Did new treatments contribute to a decrease in melanoma deaths?

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ABSTRACT

Melanoma is one of the most common cancers diagnosed in New Zealand, and New Zealand has one of the highest rates of melanoma incidence and mortality in the world. Monitoring by Environmental Health Intelligence NZ (EHINZ) has found a recent sharp decline in melanoma mortality rates in New Zealand. Since 2014 and 2015 (with 376 and 378 melanoma deaths, respectively), melanoma deaths have declined to 362 deaths in 2016, 308 deaths in 2017, and 296 deaths in 2018. We believe that two new PD-1 inhibitor drug treatments introduced in New Zealand in 2016—nivolumab (Opdivo, BMS) and pembrolizumab (Keytruda, MSD)—may have contributed to this decrease in melanoma mortality. Other factors are unlikely to have had such a major effect, with the drop unlikely due to random variation, and no major changes in melanoma registrations or melanoma thickness at diagnosis over the past decade. While our monitoring of the time trend is descriptive only, and cannot attribute causality, it does suggest a recent decrease in melanoma mortality rates at the population level. These national-level statistics reflect both what might be expected in the New Zealand situation with the introduction of PD-1 inhibitor treatments, based on clinical trials, and what oncologists are seeing at an individual level. Further studies could investigate this observational finding, to confirm whether PD-1 inhibitor drug treatments are having an impact on melanoma mortality and survival rates in New Zealand.

Melanoma is one of the most common cancers diagnosed in New Zealand, and New Zealand has one of the highest rates of melanoma incidence and mortality in the world.1,2 These high rates are believed to be due to high UV levels, as well as a high proportion of New Zealanders being fair-skinned and at greater risk of skin damage from high UV exposure.3 Given these high melanoma rates and the link to an environmental exposure, melanoma incidence and mortality are routinely monitored as part of the Environmental Health Intelligence NZ (EHINZ) surveillance programme, which provides information for action on environmental health issues in New Zealand. Decreasing the burden of melanoma in New Zealand would have a substantial impact on the health of many New Zealanders.

EHINZ's monitoring has recently found a sharp decline in melanoma mortality rates in New Zealand from 2016 onwards. From 2011 to 2015, at least 350 people died each year from melanoma, with 376 and 378 deaths in 2014 and 2015, respectively. Since 2015, deaths have declined, with 362 deaths in 2016, 308 deaths in 2017, and 296 deaths in 2018 (Figure 1). There has been a statistically significant decline in the age-standardised mortality rates over this time period, from 4.9 per 100,000 in 2015, to 3.3 per 100,000 in 2018 (Figure 2).

Additionally, preliminary mortality data for 2019, recently published on the Ministry of Health website, report 328 melanoma deaths in 2019, and an age-standardised rate of 3.6 per 100,000—a slight increase from 2018, but a similar age-standardised rate to 2017 (3.7 per 100,000) and still lower than counts and rates from 2011 to 2015. Preliminary data are subject to change and need to be interpreted with caution; however, they suggest a potential continuation of lower counts and rates of melanoma deaths compared with previous years, which would need to be confirmed at a later date.

A potential explanation for the decline in melanoma mortality rates is the introduction of new treatments for advanced (metastatic) melanoma over this time period. Advanced melanoma has historically been associated with low survival rates.5 In New Zealand, PHARMAC started funding the new treatments of (i) nivolumab (Opdivo, BMS) in July 2016, then (ii) pembrolizumab (Keytruda, MSD) in September 2016, for people with unresectable stage IIIC or stage IV disease (i.e., advanced melanoma unable to be treated with surgery).6,7 Prior to 2016, the only funded therapies in New Zealand for advanced melanoma were dacarbazine and interferon, neither of which had been shown to improve overall survival in clinical trials, and were associated with significant morbidity.8 In 2010, ipilimumab, a CTLA-4 receptor monoclonal antibody, was the first therapy that demonstrated improved overall survival for met-
**Figure 1:** Number of melanoma deaths each year in New Zealand, 2001–2018.

![Bar chart showing the number of melanoma deaths each year from 2001 to 2018.](source: New Zealand Mortality Collection.)

**Figure 2:** Age-standardised rate of melanoma mortality in New Zealand, 2001–2018.

![Line chart showing the age-standardised rate of melanoma mortality from 2001 to 2018.](source: New Zealand Mortality Collection.)

*Note: Age-standardised to the WHO world standard population. 95% confidence intervals are shown.*

*Source: New Zealand Mortality Collection.*
astatic melanoma in any clinical study; however, the list price was approximately $150,000 per course and it did not receive PHARMAC funding.

Subsequent studies demonstrated that nivolumab and pembrolizumab improved overall survival in phase 3 clinical trials. These drugs are PD-1 inhibitors, a novel class of monoclonal antibodies that bind to the programmed cell death receptor on T-lymphocytes, preventing inhibition of cytotoxic T-cells by the PD-L1 ligand on cancer cells, preventing immune escape. The pivotal CHECKMATE-066 study demonstrated that compared to chemotherapy, nivolumab improved the rate of one-year overall survival from 42.1% to 72.9% (hazard ratio for death, 0.42; 99.79% CI, 0.25–0.73, p<0.001) in patients with metastatic cutaneous melanoma without an activating BRAF mutation. Similarly, the KEYNOTE-006 study compared pembrolizumab at one of two dose schedules with ipilimumab. Patients were eligible irrespective of BRAF mutation status. Estimated one-year overall survival was improved from 58.2% with ipilimumab, to 68.4% and 74.1% with the three-weekly and two-weekly dose groups of pembrolizumab, respectively. These results were durable at five years. It is important to note that in both studies, eligibility was restricted to patients with good physical fitness (ECOG performance status 0 or 1) and with no evidence of brain metastases, which are discovered in a high proportion of patients with stage IV disease. This means it was not certain that clinical trial results would translate into a discernible improvement in population-level outcomes, if the benefit of the medicines were restricted to a small sub-group.

Starting in 2016, when nivolumab and pembrolizumab were introduced in New Zealand, we have observed a reduction in melanoma mortality rates, with further reductions in subsequent years. It is plausible that these new PD-1 inhibitor drug treatments have contributed to the decrease in melanoma deaths. The slight decrease in the melanoma mortality rate in 2016, followed by two years of sustained drops, suggests that something pivotal occurred in 2016 to impact mortality rates. The sustained reduction in mortality rates is also of note. Where a new drug improves disease control for a short period, it could be expected that there would be a displacement of deaths from one year to the following year(s). To date, we have observed a reduction in mortality rates from 2016 to 2018 (and a similarly low mortality rate in 2019 as in 2017, based on preliminary data). If the new treatments were indeed having an impact, we might expect a reduction in deaths, with two parts: a proportion of patients being cured, and a proportion having delayed death. We would see both as contributing in the early years, but in the following years we might see a slight attenuation due to delayed deaths (given an overall median survival time of about 2.75–3 years in clinical trials).

Furthermore, the size of the reduction in deaths aligns with what could be expected from these new treatments. Although patient numbers and stage-specific information is not routinely available, approximately 300 people who die from melanoma each year in New Zealand could be considered eligible for treatment with these agents (subject to performance status and co-morbidity, and assuming 100% uptake). This is a reasonable estimate, given that (i) in 2016/17 there were a total of 367 new patients for PD-1 inhibitors (pembrolizumab or nivolumab) for first-line melanoma treatment, and (ii) in 2018/19, 316 new Special Authority initiations for pembrolizumab and nivolumab were approved for first-line melanoma treatment. Phase 3 studies for patients with advanced melanoma suggest an objective response rate (absence of disease or decrease in extent of cancer after treatment) of 42–45% for these treatments, and a complete response rate (absence of disease after treatment) of 14% and 18% for pembrolizumab and nivolumab, respectively. Based on clinical trials, and approximately 300 patients each year, 60–70 fewer deaths each year in New Zealand is within the range of what could be expected due to these new PD-1 inhibitor treatments.

Other potential explanations are unlikely to account for the observed decrease in melanoma mortality rates. Firstly, random or stochastic variation is unlikely as the 95% confidence intervals do not overlap, and the decrease has been sustained over the three years 2016–2018. While the 2019 preliminary data shows a small increase in melanoma deaths to 328, the age-standardised mortality rate (3.6 per 100,000) is similar to that of 2017, and remains substantially lower than 5 per 100,000, the approximate level from 2008 to 2015. Secondly, our monitoring of melanoma registrations also shows no statistically significant change in melanoma registration (incidence) rates over this time period, with relatively stable rates from 2011 to 2020 (Figure 3). Thirdly, there has been no statistically significant change in registration rates of thicker melanoma since 2011 (Figure 3), suggesting that stage migration has not occurred. The thickness (measured
as the Breslow thickness) is a measure of severity, with thicker melanoma associated with a reduced survival rate.

This analysis has some limitations. Our monitoring of the time trend is descriptive only and cannot attribute causality. The analysis uses population-level data, rather than individual-level patient data, and therefore cannot definitively comment on whether the drug treatments have led to a lower mortality rate. Confirming these observational findings, for example through time-dependent survival analyses, would need information on number of patients treated, duration of treatment, and individual patient outcomes, which is not currently available in New Zealand. However, these data may become available in future years with the implementation of the national systemic therapies library known as the ACT-NOW (Anti-Cancer Therapy – Nationally Organised Workstreams) programme, implemented by Te Aho o Te Kahu – The Cancer Control Agency.

Nonetheless, our monitoring suggests a recent decrease in melanoma mortality at the population level. These national-level statistics reflect what might be expected in the New Zealand situation with the introduction of PD-1 inhibitors, based on clinical trials and what oncologists are seeing at an individual level. These results also suggest that the likely benefits attributed to nivolumab and pembrolizumab seen in the restricted population entered into registration trials may have been maintained when translated to a more heterogeneous real world population. Future research could investigate whether these new PD-1 inhibitor treatments are indeed having an impact, and if so, whether this impact is maintained over time. This analysis has provided an example of the critical importance and necessity of ongoing regular monitoring of the national health data, and an inquisitive questioning of the potential reasons for unexpected changes.

Figure 3: Age-standardised rates of melanoma registrations in New Zealand, total registrations and by Breslow thickness, 2001–2019.

Note: Age-standardised to the WHO world standard population. 95% confidence intervals are shown. Source: New Zealand Cancer Registry.
COMPETING INTERESTS
Nil.

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