KEYNOTE-091 CLINICAL TRIAL SUMMARY

KEYTRUDA® (pembrolizumab)

KEYTRUDA® (pembrolizumab) is a Prescription Medicine and is available as a 100 mg/4 mL concentrate for solution for infusion.

Please review the KEYTRUDA Data Sheet before prescribing. The Data Sheet is available at www.medsafe.govt.nz.

INDICATIONS: In combination with pemetrexed and platinum chemotherapy for first-line treatment of metastatic non-squamous non-small cell lung carcinoma (NSCLC), with no EGFR or ALK genomic tumour aberrations. In combination with carboplatin and either paclitaxel or nab-paclitaxel for first-line treatment of metastatic squamous NSCLC. As monotherapy for first-line treatment of patients with NSCLC whose tumours express PD-L1 [tumour proportion score (TPS) ≥1%] as determined by a validated test, with no EGFR or ALK genomic tumour aberrations and are either; metastatic, or stage III where patients are not candidates for surgical resection or definitive chemoradiation. As monotherapy for the treatment of patients with advanced NSCLC with a PD-L1 TPS level ≥1% 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. As monotherapy for the adjuvant treatment of patients with Stage IB (T2a ≥4 cm), II, or IIIA NSCLC who have undergone complete resection. See Data Sheet for other indications.

CONTRAINDICATIONS: Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of the Data Sheet. See Data Sheet for further information.

PRECAUTIONS: Severe and fatal cases of immune-mediated adverse reactions have occurred. Immune-related adverse reactions have occurred after discontinuation of treatment with KEYTRUDA and can affect more than one body system simultaneously. For management of immune-mediated adverse reactions, see Data Sheet. Immune-mediated adverse reactions have occurred as follows: pneumonitis (including fatal cases), colitis, hepatitis, nephritis, adrenal insufficiency, hypophysitis, type 1 diabetes mellitus, hyperthyroidism, hypothyroidism, thyroiditis, severe skin reactions (Stevens-Johnson syndrome and toxic epidermal necrolysis [including fatal cases], bullous pemphigoid), uveitis, myositis, Guillain-Barre syndrome, pancreatitis, encephalitis, sarcoidosis, myasthenic syndrome/myasthenia gravis (including exacerbation), myelitis, vasculitis, hypoparathyroidism, gastritis, haemolytic anaemia, pericarditis, myocarditis, sclerosing cholangitis, exocrine pancreatic insufficiency, solid organ transplant rejection, acute graft-versus-host-disease (GVHD) including fatal GVHD with a history of allogeneic hematopoietic stem cell transplantation, higher than expected frequencies of Grades 3 and 4 ALT and AST elevations in advanced RCC when used in combination with axitinib, increased mortality when in combination with dexamethasone and a thalidomide analogue in multiple myeloma (not indicated), severe infusion reactions including hypersensitivity and anaphylaxis. Monitor thyroid and liver function. Limited data in patients with active infections and with history of severe adverse reaction to ipilimumab – use caution. No data in severe renal impairment, or moderate or severe hepatic impairment. Pregnancy (Category D). See Data Sheet for further information.

INTERACTIONS: None expected. Avoid systemic corticosteroids or immunosuppressants prior to treatment (except as premedication in combination with chemotherapy).

ADVERSE EVENTS: Monotherapy: pneumonitis, colitis, diarrhoea, pyrexia, fatigue, pruritus, rash, nausea, hypothyroidism, hyperthyroidism, adrenal insufficiency, hepatitis, hypophysitis, nephritis, type 1 diabetes mellitus, arthralgia, cough, back pain, vitiligo, lymphopenia, hypertriglyceridemia, abdominal pain, hyponatremia, hyperglycaemia, hypoalbuminemia, increased AST and ALP, anaemia, dyspnoea, constipation, increased lipase; Combination (where not already listed under Monotherapy) *with chemotherapy:* alopecia, asthenia, decreased neutrophil count, neutropenia, thrombocytopenia, mucosal inflammation, stomatitis, vomiting, decreased white blood cell count, decreased appetite, decreased platelet count. See Data Sheet for further information.

DOSAGE AND ADMINISTRATION: Adults: 200 mg every 3 weeks or 400 mg every 6 weeks. Paediatrics (see Indications): 2 mg/kg (up to 200 mg) every 3 weeks. Administered as an intravenous infusion over 30 minutes. For use in combination, please review the Data Sheets for KEYTRUDA and the relevant concomitant therapies. KEYTRUDA should be administered first when given in combination with intravenous chemotherapy. Treat with KEYTRUDA until disease progression or unacceptable toxicity. Atypical responses (i.e. an initial transient increase in tumour size or small new lesions followed by shrinkage) have been observed. Clinically stable patients (i.e. asymptomatic and not requiring urgent intervention) with initial evidence of progression can remain on treatment until confirmed. For the adjuvant treatment of NSCLC, treat with KEYTRUDA for up to one year or until disease recurrence or unacceptable toxicity. See Data Sheet for further information. (v54.02)

KEYTRUDA is funded for the first-line treatment of patients with advanced or metastatic NSCLC. Further restrictions apply, see pharmac.govt.nz.[4]

KEYTRUDA is unfunded for the other NSCLC indications – a charge will apply.

AJCC: American Joint Committee on Cancer; **AE:** adverse event; **CI:** confidence interval; **DFS:** disease-free survival; **HR:** hazard ratio; **imAEs:** immune-mediated adverse events; **ITT:** intention-to-treat; **IV:** intravenous; **NR:** not reached; **NSCLC:** non-small cell lung carcinoma; **OS:** overall survival; **PD-L1:** programmed-death protein ligand 1; **Q3W:** every 3 weeks; **Q6W:** every 6 weeks; **RECIST v1.1:** Response Evaluation Criteria In Solid Tumors v1.1; **TPS:** tumour proportion score.

References: 1. KEYTRUDA Data Sheet. **2.** O'Brien M *et al. Lancet Oncol* 2022;23:1247–1286. **3.** Besse B *et al.* Adjuvant Pembrolizumab versus Placebo for Early-Stage NSCLC After Resection and Optional Chemotherapy: Updated Results From PEARLS/KEYNOTE-091. Slide deck presented at: ESMO; October 2023. **4.** PHARMAC. Pharmaceutical Schedule. Available at: https://pharmac.govt.nz/pharmaceutical-schedule Accessed 30 October 2024.

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MSD

KEYTRUDA®
(pembrolizumab)

KEYTRUDA is indicated as monotherapy for the adjuvant treatment of patients with Stage IB (T2a ≥4 cm), II, or IIIA non-small cell lung cancer (NSCLC) who have undergone complete resection.[1,a]

A Key to Treating Your Appropriate Patients with Resected NSCLC, Regardless of PD-L1 Expression[1]

[a]As defined by American Joint Committee on Cancer (AJCC) 7th edition.

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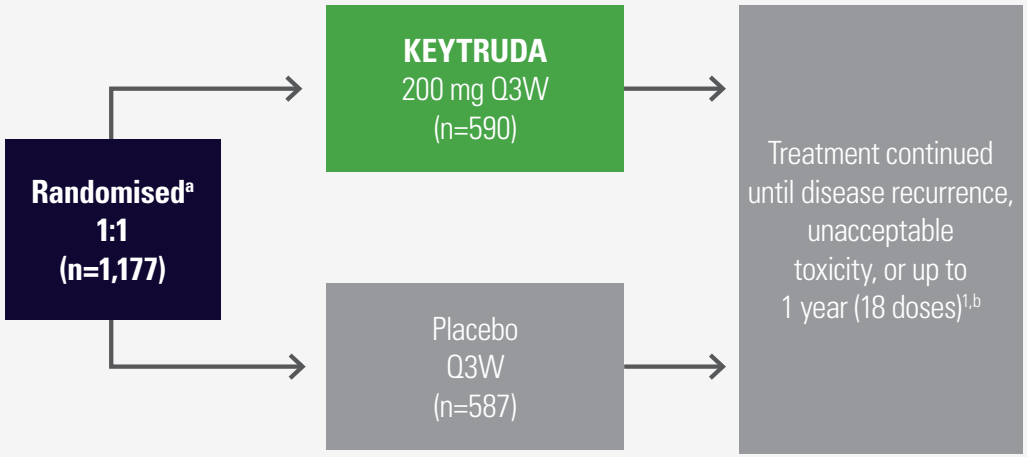
KEYNOTE-091: Study design

A multicentre, randomised, triple-blind, placebo-controlled trial[1]



Selected baseline characteristics[1]

Characteristics	ITT population (n=1,177)
Age: median age in years (range)	65 (31–87)
Age ≥65 years	53%
Sex: male / female	68% / 32%
Ethnicity: White / Asian	77% / 18%
Region: Western Europe	51%
ECOG PS: 0 / 1	61% / 39%
Stage: IIB (T2a ≥4 cm) / II / IIIA	14% / 57% / 29%
Received adjuvant chemotherapy: Y / N	86% / 14%
Tumour PD-L1 expression TPS: <1% / 1–49% / ≥50%	40% / 32% / 28%

Key eligibility criteria[1]

- Completely resected Stage IB (T2a ≥4 cm), II, or IIIA NSCLC per AJCC 7th ed, regardless of tumour PD-L1 expression
- No prior neoadjuvant radiotherapy and/or neoadjuvant chemotherapy
- No prior or planned adjuvant radiotherapy for the current malignancy
- May or may not have received adjuvant chemotherapy

Key exclusion criteria[1]

- Autoimmune disease requiring systemic therapy within 2 years of treatment
- A medical condition requiring immunosuppression
- More than 4 cycles of prior adjuvant chemotherapy

Dual primary efficacy endpoints[1]

- Disease-free survival (DFS)[c] in the overall (ITT) population
- DFS[c] in the tumour PD-L1 expression TPS ≥50% population

Secondary efficacy endpoints[1]

- DFS[c] in the tumour PD-L1 expression TPS ≥1% population
- OS in the overall population and in the populations with tumour PD-L1 expression TPS ≥50% and TPS ≥1%

a. Randomisation was stratified by Stage (IB vs II vs IIIA), adjuvant chemotherapy (no adjuvant chemotherapy vs adjuvant chemotherapy), PD-L1 status (TPS <1% [negative] vs TPS 1%–49% vs TPS ≥50%), and geographic region (Western Europe vs Eastern Europe vs Asia vs rest of world).[1]
b. RECIST v1.1–defined disease recurrence as determined by the investigator.[2]
c. Investigator-assessed DFS was defined as the time between the date of randomisation and the date of first recurrence (local/regional recurrence, distant metastasis), a second malignancy, or death, whichever occurred first.[1]

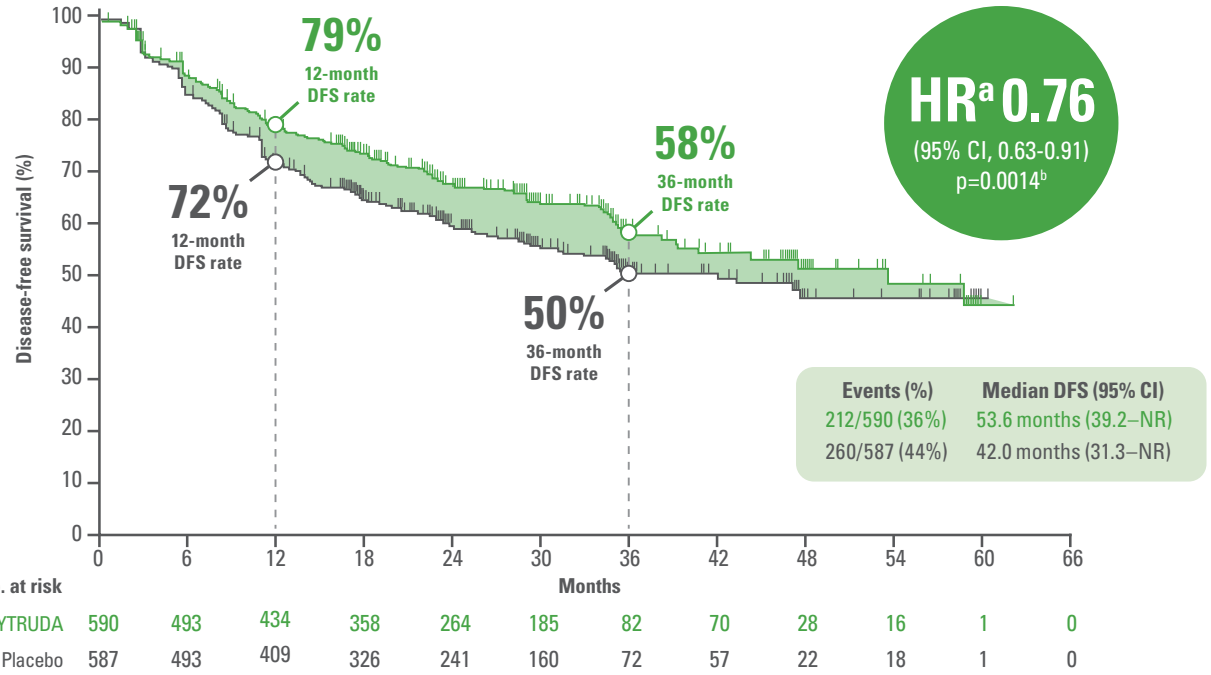
KEYNOTE-091: Disease-free survival

INTERIM ANALYSIS 2

SUPERIOR DISEASE-FREE SURVIVAL (DFS)*

***HR[a] 0.76, 95% CI: 0.63–0.91, p=0.0014[b]** for KEYTRUDA vs. placebo in the overall (ITT) population[1]

Kaplan-Meier estimates for DFS in the overall (ITT) population at median follow up 32.4 months[1,2]



- DFS in the population with tumour PD-L1 expression TPS ≥50% (dual primary endpoint) was not statistically significant: **HR[a] 0.82** (95% CI, 0.57–1.18), p=0·14.[2]
- At the time of this analysis, the overall survival results were not mature (18% with events in the overall [ITT] population).[1]

a. HR based on the multivariate Cox regression model.
b. Based on the permutation test with multivariate Cox regression model.

INTERIM ANALYSIS 3

KEYNOTE-091 follow-up analysis[3]

Final DFS analysis at median follow-up time of 51.7 months.

***LIMITATION:** No formal statistical testing was performed for the updated analysis and, therefore, no conclusions can be drawn.

DFS in the overall (ITT) population at the final analysis:

HR 0.81*
(95% CI: 0.68–0.96)[3]

KEYNOTE-091: Safety profile (median follow up 51.7 months)

Adverse events (as-treated population)[3]

	KEYTRUDA (N=580)	Placebo (n=581)
Any grade	556 (95.9)	529 (91.0)
Grade 3–5	198 (34.1)	150 (25.8)
Led to treatment discontinuation	116 (20.0)	34 (5.9)
Led to death	11 (1.9)	6 (1.0)
Treatment-related AEs	436 (75.2)	305 (52.5)
Grade 3-5	89 (15.3)	25 (4.3)
AEs of any cause occurring in ≥15% of patients in either treatment group		
Increased weight	132 (22.8)	168 (28.9)
Pruritus	125 (21.6)	74 (12.7)
Hypothyroidism	120 (20.7)	27 (4.6)
Arthralgia	107 (18.4)	72 (12.4)
Diarrhoea	106 (18.3)	83 (14.3)
Fatigue	96 (16.6)	89 (15.3)
Cough	87 (15.0)	98 (16.9)

- Adverse events led to death in 11 (2%) patients treated with KEYTRUDA. Four (1%) patients treated with KEYTRUDA died due to events attributed to treatment by the investigator: cardiogenic shock and myocarditis (n=1), septic shock and myocarditis (n=1), pneumonia (n=1), and sudden death (n=1).[2,3]

Immune-mediated adverse events (imAEs)[a] and infusion reactions (as-treated population)[3]

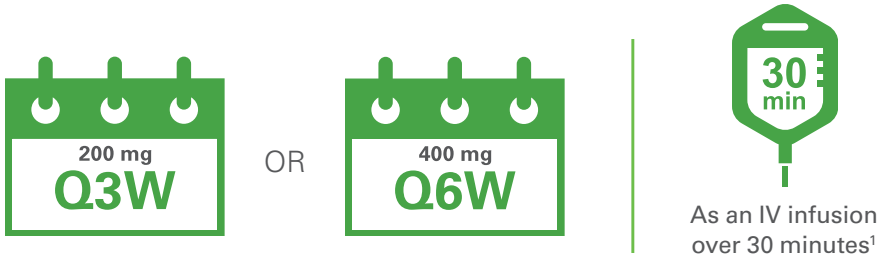
	KEYTRUDA (N=580)	Placebo (n=581)
Any grade	227 (39.1)	76 (13.1)
Grade 3–5	46 (7.9)	11 (1.9)
Occurring in ≥1% of patients in either treatment group		
Hypothyroidism	120 (20.7)	27 (4.6)
Hyperthyroidism	62 (10.7)	17 (2.9)
Pneumonitis	40 (6.9)	17 (2.9)
Severe skin reactions	16 (2.8)	4 (0.7)
Colitis	14 (2.4)	5 (0.9)
Adrenal insufficiency	10 (1.7)	0
Hepatitis	9 (1.6)	4 (0.7)
Hypophysitis	7 (1.2)	0
Thyroiditis	6 (1.0)	1 (0.2)

- Among the 580 patients treated with KEYTRUDA, the adverse reactions were generally similar to those occurring in other patients with NSCLC receiving KEYTRUDA as monotherapy with the exception of hypothyroidism (21%) and hyperthyroidism (11%).[1]

a. imAEs and infusion reactions were based on a list of preferred terms intended to capture known risks of KEYTRUDA and were considered regardless of attribution to study treatment by the investigator.

Dosing and immune-mediated adverse reactions

KEYTRUDA RECOMMENDED DOSING IN COMPLETELY RESECTED STAGE IB (T2a ≥4 cm), II, OR IIIA NSCLC[1]



- For the adjuvant treatment of NSCLC, KEYTRUDA should be administered for up to one year or until disease recurrence or unacceptable toxicity.[1]
- Treatment must be initiated and supervised by healthcare professionals experienced in the treatment of cancer.[1]

IMMUNE-MEDIATED ADVERSE REACTIONS

Immune-mediated adverse reactions, including severe and fatal cases, have occurred in patients receiving KEYTRUDA. In clinical trials, most immune-mediated adverse reactions occurred during treatment, were reversible and managed with interruptions of KEYTRUDA, administration of corticosteroids and/or supportive care. Immune-related adverse reactions have also occurred after the last dose of KEYTRUDA. Immune-mediated adverse reactions affecting more than one body system can occur simultaneously.[1]

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.[1]

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.[1]

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.[1]

Withhold or discontinue KEYTRUDA to manage adverse reactions as described in the Data Sheet.[1]