PRODUCT INFORMATION
KEYTRUDA®
pembrolizumab (rch)

NAME OF THE MEDICINE

pembrolizumab (rch)

CAS No.: 1374853-91-4

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies
ATC code: L01XC18.

DESCRIPTION

KEYTRUDA (pembrolizumab) is a selective humanized monoclonal antibody designed to block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab is an IgG4 kappa immunoglobulin with an approximate molecular weight of 149 kDa. Pembrolizumab is produced in Chinese hamster ovary cells by recombinant DNA technology.

KEYTRUDA 50 mg powder for injection
KEYTRUDA 50 mg powder for injection is a sterile, preservative-free, white to off-white lyophilised powder.
One vial contains 50 mg of pembrolizumab.
After reconstitution, 1 mL of solution contains 25 mg of pembrolizumab.
Not for direct infusion or injection (see ***DOSAGE AND ADMINISTRATION***).

KEYTRUDA 100 mg/4 mL concentrated injection
KEYTRUDA 100 mg/4 mL concentrated injection is a sterile, preservative-free, clear to slightly opalescent, colourless to slightly yellow solution.
One vial contains 100 mg of pembrolizumab in 4 mL of solution.
Not for direct infusion or injection (see ***DOSAGE AND ADMINISTRATION***).

List of excipients

Histidine
Histidine hydrochloride monohydrate
Sucrose
Polysorbate-80
Water for Injections

PHARMACOLOGY

Pharmacology and pharmacological actions

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 and reactivates anti-tumour immunity.

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

Pharmacokinetics

The pharmacokinetics of pembrolizumab was studied in 2188 patients with metastatic or unresectable melanoma, NSCLC, or other carcinomas who received doses in the range of 1 to 10 mg/kg every 2 or 3 weeks. The pharmacokinetics of pembrolizumab was consistent across indications.

Absorption

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

Distribution

Consistent with a limited extravascular distribution, the volume of distribution of pembrolizumab at steady state is small (~7.5L; CV: 21%). As an antibody, pembrolizumab is not expected to bind to plasma proteins in a specific manner.

Metabolism

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

Elimination

The systemic clearance of pembrolizumab is ~0.2 L/day (CV: 37%) and the terminal half-life ($t_{½}$) is ~26 days (CV: 39%).

Exposure to pembrolizumab as expressed by peak concentration (C_{max}) or area under the plasma concentration time curve (AUC) increased dose proportionally within the dose range for efficacy. Upon repeated dosing, the clearance of pembrolizumab was found to be independent of time, and systemic accumulation was approximately 2.2-fold when administered every 3 weeks. Near steady-state concentrations of pembrolizumab were achieved by 18 weeks; the median C_{min} 18 weeks is 22.8 µg/mL at a dose of 2 mg/kg every 3 weeks.

Special populations

The effects of various covariates on the pharmacokinetics of pembrolizumab were assessed in population pharmacokinetic analyses. The following factors had no clinically important effect on the clearance of pembrolizumab: age (range 15-94 years), gender, race, mild or moderate renal impairment, mild hepatic impairment, and tumour burden. The relationship between body weight and clearance supports the use of either fixed dose or body weight-based dosing to provide adequate and similar control of exposure.

Renal Impairment

The effect of renal impairment on the clearance of pembrolizumab was evaluated by population pharmacokinetic analysis in patients with mild (GFR <90 and ≥60 mL/min/1.73 m^2) or moderate (GFR <60 and ≥30 mL/min/1.73 m^2) renal impairment compared to patients with normal (GFR ≥90 mL/min/1.73 m^2) renal function. No clinically important differences in the clearance of pembrolizumab were found between patients with mild or moderate renal impairment and patients with normal renal

function. KEYTRUDA has not been studied in patients with severe (GFR <30 and ≥15 mL/min/1.73 m^2) renal impairment *[See DOSAGE AND ADMINISTRATION]*.

Hepatic Impairment

The effect of hepatic impairment on the clearance of pembrolizumab was evaluated by population pharmacokinetic analysis in patients with mild hepatic impairment (total bilirubin (TB) 1.0 to 1.5 x ULN or AST >ULN as defined using the National Cancer Institute criteria of hepatic dysfunction) compared to patients with normal hepatic function (TB and AST ≤ULN). No clinically important differences in the clearance of pembrolizumab were found between patients with mild hepatic impairment and normal hepatic function. KEYTRUDA has not been studied in patients with moderate (TB >1.5 to 3 x ULN and any AST) or severe (TB >3 x ULN and any AST) hepatic impairment *[See DOSAGE AND ADMINISTRATION]*.

CLINICAL TRIALS

Clinical Studies in Unresectable or Metastatic Melanoma

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

The safety and efficacy of KEYTRUDA were investigated in KEYNOTE 006, a multicenter, controlled, Phase III study for the treatment of unresectable or metastatic melanoma in patients who were naïve to ipilimumab and who received no or one prior systemic therapy. Patients were 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 (n=278). Randomization was stratified by line of therapy, ECOG performance status, and PD-L1 expression status. The study excluded patients with autoimmune disease or those receiving immunosuppression; previous severe hypersensitivity to other monoclonal antibodies; and HIV, hepatitis B or hepatitis C infection. Patients with BRAF V600E mutant melanoma were not required to have received prior BRAF inhibitor therapy.

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

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

The primary efficacy outcome measures were overall survival (OS) and progression free survival (PFS; as assessed by Integrated Radiology and Oncology Assessment [IRO] review using Response Evaluation Criteria in Solid Tumours [RECIST 1.1]). Secondary efficacy outcome measures were overall response rate (ORR) and response duration. Table 1 summarizes key efficacy measures, and the Kaplan-Meier curves for OS and PFS are shown in Figures 1 and 2.

Table 1: Response to KEYTRUDA 10 mg/kg every 2 or 3 weeks in patients with KEYTRUDA naïve advanced melanoma in KEYNOTE-006

Endpoint	KEYTRUDA 10 mg/kg every 3 weeks n=277	KEYTRUDA 10 mg/kg every 2 weeks n=279	Ipilimumab n=278
OS			
Number (%) of patients with event	92 (33%)	85 (30%)	112 (40%)
Hazard ratio† (95% CI)	0.69 (0.52, 0.90)	0.63 (0.47, 0.83)	---
p-Value‡	0.00358	0.00052	---
Median in months (95% CI)	Not reached (NA, NA)	Not reached (NA, NA)	Not reached (13, NA)
PFS by IRO*			
Number (%) of patients with event	157 (57%)	157 (56%)	188 (68%)
Hazard ratio† (95% CI)	0.58 (0.47, 0.72)	0.58 (0.46, 0.72)	---
p-Value‡	<0.00001	<0.00001	---
Median in months (95% CI)	4.1 (2.9, 6.9)	5.5 (3.4, 6.9)	2.8 (2.8, 2.9)
Best overall response by IRO*			
ORR % (95% CI)	33% (27, 39)	34% (28, 40)	12% (8, 16)
Complete response %	6%	5%	1%
Partial response %	27%	29%	10%
Response duration§ by IRO*			
Median in months (range)	Not reached (1.4+, 8.1+)	8.3 (1.4+, 8.3)	Not reached (1.1+, 7.9+)
% ongoing	97%	89%	88%

* IRO = Independent radiology plus oncologist review using RECIST 1.1
† Hazard ratio (KEYTRUDA compared to ipilimumab) based on the stratified Cox proportional hazard model
‡ Based on stratified Log rank test
§ Based on patients with a best overall response as confirmed complete or partial response
NA = not available

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

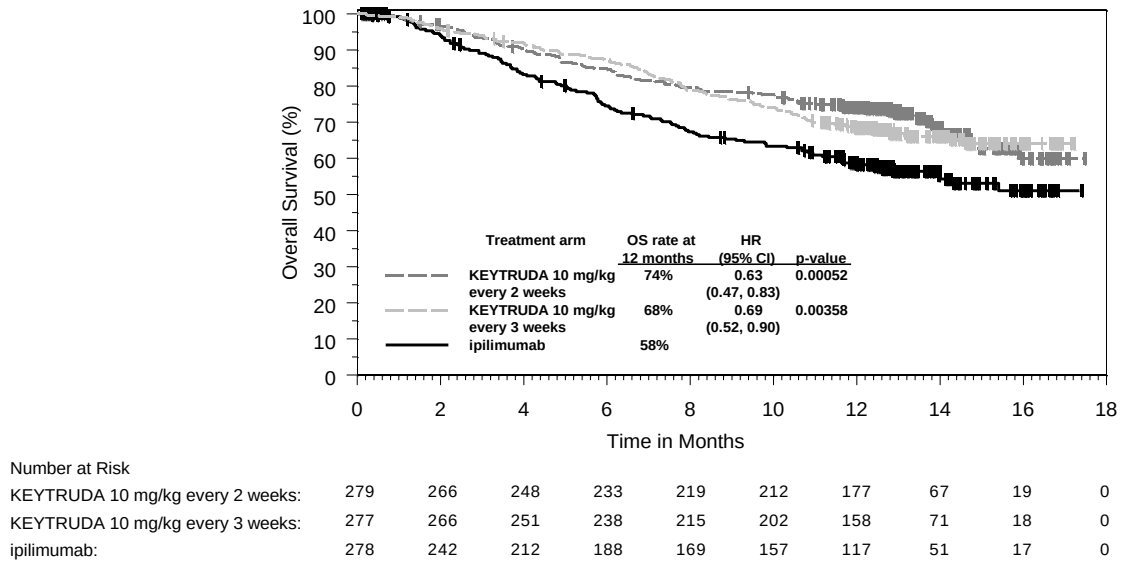
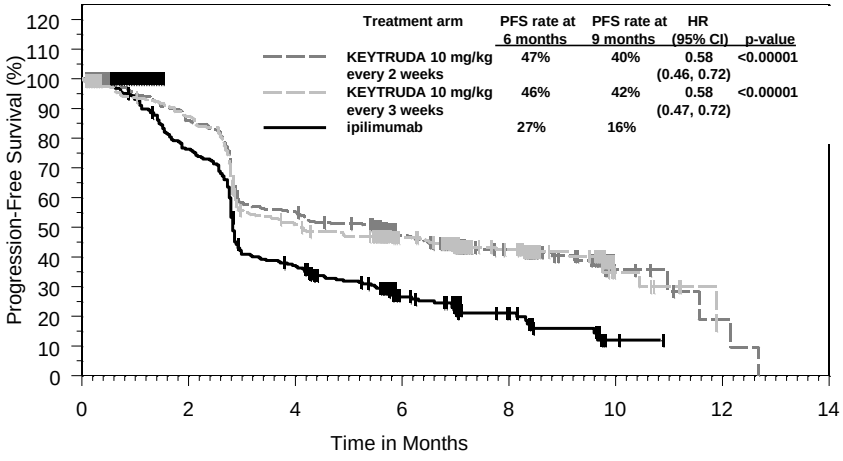


Figure 2: Kaplan-Meier curve for progression-free survival (based on IRO) by treatment arm in KEYNOTE-006 (intent to treat population)



Number at Risk

KEYTRUDA 10 mg/kg every 2 weeks:	279	231	147	98	49	7	2	0
KEYTRUDA 10 mg/kg every 3 weeks:	277	235	133	95	53	7	1	1
ipilimumab:	278	186	88	42	18	2	0	0

Sub-population analysis by BRAF mutation status

A subgroup analysis of KEYNOTE 006 in patients who were BRAF wild type, BRAF mutant without prior BRAF treatment and BRAF mutant with prior BRAF treatment was performed. The PFS hazard ratios (HRs) (pooled KEYTRUDA [10 mg/kg every 2 or 3 weeks] vs. ipilimumab) were 0.57 (95% CI: 0.45, 0.73) for BRAF wild type, 0.50 (95% CI: 0.32, 0.77) for BRAF mutant without prior BRAF treatment, and 0.73 (95% CI: 0.48, 1.11) for BRAF mutant with prior BRAF treatment. The OS HRs for pooled KEYTRUDA vs. ipilimumab were 0.61 (0.46, 0.82) for BRAF wild type, 0.69 (0.33, 1.45) for BRAF mutant without prior BRAF treatment, and 0.75 (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.

Sub-population analysis by PD-L1 status

A subgroup analysis of KEYNOTE 006 in patients who were PD L1 positive vs. PD L1 negative was performed. The PFS HRs (pooled KEYTRUDA [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 KEYTRUDA 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.

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

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

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

The primary efficacy outcome measures were PFS (as assessed by IRO review using RECIST 1.1) and overall survival (OS). Secondary efficacy outcome measures were PFS as assessed by Investigator using RECIST 1.1, ORR and response duration. Table 2 summarizes key efficacy measures in patients previously treated with ipilimumab, and the Kaplan-Meier curve for PFS is shown in Figure 3. OS data were not mature at the time of the PFS analysis. There was no statistically significant difference between KEYTRUDA and chemotherapy in the preliminary OS analysis that was not adjusted for the potentially confounding effects of crossover. Of the patients randomized to the chemotherapy arm, 48% crossed over and subsequently received treatment with KEYTRUDA.

Table 2: 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)
Mean in months (95% CI) §	5.4 (4.7, 6.0)	5.8 (5.1, 6.4)	3.6 (3.2, 4.1)
PFS by INV¶			
Number (%) of patients with event	122 (68%)	112 (62%)	157 (88%)
Hazard ratio† (95% CI)	0.49 (0.38, 0.62)	0.41 (0.32, 0.52)	---
p-Value‡	<0.0001	<0.0001	---
Median in months (95% CI)	3.7 (2.9, 5.4)	5.4 (3.8, 6.8)	2.6 (2.4, 2.8)
Mean in months (95% CI) §	5.8 (5.2, 6.4)	6.5 (5.8, 7.1)	3.7 (3.2, 4.1)
Best overall response by IRO*			
ORR % (95% CI)	21% (15, 28)	25% (19, 32)	4% (2, 9)
Complete response %	2%	3%	0%
Partial response %	19%	23%	4%
Response duration# by IRO*			
Median in months (range)	Not reached (1.4+, 11.5+)	Not reached (1.2+, 11.1+)	8.5 (1.6+, 9.5)
% ongoing	87%	80%	63%

* IRO = Independent radiology plus oncologist review using RECIST 1.1

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

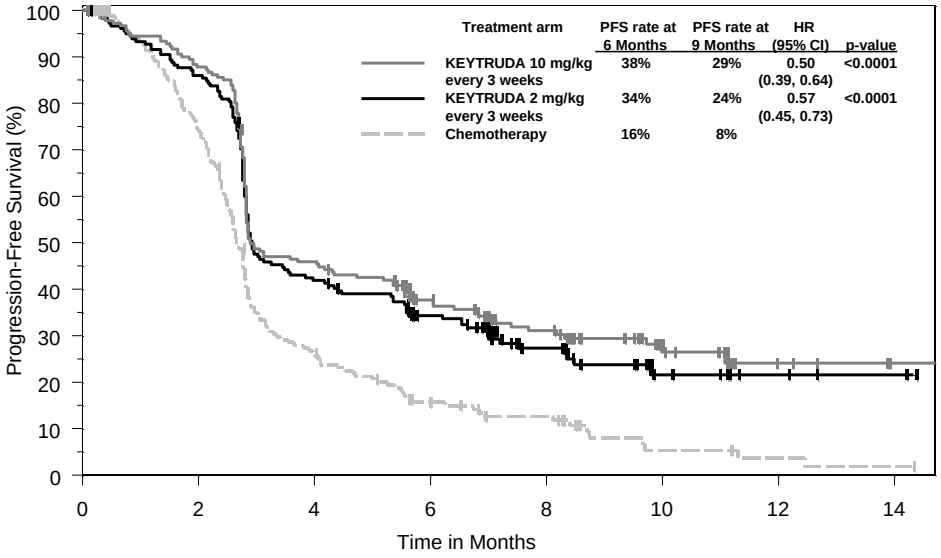
‡ Based on stratified Log rank test

§ Restricted mean progression free survival time based on follow up of 12 months

¶ INV = Investigator assessment using RECIST 1.1

Based on patients with a best overall response as confirmed complete or partial response

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



Number at Risk

KEYTRUDA 10 mg/kg:	181	158	82	55	39	15	5	1
KEYTRUDA 2 mg/kg:	180	153	74	53	26	9	4	2
Chemotherapy:	179	128	43	22	15	4	2	1

KEYNOTE-001: Open label study in melanoma patients

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

Of the 89 patients receiving 2 mg/kg of KEYTRUDA who were previously treated with ipilimumab, 53% were male, 33% were ≥65 years of age and the median age was 59 years (range 18-88). All but two patients were white. Eighty-four percent of patients had M1c stage and 8% of patients had a history of brain metastases. Seventy-eight percent of patients had at least two and 35% of patients had three or more prior systemic therapies for advanced melanoma. BRAF mutations were reported in 13% of the study population.

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

The primary efficacy outcome measure was ORR as assessed by independent review using confirmed responses and RECIST 1.1. Secondary efficacy outcome measures were disease control rate (DCR; including complete response, partial response and stable disease), response duration, PFS, and OS. Tumour response was assessed at 12-week intervals. Table 3 summarises key efficacy measures in patients previously treated or naïve to treatment with ipilimumab, receiving KEYTRUDA at the recommended dose.

Table 3: Response to KEYTRUDA 2 mg/kg every 3 Weeks in Patients with Unresectable or Metastatic Melanoma in KEYNOTE-001

Endpoint	**KEYTRUDA 2 mg/kg every 3 weeks in patients previously treated with ipilimumab n=89**	**KEYTRUDA 2 mg/kg every 3 weeks in patients naïve to treatment with ipilimumab n=51**
Best Overall Response* by IRO†		
ORR %, (95% CI)	25% (16, 35)	33% (21, 48)
Disease Control Rate %‡	49%	49%
Complete response	3%	10%
Partial response	21%	24%
Stable disease	25%	16%
Response Duration§		
Median in months (range)	Not reached (2.8+, 14.3+)	Not reached (1.6+, 13.8+)
% ongoing	86%¶	82%#
PFS		
Median in months (95% CI)	4.9 (2.8, 8.3)	5.5 (2.8, 14.0)
PFS rate at 6 months	43%	50%
OS		
Median in months (95% CI)	Not reached (11, not available)	Not reached (14, not available)
OS rate at 12 months	60%	72%

* Includes patients without measurable disease at baseline by independent radiology
† IRO = Independent radiology plus oncologist review using RECIST 1.1
‡ Based on best response of stable disease or better
§ Based on patients with a confirmed response by independent review, starting from the date the response was first recorded; n=22 for patients previously treated with ipilimumab; n=17 for patients naïve to treatment with ipilimumab
¶ Responders were followed for a minimum of 12 months after initiation of therapy
# Responders were followed for a minimum of 15 months after initiation of therapy

Results for patients previously treated with ipilimumab (n=84) and naïve to treatment with ipilimumab (n=52) who received 10 mg/kg of KEYTRUDA every 3 weeks were similar to those seen in patients who received 2 mg/kg of KEYTRUDA every 3 weeks.

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, 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; who had received more than 30 Gy of thoracic radiation within the prior 26 weeks; with an ECOG performance status > 1; with significant organ dysfunction; or with untreated brain metastases were ineligible. Patients with

treated brain metastases were eligible if neurologically returned to baseline prior to enrolment and off corticosteroids. Patients were randomized (1:1) to receive KEYTRUDA 200 mg every 3 weeks (n=154) or investigator's choice platinum-containing chemotherapy (n=151; including pemetrexed+carboplatin, pemetrexed+cisplatin, gemcitabine+cisplatin, gemcitabine+carboplatin, or paclitaxel+carboplatin. Non-squamous patients could receive pemetrexed maintenance). Patients were treated with KEYTRUDA until unacceptable toxicity or disease progression, up to a maximum of 35 treatments (24 months). Treatment could continue beyond disease progression if the patient was clinically stable and was considered to be deriving clinical benefit by the investigator. Assessment of tumour status was performed every 9 weeks. Patients on chemotherapy who experienced independently-verified progression of disease were able to crossover and receive KEYTRUDA.

Among the 305 patients in KEYNOTE-024, baseline characteristics were: median age 65 years (54% age 65 or older); 61% male; 82% White and 15% Asian; and 35% and 65% with an ECOG performance status 0 and 1, respectively. Subjects with ECOG performance status > 1 and subjects with significant organ dysfunction were ineligible. Disease characteristics were squamous (18%) and non-squamous (82%); M1 (99%); and brain metastases (9%).

The primary efficacy outcome measure was PFS as assessed by blinded independent central review (BICR) using RECIST 1.1. Secondary efficacy outcome measures were OS and ORR (as assessed by BICR using RECIST 1.1). Table 4 summarizes key efficacy measures for the entire ITT population.

Table 4: Efficacy Results in KEYNOTE-024

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

* Assessed by BICR using RECIST 1.1
† Hazard ratio (KEYTRUDA compared to chemotherapy) based on the stratified Cox proportional hazard model
‡ Based on stratified Log rank test
§ Based on patients with a best overall response as confirmed complete or partial response
¶ Based on Kaplan-Meier estimates; includes 43 patients with responses of 6 months or longer
# Based on Kaplan-Meier estimates; includes 16 patients with responses of 6 months or longer
NA = not available

Figure 4: Kaplan-Meier Progression-Free Survival by Treatment Arm in KEYNOTE-024 (Intent to Treat Population)

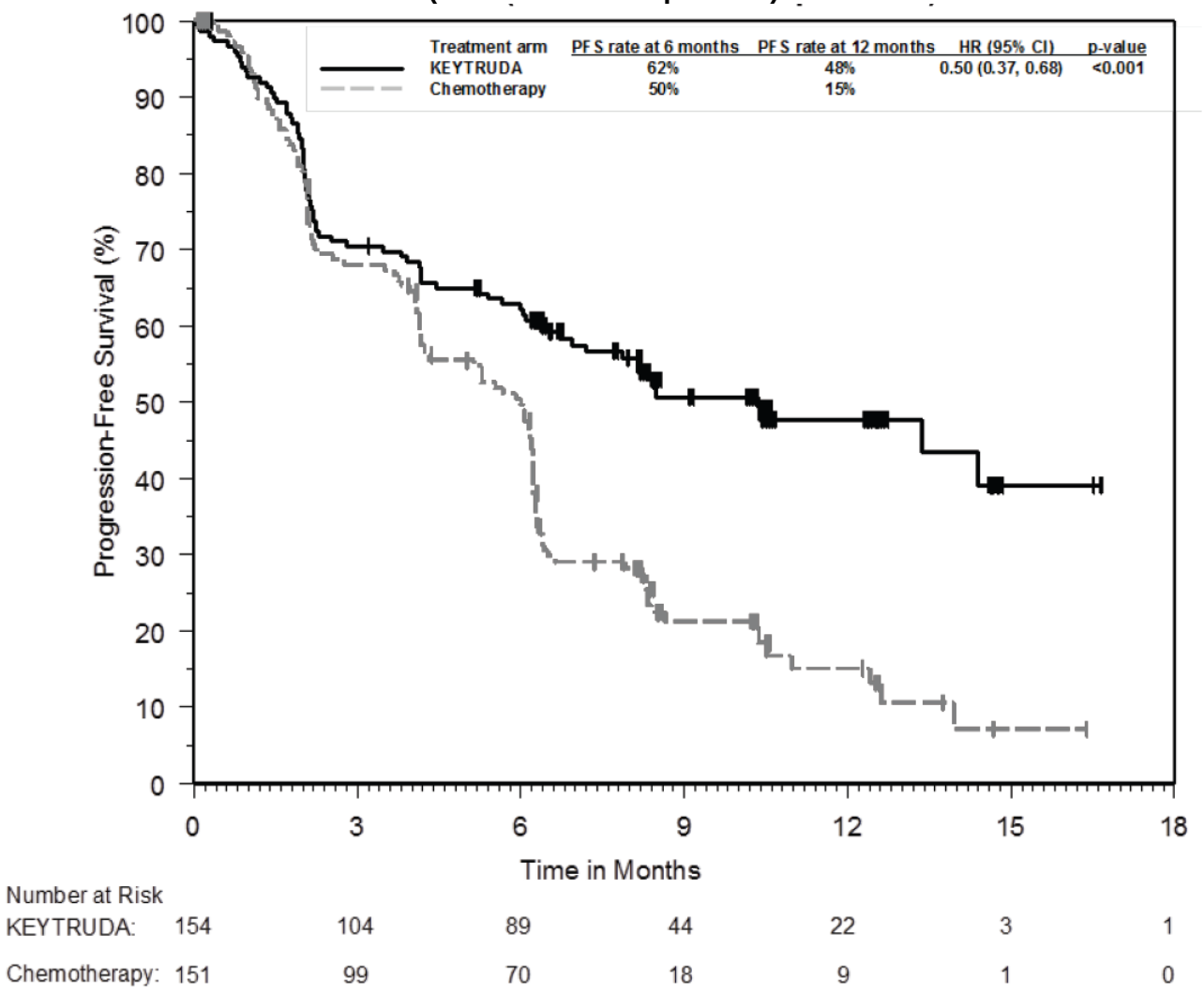
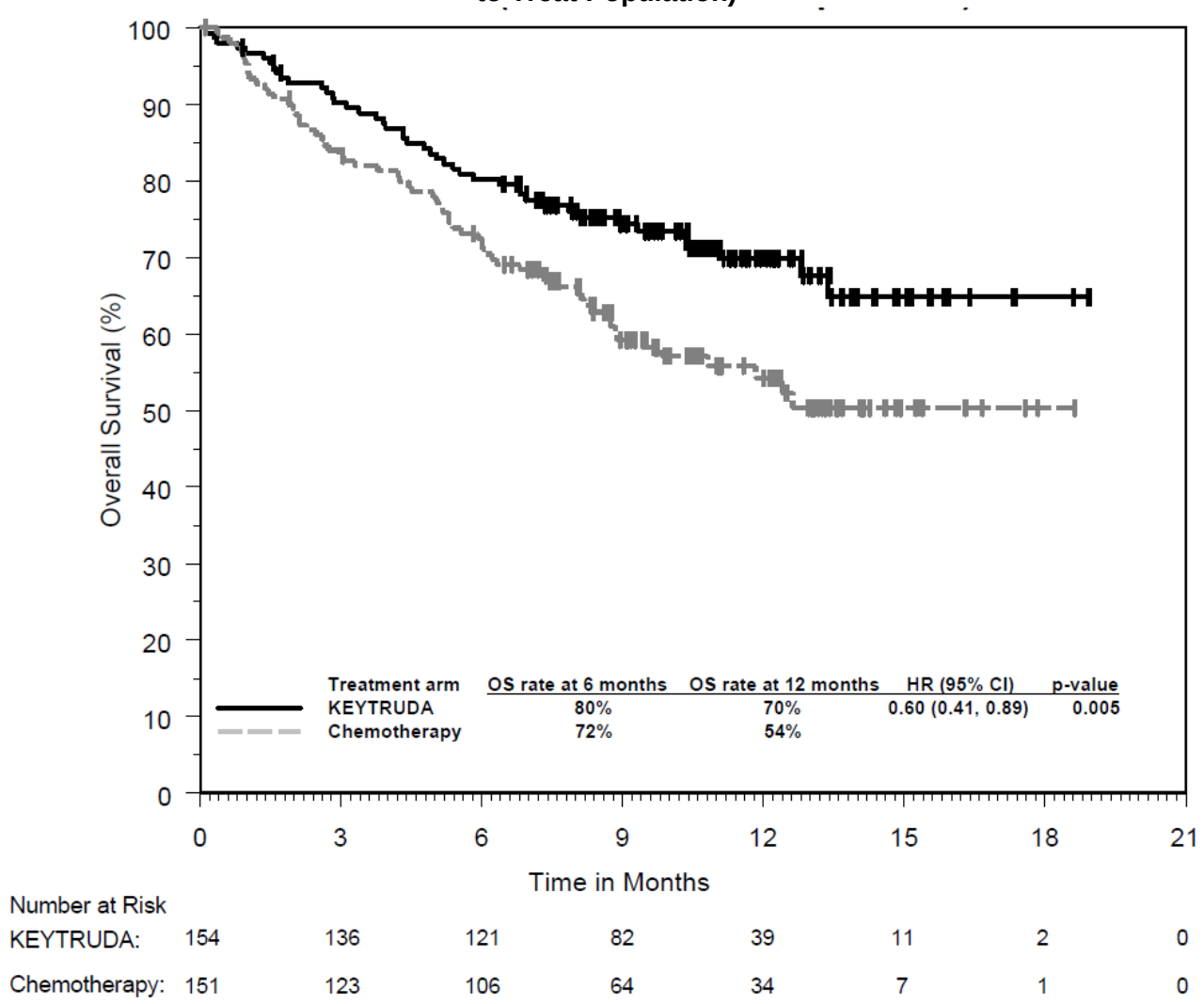


Figure 5: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-024 (Intent to Treat Population)



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

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

The efficacy of KEYTRUDA was investigated in KEYNOTE-010, a multicenter, randomized, controlled trial. Key eligibility criteria were advanced NSCLC that had progressed following platinum-containing chemotherapy, and if appropriate, targeted therapy for ALK or EGFR mutations, and PD-L1 expression TPS of 1% or greater by a clinical trial assay version of the PD-L1 IHC 22C3 pharmDx™ kit. Patients with autoimmune disease; a medical condition that required immunosuppression; who had received more than 30 Gy of thoracic radiation within the prior 26 weeks; or with untreated brain metastases were ineligible. Patients with treated brain metastases were eligible if neurologically returned to baseline prior to enrolment and off corticosteroids. Patients were randomized (1:1:1) to receive 2 mg/kg (n=344) or 10 mg/kg (n=346) of KEYTRUDA every 3 weeks or 75 mg/m^2 of docetaxel every 3 weeks (n=343). Patients were treated with KEYTRUDA until unacceptable toxicity or disease progression, up to a maximum of 35 treatments (24 months). Assessment of tumour status was performed every 9 weeks.

Among the 1033 patients in KEYNOTE-010, baseline characteristics were: median age 63 years (42% age 65 or older); 61% male; 72% White and 21% Asian; and 34% and 66% with an ECOG performance status 0 and 1, respectively. Disease characteristics were squamous (21%) and non-squamous (70%); M1 (91%); brain metastases (15%); and the incidence of genomic aberrations was EGFR (8%) or ALK (1%). Prior therapy included platinum-doublet regimen (100%); patients received one (69%), or two or more (29%) prior therapies.

The primary efficacy outcome measures were OS and PFS as assessed by an independent review committee using RECIST 1.1. Secondary efficacy outcome measures were ORR and response duration. Table 5 summarizes key efficacy measures for the entire ITT population (TPS ≥1%) and for the subgroup of patients with TPS ≥50%. Kaplan-Meier curves for OS (TPS ≥1% and TPS ≥50%) are shown in Figures 6 and 7.

Table 5: Response to KEYTRUDA 2 or 10 mg/kg every 3 Weeks in Previously Treated Patients with NSCLC in KEYNOTE-010

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

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

† Based on stratified Log rank test

‡ Assessed by BICR using RECIST 1.1

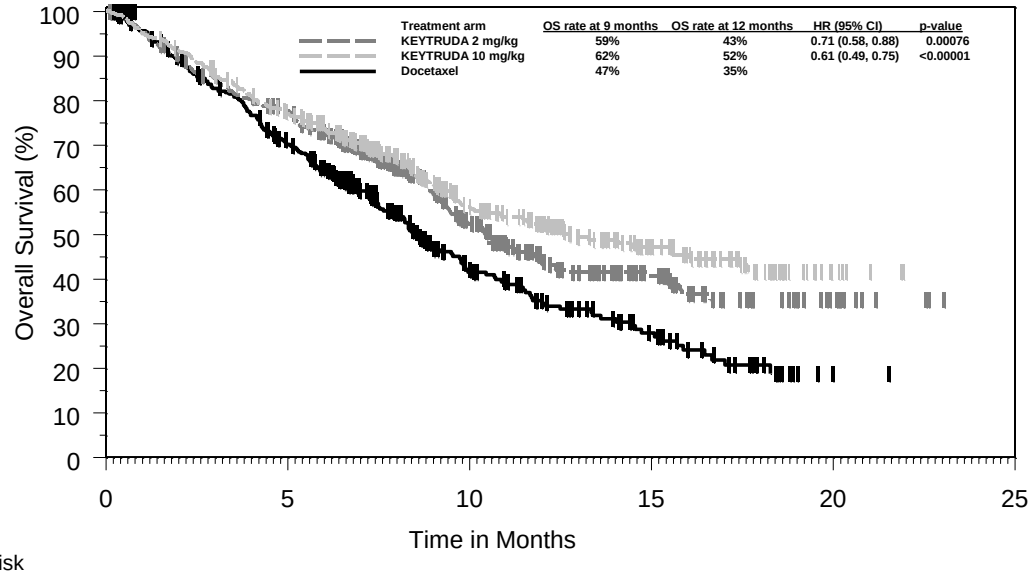
§ All responses were partial responses

¶ Based on patients with a best overall response as confirmed complete or partial response

\# Includes 30, 31, and 2 patients with ongoing responses of 6 months or longer in the KEYTRUDA 2 mg/kg, KEYTRUDA 10 mg/kg, and docetaxel groups respectively

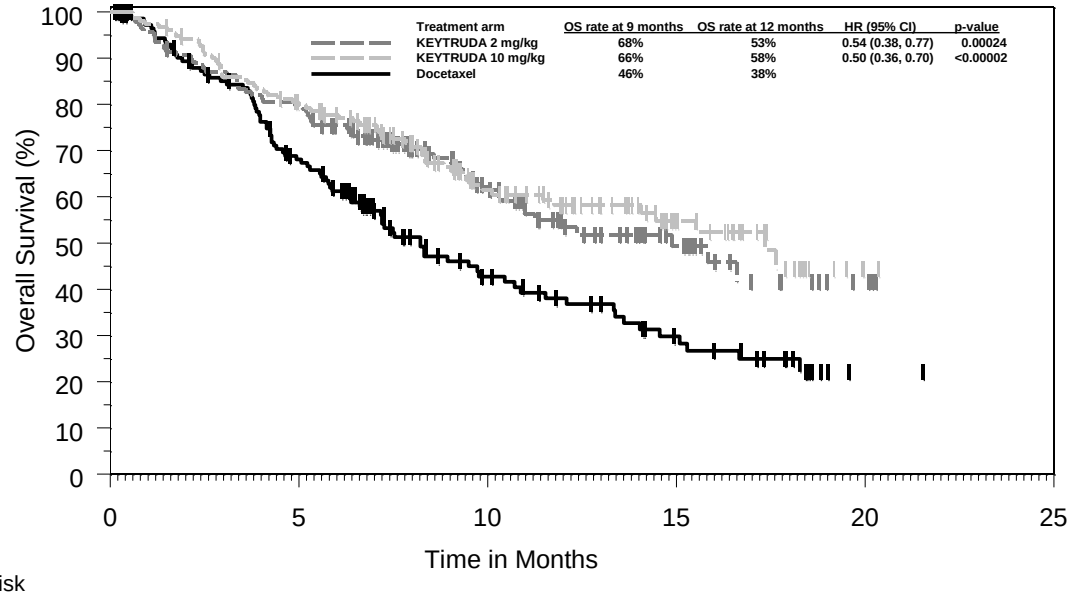
Þ Includes 22, 24, and 1 patients with ongoing responses of 6 months or longer in the KEYTRUDA 2 mg/kg, KEYTRUDA 10 mg/kg, and docetaxel groups respectively

Figure 6: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-010 (TPS ≥ 1%, Intent to Treat Population)



Number at Risk						
KEYTRUDA 2 mg/kg:	344	259	115	49	12	0
KEYTRUDA 10 mg/kg:	346	255	124	56	6	0
Docetaxel:	343	212	79	33	1	0

Figure 7: Kaplan-Meier Curve for Overall Survival by Treatment Arm in KEYNOTE-010 (TPS ≥ 50%, Intent to Treat Population)



Number at Risk						
KEYTRUDA 2 mg/kg:	139	110	51	20	3	0
KEYTRUDA 10 mg/kg:	151	115	60	25	1	0
Docetaxel:	152	90	38	19	1	0

Efficacy results were similar for the 2 mg/kg and 10 mg/kg KEYTRUDA arms. Efficacy results for OS were consistent regardless of the age of tumour specimen (new versus archival).

Sub-population analysis of patients with 1% ≤ TPS ≤ 49% in KEYNOTE-010

A subgroup analysis of KEYNOTE 010 in patients with TPS 1-49% was performed. The OS HRs for KEYTRUDA vs. docetaxel were 0.79 (95% CI: 0.61,1.04) for patients treated with 2 mg/kg every three weeks and 0.71 (95% CI: 0.53, 0.94) for patients treated with 10 mg/kg every 3 weeks. The median OS was 9.4 months (95% CI: 8.7, 10.5), 10.8 months (95% CI: 8.9, 13.3) and 8.6 months (95% CI: 7.8, 9.9) for patients treated with KEYTRUDA 2 mg/kg every three weeks (n=205), 10 mg/kg every three weeks (n=195) and docetaxel (n=191) respectively. The PFS HRs (KEYTRUDA vs. docetaxel) were 1.07 (95% CI: 0.85, 1.34) for patients treated with 2 mg/kg every three weeks and 0.99 (95% CI: 0.78, 1.25) for patients treated with 10 mg/kg every 3 weeks. The median PFS was 3.1 months (95% CI: 2.1, 3.8), 2.3 months (95% CI: 2.1, 4.0) and 3.9 months (95% CI: 2.5, 4.3) for KEYTRUDA 2 mg/kg every three weeks, 10 mg/kg every three weeks and docetaxel respectively. The ORR was 10% (95% CI: 6, 15), 10% (95% CI: 6, 15) and 10% (95% CI: 7, 16) for KEYTRUDA 2 mg/kg every three weeks, 10 mg/kg every three weeks and docetaxel respectively. Furthermore, the median duration of response was 10.6 months (range: 2.1+, 20.1+), 10.4 months (range: 3.0+, 17.1+) and 6.0 months (range: 1.4+, 7.2) for KEYTRUDA 2 mg/kg every three weeks, 10 mg/kg every three weeks and docetaxel respectively.

Head and Neck Cancer

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

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

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

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

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

Efficacy results are summarized in Table 6.

Table 6 Efficacy Results in Patients with HNSCC

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

* Assessed by blinded independent central review using RECIST 1.1

† Based on patients (n=28) with a confirmed response by independent review

¶ Based on Kaplan-Meier estimates; includes 23 patients with responses of 6 months or longer including 14 patients with response of 12 months or longer.

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

Immunogenicity

In clinical studies in patients treated with pembrolizumab at a dose of 2 mg/kg every 3 weeks 200 mg every 3 weeks or 10 mg/kg every 2 or 3 weeks, 26 (2.0%) of 1289 evaluable patients tested positive for treatment-emergent antibodies against pembrolizumab during treatment with KEYTRUDA. There was no evidence of an altered pharmacokinetic or safety profile with anti-pembrolizumab binding antibody development.

INDICATIONS

KEYTRUDA® (pembrolizumab) is indicated as monotherapy for the treatment of unresectable or metastatic melanoma in adults.

KEYTRUDA® is indicated for the first-line treatment of patients with metastatic non-small cell lung carcinoma (NSCLC) whose tumours express PD-L1 with a ≥50% tumour proportion score (TPS) as determined by a validated test, with no EGFR or ALK genomic tumour aberrations.

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

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

CONTRAINDICATIONS

KEYTRUDA is contraindicated in patients with hypersensitivity to pembrolizumab or any of the inactive ingredients *[See DESCRIPTION]*.

PRECAUTIONS

Immune-mediated Adverse Reactions

Immune-mediated adverse reactions occurred in patients receiving KEYTRUDA. In clinical trials, most immune-mediated adverse reactions occurred during treatment, were reversible and managed with interruptions of KEYTRUDA, administration of corticosteroids and/or supportive care. Immune-related adverse reactions have 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-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered. Restart KEYTRUDA if the adverse reaction remains at Grade 1 or less following corticosteroid taper. If another episode of a severe adverse reaction occurs, permanently discontinue KEYTRUDA *[See DOSAGE AND ADMINISTRATION and ADVERSE EFFECTS]*.

Immune-mediated pneumonitis

Pneumonitis (including fatal cases) has been reported in patients receiving KEYTRUDA *[See ADVERSE EFFECTS]*.

Monitor patients for signs and symptoms of pneumonitis. If pneumonitis is suspected, evaluate with radiographic imaging and exclude other causes. Administer corticosteroids for Grade 2 or greater events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper), withhold KEYTRUDA for moderate (Grade 2) pneumonitis, and permanently discontinue KEYTRUDA for severe (Grade 3), life-threatening (Grade 4) or recurrent moderate (Grade 2) pneumonitis *[See DOSAGE AND ADMINISTRATION, ADVERSE EFFECTS and Immune-mediated Adverse Reactions above]*.

Immune-mediated colitis

Colitis has been reported in patients receiving KEYTRUDA *[See ADVERSE EFFECTS]*.

Monitor patients for signs and symptoms of colitis and exclude other causes. Administer corticosteroids for Grade 2 or greater events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper), withhold KEYTRUDA for moderate (Grade 2) or severe (Grade 3) colitis, and permanently discontinue KEYTRUDA for life-threatening (Grade 4) colitis *[See DOSAGE AND ADMINISTRATION, ADVERSE EFFECTS and Immune-mediated Adverse Reactions above]*. The potential risk of gastrointestinal perforation should be taken into consideration.

Immune-mediated hepatitis

Hepatitis has been reported in patients receiving KEYTRUDA *[See ADVERSE EFFECTS]*.

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

Immune-mediated nephritis

Nephritis has been reported in patients receiving KEYTRUDA *[See ADVERSE EFFECTS]*.
Monitor patients for changes in renal function and exclude other causes. Administer corticosteroids for Grade 2 or greater events (initial dose of 1-2 mg/kg/day prednisone or equivalent followed by a taper), withhold KEYTRUDA for moderate (Grade 2), and permanently discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) nephritis. *[See DOSAGE AND ADMINISTRATION, ADVERSE EFFECTS and Immune-mediated Adverse Reactions above]*.

Immune-mediated endocrinopathies

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

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

Thyroid disorders have been reported in patients receiving KEYTRUDA and can occur at any time during treatment, therefore monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) and clinical signs and symptoms of thyroid disorders. Hypothyroidism may be managed with replacement therapy without treatment interruption and without corticosteroids. Hyperthyroidism may be managed symptomatically. Withhold or discontinue KEYTRUDA for severe (Grade 3) or life-threatening (Grade 4) hyperthyroidism *[See DOSAGE AND ADMINISTRATION, ADVERSE EFFECTS and Immune-mediated Adverse Reactions above]*.

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

Severe skin reactions

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

Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some with fatal outcome, have been reported in patients treated with KEYTRUDA. For signs or symptoms of SJS or TEN, withhold KEYTRUDA and refer the patient for specialized care for assessment and treatment. If SJS or TEN is confirmed, permanently discontinue KEYTRUDA. [*See DOSAGE AND ADMINISTRATION*].

Other immune-mediated adverse reactions

The following additional clinically significant, immune-mediated adverse reactions were reported in less than 1% of patients treated with KEYTRUDA in KEYNOTE-001, KEYNOTE-002, KEYNOTE-006, and KEYNOTE-010: uveitis, myositis, Guillain-Barre syndrome, myasthenic syndrome, and pancreatitis. The following was reported in other clinical studies with KEYTRUDA or in post-marketing use: myocarditis.

Cases of these immune-mediated adverse reactions, some of which were severe, have been reported in clinical trials or in post-marketing use.

Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with KEYTRUDA. Treatment with KEYTRUDA may increase the risk of rejection in solid organ transplant recipients. Consider the benefit of treatment with KEYTRUDA versus the risk of possible organ rejection in these patients.

Infusion-related reactions

Severe infusion reactions have been reported in 6 (0.2%) of 2799 patients receiving KEYTRUDA in KEYNOTE-001, KEYNOTE-002, KEYNOTE-006 and KEYNOTE-010. For severe infusion reactions, stop infusion and permanently discontinue KEYTRUDA *[See 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.

Patients excluded from clinical trials

Patients with HIV, HBV, HCV, other active infections requiring therapy; and patients with a history of severe immune-mediated adverse reactions with ipilimumab, defined as any Grade 4 toxicity requiring treatment with corticosteroids or Grade 3 toxicity requiring corticosteroid treatment (greater than 10 mg/day prednisone or equivalent dose) for greater than 12 weeks were excluded from the trial. No clinical data is available. Caution should be used in these patient populations.

Patients who experienced less severe adverse reactions (including immune-mediated) on ipilimumab that resolved or improved to Grade 0-1 and ≤10 mg/day prednisone (or equivalent dose) for immune-mediated adverse events for at least two weeks prior to first dose of KEYTRUDA were included in the clinical trial. Caution should be used in this patient population.

Patient Alert Card

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

Effects on Fertility

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

Use in Pregnancy (Category D)

There are no data on the use of pembrolizumab in pregnant women. Animal reproduction studies have not been conducted with pembrolizumab; however, blockade of the PD-1 pathway has been shown in mouse models of pregnancy to disrupt tolerance to the foetus and to result in an increase in foetal loss. These results indicate a potential risk, based on its mechanism of action, that administration of KEYTRUDA during pregnancy could cause foetal harm, including increased rates of abortion or stillbirth. Human IgG4 (immunoglobulin) is known to cross the placental barrier and pembrolizumab is an IgG4; therefore, pembrolizumab has the potential to be transmitted from the mother to the developing foetus. KEYTRUDA is not recommended during pregnancy unless the clinical benefit outweighs the potential risk to the foetus. Women of childbearing potential should use effective contraception during treatment with KEYTRUDA and for at least 4 months following the last dose of KEYTRUDA.

Use in Lactation

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

Paediatric Use

Safety and efficacy of KEYTRUDA in children below 18 years of age have not yet been established.

Use in the elderly

No overall differences in safety or efficacy were reported between elderly patients (65 years and over) and younger patients (less than 65 years). No dose adjustment is necessary in this population.

Genotoxicity

The genotoxic potential of pembrolizumab has not been evaluated. As a large protein molecule, pembrolizumab is not expected to interact directly with DNA or other chromosomal material.

Carcinogenicity

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

Effect on Laboratory Tests

Thyroid and liver (hepatic transaminase and bilirubin levels) function tests should be performed at the start of treatment, periodically during treatment and as indicated based on clinical evaluation *[see PRECAUTIONS and DOSAGE AND ADMINISTRATON].*

INTERACTIONS WITH OTHER MEDICINES

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

The use of systemic corticosteroids or immunosuppressants before starting KEYTRUDA should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of KEYTRUDA. However, systemic corticosteroids or other immunosuppressants can be used after starting KEYTRUDA to treat immune-mediated adverse reactions *[See PRECAUTIONS]*.

ADVERSE EFFECTS

Clinical trials experience

The safety of KEYTRUDA was investigated in three controlled, randomised studies (KEYNOTE-002, KEYNOTE-006 and KEYNOTE-010) for the treatment of unresectable or metastatic melanoma or metastatic NSCLC and in an uncontrolled, open-label study (KEYNOTE-001) 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 was evaluated in 2799 patients (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 adverse events in 5% of patients. Treatment-related serious adverse events (SAEs) reported up to 90 days after the last dose occurred in 10% of patients receiving KEYTRUDA. Of these treatment-related SAEs, the most common were: pneumonitis, colitis, diarrhoea, and pyrexia. The most common treatment-related adverse reactions (reported in >10% of patients) were: fatigue (24%), pruritus (17%), rash (14%), diarrhoea (12%), and nausea (11%). The safety profile was generally similar for patients with melanoma and NSCLC.

Immune-mediated adverse reactions [see PRECAUTIONS]

Immune-mediated adverse reactions are presented based on 2799 patients with melanoma and NSCLC. The safety profile was generally similar for patients with melanoma and NSCLC. Table 7 presents the incidence of immune-mediated adverse reactions by Grade that occurred in patients receiving KEYTRUDA.

Table 7: Immune-mediated Adverse Reactions

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

* In patients with HNSCC (n=192) the incidence of hypothyroidism was 14.6% (all Grades) with 0.5.% Grade 3.

Incidences of pneumonitis in individual studies in melanoma and non-small cell lung cancer ranged from 1.6% to 5.8%.

Endocrinopathies: The median time to onset of hypophysitis was 3.7 months (range 1 day to 11.9 months). The median duration was 4.7 months (range 8+ days to 12.7+ months). Hypophysitis led to discontinuation of KEYTRUDA in 4 (0.1%) patients. Hypophysitis resolved in 7 patients. The median time to onset of hyperthyroidism was 1.4 months (range 1 day to 21.9 months). The median duration was 2.1 months (range 3 days to 15.0+ months). Hyperthyroidism led to discontinuation of KEYTRUDA in 2 (<0.1%) patients. Hyperthyroidism resolved in 71 patients. The median time to onset of hypothyroidism was 3.5 months (range 1 day to 18.9 months). The median duration was not reached (range 2 days to 27.7+ months). One (<0.1%) patient discontinued KEYTRUDA due to hypothyroidism.
Pneumonitis: The median time to onset of pneumonitis was 3.3 months (range 2 days to 19.3 months). The median duration was 1.5 months (range 1 day to 17.2+ months). Pneumonitis led to discontinuation of KEYTRUDA in 36 (1.3%) patients. Pneumonitis resolved in 55 patients.
Colitis: The median time to onset of colitis was 3.5 months (range 10 days to 16.2 months). The median duration was 1.3 months (range 1 day to 8.7+ months). Colitis led to discontinuation of KEYTRUDA in 15 (0.5%) patients. Colitis resolved in 41 patients.
Hepatitis: The median time to onset of hepatitis was 1.3 months (range 8 days to 21.4 months). The median duration was 1.8 months (range 8 days to 20.9+ months). Hepatitis led to discontinuation of KEYTRUDA in 6 (0.2%) patients. Hepatitis resolved in 15 patients.
Nephritis: The median time to onset of nephritis was 5.1 months (range 12 days to 12.8 months). The median duration was 3.3 months (range 12 days to 8.9+ months). Nephritis led to discontinuation of KEYTRUDA in 3 (0.1%) patients. Nephritis resolved in 5 patients.

Other adverse events

Melanoma
Table 8 summarizes the adverse events that occurred in at least 10% of patients with melanoma treated with KEYTRUDA in KEYNOTE-006. The most common adverse events (reported in at least 15% of patients) were arthralgia and cough.

Table 8: Adverse Events Occurring in ≥10% of Patients treated with KEYTRUDA and at a Higher Incidence than in the Ipilimumab Arm (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grade 3]) (KEYNOTE-006)

	KEYTRUDA 10 mg/kg every 2 or 3 weeks n=555		Ipilimumab 3 mg/kg every 3 weeks n=256	
Adverse Events	**All Grades (%)**	**Grade 3* (%)**	**All Grades (%)**	**Grade 3* (%)**
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	18	0	10	1
Back pain	12	1	7	1
Respiratory, Thoracic and Mediastinal Disorders				
Cough	17	0	7	0
Skin And Subcutaneous Tissue Disorders				
Vitiligo	11	0	2	0

* Of these ≥10% adverse events, none was reported as Grade 4.

Table 9: Laboratory Abnormalities Worsened from Baseline in ≥20% of Patients with Unresectable or Metastatic Melanoma and at a Higher Incidence than in the Ipilimumab Arm (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-4]) (KEYNOTE-006)

	KEYTRUDA 10 mg/kg every 2 or 3 weeks n=555		Ipilimumab n=256	
Laboratory Test	**All Grades %**	**Grades 3-4 %**	**All Grades %**	**Grades 3-4 %**
Hematology				
Lymphopenia	45	5	36	5
Chemistry				
Hypertriglyceridemia	40	2	33	1

Table 10 summarises the adverse events that occurred in at least 10% of patients treated with KEYTRUDA at the recommended dose in KEYNOTE-002. The most common adverse event (reported in at least 20% of patients) was pruritus.

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

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

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

Table 11: Laboratory Abnormalities Worsened from Baseline in ≥20% of Patients with Unresectable or Metastatic Melanoma and at a Higher Incidence than in the Chemotherapy Arm (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grades 3-4]) (KEYNOTE-002)

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

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

Non-Small Cell Lung Carcinoma

Table 12 summarizes the adverse events that occurred in at least 10% of previously treated patients with NSCLC receiving KEYTRUDA in KEYNOTE-010. The most common adverse event (reported in at least 15% of patients) was cough. Adverse events occurring in previously untreated patients

with NSCLC receiving KEYTRUDA in KEYNOTE-024 were generally similar to those occurring in patients in KEYNOTE-010.

Table 12: Adverse Events Occurring in ≥10% of NSCLC Patients Treated with KEYTRUDA and at a Higher Incidence than in the Docetaxel Arm (Between Arm Difference of ≥5% [All Grades] or ≥2% [Grade 3]) (KEYNOTE-010)

	KEYTRUDA 2 or 10 mg/kg every 3 weeks n=682		Docetaxel 75 mg/m^2 every 3 weeks n=309	
Adverse Event	**All Grades (%)**	**Grades 3* (%)**	**All Grades (%)**	**Grades 3* (%)**
Respiratory, Thoracic and Mediastinal Disorders				
Cough	19	1	14	0
Skin and Subcutaneous Tissue Disorders				
Rash	14	<1	7	0
Pruritis	11	0	3	<1

* Of these ≥10% adverse events, none was reported as Grade 4.

Head and Neck Cancer
Adverse events occurring in patients with HNSCC were generally similar to those occurring in patients with melanoma or NSCLC, except with respect to the higher rate of hypothyroidism observed in patients with HNSCC (see Table 7). Of these 28 patients, 15 had no prior history of hypothyroidism.

DOSAGE AND ADMINISTRATION

Treatment must be initiated and supervised by healthcare professionals experienced in the treatment of cancer.

Patient Selection

Non-Small Cell Lung Carcinoma
Patients should be selected for treatment of advanced NSCLC with KEYTRUDA based on the presence of positive PD-L1 expression *[see CLINICAL TRIALS]*.

Determination of PD-L1 expression should be performed by laboratories with demonstrated proficiency in the *in-vitro* diagnostic technology being employed.

Recommended Dosing

KEYTRUDA is administered as an intravenous infusion over 30 minutes every 3 weeks.

The recommended dose of KEYTRUDA is:
- 200 mg for head and neck cancer or previously untreated NSCLC.
- 2 mg/kg for melanoma or previously treated NSCLC.

Patients should be treated with KEYTRUDA until disease progression or unacceptable toxicity. Patients with NSCLC without disease progression can be treated for up to 24 months *[see CLINICAL TRIALS].* Atypical responses (i.e., an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed. Clinically stable patients with initial evidence of disease progression can under some circumstances remain on treatment until disease progression is confirmed (see CLINICAL TRIALS section for a description of the circumstances where such continued treatment was allowed in the pivotal studies).

Dose Modifications

Withhold KEYTRUDA for immune-mediated adverse reactions including *[see PRECAUTIONS]***:**

- Pneumonitis - moderate (Grade 2; US National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE v.4))
- Colitis - moderate or severe (Grade 2 or 3)
- Nephritis - moderate (Grade 2)
- Endocrinopathies - severe or life-threatening (Grade 3 or 4)
- Hepatitis associated 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
- Severe skin reactions (Grade 3) or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)

Resume KEYTRUDA in patients whose adverse reactions recover to Grade 0-1.

Permanently discontinue KEYTRUDA *[see PRECAUTIONS]***:**

- If corticosteroid dosing cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks
- If a treatment-related toxicity does not resolve to Grade 0-1 within 12 weeks after last dose of KEYTRUDA
- If another episode of any severe toxicity occurs
- For adverse reactions including:
    - Life-threatening (Grade 4) toxicity except for endocrinopathies that improve to Grade 2 or lower and are controlled with replacement hormones
    - Immune-mediated pneumonitis - severe or life-threatening (Grade 3 or 4) or recurrent moderate (Grade 2)
    - Immune-mediated nephritis - severe or life-threatening (Grade 3 or 4)
    - Immune-mediated hepatitis associated with:
        - AST or ALT >5 times ULN or total bilirubin >3 times ULN
    - For patients with liver metastasis who begin treatment with moderate (Grade 2) elevation of AST or ALT, if AST or ALT increases ≥50% relative to baseline and lasts ≥1 week
    - Severe skin reactions (Grade 4) or confirmed SJS or TEN
    - Infusion-related reactions - severe or life-threatening (Grade 3 or 4)

Preparation and Administration

Preparation of KEYTRUDA 50 mg powder for injection

- Prior to reconstitution, the vial of lyophilised powder can be out of refrigeration (temperatures at or below 25°C) for up to 24 hours.
- Aseptically add 2.3 mL of sterile water for injection to yield a 25 mg/mL (pH 5.2-5.8) solution of KEYTRUDA.
- To avoid foaming, deliver the water along the walls of the vial and not directly on the lyophilised powder.
- Slowly swirl the vial to allow reconstitution of the lyophilised powder. Allow up to 5 minutes for the bubbles to clear. Do not shake the vials.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Reconstituted KEYTRUDA is a clear to slightly opalescent, colourless to slightly yellow solution. Discard the vial if visible particles are observed.
- Withdraw the required volume up to 2 mL (50 mg) of KEYTRUDA and transfer into an intravenous bag containing 0.9% sodium chloride or 5% glucose (dextrose) to prepare a diluted solution with a final concentration ranging from 1 to 10 mg/mL. Mix diluted solution by gentle inversion (**see *Administration***).

Preparation of KEYTRUDA 100 mg/4 mL concentrated injection

- Protect from light. Do not freeze. Do not shake.
- Equilibrate the vial of KEYTRUDA to room temperature.
- Prior to dilution, the vial of liquid can be out of refrigeration (temperatures at or below 25°C) for up to 24 hours.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. KEYTRUDA is a clear to slightly opalescent, colourless to slightly yellow solution. Discard the vial if visible particles are observed.
- Withdraw the required volume up to 4 mL (100 mg) of KEYTRUDA and transfer into an intravenous bag containing 0.9% sodium chloride or 5% glucose (dextrose) to prepare a diluted solution with a final concentration ranging from 1 to 10 mg/mL. Mix diluted solution by gentle inversion (**see *Administration***).

Administration

- Do not freeze the infusion solution.
- The product does not contain preservative. The reconstituted and/or diluted product should be used immediately. If not used immediately, reconstituted and diluted solutions of KEYTRUDA solutions may be stored at room temperature for a cumulative time of up to 6 hours. Reconstituted and diluted solutions of KEYTRUDA may also be stored under refrigeration at 2°C to 8°C; however, the total time from reconstitution or dilution of KEYTRUDA to completion of infusion should not exceed 24 hours. If refrigerated, allow the vials and/or IV bags to come to room temperature prior to use.
- Administer infusion solution intravenously over 30 minutes using a sterile, non-pyrogenic, low-protein binding 0.2 to 5 µm in-line or add-on filter.
- Do not co-administer other drugs through the same infusion line.
- Product is for single use in one patient only, Discard any residue.

Paediatric Patients

Safety and efficacy of KEYTRUDA in children below 18 years of age have not yet been established.

Geriatric Patients

No overall differences in safety or efficacy were reported between elderly patients (65 years and over) and younger patients (less than 65 years). No dose adjustment is necessary in this population.

Renal Insufficiency

No dose adjustment is needed for patients with mild or moderate renal impairment. KEYTRUDA has not been studied in patients with severe renal impairment *[See PHARMACOLOGY].*

Hepatic Insufficiency

No dose adjustment is needed for patients with mild hepatic impairment. KEYTRUDA has not been studied in patients with moderate or severe hepatic impairment *[See PHARMACOLOGY].*

OVERDOSAGE

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

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

PRESENTATION AND STORAGE CONDITIONS

Carton of one 50 mg powder for injection or one 100 mg/4 mL concentrated injection single-use vial.

Store in a refrigerator (2°C to 8°C).

Protect from light. Do not freeze. Do not shake.

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

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

Prescription only medicine (Schedule 4)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG)

16 April 2015

DATE OF MOST RECENT AMENDMENT

20 MARCH 2017