for the two pairwise comparisons versus docetaxel using a Hochberg procedure.
††† The initial one-sided type 1 error rate level for OS was 0.023. The corresponding *p*-value bounds at the interim analysis for OS was 0.0001.

Efficacy data across multiple clinical trials

Patients in some of the KEYNOTE trials were administered a dose of 2 mg/kg or 10 mg/kg every 3 weeks or 10 mg/kg every 2 weeks. These doses differ from the recommended dosing in the KEYTRUDA® Product Monograph. The recommended dosing schedule for KEYTRUDA® is 200 mg every 3 weeks.

MELANOMA

KN-002[1a]

Unresectable or metastatic melanoma – prior treatment with ipilimumab

PFS[†] (co-primary endpoint)	KEYTRUDA® 2 mg/kg every 3 weeks (n=180)		Chemotherapy (n=179)
% of patients with event	**72%**	vs.	87%
	HR[‡] 0.57 (95% CI: 0.45, 0.73); $p<0.0001$[§]		

There was no statistically significant difference between KEYTRUDA® and chemotherapy in the final OS analysis (co-primary endpoint) that was not adjusted for the potentially confounding effects of crossover.

KN-006[1b]

Unresectable or metastatic melanoma – no prior treatment

OS (primary endpoint)	KEYTRUDA® 10 mg/kg every 3 weeks (n=277)		Ipilimumab (n=278)
% of patients with event	**33%**	vs.	40%
	HR[‡] 0.69 (95% CI: 0.52, 0.90); $p=0.0036$[§]		
OS at 1 year	**68%** (95% CI: 62.5, 73.6)	vs.	58% (95% CI: 51.8, 64.0)

KN-054[1,2c]

Adjuvant treatment in Stage III melanoma

RFS (primary endpoint)	KEYTRUDA® 200 mg every 3 weeks (n=514)		Placebo (n=505)
% of patients with event	**26%**	vs.	43%
	HR[‡] 0.57 (98% CI: 0.43, 0.74); $p<0.0001$[§]		
RFS at 1 year	**75%**	vs.	61%

RFS was defined as the time between the date of randomization and the date of first recurrence (local, regional or distant metastasis) or death.

PMBCL

KN-170[1e]

Relapsed or refractory PMBCL

Single-arm trial

ORR[††] (primary endpoint)	KEYTRUDA® 200 mg every 3 weeks (n=29)
	41% (95% CI: 24, 61)
CR	14%
PR	28%

RCC

KN-426[1m]

Combination with axitinib in patients with advanced RCC naive to treatment

Open-label trial
Results are from the prespecified first interim analysis

OS[†††] (co-primary endpoint)	KEYTRUDA® 200 mg every 3 weeks (n=432)		Sunitinib (n=429)
% of patients with event	**14%**	vs.	23%
	HR[‡] 0.53 (95% CI: 0.38, 0.74); $p<0.00005$[§]		

MSI-H/dMMR

Advanced MSI-H or dMMR colorectal and endometrial cancer

Single-arm, open-label trials

	KN-164[1l] Colorectal cancer	KN-158[1l] Endometrial cancer
ORR[‡‡] (primary endpoint)	KEYTRUDA® 200 mg every 3 weeks (n=61)	KEYTRUDA® 200 mg every 3 weeks (n=24)
	28% (95% CI: 17.1, 40.8)	**54%** (95% CI: 32.8, 74.4)
CR	0%	4%
PR	28%	50%

§§ Based on the stratified Cox proportional hazard model. The confidence levels correspond to the allocated type 1 error of 0.00825 and 0.001 for the OS and PFS endpoints, respectively.
¶¶ Statistically significant based on a prespecified alpha level of 0.00825 for the two pairwise comparisons versus docetaxel using a Hochberg procedure.
††† The initial one-sided type 1 error rate level for OS was 0.023. The corresponding *p*-value bounds at the interim analysis for OS was 0.0001.

cHL

Patients with refractory or relapsed classical Hodgkin Lymphoma, or those who have relapsed after ≥3 prior lines of therapy

Non-randomized trials

	KN-087[1d]	KN-013[1d]
ORR[††] (primary endpoint)	KEYTRUDA® 200 mg every 3 weeks (n=210)	KEYTRUDA® 10 mg/kg every 2 weeks (n=31)
	68% (95% CI: 61.3, 74.3)	**58%** (95% CI: 39.1, 75.5)
CR	22%	19%
PR	46%	39%

UC

KN-045[1f]

Locally advanced or metastatic urothelial carcinoma – previously treated with platinum-containing chemotherapy

Median OS at the final descriptive analysis (primary endpoint)	KEYTRUDA® 200 mg every 3 weeks (n=270)		Chemotherapy (n=272)
• Based on the final analysis of a total of 419 deaths (200 for KEYTRUDA® and 219 for chemotherapy)	**10.1** months (95% CI: 8.0, 12.3)	vs.	7.3 months (95% CI: 6.1, 8.1)
	HR 0.70 (95% CI: 0.57, 0.85)		

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

KN-052[1g]

Locally advanced or metastatic urothelial carcinoma – not eligible for cisplatin-containing chemotherapy

Single-arm trial

ORR[‡‡] assessed by BICR (primary endpoint)	KEYTRUDA® 200 mg every 3 weeks (n=370)
	29% (95% CI: 25, 34)
CR	8%
PR	21%

NSCLC

KN-189[1h]

Unresectable or metastatic non-squamous NSCLC – combination treatment

KEYTRUDA® + pemetrexed + IC of platinum chemotherapy

OS (primary endpoint)	KEYTRUDA® + pemetrexed + IC of platinum chemotherapy (carboplatin or cisplatin) (n=410)		Placebo + pemetrexed + IC of platinum chemotherapy (carboplatin or cisplatin) (n=206)
% of patients with event	**31%**	vs.	52%
	HR[‡] 0.49 (95% CI: 0.38, 0.64); $p<0.00001$[§]		
OS at 9 months	**78%**	vs.	56%

KN-024[1,3i]

Unresectable or metastatic NSCLC – no prior treatment

OS (secondary endpoint)	KEYTRUDA® 200 mg every 3 weeks (n=154)		IC of chemotherapy (n=151)
% of patients with event	**29%**	vs.	42%
	HR[‡] 0.60 (95% CI: 0.41, 0.89); $p=0.005$[§]		

KN-010[1,4j]

Metastatic NSCLC patients previously treated with chemotherapy

OS (primary endpoint)	KEYTRUDA® 2 mg/kg every 3 weeks (n=344)		Docetaxel (n=343)
% of patients with event	**50%**	vs.	56%
	HR[¶¶] 0.71 (98.35% CI: 0.55, 0.92); $p<0.001$[¶¶]		

KN-407[1,5k]

Combination carboplatin and either paclitaxel or nab-paclitaxel in metastatic squamous NSCLC patients naive to treatment

OS (primary endpoint)	KEYTRUDA® + carboplatin + paclitaxel or nab-paclitaxel (n=278)		Placebo + carboplatin + paclitaxel or nab-paclitaxel (n=281)
% of patients with event	**31%**	vs.	43%
	HR[‡] 0.64 (95% CI: 0.49, 0.85); $p=0.0008$[§]		

Pr KEYTRUDA® (pembrolizumab)

The study parameters relating to the data presented can be found on pages 8 and 9.

BICR=blinded independent central review; CI=confidence interval; CR=complete response; HR=hazard ratio; IC=investigator's choice; IRO=independent radiology plus oncology; IWG=International Working Group; ORR=objective response rate; OS=overall survival; PR=partial response; PFS=progression-free survival; RCC=renal cell carcinoma; RECIST=Response Evaluation Criteria in Solid Tumors; RFS=recurrence-free survival

† Based on second interim analysis. IRO review using RECIST 1.1.
‡ Based on the stratified Cox proportional hazard model.
§ Based on stratified log rank test.
¶ *p*-value (based on stratified log rank test) is compared with 0.008 of the allocated alpha for this interim analysis.
†† Assessed by BICR according to the 2007 revised IWG criteria.
‡‡ Assessed by BICR using RECIST 1.1.

Important safety information

Clinical use:

Safety and efficacy of KEYTRUDA® in pediatric patients have not been established for patients with conditions other than relapsed or refractory PMBCL.

Relevant warnings and precautions:

- Immune-mediated adverse reactions, including severe and fatal cases:
  - Pneumonitis
  - Colitis
  - Hepatitis
  - Nephritis and renal dysfunction
  - Endocrinopathies including adrenal insufficiency (primary and secondary), hypophysitis, type 1 diabetes mellitus and thyroid disorders
  - Severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis
- Other immune-mediated adverse events, including uveitis, arthritis, myositis, encephalitis, sarcoidosis, myasthenic syndrome/myasthenia gravis (including exacerbation), vasculitis, Guillain-Barré syndrome, hemolytic anemia and pancreatitis
- Elevated liver enzymes when given in combination with axitinib for RCC
- Myocarditis
- Solid organ transplant rejection
- Increased mortality in patients with multiple myeloma when KEYTRUDA® is added to a thalidomide analogue and dexamethasone
- Complications of allogeneic HSCT
- Severe infusion-related reactions, including hypersensitivity and anaphylaxis
- Embryofetal toxicity
- Not recommended in pregnant women
- In nursing women, a decision should be made whether to discontinue breast-feeding or KEYTRUDA® taking into account the benefit of breast-feeding for the child and the benefit of KEYTRUDA® therapy for the woman
- Has not been studied in patients with moderate or severe hepatic impairment
- Has not been studied in patients with severe renal impairment
- Monitor liver and thyroid function tests and electrolytes during treatment

For more information:

Before prescribing KEYTRUDA®, please consult the product monograph available at www.merck.ca/static/pdf/KEYTRUDA-PM_E.pdf for important information relating to adverse reactions, drug interactions and dosing information which have not been discussed in this document.

The product monograph is also available by calling us at 1-800-567-2594 or by email at medinfocanada@merck.com.

[a] The safety and efficacy of KEYTRUDA® were investigated in KEYNOTE-002, a phase 2, open-label, multicentre, 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 (n=180) or 10 mg/kg (n=181) intravenously every 3 weeks or investigator's choice of any of the following chemotherapy regimens (n=179): dacarbazine 1000 mg/m^2 intravenously every 3 weeks (26%), temozolomide 200 mg/m^2 orally once daily for 5 days every 28 days (25%), carboplatin AUC 6 intravenously plus paclitaxel 225 mg/m^2 intravenously every 3 weeks for 4 cycles then carboplatin AUC of 5 plus paclitaxel 175 mg/m^2 every 3 weeks (25%), paclitaxel 175 mg/m^2 intravenously every 3 weeks (16%), or carboplatin AUC 5 or 6 intravenously every 3 weeks (8%). 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. 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.

[b] The safety and efficacy of KEYTRUDA® were investigated in KEYNOTE-006, a multicentre, controlled, phase 3 study for the treatment of unresectable or metastatic melanoma in patients who were naive 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. Patients were treated with KEYTRUDA® until disease progression or 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.

[c] Data were obtained from a multicentre, randomized, double-blind, placebo-controlled trial in patients with completely resected Stage IIIA (>1 mm lymph node metastasis), IIIB or IIIC melanoma. Patients (N=1,019) 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. Patients must have undergone lymph node dissection and if indicated, radiotherapy, within 13 weeks prior to starting treatment. Patients underwent imaging every 12 weeks after the first dose of KEYTRUDA® for the first 2 years, then every 6 months from year 3 to 5, and then annually.

[d] The efficacy of KEYTRUDA® was investigated in 241 patients with refractory classical Hodgkin Lymphoma, or who have relapsed after three or more prior lines of therapy including ASCT, enrolled in two multicentre, non-randomized, open-label studies (KEYNOTE-013 and KEYNOTE-087). Both studies included patients regardless of PD-L1 expression. Patients with active, non-infectious pneumonitis, an allogeneic HSCT within the past 5 years (or greater than 5 years but with GVHD), active autoimmune disease or a medical condition that required immunosuppression were ineligible for either trial. Patients received KEYTRUDA® 10 mg/kg every 2 weeks (n=31; KEYNOTE-013) or 200 mg every 3 weeks (n=210; KEYNOTE-087) until unacceptable toxicity or documented disease progression. 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. Response was assessed using the revised lymphoma criteria by PET-CT scans, with the first planned post-baseline assessment at week 12.

[e] The efficacy of KEYTRUDA® was investigated in KEYNOTE-170, a multicentre, 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.

[f] In a phase 3, open-label trial (KEYNOTE-045), 542 patients with advanced urothelial cancer that had recurred or progressed after platinum-based chemotherapy were randomly assigned in a 1:1 ratio to KEYTRUDA® 200 mg (n=270), or the investigator's choice of chemotherapy with paclitaxel 175 mg/m^2 (n=84), docetaxel 75 mg/m^2 (n=84) or vinflunine 320 mg/m^2 (n=87) administered intravenously every 3 weeks. 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. Co-primary endpoints were overall survival and progression-free survival. Objective response rates, defined as the percentage of patients who had a confirmed complete or partial response, were also assessed.

[g] The efficacy of KEYTRUDA® was investigated in KEYNOTE-052, a multicentre, open-label, single-arm trial of 370 patients with locally advanced unresectable or metastatic urothelial carcinoma who were not eligible for cisplatin-containing chemotherapy. 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.

[h] Data were obtained from a multicentre, randomized, active-controlled, double-blind, phase 3 trial. Patients (n=616) with metastatic non-squamous NSCLC, without sensitizing EGFR or ALK mutations and who had received no previous treatment for metastatic disease, were randomly assigned (2:1) to receive one of the following regimens: KEYTRUDA® combination treatment, which included KEYTRUDA® 200 mg with pemetrexed 500 mg/m^2 and IC of cisplatin 75 mg/m^2 or carboplatin AUC 5 mg/mL/min intravenously every 3 weeks for 4 cycles followed by KEYTRUDA® 200 mg and pemetrexed 500 mg/m^2 intravenously every 3 weeks (n=410); or, placebo combination treatment, which included placebo with pemetrexed 500 mg/m^2 and IC of cisplatin 75 mg/m^2 or carboplatin AUC 5 mg/mL/min intravenously every 3 weeks for 4 cycles followed by placebo and pemetrexed 500 mg/m^2 intravenously every 3 weeks (n=206). 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 a 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.

[i] A randomized, open-label, multicentre, controlled, phase 3 trial, which included patients with no prior systemic treatment for metastatic NSCLC whose tumours had high PD-L1 expression (TPS ≥50%). Patients were randomized (1:1) to receive KEYTRUDA® 200 mg intravenously every 3 weeks (n=154) or IC platinum-containing chemotherapy regimens (n=151); pemetrexed 500 mg/m^2 every 3 weeks and carboplatin AUC 5 to 6 mg/mL/min every 3 weeks on day 1 for 4 to 6 cycles followed by optional pemetrexed 500 mg/m^2 every 3 weeks for patients with non-squamous histologies; pemetrexed 500 mg/m^2 every 3 weeks and cisplatin 75 mg/m^2 every 3 weeks on day 1 for 4 to 6 cycles followed by optional pemetrexed 500 mg/m^2 every 3 weeks for patients with non-squamous histologies; gemcitabine 1250 mg/m^2 on days 1 and 8 and cisplatin 75 mg/m^2 every 3 weeks on day 1 for 4 to 6 cycles; gemcitabine 1250 mg/m^2 on days 1 and 8 and carboplatin AUC 5 to 6 mg/mL/min every 3 weeks on day 1 for 4 to 6 cycles; paclitaxel 200 mg/m^2 every 3 weeks and carboplatin AUC 5 to 6 mg/mL/min every 3 weeks on day 1 for 4 to 6 cycles followed by optional pemetrexed maintenance (for non-squamous histologies). Treatment with KEYTRUDA® continued until disease progression 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 could be treated for up to 24 months or 35 administrations, whichever was longer.

[j] The efficacy of KEYTRUDA® was investigated in KEYNOTE-010, a multicentre, randomized, open-label, controlled trial. Key eligibility criteria were metastatic NSCLC that had progressed following platinum-containing chemotherapy, and if appropriate, targeted therapy for ALK or EGFR mutations, and PD-L1 expression TPS of 1% or greater by a clinical trial assay version of the PD-L1 IHC 22C3 pharmDx® kit. Patients were randomized (1:1:1) to receive KEYTRUDA® 2 mg/kg intravenously every 3 weeks (n=344), KEYTRUDA® 10 mg/kg intravenously every 3 weeks (n=346) or docetaxel 75 mg/m^2 intravenously every 3 weeks (n=343). Patients randomized to KEYTRUDA® were permitted to continue until disease progression that was symptomatic, rapidly progressive, required urgent intervention, occurred with a decline in performance status, or confirmation of progression at 4 to 6 weeks with repeat imaging or for up to 24 months without disease progression.

[k] The efficacy of KEYTRUDA® in combination with carboplatin and either paclitaxel or nab-paclitaxel was investigated in KEYNOTE-407, a randomized, double-blind, multicentre, placebo-controlled study. Key eligibility criteria were metastatic squamous NSCLC, regardless of tumour PD-L1 expression status, and no prior systemic treatment for metastatic disease. 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. Patients were randomized (1:1) to one of the following treatment arms: KEYTRUDA® 200 mg and carboplatin AUC 6 mg/mL/min on day 1 of each 21-day cycle for 4 cycles, and paclitaxel 200 mg/m^2 on day 1 of each 21-day cycle for 4 cycles or nab-paclitaxel 100 mg/m^2 on days 1, 8 and 15 of each 21-day cycle for 4 cycles, followed by KEYTRUDA® 200 mg every 3 weeks (n=278). KEYTRUDA® was administered prior to chemotherapy on day 1; or placebo and carboplatin AUC 6 mg/mL/min on day 1 of each 21-day cycle for 4 cycles and paclitaxel 200 mg/m^2 on day 1 of each 21-day cycle for 4 cycles or nab-paclitaxel 100 mg/m^2 on days 1, 8 and 15 of each 21-day cycle for 4 cycles, followed by placebo every 3 weeks (n=281). All study medications were administered via intravenous infusion. Treatment with KEYTRUDA® or placebo continued until RECIST 1.1-defined progression of disease as determined by 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. Assessment of tumour status was performed every 6 weeks through week 18, every 9 weeks through week 45 and every 12 weeks thereafter.

[l] Data were obtained from 85 patients with MSI-H or dMMR cancer enrolled in two single-arm, multicentre, non-randomized, open-label, multi-cohort phase 2 studies. Regardless of histology, MSI or MMR tumour status was determined using polymerase chain reaction or immunohistochemistry, respectively. Efficacy was evaluated in 61 patients enrolled in KEYNOTE-164 with advanced MSI-H or dMMR colorectal cancer that progressed following treatment with a fluoropyrimidine, oxaliplatin and irinotecan. Efficacy was also evaluated in 24 patients enrolled in KEYNOTE-158, cohorts D and K, with advanced MSI-H or dMMR endometrial cancer who had disease progression following prior therapy and had no satisfactory alternative treatment options. Patients received KEYTRUDA® 200 mg every 3 weeks until unacceptable toxicity or disease progression. Clinically stable patients with initial evidence of disease progression were permitted to remain on treatment until disease progression was confirmed. Patients without disease progression were treated for up to 24 months. Treatment with pembrolizumab could be reinitiated for subsequent disease progression and administered for up to one additional year. Assessment of tumour status in KEYNOTE-164 was performed every 9 weeks and in KEYNOTE-158 every 9 weeks through the first year, then every 12 weeks thereafter.

[m] The efficacy of KEYTRUDA® in combination with axitinib was investigated in a randomized, multicentre, 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 IMDC risk group categories. 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. 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 1 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.

AUC=area under the curve; ECOG=Eastern Cooperative Oncology Group; GVHD=graft-versus-host-disease; HSCT=hematopoietic stem cell transplant; IMDC=International Metastatic RCC Database Consortium; PET-CT=positron emission tomography-computed tomography

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