Patients with Metastatic or Unresectable Melanoma: Exploration of Pembrolizumab Treatment Outcomes Across Adult Cohorts

Kathy (Kyungmi) Lee

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Abstract

Introduction: The risk for melanoma increases as people age and due to an increasingly older population, more older adults are being diagnosed with melanoma in New Zealand. Pembrolizumab, a highly selective monoclonal antibody medication is the first-line treatment for metastatic and unresectable melanoma. While pembrolizumab is generally well-tolerated, immune-related adverse events and systemic toxicities threaten the completion of treatment for some patients. This research investigated whether there are any differences in outcomes between patients aged 50 years and under, 51-65 years, 66-80 years, and 81 years and older.

Methods: A database was provided by the Data and Analytics department of the hospital of patients who had received pembrolizumab between January 2017 to June 2021 and this was anonymised before analysis. Descriptive statistics were used to characterise the study population: gender, age, ethnicity, district health board (DHB) of enrolment, and any comorbidities. Independent T-test measured mean scores and associations between continuous variables and categorical predictors. One-way analysis of variance (ANOVA) explored associations among continuous variables and two or more categories, with Tukey HSD post hoc testing applied to detect the influential variable(s). Chi-square analysis for independence tested relationships among categorical predictors and outcomes. Fisher's Exact test (two-sided) was applied when cell size did not meet assumptions for chi-square analysis. Regression analyses were applied to predict categorical outcomes with two or more categories (using binary logistic regression) to test the effects of study factors on three models: (1) *Response to Treatment*, (2) *Disease Progression*, and (3) *Toxicity*.

Results: A total of 300 patients were included in the study. The overall treatment efficacy for pembrolizumab was 35% (n=135/300) across all age bands. The 81 years and older age group were less likely than other age groups to experience *disease progression* (β = -.61(.18), $p < .001$). However, *disease progression* was more likely in patients with *cardiovascular comorbidity*, indicating it is an important comorbidity to be aware of (β = 1.36(.38), $p < .001$). There were no significant differences in *cardiovascular comorbidity* by *DHB* (p = .09), or *gender* (p=.06).

Increasing age was significantly related to higher toxicity (β = .96(.24), $p < .001$). However, there were no statistically significant differences for *toxicity* by *DHB* (p = .34), or *gender* (p = .99). By *gender*, *age*, or *DHB*, there were no statistically significant differences regarding the *number of treatments* (p values all greater than .79) or *response to treatment* (p values all greater than .6). There were significant associations between age and toxicity ($F(3, 296) = 6.813$, $p < .001$), with the 81 years and older age group experiencing significantly more toxicity. There were no statistically significant differences for *toxicity* by *DHB* (p = .34), or *gender* (p = .99).

The number of comorbidities for males (M = 1.41, SD = 1.63) was significantly (p = .039) different to females (M = 1.03, SD = 1.21). These results support that comorbidity occurs more frequently as patients age and that males have more comorbidities than females. There were no differences in comorbidities and the DHB that patients attended.

Conclusion: This retrospective cohort study confirms that age is not a limiting factor in receiving pembrolizumab for metastatic or unresectable melanoma, as supported by the tumour response within patients. Older old adults (81 years and older) can benefit as much as their younger cohorts to achieve stable disease, a partial or complete response. Therefore, this means age is not an exclusion criterion for pembrolizumab. Indeed, older adults over 81 years old were less likely to suffer from disease progression than those under 50, supporting the resiliency that age brings in some circumstances. Cardiovascular comorbidity decreases the likelihood of responding to treatment and increases the likelihood of disease progression. There is a higher likelihood of toxicity experienced as people age. Gender and DHB are not significantly related to toxicity, response to treatment or number of treatments, nor specifically are diabetes or other cancer comorbidities.

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Attestation of Authorship

I hereby declare that this submission is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person (except where explicitly defined in the acknowledgements), nor material which to a substantial extent has been submitted for the award of any other degree or diploma of a university or other institution of higher learning.

22/08/2022

Signature _____ *Date*

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List of Abbreviations

Auckland District Health Board	ADHB
Activities of daily living	ADL
Adverse events	AE
Analysis of variance	ANOVA
Analysis of covariance	ANCOVA
Auckland University of Technology	AUT
Auckland University of Technology Ethics subcommittee	AUTEC
Best Practice Advocacy Centre New Zealand	BPAC NZ
B-Raf proto-oncogene	BRAF
Classical Hodgkin Lymphoma	cHL
Counties Manukau District Health Board	CMDHB
Common Terminology Criteria for Adverse Events	CTCAE
Cumulative Index to Nursing and Allied Health Literature	CINAHL
District health board	DHB
Mismatch repair deficient	dMMR
Dimethyl triazeno imidazole carboxamide	DTIC
Eastern Cooperative Oncology Group performance status	ECOG PS
Environmental Health Intelligence New Zealand	EHINZ
Food and Drug Administration	FDA
Head and neck squamous cell carcinoma	HNSCC
Health Services Research Centre	HSRC
Immune checkpoint inhibitor	ICI
Immune-related adverse effects	irAE
Lactate dehydrogenase	LDH
Least significant difference	LSD
Lentigo malignant melanoma	LMM
Lipopolysaccharide	LPS
Medical Literature On-Line	MEDLINE
Millimetre	mm
Ministry of Health	MoH
Microsatellite instability-high	MSI-H
Nodular melanoma	NM
Non-small cell lung cancer	NSCLC
New Zealand	NZ
New Zealand Institute for Research on Ageing	NZiRA
Organisation for Economic Co-operation and Development	OECD
Overall survival	OS
Programmed cell death-1	PD-1
Progression free survival	PFS
Pharmaceutical Management Agency	Pharmac
Renal cell carcinoma	RCC
School of Clinical Sciences	SoCS
Superficial spreading melanoma	SSM
Therapeutic Goods Administration	TGA
United States of America	USA
Ultraviolet	UV
Waitemata District Health Board	WDHB

Chapter 1 Introduction

This chapter will describe the incidence and prevalence of melanoma in New Zealand and explain why older adults are at an increased risk for this disease. The current standard of care for treatment for melanoma is the immunotherapy drug pembrolizumab. This medication will be briefly described it relates to the older adult population. The aim of this research and guiding research questions will also be defined.

1.1 Background

Melanoma is the most serious type of skin cancer with a high mortality burden worldwide (Boozer, 2021). New Zealand has one of the highest age-standardised incidence rates of melanoma in the world, with approximately 35 to 40 people per 100,000 population being diagnosed each year. An individual's lifetime risk of melanoma is two to three times higher than other western countries with 3.6% in New Zealand compared to 1.9% in the United States of America (USA) (Best Practice Advocacy Centre New Zealand (BPAC NZ), 2020). The high prevalence in New Zealand is likely due to the high ambient levels of ultraviolet (UV) radiation across the country (Sneyd & Cox, 2013). Four out of five skin cancer-related deaths in New Zealand are caused by melanoma versus the more common skin cancers like basal cell and squamous cell carcinomas (BPAC NZ, 2020).

A population at risk for melanoma are the older adult due to their high cumulative lifetime risk (Foo et al., 2020), and increasingly more older adults are being diagnosed with melanoma (Godby et al., 2019; Johnpulle et al., 2016). This is due to the significant acceleration in the growth of this demographic as evidenced by the doubling number of older New Zealanders since 1998 from 440,000 to 740,000 people in 2019 (Parr-Brownlie et al., 2020). Effective and safe treatment is needed to treat this expected growing burden of patients with melanoma.

There are multiple treatment options for melanoma including chemotherapy, radiation, surgery, and immunotherapy (Hao et al., 2016; Lui et al., 2007; Rai et al., 2021). However, the introduction of immunotherapy has made a significant impact for patients with increased disease-free and overall survival, a more favourable side effect profile and lower rates of severe toxicity compared to chemotherapy (Chanala et al., 2019; Cybulska-Stopa et al., 2019; Fox et al., 2020; Godby et al., 2019; Rai et al., 2021). Pembrolizumab is effective in the treatment of metastatic and unresectable melanoma because melanoma is an immunogenic malignancy which makes it responsive to targeted immunotherapy (Cybulska-Stopa et al., 2019). There is an extensive breadth of literature that showcases the efficacy of pembrolizumab as a therapy for advanced and metastatic melanoma (Robert et al., 2014; Robert et al., 2019; Schadendorf et al., 2016).

An increased likelihood of drug-induced toxicities exists for older adults which limits safe dosages available of chemotherapy (Hamilton & Henry, 2020). There is concern that this risk may extend to immunotherapy treatments such as pembrolizumab which is an alternative for older adults with a cancer diagnosis (Fox et al., 2020; Hamilton & Henry, 2020; Perier-Muzet et al., 2018).

A review of current literature which evaluated older adults' response to pembrolizumab, all showed positive outcomes for older old adults. Cybulska-Stopa et al.'s (2019) study demonstrated a similar outcome for progression-free survival and overall survival compared to younger cohorts. Additionally, the presence of chronic diseases did not affect the effectiveness of treatment or likelihood of experiencing toxicities. Ben-Betzalel et al. (2019) found the same outcomes in older cohorts for progression-free survival, overall survival, and toxicity. Interestingly, they showed patients 80-100 years of age had an increased overall response and complete response compared to patients aged 65- 79 years.

Fox et al. (2020) demonstrated a clinical benefit (stable disease, partial response, and complete response) for the majority (50-80%) of their older adult patients and similar toxicity profile. Cybulska-Stopa et al. (2021) also found a similar overall response rate (partial and complete response), disease control rate (stable disease, partial and complete response) and toxicity. There were no statistically significant differences in overall survival, progression-free survival, or melanoma specific survival across age groups.

All these studies showed positive results with the efficacy of immunotherapy not being affected by older age. However, there is a gap in the literature for older old adult patient populations (those greater than 80 years of age) in large-scale oncology research or clinical trials (Chanala et al, 2019; Hamilton & Henry, 2020; Rai et al., 2021). There is also a lack of New Zealand based research studies on this topic, so this research project aims to contribute to this gap in knowledge. This study will analyse stratified age data of New Zealand patients who have received pembrolizumab to understand more about treatment outcomes for older adults within a New Zealand context.

1.2 **Research Aim**

The aim of this study is to explore the treatment outcomes of pembrolizumab treatment for metastatic and unresectable melanoma across adult aged cohorts. The findings will provide information about which age groups tolerate treatment (toxicity experienced) better than others and who have improved treatment outcomes (tumour response vs disease progression). This will be valuable information as by identifying and mitigating reasons why some age groups do not do so well means there is a chance to improve treatment outcomes of future patients regardless of their age. The significance of these findings is that health practitioners can achieve both a

more tolerable and successful treatment for all their melanoma patients. The results may also confirm that pembrolizumab is a viable treatment option for older old adult patients.

1.3 Research Questions

1. How do treatment outcomes (tumour response or disease progression) experienced by older old adults (81 years and older) receiving pembrolizumab, compare with the treatment outcomes experienced by i) patients aged 66-80 years old and ii) patients aged 51-65 years old and iii) patients aged 50 years and younger?

2. How frequently do older old adults (81 years and older) receiving pembrolizumab experience toxicities compared with other adult groups (under 81 years old)?

3. Does the presence of comorbidities affect the treatment outcome of patients?

4. Does a patient's local district health board (DHB) influence treatment outcome of patients?

1.4 Summary

This chapter (**Chapter 1. Introduction**) has set the context of this research project by introducing melanoma prevalence in New Zealand, the older adult population and current treatment of pembrolizumab. The aim and guiding questions of this research project were stated. The layout of this dissertation will compromise of four more chapters.

Chapter 2. Literature Review. The next chapter will give an in-depth overview of melanoma and pembrolizumab. It will define melanoma, how it is diagnosed and its prevalence in New Zealand. It will detail New Zealand's ageing population and explore treatment options with a focus on pembrolizumab. The chapter ends by examining the existing literature on pembrolizumab as it relates to older adult treatment outcomes. Therefore, the research gap will be identified and where this research study can contribute.

Chapter 3. Methodology. This chapter will explain the theoretical underpinnings of positivism and associated research design used for this study. It will explain the methods used, study population, treatment setting and study protocol. The rationalisation of using statistics will be elaborated on alongside outcome measures, data analysis and ethics. Correlation analysis measured the strength that two variables are linearly related. The correlation was positive if one variable increased as the other one increased or was negative if one variable decreased as the other increased (Campbell & Swinscow, 1997). Regression analysis identified which predictor variables had an impact on the studied outcome and gave a summary of the relationship between variables (Campbell & Swinscow, 1997).

Chapter 4. Results. This chapter will display results of this research study with descriptions of the statistics and in table format. The key variables looked at included the number of treatments,

response to treatment, disease progression, toxicity, and comorbidities. Inferential statistics used include T tests, ANOVA, ANCOVA, regression model correlation and binary logistic regression analysis which demonstrate the relationship between the variables, gender and DHB across four age groups.

Chapter 5. Discussion. The final chapter will synthesise the results from this research study and answers the research questions posed. It will cover treatment outcomes (disease progression vs response to treatment), toxicity, and comorbidities as it relates to existing literature. The strengths and limitations of this research will be explained and consequently, recommendations for future research will be made. The dissertation will conclude with a summary of the findings and implications for clinical practice.

Chapter 2 Literature Review

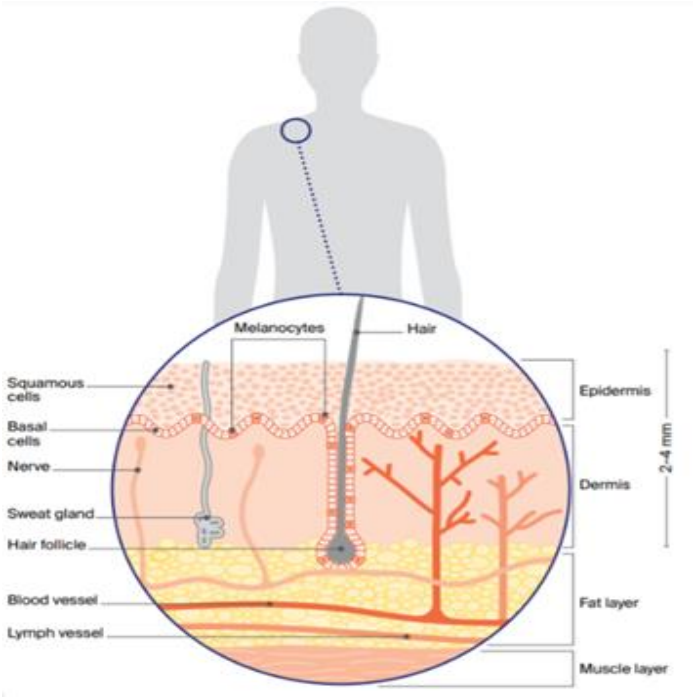
This chapter will provide a comprehensive literature review to understand melanoma as a disease, to define how pembrolizumab works as a treatment and will define the older old adult patient population. It will outline 1. Risk factors for melanoma 2. Diagnosis of melanoma 3. Melanoma in New Zealand 4. New Zealand's ageing population 5. Pembrolizumab 6. Older adult patients and 7. Existing literature about the effectiveness of pembrolizumab as a treatment in relation to the older adults. This thorough review will identify the gap which exists in current knowledge and how this research study can contribute to this.

2.1 Melanoma Definition and Risk Factors

The skin is one of the largest organs in the body and is designed to protect, regulate, and provide sensation (Dréno, 2009). Anatomically, skin consists of three layers (Figure 1). The most superficial being the epidermis, beneath this lies the dermis and deeper still the hypodermis (Boozer, 2021).

Figure 1

Layers of Skin



Note. Cross section of skin showing the different layers. From Understanding Melanoma- A guide for people with cancer, their families, and friends [Brochure]. Cancer Council NSW. (2021). Reprinted with permission.

Skin cancer is the mutation of one of three cells located in the epidermis. These include basal cells, which are responsible for new cell regeneration, flat squamous cells that make up the epidermis and melanocytes (Cancer Council NSW, 2021). Melanocytes synthesise melanin to

provide colour to skin and are found in the basal layer of the epidermis (Dréno, 2009; Ryan, 2020). When categorising skin cancer, diagnosis falls into two categories and is either non-melanoma (basal cell carcinoma or squamous cell carcinoma) or melanoma (Ryan, 2020). B-Raf proto-oncogene (BRAF) is a protein found in cells involved in the signalling pathway for normal cell growth. In 40-50% of melanoma cases this BRAF mutation exists which causes abnormal cell division (Ryan, 2020).

Melanoma can present in a variety of sites in the body. However, it usually occurs in areas of the body that have been overexposed to the sun (Ryan, 2020). Although in 90% of cases, melanoma occurs in the skin, there is a small proportion that develops in the mucosa (referred to as a mucosal melanoma) or eye (ocular melanoma). Melanoma can develop from either a new skin lesion (de novo) or can form from an existing skin lesion or nevus that progressively changes. A nevus is a common mole made up of a benign cluster of melanocytes and is a non-cancerous skin lesion (Boozer, 2021). However, having an increased number of nevi is related to an increased risk of melanoma (Berwick et al., 2016).

Melanoma is the most serious type of skin cancer, responsible for causing 75% of deaths from cutaneous cancers (Boozer, 2021). Abnormal cell growth in the melanocytes is triggered by unrepaired DNA damage (Ryan, 2020). This damage is typically caused by overexposure to ultraviolet (UV) radiation which has a genotoxic effect (Rastrelli et al., 2014; Ryan, 2020). The entire UV spectrum is carcinogenic to humans, however as most of UVB and all UVC are removed by the stratospheric ozone, it is predominantly UVA (95%) that reaches people followed by a small amount of UVB (5%) (Berwick et al., 2016). The greatest environmental risk factor for melanoma development is UV light exposure, from both natural exposure such as the sun and artificial sources including tanning beds (Bolick & Geller, 2021; Boozer, 2021; Sneyd & Cox, 2013; Ryan, 2020). This risk increases through the accumulation of intermittent sun exposure over a lifetime (Berwick et al., 2016).

There are some industries that may have an increased risk for developing melanoma related to occupational hazards. Such occupations are those working in the printing, electronic, chemical or airline industries (Berwick et al., 2016). These professions have increased exposure to carcinogenic triggers such as ionising radiation, chromium or organochlorine compounds, chlorine-based pesticides, and cosmic radiation from high altitude flights respectively, placing workers at risk (Berwick et al., 2016).

Trends show that the incidence of melanoma has stabilised for patients under 50 years old for both genders (Foo et al., 2020), while there is a significant increase for those 50 years old and older due to the high cumulative lifetime risk for melanoma (Foo et al., 2020). Overall, there has also been a rapid rise of melanoma for older adult males compared to other demographic subsets (Berwick et al., 2016; Johnpulle et al., 2016). From age 75 years and older, males are

three times more likely to develop melanoma than females (Rastrelli et al., 2014). The sites of occurrence differ between genders with men typically developing melanoma on their back while women develop them on their arms and legs (Rastrelli et al., 2014).

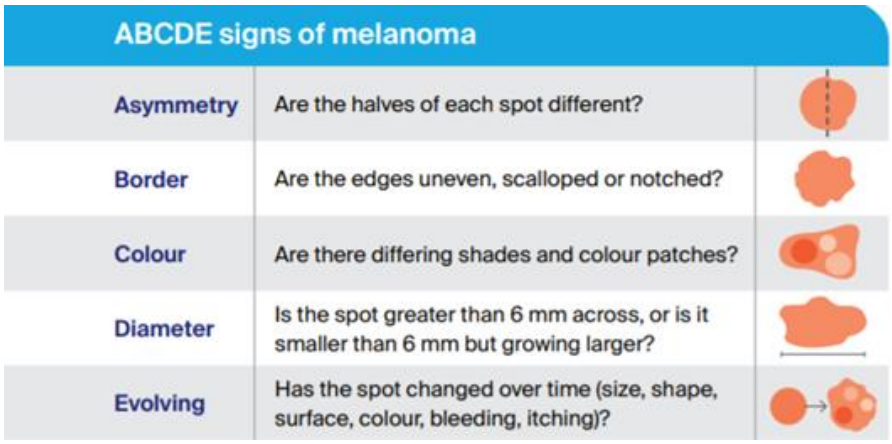
The clinical characteristics and incidence of melanoma also differs between various ethnic groups (Hao et al., 2016). Globally melanoma is a disease that predominantly affects Caucasians compared to other ethnicities. This is due to the phenotypic characteristics of fair skin and fair hair (red or blonde), freckles and light eyes (blue or green) which are more susceptible to the sun (Berwick et al., 2016; Rastrelli et al., 2014; Sneyd & Cox, 2013; Sneyd & Cox, 2009). The increased propensity to burn and inability to tan gives these individuals an approximately 10-fold risk of developing melanoma compared to people with darker skin pigmentation who have increased protection against UV rays (Berwick et al., 2016; Bolick & Geller, 2021; Johnpulle et al., 2016; Rastrelli et al., 2014).

2.2 Diagnosis of Melanoma

When assessing the skin for melanoma, there are specific signs and symptoms that can lead to a diagnosis. These include a bleeding, ulcerated or non-healing skin lesion, changes to a current nevus or new skin growth that meets the ABCDE mnemonic tool (Figure 2). ABCDE represents assessment points for the clinical presentation of melanoma with asymmetry indicating two sides of the mole do not match, border irregularity when there are irregular edges to the mole and where there is colour variation throughout. Another consideration is the diameter of the mole, which is greater than 6mm in width, and finally whether the mole is changing in size, shape, colour, or texture which is referred to as evolving (Boozer, 2021; Rastrelli et al., 2014).

Figure 2

ABCDE Tool



Note. Signs of melanoma. From Understanding Melanoma- A guide for people with cancer, their families, and friends [Brochure]. Cancer Council NSW. (2021). Reprinted with permission.

There are three major subtypes of cutaneous melanoma including superficial spreading, nodular and lentigo malignant melanoma (Hao et al., 2016). Superficial spreading melanoma (SSM) is the most common type people are diagnosed with, representing 70% of melanoma cases. It typically affects the backs of legs in women and the backs of men. It can arise from either an existing nevus or de novo and presents either flat or slightly raised, with irregular colours and asymmetric border. It takes years to become invasive (Boozer, 2021; Rastrelli et al., 2014).

Nodular melanoma (NM) accounts for 10-15% of cases and mainly affects men. It typically occurs de novo in the trunk, head and neck with rapid growth and high rates of metastasis. It often presents ulcerated with a uniform colour of brown, blue-black, black, pink, red but can also be a smooth surface nodule or elevated plaque with irregular borders (Boozer, 2021; Rastrelli et al., 2014).

Whilst SSM and NM are related to intermittent sun exposure, lentigo malignant melanoma (LMM) is linked to long term sun exposure. It typically affects the most sun-exposed skin such as on the head, neck, nose, and cheeks. It presents as a large, flat, irregular surface with a variegated pigment pattern (Boozer, 2021; Rastrelli et al., 2014).

Melanoma staging is a numerical range on a scale of 0-4. Stage 0 is melanoma in situ with it confined to cells in the epidermis and no invasion of the dermis. Stage 1 has 2-millimetre (mm) thickness without ulceration and 1mm in thickness with ulceration. Stage 2 has greater than 2mm thickness with or without ulceration or between 1-2mm thickness with ulceration. Stages 0-2 is classified as localised melanoma. Stage 3 is any thickness melanoma with involvement of nearby lymph nodes or tissues and is now regional melanoma. Stage 4 is any thickness melanoma with spread to distant lymph nodes or distant sites. This is classified as advanced or metastatic melanoma (Ryan, 2020).

When assessing a potential melanoma, clinicians will often use the Breslow depth score or the Clark level to stage lesions. The Breslow depth is a vertical measurement of how much the melanoma has invaded the cutaneous tissue, starting from the superficial ulceration to the deepest point of tumour involvement. It is a strong predictor of patient outcome with a thicker mole having a higher chance of metastasising (Boozer, 2021). The Clark Level also measures melanoma depth with a range of 1-5 levels, where level 1 means in situ, to level 5 which has invaded subcutaneous tissues and has the greatest risk of metastasis (Boozer, 2021).

Overall survival (OS) and progression-free survival (PFS) for patients is dependent on the anatomical site of the primary lesion (Hao et al., 2016). Acral lesions are those involving the upper and lower extremities and have a better survival time compared to non-acral lesions which include the head, neck, and trunk (Hao et al., 2016). The presence of ulceration also suggests a more rapidly growing melanoma (Ryan, 2020).

Prognosis is also associated with the stage and thickness of the melanoma which therefore highlights the importance of screening (Bolick & Geller, 2021). Early recognition, diagnosis and treatment are important to minimise morbidity and mortality. Surgery is a curative modality in the initial stages of melanoma with localised disease (Lui et al., 2007; Johnpulle et al., 2016). A local stage melanoma with early recognition and surgical excision has a 5-year 98% survival rate (Boozer, 2021; Hao et al., 2016). Whereas comparatively, a metastasized melanoma has a greatly reduced 25% survival rate (Boozer, 2021). Non-resectable Stage III and malignant Stage IV melanoma has a poor prognosis with a 1-year survival rate of 30-60% and 5-year survival rate of 16% (Hao et al., 2016).

Primary prevention of melanoma is being "SunSmart." This includes the reduction of sun exposure and use of sun protection through sunscreen and clothing to prevent sunburns. Whilst secondary prevention of melanoma is the early detection and reduction of associated deaths from melanoma (Kai Tiaki Nursing New Zealand, 2016). Skin self-examinations can be useful to have a baseline of spots, moles and freckles and observe if any changes occur over time (Berwick et al., 2016; Boozer, 2021; Hao et al., 2016).

2.3 **Melanoma in New Zealand**

New Zealand has one of the world's highest incidence and mortality rates from cutaneous melanoma (Ryan 2020; Sneyd & Cox, 2009). This is likely related to the high levels of ambient UV radiation levels in the country (Sneyd & Cox, 2013). UV radiation levels have been linked to the geographical distribution of melanoma around the world (Berwick et al., 2016). In 2018, melanoma was the third most common cancer for both males and females in New Zealand (Ministry of Health, 2018).

Trends in melanoma diagnosis in New Zealand have shown a slight increase over time, except for a decrease between 2016 and 2017. However, there has been a 12.8% increase when comparing total registrations between 2015 and 2018 (Table 1) (Ministry of Health, 2018). Not only has there been a rise in registrations, but there has been a trend in increasing mortality rates showing a 1.5% rise per year from 2001 to 2011 (Bolick & Geller, 2021). This is likely to be attributable to the ageing population in New Zealand.

Table 1

Display of Ministry of Health Statistics for Melanoma 2015-2018

Year	Male	Female	Total
2018	1538	1200	2738
2017	1412	1140	2552
2016	1431	1140	2571
2015	1361	1066	2427

Note. Adapted from statistics https://www.health.govt.nz/publication/selected-cancers-2015-2016-2017 and https://www.health.govt.nz/publication/new-cancer-registrations-2018. CC-BY 4.0. (Ministry of Health, 2018; Ministry of Health, 2019)

New Zealand is a multicultural nation with people from a diverse range of ethnic groups. According to 2018 census data, the New Zealand population was made up of European (70.2%), Māori (16.5%), Pacific peoples (8.1%), Asian (15.1%), Middle Eastern/ Latin American/ African (1.5%), and 'other' ethnicity (1.2%) (Table 2) (Statistics New Zealand, 2018).

Māori, Pacific Islander and Asian populations are less frequently diagnosed with melanoma compared to their NZ European counterparts. However, minority ethnicities in New Zealand are at higher risk of being diagnosed with thicker lesions and more advanced stage melanoma as well as having a poorer prognosis (Sneyd & Cox, 2009). Māori have a higher incidence of melanoma compared to Pacific Islander and Asian groups (Sneyd & Cox, 2009).

Table 2

Display of Ethnic Groups for People in New Zealand, 2006–18 Censuses

Ethnic group	2006 (%)	2013 (%)	2018 (%)
European	67.6	74.0	70.2
Māori	14.6	14.9	16.5
Pacific peoples	6.9	7.4	8.1
Asian	9.2	11.8	15.1
Middle Eastern/Latin American/African	0.9	1.2	1.5
'Other' ethnicity	11.2	1.7	1.2

Note. Where an individual reported more than one ethnic group, they were counted in each applicable group and therefore it does not total 100%. Adapted from statistics https://www.stats.govt.nz/tools/2018-census-place-summaries/new-zealand#ethnicity-culture-and-identity. CC-BY 4.0. (Statistics New Zealand, 2018).

When evaluating the age of melanoma patients, the 2018 statistics demonstrate that most patients belong to the 45-64 years old group. This is followed by those who are 75+ years and then 65-74 years old (Table 3).

Table 3

Display of Ministry of Health Statistics for Life Stage (Years) Breakdown of Melanoma in 2018

Life stage (years)	Male	Female	Total
0-24	3	10	13
25-44	98	126	224
45-64	495	450	945
65-74	445	279	724
75+	497	335	832

Note. Adapted from statistics https://www.stats.govt.nz/tools/2018-census-place-summaries/new-zealand#ethnicity-culture-and-identity. CC-BY 4.0. (Statistics New Zealand, 2018).

The domicile breakdown of those diagnosed with melanoma in 2018, showed most patients belonged to a district health board (DHB) within Auckland i.e., Waitemata district health board (WDHB), Auckland district health board (ADHB) and Counties Manukau district health board (CMDHB), with a total of 857 patients (Appendix A). This is unsurprising as Auckland boasts one third (33.4%) of the total New Zealand population (Statistics New Zealand, 2020).

There is much heterogeneity across the three Auckland DHBs. According to the Ministry of Health (MoH) (2021), ADHB serves the smallest population of 493,990 people, while CMDHB serves 578,650 people and WDHB serves the largest cohort consisting of 628,770 people (MoH, 2021a; MoH, 2021b; MoH, 2021c). There is diversity in age also, with CMDHB having the youngest population, boasting an average age of 32.9 years old (Statistics New Zealand, 2020). The ADHB population has an average age of 34.1 years, whilst WDHB has a similar population to the national average at 36.7 years (MoH, 2021a; MoH, 2021b; MoH, 2021c; Statistics New Zealand, 2020).

CMDHB has a higher proportion of Pacific people and similar proportion of Māori people compared to the national average. ADHB has a lower proportion of Māori people and higher proportion of Pacific people compared to the national average. WDHB has a lower proportion of Māori people and a similar proportion of Pacific Island people compared to the national average (MoH, 2021a; MoH, 2021b; MoH, 2021c).

Deprivation scores can also be broken down according to DHB, and the three Auckland DHBs have differing deprivation scores. WDHB is the least deprived, where CMDHB has proportionally more people who are living in deprivation. (MoH, 2021a; MoH, 2021b; MoH, 2021c). When evaluating the breakdown of patient's deprivation scores from the 2018 melanoma statistics, there were more people who had melanoma in the least deprived locations

then most deprived locations- suggesting that this disease does not discriminate by deprivation (Table 4).

Table 4

Display of Ministry of Health Statistics for Deprivation Quintile of Melanoma Patients in New Zealand 2018

Deprivation quintile	Male	Female	Total
1	417	305	722
2	330	232	562
3	322	277	599
4	286	245	531
5	181	137	318

Note. The deprivation score is represented by Quintile 1 to Quintile 5. Quintile 1 represents the least deprived section of the population while on the other end, Quintile 5 represents the most deprived section. Nationally, each quintile represents 20% of the population (MoH, 2021a; MoH, 2021b; MoH, 2021c). Adapted from statistics https://www.stats.govt.nz/tools/2018-census-place-summaries/new-zealand#ethnicity-culture-and-identity. CC-BY 4.0. (Statistics New Zealand, 2018).

2.4 New Zealand's Ageing Population

The New Zealand population is living longer, a trend reflected in other Organisation for Economic Co-operation and Development (OECD) countries around the world (Ben-Betzalel et al., 2019; Khawaja & Boddington, 2010). New Zealand has a population of 4.9 million, with 15% of people being 65 years old or older (Parr-Brownlie et al., 2020). Older adulthood is often broken down into further classifications. For example, terms that can be used are the 'young old', those greater than 65 years of age to 80 and 'older old' who are 80-85 years old and older (Cornwall & Davey, 2004).

The median age of the New Zealanders has increased from 25.6 years in 1870 to 37.1 years in 2016, which demonstrates the trend in growth for older adults (Office for Seniors, 2017). The number of older New Zealanders has doubled since 1998 from 440,000 to 740,000 people in 2019 (Parr-Brownlie et al., 2020). All regions across the country are expected to age at different paces (Khawaja & Boddington, 2010). These trends mean that the older New Zealand population is also becoming more diverse, with Māori, Pacific Island, Asian and other ethnic minorities making up a significant proportion of the older population (Office for Seniors, 2017).

The ageing population is an epidemiological transition due to many factors such as an improved standard of living, increased medical advances and public health strategies. This is alongside declining birth rates, decreasing mortality, and longer life expectancy (Cornwall & Davey, 2004; Khawaja & Boddington, 2010; Office for Seniors, 2017). The baby boomer cohort born

post World War II are also becoming a pensionable age which shifts the age structure and distribution of populations (Khawaja & Boddington, 2010).

Even though the population is living longer, there is an association between ageing and the prevalence of degenerative disorders such as neoplasms compared to communicable diseases (Cornwall & Davey, 2004). Advancing age is a significant risk factor for cancer development, with 60% of diagnoses and 70% of cancer deaths being within the patient demographic of those 65 years and older (Fox et al., 2020; Godby et al., 2019; Hamilton & Henry, 2020). The older adult population also has an increasing prevalence of chronic diseases and conditions related to a decline in the severity of the diagnoses and therefore decreased old-age mortality (Christensen et al., 2008). Specifically, the incidence of cardiovascular disease has risen significantly. Early diagnosis and improved medical care have resulted in patients living with less disability and for a longer duration with these diseases (Christensen et al., 2009).

The physiological changes which occur as we age need to be considered when assessing older adults and how they may respond to disease processes and treatment. There is a natural decline in biological and physiological response systems with increasing age (Fox et al., 2020; Hamilton & Henry, 2020). However, heterogeneity exists within the functional status of the older adult population (Rai et al., 2021). This is due to the variability in organ reserve, comorbidities, polypharmacy, and organ dysfunction (Cybulska-Stopa et al., 2021; Fox et al., 2020; Godby et al., 2019; Johnpulle et al., 2016).

These features of older adult patients are known to alter pharmacodynamics and pharmacokinetics, limiting therapeutic options (Johnpulle et al., 2016). While absorption is not generally an issue, drug distribution, metabolism and excretion can affect the safety and efficacy of drugs (Chung, 2014). Baseline factors to consider include geriatric syndromes such as frailty and sarcopenia (Godby et al., 2019), which can affect the volume distribution of the medication and therefore, exposure (Chung, 2014). Changes in hepatic function affect metabolism while reduced renal clearance affects drug excretion (Chung, 2014). Hepatic function is also affected by comorbidities and associated polypharmacy (Perier-Muzet et al., 2018).

2.5 Current Melanoma Treatment: Pembrolizumab

Several options are available for melanoma treatment, including chemotherapy, radiation, surgery, and immunotherapy (Hao et al., 2016; Lui et al., 2007; Rai et al., 2021).

Pembrolizumab is targeted immunotherapy and effective in treating unresectable and metastatic melanoma (Cybulska-Stopa et al., 2019). Pembrolizumab (Brand name Keytruda) is an immune checkpoint inhibitor (ICI) that can be used to treat multiple cancers. These include melanoma, non-small cell lung cancer (NSCLC), classical Hodgkin Lymphoma (cHL), urothelial carcinoma, renal cell carcinoma (RCC), head and neck squamous cell carcinoma (HNSCC) or

microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) cancers found anywhere in the body (Medsafe, 2021). However, pembrolizumab is only funded for treating unresectable or metastatic (Stage 3 or Stage 4) melanoma in New Zealand by the Special Authority (Medsafe, 2021). Pembrolizumab comes in a 4mL vial with 25mg per millilitre. Each 100mg vial costs $4680 according to PHARMAC (2021).

Pembrolizumab is a monoclonal antibody that works as a programmed cell death-1 (PD-1) inhibitor. PD-1 is an immune checkpoint transmembrane receptor that primarily functions in the peripheral tissues and is expressed on activated T lymphocytes to limit their activity and cause immune suppression (Godby et al., 2019; Ranaweera, 2018; Topalian et al., 2012). T cells encounter the primary ligands PD-L1 and PD-L2 expressed by tumour cells to achieve immune evasion (Godby et al., 2019; Topalian et al., 2012). Pembrolizumab has a high affinity against this pathway and blocks the interaction between the PD-1 receptor and its dual ligands. This modulation enhances T-cell effector functions and promotes an anti-tumour immune response through the proliferation and reactivation of tumour-specific cytotoxic T lymphocytes and other immunomodulatory mechanisms (Cybulska-Stopa et al., 2019; Godby et al., 2019; Poole, 2014; Topalian et al., 2012).

Prior to pembrolizumab, dacarbazine was the primary chemotherapy funded for the treatment of melanoma. Dacarbazine (also known as Dimethyl triazeno imidazole carboxamide (DTIC)) is a biochemical analogue of the 5-amino-imidazole-4-carboxamide ribonucleotide, which is an intermediate of purine biosynthesis (Hill et al., 1984). It inhibits cell replication; however, the exact mechanism is unknown. This treatment was difficult for patients to tolerate because a severe toxicity is haematopoietic depression. Common side effects include nausea and vomiting, bone marrow depression with leukocytopenia and thrombocytopenia (Medsafe, 2019).

Traditional chemotherapy has a low response rate, short response duration, and a poor toxicity profile for melanoma patients (Lui et al., 2007; Johnpulle et al., 2016). However, systemic chemotherapy such as Dacarbazine was considered the 'gold standard' of treatment for advanced melanoma as there were no placebo-controlled studies despite its limited success (Lui et al., 2007). Immune checkpoint inhibitors (ICI) are less aggressive than chemotherapy and radiation (Rai et al., 2021) and are better tolerated by patients. Evidence exists that they have a more favourable side effect profile and lower rates of severe toxicity than traditional chemotherapy or Dacarbazine (Fox et al., 2020; Godby et al., 2019). Additionally, ICI treatment has demonstrated benefits of increased disease-free and overall survival for patients with late-stage melanoma (Chanala et al., 2019; Cybulska-Stopa et al., 2019; Foo et al., 2020; Rai et al., 2021).

There are other immunotherapy treatments available. However, pembrolizumab was the first anti-PD-1 therapy that had accelerated, conditional approval by the Food and Drug Administration (FDA) in the United States of America (USA) in September 2014 for

unresectable and metastatic melanoma based on Phase I data (PHARMAC, 2015; Poole, 2014). Pembrolizumab was approved by the Therapeutic Goods Administration (TGA) in Australia in April 2015 for first and second-line treatment of unresectable and metastatic melanoma at 2mg/kg every three weeks (PHARMAC, 2015). PHARMAC approved its use in New Zealand in 2016 based on clinical evidence that showed efficacy and long-term benefits. This evidence predominantly came from the Phase I, II and III Keynote studies which demonstrated a durable response rate, improved overall survival and progression-free survival (Robert et al., 2014; Robert et al., 2019; Schadendorf et al., 2016).

Anti PD-1 immunotherapy studies have shown a response rate (RR) of 35-45%, and a durable response rate is seen in survival rates of over 50% at two years. It has been shown that 90% of patients with metastatic melanoma remain progression-free at 24 months after achieving a complete response and completing two years of therapy (Ben-Betzalel et al., 2019; Johnpulle et al., 2016). Comparatively, the median overall survival for chemotherapy and radiation is 6-8 months (Rai et al., 2021).

Pembrolizumab treatments are given as a 30-minute infusion on a 3-weekly schedule (Godby et al., 2019). Patients discontinue treatment due to progression of disease that has worsened or spread, unacceptable levels of toxicity, if the patient has removed their consent, or the patient dies. According to multiple keynote studies by Medsafe, it is possible to reinstate pembrolizumab for up to one additional year if there is disease progression (Robert et al., 2014; Robert et al., 2019; Schadendorf et al., 2016).

Common side effects of pembrolizumab include diarrhoea, nausea, pruritus, rash, arthralgia, fatigue, and stomach pain (Poole, 2014; Medsafe, 2021). Common side effects differ from immune-related adverse effects (irAE), where there is a lowered threshold of self-tolerance and increased T-cell activity against healthy cells (Cybulska-Stopa et al., 2021; Godby et al., 2019). Immune-related adverse effects can occur at any time during treatment, although is most common in the first three months of therapy. It can even occur up to 6 months after the discontinuation of the immunotherapy (Godby et al., 2019; Medsafe, 2021).

Immune-mediated adverse effects (that can become life-threatening or lead to death) can affect multiple body systems (Medsafe, 2021). Specifically, this can be observed as dermatitis, pneumonitis, colitis, hepatitis, thyroiditis, hypophysitis, nephritis, hyperthyroidism, or hypothyroidism (Godby et al., 2019; Poole, 2014). The standard treatment for irAEs is high-dose corticosteroids or other immunosuppressive therapies (Johnpulle et al., 2016). Further management includes delaying the next dose of pembrolizumab or withdrawing from treatment depending on the severity of these adverse effects (Medsafe, 2021).

The National Cancer Institute created the Common Terminology Criteria for Adverse Events (CTCAE) to grade the severity of adverse events (AE). Grade 3 is severe and is for medically significant symptoms though not immediately life-threatening. It requires hospitalisation or the prolongation of hospitalisation and causes limited self-care activities of daily living (ADL). Grade 4 is life-threatening, requiring urgent intervention (National Cancer Institute, 2017). Serious adverse events are relatively uncommon with pembrolizumab, and clinically severe toxicities (CTCAE Grade 3-4) occur in only 10-15% of patients (Ben-Betzalel et al., 2019; Johnpulle et al., 2016). Grade 5 events result in death and fatal events occur in 1 of 300 patients who have received pembrolizumab (Godby et al., 2019).

2.6 Research on Older Adult Ageing Processes and Melanoma Treatment With Pembrolizumab

Age is an important clinical factor to consider in the treatment response of patients. Older patients with unresectable and metastatic melanoma possess different disease characteristics than their younger counterparts. Older adults are more likely to have a delayed diagnosis and high Breslow thickness of their primary melanoma, which provides an inferior prognosis (Chanala et al., 2019; Cybulska-Stopa et al., 2019; Johnpulle et al., 2016). Delayed diagnosis and high Breslow thickness, combined with more aggressive biologic behaviour (high mitotic index) and a lower percentage of the targeted therapy-sensitive V600E BRAF-mutant genotype, lowers the disease-specific survival rate (Chanala et al., 2019; Cybulska-Stopa et al., 2019; Johnpulle et al., 2016). The prognosis for older adults is also related to the tumour burden, elevation of lactate dehydrogenase (LDH) and their multimorbidities (Chanala et al., 2019). It is common for older adults to have comorbidities. The concern lies with the fear of worsening these other chronic conditions while treating their melanoma (Rai et al., 2021).

Immunosenescence is the natural, ageing-associated loss of immune homeostasis, biological and physiological responses within the body (Fox et al., 2020; Hamilton & Henry, 2020). The global immune system is modified by immune dysfunction (Perier-Muzet et al., 2018) from thymic involution and decreased haematopoiesis (Cybulska-Stopa et al., 2019; Godby et al., 2019), with derangements in adaptive, cell-mediated immunity (Fox et al., 2020). This can be observed through the elevated circulating levels of pro-inflammatory cytokines and autoantibodies, attenuated production, and reduced function of lymphoid cells (Godby et al., 2019; Hamilton & Henry, 2020). The reduced proliferative capacity and survival of T lymphocytes also reduce T lymphocyte-mediated cytotoxicity functions (Foo et al., 2020; Fox et al., 2020). Additionally, the autonomous cell changes with increased DNA damage, mitochondrial dysfunction and oxidative stress also compromise the function of aged immune cells (Hamilton & Henry, 2020).

2.7 **Previous Literature**

A literature search was conducted to see what is known about older adults and how they respond to pembrolizumab. Sixty-one journal articles were found. Relevant research articles were collated using databases including Cumulative Index to Nursing and Allied Health Literature (CINAHL) Complete, MEDLINE (Medical Literature On-Line) and Google Scholar.

The following keywords and combination of them were used:

•immunotherapy, immune checkpoint inhibitors, pembrolizumab, anti-PD1, dacarbazine, melanoma, metastatic melanoma

•older patients, elderly, geriatrics, octogenarian and nonagenarian, ageing, immunosenescence

A literature review was conducted to see if any previous studies had found that age impacted treatment outcomes for those receiving pembrolizumab. It included articles published between the period 2011- 2021. Older articles were referenced to provide historical context. Several studies found no differences between older and younger adults regarding toxicity, response rates and survival rates.

Cybulska-Stopa et al. (2019) looked at 82 patients above 70 (70-90 years age range) out of 318 patients who received ICI. They found a similar progression-free survival and overall survival rate for this older adult group. Within this group, 84% of people had comorbidities; however, other chronic diseases (including diabetes, arterial hypertension, and cardiovascular disease) showed no impact on the effectiveness of treatment in the older adult or the likelihood of experiencing toxicities.

Ben-Betzalel et al. (2019) compared two groups of patients over 65 who had previously received anti-PD-1 therapy; 75% of patients received pembrolizumab, while the other 25% received Nivolumab. Group A had 82 people aged 65- 79 years old, and Group B had 62 people who were 80-100 years of age. Their study showed an increased overall response rate and significantly increased complete response (22% in Group A versus 47.9% in Group B) in Group B. Therefore, older old adults have an enhanced response to anti-PD-1 inhibitors. There were no significant differences between groups in progression-free survival or overall survival rates. Additionally, both groups had similar toxicity experienced for grade 2 to grade 4 adverse events.

Fox et al.'s (2020) study looked at 20 patients aged 75-94 years with polypharmacy, and 95% of the group had comorbidities. A clinical benefit (stable disease, partial response, complete response) was observed in 13 out of 20 patients. Out of the 20 patients, 80% were in the age range of 75-79 years and 50% those older than 79. The toxicity profile was shown to be similar to younger patients. A critique of this study would be that a small number of patients were

included and a wide range of cancer diagnoses including non-small-cell lung cancer, urothelial bladder carcinoma, renal cancer, and Merkel cell carcinoma.

Cybulska-Stopa et al. (2021) compared three groups of older adult patients those under 65 years of age, 65-79 years, and those 80-100 years old. They found a similar overall response rate and disease control rate as well as grade 3 and grade 4 immune-related adverse event rate. Overall response rate was defined as a complete response and partial response of the tumour. Disease control rate was defined as complete response, partial response, and stable disease of the tumour. There were no statistically significant differences in overall, progression-free, or melanoma-specific survival. Therefore, treatment efficacy and toxicity were the same for octogenarians and nonagenarians compared to their younger counterparts.

These four studies recruited patients from the European and Asian continent (specifically Spain, Poland, and Israel), and it is uncertain if these results could also translate to Oceania. Therefore, this research study could contribute new knowledge from a New Zealand context. There was also a mix of immunotherapy drugs used across these studies, including nivolumab, atezolizumab, ipilimumab and pembrolizumab. Therefore, this provides mixed results about the efficacy and tolerability of pembrolizumab as a treatment option. This study will provide clarity by focussing solely on pembrolizumab as a treatment. All studies except Fox et al. (2020) (only 20 patients) had a reasonable-sized cohort of the older old adult population (62-82 patients). This research aims to recruit as many older old adults as possible. Regardless of the study's population size, all four studies shared a common theme that older adults have a similar disease response to immunotherapy and toxicity profile to their younger counterparts. Positively the results of these studies also demonstrated that the older old adult was not disadvantaged by their comorbidity profile. These studies suggest a positive outcome is also possible for the older old New Zealand patients receiving pembrolizumab.

2.8 **Summary**

This chapter has explored melanoma, what it is and how it is diagnosed, pembrolizumab treatment within a New Zealand context, and how it relates to the ageing patient population. Although research shows that age is not a barrier to effective treatment outcomes with pembrolizumab, cohort numbers of older adults in studies are small. Few studies exist that evaluate the older old adult (80 years and older). There are also no studies that have looked at older adults receiving pembrolizumab from a New Zealand context. The following chapter will explain the methods and methodology used for this study that will answer the research question of this study which is to explore the treatment outcomes of pembrolizumab treatment for metastatic and unresectable melanoma across adult aged cohorts.

Chapter 3 Methodology

This chapter will cover the methodology which underpins this dissertation. It includes a discussion about the philosophical worldview held by the researcher and associated research design used for this study. This will expand further into the methods used, including the study population, treatment setting, study protocol, outcome measures, data analysis and ethical approval for the research.

The aim of this study was to explore the treatment outcomes of pembrolizumab treatment for metastatic and unresectable melanoma across adult aged cohorts: (50 years old and younger, 51-65 years, 66-80 years, 81 years and older). The treatment outcomes being explored were tumour response, disease progression and toxicities, compared across age cohorts. Covariates that potentially influenced outcomes were also included (comorbidities, district health board of enrolment (DHB) gender).

3.1 Philosophical Worldview

A paradigm is a belief system and way of viewing the world. This philosophical assumption underpins the foundation of different approaches to research and the components include ontology (nature of reality and truth), epistemology (nature of knowledge), axiology (nature of values) and methodology (strategy and rationale) (Davies & Fisher, 2018).

The guiding philosophical worldview used in this research is positivism which is also known as the scientific paradigm. It is a form of empiricism and arises from a branch of philosophy called logical positivism where there are strict rules of logic, universal truth, and predictions (Clark, 1998; Gillis & Jackson, 2002). The ontology assumes there is a single objective reality (Creswell, 2009; Davies & Fisher, 2018) with general laws of cause and effect i.e., human behaviour is the outcome of natural forces acting on individuals (Gillis & Jackson, 2002). Deductive reasoning is used to test predetermined hypotheses or theories to reach a conclusion (Davies & Fisher, 2018). Epistemology means the phenomena studied can be undertaken with objectivity, impartiality, and a high level of control (Clark, 1998). Therefore, it will produce replicable data that is generalisable to the population or situation (Clark, 1998; Davies & Fisher, 2018).

Positivist inquiry is a value free, relativistic research where detachment is held in high regard (Clark, 1998) with researchers separated from the participants. This purports to eliminate biases and allow predictive data to be produced (Davies & Fisher, 2018; Gillis & Jackson, 2002). Theories and knowledge can be established deductively through empirical testing and evidence between rival hypotheses (Creswell, 2009). The traditional methodological design associated with positivism is quantitative in orientation with data often presented in numerical indices

(Davies & Fisher, 2018; Gillis & Jackson, 2002). This study will predominantly use inferential statistics and therefore fall under positivism. The use of inferential statistical testing means that the true results cannot be 'proven'. However, a statistical significance value of $p \leq 0.05$ strongly supports that the results received are the true results.

3.2 **Research Design**

The choice between carrying out quantitative versus qualitative research or mixed methods research is influenced by the nature of questions asked, the research topic, and the philosophy of the researcher (Creswell, 2009; Gillis & Jackson, 2002). A quantitative methodology was chosen as the research questions posed are close ended (Clark, 1998). This research involves counting the pembrolizumab cycles completed by patients belonging to various age-band groups and comparing their treatment outcomes, while considering influential covariables. To achieve this, statistical testing is needed to find associations between a patient's age and their treatment outcomes and other related variables. Therefore, inferences can be made about the relationships that exist between the variables (Welford et al., 2012).

The role of the researcher will be detached from the data fields. The research is a retrospective observational study of the outcomes of pembrolizumab. This data was obtained in the naturalistic setting instead of a controlled research setting that compares an intervention versus control group (Creswell, 2009) for the pembrolizumab treatment. For quantitative research, the researcher must identify, measure, and express the relationship between variables with mathematical precision (Gillis & Jackson, 2002).

The researcher acknowledges the results are limited in precision by the lack of controls over the data collection process before the statistical analysis takes place. The researcher will have a heavy reliance on the data that has been collected by others and therefore be limited by what is available to access at the data collection stage. There is potential for error in reporting (misclassification) or absent data points (Sedgwick, 2014). This is one of the drawbacks of working with a retrospective design. However, in contrast, a benefit of pre-existing data is that there is no dependence on a patients' willingness to participate in the study. Additionally, it is a less resource intensive study design to carry out with a smaller research team required and therefore cost-effective. It is also less time consuming and will allow for faster data analysis (Sedgwick, 2014).

The nature of working with cancer patients means it is unethical to run a randomised controlled trial (RCT) with an active versus placebo treatment. This is because some patients will miss out on effective treatment if they are in the placebo group (Caparrotta et al., 2019). Therefore, an advantage of using a retrospective naturalistic design is that this specific patient group can still be included within research studies to further increase our knowledge about how to improve outcomes. Other benefits include observing outcomes without any interference from the

researcher which will reduce bias (Caparrotta et al., 2019; Welford et al., 2012). Overall, it is most appropriate to conduct a retrospective observational study to observe the treatment outcome phenomenon in a natural setting.

3.3 Methods

A retrospective cohort design will be used as the relative timing of the data collected will be looking backwards (Polit & Beck, 2017). This method means that the participants will be identified at the beginning of the study from past health records and their outcome will then be able to be assessed (Celentano & Szklo, 2019).

3.4 Study Population

Inclusion: The participants of this study are any patients over the age of eighteen years old who have been diagnosed with unresectable or metastatic melanoma and received pembrolizumab immunotherapy in Auckland between January 2017 and June 2021. Patients were included only if they had completed their full treatment regime.

Exclusion: Patients still currently on active treatment were removed. Patients under the age of 18 years old were removed from the database as there was no guardians' permission for their data to be included in this study. Additionally, patients recruited to a clinical research trial were excluded as they would not represent a standard of care patient.

3.5 Treatment Setting

The location of the study will be at a single institution. This will be a tertiary level hospital that operates in Auckland, New Zealand and treats citizens and permanent residents free of charge for pembrolizumab. The district health board (DHB) of this hospital will have received allocated funding for this (Parr-Brownlie et al., 2020). Patients will arrive on a three weekly schedule to receive their half hour pembrolizumab infusion at either the day stay or infusion room as an outpatient. The researcher will not be identifying the DHB and hospital to provide anonymity to the patients involved in this study.

3.6 Study Protocol

A database was provided by the Data and Analytics department of the hospital with 345 patients who had received pembrolizumab between January 2017 to June 2021. Data fields included date of birth, gender, start and end date of treatment and local district health board.

Additional data fields were collected by a Research Officer and provided a full de-identified data set to the researcher. Additional data collected included ethnicity, postcode, list of comorbidities, number of pembrolizumab cycles completed and reasons treatment was discontinued. The data was collected once and at a single point in time, which made the data

cross-sectional in nature (Gillis & Jackson, 2002; Polit & Beck, 2017). A data management plan was created (Appendix B).

3.7 Predictor and outcome variables

Predictor variables

- Age (in bands: 1= 50 years and under, 2= 51-65 years, 3= 66-80 years, 4= 81 years and above). Age was arranged into quartiles, with those 50 years old and under who would represent our younger cohort. Middle-aged people were those 51-65 years old, and this group was capped at the current retirement age in New Zealand. There were two more age categories with those 66-80 years old and 81 years and older
- Number of treatments
- Number of comorbidities (total number of comorbidities).
- Category of comorbidity.
- Gender (1= females, 0= males).
- District Health Board (DHB) (Table 6).

Outcome variables

- *Response to treatment* (patients who have responded to pembrolizumab). Tumour response to treatment can be defined as either complete or partial response or stable disease. Complete response is defined as a disappearance of all target lesions in response to treatment while partial response is a decrease in the sum of diameters of target lesions from baseline. Stable disease means neither a response nor progressive disease (Ribas et al., 2016).
- *Disease progression* (number of patients who have/have not responded to pembrolizumab).
- *Toxicity* (number of patients that have/have not been afflicted with toxicity issues such as fatigue and skin rash).

Secondary analysis were the associations between category of comorbidities and treatment outcomes. Secondary analysis also looked at associations between predictor variables. Classification of comorbidity category was agreed upon by between the author and the supervisor with a third agreement with a senior lecturer at AUT, until consensus was met (Table 5).

Table 5

Classification of comorbidities

1	Cancer
2	Cardiovascular
3	Diabetes
4	Autoimmune
5	Infection
6	Haematology
7	Other

For analysis we focused on the top three occurring comorbidities: Cardiovascular (cardiovascular comorbidity 1= yes, 0= no). Diabetes (diabetes comorbidity 1= yes, 0= no). Cancer (cancer comorbidity 1= yes, 0= no).

Because Caucasian respondents (New Zealand Europeans and other Europeans) made up 93% of respondents, no analysis was conducted by ethnicity due to a lack of population variance.

3.8 **Data Analysis**

Descriptive statistics were applied to summarise *gender, age, ethnicity* and *DHB*. Descriptive analysis characterises the data set and provides a summary of the collected data. There were only binary genders provided in the data set and therefore not all gender categories could be reflected. In this study, the central tendency measure (mean, median, mode), variability (range, standard deviation) and statistical significance (probability value) will be used for continuous or interval scale variables (Creswell, 2009).

The data was assessed for normality in SPSS V28 prior to statistical analysis. Therefore, this assumption would be met for statistical testing. All statistical analyses were performed using SPSS V28. The differences were considered statistically significant if the p-values were less than 0.05.

An independent T- test was used to measure associations and mean scores between continuous variables and categorical predictors. One way analysis of variance (ANOVA) was conducted to explore associations on continuous variables between two or more categories (Creswell, 2009). For significant ANOVA, Tukey's HSD post hoc testing was applied to detect the influential variable(s) for significant ANOVA results. Following discussion with the biostatistician, analysis of covariance (ANCOVA) was used to adjust for differences between groups based on the covariate (Leech et al., 2005). A one-way ANCOVA was run to examine whether age

differences exist across *age* while controlling for *DHB*. This was because *age* and *DHB* are not independent of each other. Therefore, the ANCOVA would demonstrate the similarity of statistical results to the ANOVA and show that error was not introduced because of concurrent ANOVAS on related variables.

Chi-square analysis for independence tested relationships among categorical predictor variables (*DHB, gender*) and outcome categorical variables of *treatment outcome, disease progression,* and *toxicity*. Fisher's Exact test (two-sided) was applied when cell size did not meet assumptions for chi-square analysis.

Regression analysis was also used to predict categorical outcomes with two or more categories (using binary logistic regression) to test the effects of study factors on three models: (1) Response to Treatment, (2) Disease Progression, and (3) Toxicity. The three main comorbidities were studied (cardiovascular, diabetes and cancer) as well as the primary outcomes of response to treatment, disease progression and toxicity.

3.9 **Ethics**

Auckland University of Technology Ethics subcommittee (AUTEC) approved this research (21/96) (Appendix C) and it was granted in July 2021. A data management plan was created for the ethics approval process (Appendix B) however, was not used as ethics approval was conditional on the student researcher not having access to identifiable information. This was despite the researcher's role as a staff member at the DHB which gave rights to access this data for audit purposes. However, this would not translate to the right to access data for the student researcher role.

Auckland University of Technology (AUT) School of Clinical Sciences (SoCS) Seed Funding was used to hire an independent research officer to collect data and provide a complete de-identified data set. Provisions were put in place to prevent re-identification to protect patients' confidentiality.

An audit proposal was provided to the Outpatients Oncology Department to provide details of the research project. The researcher signed the 'Confidentiality of Information' form (see Appendix D) to provide guarantee of patient privacy and confidentiality. The approval for this was signed by the charge nurse manager. This form was not required for the research assistant as they were currently employed by the same district health board, and this was part of their work contract. The 'Access to Patient Information' form was completed by the researcher on behalf of our research assistant as shown in Appendix E. This received departmental approval through the signature of the Clinical Director.

3.10 **Summary**

This chapter has explained the philosophical worldview guiding the research and detailed the specific methods undertaken to achieve the research aim, and why both are suitable to answer the research question. Details were provided about the study population who are unresectable or metastatic melanoma patients attending a tertiary level hospital for pembrolizumab immunotherapy. The inclusion and exclusion criteria were stated, along with the variables of interest which included age, gender, DHB, number of treatments, comorbidities, and treatment outcomes. The ethical process was explained, including locality agreements and AUTEC applications. The next chapter will present the results of this study.

Chapter 4 Results

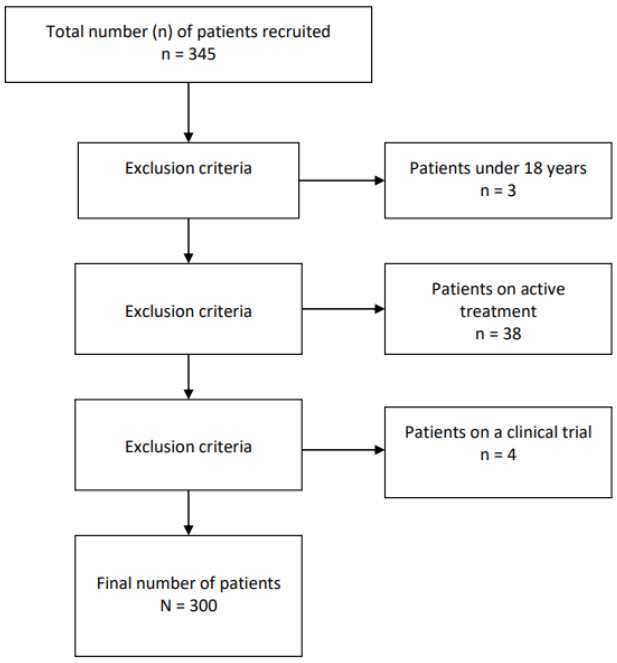
In this chapter, the results of this research study will be presented in both table format and in-text descriptions. The study population will be described prior to the results of number of treatments, response to treatment, disease progression, toxicity, number of comorbidities, and associations with cardiovascular, diabetes and cancer comorbidities. The associations between study variables are reported through t-tests, ANOVA, ANCOVA, Chi-square analysis for independence and Fisher's Exact test, and binary logistic regression.

4.1 Patient Population

There was a total population of 345 patients able to be evaluated for this study, three patients were excluded as they were under 18 years of age, and we did not have parental or guardian permission to include these patients in the research study. An additional 38 patients were removed as they were still on active treatment. Therefore, they would not have completed their treatment course and would have no treatment outcome data available to be evaluated. Four patients that were involved on a clinical trial were also excluded as there are strict inclusion and exclusion criteria to be met to be recruited onto a clinical trial. Due to this, they would not represent the general population of patients. There was a total of 300 patients remaining who were able to be included (Figure 3).

Figure 3

The Data Collection Process



Note. Flow diagram of study population

Table 6

Participant Demographic Characteristics

Demographic variable	*n*	*%*
Gender		
Female	102	34%
Male	198	66%
Total	**300**	**100**
Age (years)		
50 years and under	27	9.0%
51-65 years	90	30%
66-80 years	131	44%
81+ years	52	17%
Total	**300**	**100**
Ethnicity		
NZ Europeans	239	80%
Other Europeans	38	12.5%
Cook Island Māori	1	0.3%
Chinese	5	1.7%
European NFD	6	2.0%
Indian	1	0.3%
Latin American	1	0.3%
Māori	6	2.0%
Middle Eastern	1	0.3%
Samoan	1	0.3%
Other Ethnicity	1	0.3%
Total	**300**	**100**
District Health Board		
Waitemata	118	39%
Auckland	83	28%
Counties Manukau	74	25%
Northland	22	7.0%
Bay of Plenty	2	0.7%
Lakes	1	0.3%
Total	**300**	**100**

Table 7

Participant Treatment Characteristics

Treatment Outcomes	*n*	*%*
*Disease progression	133	44%
# Response to treatment	105	35%
*Toxicity	47	16%
*Other disease	15	5%
Total	**300**	**100%**
Number of comorbidities		
0 comorbidities	124	41%
1 comorbidity	73	24%
2 comorbidities	42	14%
3 comorbidities	38	13%
4 comorbidities	12	4.0%
5 or more	11	4.0%
Total	**300**	**100%**
Comorbidity Types (most frequent):		
Cardiovascular	120	40%
Diabetes	25	8.0%
Cancer	18	6.0%
Total	**163**	**54%**

Notes: *Treatment outcome that prompted treatment discontinuation or completion (number of participants). # Number of participants who responded favourably to treatment.

Table 8

Descriptive treatment characteristics

Overall	*N*	Minimum score	Maximum score	*M*	*SD*
Average age of participants	300	20	101	68.45	13.3
Number of treatments	300	1	64	14	13.2

4.2 Number of Treatments

Across all 300 participants, the mean number of treatments for males was 13.9 (*SD* = 12.90) and females was 14.3 (*SD* = 14.03). (Table 10).

ANOVA conducted on *number of treatments* by *age* found no significant differences across the age bands, F(3, 296) = 1.677, p = .172. Similarly, there were no significant differences on *number of treatments* by *DHB*, F(3, 296) = 1.612, p = .187. (Table 9).

T-test similarly found no significant difference regarding the *number of treatments* by the *gender* of the patient, t(2, 298) = .265, p = .791. (Table 10). This supported that the *number of treatments* was not significantly affected by patient *gender*, *age*, and the *DHB* they attended.

4.3 Response to Treatment

Thirty-five percent of patients (*n* = 105) responded to treatment (Table 7). This meant they had stable disease, a partial response or complete response (see page 32 for definitions).

ANOVA was conducted on response to treatment by *age.* There was no significant difference by *age* in response to treatment, F(3, 296) = .734, p = .609. There was also no significant difference by *DHB* in response to treatment (n=300), X2 (df, 5) = 3.4, p = .63.

Two-sided Fisher's Exact test found no significant difference regarding response to treatment by *gender*, p = .6 (Table 10). This supports that the response to treatment is uniform across patient *age*, *gender*, and the *DHB* they attended.

4.4 Disease Progression

Forty-four percent of patients (*n* = 133) had *disease progression* (Table 7).

ANOVA was conducted on the outcome measure of disease progression by the variables of *age*. There was a significant difference across *age* on *disease progression*, F(3, 296) = 2.800, p = .040. The highest age-band with disease progression was in the 50 years and under group (59%), had a higher percentage with *disease progression* than all other age groups. The next highest percentage for *disease progression* was in the 66-80 years group (48%), followed by the

51-65 years group (43%). The group with the lowest percentage with *disease progression* was the 81 years and older group (29%). There was no significant difference by *DHB* for *disease progression* (p=.75), or by *gender* (n=300), X2 (df,4) = 1.4, p = .85.

The above results support that for the study population, the risk for *disease progression* was highest for the youngest age group and lowest for the oldest age group. Risk for disease progression was not significantly associated with *gender* or the *DHB* they attended for treatment.

4.5 **Toxicity**

Treatment toxicity occurred in 16% of patients (*n* = 47) (Table 7).

ANOVA, conducted on whether the toxicity experienced by patients differed by *age* found a statistically significant difference across *age* for *toxicity*, F(3, 296) = 6.813, p < .001. The highest presentation of *toxicity* occurred in the 81 years and older age group (35%). Presentation of toxicity reactions were different between all other age bands; 50 years and under (4%), 51-65 years group (10%), and 66-80 years group (15%). However, Fisher's Exact test found no significant difference for *toxicity* by *DHB* (p = .34), or *gender* (p = .99).

4.6 **Number of Comorbidities**

Overall, 41% of patients (*n* = 124) had no comorbidities (Table 7). Patients with comorbidities recorded between one to eight comorbidities, with a mean of 1.28 (*SD* = 1.51) comorbidities.

ANOVA was conducted for associations between the *number of comorbidities* by *age* or *DHB*. By *age*, there was a significant difference across *age* for *number of comorbidities*, F(3, 296) = 20.509, p < .001. The highest *number of comorbidities* (*M* = 2.31, *SD* = 1.821) was for those aged 81 years and older, which was significantly higher (p < .001) than comorbidities in those aged 66-80 years (*M* = 1.49, *SD* = 1.490). In turn, the next groups were significantly lower: 51-65 years group (*M* = .63, *SD* = .965) and the 50 years and under group (*M* = .44, *SD* = .934). However, there was no significant difference in *number of comorbidities* by *DHB*, F(2, 298) = 1.109, p = .346. (Table 9).

T-test supported that there was a significant difference in the *number of comorbidities* by *gender*, F(2, 298) = -2.076, p = .039. The *number of comorbidities* for males (*M* = 1.41, *SD* = 1.63) was significantly (p = .039) different to females (*M* = 1.03, *SD* = 1.21) (Table 10). These results support that comorbidity occur more frequently as patients get older, and that males have a higher number of comorbidities than females.

4.6.1 **Comorbidity: Cardiovascular**

Overall, 40% of patients (*n* = 120) had a cardiovascular comorbidity (Table 7).

ANOVA was conducted on whether patients differed on cardiovascular comorbidity by age. By *age*, there was a significant difference for *cardiovascular morbidity* F(3, 296) = 23.263, p < .001. The highest percentage of *cardiovascular comorbidity* was in the 81 years and older age band (67%,) and those aged 66-80 years (52%). Both these groups recorded a higher percentage with *cardiovascular comorbidity* than those aged 51-65 years (18%) and the 50 years and under group (4%). Chi-square analysis found no significant difference in *cardiovascular comorbidity* by *gender*, (X2 [df,1], = 2.9, p = .06). There was no significant difference for *cardiovascular comorbidity* by *DHB* (p = .95).

4.6.2 **Comorbidity: Diabetes**

Overall, 8% of patients (*n* = 25) had a comorbidity of diabetes (Table 7).

ANOVA was conducted on differences in the *diabetes comorbidity* by *age*.. By *age*, there was not a significant difference across the age bands for *diabetes comorbidity*, F(3, 296) = .539, p = .656.

The independent Chi-Square analysis found no significant difference in diabetes comorbidity by gender, (X2 [df,1], = 2.4, p = .12). There was no significant difference for diabetes comorbidity by DHB (p = .74).

4.6.3 **Comorbidity: Cancer**

Overall, 6.0% of patients (*n* = 18) recorded a comorbidity of another cancer (Table 7).

ANOVA was conducted on whether patients differed in *cancer comorbidity* by *age.* By *age*, there was no significant difference *cancer comorbidity* , F(3, 296) = .611, p = .608. Chi-square analysis found no significant difference in *cancer comorbidity* by *gender*, (X2 [df,1], = .2, p = .65). There was no significant difference for *cancer comorbidity* by *DHB* (p = .19).

Table 9

Statistical results by Age and DHB

Variables by age	*F-Statistic*	*p*	*Significant Difference (Tukey HSD Post-hoc Test) – where applicable*
Number of treatments	1.677	.172	N/A
Response to treatment	.734	.609	N/A
Disease progression	2.800	.040*	50 years and under (59%)> 66-80 years (48%) > 51-65 years (43%)> 81 years plus (29%)
Toxicity	6.813	< .001***	81 years plus (35%) > 66-80 years (15%) + 51-65 years (10%) + 50 years and under (04%)
Number of Comorbidities	20.509	< .001***	81 years plus (2.31) > 66-80 years (1.49) > 51-65 years(0.63)> 50 years and under (0.44)
Comorbidities:			N/A
Cardiovascular	23.263	< .001***	81 years plus (67%)> 66-80 years (52%) > 51-65 years (18%) + 50 years and under (4%)
Diabetes	.539	.656	N/A
Cancer	.611	.608	N/A
Variable by DHB	*Chi-square X2*	*p*	*Fishers Exact test*
Variable by DHB			
Response to treatment	3.4	.63	
Disease progression			.75
Toxicity			.34
Comorbidities			
Cardiovascular			.95
Diabetes			.74
Cancer			.19

*p < .05, **p < .01, ***p < .001

Table 10

T- Test Results Variables to Gender

	Females (*n* = 102)		Males (*n* = 198)					
Variables	*M*	*SD*	*M*	*SD*	*t (df* = 298*)*	*p*	*Chi-square* [#]	*Fishers Exact test*[#]
Number of treatments	14.32	14.03	13.89	12.90	.265	.791		
Response to treatment								.60[#]
Disease progression						.85	1.4 (df,4)[#]	
Toxicity								.99[#]
Comorbidity – cardiovascular						.06	2.9(df,1)[#]	
Comorbidity – diabetes						.12	2.4(df,1)[#]	
Comorbidity – cancer						.65	.2(df,1)[#]	

*p < .05, **p < .01 *SD*= Standard Deviation, *M*= Mean score of variables, [#] 2 sided Fishers Exact test or chi-square

4.7 **ANCOVA Results**

ANCOVA conducted on number of treatments by *age* found non-significant differences across the age bands, $F(3, 297) = 1.726$, $p = .162$. The control variable *DHB* was non-significant, $F(1, 299) = 0.463$, $p = .497$.

ANCOVA conducted on number of comorbidities by *age* found significant differences across *age* , $F(3, 297) = 20.076$, $p < .001$. Across the age bands, the category of 81 plus years had a significantly higher number of comorbidities than the under 50 years age band (mean difference= 1.863, $p < .001$). This was significantly higher than 51-65 years category (mean difference= 1.655, $p < .001$) and significantly higher than 66-80 years category (mean difference= .827, $p < .001$). The control variable *DHB* was non-significant, $F(1, 299) = 2.359$, $p = .126$. Thus, participants in the oldest age category were more likely to have multiple comorbidities than younger participants.

4.8 Regression Model Correlations with Study Variables

The analysis supported that *age* was significantly correlated with *disease progression* (r = -.12, p = .040) and *toxicity* (r = .23, p < .001), but not *response to treatment* (r = -.03, p = .594). As age increased, there was less *disease progression*, but more *toxicity* experienced. *Number of treatments* was significantly correlated with *response to treatment* (r = .63, p < .001), *disease progression* (r = -.42, p < .001) and toxicity (r = -.20, p < .001). With an increasing number of treatments, there was more response to treatment, less disease progression, and less toxicity.

While *number of comorbidities* were not significantly correlated with any key outcomes (all p > .05), *cardiovascular comorbidity* was significantly correlated with *response to treatment* (r = -.13, p = .026), *disease progression* (r = .13, p = .020) but not *toxicity* (r = .04, p = .477). The presence of cardiovascular comorbidity was related to a decreased response to treatment and increased disease progression. *Diabetes comorbidity* is not significantly correlated with any key outcomes (all p > .05). Finally, *cancer comorbidity* is also not significantly correlated to response with any key outcomes (all p > .05).

Results of the regression model are shown in Table 11.

Table 11

Regression Model Correlations with Study Variables

Variables	1	2	3	4	5	6	7	8	9
1. Age	--								
2. Number of Treatments	-.07	--							
3. Number of Comorbidities	.40**	-.16**	--						
Comorbidities:									
4. Cardiovascular	.43**	-.13*	.65**	--					
5. Diabetes	.07	-.16**	.29**	.05	--				
6. Cancer	.07	-.04	.12*	-.06	.08	--			
Key Outcomes:									
7. Response to Treatment	-.03	.63**	-.07	-.13*	-.12*	-.04	--		
8. Disease Progression	-.12*	-.42**	.02	.13*	.10	-.03	-.66**	--	
9. Toxicity	.23**	-.20**	.05	.04	.07	-.03	-.32**	-.39**	--

N = 300, *p < .05, ** p < .01

4.9 **Binary Logistic Regression Analyses with Study Variables**

Model 1 looked at the outcome of *response to treatment*. Results showed that both the *number of treatments* (β = .13(.01), p < .001) and *number of comorbidities* (β = .30(.15), p = .040) are significantly related. This was the most significant for *cardiovascular comorbidity* (β = -1.1(.48), p < .023). Overall, model 1 is significant and accounts for sizeable variance (37.1%). A patient is more likely to respond successfully to pembrolizumab the greater the number of cycles. While *number of comorbidities* is positively related, this is distinct from the correlation which is non-significant and is likely a spurious effect. Patients with a *cardiovascular comorbidity* are less likely to respond to treatment.

Model 2 looked at the outcome of *disease progression*. Multiple variables were significantly related including patient *age* (β = -.61(.18), p < .001), *number of treatments* (β = -.08(.01), p < .001) and *number of comorbidities* (β = -.28(.13), p = .031). Again, specifically *cardiovascular comorbidity* was significantly related (β = 1.36(.38), p < .001). Model 2 is significant and accounts for sizeable variance (23.6%). A patient is less likely to have *disease progression* with a greater number of treatments which aligns with response to treatment in Model 1. Older patients are less likely to have *disease progression*. Again, *number of comorbidities* is significantly related, but again, this is distinct from the correlation which is non-significant and is similarly a spurious effect like model 1. Patients with a *cardiovascular comorbidity* are more likely to have *disease progression*, indicating it is an important comorbidity to be aware of.

Finally, model 3 looked at the outcome of *toxicity*. Patient *age* (β = .96(.24), p < .001) was significantly related to *toxicity* while *number of treatments* was significantly, but inversely related (β = -.05(.02), p = .003).. However,, *number of comorbidities* or specific comorbidities are not significantly related (all p > .05). The model is significant but accounts for only a modest amount of variance (10.7%). Patients of greater age are more likely to experience toxicity while a lesser number of treatments is related to a lower chance of experiencing toxicity.

Results of the binary logistic regression analyses are shown in Table 12.

Table 12

Binary Logistic Regression Analyses With Study Variables

	Response to treatment			Disease progression			Toxicity		
	β	SE	P	β	SE	P	β	SE	P
Constant	-2.2	.72	.003**	2.30	.62	<.001***	-4.23	.88	<.001***
Gender	-.37	.36	.312	-.11	.29	.700	.37	.37	.315
Age Bands	.08	.22	.717	-.61	.18	<.001***	.96	.24	<.001***
DHB	-.21	.17	.224	-.02	.14	.870	.22	.17	.190
Number of Treatments	.13	.01	<.001***	-.08	.01	<.001***	-.05	.02	.003**
Number of Comorbidities	.30	.15	.040*	-.28	.13	.031	-.04	.15	.811
Comorbidities									
Cardiovascular	-1.1	.48	.023*	1.36	.38	<.001***	-.41	.46	.381
Diabetes	-.62	.72	.387	.65	.51	.198	.21	.59	.714
Cancer	-.62	.72	.352	.01	.59	.986	-.71	.83	.386
-2 Log likelihood	249	.484	.001	331	.145	<.001	226	.399	<.001
Cox & Snell R squared		.371			.236			.107	

*p < .05, **p < .01, ***p < .001

4.10 **Summary**

This chapter covered the findings of the research study as it related to the key variables, three main comorbidities studied and key outcomes of the pembrolizumab treatment. While there was no difference between the age bands for number of treatments and response to treatment, the youngest age group (50 years and under) had a significantly high risk for disease progression while the oldest age group (81 years and older) had the least risk. There was no difference demonstrated in the number of treatments, response to treatment, disease progression and toxicity experienced when relating to district health board (DHB) and gender. The number of comorbidities and presence of cardiovascular comorbidities were highest in the oldest age group and lowest in the youngest age group. There was no difference in age bands for diabetes and cancer comorbidities. There was also no significant difference in the number of comorbidities, cardiovascular, diabetes and cancer comorbidity across DHB and gender.

Chapter 5 Discussion

This chapter will critically discuss the results of the study. It will fulfil the primary objective of this research which was to evaluate how treatment outcomes (response to treatment, disease progression and toxicity) experienced by the older old adults (81 years and older) receiving pembrolizumab, compare with the treatment outcomes experienced by i) patients aged 66-80 years and ii) patients aged 51-65 years old and iii) patients aged 50 years and younger. The influence of a patient's gender, local district health board (DHB) and comorbidities will also be compared across the patient population. The strengths and limitations of this research will be covered and end with a conclusion.

5.1 Response to Treatment

This study showed that 35% of the patient population had a response to treatment, defined as having stable disease, a partial or complete tumour response. Similarly, anti-PD-1 immunotherapy studies completed by Ben-Betzalel et al. (2019) and Johnpulle et al. (2016) also had a 35-45% response rate. The Keynote-002 and Keynote-006 showed a 21-25% and 33-34% overall response respectively (Medsafe, 2021). Our data also showed a significant relationship between the number of treatments received and whether the patient will have a tumour response or disease progression. A patient is more likely to respond successfully to pembrolizumab with increased cycles. This indicates that persistence with treatment is favourable to have an improved treatment outcome. However, the number of pembrolizumab cycles are affected by radiology imaging results and toxicity experienced by the patient.

Our results showed that pembrolizumab can induce a tumour response in patients regardless of age. Patients older than 81 were not disadvantaged by their chronological age. Other studies have similar results in that age does not influence the effectiveness of treatment (Perier-Muzet et al., 2018; Ranaweera, 2018). According to Kugel et al. (2018), the likelihood of a tumour response increases with age. The results showed that 52% of patients below 62 years of age failed to respond compared to 37% of those greater than 62 years. Jain et al. (2020) conducted a retrospective audit with 4102 patients and found that those 60 years and older had a more significant survival benefit than those under 60 years. This remained consistent with a propensity score-weighted and sensitivity analysis with age stratification of 55, 65 and 70 years.

Like Kugel et al. (2018), we were surprised that the oldest patient age band had better outcomes than their younger counterparts. This is because older adults have inferior prognoses due to a higher Breslow thickness and aggressive melanoma (Chanala et al., 2019; Cybulska-Stopa et al., 2019; Johnpulle et al., 2016). There is also the natural process of immunosenescence which is a global immune system decline as people age (Perier-Muzet et al., 2018). Our results showed that the oldest patient age (81 years and older) band had the lowest percentage (29%) of patients

with disease progression, while the youngest patient age group (50 years and under) had the highest percentage of 43%. This pattern of 'older' old adults having an advantage was similar to a study conducted by Kugel et al. (2018). Their study found that the odds ratio for disease progression decreased by 13% for every decade of a patient's age, independent of gender.

This phenomenon is surprising as people generally gain comorbidities and experience a natural decline in their biological, physiological, and immune systems as they age (Fox et al., 2020; Hamilton & Henry, 2020). However, older adults also have increased chronic inflammation, which suggests increased immune function (Kugel et al., 2018). Johnpulle et al. (2016) and Perier-Muzet et al. (2018) found that older adults (greater than 80 years old) demonstrated an enhanced response to anti-PD-1 therapy. This was possibly due to the imbalanced immune system between the native and adaptive systems found in older adults, favouring anti-tumour activity and providing resilience against disease progression. It is also theorised that the increasing dominance of the PD-1 mediator immune senescence mechanisms of older adults could make patients more amenable to PD-1 blockade and therefore have better treatment outcomes (Ben-Betzalel et al., 2019; Hamilton & Henry, 2020).

Maggiorani and Beauséjour (2021) found that ageing and cellular senescence modifies the tumour microenvironment (TME) with an accumulation of immunosuppressive cells. Kugel et al. (2018) found regulatory T cells (Tregs) were decreased and CD8+ T cells were increased within the TME of older adults, and this enhanced their response to pembrolizumab. Perier-Muzet et al. (2018) did not evaluate the underlying mechanisms for why older adults fared better than their younger counterparts. However, they hypothesised the age-related changes of high levels of Il-2 soluble receptors at baseline, high levels of myeloid-derived suppressor cells, low neutrophil count, high PD-L1 expression by the tumour, high PD1 expression on CD8-positive T cells and CD8-positive T-cell tumour infiltration had an influence. It is also speculated that older adults' reduced immune cell fitness is compensated by the compounding reduced growth rate of tumours (Maggiorani & Beauséjour, 2021).

Another theory relates to the differences in gut microbiota composition between young and older hosts, with more pro-inflammatory bacteria found in older adults. These increase the lipopolysaccharide (LPS) level, eliciting a robust immune response which could explain improved treatment efficacy (Machiraju et al., 2021). A study by Gopalakrishnan et al. (2018) demonstrated the importance of the microbiome on response to PD-1 immunotherapy for melanoma patients. Their results showed significant differences in the oral and gut microbiome between responders versus non-responders to treatment. Greater alpha diversity and relative abundance of Ruminococcaceae bacteria were observed in responders. In this study, the age of patients in both the non-responder and responder groups were similar (Gopalakrishnan et al., 2018).

This finding could also be attributed to a higher resilience level in older adults than their younger counterparts. Resilience is an individual's ability to maintain or restore stable psychological and physical functioning (Seiler & Jenewein, 2019) despite health setbacks such as cancer. It is a multi-dimensional concept that is affected by biological factors, individual personal factors (baseline physical and mental health) and environmental factors, particularly social support (Duan-Porter et al., 2016; MacLeod et al., 2016; Seiler & Jenewein, 2019). This adaptive capacity allows individuals to maintain independent functioning and achieve good well-being. The review conducted by MacLeod et al. (2016) of existing literature showed that adults with high resilience had adaptive coping styles, optimism, social support, community involvement, ADL independence, and were physically active.

Specifically, physical resilience is defined as resistance to decline in physical function or regain of lost function after a decline (Duan-Porter et al., 2016). Though it is assumed that resilience weakens with age, other studies have shown increased resilience with older age (Seiler & Jenewein, 2019). A study by Duan-Porter et al. (2016) showed that most older cancer survivors (65 years and older) had high physical resilience despite being at-risk. The mean age of patients included was 73.1 years, and (89.1%) of the study population were Caucasian, similar to this study's demographic. Older adults (85 years and older) have also demonstrated an equal or greater capacity for resilience compared to their younger counterparts (MacLeod et al., 2016). This infers that older old adults can still have positive treatment outcomes, reduced mortality, and increased longevity (MacLeod et al., 2016; Seiler & Jenewein, 2019) despite their age.

5.2 **Toxicity**

This study showed 16% of patients experienced toxicities and therefore had to stop treatment. Serious adverse events are relatively uncommon with pembrolizumab, and clinically severe toxicities (CTCAE Grade 3-4) occur in only 10-15% of patients (Ben-Betzalel et al., 2019; Johnpulle et al., 2016). According to Joshi et al. (2020), toxicity is an indirect marker for the efficacy of immunotherapy. In their study, overall immune related adverse events (irAEs) occurred in 66.7% of responders to treatment versus 40% of non-responders. This included adverse events of all severities, regardless of the patient's age.

There was a significant difference across the age bands in this study concerning toxicity, with those aged 81 years and older experiencing a 35% chance of toxicity. This was much lower in all other age groups: 50 years and under (4% chance), 51-65 years (10% chance), and 66-80 years group (15% chance). The chance of toxicity was significantly worse only for the oldest age group of patients, with no difference by patient gender or the DHB they attended.

Chanala et al. (2019) showed a tumour response from pembrolizumab for older adults, but this was associated with high-risk toxicity and impaired autonomy. However, their study only included nine patients older than 85 years, seven of whom experienced Grade 3 or Grade 4

adverse events (Chanala et al., 2019). The researchers did not rationalise why they received the results they did. A theory exists that adverse effects occur more often and with greater severity in patients greater than 80 years old with comorbidities (Rai et al., 2021). These comorbidities are associated with polypharmacy, possible organ dysfunction and decreased organ reserve (Cybulska-Stopa et al., 2021; Fox et al., 2020; Godby et al., 2019; Johnpulle et al., 2016), which could affect the patient outcome negatively.

This contradicts other studies that showed pembrolizumab is a safe treatment option for older adults. According to Ranaweera (2018), no differences are seen in the safety profile. This is supported by research carried out by Ben-Betzalel et al. (2019), Cybulska-Stopa et al. (2019), Cybulska-Stopa et al. (2021) and Fox et al. (2020), who looked at the patient groups above 65-75 years old and showed a mild toxicity profile. This could be because a patient's chronological age does not accurately reflect their physiological age. The complex interplay of genetics, lifestyle, and pathogenic exposures can cause individuals' immune systems to decline at varying ages (Wong et al., 2021). Perier-Muzet et al. (2018) also found that older patients did not have a higher incidence of irAE or suffer from more severe (grade) adverse events compared to their younger counterparts. However, their study included patients that received a range of immunotherapy treatments, including ipilimumab, nivolumab and pembrolizumab.

Ben-Betzalel et al. (2019) found that their older old adult group (80-100 years old) developed toxicities significantly earlier compared to their other group (65-79 years old). It is believed to be related to the quicker response dynamics of immune activation within older adults due to senescence mechanisms. Overall, it is suggested that the toxicity incidence is likely similar across age ranges (Hamilton & Henry, 2020), but the recovery may be more challenging in older patients with limited functional status (Godby et al., 2019). The risk-to-benefit assessment of this treatment suggests pembrolizumab is a viable treatment option for the older adult population; however, to be aware that those older than 81 years may have an increased risk for toxicity.

5.3 **Comorbidity**

Our results demonstrated a significant difference across the age bands in comorbidities, with the highest number of comorbidities noted for those aged 81 years and older. This is not surprising with the knowledge that there is an increase in chronic diseases and conditions as patients get older. However, due to early diagnosis and improved medical care, patients are now living longer and experiencing less disability from these comorbidities (Christensen et al., 2008). There are no differences in comorbidity dependent on the DHB that patients attended, suggesting that the deprivation score of each DHB did not have an impact.

This study showed that males possessed a higher number of comorbidities than females. Most research into gender differentials has concluded that this is because men engage in riskier health

behaviours such as heavy drinking and smoking (Crimmins et al., 2010). However, the differences between men and women result from the complex interplay of biological, social, and behavioural factors and are difficult to quantify (Crimmins et al., 2010).

A misconception exists that cardiovascular disease is predominantly a male disease. However, a breadth of research demonstrates the female burden and evaluates the gender differences in the morbidity and mortality of cardiovascular disease (Bots et al., 2017; Gao et al., 2019; Singh-Manoux et al., 2008). Overall, it is a complex topic to address due to the range of cardiovascular diseases, e.g., coronary heart disease, stroke, and heart failure, as well as factors such as genetic, hormonal, social and cultural influences (Gao et al., 2019; Singh-Manoux et al., 2008). It is beyond the scope of this study to address this gender-related variable. However, our research showed no differences in cardiovascular comorbidity by patient gender or the DHB they attended.

In this current study, 40% of patients had cardiovascular comorbidity. This high percentage is not surprising as the incidence of cardiovascular disease has risen significantly over time (Christensen et al., 2009). The highest incidence of cardiovascular comorbidity was for those aged 81 years and older (67%) and those aged 66-80 years (52%). Both these groups were significantly higher than those aged 51-65 years (18%) and the 50 years and under group (4% chance). This shows that cardiovascular comorbidity occurs more numerously as people age. This was evidenced in Ben-Betzalel et al.'s (2019) study with more cardiovascular comorbidities for their older old adult group (80-100 years old) with ischaemic heart disease and arrhythmias compared to those 65-79 years old.

There is concern of worsening a patient's multi-morbidities while treating their melanoma (Rai et al., 2021). This is especially the case for patients who suffer from an irAE and will require high-dose corticosteroids to treat them (Cybulska-Stopa et al., 2021; Foo et al., 2020; Godby et al., 2019). Possible side effects of steroid treatment include hyperglycaemia, delirium, arrhythmia, and infection (Wong et al., 2021) which will increase the morbidity burden of patients (Foo et al., 2020).

5.4 **Patient Demographics**

This study demonstrated that treatment was uniform across patients' gender, age, and the DHB attended. Therefore, pembrolizumab treatment is valuable regardless of gender, age, or deprivation code (as related to DHB).

The demographic breakdown of this cohort was comparable to existing data in New Zealand. In 2018, 56% of men were diagnosed with melanoma versus 44% of women (Ministry of Health, 2018). This was slightly lower than the 66% of men in our study and might reflect the different gender composition of other cities in New Zealand. The registration rate for melanoma has

always been higher for males than females over the past 19 years (Environmental Health Intelligence New Zealand (EHINZ), 2021). A large body of literature exists which reflects that it is predominantly men being diagnosed with melanoma (Berwick et al., 2016; Johnpulle et al., 2016; Rastrelli et al., 2014).

In 2019, almost all (96%) melanoma cancer registrations were for European/Other ethnicity patients. A small number of registrations were for Maori (70 cases), Pacific people (six cases) and Asian (seven cases) people (EHINZ, 2021). This is comparable to the 93% of patients in this study that identified as New Zealand European or Other European. This supports the existing literature that states it is predominantly Europeans diagnosed with melanoma (Berwick et al., 2016; Rastrelli et al., 2014; Sneyd & Cox, 2013).

The complete cohort of patients and their aggregated data were divided into quartiles. The defined groups used were 50 years and under, 51-65 years, 66-80 years, and 81 years of age and above. This is comparable to the study conducted by Cybulska-Stopa et al. (2021), who used three age groups under 65, 65-79 years, and 80-100 years old. As 39% of our study population were under 65 years of age, a fourth age group was created to disperse the bulk of this data. Therefore, we could gain greater insight into the differences between those aged 50 and under versus 51-65 years old. We analysed if there were any differences in the variables between the four age groups and compared the impact (Gillis & Jackson, 2002) of pembrolizumab across this patient population.

5.5 **Strengths**

New Zealand has a high incidence of melanoma, with an incidence of 35.5 people per 100,000 population being diagnosed in 2019 (Ministry of Health, 2021). Therefore, this study gives cross-sectional data on a large group of patients who have received pembrolizumab. The research results from this sample could be used to generalise the total patient population receiving pembrolizumab treatment in New Zealand and globally.

The inclusion of older old adults into this study- a demographic group that usually do not qualify for clinical trials and are typically underrepresented in research, allows a greater understanding of their treatment outcomes. New and valuable insights can be gained through the involvement of this age group in research to guide future treatment. It is another strength of this study that there were a good number of older adults included with131 patients (44%) between 65-80 years and 52 patients (17%) over 81 years old. As a result, the results of this study are more reflective of the growing older adult population in New Zealand.

5.6 **Limitations**

Several limitation*s exist* in this study that should be considered when interpreting the findings. Information on several vital variables were not available in our data set. For example, the

baseline tumour size was not collected for everyone, i.e., Stage 3 versus Stage 4 melanoma. We also did not record if there were brain metastases present which could affect outcomes. In addition, we did not record if pembrolizumab was the first-line treatment; this means we do not have a complete picture of what the patient received prior to these infusions. For example, if they received privately funded treatment such as MEK inhibitor or BRAF inhibitor therapy. We also did not record intermittent other treatment received during the pembrolizumab course, which may have included surgery or radiation therapy. These would all have an impact on a patient's overall tumour response.

Furthermore, biological blood characteristics such as lactate dehydrogenase (LDH) level and the patient's Eastern Cooperative Oncology Group performance status (ECOG PS) were not recorded. Both are considered prognostic survival indicators (Joseph et al., 2018; Liu et al., 2019). However, the quantity of data that corresponds to both variables were beyond this research study.

Another limitation was the unequal groups of participants across the age bands. The bulk of patients in the study were between 51-65 years (90 patients) and 66-80 years (131 patients) compared with the other patient groups of 50 years and under (27 patients) and patients 81 years and older (52 patients). To mitigate this, we could have split up our study population across more age stratifications for a better spread of the patients. We used the specific age ranges for reasons explained previously: to capture the older old, those before and after the retirement age in New Zealand of 65 years, and those under 50 years of age.

Some patient data points were missing, such as the tumour response to treatment. These points were missing as oncologists were not always entering this information when writing their clinic letters. Specifically, we are unsure if the patient had stable disease, partial or complete response by the end of their treatment course and therefore grouped all three of these tumour responses into one category.

5.7 Recommendations for Future Research

There is excellent potential to expand on this preliminary study and research other relevant variables to gain more information. This includes those previously mentioned in the limitations section, such as baseline tumour size, sites of metastasis, prior lines of therapy received, LDH level (elevated or normal serum level) and ECOG PS. These prognostic factors could provide a greater understanding of their influence on the treatment outcomes for patients across all age groups.

Melanoma characteristics such as the primary site of disease, PD-L1 positivity status and mutational status for BRAF were not included as the complexity of these genes and proteins

were beyond the scope of this study. However, it would be interesting to see how much of an influence these underlying genes and proteins played in treatment outcomes.

It is essential to acknowledge the possible limitations of radiologic imaging reviewed by multiple radiologists for different patients over a long period of time. The risk exists that different interpretations of tumour response for patients may exist. A possible future study involves using a single radiologist who could examine all the imaging throughout a patient's treatment duration to ensure consistency. This would not be easy to achieve in a typical hospital setting due to staff rosters and rotating professionals in the department.

A quantitative study was used to observe the outcomes experienced by metastatic and unresectable melanoma patients that have completed their pembrolizumab treatment. However, a qualitative format could be used to gain insight into a patient's perspective of how they tolerate treatment and what they gain from receiving it. This could be done through regular questionnaires that ask about treatment access, their quality of life and side effects. Alternatively, interviews could be conducted with a small group of patients about their personal experience of their treatment course. This would provide a qualitative dimension to the outcome of pembrolizumab not able to be captured by statistical modelling.

Evaluating the impact of Covid-19 was considered. However, because treatment can span over a long period, it was challenging to track treatment for those that started prior to 2019 and those after 2021. It would be interesting to see if COVID-19 impacted patient access to treatment and their tumour response. This could be quantitatively measured and compared against other years before the coronavirus pandemic to see if there were any differences.

A future research project could also be to conduct a cost analysis of the overall treatment. This involves a projection of the estimated costs associated with the average patient's pembrolizumab treatment compared with the benefits gained by patients. Possible indicators of a positive impact could include the measurement of tumour response.

Finally, the delayed treatments (due to side effects) or time between treatments warrant further investigation for patients. Important information could be gained if a particular age group experienced these deferred treatments more and how it affected their overall treatment course. This finding would be relevant to clinical practice to be more aware of potential side effects that cause treatment deferrals and how to better manage them.

5.8 **Conclusion**

This quantitative study provided a snapshot of patients had received pembrolizumab for their unresectable or metastatic melanoma in Auckland between January 2017 and June 2021. We ran multiple statistical analyses to answer several key questions posed. These were to compare the

tumour response or disease progression experienced by patients over four age cohorts of: 50 years and younger, 51-65 years, 66-80 years, and 81 years and older. The incidence of toxicities, influence of comorbidities and district health board (DHB) were also evaluated.

The stratification of patients by age demonstrated that there was no significant relationship between age and response to treatment. Older old adults (81 years and older) can benefit as much as their younger cohorts to achieve stable disease, a partial response or complete response of their melanoma. They are also the least likely to suffer from disease progression than those patients under 50 years of age. Therefore, age is not an exclusion criterion for pembrolizumab, and the older age may provide an advantage to those patients. However, the older old adults are the most likely to experience toxicities compared to their younger counterparts. Through close monitoring and timely management of toxicities, pembrolizumab can be a safe and effective treatment for the older old adults.

Though ethnicity was collected, it was unable to be analysed as there was no variance. Gender and DHB were not significantly related, and neither was diabetes or other cancer comorbidities. The presence of a cardiovascular comorbidity decreased the likelihood of responding to treatment and increased the likelihood of disease progression. Therefore, making it an important comorbidity to be mindful of.

Through the inclusion of older old adults within the study, we have demonstrated the relevance of pembrolizumab as a viable treatment for this population. Future clinical trials should make it a priority to enrol and study the outcomes of older adults over the age of 80 years instead of excluding them due to their comorbidities and polypharmacy. Therefore, the reported outcomes can inform complex, bedside decision-making between providers and older old patients.

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Appendix A Melanoma Patient Breakdown in 2018 by District Health Board

District Health Board	Male	Female	Total
Northland	58	39	97
Waitemata	243	154	397
Auckland	151	104	255
Counties Manukau	109	96	205
Waikato	123	124	247
Lakes	34	21	55
Bay of Plenty	97	81	178
Tairāwhiti	11	15	26
Hawke's Bay	65	25	90
Taranaki	63	63	126
MidCentral	48	38	86
Whanganui	22	16	38
Capital & Coast	86	75	161
Hutt Valley	32	31	63
Wairarapa	19	10	29
Nelson Marlborough	67	50	117
West Coast	7	5	12
Canterbury	179	129	308
South Canterbury	18	22	40
Southern	106	99	205

(Ministry of Health, 2018)

Appendix B Data Management Plan

1.	
a. Project title	A comparison of treatment health outcomes experienced by melanoma patients from various three age groups cohorts receiving pembrolizumab immunotherapy in a COVID 19 year (2020)
b. ID	
c. Grant reference number	NA
d. Ethics approval Number	Ethics Application:21/96
e. PI Name(s)	Name of Principal Investigator: Rebecca Mowat (Primary supervisor) Name of Master's Student: Kathy Lee
f. RDMP author name	Rebecca.marie.mowat@aut.ac.nz
g. School / Department	Auckland university of Technology, School of Environmental Sciences
h. Project start & end dates	This research will start May 2021 and end August 2021
i. Project description	This study is a retrospective cohort study using prospectively collected data. Retrospective data will be obtained from all patients who have received Pembrolizumab from Auckland Hospital (excluding those under 18 years of age). Patient demographic data collected includes patient age, gender, ethnicity, number of cycles of Pembrolizumab completed, local district health board (DHB), postcode and reasons for discontinuing treatment (if applicable).
j. Related policies & guidelines	This study has approval from ADHB (Auckland Hospital) and the hospital is aware Kathy (the student researcher) will be retrieving the data (see approval on ADHB connected to Ethics). Initially Kathy will be provided with a database of relevant patients (those who received Pembrolizumab treatment in 2020) from which she will then retrieve more in-depth information than is currently provided. Additional data to be retrieved includes Level 1 ethnicity and reason for incompletion of treatment. The ADHB provided datasheet is all information that Kathy would normally have access to in her role as a senior registered nurse undertaking an audit in the ADHB oncology service. Kathy will assign the patients with a participant ID number (based on their line in the datasheet). This updated ADHB datasheet becomes spreadsheet V1. An anonymised pivot table of data will then be created as a new spreadsheet-V2 (section 2). This is where the deidentification process begins as only the participant study ID, gender, age -range, postcode, DHB, and completion/reason for incompletion are included in spreadsheet V2 (see example of attached Excel spreadsheet). Spreadsheet V2 will be sent to an independent staff member not from the research team for checking of deidentification. To ensure further anonymity during analysis, the already deidentified data will be re-shuffled into spreadsheet V3 so the order of participants is completely different to the original spreadsheets. The nominated staff member to undertake this process is Dr Michelle Wilson at the ADHB.

	Once the shuffled and deidentified spreadsheet V3 is finalsed, Kathy will no longer have access to identifying data on these participants. All data will be stored on a computer on ADHB premises with a code that only the researcher can access via a secured password. Kathy has a signed confidentiality agreement.

2. Developing your RDMP (about your data)		
a.	*Data types*	Patient data will be made available to Kathy initially with NHI numbers and age of patients who attended treatment cycles of Pembrolizumab in 2020. The researcher will then access the individual files to obtain the following information regarding the patient: 1a) age ≥ 80 years 1b) 65- 79 years 1c) Patients aged < 65 years). 2: Ethnicity of the patient, 3: Gender of the patient 4: Post code, 5: DHB usually attends, 6) Number of cycles completed, and if dropped out why? 6a) Due to adverse effects=1 6b) Death=2 6c) Did Not Attend/no show =3 6d) Other=4 This will be systematically entered a excel spreadsheet under a new patient code of numerical numbering from 1-180.
b.	*File formats*	***Resources*** As future access and reuse of data may be affected by proprietary formats, it is advisable to use open formats such as Rich Text Format (RTF) or Open Document Format (ODF) for preservation purposes. We will check and make sure that this is the case.
c.	*Organisation*	An excel folder will be created by the primary researcher that is labelled "Pembrolizumab cycle research" see attachment with the data dictionary. Only one excel spreadsheet (V3) is needed as a file. Kathy will log in with her staff ID login and then access a personal storage space that she has access to along with the collective shared DHB folders. And will save the work in progress on an excel spreadsheet in her personal storage space/ my documents. In the department, there is an Oncology Outpatients Nurses folder that only nurses who work in that department can access. Kathy will store her password-protected excel file here in a separate folder (when the file is no longer being worked on/ completed data collection). The files will be Backed upon the local drive of the computer with the password code.

5.9

3. Ethics and Legal Issues	
a. Ethics and Legal	Because all patients will be placed into general age category i.e. a patient that is 103 of age will be categorised (>/= 80) this will make identification difficult. See Section 1j regarding the creation of deidentified spreadsheet V3. This research is transparent and has been permitted through the research department at ADHB and the AUTEC committee at AUT.
b. Copyright and IP	This data is copyright of the Auckland DHB and any research published will acknowledge the Auckland DHB.
c. Cultural	See Ethics application

4. Access, confidentiality and security	
a. Secure storage and backup	Back up will be done frequently and storage will on the hospital computer. This will be made available to the ADHB so that more research can be done if they should require.
b. Access, confidentiality and security	As this data is confidential to Kathy who has signed a confidentiality agreement, she is the only researcher that will have access to the original datasheet in the data collation phase. Once this data is de-identified, Kathy will share the data collected with one of the hospital service consultants, Dr Michelle Wilson. See section 1j. **This research is secondary retrospective data -** This is pre-existing data that has already been collected as part of hospital protocol. This data is an audit of completion of cycles related to age and gender at ADHB. This information in available to anyone who has password access to the files. • Although anyone with a password can find this data, Kathy's specific data will be kept on a file on a computer at the hospital (see section 1j). This data management plan will be shared with the facility Kathy is working with. As the data may be of benefit for future audits.

5. Documenting and Describing your Data/ Data dictionary	
a. Documentation	**Age** 1a) age ≥ 80 years

	1b) 65- 79 years 1c) Patients aged < 65 years). **The statistics identification of ethnicity will be used Ministry of Health Level 1 ethnic codes** **Ethnic Group code description** 1 European 2 Maori 3 Pacific Peoples 4 Asian 5 Middle Eastern/Latin American/African 6 Other Ethnicity 9 Residual Categories **Post code** This will likely to be many patients in the Auckland catchment but there will be patients form many parts of New Zealand. This will also tell us about deprivation areas and potentially how transport can impact on access to treatment**.**

6. Sharing and Preserving your Data	
a. Sharing	As the data will be the property of ADHB and be used for auditing purpose, the data once it is de identified will be accessible to relevant ADHB with authority to use this datasheet. It will also be viewed by Kathy's supervisors only outside of the ADHB and this is for student supervision purposes.
b. Restrictions	No.

Appendix C Approval from Auckland University of Technology Ethics Committee (AUTEC)

5 July 2021

Rebecca Mowat
Faculty of Health and Environmental Sciences
Dear Rebecca

Re Ethics Application: **21/96 The health outcomes experienced by various age groups of melanoma patients receiving Pembrolizumab in a Covid year (2020)**

Thank you for providing evidence as requested, which satisfies the points raised by the Auckland University of Technology Ethics Committee (AUTEC).

Your ethics application has been approved for three years until 2 July 2024.

Standard Conditions of Approval

1. The research is to be undertaken in accordance with the Auckland University of Technology Code of Conduct for Research and as approved by AUTEC in this application.
2. A progress report is due annually on the anniversary of the approval date, using the EA2 form.
3. A final report is due at the expiration of the approval period, or, upon completion of project, using the EA3 form.
4. Any amendments to the project must be approved by AUTEC prior to being implemented. Amendments can be requested using the EA2 form.
5. Any serious or unexpected adverse events must be reported to AUTEC Secretariat as a matter of priority.
6. Any unforeseen events that might affect continued ethical acceptability of the project should also be reported to the AUTEC Secretariat as a matter of priority.
7. It is your responsibility to ensure that the spelling and grammar of documents being provided to participants or external organisations is of a high standard and that all the dates on the documents are updated.

AUTEC grants ethical approval only. You are responsible for obtaining management approval for access for your research from any institution or organisation at which your research is being conducted and you need to meet all ethical, legal, public health, and locality obligations or requirements for the jurisdictions in which the research is being undertaken.

Please quote the application number and title on all future correspondence related to this project. For any enquiries please contact ethics@aut.ac.nz. The forms mentioned above are available online through http://www.aut.ac.nz/research/researchethics

The AUTEC Secretariat
Auckland University of Technology Ethics Committee

Appendix D Auckland District Health Board (ADHB) Confidentiality of Information

Careers Centre

HR HUMAN RESOURCES

Confidentiality Of Information

Your attention is drawn to the obligations of ADHB as set out in the Privacy Act 1993, the Privacy Code of Practice 1993 and Health Amendment Act No. 2 1993. As a contractor or agency employee, you are required to comply with these Acts and Codes.

The individual named below shall not disclose to any person information concerning the condition or medical history, treatment or other details of any patient who is receiving, or has received services provided by the ADHB, whether or not the patient is in hospital. The exception to this is where staff are specifically authorised by legislation or are entitled to the information because of their job.

The individual shall not at any time during or after their term of engagement discuss or disclose information, processes, materials, costs or secrets relating to any aspect of the ADHB to any person without the ADHB's express agreement, except as is required in the performance of their duties.

In addition, on termination of their term of engagement, any ADHB information held in writing or on computer storage format must be returned to the ADHB.

Any breach of these provisions shall be considered as grounds for legal action against the individual and/or agency concerned.

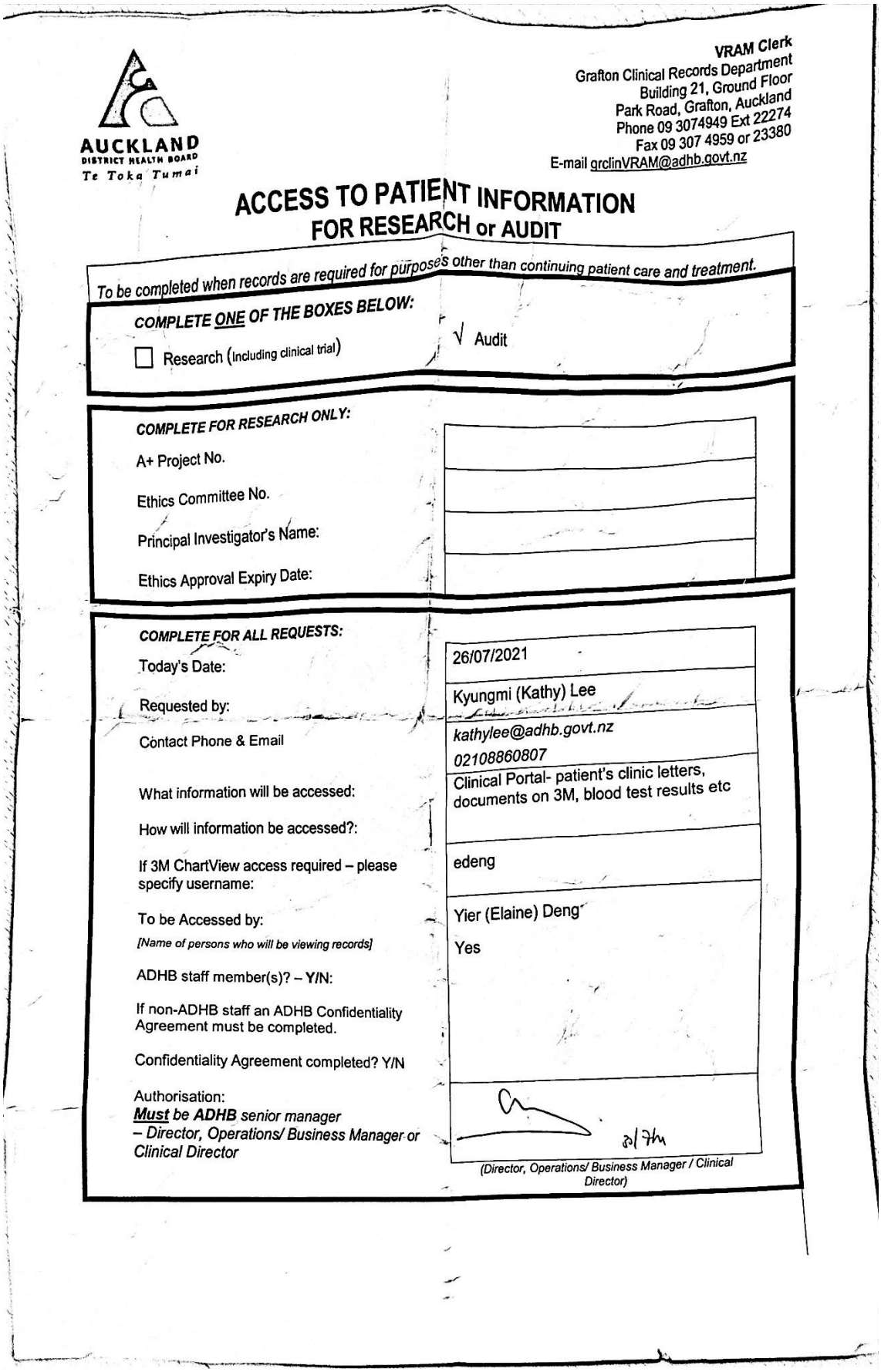
Please note that a witness must sight and sign below to verify that you read this form

Acceptance		
Printed name	Signature	Date
Kyungmi (Kathy) Lee		3/5/2021
Printed name	Witness Signature	Date
L M Wilson CN		12/05/21

Date Updated: 09/08/05
Home Page

AUCKLAND DISTRICT HEALTH BOARD Te Toka Tumai

Appendix E Auckland District Health Board (ADHB) Access to Patient Information



AUCKLAND DISTRICT HEALTH BOARD
Te Toka Tumai

VRAM Clerk
Grafton Clinical Records Department
Building 21, Ground Floor
Park Road, Grafton, Auckland
Phone 09 3074949 Ext 22274
Fax 09 307 4959 or 23380
E-mail grclinVRAM@adhb.govt.nz

ACCESS TO PATIENT INFORMATION FOR RESEARCH or AUDIT

To be completed when records are required for purposes other than continuing patient care and treatment.

COMPLETE ONE OF THE BOXES BELOW:

☐ Research (Including clinical trial)

√ Audit

COMPLETE FOR RESEARCH ONLY:

A+ Project No.	
Ethics Committee No.	
Principal Investigator's Name:	
Ethics Approval Expiry Date:	

COMPLETE FOR ALL REQUESTS:

Today's Date:	26/07/2021
Requested by:	Kyungmi (Kathy) Lee
Contact Phone & Email	*kathylee@adhb.govt.nz* *02108860807*
What information will be accessed:	Clinical Portal- patient's clinic letters, documents on 3M, blood test results etc
How will information be accessed?:	
If 3M ChartView access required – please specify username:	edeng
To be Accessed by: *[Name of persons who will be viewing records]*	Yier (Elaine) Deng
ADHB staff member(s)? – Y/N:	Yes
If non-ADHB staff an ADHB Confidentiality Agreement must be completed.	
Confidentiality Agreement completed? Y/N	
Authorisation: ***Must** be **ADHB** senior manager – Director, Operations/ Business Manager or Clinical Director*	26/7/21 *(Director, Operations/ Business Manager / Clinical Director)*