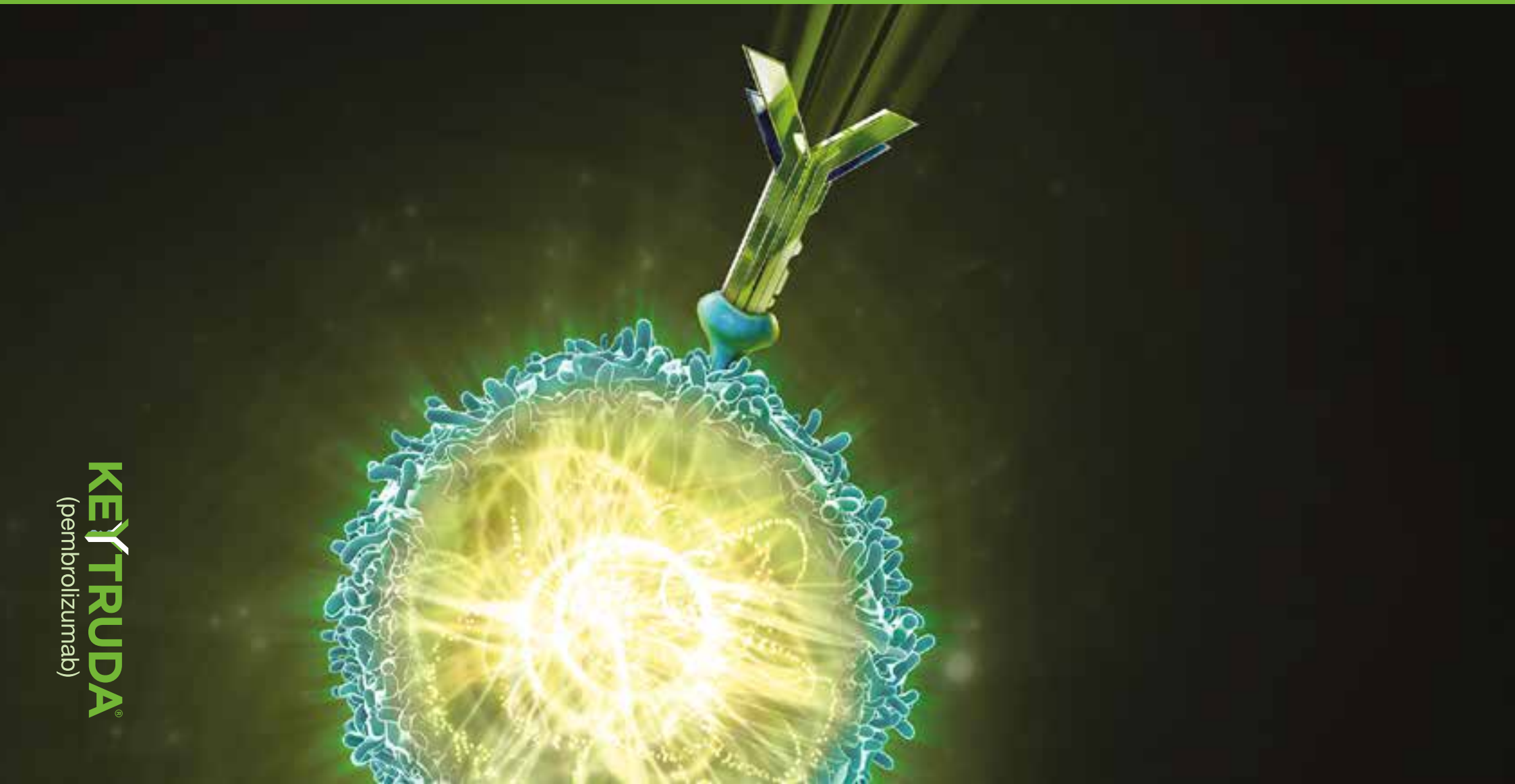
A guide to KEYTRUDA
Providing a treatment option for cancer patients

www.keytruda.co.nz

KEYTRUDA®



KEYTRUDA®
(pembrolizumab)

In New Zealand, KEYTRUDA® (pembrolizumab) is currently indicated:[1]

- as monotherapy for the treatment of unresectable or metastatic **melanoma** in adults.*
- as monotherapy 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.**
- in combination with platinum-pemetrexed chemotherapy for the first line treatment of patients with metastatic non-squamous **NSCLC**.**
- as monotherapy 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.**
- for the treatment of patients with refractory classical **Hodgkin Lymphoma (cHL)**, or who have relapsed after 3 or more prior lines of therapy.**
- for the treatment of patients with locally advanced or metastatic **urothelial carcinoma** who are not eligible for cisplatin-containing chemotherapy.**
- for the treatment of patients with locally advanced or metastatic **urothelial carcinoma** who have received platinum-containing chemotherapy.**

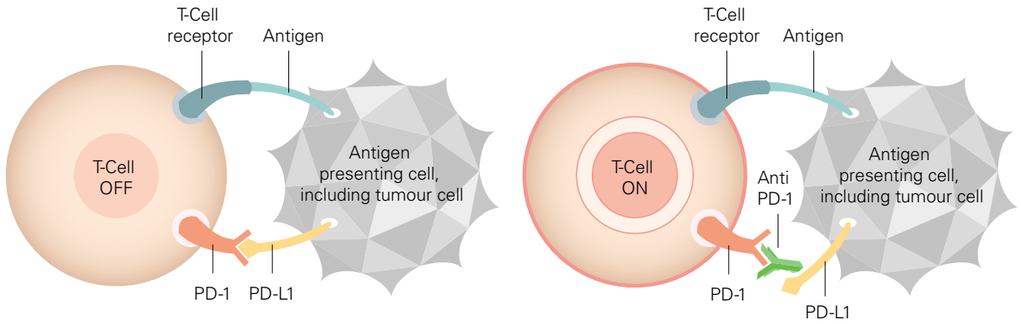
KEYTRUDA is a type of immuno-oncology (or immunotherapy) that is currently being trialled in a number of new cancer types, and works with the immune system to help find and destroy cancer cells.

KEYTRUDA is a selective humanised monoclonal antibody designed to block the interaction between the PD-1 receptor and its ligands, PD-L1 and PD-L2.[1]

Immunotherapy: Checkpoint Inhibition

PD-1 is an immune-checkpoint receptor that limits the activity of T lymphocytes in peripheral tissues. This PD-1 pathway 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.[1]



KEYTRUDA and the PD-1 pathway[2]

Adapted from Cancer Immunology: PD-1 and Beyond. Smart Patients. Available from: www.smartpatients.com/pathways/pd-1; Last accessed November 2017.

The PD-1 Pathway may be exploited to evade the immune response[1,3]

- Emerging research has identified PD-1 as a key immune checkpoint pathway involved in inhibiting the T-cell–mediated immune response.
- Tumour cells can downregulate T-cell activity by exploiting the PD-1 checkpoint pathway through expression of the PD-1 ligands, PD-L1 and PD-L2.
- PD-L1 and PD-L2 engage the PD-1 receptor on T-cells to inactivate them, which may allow tumour cells to evade the immune response.

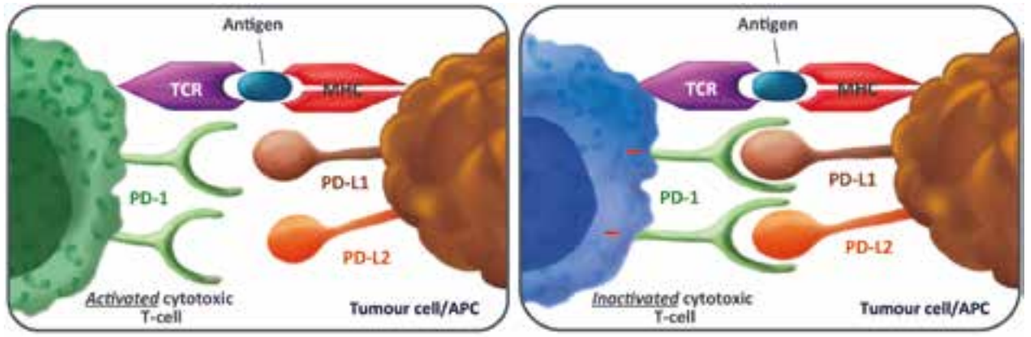


Image adapted from Pardoll DM. *Nat Rev Cancer.* 2012;12(4):252–264[3]

*KEYTRUDA is fully funded under special authority criteria for people with advanced stage 3-4 melanoma that has spread and cannot be removed by surgery.

**KEYTRUDA is now registered for the treatment of NSCLC, Hodgkin Lymphoma and urothelial cancer, is not currently funded but is available privately. Funding applications have been sent to PHARMAC for both NSCLC and Hodgkin Lymphoma.

APC, antigen-presenting cell; **MHC**, major histocompatibility complex; **mUC**, metastatic urothelial carcinoma; **PD-1**, programmed death receptor-1; **PD-L1**, programmed death ligand 1; **PD-L2**, programmed death ligand 2; **TCR**, T-cell receptor.

Advances in Cancer Immunotherapy

Cancer immunotherapy – over a century in the making

It has taken scientists more than a century to understand how to harness the immune system to treat cancer.[4] Several methods have been investigated but one – blocking immune checkpoints – has proved to be particularly effective in several cancers.[4]

The history of the development of cancer immunotherapy[5-8]

1891
First attempt to harness the immune system to treat cancer by William B Coley

1957
Thomas and Burnet propose the theory of cancer immunosurveillance

1970s
Large doses of IL-2 to enhance T-cell production shown to be effective in treating metastatic cancers

1997
First monoclonal antibody to treat non-Hodgkin lymphoma approved by the FDA

1998
First immunostimmulatory agent to treat bladder cancer approved by the FDA

2011
First antibody targeting CTLA-4 approved by the FDA to treat melanoma

2014
First PD-1 inhibitor approved in Japan to treat unresectable melanoma

2014
First PD-1 inhibitors (including KEYTRUDA) approved by the FDA to treat metastatic melanoma

2016+2017
Cancer immunotherapy described by ASCO as the Advance of the Year

ASCO, American Society of Clinical Oncology; **CTLA-4**, cytotoxic T-lymphocyte-associated protein 4; **FDA**, Food and Drug Administration; **IL-2**, interleukin-2; **PD-1**, programmed cell death receptor-1. Figure adapted from references 5-8

Progress with immune checkpoint inhibitors

Since 2011 when the first reports of immune checkpoint inhibitors shrinking advanced melanoma were published, considerable research has been undertaken.[4] Medsafe New Zealand has approved several immune checkpoint inhibitors for use in the following cancer types:

Bladder Cancer[1,10]	**Hodgkin Lymphoma[1]**	**Kidney Cancer[9]**	**Melanoma[1,9,11]**	**Lung Cancer[1,9,10]**

Immunotherapy – future perspectives

Although current immunotherapies targeted at the immune checkpoints, PD-1 and CTLA-4, have demonstrated huge potential to treat cancer, there are some tumour types that are refractory to therapy with patients deriving little or no benefit from treatment.[3] Moreover, among patients with the same type of cancer, some patients will respond well to treatment while others will not.[3] An ongoing challenge in this field is the development of adequate screening of predictive biomarkers to identify patients who are most likely to benefit from treatment.[3,12]

In some cancer types, high levels of PD-L1 can be predictive of a favourable response with KEYTRUDA; however, the relationship between PD-L1 and response to PD-1 checkpoint inhibitors is complex and variable across different cancer types.[3] Considerable research is underway to identify more sensitive screening methods for existing biomarkers or to identify alternative biomarkers.

In addition, ongoing research is being undertaken on potential combination therapies with some studies raising the possibility that combinations of different immunotherapies may be more effective than immunotherapy monotherapy. Over 300 clinical trials are currently underway investigating the potential benefit of combining KEYTRUDA with other therapies.

Extensive research is currently underway to identify additional cancers that are susceptible to immune checkpoint inhibition. KEYTRUDA alone is being researched in 600 trials across more than 30 tumour types.[13]

Development in Key Populations

KEYTRUDA has the potential to extend and improve the lives of people worldwide suffering from a wide range of cancers. Significant progress has been made in the last 5 years to establish KEYTRUDA as a foundation cancer treatment in monotherapy and in combination across multiple tumour types.[13]

KEYTRUDA **has a broad PD-1/PD-L1 clinical research programme** with more than 600 trials in more than 30 tumour types, and more than 300 combination trials underway

KEYTRUDA monotherapy has **shown activity in more than 20 tumours** resulting in approvals across 5 tumour types in New Zealand: melanoma, non-small cell lung cancer (NSCLC), urothelial cancer, classic Hodgkin Lymphoma (cHL)

KEYTRUDA **has received FDA Breakthrough Designation in 8 tumours,** has been approved in 10 different indications, and has received the first ever approval based on genetic traits and not on tumour location

Ongoing clinical trials demonstrate positive results across numerous cancer types:*

Lung Cancer

KEYNOTE-021G
KEYTRUDA + pemetrexed and carboplatin as first line therapy in lung cancer (n = 123)[14]

- Significant improvement in ORR (KEYTRUDA + PC: 55%, PC alone: 29%; P = 0.0016 [95% CI, 9% - 42%) and PFS estimated at 6 months (KEYTRUDA + PC: 77% (95% CI, 64 - 86), PC alone: 63% (49 - 74))

KEYNOTE-024
KEYTRUDA vs. chemotherapy as first line therapy in NSCLC (TPS≥50%) (n = 305)[15]

- OS benefit at 6 months with KEYTRUDA 80.2% (95% CI, 72.9 - 85.7) vs. chemotherapy 72.4% (95% CI, 64.5 - 78.9) for metastatic NSCLC with PD-L1 TPS ≥50%
- PFS estimates at 6 months, KEYTRUDA 62.1% vs. chemotherapy 50.3% (95% CI, 53.8 - 69.4)

KEYNOTE-010
KEYTRUDA vs. chemotherapy as second line therapy in NSCLC (TPS >= 1%) (n=1,033)[16]

- Superior OS benefit with KEYTRUDA vs. docetaxel with PD-L1 TPS>=1% (HR = 0.71 [95% CI, 0.58 - 0.88; p=0.0008])
- PFS significantly longer with KEYTRUDA vs. docetaxel PD-L1 TPS>=50% (HR = 0.59 [95% CI, 0.44 - 0.78; p<=0.001])

Urothelial Cancer

KEYNOTE-045
KEYTRUDA as second line therapy in bladder cancer (n = 542)[17]

- Demonstrates OS benefit in second line setting vs. chemotherapy (HR= 0.73 (95% CI, 0.59 - 0.91) [p = 0.002])

KEYNOTE-052
KEYTRUDA as first line therapy in bladder cancer (n = 370)[18]

- 58% of patients experienced a decrease in target lesions
- ORR of 24% in all patients

Melanoma

KEYNOTE-006
KEYTRUDA vs. ipilimumab as second line therapy in advanced melanoma (n=834)[19]

- KEYTRUDA median OS was not reached. Ipilimumab was 16 months (range 13·5 - 22·0)
- KEYTRUDA was superior to ipilimumab for OS (HR 0·68; 95% CI 0·53 - 0·86; [p=0·0008] 3-weekly KEYTRUDA vs ipilimumab)
- Median PFS for 3-weekly KEYTRUDA was 4·1 months (range 2·9 - 7·2), and 2·8 months (range 2·8-2·9) for ipilimumab (HR 0.61; 95% CI 0·50 - 0·75; [p<0·0001])

Hodgkin Lymphoma

KEYNOTE-087
KEYTRUDA in patients with refractory classic Hodgkin Lymphoma or those who have relapsed after ≥3 prior lines of therapy (n=210)[20]

- ORR was 69% (95% CI, 62.3 - 75.2) with 22% of patients achieving CR and 47% patients achieving PR
- Across all cohorts, >90% of patients experienced a decrease in tumour burden
- At 6 months, the OS rate was 99.5%, and the PFS rate was 72.4%. Median OS was not reached. 31 patients had a response ≥ 6 months

Additional information about clinical trials is available at www.clinicaltrials.gov and www.merck.com/research/pipeline

* Clinical trial summaries for each study are available on page 14.

CI, confidence interval; **HR**, hazard ratio; **NSCLC**, non-small cell lung cancer; **ORR**, objective response rate; **OS**, overall survival; **PC**, platinum chemotherapy; **PD-L1**, programmed death-ligand 1; **PFS**, progression-free survival; **TPS**, tumour proportion score; **PR**, partial response; **CR**, complete response

Understanding KEYTRUDA clinical trials

Well-designed, randomised clinical trials are essential to improve cancer care. KEYTRUDA clinical trials conform to strict criteria to ensure rigorous evaluation of the drug in different cancer types and patient populations prior to licensing by regulatory authorities.

Clinical trial phases[21]

Phase I
Safety evaluation and dose determination

A Phase I trial is commonly conducted in a small number of healthy volunteers to determine how the drug is absorbed, distributed and metabolised within the body.

Phase II
Efficacy evaluation in a small patient population

Typically, a **Phase II single-arm trial** is used to investigate the clinical efficacy of the investigational drug in a small population of patients with the disease. These studies are also used to determine the dose, tolerability profile of the drug and identify any associated safety concerns.

Phase III
Confirm findings with randomised, controlled trials in a large patient population

Confirmatory **Phase III head-to-head trials** are then initiated to compare the investigational drug with the best existing treatment or standard of care for the disease. These studies are usually carried out in large numbers of patients and can be used to support applications to regulatory authorities to receive regulatory approval for the investigational drug.

Phase IV
Assess treatment in clinical practice

Phase IV trials are commonly known as post-marketing studies and are conducted after the drug is approved by regulatory authorities to evaluate the long-term safety and efficacy of the drug in a "real world" setting.

Within the oncology setting, **placebo-controlled trials** are rarely conducted for ethical reasons, as it would be unethical to treat patients who have a life-threatening condition such as cancer with inactive placebos.

Study endpoints

The efficacy of KEYTRUDA is usually assessed in clinical trials by analysing outcomes such as overall survival and tumour response. Overall survival is widely regarded as the most reliable cancer endpoint; however, it requires long follow-up periods in large trials and may be compounded by crossover. Thus, interim or surrogate endpoints are often used, which enable researchers to identify trends in treatment effects earlier in the trial.

Commonly used endpoints in KEYTRUDA clinical trials are described below:

Common clinical trial endpoints[22-24]

Endpoints based on survival	
Overall Survival (OS)	The time from randomisation until death from any cause.
Endpoints based on tumour response evaluation	
Progression-Free Survival (PFS)	The time from randomisation until objective tumour progression or death.
Response Rate (RR)	Response rate is usually determined using a scan or X-ray to measure tumour size. A reduction in tumour size indicates a response. The internationally recognised Response Evaluation Criteria In Solid Tumours (RECIST)guidelines are frequently used to determine the response rate.[24] **Complete response (CR)**: Disappearance of all clinical evidence of disease. **Partial response (PR)**: A ≥30% decrease in the sum of target lesions. **Stable Disease (SD)**: Between a 30% reduction or <25% increase in the size of all detectable tumours. **Progressive Disease (PD)**: Patients or proportion of patients with a ≥25% increase in size of tumours since previous measurement.
Objective Response Rate (ORR)	Percentage of patients who experience a partial response or complete response to treatment (CR +PR).

Interpreting measures of treatment effect in KEYTRUDA clinical trials

Measures of a treatment effect in cancer clinical trials are often summarised using odds ratios (ORs) and hazard ratios (HRs) derived using logistic regression (tumour response data), and Cox's proportional hazards regression (survival data), respectively. Data may also be described using absolute risk reduction (ARR) or relative risk reduction (RRR).

Hazard Ratio (HR)[25,26]	The measure of an effect of a treatment intervention on an outcome of interest (e.g. disease progression) in one trial arm compared with the other, over the entire time period of the trial. HR of 1 = no difference between the groups HR of 2 = double the risk HR of 0.5 = half the risk *Example*: A HR for OS of 0.74 indicates a 26% reduction in the risk of progression or death in treatment arm A vs treatment arm B (-1 – 0.74 [the HR] x 100 = 26% risk reduction).
Odds Ratio (OR)[25,26]	The odds of having an event compared with not having an event in two different groups. The closer the OR is to 1, the smaller the difference in effect between the treatment group and the control group. An OR greater (or less) than 1 indicates that the treatment effect is more (or less) than that of the control group.
Absolute Risk Reduction (ARR)[26]	The absolute difference between the number of events that occurred in the treatment group and the number of those events in the control group. *Example:* 15% of patients treated with treatment A progressed versus 10% of patients treated with treatment B thus there is a 5% ARR in disease progression with treatment B versus treatment A (15% - 10% = 5% ARR).
Relative Risk Reduction (RRR)[26]	The reduction in risk of an event associated with one intervention relative to the risk of the event in the control group. *Example:* 15% of patients treated with treatment A progressed versus 10% of patients treated with treatment B thus the RRR of progression is reduced by 33% with drug B vs. Drug A ([15-10]/15 = 5/15 =33.3% RRR).

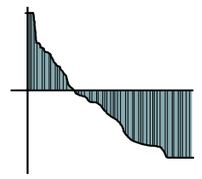
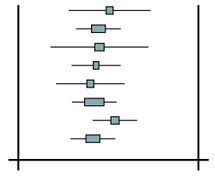
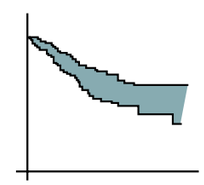
Measurement of PD-L1 expression

Programmed death ligand 1 (PD-L1) has been shown to be an effective biomarker that can help to predict responses to immunotherapies targeted against PD-L1 and its receptor (PD-1), an example of which would be in lung cancer.[27] Bioassays can be used to detect PD-L1 expression on tumour cells and identify patients who are most likely to derive benefit from treatment.[27] The level of PD-L1 expression is determined by using the tumour proportion score (TPS)[27] or the combined positive score (CPS).[17]

In clinical trials investigating cancer types where PD-L1 has been shown to be a valuable biomarker, high PD-L1 expression may be an inclusion criterion to ensure that patients who are most likely to derive a benefit from treatment are enrolled in the trial, such as in Keynote-024.

Combined Positive Score (CPS)[17]	The percentage of PD-L1–expressing tumour and infiltrating immune cells relative to the total number of tumour cells. Positive PD-L1 expression is defined as a CPS ≥1% and a specimen is considered to have high PD-L1 expression if the CPS is ≥10%.
Tumour Proportion Score (TPS)[27]	The percentage of tumour cells showing partial or complete membrane staining at any intensity. Positive PD-L1 expression is defined as a TPS ≥1%, and a specimen is considered to have high PD-L1 expression if the TPS is ≥50%.

Presenting clinical trial results

	**Waterfall plot[28]** A waterfall plot **plots the response rate status (CR, PR, SD or PD) for individual patients.** Each vertical bar represents an individual patient, and tumour response can be easily interpreted as shrinkage if it is below the baseline and tumour progression if it is above.
	**Forest plot[28]** A forest plot **compares different groups of data,** for example, subgroups of patients within a study who may respond differently to treatment. Generally, data that fall on the left of the vertical line indicate that the intervention treatment is more effective than the comparator in a specific subgroup, while if the data falls to the right of the line the intervention treatment is less effective than the comparator in the subgroup.
	**Kaplan-Meier (K-M) curve[28]** A K-M curve is often **used to represent overall survival or efficacy and shows the proportion of the study population still surviving (or free of disease or some other outcome) at successive times.** The number of subjects in each group and at each time point is given numerically, as are the hazard ratio, confidence interval, and P value. The greater the separation of the curves the greater the difference between the treatment groups.

Access to KEYTRUDA

Current access to KEYTRUDA when treatment is not fully funded

If KEYTRUDA is a potential treatment for your patient but they have a cancer type other than melanoma, and don't qualify for PHARMAC funding, here are some other avenues to consider:

- **Health insurance:** Around 1.4 million New Zealanders have health insurance, which is approximately 30% of the population. If they have health insurance, they can check with their provider to find out if any of their cancer care is covered.
- **Life insurance or trauma cover:** Often life insurance and trauma cover policies will provide some or all of the cost of cancer treatment, so it is worth patients checking with providers about what cover they have.
- **ACC:** If the patient has had a previous misdiagnosis (also known as "treatment injury"), delayed diagnosis or probable occupational exposure, ACC may be an option for providing funding for KEYTRUDA.
- **Crowd funding:** Some patients have raised money for treatments through crowd funding websites such as Givealittle.
- **Private Providers:** KEYTRUDA is not funded in New Zealand for all registered indications. Patients may need to see a private provider to have KEYTRUDA prescribed for any cancer type other than melanoma. A list of private providers across New Zealand is available at www.fightcancer.co.nz/about-keytruda/access-to-keytruda.
- **Clinical trials:** KEYTRUDA is being studied across more than 30 types of cancer and more than 4,000 patients are estimated to be enrolled in these trials. Patients may be eligible for a current clinical trial either in New Zealand or overseas (www.clinicaltrials.gov).
- **MSD Patient Programmes:** MSD run patient programmes to help patients access KEYTRUDA treatment. For further details about these programmes email **dpoc.nz@merck.com.**

What can you do to improve funding for KEYTRUDA?

If you feel funding for KEYTRUDA should be broadened, you can help to support your patients by making a funding application to PHARMAC. Anyone can make a submission for the funding of a medicine by completing the online form available at www.pharmac.govt.nz/medicines/how-medicines-are-funded/new-funding-applications.

Other information about the cost of KEYTRUDA treatment

When patients receive treatment privately, the cost of KEYTRUDA is just one part of the total costs. Cost components can also include: courier to transport KEYTRUDA, reconstitution for infusion, dispensing fee, clinic time and administration fees. Other charges may also apply. It is essential for patients to be aware of all cost implications prior to proceeding.

In some indications the number of vials needed to treat will depend on the patient's weight (eg melanoma), other indications follow a flat dose regimen (eg urothelial). KEYTRUDA is given via an infusion every three weeks, until disease progression.[1]

Discussing the costs of KEYTRUDA with your patients

In situations where patients are ineligible to receive fully funded treatment, they have the option of going privately to pay for treatment. With the speed at which new therapies are becoming available in the oncology field this is going to be a growing area of discussion for health providers with their patients.

The discussion around cost is always difficult, especially when a patient may have received devastating news. The decision around the ability to finance private treatment is a very personal one that lies with the patient and their family. Therefore, it is important to give patients the information and time they need to consider all treatment options available.

Research shows that most patients want to be fully informed of all treatment options, including those that incur high-costs, and consider discussions with their doctor about out-of-pocket expenses to be very important.[29,30] In 2009, the American Society of Clinical Oncology addressed this issue and released a statement affirming that *"communication with patients about the cost of care is a key component of high-quality care."*[31]

There are several areas to support your discussions that will help patients and their families make fully informed decisions at this challenging time:

- **Funded vs non-funded:** Ensuring patients understand the difference between access to funded and non-funded treatment options, and potential related costs, including peripheral costs such as tests and clinic visit fees.
- **Clinical research/NPPA:** The patient may potentially qualify for a Clinical Research programme either in New Zealand or overseas (www.clinicaltrials.gov), or be suitable for an application to Pharmac for the Named Patient Pharmaceutical Assessment (www.pharmac.govt.nz).
- **Where to inquire about private treatment:** Providing patients with information around suitable private clinics in their area. Please refer to www.fightcancer.co.nz/about-keytruda/access-to-keytruda.
- **How to inquire about private treatment:** Patients will require a referral letter, pathology report/s and any relevant radiology reports when booking in for treatment. Additional supporting documentation, such as hospital letters or operation notes, can also be useful.
- **Patient programmes:** MSD run patient programmes that can help support the cost of treatment. To contact MSD to inquire further about our current patient programmes please email **dpoc.nz@merck.com.**
- **Funding private medicines:** Patients may choose to raise money through crowdfunding, or have the option for some or all of the costs to be covered by their health or life insurance policies.

Where possible, it is important to provide resources that can support your patient's decision-making process.

KEYTRUDA clinical trial study designs

These summaries relate to the Keynote studies on pages 6-7.

KEYNOTE-021G Lung Cancer

An open-label, randomised, controlled, phase 2 study of KEYTRUDA plus pemetrexed and carboplatin vs pemetrexed and carboplatin alone in chemotherapy-naïve patients, stage IIIB or IV histologically or cytologically confirmed nonsquamous NSCLC without targetable EGFR mutations of ALK translocations. All patients were randomly assigned (1:1) in blocks of four stratified by PD-L1 tumour proportion score (<1% vs ≥ 1%) to 4 cycles of KEYTRUDA 200mg plus carboplatin AUC 5mg/ml/min and pemetrexed 500mg/m2 Q3W followed by KEYTRUDA for 24 months and pemetrexed maintenance. Or to 4 cycles of carboplatin and pemetrexed alone followed by pemetrexed maintenance. The primary endpoint was the proportion of patients who achieved an objective response, defined as the percentage of patients with radiologically confirmed complete or partial response according to RECIST v1.1.[14]

KEYNOTE-024 Lung Cancer

An open-label, multicentre, randomised, phase 3 trial comparing single-agent KEYTRUDA vs the investigator's choice of platinum-containing chemotherapy in 305 patients with previously untreated, squamous or non-squamous metastatic NSCLC. All randomised patients had tumours with high PD-L1 expression based on a TPS ≥ 50%, as determined by the PD-L1 immunohistochemistry 22C3 pharmDx assay and without EGFR or ALK genomic tumour aberrations. Patients received KEYTRUDA 200mg Q3W (n=154) or platinum-containing chemotherapy for 4-6 cycles (n=151) until the specified number of cycles, disease progression or unacceptable toxicity. Tumour status was assessed every 9 weeks. The primary endpoint was progression-free survival defined as disease progression or death from any cause.[15]

KEYNOTE-010 Lung Cancer

An open-label, multicentre, randomised, phase 3 trial of single-agent KEYTRUDA vs docetaxel in 1,033 patients with squamous or nonsquamous mNSCLC. The trial included patients whose tumours were PD-L1 positive based on a TPS ≥1%, as determined by the PD-L1 immunohistochemistry 22C3 pharmDx assay. Patients also had disease progression following platinum-containing chemotherapy and, if appropriate, targeted therapy for EGFR or ALK genomic tumour aberrations. Patients received KEYTRUDA 2mg/kg (n=344) or 10mg/kg* (n=346) or docetaxel 75mg/m2 (n=343) Q3W until unacceptable toxicity or disease progression. Tumour status was assessed every 9 weeks. Co-primary endpoints were OS and PFS, as assessed by BICR review using RECIST 1.1.[16]

KEYNOTE-045 Urothelial Cancer

An open-label, multicentre, randomised, phase 3 trial in 542 patients, KEYTRUDA was associated with superior survival versus investigator's choice of chemotherapy with paclitaxel, docetaxel or vinflunine with advanced urothelial carcinoma who had recurred or progressed after platinumbased chemotherapy. Clinically stable patients with initial evidence of PD were permitted to remain on treatment until PD was confirmed. Co-primary endpoints were OS and PFS, as assessed by blinded independent central review per RECIST v1.1 criteria at 9 weeks after randomisation, then every 6 weeks through the first year of treatment, followed by every 12 weeks thereafter. Secondary endpoints included ORR, DOR and safety.[17]

KEYNOTE-052 Urothelial Cancer

A single-arm, multicentre, randomised, phase 2 trial in 370 patients, KEYTRUDA 200mg every 3 weeks elicited antitumour activity in cisplatin-ineligible patients with locally advanced or metastatic urothelial carcinoma. Primary efficacy endpoint was ORR in patients with PD-L1 expressing tumours, as assessed by blinded independent central review per RECIST v1.1 criteria at 9 weeks after randomisation, then every 6 weeks through the first year of treatment, followed by every 12 weeks thereafter. Secondary endpoints included ORR, DOR and safety.[18]

KEYNOTE-006 Melanoma

A multicentre, 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 randomised (1:1:1) to receive KEYTRUDA at a dose of 10mg/kg every 2 (n=279) or 3 weeks (n=277) or ipilimumab (n=278). Randomisation 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.[19]

KEYNOTE-087 Hodgkin Lymphoma (cHL)

A multicentre, open-label, non randomised study of single agent KEYTRUDA, investigated in 210 patients, regardless of PD-L1 expression, with refractory cHL or who relapsed after 3 or more prior lines of therapy. Patients with active, noninfectious pneumonitis, an allogeneic hematopoietic SCT within the past 5 years (or greater than 5 years, but with graft-versus-host disease), active autoimmune disease, or a medical condition that required immunosuppression were ineligible. Patients received KEYTRUDA 200mg every 3 weeks until unacceptable toxicity or documented disease progression. Response was assessed using the revised lymphoma criteria by positron emission tomography/computed tomography scans, with the first planned post-baseline assessment at week 12. The major efficacy outcome measures were ORR, CRR, and DOR, assessed by blinded independent central review according to the 2007 revised International Working Group criteria.[20]

KEYTRUDA registration and funding in New Zealand[32]

TYPE OF CANCER	REGISTERED?	FUNDED?	DETAILS
Melanoma	✓	✓	KEYTRUDA is fully funded by PHARMAC for people with advanced (stage 3-4) melanoma that has spread and can't be removed by surgery.
Lung cancer	✓	X	KEYTRUDA is registered for the treatment of non-small cell lung cancer (NSCLC) in PD-L1-positive patients, is not currently funded but is available privately. A funding application has been sent to PHARMAC.
Hodgkin lymphoma	✓	X	KEYTRUDA is registered for the treatment of Hodgkin lymphoma, is not currently funded but is available privately. A funding application has been sent to PHARMAC.
Urothelial carcinoma	✓	X	KEYTRUDA is registered for the treatment of urothelial carcinoma, is not currently funded but is available privately. A funding application has been sent to PHARMAC.

Overview of KEYTRUDA treatment

Start

Appropriate patients will be treated with KEYTRUDA every 3 weeks until disease progression or unacceptable toxicity.[1]

Monitor

Patients will be monitored for adverse reactions during treatment.

Manage

Adverse reactions are managed on the basis of grade in accordance with the prescribing information.

Start

Appropriate patients will be treated with KEYTRUDA every 3 weeks until disease progression or unacceptable toxicity.[1]

Starting treatment with KEYTRUDA[1]

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

KEYTRUDA is administered intravenously over 30 minutes every 3 weeks. The recommended dose of KEYTRUDA for melanoma is 2mg/kg. The recommended dose of KEYTRUDA for NSCLC, cHL and mUC is a 200mg flat dose.

Intravenous infusion

Over 30 minutes

Once every 3 weeks

Patients should be treated with KEYTRUDA until disease progression or unacceptable toxicity.

Atypical responses (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 should remain on treatment until disease progression is confirmed.

Age (range 18-94 years), gender, mild or moderate renal impairment, mild hepatic impairment and tumour burden do not significantly impact clearance of KEYTRUDA; no dose adjustment is required.

Special populations considerations[1]

Fertility

Fertility studies have not been conducted with pembrolizumab. There were no notable effects in animal studies.

Pregnancy

Category D. There are no data on the use of pembrolizumab in pregnant women. KEYTRUDA 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.

Lactation

It is unknown whether KEYTRUDA is 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

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

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.

Renal impairment

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

Hepatic impairment

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

KEYTRUDA®
(pembrolizumab) for Injection 50 mg

Monitor

Patients will be monitored for adverse reactions during treatment.

Monitoring for immune-mediated adverse events[1]

When discussing adverse events with your patients that can occur during treatment with KEYTRUDA, emphasise the importance of monitoring for symptoms of immune-mediated reactions.

In clinical trials, most immune-mediated adverse events that occurred during treatment were reversible and managed with interruptions of KEYTRUDA, administration of corticosteroids and/or supportive care. Immune-related adverse events have also occurred after the last dose of KEYTRUDA.

KEYTRUDA treatment can be continued, with appropriate monitoring and management, during mild (Grade 1) adverse events.

For suspected immune-mediated adverse reactions, ensure adequate evaluation to confirm aetiology or exclude other causes. Based on the severity of the adverse reaction, withhold KEYTRUDA and administer corticosteroids.

Please refer to pages 26–27 for guidance on managing immune-mediated adverse events.

Monitoring for adverse events is also important during and after KEYTRUDA treatment, not only at the start of treatment.

Treatment-related serious adverse events reported up to 90 days after the last dose occurred in 10% of patients receiving KEYTRUDA.

Immune-mediated adverse events reported with KEYTRUDA[1]

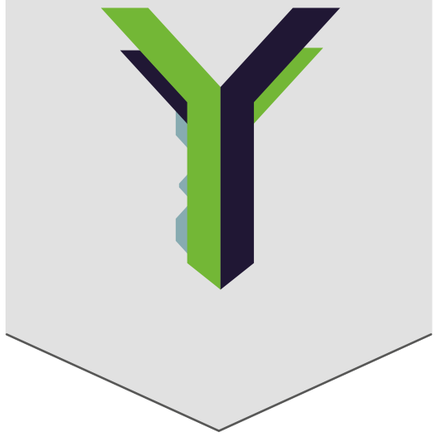
The immune-mediated adverse reactions in the table below were based on 2799 patients with melanoma and non-small cell lung cancer (NSCLC), studied across three doses (2mg/kg every 3 weeks or 10mg/kg every 2 or 3 weeks).

	Immune-mediated adverse events by grade				
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 cHL (n=241) the incidence of hypothyroidism was 14.1% (all grades) with 0.4% Grade 3.

	Immune-mediated adverse events by median time to onset and duration			
Adverse Reaction	**Median time to onset (months)**	**Median Duration (months)**	**Discontinuation in KEYTRUDA patients (%)**	**Resolution (patients)**
Hypothyroidism	3.5 (1 day to 18.9 months)	Not reached (2 days to 27.7+ months)	1 (<0.1)	-
Hyperthyroidism	1.4 (1 day to 21.9 months)	2.1 (3 days to 15+ months)	2 (<0.1)	71
Pneumonitis	3.3 (2 days to 19.3 months)	1.5 (range 1 day to 17.2+ months)	36 (1.3)	55
Colitis	3.5 (10 days to 16.2 months)	1.3 (1 day to 8.7+ months)	15 (0.5)	41
Hepatitis	1.3 (8 days to 21.4 months)	1.8 (8 days to 20.9+ months)	6 (0.2)	15
Hypophysitis	3.7 (1 day to 11.9 months)	4.7 (8+ days to 12.7+ months)	4 (0.1)	7
Nephritis	5.1 (12 days to 12.8 months)	3.3 (12 days to 8.9+ months)	3 (0.1)	5

Manage



Adverse reactions are managed on the basis of grade in accordance with the prescribing information.

Overview of managing adverse events[1]

If you suspect your patient is experiencing an adverse event, evaluate to confirm aetiology or exclude other causes. Based on the severity of the adverse event, withhold KEYTRUDA and administer corticosteroids as recommended below.

Adverse event[a]	Management	Follow-up
Any Grade 1 (mild)	**Supportive care**	**Continue treatment with KEYTRUDA and monitor**
Grade 2 (moderate): ■ Pneumonitis ■ Hypophysitis[b] ■ Nephritis **Grade 2 or 3 (moderate or severe) colitis, other immune-mediated events** **Grade 3 (severe) hyperthyroidism, symptomatic hypophysitis[b], severe skin reactions, SJS, TEN** **Grade 4 (life-threatening) haematological toxicity**	**Withhold treatment and administer corticosteroids** ■ Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month	**Resume treatment with KEYTRUDA when** ■ Adverse event recovers to Grade 0-1 within 12 weeks after last dose ■ Corticosteroid dose is reduced to ≤10 mg prednisolone or equivalent per day **Permanently discontinue KEYTRUDA when** ■ Adverse event does not resolve to Grade 0-1 within 12 weeks after last dose ■ Corticosteroid dosing cannot be reduced to ≤10 mg prednisolone or equivalent per day ■ Any severe (Grade 3) treatment-related adverse event recurs
Hepatitis associated with ■ AST/ALT >3 to 5 x ULN ■ Total bilirubin >1.5 to 3 x ULN		
Hepatitis associated with ■ AST/ALT >5x ULN ■ AST/ALT increases ≥50% relative to baseline and lasts ≥1 week in patients with liver metastasis who begin treatment with moderate (Grade 2) elevation of AST/ALT ■ Total bilirubin >3 x ULN	**Permanently discontinue KEYTRUDA**	
Grade 3 or 4 (severe or life-threatening): ■ Pneumonitis ■ Nephritis ■ Infusion-related reaction ■ Hypophysitis[b] ■ Severe skin reactions (Grade 4 only) ■ Confirmed SJS (Grade 4 only) ■ TEN ■ Myocarditis ■ Colitis ■ Other immune-mediated events **Any Grade 4 (life-threatening) adverse event**		
Isolated hypothyroidism (Manage other thyroid disorders as described above by grade)	May be managed with replacement therapy, without KEYTRUDA treatment interruption and without corticosteroids	

Continue monitoring for adverse events during and after KEYTRUDA treatment. Treatment related adverse events can also occur after the last dose of KEYTRUDA.

Please report all adverse effects to our pharmacovigilance team at dpoc.australia@merck.com

a Grades are defined according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE)v4.0; **b** Pituitary gland inflammation; **ALT** = alanine aminotransferase, **AST** = aspartate aminotransferase, **ULN** = upper limit of normal, **SJS** = Stevens-Johnson syndrome, **TEN** = toxic epidermal necrolysis

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KEYTRUDA (pembrolizumab) 50mg powder for infusion

Before prescribing KEYTRUDA, read the data sheet for information on dosage, contraindications, precautions, interactions and adverse effects available at www.medsafe.govt.nz or on request from Merck Sharp & Dohme (New Zealand) Limited. Prescription Only Medicine Indication: As monotherapy for the treatment of unresectable or metastatic melanoma in adults. In combination with platinum-pemetrexed for first-line treatment of metastatic non-squamous NSCLC. As monotherapy for first-line treatment of patients with metastatic NSCLC whose tumours express PD-L1 ≥50% tumour proportion score (TPS) on a validated test, with no EGFR or ALK genomic tumour aberrations. As monotherapy for the treatment of patients with advanced NSCLC with a PD-L1 TPS level ≥1% 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 refractory/ relapsed classical Hodgkin Lymphoma (cHL). As monotherapy for patients with locally advanced/ metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy, or who have received platinum-containing chemotherapy. See full data sheet. **Contraindications:** None. **Precautions:** Immune-mediated adverse reactions, including pneumonitis, colitis, hepatitis, nephritis, hypophysitis, type 1 diabetes mellitus, hyperthyroidism, hypothyroidism, thyroiditis, uveitis, myositis, Guillain-Barre syndrome, pancreatitis, encephalitis, sarcoidosis, myasthenic syndrome, severe skin reactions (including Stevens-Johnson syndrome and toxic epidermal necrolysis), and severe infusion reactions including hypersensitivity and anaphylaxis. Increased mortality when in combination with dexamethasone and a thalidomide analogue in multiple myeloma (not indicated). Immune-mediated adverse reactions affecting more than one body system can occur simultaneously. For management of immune-mediated adverse events, see full data sheet. Limited information in patients with active infection and patients with on-going adverse reaction to ipilimumab – use caution. Acute graft-versus-host-disease in patients with history of allogeneic HSCT. Post-marketing: solid organ transplant rejection and myocarditis. See full data sheet for further information. **Interactions:** None expected. Avoid corticosteroids or immunosuppressants prior to treatment. **Side effects:** Clinical trials (treatment-related only): nasopharyngitis, anaemia, hypothyroidism, decreased appetite, dizziness, headache, cough, dyspnea, abdominal pain, constipation, diarrhea, nausea, vomiting, erythema, pruritus, rash, vitiligo, arthralgia, back pain, myalgia, pain in extremity, asthenia, chills, fatigue, oedema peripheral, pyrexia, colitis, hepatitis, hyperthyroidism, hypophysitis, nephritis, pneumonitis, type 1 diabetes mellitus, adrenal insufficiency, autoimmune hepatitis, alopecia, upper respiratory tract infection. **Dosage and administration:** The recommended dose of KEYTRUDA is 200 mg for previously untreated NSCLC, cHL, and urothelial carcinoma, and 2 mg/kg or 200 mg for melanoma or previously treated NSCLC (administered as an intravenous infusion over 30 minutes every 3 weeks). KEYTRUDA should be administered first when given in combination with pemetrexed and carboplatin. 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. See full data sheet for further information, including details on PD-L1 testing KEYTRUDA is a funded medicine for melanoma patients– restrictions apply. KEYTRUDA is a private purchase medicine for NSCLC, cHL and urothelial carcinoma patients. Based on data sheet prepared 25 January 2018. ONCO-1230760-0022 DA1827MW essence MSD8507 March 2018 v1

MSD

KEYTRUDA® (pembrolizumab) for Injection 50 mg