

Research Review

PRODUCT REVIEW

Pembrolizumab (Keytruda®) in the treatment of malignant melanoma

About the Reviewer



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Rosalie Fisher is a medical oncologist at Auckland Hospital specialising in the treatment of patients with melanoma, breast and gynaecological cancers.

Rosalie graduated from the University of Auckland School of Medicine in 2004 and completed specialist training in oncology in 2010. Between 2010 and 2013 she completed a fellowship at the Royal Marsden Hospital in London, and undertook clinical and translational research in melanoma, kidney, breast and gynaecological cancers. She is published widely in peer-reviewed journals in these areas and contributes to patient and public education. Rosalie is now completing a post-graduate degree (MD Res) through the University of London focussing on tumour biology and evolution.

Rosalie is a Trustee on the board of Melanoma NZ and a member of the NZ Gynaecological Cancer Group. Melanoma is an active research focus, aiming to improve patient outcomes by access to new, improved therapies.

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This review is a concise summary of the important pharmacological and clinical characteristics of pembrolizumab (Keytruda®), which is available in New Zealand for the treatment of unresectable or metastatic melanoma. Expert commentary on the use of pembrolizumab from a clinical practice perspective is provided by Dr Rosalie Fisher, medical oncologist at Auckland Hospital. This review is sponsored by MSD (NZ) Ltd.

New Zealand has one of the highest rates of invasive melanoma in the world, with an incidence rate of approximately 41 per 100,000 people, per year.^{1,2} In 2011, 359 people died from malignant melanoma in New Zealand, accounting for 4% of all cancer deaths.³

Historically, the 5-year survival rate for patients with stage IV malignant melanoma is only about 6%.⁴⁻⁶ Two therapeutic strategies have improved survival for patients with advanced melanoma in recent years: targeted therapies blocking BRAF* and MEK*, and immunotherapy with checkpoint inhibitors.⁷ BRAF and MEK inhibitors are indicated for the approximately 40% to 50% of patients with BRAF V600 mutations,⁷ but most patients eventually develop resistance leading to disease progression.^{8,9}

Immunotherapy in cancer background

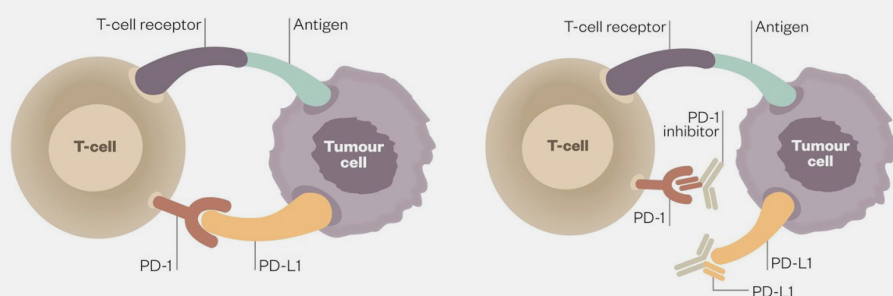
The goal of immunotherapy is to elicit antitumour immune responses.¹⁰ Under normal conditions, both stimulatory and inhibitory pathways control the inflammatory immune response to pathogens and maintain tolerance to self-antigens.¹⁰ In order to protect healthy tissues from damage, this response is regulated by immune checkpoints.¹¹ Exploitation of these immune checkpoint pathways is one of the mechanisms by which tumours escape the immune system.¹¹ The cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed death-1 (PD-1) pathways are immune checkpoints that are clinically relevant and have been the initial focus of cancer immunotherapy. The CTLA-4 and PD-1 pathways are thought to operate at different stages of the immune response.¹² CTLA-4 modulates the immune response early, at the time of T cell activation by antigen presenting cells.¹⁰ In contrast, the PD-1 pathway seems to affect the T-cell response at the later effector stage.

Advances in the understanding of immunology and its role in cancer have led to the development of immune checkpoint inhibitors that block CTLA-4* and PD-1 and result in durable responses in patients with a wide range of cancers including melanoma.¹³⁻²³

The PD-1/PD-L1 pathway

PD-1 is upregulated on T-cells after persistent antigen exposure, i.e. in response to tumours.¹⁰ The ligands for PD-1, PD-L1 and PD-L2, are expressed by tumour or other immune cells including macrophages and dendritic cells; when PD-1 binds to its ligand, the T-cell receives an inhibitory signal and dampens ongoing antitumour immune response (see Figure 1).¹⁰ PD-1 and PD-L1 inhibitors target the interaction between PD-1 and PD-L1 and are able to reverse this T-cell suppression and induce long-lasting antitumour responses.¹⁵⁻²³

The PD-1 inhibitor pembrolizumab (Keytruda, MK-3475, lambrolizumab) was associated with a response rate of 34% in patients with advanced melanoma in the KEYNOTE-001 trial.¹⁶ Median overall survival (OS) has not been reached. In the KEYNOTE-006 trial of pembrolizumab every 2 or 3 weeks versus ipilimumab, OS at 1 year was 74.1% and 68.4% vs 58.2%, respectively.²¹ These trials are discussed in more detail below.



Deactivated T-cell: When PD-1 on the T-cell binds to PD-L1 on the tumour cell, the T-cell becomes deactivated, allowing the cancer cell to evade immune attack.

Activated T-cell: Inhibitors of PD-1 and PD-L1 can prevent the tumour cell from binding to PD-1, enabling the T-cell to remain active and co-ordinate an attack.

Figure 1. The PD-1/PD-L1 pathway in cancer²⁴

Focus on pembrolizumab

In New Zealand, pembrolizumab is a prescription medication that is indicated as monotherapy for the treatment of unresectable or metastatic melanoma. The following section summarises important pharmacological properties of pembrolizumab. Full details can be obtained from the [Keytruda Data Sheet](#).

*BRAF inhibitors, MEK inhibitors, and CTLA-4 inhibitors are not registered for the treatment of melanoma in New Zealand.

Mechanism of action

Pembrolizumab is a highly selective, humanised monoclonal IgG4-kappa isotype 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, pembrolizumab reactivates tumour-specific cytotoxic T-cells in the tumour microenvironment and reactivates anti-tumour immunity (see Figure 1).²⁵

Pharmacokinetics

Pembrolizumab is dosed via the IV route and therefore is immediately and completely bioavailable. Consistent with a limited extravascular distribution, the volume of distribution of pembrolizumab at steady state is small (~7.7 L; CV: 14%). As an antibody, pembrolizumab is not expected to bind to plasma proteins in a specific manner. The systemic clearance of pembrolizumab is ~0.2 L/day and the terminal half-life ($t_{1/2}$) is ~26 days. 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-fold when administered every 3 weeks. Steady-state concentrations of pembrolizumab were reached by 18 weeks; the mean C_{min} at steady-state was 23 µg/mL during a regimen of 2 mg/kg every 3 weeks.²⁵

Dosage and administration

The recommended dose of pembrolizumab is 2 mg/kg administered intravenously over 30 minutes every 3 weeks. Patients should be treated with pembrolizumab until disease progression or unacceptable toxicity. 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.²⁵

Tolerability and safety

In general, adverse events (AEs) related to pembrolizumab are usually mild and easily manageable. Dose interruptions may be required. The most common treatment-related AEs are fatigue, pruritus, rash, arthralgia, diarrhoea, asthenia, cough and nausea.^{16,21,25} Pembrolizumab has also been associated with immune-related AEs that can be severe, including colitis, hepatitis, hyperthyroidism, hypophysitis, hypothyroidism, nephritis, pneumonitis, and type 1 diabetes.^{16,21,25} One case of reversible acute heart failure due to autoimmune myocarditis has been reported.²⁶ The understanding, diagnosis and early management of these AEs are essential for the optimal care of patients treated with pembrolizumab. It is important to recognise the role of corticosteroids in the treatment of immune-related AEs.

Dose modifications

Withhold pembrolizumab for potential immune-mediated adverse reactions including:²⁵

- Pneumonitis - moderate (grade 2)
- Colitis - moderate or severe (grade 2 or 3)
- Symptomatic hypophysitis
- Nephritis - moderate (grade 2)
- Hyperthyroidism - severe (grade 3)
- 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

Resume pembrolizumab in patients whose adverse reactions recover to grade 0–1 within 12 weeks after the last dose of pembrolizumab and with a corticosteroid dose of ≤10mg prednisone or equivalent per day.²⁵

Withhold pembrolizumab for any other severe or grade 3 treatment-related adverse reaction.²⁵

Permanently discontinue pembrolizumab:²⁵

- If corticosteroid dosing cannot be reduced to ≤10mg prednisone or equivalent per day
- If a treatment-related toxicity does not resolve to grade 0–1 within 12 weeks after last dose of pembrolizumab
- If another episode of any severe toxicity occurs
- For adverse reactions including:
 - Life-threatening (grade 4) toxicity
 - Potential immune-mediated pneumonitis - severe or life-threatening (grade 3 or 4)
 - Potential immune-mediated nephritis - severe or life-threatening (grade 3 or 4)
 - Potential 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
 - Infusion-related reactions - severe or life-threatening (grade 3 or 4)

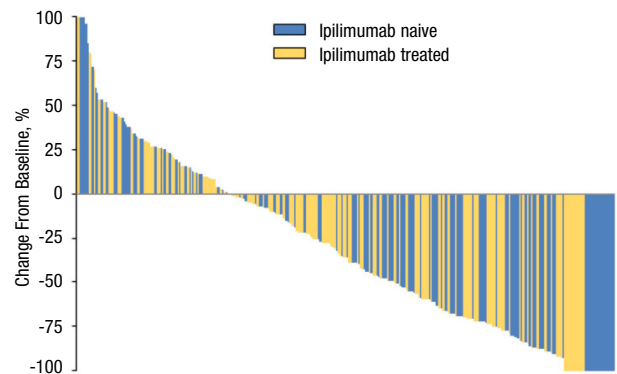
Key clinical trials

KEYNOTE-001

The safety and efficacy of pembrolizumab was investigated in an uncontrolled, open-label study (KEYNOTE-001) for the treatment of unresectable or metastatic melanoma (n=411).^{16,21,25} Patients received pembrolizumab 2 mg/kg every 3 weeks, 10 mg/kg every 2 weeks, or 10 mg/kg every 3 weeks, and were previously treated with ipilimumab (n=221) or naïve to ipilimumab (n=190). This cohort excluded patients with severe immune-related toxicity to ipilimumab. The primary endpoint was overall response rate (ORR) as assessed every 12 weeks by RECIST 1.1 criteria and by immune-related response criteria (irRC) by investigator.

The average treatment duration was 239 days including 115 patients treated for longer than one year. Among 365 patients with measurable disease at baseline, ORR was 34% by RECIST and 37% by irRC. The disease control rate was 54% and 63%, respectively. Responses were durable, with 88% ongoing at analysis and median response duration not reached (see Figure 2). Pembrolizumab demonstrated antitumour benefit at all doses and schedules regardless of prior ipilimumab, ECOG status, or LDH levels. Baseline tumour size was identified as an independent predictor of response. As of May 2014, median OS was not reached, with a 69% 1-year OS rate and 62% 18-month OS rate.

Maximum Percentage Change from Baseline in Tumour Size



Time to Durability of Response

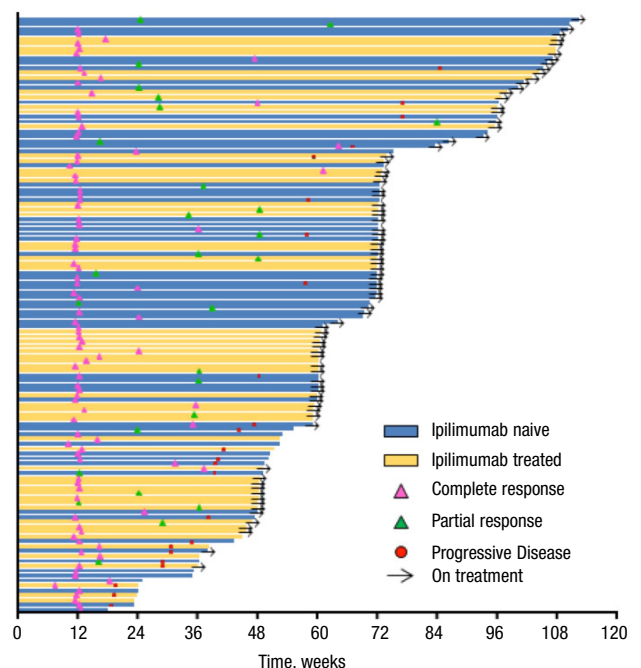


Figure 2. Pembrolizumab efficacy in unresectable or metastatic melanoma: KEYNOTE-001²⁷

Pembrolizumab was discontinued for treatment-related AEs in 4% of patients. Treatment-related serious AEs reported up to 90 days after the last dose occurred in 9% of patients. In the pembrolizumab 2 mg/kg group, the most common treatment-related AEs (reported in >10% of patients) included fatigue (30.2%), pruritus (22.8%), rash (19.8%), arthralgia (14.8%), diarrhoea (14.8%), cough (11.1%) and nausea (10%). Overall, the safety profile was similar among the low and high dose groups and between patients previously treated with ipilimumab and patients naïve to ipilimumab. Treatment-related potential immune-mediated adverse reactions for all patients in the KEYNOTE-001 trial are shown in Table 1.

Table 1. Select treatment-related, potential immune-mediated adverse reactions in KEYNOTE-001²⁵

Adverse Reaction	Pembrolizumab 2 mg/kg every 3 weeks n=162			Pembrolizumab 2 mg/kg every 3 weeks or 10 mg/kg every 2 or 3 weeks n=411		
	All Grades (%)	Grade 3 (%)	Grade 4* (%)	All Grades (%)	Grade 3 (%)	Grade 4* (%)
Colitis [†]	1.2	1.2	0	1.0	0.5	0
Hepatitis [‡]	1.2	0	0.6	0.5	0	0.2
Hyperthyroidism	0.6	0	0	1.0	0.2	0
Hypophysitis	1.2	0	0.6	0.5	0	0.2
Hypothyroidism	9.3	0	0	8.3	0.2	0
Nephritis [§]	0	0	0	0.7	0.2	0.2
Pneumonitis	1.2	0.6	0	2.7	0.2	0

* There were no Grade 5 treatment-related potential immune-mediated adverse reactions reported with Pembrolizumab.

[†] Includes colitis microscopic

[‡] Includes autoimmune hepatitis

[§] Includes autoimmune nephritis and renal failure with evidence of interstitial nephritis

Reviewer's comment on KEYNOTE 001

The KEYNOTE 001 trial enrolled an exceptionally large number of melanoma patients and thus was considered a landmark trial, despite its early phase. An important finding was that both ipilimumab-treated and -naïve patients had similar response rates to pembrolizumab. Most impressive was the durability of response in advanced melanoma patients observed in this study, and this is expected to translate to marked improvement in OS but mature survival data from this trial has not been presented.

KEYNOTE-006

Safety and efficacy was also investigated in a randomised, controlled trial (KEYNOTE-006) of pembrolizumab (10 mg/kg every 2 or 3 weeks) versus ipilimumab (four cycles of 3 mg/kg every 3 weeks) in patients with advanced melanoma (n=834).²¹ Patients were required to be CTLA-4, PD-1, or PD-L1 inhibitor-naïve. Primary endpoints were progression-free survival (PFS) and OS.

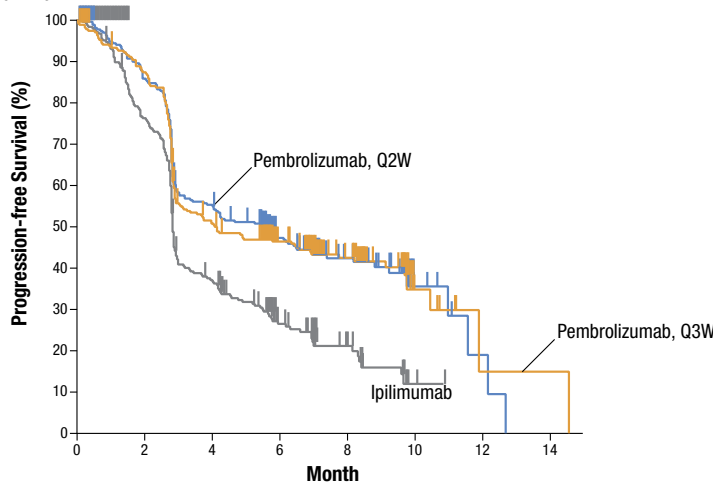
The median duration of follow-up was 7.9 months. Six-month PFS was 47.3% for pembrolizumab every 2 weeks, 46.4% for pembrolizumab every 3 weeks, and 26.5% for ipilimumab (hazard ratio [HR] for disease progression = 0.58; p<0.001 for both pembrolizumab regimens vs ipilimumab; 95% CI 0.46–0.72 and 0.47–0.72, respectively) (see Figure 3). OS at 1 year was 74.1% for those receiving pembrolizumab every 2 weeks (HR for death vs ipilimumab = 0.63; 95% CI 0.47–0.83; p<0.0005), 68.4% for those receiving pembrolizumab every 3 weeks (HR for death vs ipilimumab = 0.69; 95% CI 0.52–0.90; p=0.0036), and 58.2% for those receiving ipilimumab (see Figure 3). The relative risk of progression or death was decreased by 42% with the two pembrolizumab regimens and the relative risk of death was decreased by 31% to 37%. Responses were durable in all groups, with ongoing responses in 93% of patients in the combined pembrolizumab groups and 87.9% of those in the ipilimumab group. There were no apparent differences in efficacy between the two pembrolizumab regimens, neither of which is the dose approved in New Zealand (2 mg/kg every 3 weeks). The lack of a dose-response relationship is consistent with the results of other large trials of pembrolizumab.^{15-18,28}

While the average treatment duration was longer among patients receiving pembrolizumab every 2 or 3 weeks compared to patients receiving ipilimumab (164 days and 151 days vs 50 days), therapy discontinuation for AEs was lower (4% and 6.9% vs 9.4%, respectively), as was the incidence of grade 3–5 treatment-related AEs (13.3% and 10.1% vs 19.9%, respectively). The most common treatment-related AEs (reported in ≥10% of patients) in all treatment groups were fatigue, diarrhoea, rash, pruritus, asthenia, nausea, arthralgia, and vitiligo (see Figure 4). Potential immune-mediated adverse reactions most common in the pembrolizumab groups were hypo- and hyperthyroidism (see Figure 4).

Reviewer's comment on KEYNOTE 006

KEYNOTE 006 confirms the previously anecdotal view that pembrolizumab is superior to ipilimumab, with regard to efficacy and tolerability, in untreated patients with advanced melanoma. It is highly relevant to clinical practice in New Zealand, where both agents remain unfunded and a pragmatic decision to use one or the other is usually required. Level 1 evidence reporting further improvement upon the current standard of first line care (ipilimumab) is highly encouraging.

Progression-free Survival



Overall Survival

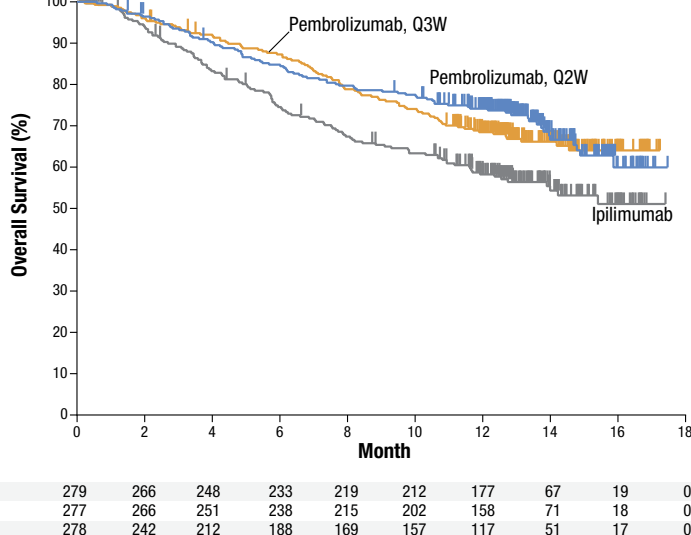
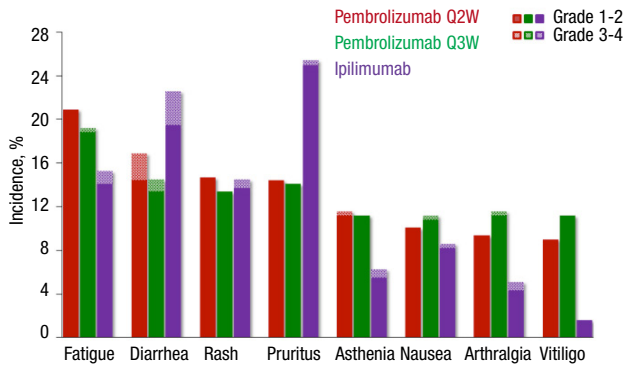


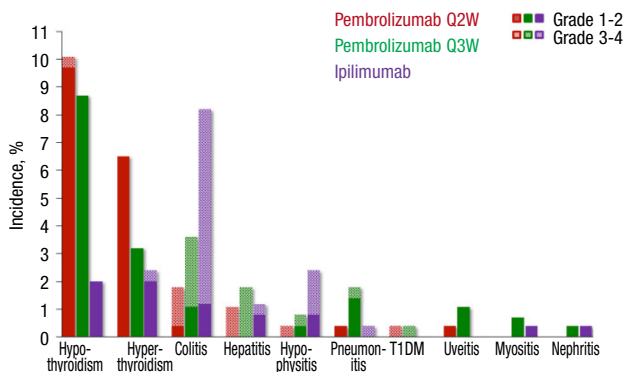
Figure 3. Efficacy of pembrolizumab vs ipilimumab in ipilimumab-naïve advanced melanoma: KEYNOTE-006²¹

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Pembrolizumab (Keytruda®) in the treatment of malignant melanoma



AEs reported in ≥10% of patients



AEs of special interest

Figure 4. Adverse events in patients with ipilimumab-naïve, advanced melanoma treated with pembrolizumab vs ipilimumab: KEYNOTE-006.²⁹

PD-L1 as predictive biomarker

Many trials are now investigating whether PD-L1 expression by tumours can be used as a predictive biomarker of response to PD-1 inhibitors. A number of studies evaluating PD-1 inhibitors in different tumour types found that antitumour activity was generally higher against PD-L1-positive tumours versus tumours with low or negative staining for PD-L1.³⁰⁻³³ However, the methodology, cut-off required to qualify as a PD-L1-positive tumour, and timing of sample collection varied across studies.³⁴ Thus, while these preliminary findings are encouraging, further prospective evaluation of PD-L1 as a potential biomarker is needed and at this time it should not be used to inform the treatment decision.

TAKE HOME MESSAGES FROM THE REVIEWER

- Pembrolizumab received accelerated regulatory approval based on data from large phase I studies but there is now randomised evidence to support its use as first line treatment for metastatic melanoma patients; this is a major advance in the field.
- When used in treatment-naïve patients or those previously treated with agents such as ipilimumab or BRAF inhibitor treatments, pembrolizumab is the most efficacious agent against advanced melanoma that has been reported to date and it is a key element of an increasingly complex treatment algorithm.
- Pembrolizumab is generally well tolerated; immune-related side effects can be severe and early recognition and management of these, often involving the use of corticosteroids, is vital.
- Research into clinical factors that may predict benefit from treatment and improved understanding of the biological mechanisms underpinning pembrolizumab response is key to patient selection; this is critically relevant to the New Zealand population where access to high-cost drugs is limited.

REFERENCES

1. Dermnet NZ. Clinical Topics A-Z. Dermatological Society of New Zealand, 2015. www.dermnet.org.nz
2. Liang J, Robinson E, Martin R. Cutaneous melanoma in New Zealand: 2000-2004. *A NZ J Surg.* 2010;80:312-16.
3. Ministry of Health. Mortality and demographic data 2011. Wellington: Ministry of Health, 2014.
4. Barth A, et al. Prognostic factors in 1,521 melanoma patients with distant metastases. *J Am Coll Surg.* 1995;181:193-201.
5. Manola J, et al. Prognostic factors in metastatic melanoma: a pooled analysis of Eastern Cooperative Oncology Group trials. *J Clin Oncol.* 2000;18:3782-93.
6. Unger JM, et al. Gender and other survival predictors in patients with metastatic melanoma on Southwest Oncology Group trials. *Cancer.* 2001;91:1148-55.
7. McArthur GA, et al. Targeting oncogenic drivers and the immune system in melanoma. *J Clin Oncol.* 2013;31:499-506.
8. Luke JJ, et al. Ipilimumab, vemurafenib, dabrafenib, and trametinib: synergistic competitors in the clinical management of BRAF mutant malignant melanoma. *Oncologist.* 2013;18:717-25.
9. Sosman JA, et al. Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib. *N Engl J Med.* 2012;366:707-14.
10. Luke JJ, et al. PD-1 pathway inhibitors: The next generation of immunotherapy for advanced melanoma. *Oncotarget.* 2015;6:3479-91.
11. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer.* 2012;12:252-64.
12. Fife BT, et al. Control of peripheral T-cell tolerance and autoimmunity via the CTLA-4 and PD-1 pathways. *Immunol Rev.* 2008;224:166-82.
13. Hodi F, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med.* 2010;363:711-23.
14. Delyon J, et al. The ipilimumab lesson in melanoma: achieving long-term survival. *Semin Oncol.* 2015;42(3):387-401.
15. Hamid O, et al. Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. *N Engl J Med.* 2013;369:134-44.
16. Ribas A, et al. Updated clinical efficacy of the anti-PD-1 monoclonal antibody pembrolizumab (MK-3475) in 411 patients (pts) with melanoma (MEL). *Pigment Cell Melanoma Res.* 2014;27:1222.
17. Robert C, et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. *Lancet.* 2014;382:1109-17.
18. Dummer R, et al. A randomized controlled comparison of pembrolizumab and chemotherapy in patients with ipilimumab-refractory melanoma. *J Trans Med.* 2015;13(Suppl 1):05.
19. Wolchok JD, et al. Nivolumab plus ipilimumab in advanced melanoma. *N Engl J Med.* 2013;369:122-33.
20. Topalian SL, et al. Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. *J Clin Oncol.* 2014;32:1020-30.
21. Robert C, et al. Pembrolizumab versus ipilimumab in advanced melanoma. *N Engl J Med.* 2015. Apr 19. [Epub ahead of print]
22. Robert C, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med.* 2015;372:320-30.
23. Weber JS, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. *Lancet Oncol.* 2015 Apr;16(4):375-84.
24. Guha M. The new era of immune checkpoint inhibitors. *The Pharmaceutical Journal.* 2014;293:7837/8. online | URL: 20067127.
25. Product Information: Keytruda. 16 April 2015. Merck Sharp & Dohme (Australia) Pty Ltd.
26. Läubli H, et al. Acute heart failure due to autoimmune myocarditis under pembrolizumab treatment for metastatic melanoma. *J Immunother Cancer.* 2015 Apr 21;3:11.
27. Daud A, et al. Society for Melanoma Research 2014 Annual Meeting; November 13-16, 2014; Zurich, Switzerland.
28. Robert C, et al. Pembrolizumab for advanced melanoma: randomized comparison of two dosing schedules. *Ann Oncol.* 2014;25(Suppl 5):v1-v41. LBA34.
29. Ribas A, et al. KEYNOTE-006: phase III study of pembrolizumab (MK-3475) versus ipilimumab in patients with ipilimumab-naïve advanced melanoma. American Association for Cancer Research Annual Meeting, Philadelphia, USA. 2015. Abstract CT101.
30. Kefford R, et al. Clinical efficacy and correlation with tumor PD-L1 expression in patients with melanoma treated with the anti-PD-1 monoclonal antibody MK-3475. *J Clin Oncol.* 2014;32(15 suppl):abstr 3005.
31. Gandhi L, et al. MK-3475 (anti-PD-1 monoclonal antibody) for non-small cell lung cancer (NSCLC): antitumor activity and association with tumor PD-L1 expression. American Association for Cancer Research Annual Meeting 2014; April 5-9, 2014; San Diego. Abstr CT105.
32. Hodi FS, et al. Long-term survival of ipilimumab-naïve patients with advanced melanoma treated with nivolumab (anti-PD-1; BMS-936558; ONO-4538) in a phase I trial. *J Clin Oncol.* 2014;32(15 suppl):abstr 9002.
33. Gettinger S, et al. First-line nivolumab (anti-PD-1; BMS-936558; ONO-4538) monotherapy in advanced NSCLC: safety, efficacy and correlation of outcomes with PD-L1 status. *J Clin Oncol.* 2014;32(15 suppl):abstr 8024.
34. Shih K, et al. Clinical impact of checkpoint inhibitors as novel cancer therapies. *Drugs.* 2014;74:1993-2013.



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