University of Strathclyde Glasgow

Real-World Outcomes in Advanced Melanoma: The Impact of Immunotherapy and Targeted Therapy

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Date: 19/04/2025

Signed: Pedro Nuno Ferreira de Fontes

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- I did a thing! -

Jeremy Clarkson, Clarkson's Farm

Abstract

The increasing global life expectancy has brought about a surge in age-related diseases, notably cancer, as cells accumulate mutations over time. Melanoma has witnessed a rise in diagnoses, with advanced melanoma accounting for 90% of skin cancer-related deaths. Before 2010, treatment options were limited, leading to a poor prognosis. However, the introduction of systemic anti-cancer therapy in the form of immunotherapy and targeted therapy revolutionised the outcomes for metastatic melanoma patients.

This thesis focuses on the use of real-world evidence to explore the implications of systemic anti-cancer therapy for advanced melanoma patients. The research aims were reached through statistical and survival analysis techniques, including Kaplan-Meier estimates and Cox proportional-hazards models, to assess survival probabilities and analyse the impact of covariates on outcomes. Notably, time-dependency adjusted models were developed to explore the influence of body-mass index and therapy type on survival.

A continuous time multi-state Markov model is used to investigate the treatment routes of advanced melanoma patients. The focus shifts to patients undergoing treatment changes between immunotherapy and targeted therapy, with particular emphasis on patients with progressive disease. This model provides valuable insights into the active treatment pathways in a real-world setting.

A health economic evaluation is also introduced to this cohort, examining the cost-effectiveness of advanced melanoma treatments. Using a state transition model, the study includes outcomes such as quality-adjusted life years and incremental cost-utility ratios in the cost-effectiveness analysis. The economic model's robustness is tested through a probabilistic sensitivity analysis.

In conclusion, this thesis investigates the complexities of advanced melanoma treatments in a real-world setting. The findings contribute to a better understanding of treatment outcomes, paving the way for more informed clinical decisions and health policies in the ever-evolving landscape of cancer care.

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ACD	Appraisal consultation document
AIC	Akaike Information Criterion
AJCC	American Joint Committee on Cancer
ASR	Age-standardised rate
AWMSG	All Wales Medicines Strategy Group
BRAF	B-Raf oncogene
BMI	Body-mass index
CDF	Cancer Drug Fund
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CEAF	Cost-effectiveness acceptability frontier
CEPAS	Chemotherapy Electronic Prescribing and Administration System
CI	Confidence interval
CMOP	Cancer Medicines Outcomes Programme
CTLA-4	Cytotoxic T-lymphocyte-associated antigen 4
DAB	Dabrafenib
DABTRA	Dabrafenib plus trametinib
DHSSPS	Department of Health, Social Services and Public Safety
DNA	Deoxyribonucleic acid
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
ERK	Extracellular signal-regulated kinase
EU	European Union
FAD	Final appraisal document
FDA	Food and drug administration
GB	Great Britain
HR	Hazard ratio
HSC	Health and Social Care
HTA	Health technology assessment

ICUR	Incremental cost-utility ratio
ICI	Immune checkpoint inhibitor
ICTSTM	Individual continuous time state transition model
IPD	Individual patient-level data
IPI	Ipilimumab
IPINIVO	Ipilimumab + nivolumab
IQR	Interquartile range
irAE	Immune-related adverse events
LCL	Lower confidence level
LDH	Lactate dehydrogenase
LYs	Life years
KM	Kaplan-Meier
MAH	Marketing authorisation holder
MAPK	Mitogen-activated protein kinase
MEK	Mitogen-activated protein kinase kinase
MHRA	Medicines and Healthcare Products Regulatory Agency
MTA	Multiple technology appraisal
NA	Not applicable
NCT	National Clinical Trial
NDC	New Drugs Committee
NF1	Neurofibromin 1
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NIVO	Nivolumab
NPAF	New Product Assessment Form
NR	Not reached
OS	Overall survival
PACE	Patient and Clinician Engagement
PBPP	Public Benefit and Privacy Panel
PD-1	Programmed cell death 1
PEM	Pembrolizumab
PFS	Progression-free survival

PH	Proportional-hazards
PLGB	Product licence for Great Britain
PSA	Probabilistic sensitivity analysis
RR	Response rate
RCT	Randomised controlled trial
RTK	Receptor tyrosine kinase
QALYs	Quality-adjusted life years
SACT	Systemic anti-cancer therapy
SE	Standard error
SIMD	Scottish Index of Multiple Deprivation
SMC	Scottish Medicines Consortium
STA	Single technology appraisal
UCL	Upper confidence level
UV	Ultraviolet
UK	United Kingdom
VEM	Vemurafenib
WoSCAN	West of Scotland Cancer Network
WHO	World Health Organization
WTP	Willingness-to-pay

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Chapter 1 Introduction

1.1. Background on melanoma

As a result of better conditions, life expectancy is greater. However, the additional years lived lead to an increased risk of disease development such as cancer [1], [2]. As a person ages cells can suffer mutations due to toxic compounds, environmental factors, or inner cell mechanisms' malfunction. Cells can recover from these mutations but the ageing process reduces cells' ability to reverse them which results in the accumulation of mutations that can lead to cancer [1], [3].

Melanoma is a type of cancer that can develop without a major manifestation of symptoms leading to more advanced stages where cancer cells can spread to different locations by metastasising. This stage is called advanced, metastatic or unresectable melanoma [4]. Advanced melanoma is the deadliest form of skin cancer in the world accounting for 90% of all skin cancer-related deaths [5]. Despite the preventive campaigns and information to increase global awareness of this deadly disease, the number of diagnoses has increased at a global level over the last 50 years [2]. Prior to 2010, dacarbazine which is a chemotherapy medicine was the standard treatment for advanced melanoma. However, treatment with dacarbazine did not significantly affect outcomes and people diagnosed with advanced melanoma had a poor prognosis, with a median overall survival (OS) under 1-year usually between 6 to 9 months [5]. Since 2011 SACT with immunotherapy and targeted therapy has revolutionised cancer treatment for advanced melanoma [3], [5], [6]. With the new SACT treatments, 50% of patients reach an OS of 5 years despite having metastatic melanoma which was unrealistic with previous standard treatments [6], [7], [8], [9], [10].

The advances made in metastatic melanoma treatment come from treatment evaluations primarily conducted through clinical trials aimed at assessing the clinical safety and efficacy of novel therapeutic interventions such as immunotherapy and targeted therapy regimens. These trials typically employ randomised controlled designs to compare the outcomes of patients receiving the experimental treatment against those receiving standard of care or placebo. Examples of such trials include MDX010-20,

which evaluated ipilimumab, an immunotherapy regimen, with or without gp100, versus the gp100 peptide vaccine alone. In this clinical trial ipilimumab, alone or in combination, demonstrated improved OS in comparison with the gp100 peptide vaccine alone (NCT00094653) [11]. Similarly, for targeted therapy treatments, clinical trials such as BRIM 3 have assessed vemurafenib versus dacarbazine in previously untreated patients with *BRAF*-mutant metastatic melanoma, revealing improved progression-free and OS outcomes in comparison with chemotherapy (NCT01006980) [12].

These trials are conducted in a strict, controlled environment to decrease the risk of confounding variables that could compromise the treatment comparisons such as the presence of brain metastasis or difference in primary location of the tumour, ocular or mucosal instead of cutaneous melanoma [11]. Researchers follow a cohort of patients that fulfil the criteria to participate in the study and analyse the outcomes of the trial [13], [14]. Randomisation in clinical trials can ensure the balance between the control and treatment groups, ensuring they have similar distributions of baseline characteristics [13], [14].

Results from randomised clinical studies may not always fully translate to real-world practise as this population treated might include patients that would not fit the inclusion criteria to participate in the clinical trials for the clinicians proposed anti-cancer treatment. Reasoning for exclusion from such trials could be due to the presence of comorbidities, age, and/or a more severe degree of disease, leading to unexpected outcomes [13], [14].

Observational studies are another research tool that can provide additional information to clinical trials, such as testing hypothesis that could not be tested in a randomised clinical trial. An example of such hypothesis was the study from 1950 describing the association between smoking and lung carcinoma, which revealed that smokers were at a significantly higher risk of developing carcinoma of the lung compared to non-smokers [15]. Also, observational studies can help assess the treatment efficacy in real-world clinical practice by examining the treatment outcomes in a broader population. Patients who are not eligible for trials usually tend to have a poorer prognosis, resulting in a less positive treatment outcomes in the population than in clinical trials such as OS. These studies can enable a more informed discussion of the expected treatment outcomes, especially for the group of patients that do not fulfil trial

eligibility criteria [16]. However, there are limitations inherent in retrospective observational studies. Retrospective studies depend on data already available in clinical databases and not collected for the research in accordance with the requirements and pre-design of the study. It is inevitable that in most cases some data will be missing, and certain variables that could potentially impact the outcome may not have been recorded [17]. Therefore, it is necessary to consider these limitations when analysing the results and making inferences about them.

Advanced melanoma patients that are non-eligible for trials can be treated in real-world practice with any anti-cancer medicine approved according to clinicians' selection. Since there is no randomisation in clinical practice, melanoma patients may experience treatments with different drugs, switching from targeted therapy to immunotherapy in the pursuit of better treatment outcomes. Treatment changes between different types of therapy may improve treatment outcomes by rechallenging *BRAF*-mutant patients. As previously described in a case-report in 2018 by Kato *et al.*, a patient with nivolumab-resistant melanoma showed an improved response to a rechallenge with nivolumab after vemurafenib targeted therapy where no adverse events were observed, and the patient maintain a progression-free status [18].

Melanoma arises from melanocytes which are cells present in the epidermis responsible for the production of melanin. The most common form of melanoma is cutaneous, although it can be found in other tissues developing into, for example, ocular or mucosal melanoma [5]. Despite being the least common form of skin cancer, malignant melanoma is the deadliest, accounting for around 90% of all deaths associated with skin cancer [5]. Melanoma incidence has risen quickly in the last 50 years despite all the preventive campaigns and information to improve awareness of this disease [2].

If melanoma is diagnosed early, surgery to resect the lesion is possible and is associated with higher survival rates [2], [19]. Nevertheless, the aggressiveness of this disease can lead to metastases beyond the primary site, making resection unviable. This condition is called advanced or metastatic melanoma and treating this disease is harder than its initial stage [2]. The heterogeneity of metastatic melanoma can provoke differences in disease progression, treatment outcomes and site of metastatic lesions [5]. Additionality, patients detected with brain and visceral organ metastases tend to be

incapable of achieving long-lasting remissions from either targeted therapy or immunotherapy [20]. Due to the lethality of this form of skin cancer, efforts have been made during the last decade to develop new therapies to such as immunotherapy with immune checkpoint inhibitors (ICI) and targeted therapy in order to improve the quality of life and survival of patients dealing with this disease [21].

In this research project, it was investigated the clinical effectiveness of different therapeutic regimens with immunotherapy and targeted therapy in real-world patients with advanced melanoma from the Scottish population. Treatment outcomes of this cohort were examined through statistical and survival analyses in order to assess the possible existence of clinical and/or survival benefits, and the impact of prognostic factors. After these analyses, the research focuses on patients experiencing treatment changes between immunotherapy and targeted therapy. A multi-state model was developed to incorporate these treatment changes using real-world evidence. Further, the multi-state model was used to conduct a health economic evaluation in order to investigate the cost-effectiveness in a real-world setting of the different immunotherapy and targeted therapy regimens approved in Scotland by the SMC for treatment of advanced melanoma.

1.2. Genetic landscape of melanoma

Genetic factors have a predominant role in the pathogenesis of melanoma. Different mutations that result in the activation of melanoma cancer cells have been described, and various targeted drugs were developed, investigated to target these mutations. In 2005, researchers found that patients with melanoma who had not sustained long-term ultraviolet (UV) damage had higher levels of *BRAF* mutations [14], [22]. About half of cutaneous melanomas reveal an oncogenic mutation in the *BRAF* gene [21].

This gene belongs to the family of mitogen-activated protein kinase (MAPK) and codes for a serine/threonine protein kinase constituting part of RAS-RAF-MEK signalling pathway [3]. The RAS-RAF-MEK or MAPK pathway is a chain of proteins in the cell that transmits a signal from a receptor on the surface of the cell to the DNA in the nucleus.

In mammalian cells, the MAPK signalling pathway is crucial in the transduction of extracellular signals to cellular responses in order to control cell division, differentiation, development, and growth [23]. The proper growth and multiplication of multicellular organisms depend on the control of this cycle, and dysregulation in this pathway can lead to cancer like melanoma [23]. The hyperactivation of the MAPK pathway caused by a *BRAF* mutation results in cell division and survival signalling. A *BRAF* mutation induces hyperactivation of the MAPK pathway, leading to cell division and survival signalling [24].

The most common alterations in the MAPK pathway are *BRAF* mutations accounting for 40-50% of the mutations cases, while 20-30% are *NRAS* mutations and 10-15% with *NF1* mutations [14]. There are several mutations involving *BRAF* or *NRAS*, and the most commonly observed *BRAF* mutations are V600E, which represents 80 to 90% of the total, while V600K, V600D, and non-V600 mutations account for the remaining 10 to 20% [21], [24]. The MAPK signalling pathway in melanoma and the likelihood of mutations occurring are shown in Figure 1. As illustrated in the figure below, it is estimated that more than 80% of melanomas have genetic mutations in one or more important MAPK signalling pathway nodes [21].

The presence or absence of a *BRAF* mutation are a key feature in assessing the administration of immunotherapy or targeted therapy during the clinical decision-making process [21]. Hence, highly selective inhibitors to this mutation, such as *BRAF* and MEK inhibitors, have been developed to treat *BRAF*-mutant melanoma [3], [5], [14].

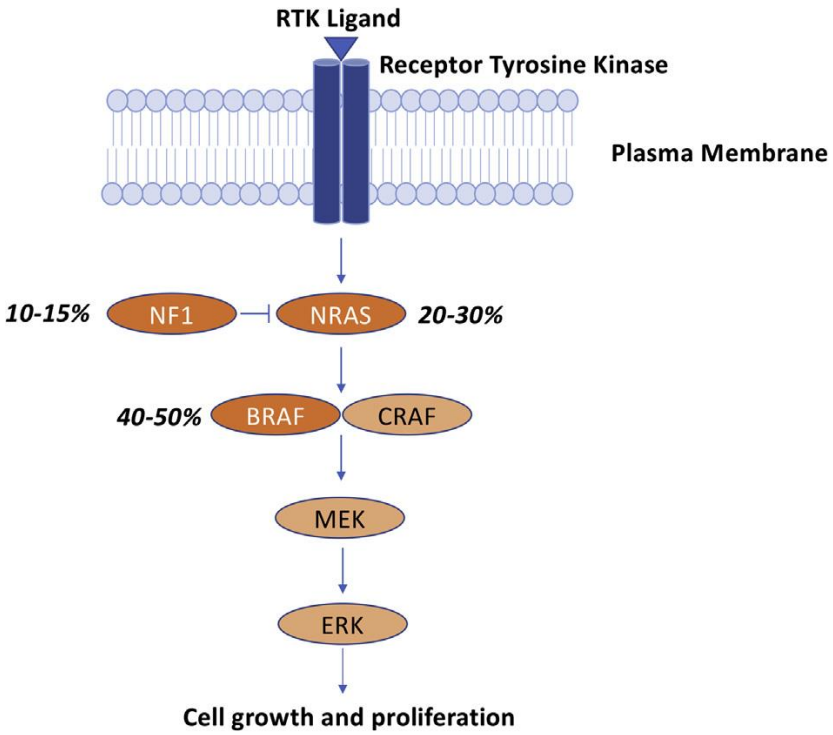

Figure 1.1 – Regulation mechanism of the MAPK signalling pathway in melanoma

Note: The figure illustrates the MAPK signalling pathway and its nodes that leads to cell growth and proliferation. Dark oranges circles represent oncogenes. The blue arrows point the direction of the cascade reaction after a cell receives an extracellular signal. **Abbreviations:** BRAF – B-Raf oncogene; CRAF – C-Raf or RAF1; ERK – Extracellular signal-regulated kinase; MEK – Mitogen-activated protein kinase kinase; NF1 – Neurofibromin 1; RTK – Receptor tyrosine kinase

1.3. Epidemiology

Skin cancers are the most often diagnosed type of cancer globally, with an estima ted 1.5 million new cases in 2020 [25]. Malignant or advanced melanoma accounts for approximately 20% of all skin cancer diagnosis, with approximately 325,000 cases estimated globally in 2020 [25]. Melanoma affects populations across the world differently due to the differences in skin pigmentation and sun exposure habits [5]. Despite being a historically uncommon disease, during the past 50 years, melanoma incidence rates have been rising in fair-skinned European populations [26], [27].

The pathogenesis of melanoma is influenced by factors including environmental genetic, and immunological factors that may be responsible for the global rise of melanoma cases [3]. Research has shown environmental factors and UV radiation exposure play an important role in the development of melanoma [3]. With the global

populations being exposed to more UV radiation, which is both naturally occurring from the sun and artificially produced, UV radiation is a potent and widespread risk factor for melanoma [25]. According to global estimates, more than three-quarters of all newly diagnosed cases of melanoma worldwide can be linked to UV exposure [25]. In regards to environmental factors, in a study published in 1956, Lancaster found that melanoma mortality rates increased with the distance from the equator, a phenomenon he named 'latitude gradient' [28]. Since then, reports of comparable global melanoma incidence patterns have been made, and melanoma annual incidence is typically higher in lower latitudes than in higher latitudes [3]. As a result, a higher incidence of melanoma is observed in countries such as Australia, New Zealand and regions such as North America and Scandinavian Europe in comparison with population with a predominantly darker skin tone like Africa and some countries in Asia [2], [25].

As previously mentioned in this thesis, genetic factors have a predominant role in the pathogenesis of melanoma. Researchers found that patients with melanoma who had not sustained long-term UV damage had higher levels of *BRAF* mutations [21]. It is estimated that nearly half of cutaneous melanomas have a oncogenic mutation in the BRAF gene [14], [22]. Additionally, the immunogenicity (ability to stimulate an immune response) of melanoma is the base the disease pathogenesis [3]. Melanoma disease progression is based on a lack of activation of the immune system, and the ability of the tumour to evade the immune system. This is corroborated by the fact that some melanoma patients have progressed to a metastatic disease state without an evident primary lesion; these cases are also known as 'melanoma of unknown primary' [3].

These factors have contributed to the worldwide total of 325,000 new melanoma cases (174,000 males, 151,000 females) and 57,000 deaths (32,000 males, 25,000 females) estimated in 2020. Furthermore, cutaneous melanoma accounted for 1.7% of global cancer diagnoses in 2022 with an estimation over 330,000 cases of melanoma according to Global Cancer Observatory from the World Health Organization (WHO) [29]. The age-standardised incidence rate for males and females was 3.8 and 3.0 per 100,000, with cumulative lifetime risks of 0.42% and 0.33%, respectively [29].

The burden of melanoma is predicted to rise by approximately 50% to 510,000 new cases, and to 96,000 deaths (68% increase) by 2040 if the rates for 2020 hold stable [25]. It is estimated that in order to ensure fewer cases of melanoma in 2040 than there

were in 2020, the yearly incidence and mortality rates need to decrease more than 2% globally [25].

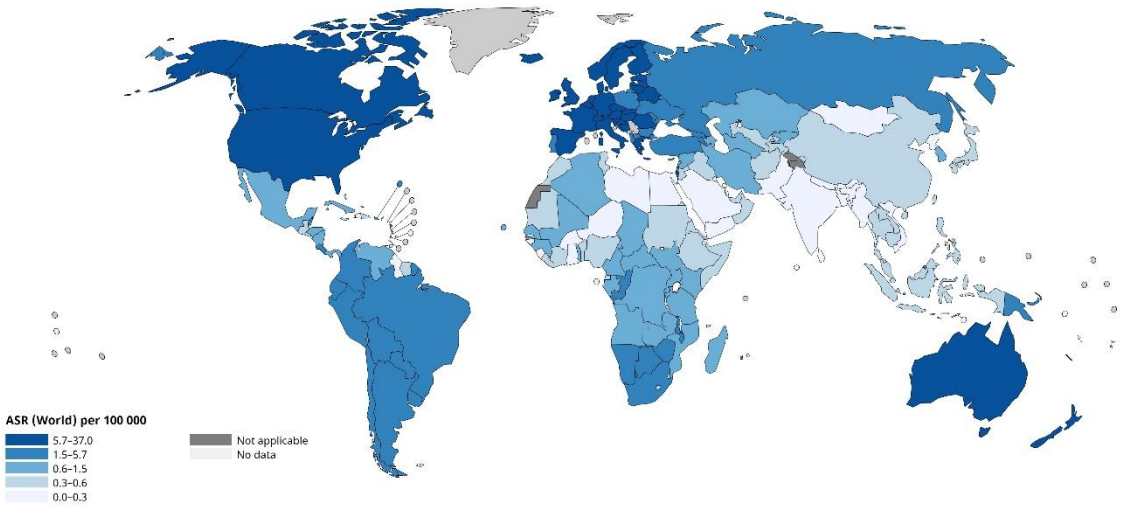

Figure 1.2 – Age-standardised rate incidence of melanoma per 100,000 in 2022 [29]

Abbreviation: ASR – Age-standardised rate

The rising number of melanoma cases also affected the UK as its incidence was found to increase from 5.8 to 19.8 from 1982 to 2011 [30]. In 2022, the age-standardised incidence rate for melanoma in the UK was 15.3, representing 4.3% of the cancer diagnosis with 19,712 cases and 2,626 deaths (Figure 1.2) [29]. Despite the difference in total population number, Scotland accounts for 44% of the total deaths by melanoma registered in 2017 within the UK [31].

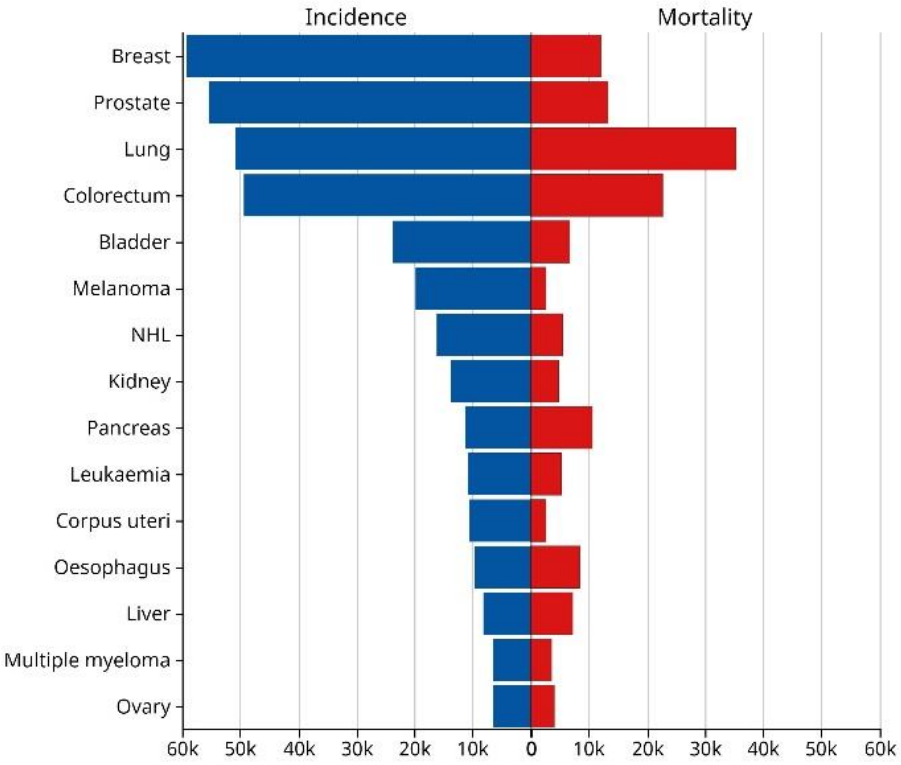

Figure 1.3 – Absolute numbers for cancer incidence and mortality in the United Kindgom (2022) [18]

Abbreviation: NHL – Non-Hodgkin lymphoma

1.4. Stages of melanoma

The clinical diagnosis of melanoma is provided by a dermatologist based on the analyses of a pigmented lesion. During the examination with the naked eye, specialist consider the ABCDE rule: asymmetry, borders, colour, diameter, and evolution. Characteristic features of a melanoma lesion are asymmetrical shape, irregular borders, differences in pigmentation or irregular colour, streaks and increasing diameter (>5 mm). Besides the mentioned characteristics, it is of equal significance to look for an evolution of lesions involving changes in shape, size and pigmentation [3], [5].

In 2009, the American Joint Committee on Cancer (AJCC) proposed a new tumour classification and staging for melanoma which is now the foundation for the classification of melanomas [5]. The TNM Staging System was created in order to standardise the criteria to assess tumour stages. This system is based on original location or primary site of the tumour (T), the spread degree to nearby lymph nodes (N) and the

existence of metastasis (M) [5], [32]. The classification and differences between classification stages are displayed in Table 1.1.

Advanced or metastatic melanoma is represented by the latest stage (stage IV) and is it defined by the presence of distance metastases (Table 1.1). The proportion of patients with metastatic melanoma is unknown, however, if untreated the median OS ranges between 6 to 9 months [3], [5].

Table 1.1 – Classification of TNM staging for melanoma [5], [21]

Stage	Primary tumour (T)	Regional lymph node metastases (N)	Distant metastatses (M)
0	*In situ* tumour	None	None
IA	≤ 1.0 mm, no ulceration	None	None
IB	≤ 1.0 mm with ulceration or mitotic rate ≥ 1/mm^2	None	None
	1.01−2.0 mm, no ulceration	None	
IIA	1.01−2.0 mm with ulceration	None	None
	2.01−4.0 mm, no ulceration	None	
IIB	2.01−4.0 mm with ulceration	None	None
	> 4.0 mm, no ulceration	None	
IIC	> 4.0 mm with ulceration	None	None
IIIA	Any tumour thickness, no ulceration	Micrometastases	None
IIIB	Any tumour thickness with ulceration	Micrometastases	None
	Any tumour thickness, no ulceration	Up to three macrometastases	
	Any tumour thickness ± ulceration	None but satellite and/or in-transit metastases	
IIIC	Any tumour thickness with ulceration	Up to three macrometastases	None
	Any tumour thickness ± ulceration	Four or more macrometastases, or lymph node involvement extending beyond capsule, or satellite and/or in-transit metastases with lymph node involvement	None
IV			Distant metastases

1.5. Treatments for advanced melanoma

Due to the existence of distant metastases (stage IV) these tumours are usually inoperable meaning that the resection of the tumour cannot be achieved [5]. The course of action to treat these tumours is through SACT. Examples of such therapies are immunotherapy and targeted treatment. With such therapies medical professionals intend to increase the survival time of their patients, reduce the tumour size and decrease the symptoms from this disease [5].

Prior to 2010, despite complete responses being rare, dacarbazine was the standard treatment for melanoma for many years. Only between 10 to 20% of patients would respond to this treatment and median OS under 1-year was usually between 6 to 9 months [3], [5].

Establishing the immunologic origin of melanoma has propelled the development of novel therapeutics like immunotherapy. Immunotherapy is the treatment that has been most extensively studied through the last decade for metastatic melanoma, and it can be divided into four groups: biological medications, vaccination, adoptive cell therapy and ICIs [3], [5]. ICI target tumour cell pathways that allow these cells to evade the immune system, enabling tumour cells to grow and spread. Melanoma therapy with ICIs has two targets: programmed cell death 1 (PD-1), and cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4). The blockade of these two molecules abrogates the downregulation of lymphocytes from the immune system allowing them to identify and eliminate tumour cells. Although this immunostimulation process is non-specific for tumour cells, it relies on the overexpression in those cells [5]. During the last decade, new antibodies directed to these specific targets PD-1 and CTLA-4 have drastically increased the OS of advanced melanoma patients [3], [5].

1.5.1. Immune checkpoint inhibitors

In 2011, ipilimumab was the first immune checkpoint inhibitor approved for the treatment of advanced melanoma after demonstrating benefit in OS in controlled

clinical trial (NCT00094653) [11]. Results from the clinical trial showed that median OS of patients treated with only ipilimumab was 10.1 months, in comparison with 6.4 months among patients receiving gp100 peptide vaccine alone (Hazard ratio [HR]: 0.66; p=0.003) [11]. These results lead researchers to conclude that ipilimumab, with or without gp100, improved OS in patients with previously treated advanced melanoma [10]. Consequently, this antibody was approved to treat melanoma patients in the USA and in Europe. Despite only 15% of patients having a response to monotherapy with ipilimumab, durable remissions were observed in patients previously treated with other drugs [5], [7].

Tremelimumab is a CTLA-4 inhibitor tested in clinical trials (NCT00257205) for advanced melanoma [33]. Results from this clinical trial revealed an OS was 12.6 months (95% CI: 10.8−14.3) for tremelimumab and 10.7 months (95% CI: 9.36−11.96) for chemotherapy (HR: 0.88; p=0.127) [33]. The monoclonal antibody tremelimumab failed to demonstrated a statistically significant advantage over standard of care chemotherapy in patients with advanced melanoma, therefore not receiving approval for its used in metastatic melanoma [7], [33].

In 2014, results from clinical trials of monoclonal antibodies targeting PD-1 demonstrated clinical activity not only in melanoma, but also non-small cell lung cancer, and renal cell carcinoma. Nivolumab and pembrolizumab are two PD-1-blocking monoclonal antibodies approved for therapy of unresectable or metastatic melanoma [7].

In a clinical trial (CheckMate 066) nivolumab was compared with dacarbazine among patients with previously untreated *BRAF*-wild-type metastatic melanoma. In this trial, nivolumab demonstrated significant improvements in OS and progression-free survival (PFS) in comparison with dacarbazine [34]. After 1 year, the OS rate was 72.9% (95% CI: 65.5−78.9) as compared with dacarbazine patients with 42.1% (HR: 0.42; p<0.001) [34]. In the clinical study CheckMate 067, the clinical outcomes of nivolumab alone or in combination with ipilimumab were compared with ipilimumab only treatment [35]. This study revealed that the combination of nivolumab and ipilimumab provides greater benefits, resulting in longer PFS and OS in comparison with ipilimumab alone; nivolumab only group also had better results in comparison with ipilimumab only group [5], [7].

Pembrolizumab was also tested in comparison with ipilimumab in randomised phase III clinical trial (KEYNOTE-066). After a median follow-up of 57.7 months among the surviving patients, it was observed a median OS of 32.7 months (95% CI: 24.5–41.6) in the pembrolizumab group; patients in the ipilimumab group had and OS of 15.9 months (HR: 0.73; p=0.00049) [36]. Alongside with OS, pembrolizumab presented clinical benefits in terms of PFS and the development of severe-grade adverse events. These results suggest a superiority from pembrolizumab over ipilimumab, supporting the use of pembrolizumab a new viable option for the treatment of advanced melanoma [5], [36], [37].

1.5.2. Targeted therapy

The identification of *BRAF* mutations in metastatic melanoma marked the dawning of molecular targeted therapy. Such discovery led to the evaluation of *BRAF* inhibitors in clinical trial settings for the treatment of advanced melanoma [21]. In light of the clinical efficacy of single-agent MEK inhibition, and the understanding of the significance of downstream MAPK signalling pathway, combinations of *BRAF* and MEK inhibitors were subsequently evaluated [21], [38].

The first combination of *BRAF* and MEK inhibitors approved for advanced melanoma was dabrafenib plus trametinib based on the results from two phase III clinical trials, COMBI-v [39] and COMBI-d [40], which evaluated the combination treatment against single-agent treatment with vemurafenib and dabrafenib, respectively. In COMBI-v, patients who received dabrafenib plus trametinib demonstrated a significant improvement in OS in comparison with vemurafenib [39]. Regarding COMBI-d, patients who received the *BRAF* plus MEK inhibitors combination demonstrated a statistically significant improvement in PFS in comparison with the single-agent arm with dabrafenib [40]. Patients receiving the combination had a PFS of 9.3 months, whilst patients receiving only dabrafenib had a PFS of 8.8 months (HR: 0.75; p=0.035) [40]. Later, a pooled analysis of both clinical trials reported the findings of a five-year analysis of patients treated with dabrafenib plus trametinib for metastatic melanoma [41]. In this study, authors reported PFS rates of 21% (95% CI: 17-24) at 4 years, and 19% (95% CI: 15−22) at 5 years. The OS rates were 37% (95% CI: 33−42) at 4

years, and 34% (95% CI: 30−38) at 5 years [41]. Additionally, a complete response occurred in 109 patients (19%), and it was associated with an improved long-term outcome, with an OS rate of 71% (95% CI: 62−79) at 5 years [41].

Another clinical trial (coBRIM) investigated the PFS of *BRAF*^{V600} mutation-positive metastatic melanoma patients treated with a *BRAF* inhibitor plus a MEK inhibitor [42]. Two patient groups were compared: one patient group was treated with a combination of *BRAF* and MEK inhibitors, vemurafenib plus cobimetinib; the control group was treated with vemurafenib alone [42]. This clinical trial revealed a statistically significant improvement in PFS among the patients receiving the combination treatment. This group had a PFS of 9.9 months, in comparison with the PFS of 6.2 months in the control group (HR: 0.51 [95% CI: 0.39−0.68]; p<0.001) [42]. However, the longer PFS in the group receiving the combination treatments was associated with an increased incidence of adverse events [42].

A third combination of *BRAF* inhibitor (encorafenib) plus MEK inhibitor (binimetinib) was evaluated in a randomised phase III clinical trial (COLUMBUS) [43]. In this clinical trial, patients were randomly assigned into three arms: combination of encorafenib plus binimetinib; encorafenib; and vemurafenib [43]. The results from this study showed favourable efficacy of encorafenib plus binimetinib, and encorafenib monotherapy in comparison with vemurafenib as a single-agent. The median PFS for the combination of *BRAF* and MEK inhibitors was 14.9 months (95% CI: 11.0–18.5), and 7.3 months (95% CI: 5.6–8.2) in the vemurafenib group [43]. Also, patients treated with encorafenib plus binimetinib demonstrated a HR of 0.54 (95% CI: 0.41–0.71; p<0.0001) in comparison with vemurafenib alone, revealing a statistically significant difference in the probability of disease progression [43].

These clinical trials have shown that MEK inhibitors can supplement the inhibition provided by *BRAF* inhibitors, resulting in a significant increase in objective response rate, PFS, and OS [3]. The currently available combinations of *BRAF* and MEK inhibitors are comparable in terms of efficacy, with response rates between 60% and 70% [21]. Therefore, the current standard of care for metastatic melanoma patients with a *BRAF* mutation has transformed thanks to the encouraging outcomes of these clinical trials investigating the potential benefits of a combination of *BRAF* and MEK inhibitors [21].

1.5.3. Emerging treatments

Treatment guidelines for advanced melanoma have evolved over the course of the last decade. However, despite the current improvements, the optimal regimen that can harness the best benefits from therapies available at present is still unknown [3]. Researchers are pursuing the ideal treatment either through the development of new drugs or the combination of existing ones. A possible new treatment strategy that is currently under study is the combination of both targeted treatments (*BRAF*/MEK inhibitors) and immunotherapy in patients with a BRAF gene mutation. Previous studies have suggested the use of *BRAF*/MEK inhibitors can potentially activate the immune system, resulting in a synergetic action between targeted agents and immunotherapy drugs [44], [45], [46]. However, some challenges may arise from this combination, such as tolerability problems and immune-related adverse events like hepatotoxicity from the combination of ipilimumab and vemurafenib [44], [47].

Another important aspect of the combination treatment of the two drug classes is the required attention to sequential dosing as a possible treatment strategy. To address this issue, it is necessary to understand the individual mechanisms of action and treatment purposes of each drug class. Targeted therapy is associated with an early response and a high response rate but lacks an extended response [46]. Conversely, immunotherapy has a longer response rate, exhibiting greater potential for long-term benefits [46]. Theoretically, the early response from targeted therapy followed by the longer response rate from immunotherapy would suggest the best course of action for drug class combination would be immunotherapy followed by targeted treatment further into the treatment journey in cases of disease progression. However, targeted agents might be chosen as first-line treatment for cases of severe disease due to the quicker response rate. Patients not responding to this treatment could lead to rapid disease progression, which compromises the use of immunotherapy as a subsequent line of therapy [47].

1.5.3.1. Sequential treatment with targeted therapy and immune checkpoint inhibitors

The potential synergy effect between targeted therapy and immunotherapy has been previously explored. This review revealed examples of published retrospectives studies with results from the sequential treatment of targeted therapy and immunotherapy. In a 2017 retrospective study performed by Simeone, Grimaldi *et al.*, the authors investigated the correlation between previous treatment with *BRAF* inhibitors and clinical response to pembrolizumab [47]. In this study, 42 patients with advanced melanoma (16 patients *BRAF*-mutant; 26 patients *BRAF*-wild-type) who had received previous treatment with ipilimumab were treated with pembrolizumab as part of the Italian expanded access programme. The patients diagnosed with a mutation in the BRAF gene were also previously treated with targeted therapy with either vemurafenib or dabrafenib. Results have shown that patients with *BRAF*-mutant melanoma who had previously been treated with *BRAF* inhibitors had a significantly lower median PFS (3 months [range: 2.3–3.7 months] vs not reached [range: 2–8+ months]; p-value = 0.001) and disease control rate (18.6% vs 65.4%; p-value = 0.005) in comparison with *BRAF*-wild-type patients [47].

Another retrospective study from Ackerman, Allison *et al.* (2014) describes the outcomes of metastatic melanoma patients treated with either *BRAF* inhibitors before immunotherapy or vice-versa [48]. Response rate (RR), OS, and PFS were evaluated for the entire cohort, subdivided by *BRAF* inhibitor prior to or after immunotherapy. A total of 193 patients had discontinued *BRAF* inhibitor treatment and a subset 40 patients subsequently received ipilimumab but only half completed the full 4-dose treatment. Results from this study showed that prior treatment with immunotherapy does not appear to negatively influence clinical response to subsequent treatment with targeted agents whilst the outcomes for immunotherapy with ipilimumab following *BRAF* inhibitor discontinuation are poor [48].

The potential synergetic effect with the use of immunotherapy following a previous course of targeted therapy has also been investigated through clinical trials

such as DREAMseq (NCT02224781) [49], SECOMBIT (NCT02631447) [50], and EBIN (NCT03235245) [51]. In the DREAMseq clinical trial, patients were randomised to receive either dabrafenib plus trametinib followed by ipilimumab plus nivolumab or ipilimumab plus nivolumab followed by dabrafenib plus trametinib [49], [52]. Similarly, the SECOMBIT clinical trial explored sequential treatment strategies across three treatment arms: Arm A received encorafenib plus binimetinib until disease progression followed by ipilimumab plus nivolumab; Arm B received ipilimumab plus nivolumab until disease progression followed by encorafenib plus binimetinib; and Arm C received encorafenib plus binimetinib for an 8-week course, followed by ipilimumab plus nivolumab until disease progression followed encorafenib plus binimetinib [50]. Additionally, the randomised phase II EBIN clinical trial (NCT03235245) is further exploring the effect of ipilimumab plus nivolumab, preceded or not by encorafenib plus binimetinib, in patients with *BRAF* mutation-positive unresectable or metastatic melanoma [53]. However, no conclusions have been reached [53].

The primary endpoint in the DREAMseq and SECOMBIT trials were 2-year OS rates. Results from the DREAMseq clinical trial revealed a higher proportion of patients surviving when immunotherapy was administered first-line, followed by targeted therapy second-line, with 71.8% (95% CI: 62.5−79.1) compared to 51.5% (95% CI: 41.7−60.4) for those receiving targeted therapy first-line [52]. SECOMBIT results for OS demonstrated varying rates across the arms, with 65% for Arm A, 73% for Arm B, and 69% for Arm C [54]. A follow-up study reporting the 4-year survival outcomes of the SECOMBIT clinical trial revealed that the 4-year OS rates for patients in treatment arms B C were 59% (95% CI: 53–76) and 63% (95% CI: 47–71), compared to 46% (95% CI: 33–59) for treatment Arm A [55]. The sandwich technique with Arm C (*BRAF*/MEK inhibitors followed by ICI treatment as second-line treatment, followed *BRAF*/MEK inhibitors as a third-line treatment) is one of the main distinctions between the DREAMseq and SECOMBIT trials, which also demonstrated clinical benefits. These findings of DREAMseq [49] and SECOMBIT [50] trials collectively suggest a potential survival benefit associated with the administration of combination immunotherapy as a first-line treatment followed by targeted therapy in patients with advanced melanoma. Nevertheless, it is still unclear if some patients may benefit more from a brief course of targeted therapy prior to starting immunotherapy which warrants further research.

Table 1.2 – Clinical trials using a sequential treatment of *BRAF*/MEK inhibitors with immune checkpoint inhibitors for melanoma

Clinical trial (NCT number)	Population	Treatment schedule	Study design	Outcomes
DREAMSeq (NCT02224781)	Unresectable stage III or stage IV, BRAF V600 mutant CM	Ipilimumab + nivolumab followed by crossover to dabrafenib plus trametinib vs. dabrafenib plus trametinib followed by crossover to ipilimumab + nivolumab	Randomised, open-label, phase III	2-year OS rate: 72% vs. 52%
SECOMBIT (NCT02631447)	Unresectable stage III or stage IV, BRAF V600 mutant CM; BRAF V600 mutant MM	Ipilimumab + nivolumab followed by crossover to encorafenib + binimetinib vs. encorafenib + binimetinib followed by crossover to ipilimumab + nivolumab vs.8-weeks induction with encorafenib + binimetinib, then ipilimumab + nivolumab followed by crossover to encorafenib + binimetinib	Randomised, open-label, phase II	2-year OS rate: 73% vs. 65% vs. 69%

Abbreviation: CM – Cutaneous melanoma; NCT – National Clinical Trial; OS – Overall survival

1.5.3.2. Combination therapy using immune checkpoint inhibitors with targeted therapy treatments

Following early preclinical evidence, several clinical trials have investigated the efficacy of triple combination of *BRAF*/MEK inhibitors and ICIs in patients with advanced *BRAF*-mutant melanoma such as TRIDeNT/TRIBECA (NCT02910700) [56], KEYNOTE-022 (NCT02130466) [57], COMBI-i (NCT02967692) [58], and IMspire150 (NCT02908672) [59]. There are reported outcomes for the KEYNOTE-022 [57], [60], COMBI-i [61], and IMspire150 [62] trials, however others clinical trials such as STARBOARD [63] and TRIDeNT/TRIBECA [56] are still ongoing, without any reported

outcomes**.** The details for the clinical trials investigating the combination of *BRAF*/MEK inhibitors with ICI are displayed in Table 1.3 and Table 1.4.

These clinical trials involved patients with *BRAF*-mutant metastatic or advanced melanoma, and the primary endpoint focused on the PFS, with secondary endpoints including OS. The treatment combinations under investigation in the KEYNOTE-022, COMBI-i, and IMspire150 clinical trials were the combination of pembrolizumab plus dabrafenib plus trametinib; the combination of spartalizumab plus dabrafenib plus trametinib; and the combination of atezolizumab plus cobimetinib plus vemurafenib, respectively [57], [58], [59]. The KEYNOTE-022 found that after a median follow-up of 61.2 months, the median PFS was 17 months in the triplet arm and 9.9 months in the doublet arm [57], [60]. Additionally, median OS was 46.3 months (95% CI: 23.9–NR) in the triplet arm, and 26.3 months (95% CI: 18.2–38.6) was observed in the doublet arm [57], [60]. Furthermore, patients in the doublet arm were more likely to achieve an objective RR (63.3% vs. 71.7%), but a complete response was more frequent in the triplet group (20% vs. 15%) [64]. Despite the COMBI-i not meeting the primary endpoint, the results were consistent with those reported in the KEYNOTE-022 trial [65]. After a median follow-up of 27.2 months, the median PFS was 16.2 months in the triple group (spartalizumab plus dabrafenib plus trametinib) compared to 12.0 months in the control group (dabrafenib plus trametinib). Additionally, the median OS was not reached in the triple group, while the median OS in the control group was 40.4 months [61]. In the IMspire150, one group of patients received triple therapy (*BRAF*/MEK inhibitor plus ICI) and the control group received only the *BRAF* and MEK inhibitors [59]. Results from IMspire150 demonstrated that PFS was significantly prolonged in the triple therapy group, reaching 15.1 months, in comparison with the control group of 10.6 months (HR 0.78; 95% CI: 0.63−0.97; p=0.025) [62]. Additionally, secondary endpoint of the IMspire150 trial detected common immune-related adverse events (irAE) in over a third of the patients for both treatment groups [62]. These irAE led 13% and 16% of patients, in atezolizumab group and control group respectively, to stop their treatment entirely. Notwithstanding with the development of adverse events, results from the IMspire150 clinical trial showed the combination of atezolizumab plus cobimetinib plus vemurafenib is safe and tolerable, and can significantly improve PFS in patients with $BRAF^{V600}$-mutant metastatic melanoma [62].

On July 30, 2020, the FDA approved the use of atezolizumab (Tecentriq®) in combination with vemurafenib and cobimetinib for the treatment of patients with *BRAF*^{V600}-mutant unresectable or metastatic melanoma, citing the IMspire150 trial's benefits (safety, tolerability, and significant increase of PFS) [66]. This is the first triple combination of ICI and *BRAF*/MEK inhibitors to receive an authorisation for use in metastatic melanoma. The EMA has granted an authorisation for the use of atezolizumab in the EU, however this authorisation does not comprise metastatic melanoma. Atezolizumab is authorised in the EU for use in urothelial cancer, lung cancer, triple-negative breast cancer, and hepatocellular carcinoma [67]. No approval has been granted yet for the use of atezolizumab in metastatic melanoma in the EU [67].

Table 1.3 – Clinical trials investigating a combination of *BRAF*/MEK inhibitors with immune checkpoint inhibitors for metastatic melanoma with published outcomes

Clinical trial (NCT number)	Population	Treatment arms	Study design
KEYNOTE-022 (NCT02130466) [93]	Unresectable stage III or stage IV, *BRAF*^{V600}-mutant metastatic melanoma	Pembrolizumab + dabrafenib + trametinib vs. Placebo + dabrafenib + trametinib	Phase II, randomised, double-blind, placebo-controlled
COMBI-i (NCT02967692) [94]	Unresectable stage III or stage IV, *BRAF*^{V600}-mutant metastatic melanoma	Spartalizumab + dabrafenib + trametinib vs. Placebo dabrafenib + trametinib	Randomised, double-blind, placebo-controlled phase III
IMspire150 (NCT02908672) [95]	Unresectable stage IIIC or stage IV, BRAF V600 mutant CM	Atezolizumab vemurafenib + cobimetinib vs. Placebo + vemurafenib + cobimetinib	Randomised, double-blind, placebo-controlled phase III
NCT02027961	Unresectable stage III or stage IV CM	Cohort A: BRAF V600 mutant CM treated with dabrafenib + trametinib + durvalumab; Cohort B: BRAF wild-type CM treated with trametinib + concurrent durvalumab; Cohort C: BRAF wild-type CM treated with trametinib + sequential durvalumab	Open-label, dose escalation and expansion phase I

Abbreviations: CM – Cutaneous melanoma; NCT – National Clinical Trial

Table 1.4 – Ongoing clinical trials investigating the combination of immune checkpoint inhibitors with *BRAF*/MEK inhibitors for *BRAF*-mutant melanoma without published outcomes

Clinical trial (NCT number)	Population	Treatment schedule	Study design	Status
STARBOARD (NCT04657991) [63]	Unresectable stage IIIB-D or stage IV, $BRAF^{V600}$-mutant CM	Encorafenib + binimetinib + pembrolizumab vs. placebo + pembrolizumab	Phase III, randomised, double-blind	Active, not recruiting
TRIDeNT/TRIBECA (NCT02910700) [92]	Unresectable stage III or stage IV, $BRAF^{V600}$-mutant CM	Dabrafenib + trametinib + nivolumab, or trametinib + nivolumab, or encorafenib + binimetinib + nivolumab	Phase II, non-randomised, open-label	Active, not recruiting
SWOG S2000 (NCT04511013) [100]	$BRAF^{V600}$-mutant melanoma with brain metastases	Encorafenib + binimetinib + nivolumab vs. Ipilimumab + nivolumab	Phase II, randomised	Recruiting
NCT04375527 [105]	*Unresectable or metastatic $BRAF^{V600}$-wild-type melanoma*	Binimetinib and nivolumab	Phase II, non-randomised	Recruiting

Abbreviations: CM – Cutaneous melanoma; NCT – National Clinical Trial

1.6. Drug approval process in the United Kingdom

This research aims to investigate the clinical outcomes of patients undergoing systemic anti-cancer treatment for advanced melanoma through the analysis of real-world evidence. The legal examination of such treatments by relevant regulatory agencies must first be completed based on clinical trial results provided by the submitting entity. Only then can these treatments be used in clinical practice in a real-world setting. The regulation for the introduction of new medicines or treatment regimens into the National Health Service (NHS) is a process to ensure these are safe, effective, and provide care benefits to patients.

There are two agencies able to licence drugs within the UK which are the European Medicines Agency (EMA) and Medicines and Healthcare Products Regulatory Agency (MHRA) [68]. The first provides a Europe-wide licence under the European Commission whilst MHRA issues a licence for the UK [68]. The EMA is a decentralised agency of the European Union (EU) responsible for the scientific evaluation, supervision and safety monitoring of medicines in the EU. Additionally, the EMA defends public and animal health by ensuring that the medicines available either for human or veterinary use are safe and effective. EMA follows a centralised procedure allowing pharmaceutical companies to submit a single application to the agency in order to obtain from the European Commission a centralised marketing authorisation. Once granted, this authorisation is valid in all EU, EEA and European Free Trade Association countries [69]. The MHRA is responsible to assess new medicine outside the EMA's centralised authorisation procedure. Moreover, this organisation enforces that European regulations are met in the UK and ensures the safety and efficacy of treatments [68].

Once a drug or regimen is licenced by the EMA or MHRA, other agencies assess and regulate its potential use within the NHS. The National Institute for Health and Care Excellence (NICE) and the Scottish Medicines Consortium (SMC) are the agencies responsible for the decision process to include new drugs in the NHS England and NHS Scotland, respectively [68].

However, the EU Referendum in 2016 led to the UK notifying the EU of its intention to withdraw from it, which would leave MHRA as standalone regulator for the UK [70], [71]. From 2017, in an effort to lessen the effects of Brexit on the availability of medicines in the UK, the EMA and EU member states reallocated the UK's portfolio of previously centrally authorised medications. Since January 1st 2021, EU pharmaceutical law is no longer in effect in the UK, except for Northern Ireland based on a protocol agreement between the EU and the UK. All existing centrally authorised product marketing authorisation automatically converted into Great Britain marketing authorisations, except when the marketing authorisation holders opted out [70]. The converted EU marketing authorisations are assigned a product licence for Great Britain (PLGB). Nevertheless, option of convert to PLGB remains available for MAH that initially opted out [70]. From this date onwards, marketing authorisation applications submitted to the MHRA for novel products will be valid only for Great Britain [70].

1.6.1. National Institute for Health and Care Excellence – NHS England

The NICE is an independent organisation set up by the British Government. The aim of this agency is to provide guidance to the NHS England and decide which medicines and treatments are available, making sure people have the same access to treatment and care [72].

NICE technology appraisals are recommendations on the use of new and existing drugs and treatments within the NHS England. These appraisals refer to medicines, medical devices, diagnostic techniques, surgical procedures, and health promotion activities. The appraisals are based on clinical evidence (how well the medicine or treatment works) and economic evidence (relationship between medicine or treatment and cost to the NHS England).

Technology appraisals assume one of three forms:

- A single technology appraisal (STA) – covers a single technology for a single indication;
- A fast-track appraisal – covers a single technology for a single indication but with a shorter process time. It speeds up the access to the most cost-effective new treatments;
- A multiple technology appraisal (MTA) – for more than one technology or one technology for more than one indication [73].

Technology appraisals are developed by the Centre for Health Technology Evaluation at NICE [73]. A manufacturing or sponsoring company submits a comprehensive dossier to NICE containing clinical, safety, and economic data regarding the technology under evaluation or its comparator. Then, the NICE conducts their technology appraisal based on the evidence provided. This submission adheres to strict regulatory guidelines and serves as a foundational resource for the appraisal process, informing the committee's assessments and subsequent recommendations regarding the technology's adoption within the healthcare system [73]. After weighing the available data, the appraisal committee determines whether to suggest the technology as a clinically and financially sound use of NHS resources or if it should only be

recommended for particular populations. The appraisal committee is an independent, standalone committee that evaluates evidence for various technologies and produces recommendations. Committee members are recruited by NICE through competitive advertising, serving initially for a 3-year term and representing diverse backgrounds, including the NHS, lay backgrounds (with an understanding of patient and public perspectives on healthcare issues), academia, and the pharmaceutical and medical device industries [73]. Subsequently, the appraisal committee provides its recommendations to NICE in the form of an appraisal consultation document (ACD) or a final appraisal document (FAD). If the appraisal committee provides an ACD, then NICE invites consultees, commentators, and the public to comment on it [73]. The appraisal committee will take these comments into consideration and finalise its recommendations, providing them to NICE in the form of a FAD. Then, the FAD serves as the foundation for the recommendations that NICE issues to NHS England [73].

NICE recommendations from technology appraisals may contain more than one recommendation, and are classified into five categories: '*Recommended*'; '*Optimised*'; '*Recommended for use in the Cancer Drug Fund (CDF)*'; '*Only in research*'; '*Not recommended*' [74]. When a drug or treatment receives a recommendation for use by NICE, it should be routinely available within 3 months of its date of publication, unless otherwise specified. It is recommended for use in line with the marketing authorisation from the MHRA, in line with how it is used in clinical practice in the NHS, or both [74], [75]. A technology appraisal receives an optimised verdict when the committee decides that the drug is only cost-effective as a treatment option for a specific group of patients, for example those who are resistant to or cannot tolerate other drugs [74], [75]. A recommendation for used within the CDF indicates that although demonstrated encouraging outcomes in clinical trials, there is currently insufficient data to support the recommendation of a medicine [74], [75]. The CDF aims to give physicians faster access to innovative patient therapies. After a period of up to 2 years in the CDF, NICE reviews the medication and decides whether or not to recommend it [76]. Upon a recommendation for use only in research, the drug or treatment can be used as part of a clinical trial, so researchers can collect more evidence about how well it works, the prospect of being cost-effective, and to inform future NICE guidance [74], [75]. Lastly, if a treatment is deemed to be a less cost-effective use of NHS resources when compared

to current NHS practice, or if there is insufficient evidence for its clinical effectiveness, NICE will decide not to recommend it [74], [75]. Subsequently, NHS is legally obliged to fund and resource medicines and treatments recommended by NICE's technology appraisals [72], [73].

The organisations in the UK responsible for the decision to include a medicine as part of the free healthcare in NHS and Health and Social Care (HSC) are the NICE for NHS England, the SMC for NHS Scotland, the All Wales Medicines Strategy Group (AWMSG) for NHS Wales, and the Department of Health, Social Services and Public Safety (DHSSPS) for HSC in Northern Ireland [77].

1.6.2. Scottish Medicines Consortium – NHS Scotland

The SMC is part of Healthcare Improvement Scotland which is the national healthcare improvement organisation for Scotland. The SMC provides advice to NHS Scotland and is responsible for reviewing new medicines, formulations, or new therapeutic regimes that have received a licence from either the EMA or MHRA (regulatory authorities mentioned above). Therefore, even with a previous approval by other agencies, a medicine can only be prescribed routinely in Scotland after its authorisation for use by the SMC [78].

The SMC is a committee with a wide mixture of backgrounds composed by clinicians, NHS board representatives and the public. The decision-making process is settled through a vote system at their monthly meeting, benefiting from the different backgrounds that assures a broad perspective [79], [80]. This committee is supported by a core team of pharmacists, economists, public involvement professionals and administration support. Decisions about the approval for the use of a new medicine are based on its efficacy, patient's benefits, comparison with the current treatment already in use for a particular health condition (if there is any) and its cost-effectiveness. The SMC takes these factors into account when deciding whether to accept a new medicine under review. Due to the NHS Scotland limited resources, SMC assesses carefully each new proposal submitted to the committee based on the key points mentioned [78], [79].

To determine whether a medicine is cost-effective, the committee reviews clinical and health economic evidence provided by the submitting company, as well as evidence submitted by patient groups [80]. This assessment considers various aspects beyond the medicine's purchase cost, including its comparative benefits against existing treatments, the impact on patients' quality of life and life expectancy, ease of administration, potential cost savings from reduced hospital admissions, and additional healthcare professional visits. Ultimately, this assessment aims to determine the medicine's overall value for money and cost-effectiveness in treating specific conditions within NHS Scotland [80].

It is important to highlight that the data used throughout this thesis is derived from patients treated in the Scottish healthcare system. This allows a more accurate and relevant evaluation of the clinical and cost-effectiveness of advanced melanoma treatments within the context of NHS Scotland. The findings can directly inform decision-making processes and healthcare strategies specific to Scotland, ensuring that the results are applicable and beneficial to the local population and healthcare infrastructure.

1.6.2.1. SMC appraisal decisions

An SMC appraisal can end in four decisions outcomes: accepted, accepted with some restriction(s), accepted on an interim basis, or not recommended. When SMC decides to approve a medicine with some restrictions, the medicine is only approved for use in a specific subset of patients who meet certain criteria. Usually, this happens because of the company's explicit request in their submission [78]. The SMC can decide to accept a medicine on an interim basis which indicates that the medicine is accepted for use, however it is subject to ongoing evaluation and reassessment once further evidence is available [78]. If SMC considers that the medicines may provide value for money, the SMC may decide that a medicine is accepted on an interim basis; however, additional evidence is expected that may address existing uncertainties regarding the evidence presented by the submitting company [78]. Generally, the decision to not recommend a medicine is due to a lack of a sufficiently strong economic case, not providing additional benefits in comparison with a cheaper medicine already in use, or

due to the non-submission for SMC appraisal by the holder of the marketing authorisation.

Following an approval, NHS boards are expected to make available for clinical use the medicine under consideration or an equivalent to SMC-accepted medicine. In the event of a non-recommendation by SMC, the committee advises the submitting company about the reasoning for the decision and welcomes a resubmission once the issues are addressed [78], [79].

1.6.2.2. Patient and Clinician Engagement process

When the evaluation conducted by SMC is aimed at end-of-life medicines and medicines to treat rare conditions (i.e., orphan medicines), SMC offers the submitting pharmaceutical companies the opportunity to request a Patient and Clinician Engagement (PACE) meeting, which gives patient groups and clinicians a stronger voice in the SMC decision-making process [81], [82]. A medicine is considered an end-of-life medicine if it is used to treat a condition at a stage that usually leads to death within 3 years with currently available treatments [82]. Regarding orphan medicines, these are defined as medicines with a GB orphan marketing authorisation from the MHRA, meaning that the health condition affects fewer than 2,500 people in a population of 5 million or a medicine to treat an equivalent size of population, irrespective of whether it has designated orphan status [82].

The standard SMC submission form is used to submit end-of-life and orphan medications, which are then assessed by the New Drugs Committee (NDC). In the event that the NDC advises against using the medication, the submitting pharmaceutical company can request that the SMC call a PACE meeting. The purpose of the PACE meeting is to elucidate the additional benefits of a medicine from both patient and clinician perspectives, which may not be fully captured through clinical and economic assessments [82]. During the PACE meeting, a template is completed and agreed upon by group members. The resulting PACE meeting statement is included in the medicine's SMC meeting papers along with other relevant documents that have a significant impact

on the SMC's decision-making process, such as detailed advice from the NDC, company comments, clinical expert responses, patient group submissions, and Patient Access Scheme submissions [82].

In cases where a PACE-eligible medicine is not accepted for routine use in NHS Scotland despite the added flexibility of the PACE pathway, the company has the option to resubmit to SMC. If resubmission occurs within six months of the original PACE meeting, the original PACE statement is used. However, if the resubmission is received more than six months later, SMC staff will contact the original participants in the PACE meeting in order to establish if the previous PACE statement is still valid in terms of capturing the potential added value. If the previous PACE statement is not valid, then an updated PACE statement or a further PACE meeting are required [82].

1.6.2.3. Ultra-orphan pathway

A medicine is considered to be an ultra-orphan medicine when all the following criteria are met:

- The condition, typically a recognised distinct disease or syndrome, has a prevalence of 1 in 50,000 or less in Scotland;
- The medicine has a GB orphan marketing authorisation from the MHRA;
- The condition is chronic and severely disabling;
- The condition requires highly specialised management [83].

The health condition is typically a recognised distinct disease or syndrome, and the SMC uses the description of the orphan condition within the MHRA's Orphan Register [83]. For assessing ultra-orphan medicines, the SMC has developed a specific framework following a pathway that involves four key stages:

- Validation of ultra-orphan status;
- SMC initial assessment;
- Evidence generation for a period of three years;
- SMC reassessment, followed by the issue of advice to NHS Scotland [83].

The submitting companies are encouraged to seek validation for their medicine as an ultra-orphan medicine, by completing an ultra-orphan proforma at an early stage [83], [84]. The validation process usually takes eight weeks, during which the SMC

reviews the proforma to determine whether the medication fits the ultra-orphan medicine category. The validation of an ultra-orphan medicine status has a two-year expiration period. Afterwards, if a product has Great Britain marketing authorisation from the MHRA; if there are eligible patients in NHS Scotland; and if no submission is forthcoming, SMC will move to issue a '*Not Recommended*' advice [84].

The initial SMC assessment phase involves a comprehensive evaluation of the clinical and cost-effectiveness of the medicine. Companies are required to submit the New Product Assessment Form (NPAF) for ultra-orphan medicines in order to facilitate this process [83], [84]. In order to appraise ultra-orphan medicines, the SMC considers various factors such as the condition's nature, the medicine's impact, its value for money, implications on specialist services, and the associated costs to the NHS. This assessment aims to identify any uncertainties in the evidence base, providing valuable insights for subsequent stages of the ultra-orphan pathway [83], [84].

The evidence generation and data collection can start at an early stage in parallel with the SMC's initial assessment. The main objective of this phase is to address any uncertainties identified during the initial assessment by generating additional evidence. In order to boost the SMC's confidence in the clinical and cost-effectiveness viability of the ultra-orphan medication at the time of reassessment, the submitting pharmaceutical company has a maximum of three years to collect data and generate more evidence to support the ultra-orphan medicine's clinical and economic value [85].

Following the data collection phase, the pharmaceutical company is required to provide a comprehensive updated submission to the SMC. This submission should incorporate any new evidence obtained during the data collection period, such as results from further controlled studies, observational, or other real-world data [83]. The SMC will then conduct review the updated submission alongside evidence from clinical experts, patient groups, and any outcomes from a PACE meeting. Based on this comprehensive review, the SMC makes a decision regarding the routine use of the medicine in NHS Scotland, ensuring patient access to effective and cost-effective treatments within the healthcare system [83].

1.6.2.4. Scottish Medicines Consortium approved treatments approved for advanced melanoma

The SMC has approved several treatments for advanced or metastatic melanoma over the past decade, including immunotherapy and targeted therapy regimens.

Table **1.5** presents all the SACT recommended by the SMC until January 30th, 2024. This is a summary of ICI and targeted therapy drugs and their indication recommended by SMC, some of which might follow restrictions. A second assessment regarding the use of pembrolizumab was completed on the 4th November 2016 by the SMC [86]. This assessment followed a resubmission for the use of pembrolizumab as monotherapy for the treatment of advanced melanoma in adult patients previously treated with ipilimumab. However, this approval was not authorised and the use of pembrolizumab is not recommended for use within NHS Scotland for this patient group. Despite the results in a phase III randomised study showing an improvement in PFS in comparison with chemotherapy, the submitting company failed to present a robust economic analysis to justify the relation between health benefits and treatment costs [86]. The combination of the *BRAF* and MEK inhibitors cobimetinib plus vemurafenib is approved by the Food and Drug Administration (FDA) and EMA for the treatment of adult patients with metastatic melanoma with a $BRAF^{V600}$ mutation [87], [88]. However, this combination therapy is not recommended for use within NHS Scotland. The holder of the marketing authorisation had not made a submission to the SMC regarding the indication mentioned above, resulting in the failed recommendation by the SMC [89].

Table 1.5 – Treatments recommended for use by the Scottish Medicines Consortium [90]

Medicines	Indication	Date of publication
Ipilimumab	Treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy [91].	08/03/2013
	Treatment of advanced (unresectable or metastatic) melanoma in adults (first-line use) [92].	10/11/2014
	Monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adolescents 12 years of age and older [93].	08/10/2018
Pembrolizumab	Monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adults previously untreated with ipilimumab [94].	09/11/2015
Nivolumab	Monotherapy for the treatment of advanced (unresectable or metastatic) melanoma in adult patients previously untreated with ipilimumab [95].	08/08/2016
	Combination with ipilimumab for the treatment of advanced (unresectable or metastatic) melanoma in adults as a first-line treatment [96].	07/11/2016
	Monotherapy for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection [97].	10/12/2018
Dabrafenib	Monotherapy treatment of adult patients with unresectable or metastatic melanoma with a *BRAF*^{V600} mutation who have received no prior therapy [98].	09/03/2015
	Combination with trametinib for the adjuvant treatment of adult patients with Stage III melanoma with a *BRAF*^{V600} mutation, following complete resection [99].	11/02/2019
Vemurafenib	As monotherapy for the treatment of adult patients with *BRAF*^{V600} mutation-positive unresectable or metastatic melanoma as a first-line treatment [100].	09/12/2013
Trametinib	Combination with dabrafenib for the treatment of adult patients with unresectable or metastatic melanoma with a *BRAF*^{V600} mutation as a first-line treatment [101].	12/09/2016
	Combination with dabrafenib for the treatment of adult patients with unresectable or metastatic melanoma with a *BRAF*^{V600} mutation [102].	08/03/2021
Encorafenib	Combination with binimetinib for the treatment of adult patients with unresectable or metastatic melanoma with a *BRAF*^{V600} mutation [103].	10/02/2020

1.6.3. Health economic evaluation of advanced melanoma treatments

The economic burden of advanced melanoma is substantial, requiring a thorough evaluation of the cost-effectiveness of various treatment options available. As healthcare systems attempt to allocate resources efficiently, understanding the economic value of treatments such as immunotherapy and targeted therapy is important.

Immunotherapy and targeted therapy drugs have revolutionised the treatment landscape for advanced melanoma. These therapies offer significant clinical benefits, however their high costs pose challenges for healthcare systems, making economic evaluations crucial. Cost-effectiveness studies assess the value of these treatments by comparing their costs and health outcomes, such as quality-adjusted life years (QALYs) and life years (LYs), to determine their overall economic impact. Cost-Effectiveness analysis is a critical component of the HTA process. NICE and SMC use cost-utility analysis, where the effectiveness of a drug is measured in terms of QALYs gained. The cost per QALY is then compared to a threshold, typically between £20,000 and £30,000 per QALY gained [104]. If the cost per QALY is below this threshold, the drug is considered cost-effective.

The information in this section helped the development of the health economic evaluation and cost-effectiveness model, which will be further detailed in Chapter 5.

1.6.3.1. Background on economic evaluations of immunotherapy and targeted therapy for advanced melanoma

The introduction of new treatments, including ICIs, *BRAF* and MEK inhibitors has significantly improved OS and PFS for patients with advanced melanoma. A systematic literature review was conducted to evaluate the published evidence on the cost-effectiveness of these pharmacological treatments [105]. This review was published in

May 2017 and was conducted in PubMed, EMBASE, Scopus, the Cochrane Library, the NICE databases, and the Health Technology Assessment journal [105]. The review identified nine full text pharmacoeconomic analyses of advanced melanoma treatments. According to the economic analyses, the new treatments have been shown to be more effective, providing more LYs and QALYs than chemotherapy [105]. However, the cost per QALY gained was above the commonly accepted threshold, indicating that these treatments may not be considered cost-effective under standard criteria. Additionally, due to the variability of the available analyses comparing the new treatments, the authors could not determine which treatment was the most cost-effective [105]. Despite this review having a comprehensive in scope, it was constrained by its 2017 cut-off and reliance on early evaluations with limited real-world validation.

Building on this evidence, a systematic review by Gorry *et al.* (2020) expanded the synthesis to 15 decision-analytic model-based studies published up to September 2018 [106]. This review provided a comparative assessment of model structures and assumptions. It found that PD-1 inhibitors such as nivolumab and pembrolizumab were generally cost-effective compared with ipilimumab, though their cost-effectiveness relative to chemotherapy remained uncertain due to variations in comparators and assumptions [106]. In contrast, *BRAF* monotherapies and *BRAF*/MEK combinations were consistently not cost-effective, and the nivolumab plus ipilimumab combination was unlikely to be cost-effective under any scenario. The systematic review also observed through statistical analysis that evaluations published in health economics journals tended to report higher methodological quality compared with those in clinical journals. Strengths of this review include its systematic assessment of structural and methodological consistency, which provided valuable insights into the reliability of reported outcomes. However, most studies were based on immature trial data with long-term survival extrapolated using parametric models that may over- or underestimate benefit. Additionally, the structural heterogeneity across the various models reduced comparability.

A more recent retrospective study examining health care utilisation and costs associated with systemic therapies for metastatic melanoma from 2016 to 2020 found that nivolumab surpassed pembrolizumab as the most prescribed systemic melanoma therapy during this period [107]. The treatments under studied included ICIs and

targeted therapies: nivolumab, pembrolizumab, ipilimumab plus nivolumab, and a *BRAF*/MEK inhibitors combination [107]. Relative to nivolumab, all other therapies were associated with increased total healthcare costs, with ipilimumab plus nivolumab and targeted therapies (*BRAF*/MEK inhibitors) also linked to more inpatient hospital days. Nivolumab monotherapy emerged as the most used and least costly systemic treatment from 2016 to 2020, potentially due to the earlier adoption of less frequent dosing intervals. The study found that regimens including anti-CTLA4 therapy (e.g., ipilimumab plus nivolumab) may be associated with greater immune-related adverse event (irAE) related healthcare resource utilisation and costs compared with anti-PD1 monotherapies (nivolumab or pembrolizumab) [107].

More recently, a study published in 2023 compared the cost-effectiveness of four combination therapies for the first-line treatment of metastatic melanoma with the $BRAF^{V600}$ mutation: atezolizumab-vemurafenib-cobimetinib, vemurafenib plus cobimetinib, dabrafenib plus trametinib, and encorafenib plus binimetinib [108]. Authors developed a patient-level model to project health outcomes, including direct costs, QALYs, and the incremental cost-utility ratio (ICUR), from the US payer perspective. The transition probabilities were estimated from clinical trials using a parametric survival model. This model allowed for a detailed analysis of the economic impact of each treatment strategy, considering both clinical efficacy and financial implications [108].

The results of the study indicated that the triple combination of atezolizumab-vemurafenib-cobimetinib produced the best health outcomes among the four therapies assessed. However, the least expensive option was the combination therapy of vemurafenib plus cobimetinib [108]. Additionally, ICURs were calculated to compare the cost-effectiveness of the different treatment strategies. The ICUR for dabrafenib plus trametinib versus vemurafenib plus cobimetinib was $325,113 per QALY, while the ICUR for atezolizumab-vemurafenib-cobimetinib versus dabrafenib plus trametinib was $2,247,500 per QALY. Encorafenib plus binimetinib was found to be dominated by the other three competing strategies, meaning it was less cost-effective in comparison [108]. The authors in this study concluded that the *BRAF*/MEK inhibitors combination of vemurafenib plus cobimetinib could be considered the most cost-effective treatment at the willingness-to-pay threshold of $150,000 per QALY [108].

In summary, the body of evidence demonstrates consistent improvements in health outcomes with ICIs and targeted therapies compared with chemotherapy, but their cost-effectiveness remains highly variable. The early reviews and expanded synthesis by Gorry *et al.* (2020) confirm that PD-1 inhibitors offer greater value than ipilimumab, but questions remain regarding their cost-effectiveness relative to chemotherapy, the role of combination regimens such as nivolumab plus ipilimumab, and the generalisability of findings across different jurisdictions. Strengths of the literature include the use of structured modelling approaches and the gradual incorporation of real-world utilisation data. However, persistent limitations such as heterogeneity in modelling assumptions, reliance on immature survival data, inadequate sensitivity analyses, and narrow geographical perspectives restrict the confidence with which conclusions can be drawn. These issues underscore the need for updated systematic reviews incorporating more recent data and real-world evidence to provide a more robust and contemporary understanding of the economic value of advanced melanoma therapies.

1.6.3.2. Use of real-world evidence in cost-effectiveness studies of advanced melanoma treatments

Health economic evaluations can be conducted using various types of data, including real-world data, in addition to clinical trial data. While clinical trial data are typically used when regulatory authorities like NICE and SMC request cost-effectiveness analyses of new medicines, real-world data can provide valuable insights into the actual use and economic impact of treatments in everyday clinical practice.

A real-world cohort study was conducted to assess the cost-effectiveness of second-line ipilimumab versus non-ipilimumab treatments for metastatic melanoma in Ontario, Canada [109]. This study aimed to provide insights into the economic impact of ipilimumab in a real-world setting, as opposed to controlled clinical trials. In this study ipilimumab was associated with an ICUR of $225,885 per QALY when adjusting for quality of life using utility weights (see section 5.3.2.3). Even with a 100% reduction in

the price of ipilimumab, the ICUR remained high at $111,728 per QALY. Thus, in this study it was concluded that despite its clinical benefit, ipilimumab as second-line monotherapy for metastatic melanoma patients is not cost-effective in the real-world under conventional willingness-to-pay (WTP) thresholds [109]. The incremental clinical benefit associated with ipilimumab was lower than that estimated by the manufacturer and suggested that ipilimumab monotherapy is not a cost-effective option for metastatic melanoma patients, but the immunotherapy combination of ipilimumab plus nivolumab may be a more optimal and cost-effective approach [109].

More recently, Blommestein *et al.* (2025) conducted a real-world cost-effectiveness study in the Netherlands using national cancer registry data to evaluate the cost-effectiveness of treatment sequences with immunotherapy and targeted therapy in advanced melanoma [110]. This analysis incorporated observed treatment duration, discontinuation rates, toxicity-related healthcare resource use, and sequencing patterns. The study found that combination immunotherapy (nivolumab plus ipilimumab) as a first-line treatment followed by *BRAF*/MEK inhibitor in the second-line treatment yielded the highest life expectancy and QALYs [110]. Importantly, the study highlighted that the first treatment administered in a sequence along with assumptions regarding the treatment during have a substantial impact on cost-effectiveness outcomes [110]. These findings demonstrate how treatment patterns in real-world clinical practice can modify cost-effectiveness conclusions, reinforcing the need to integrate real-world evidence into health technology assessments (HTAs).

Cost-effectiveness analyses using real-world and clinical trial data can provide different results. Clinical trials are conducted in controlled environments with strict protocols, which may not fully capture the complexities and variations of real-world clinical practice. Real-world data reflects the actual use of treatments in diverse patient populations and healthcare settings, providing a more comprehensive understanding of their economic impact.

Therefore, real-world studies can capture long-term outcomes and adverse events that may not be evident in the shorter duration of clinical trials. Additionally, cost-effectiveness analysis using real-world data might provide insights into actual healthcare resource utilisation, including hospitalisations, outpatient visits, and adverse event treatment, which are important for accurate economic evaluations. By incorporating

real-world evidence into economic evaluations, healthcare providers and policymakers can make more informed decisions about the allocation of resources for melanoma care, ensuring that treatments provide value for money and improve patient outcomes.

1.7. Literature search strategy

To inform the background presented in this chapter, a structured literature search was conducted using PubMed, Scopus, and the Cochrane Library. The search focused on studies reporting on systemic anti-cancer therapies in advanced, unresectable, or metastatic melanoma. The following search terms were applied in various combinations:

- (“advanced melanoma” OR “metastatic melanoma” OR “unresectable melanoma”) AND (“immunotherapy” OR “nivolumab” OR “ipilimumab” OR “pembrolizumab”) AND (“targeted treatment*” OR “dabrafenib +/- trametinib” OR “vemurafenib +/- cobimetinib” OR “encorafenib +/- binimetinib”);
- (“advanced melanoma” OR “metastatic melanoma” OR “unresectable melanoma”) AND ((“immunotherapy” OR “nivolumab” OR “ipilimumab” OR “pembrolizumab”) OR (“targeted treatment*” OR “dabrafenib +/- trametinib” OR “vemurafenib +/- cobimetinib” OR “encorafenib +/- binimetinib”)) AND (survival OR mortality OR death);
- (“advanced melanoma” OR “metastatic melanoma” OR “unresectable melanoma”) AND ((“immunotherapy” OR “nivolumab” OR “ipilimumab” OR “pembrolizumab”) OR (“targeted treatment*” OR “dabrafenib +/- trametinib” OR “vemurafenib +/- cobimetinib” OR “encorafenib +/- binimetinib”)) AND (survival OR mortality) AND (“clinical trial*” OR “observational”).

Searches were limited to articles published in English. Titles and abstracts were screened to identify relevant studies, with a focus on clinical trials and observational studies reporting survival outcomes, treatment efficacy, sequencing, or health economic

evaluations in advanced melanoma. Additional articles were identified through citation tracking and reference lists of key publications.

1.8. Research questions and aims

Despite the current advances in the treatment of advanced melanoma, considerable uncertainty remains regarding the optimal use and sequencing of modern SACTs in real-world clinical practice. While clinical trials have demonstrated improvements in progression-free and overall survival with immunotherapy and targeted therapy, trial populations may not fully reflect patients treated in routine care, and evidence on long-term outcomes, treatment sequencing, and cost-effectiveness in real-world settings remains limited. In particular, there is a lack of UK-based real-world evidence assessing how treatment choice and sequencing influence both clinical and economic outcomes for patients with advanced melanoma.

The overall aim of the work in this thesis is to determine the clinical outcomes of patients receiving systemic anti-cancer treatment for advanced (unresectable or metastatic) melanoma using real-world evidence from Scottish patients. To address this aim, the thesis is guided by the following overarching research questions:

- What are the real-world survival outcomes and prognostic factors for patients with advanced melanoma treated with immunotherapy and/or targeted therapy in Scotland?
- How treatment transitions between immunotherapy and targeted therapy influence survival outcomes in routine clinical practice?
- What is the cost-effectiveness of first-line immunotherapy versus first-line targeted therapy using real-world survival and treatment patterns?

These research questions are addressed through the following objectives, which reflect the topics discussed from the literature reviewed in Chapter 1:

Survival analysis:

- Identify a patient cohort for advanced melanoma patients from real-world evidence from the region of Greater Glasgow and Clyde;
- Describe the baseline characteristics of the patient cohort;
- Determine the survival outcomes of SACT treatments such as median OS, duration of treatment and time to subsequent treatment;
- Identify patient factors associated with survival outcomes.

Multi-state modelling:

- Develop a multi-state model for OS in advanced melanoma patients;
- Investigate how therapy changes impact the survival of advanced melanoma patients;
- Explore the sojourn times and transition probabilities associated with the lines of treatment for immunotherapy and targeted therapy.

Health economic evaluation:

- Develop an efficient, fast and adaptable multi-state cost-effectiveness model in R to facilitate health economic evaluations;
- Determine the cost-effectiveness of immunotherapy and targeted therapy treatments in a real-world setting;
- Investigate the influence of first- and second-line treatments (immunotherapy or targeted therapy) in QALYs.

1.9. Cancer Medicines Outcomes Programme

This research project was conducted in collaboration with the Cancer Medicines Outcomes Programme (CMOP), which played a fundamental role by offering resources to access data and conduct all analyses within this thesis. Permission for data access was obtained from Public Benefit and Privacy Panel (PBPP) [111].

The CMOP's involvement facilitated the exploration of real-world data concerning cancer patients, contributing significantly to a deeper understanding of treatment

pathways and outcomes. This research project aimed to study the effectiveness and safety of cancer medicines in routine care settings, thus aligning with CMOP's broader vision to better understand the real-life impact of cancer treatments on Scottish cancer patients [112].

1.10. Thesis outline

The initial chapter of this thesis, Chapter 1, will focus on providing an introductory background on melanoma, encompassing domains including genetics, epidemiology, available treatments for this disease, the approval processes governing them, and emerging treatments currently under study. With a specific emphasis on novel treatments such as immunotherapy and targeted therapy, this chapter prepares the reader for a deeper understanding of the complexities of melanoma, the analyses and discussions that will come later in the thesis.

0 of this thesis describes the fundamental features of the data used in all the analyses, outlining the requirements for variable inclusion along with their definitions. This chapter facilitates the understanding of the future analytical processes by providing a detailed explanation of the dataset that was used.

Chapter 3 encompassed a survival analysis study centred around a cohort of patients diagnosed with advanced melanoma. The methods employed in this analysis included statistical techniques such as Kaplan-Meier estimates and plots to assess survival probabilities over time. The study also employed the log-rank test for comparing survival curves. Additionally, Cox proportional-hazards (PH) models were used to analyse the association between covariates and survival outcome. Both univariable and multivariable survival analyses were performed to assess the impact on survival outcomes from the multiple covariates included in the study. Additionally, time-dependency adjusted Cox PH models were created to examine how this cohort's survival was affected over time by body-mass index (BMI) and type of therapy.

Following the survival analysis, Chapter 4 involved the development of a multi-state model to clarify the anti-cancer treatment route of advanced melanoma patients treated with immunotherapy or targeted therapy medicines. The primary method

employed was a continuous time multi-state Markov model, capturing the transitions between various health states during the treatment course. The health states included in this model were based on the line of treatment: first and second lines with either immunotherapy or targeted therapy. The model's assessment involved the creation and analysis of next state probability and transition probability matrices, offering insights into the probabilities of transitioning between different health states during the treatment trajectory.

In Chapter 5, a health economic evaluation was conducted focusing on the implications of drug acquisition costs and the cost-effectiveness of melanoma treatments in a real-world setting. The technique used to model the transitions between various health states according to disease progression was an individual-level continuous time state transition model (ICTSTM) using parameters from the multi-state Markov model. The assessment of QALYs, ICUR, and cost-effectiveness analysis were all integrated in this chapter. This economic model was described and displayed through cost-effectiveness planes, acceptability curves, and the exploration of expected value of perfect information, providing information on the cost-effectiveness of different treatment strategies. Additionally, probabilistic sensitivity analysis was conducted in order to test the robustness of the model.

Finally, the conclusions and further research are depicted in Chapter 6.

1.11. Conclusion

This chapter presents the findings of a literature search on the historical context of melanoma, the state of its current treatment, emerging therapies currently under study, and an overview of the disease's genetic landscape, epidemiology, drug approval procedures in the UK and health economic evaluations.

The introduction of ICIs and *BRAF*/MEK inhibitors has revolutionised the current landscape of advanced melanoma treatment. For patients with *BRAF*-mutant melanoma, combinations of *BRAF* and MEK inhibitors have become the standard of therapy due to their substantial improvements in PFS and OS. Furthermore, immunotherapy with ICI has proven to be effective in treating cases of both *BRAF*-wild-

type and *BRAF*-mutant melanoma, further expanding treatment options for patients across different genetic subtypes. The treatment landscape for advanced melanoma continues to evolve in constant and rapid evolution with the introduction of targeted and immunotherapeutic therapies. The exploration of sequential treatment strategies involving the combination of both *BRAF* and MEK inhibitors plus ICI is a potentially effective way to improve treatment results and overcome resistance mechanisms. Similarly, ongoing investigations into triple combination therapies, including ICI with *BRAF* and MEK inhibitors, possess potential for producing synergistic effects and improving the effectiveness of treatment. The most recent example is the FDA's approval of atezolimumab with *BRAF* and MEK inhibitors, vemurafenib and cobimetinib, as the first triple combination treatment for metastatic melanoma.

Furthermore, retrospective data from patients treated in real-world clinical settings offers valuable insights into current treatment practices and sequencing patterns for advanced melanoma. Though lacking the rigour and control of clinical trials, real-world data can serve as a complementary tool for informing future research and the development of new clinical trials. Researchers can enhance treatment regimens, optimise patient care, and eventually improve outcomes for patients affected by advanced melanoma by leveraging the combined knowledge obtained from clinical trials and real-world observations.

Also, health economic evaluations highlight the complexities and challenges in assessing the cost-effectiveness of advanced melanoma treatments. By focusing on real-world evidence and comprehensive economic evaluations, healthcare providers and policymakers can make informed decisions about the allocation of resources for advanced melanoma care. Furthermore, the increased costs of modern systemic therapies are not solely attributed to direct drug-related expenses but also include indirect costs related to the management of adverse events. This highlights the need for comprehensive economic evaluations that consider both direct and indirect costs to fully understand the financial impact of these treatments on healthcare systems.

Patients diagnosed with advanced melanoma and treated with immunotherapy or targeted therapy provide a valuable dataset for evaluating the economic impact of these treatments in a real-world setting. By focusing on real-world data, this research aims to fill gaps in the current literature and provide more insight into the cost-effectiveness of

new treatments from a UK perspective. Understanding the real-world cost-effectiveness of these treatments is essential for making informed decisions about resource allocation and ensuring that patients receive the most effective care.

In summary, despite the progress made in the advanced melanoma treatment landscape over the past decades, there is still uncertainty regarding the optimal course of treatment for this condition, how to use these treatments in real-world settings, how to sequence therapies to improve clinical outcomes, and how to balance clinical and economic effectiveness. The heterogeneous nature of advanced melanoma, characterised by diverse genetic mutations, presents a challenge to developing standardised treatment approaches that effectively address individual patient needs and disease characteristics. Furthermore, the long-term efficacy, durability of response, and potential for treatment resistance remain areas of ongoing investigation and debate within the scientific community. Addressing this gap forms the basis of the present thesis. The overall aim of this work is to determine the clinical outcomes of patients receiving SACT for advanced melanoma in Scotland, using real-world evidence. Specifically, the objectives are to describe survival outcomes and associated patient factors, develop and apply multi-state models to examine treatment sequencing, and evaluate the cost-effectiveness of targeted therapy and immunotherapy in this population. By linking clinical and economic perspectives, this thesis seeks to generate evidence that can guide clinical practice and policy decisions for the management of advanced melanoma.

Chapter 2 Data description

The real-world data used in this study originated from patient healthcare in health boards across the region of Greater Glasgow and Clyde. Patients were identified from the West of Scotland Cancer Network (WoSCAN) using the Chemotherapy Electronic Prescribing and Administration System (CEPAS) which contains records of all SACT prescribed within WoSCAN. This system serves about half the population of Scotland (approximately 2.5 million people) including patients from the following Scottish health boards: NHS Ayrshire and Arran; NHS Forth Valley; NHS Greater Glasgow and Clyde; and NHS Lanarkshire [113].

CEPAS is an integrated electronic platform that is used by 14 NHS Scotland health boards to manage patient scheduling and chemotherapy prescriptions [114]. It operates through three Regional Cancer Networks: the WoSCAN, the North Cancer Alliance, and the South East Scotland Cancer Network (SCAN) [114]. CEPAS supports both adult and paediatric SACT prescribing, covering every step of the treatment pathway, from initial evaluation and prescription to scheduling, dispensing, and administering SACT to tracking treatment-related effects and results [114]. Additionally, CEPAS accesses and transfers patient demographic and laboratory data from nearby NHS board repositories using the Community Health Index as the primary patient identification [114]. Thus, keeping an extensive collection of SACT regimens and supportive care that goes along with them, including unlicenced and phase I–III experimental medicines [114].

All analyses in this chapter were conducted in R programming language using RStudio® as the primary software environment on individual patient-level data (IPD) from patients diagnosed with advanced melanoma. Data was accessed through the SafeHaven from the University of Glasgow through a secure network connection.

2.1. Data manipulation

The raw data comprised four datasets: '*WoS Melanoma Chemocare*', which included CEPAS prescribing information such as diagnosis, treatment regimen, appointment dates, cycle information, and supportive clinical data such as weight and

height; the '*CHI deaths database*', which contained demographic information including date of birth, sex, and deprivation index alongside mortality records such as date of death; the '*BRAF dataset*', which provided laboratory test results for *BRAF* mutation status; and the '*SCI laboratory dataset*', which contributed additional clinical biomarkers including lactate dehydrogenase (LDH). All datasets were linked using the anonymised SafeHavenID as the unique patient identifier.

Demographic variables were extracted from the CHI deaths database. Dates of birth and death were standardised into a uniform date format. Sex was recoded into a binary male or female variable, and socioeconomic status was represented using the Scottish Index of Multiple Deprivation (SIMD) quintile, which was recategorised as a factor variable. Mortality information was used to derive a binary event indicator that distinguished between patients who had died and those who were censored at last follow-up. Follow-up time was then calculated as the difference between the date of first treatment and either the date of death or the date of the last recorded appointment if censored, and expressed in months to help interpretation.

From the CEPAS prescribing dataset, patients were filtered to include only those with a diagnosis of advanced melanoma in order to create a subset with the population of interest. The format of appointment dates was standardised to match the date format of date of birth and date of death. Treatment regimen, cycle, and diagnosis variables were encoded as factors.

The BRAF dataset was cleaned to identify patients with confirmed BRAF gene mutations. Multiple text-results entries were consolidated into a binary classification of either '*BRAF* mutation' or '*BRAF* wild-type'. The *BRAF* status variable was modified based on laboratory results from the presence of a BRAF gene mutation in the patient's biopsy samples. Patients with a detected mutation were assigned the status '*BRAF-mutant*' while those without a mutation were categorised as '*BRAF-wild-type*'. This classification is essential because the presence of a BRAF mutation determines eligibility for targeted therapies treatment.

However, the dataset contained missing BRAF gene status information for 136 patients in the cohort. To address this issue, an assumption was applied: if a patient had been prescribed targeted therapy during their course of treatment, their *BRAF* status was set to '*BRAF-mutant*'. This assumption is based on clinical practice guidelines, which

stipulate that targeted therapy drugs, such as *BRAF*/MEK inhibitors, are only administered to patients with a confirmed *BRAF* mutation. This approach corrected the status for 69 patients, filling in missing values where the treatment regimen provided a clear indication of their mutation status.

For the remaining 67 patients with no documented *BRAF* status, no further assumptions were made. These cases were left as missing data because *BRAF* status does not influence eligibility for non-targeted therapies, such as immunotherapy. This transformation ensured that the variable was as complete and accurate as possible without introducing undue bias.

Treatment-related variables included multiple names and study codes for the same therapy. These were systematically recategorised into a simplified drug variable and a therapy type variable to avoid drug misclassification. Treatment duration was also standardised. A treatment order variable was generated for each patient, in chronological order of each SACT received during course of treatment, to facilitate the evaluation of treatment sequencing. Patients with only one line of therapy were classified as monotherapy, while those who received multiple distinct drugs or types were categorised as receiving multiple lines of therapy. Switching treatment was further divided into switching by drug, defined as receiving two or more distinct drugs; and switching by therapy type, defined as receiving therapies from two or more different therapy classes. The number of distinct SACT received was also captured as a separate variable with categories of one, two, or three or more treatments.

Additionally, the covariates available in the dataset were modified and used to generate new covariates such as age, death or censoring, follow-up time, drug used in each appointment, type of therapy, BRAF gene status (*BRAF*-wild-type and *BRAF*-mutant), BMI, BMI group, Eastern Cooperative Oncology Group Performance Status (ECOG PS), and lactate dehydrogenase (LDH) blood level. Age was created based on the date of birth and appointment date in each observation. A variable for death was created based on the presence or absence of a date of death for each patient. Following this, we calculated the follow-up time for each patient. Follow-up time was the time difference between the first appointment date and the last appointment or date of death, and it was displayed in days. The drug and type of therapy covariates were modified from the regime variable, which included multiple designations for the same

treatment. The drug covariate only included the name of the drug used in each appointment. Also, a new variable with the type of therapy based on the previous drug covariate was created. Therefore, drugs were categorised into immunotherapy, targeted therapy and chemotherapy based on its drug class.

The BMI is defined as the body-mass divided by the square of the body height and is expressed in units of kg/m^2. When available, BMI was calculated based on patient's weight and height at each appointment date. Afterwards, BMI was categorised in accordance with WHO parameters represented in Table 2.1 [115].

Table 2.1 – Nutritional status according to values of BMI from the World Health Organization

BMI (kg/m^2)	Nutritional status
Below 18.5	Underweight
18–24.9	Normal weight
25.0–29.9	Overweight
30.0–34.9	Obesity class I
35.0–39.9	Obesity class II
Above 40	Obesity class III

Abbreviations: BMI – Body-mass index; kg – Kilograms; m^2 – Squared metres

Biomarkers were added by linking SCI records to the melanoma cohort. Only LDH values, defined as the first available measurement per patient, were retained in the melanoma cohort. A numerical LDH covariate and a categorical variable for LDH groups were created based on the levels in blood samples. For LDH as a categorical variable, serum levels of LDH are considered normal when these were lower or equal to 333 U/L [116]. Measurements above 334 U/L were considered high levels of LDH [117].

The ECOG Performance Status includes 5 grades that describe a patient's level of functioning in terms of their ability to selfcare, daily activities, and physical capability such as working and walking, for example [118]. The description for each grade of ECOG PS is displayed in Table 2.2 [118]. However, due to the small number of observations, ECOG PS equal to 2 or higher were compiled in a single group (ECOG PS 2+). Therefore, in this study, the ECOG PS covariate encompasses three levels: ECOG PS 0, ECOG PS 1 and ECOG PS 2+.

Table 2.2 – ECOG Performance Status grades and description

Grade	ECOG Performance Status [118]
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (E.g., light house work, office work)
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; Confined to bed or chair more than 50% of waking hours
4	Completely disabled; Cannot carry on any selfcare; Totally confined to bed or chair
5	Dead

Abbreviations: ECOG – Eastern Cooperative Oncology Group

2.2. Patient eligibility criteria

Regarding exclusion criteria, patients under 18 years old at the time of the first appointment were excluded from the cohort. Also, melanoma patients not considered to be in an advanced stage of disease were also excluded. Thus, 13 patients were excluded due to disease stage, and one patient was excluded due to age.

The final cohort included 350 patients diagnosed with advanced melanoma (stage IV) and aged 18 years old at the time of the first registry entry. Data included information from 2784 appointments between March 2008 and March 2018 with multiple appointment entries by patients.

2.3. Data limitations

It is important to recognise the limitations of the data used in this research study. Firstly, the cohort size was small which could potentially constrain the generalisability of the findings to a broader population. A small sample size may not capture the full variability and diversity of patient experiences and outcomes, thereby limiting the ability to draw robust conclusions that are applicable to a wider Scottish demographic.

Additionally, the dataset lacked components such as laboratory results and detailed information on previous treatments (i.e. other SACT, treatments for other diseases/health conditions), surgeries, and hospitalisations. The absence of this information restricts the understanding of patients full clinical history and the factors influencing their treatment outcomes. Without these data points, it is challenging to account for all variables that may affect patient survival and treatment efficacy.

Furthermore, the study did not include information regarding adverse events, which is crucial for assessing the tolerability and safety of the SACT administered to treat advanced melanoma. The ability to evaluate the incidence of adverse effects is particularly important for newer therapies, such as immunotherapy and targeted therapy, where long-term safety profiles are still being established. This gap limits the study's capacity to fully assess the risk-benefit balance of these treatments.

Another limitation involves confidentiality and statistical reliability concerns, which prevented the reporting of data points with counts were below five (absolute number).

These limitations underscore the need for thoughtful interpretation of the findings. While this study provides valuable insights into treatment outcomes for advanced melanoma, the results must be interpreted with caution when extrapolating these results to larger or different populations. The highlighted gaps in data availability and completeness suggest directions for future research. Subsequent studies should aim to include larger, more diverse cohorts and integrate comprehensive clinical histories, including laboratory results, previous treatments, and treatment-emergent adverse event reporting. Addressing these limitations will enhance the robustness and applicability of future research findings, providing a more complete picture of patient experiences and treatment outcomes for advanced melanoma in real-world practice.

Chapter 3 Survival analysis of advanced melanoma patients using real-world evidence

3.1. Introduction

Building on the information provided in the previous chapter (0) which describes the data used throughout this thesis, this chapter investigates how the results from clinical trials on immunotherapy and targeted therapy to treat advanced melanoma are mirrored in real-world practice. This chapter focuses on survival outcomes and associated prognostic factors using real-world evidence of patients diagnosed with advanced melanoma in the Greater Glasgow and Clyde region.

The overall aim of this chapter is to evaluate the real-world clinical effectiveness of SACT for advanced melanoma and to identify patient- and treatment-related factors associated with overall survival. This aim is addressed using individual-level real-world evidence to characterise survival outcomes across treatment modalities and to examine prognostic factors that may influence these outcomes in routine clinical care.

To address this aim, the chapter is guided by the following research questions:

1. What are the baseline characteristics of advanced melanoma patients treated with SACT in the Greater Glasgow and Clyde region?
2. What are the OS outcomes for advanced melanoma patients receiving SACT?
3. How do real-world survival outcomes for immunotherapy and targeted therapies compare with those observed in clinical trials for the same treatments?
4. What patient- and treatment-specific factors are associated with OS outcomes?

5. Do these associations between patient factors and survival outcomes vary over time, reflecting potential time-dependent effects?

The chapter is structured to first present the cohort selection and baseline characteristics, followed by analyses of survival outcomes for different treatment modalities, including chemotherapy, immunotherapy, and targeted therapies, to determine their relative effectiveness in a real-world setting. Comparisons are drawn with survival outcomes reported in clinical trials to assess the extent to which trial findings translate into routine clinical practice.

The analysis also investigates factors such as age, sex, comorbidities, and treatment type to identify variables associated with survival outcomes. Furthermore, it examines whether these associations vary over time, acknowledging that the impact of certain factors may shift as the disease progresses or as patients receive subsequent treatments. Thus, this chapter aims to provide insights into the real-world effectiveness of advanced melanoma treatments, identify possible prognostic factors, and compare these findings with results from controlled clinical trials. By understanding these elements, the study seeks to enhance the evidence base for treatment strategies and improve patient outcomes in clinical practice.

3.2. Aims and objectives

The general aim of the work in this chapter is to investigate survival outcomes and factors influencing prognosis in patients with advanced (unresectable or metastatic) melanoma using real-world evidence from Scottish patients. Thus, the objectives of this chapter were:

- Identify a patient cohort for advanced melanoma patients from real-world evidence from the region of Greater Glasgow and Clyde;
- Describe the baseline characteristics of real-world advanced melanoma patients;
- Assess the survival outcomes of SACT treatments such as median OS and time to subsequent treatment using survival analysis;

- Identify patient factors associated with survival outcomes.

3.3. Methods

3.3.1. Study design

This study is a retrospective cohort analysis linking routine healthcare data with SACT prescriptions for advanced melanoma patients treated with immunotherapy (ipilimumab; nivolumab; pembrolizumab; nivolumab plus ipilimumab), targeted therapy (dabrafenib; dabrafenib plus trametinib; vemurafenib), or chemotherapy in the west of Scotland.

3.3.2. Study population

The research cohort consists of patients diagnosed with advanced melanoma, encompassing patients presenting with unresectable or metastatic disease stages (stage IV). By focusing on this specific patient cohort, this research captures the real-world clinical scenario prevalent within the Greater Glasgow and Clyde region, thereby facilitating the generalisability of study findings to the broader population of advanced melanoma patients, specifically in the national context of Scotland.

Moreover, as previously mentioned in 0, the eligibility criteria stipulate that study participants must be over the age of 18 at the time of the first appointment date. By restricting the age range to adult patients only, it ensures homogeneity within the study population, thereby minimising potential confounding factors, and facilitating more robust data analysis and interpretation.

Additionally, the data included in this study includes appointments for patients treated between March 2008 and March 2018, providing a comprehensive assessment of treatment practices and outcomes over a ten-year period. This extended timeframe captures patients treated during the period of inclusion of novel treatments (immunotherapy and targeted therapy) in the current clinical practice for advanced melanoma treatment.

In conclusion, the cohort for the analysis in this chapter included 350 adult patients diagnosed with advanced melanoma (stage IV) treated in the region of Greater Glasgow and Clyde, Scotland.

3.3.3. Outcome definitions

In this study, patients were exposed to SACT with the intent to treat advanced melanoma and prolong patients' lives. The exposure in this study pertains to the administration of various SACT regimens, including immunotherapy, targeted therapy, and chemotherapy. Each of these treatment modalities has distinct mechanisms of action and potential impacts on patient outcomes. By defining exposure based on the administration of these SACTs, the study was able to systematically evaluate their effectiveness in a real-world clinical setting.

The primary outcome of interest in this analysis was OS, which is a crucial measure for assessing the effectiveness of cancer treatments. OS refers to the duration from the start of treatment until death from any cause, or censorship which occurs when a patient is lost to follow-up. By focusing on this outcome, the study aimed to provide a comprehensive evaluation of how well the different SACTs improved advanced melanoma patient survival in a real-world setting.

To explore the relationship between treatment and survival, survival analysis was conducted using HRs. Hazard ratios represent the probability of an event occurring at any given point in time, relative to a baseline. In this study, the event of interest was death, and HRs were employed to compare the relative effectiveness of immunotherapy, targeted therapy, and chemotherapy. By using HRs, the study could provide an understanding of how each treatment influenced survival outcomes. A HR less than 1 indicates a reduction in the risk of death compared to the reference group, while a HR greater than 1 indicates an increased risk. The use of HRs in survival analysis is well-supported in the literature, as they offer a robust statistical method for assessing the impact of different variables on survival [119].

Overall, this study’s methodological approach, including the definition of treatment exposure and the use of OS and HRs as key outcomes, provides a solid

foundation for evaluating the effectiveness of SACTs in treating advanced melanoma in a real-world setting.

3.3.4. Variables

The analysis in this chapter used a dataset encompassing a range of continuous, categorical, and date variables. These variables were instrumental in assessing the influence of different factors on the probability of survival during follow-up. Continuous variables included age, LDH, height, and weight. Categorical variables consisted of sex, SIMD quintile, ECOG PS, *BRAF* status, name of drug treatment, and type of therapy. Additionally, date variables regarding patients' appointment date, date of birth, and date of death were included.

To facilitate subgroup analysis and interpretability, several continuous variables were categorised. The decision to categorise variables and determine which variables to control for in this analysis was informed by discussions with clinicians and clinical oncology pharmacists, whose professional experience provided insight into the clinical relevance of different factors.

Categorical variables created from the dataset included age group, LDH group, BMI group, and censorship. Regarding age, patients were divided according to the age distribution in this cohort, thus creating three categories: '*patients under 50 years*', '*patients between 50 and 65 years'*, and '*patients over 65 years*'. Using the continuous LDH covariate, a new categorical variable was created for LDH. Therefore, LDH was dichotomised into normal LDH level, and high LDH level. Patients with a LDH blood level smaller or equal to 333 U/L were considered as having a normal LDH, and patients with a blood level equal to 334 U/L or higher were considered as having a high LDH level [117].

Additionally, BMI was calculated as a continuous variable based on available data for patients' height and weight. BMI was further manipulated into a categorical variable based on the nutritional status by the WHO as previously described in 0 (Table 2.1).

BRAF status plays a pivotal role in determining the appropriate treatment strategy for melanoma patients and therefore included in this analysis. Mutations in the BRAF gene, particularly the V600E mutation, make tumours more responsive to targeted

therapies like as *BRAF* inhibitors (e.g., dabrafenib, vemurafenib) and MEK inhibitors. Thus, patients with a *BRAF* mutation are eligible for targeted therapies, while patients without a *BRAF* mutation (*BRAF*-wild-type) are not eligible to receive targeted therapy treatment.

In summary, the variables selected for this analysis provide a robust framework for understanding the prognostic factors and treatment implications in advanced melanoma for a real-world setting. ECOG PS and LDH levels are validated as critical prognostic markers for survival, while *BRAF* status continues to guide therapeutic decisions, reflecting the personalised nature of modern oncology [120].

3.3.5. Statistical analyses

A descriptive statistical analysis (section 3.4) was performed to summarise and understand the features of the total patient cohort. Date of last follow-up was defined as the date of last appointment date or date of death, whichever occurred later. Data from this cohort regarding continuous variables, including patient age, blood LDH levels, and BMI, were described using the mean, standard deviation (SD), and range to capture their central tendencies and dispersion. Categorical variables, such as gender, BRAF gene status, and ECOG PS were summarised by absolute numbers and percentages per group.

3.3.5.1. Sankey plots

Following the descriptive statistical analysis, Sankey plots, a type of flow diagram, were used to visualise the movement or transition of data across different categories. In order to create a Sankey plot, data was first organised into nodes and flows. Nodes represent the distinct stages or categories in the analysis, such as different types of therapy in the context of this research study. Flows between these nodes represent the movement of patients between different stages (types of therapy). The width of each flow is determined by the quantity of patients transitioning from one node to another, and the flow width is proportional to the quantity of patients in flow between therapy types. Hence, these plots are designed to show how quantities are distributed and how

they change from one state to another, making it easy to compare the relative sizes of different transitions.

3.3.5.2. Kaplan-Meier estimates

The main outcome considered in this chapter is OS and the methods applied were Kaplan-Meier (KM) estimates, log-rank tests, and Cox PH models. In this chapter, these methods were applied using the input from the variables for gender, age, *BRAF* status, ECOG PS, LDH and BMI. These methods allowed to calculate the different values for median OS which correlate to the association between variables and overall survival. For the purpose of the analysis in this chapter, only categorical variables were used allowing for a subgroup analysis for these variables that explains the survival difference between the variable subgroups.

KM estimates were calculated on baseline levels for the covariates in this analysis to evaluate survival probabilities over time. This analysis also involved running the log-rank test to assess whether there were significant differences in survival between different subgroups of categorical variables. The primary hypothesis tested was that there were no survival differences between the categorical variables' treatment subgroups. To determine the statistical significance of the observed differences in survival probabilities, a p-value threshold was set. If the p-value for the log-rank test was less than or equal to 0.05 (p-value ≤ 0.05), the difference in survival probability was considered statistically significant. This means that there was less than a 5% probability that the observed differences were due to chance alone, thereby providing evidence against the null hypothesis of no difference in survival between the covariate subgroups. Such a rigorous approach ensured that the survival analysis could reliably identify whether specific treatments or patient characteristics were associated with improved or diminished survival outcomes in the cohort under study.

In order to visualise the survival probability, the KM curves were plotted. The correlation between survival probabilities and the categorical variables (sex, LDH group, ECOG PS, and BMI) can be visualised in section 3.4.4, which includes KM curves and respective results for the log-rank tests. Sankey plots were used to easily visualise the

flow of patients between the different drugs and the therapy pathways observed in this cohort as previously mentioned.

3.3.5.3. Cox Proportional-hazards model

In order to assess survival probability in advanced melanoma patients, Cox PH models were fitted using the available data. This method is well-suited for survival analysis as it allows for the examination of the relationship between survival time and multiple covariates, while effectively handling censored data, which is common in survival studies [121].

The proportional-hazards assumption was tested to ensure the validity of the Cox PH models. Schoenfeld residuals, which assesses whether the residuals are independent of time, were examined for each covariate. Both graphical diagnostics and global tests were conducted [122]. Where violations of the PH assumption were detected, time-dependent covariates or stratification were considered to account for non-proportionality.

Additionally, the Cox PH models provides HRs, offering a quantifiable measure of the effect of individual variables on survival outcomes [121]. The Cox PH models incorporated a range of variables, including demographic factors (age, gender, and SIMD quintile), BRAF gene mutation status, ECOG PS, LDH blood levels, and patients' BMI from data registry at the start of SACT (baseline). The variable selection reflects their known or potential impact on survival outcomes in oncology as previously described in section 3.3.4.

Recognising that certain variables might change over time and thus affecting survival outcomes, time-dependency adjusted Cox PH models were developed. To assess the impact of therapy and therapy changes on survival, the data were manipulated to account for time-dependent covariates, thereby avoiding the pitfalls of immortal-time bias [123], [124]. Immortal-time bias occurs when a period of follow-up during which the event of interest (e.g., death) could not occur is incorrectly attributed to a particular treatment, leading to an overestimation of the treatment's effectiveness [123], [124]. In order to mitigate the immortal-time bias, a time-dependency adjusted Cox PH model was developed where type of treatment was treated as a time-dependent

variable. By fitting each type of therapy that patients received throughout the entire course of treatment, rather than attributing survival exclusively to the first-line treatment, this method allowed the model to capture the changes in subsequent therapy administration. Each patient identified with at least one treatment change had the follow-up time split for each therapy cycle. The follow-up time measured was the time from start of therapy until a switch to another therapy type or until an event occurrence (death or censoring). Thus, the model provided a more accurate estimate of survival outcomes based on the entire treatment pathway, reflecting the real-world clinical scenario where patients often undergo multiple lines of therapy.

Additionally, a time-dependency adjusted Cox model with BMI as a time-dependent covariate was created. This method allowed for the examination of how BMI changes over time correlate with OS. The process started by selecting relevant data from the main dataset, focusing on patient ID, appointment date, follow-up time, censoring status, and BMI. Time differences between appointments were calculated, allowing the data to reflect intervals between BMI measurements. The data was then structured to track the order of BMI measurements within each patient's follow-up period, creating a time-dependent framework. Then, a time-dependent data structure was established, incorporating the follow-up period and the event of interest (i.e., death). BMI was then formally integrated as a time-dependent covariate, capturing its fluctuations over time and their impact on survival. Finally, a Cox PH model was fitted, providing hazard ratios associated with BMI at different time points, offering insights into how BMI changes during treatment influence patient survival throughout the study period.

3.3.5.4. Log-rank test

In order to ensure the robustness of the findings from the Cox PH models, log-rank tests were conducted to evaluate the statistical significance of each covariate's effect on OS [125]. Similar to its application in KM estimates, the log-rank test compares the observed survival curves and helps determine whether differences between groups are statistically significant [121], [125].

3.4. Results

3.4.1. Total cohort baseline statistics

The median age of advanced melanoma patients in this study's cohort was 64 years at the time of the first entry and patients' age ranged between 22 and 92 years old. In terms of gender, the distribution of males and females was similar with a slightly higher number of male patients (51.1 % and 48.9 %, respectively). The SIMD quintile appears to be evenly distributed along with the five ranks. The percentage range varies between 17.7% to 22% from ranks 1 to 5 (1 – 21.1 %; 2 – 21.1 %; 3 – 17.7 %; 4 – 17.7 %; 5 – 22 %) with only one patient missing SIMD quintile information.

In this cohort, 75 patients (21.2 %) did not have information about their *BRAF* status. From the remaining 276 patients, 139 (50.4 %) were *BRAF*-mutant, and 137 (49.6%) were *BRAF*-wild-type. Thus, about half of the cohort had a mutation in the *BRAF* gene which aligns with results from the literature [21].

Regarding BMI, patients had a median BMI of 26 at baseline with an interquartile range (IQR) of 23-30. Only a small percentage of patients were considered underweight at the start of their treatment (3.7%), whilst the majority of patients had a BMI above the recommended values and were considered as being overweight or obese (56.9%). Thus, for the purposes of this analysis, the small percentage of patients considered as being underweight where included in the normal group for the subgroup analysis in further sections.

The mean value for LDH at the date of first treatment was 309.9 units per litre (U/L) and the value ranges was between 83 to 5869 U/L. As described in

Table **3.1**, most patients (78%) presented an LDH level considered normal at the time of the first appointment. Also, over half of the patients (52.9%) had registered an ECOG PS of grade 0 at the time of initial treatment, indicating they were fully active at that moment these patients started receiving advanced melanoma treatment.

Table 3.1 – Baseline descriptive statistics of demographic and prognostic factors for advanced melanoma patients

Variable	Category	N
Age (years)	Median (IQR) [Range]	64 (51-74) [22-92]
Gender	Male	179 (51.1 %)
	Female	171 (48.9 %)
SIMD quintile	1	74 (21.1 %)
	2	74 (21.1 %)
	3	62 (17.7 %)
	4	62 (17.7 %)
	5	77 (22.0 %)
BMI	Median (IQR) [Range]	26 (23-30) [14-48]
	Normal	112 (32.0 %)
	Overweight	112 (32.0 %)
	Obese	87 (24.9 %)
	NA	26 (7.4 %)
LDH in units per litre (U/L)	Mean (SD) [Range]	309.9 (403.9) [83-5869]
LDH group	Normal	273 (78.0 %)
	High	62 (17.7 %)
	NA	15 (4.3 %)
ECOG PS	0	185 (52.9 %)
	1	88 (25.1 %)
	2+	40 (11.4 %)
	NA	37 (10.6 %)
BRAF gene status	Wild-type	137 (39.1 %)
	Mutation	139 (39.7 %)
	NA	75 (21.2 %)

Abbreviations: BMI – Body-mass index; BRAF - proto-oncogene B-Raf; LDH – Lactate dehydrogenase; ECOG PS - ECOG Performance Status; SIMD – Scottish Index of Multiple Deprivation; SD – Standard deviation; IQR – Interquartile range; NA – Not applicable

Descriptive statistics for cancer treatments shown that most patients started cancer treatment with drugs developed and approved for use in the last decade for metastatic melanoma: immunotherapy and targeted therapy (Table 3.2). Nearly half of the patients started treatment with an immunotherapy drug (47.1 %), roughly one-third started with a targeted drug (33.4 %), and 16.6 % of patients started chemotherapy.

Pembrolizumab was administered to approximately a quarter of patients (86 patients; 24.6 %), followed by the targeted therapy drug dabrafenib, which was administered to 66 patients (18.9 %).

Whilst most patients were treated with the same type of therapy during the entire course of treatment (65.4%) roughly a third of the cohort had a subsequent treatment with a different type of therapy (therapy switch) than the initial type of therapy for first-line treatment (34.6%).

Regarding survival, at the end of follow-up, 237 patients died (67.7 %). Furthermore, nearly a third of patients (113 [32.3 %]) were still alive at the end of follow-up, with the last death recorded on 25th March 2018.

Table 3.2 – Baseline descriptive statistics for drug treatment, therapy type and outcome for advanced melanoma patients

	Category	N (%)
Drug (first-line)	Dabrafenib	34 (9.7)
	Dabrafenib plus trametinib	42 (12.0)
	Dacarbazine	51 (14.6)
	Ipilimumab	34 (9.7)
	Nivolumab plus ipilimumab	44 (12.6)
	Pembrolizumab	86 (24.6)
	Temozolomide	7 (2.0)
	Vemurafenib	44 (12.6)
	Other	8 (2.3)
Type of therapy (first-line)	Chemotherapy	58 (16.6)
	Immunotherapy	164 (46.8)
	Targeted therapy	120 (34.3)
	Other	8 (2.3)
Therapy switch	Not switched	229 (65.4 %)
	Switched	121 (34.6 %)
Status at end of follow-up	Alive	113 (32.3)
	Dead	237 (67.7)

Notes: '*Other*' drug category includes treatments that were under study in clinical trials or considered as adjuvant treatment

3.4.2. Treatment pathways derived from switching type of therapy

As shown in Table 3.3, a patient subset in this study cohort received a second-line treatment from a different type of therapy than the first-line therapy approach (immunotherapy, targeted therapy, and chemotherapy). Following their first-line therapy course, 146 patients underwent a second-line of treatment with a therapy change. A total of 6 patients received second-line chemotherapy, while 90 and 50 patients received second-line immunotherapy and targeted therapy, respectively. Of these 146 patient who received second-line treatment, a total of 33 received a third-line therapy: 6 patients third-line targeted therapy while 27 patients received third-line immunotherapy. The plot in Figure 3.1 illustrates how patients alternated between the three types of therapy available, immunotherapy, targeted therapy, and chemotherapy. This plot serves as a helpful visual aid to show how the various therapy pathways relate to each other. The type of therapy a patient is receiving is represented by a solid vertical block, thus targeted therapy, chemotherapy, and immunotherapy are represented by a blue, green and red blocks, respectively. The grey or pink lines indicate the transitions to alternative types of therapy, and their width is proportional to the number of patients leaving or starting that type of therapy. Also, the plot should be interpreted from left to right, meaning that patients "leave" the type of therapy through the right-hand side of the block, and enter that type of therapy through the left-hand side of the block.

Table 3.3 – Total number of patients treated for advanced melanoma by type of therapy and line of treatment

	Number of patients		
Therapy type	**First-line treatment**	**Second-line treatment**	**Third-line treatment**
Chemotherapy	58	6	-
Immunotherapy	164	90	27
Targeted therapy	120	50	6
Total (%)	342 (100 %)	146 (42.81 %)	33 (9.68 %)

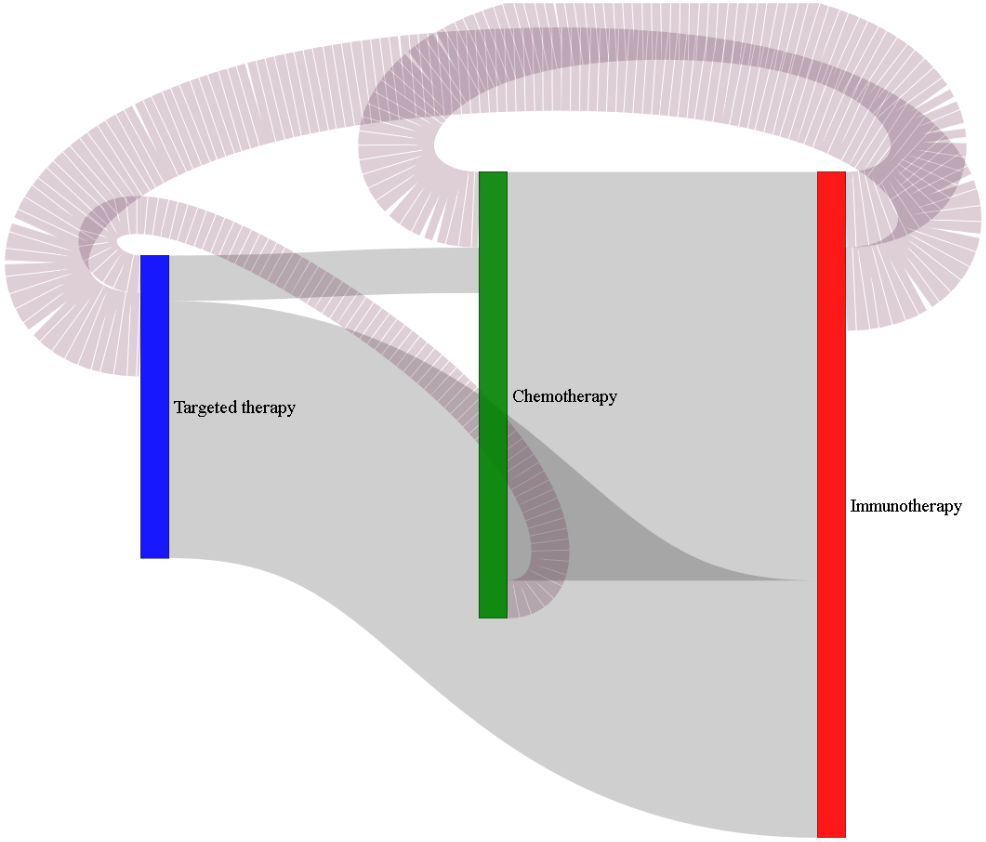

Figure 3.1 – Sankey plot representing the treatment pathways for patients switching type of therapy

3.4.3. Treatment pathways derived from switching drug treatments

The main outcome of this study, OS, is influenced by the complex combination of multiple anti-cancer drugs administered throughout the cancer therapy journey, rather than solely by the first treatment. This complexity is illustrated in the Sankey plot (Figure 3.2), which visually demonstrates the diverse treatment pathways experienced by advanced melanoma patients in real-world practice. In contrast to the more linear treatment procedures observed in clinical trials, some patients, as indicated in Table 3.4, receive up to three different lines of treatment with distinct drugs. Such real-world treatment variability can impact survival outcomes, as emerging evidence suggests that patients often experience a distinct course of treatment compared to those described

in randomised controlled trials (RCTs). Studies have shown that the flexibility in treatment adjustments based on individual responses and new drug availability can lead to differences in survival, underscoring the importance of considering the entire treatment journey rather than only the initial therapy. This highlights the need for more comprehensive and adaptable treatment strategies in clinical practice to better mirror the real-world practice scenarios and improve patient outcomes [126], [127].

Table 3.4 – Total number of patients treated for advanced melanoma by the treatment drug and line of treatment

	Number of patients		
Drug	**First-line treatment**	**Second-line treatment**	**Third-line treatment**
Dabrafenib	34	10	-
Dabrafenib plus trametinib	42	40	6
Ipilimumab	34	75	7
Nivolumab plus ipilimumab	44	5	5
Pembrolizumab	86	10	15
Vemurafenib	44	-	-
Dacarbazine	51	-	-
Temozolomide	7	6	-
Total (%)	342 (100 %)	146 (42.81 %)	33 (9.68 %)

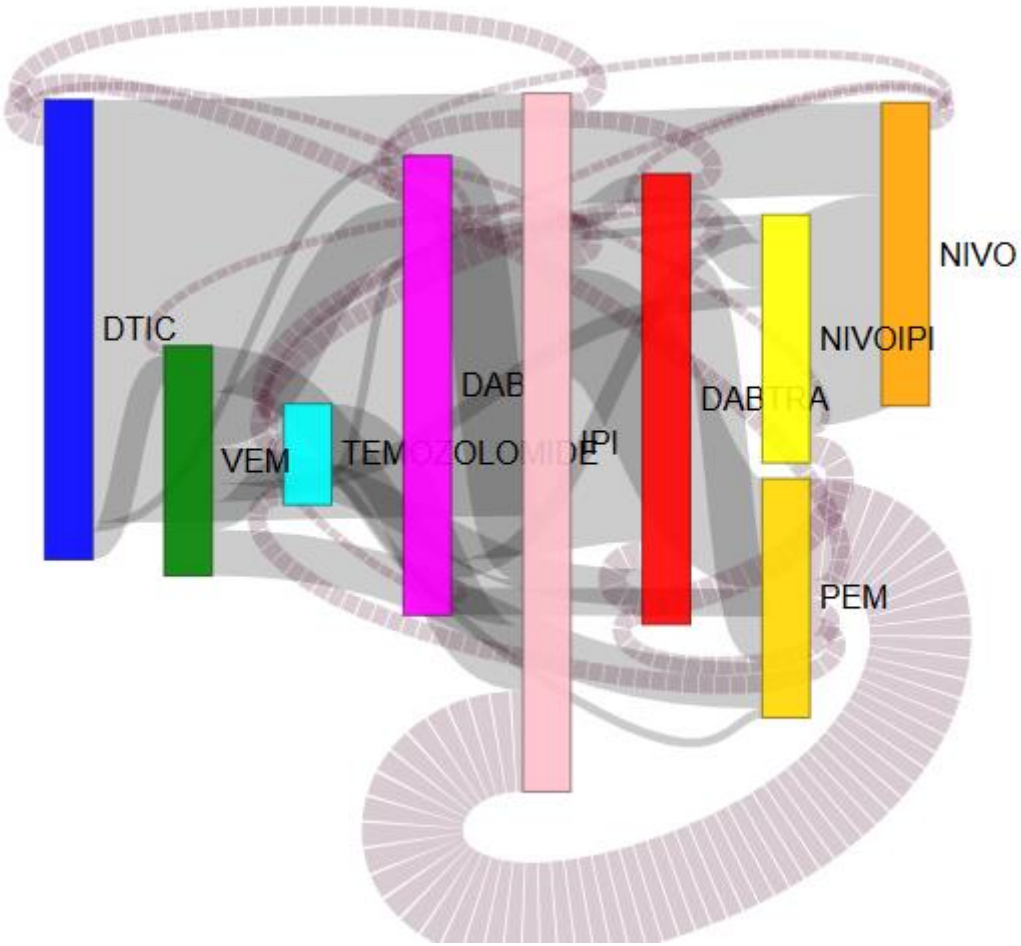

Figure 3.2 – Sankey plot of patients switching drug treatment

Abbreviations: DAB – Dabrafenib; DABTRA – Dabrafenib + trametinib; DTIC – Dacarbazine; IPI – Ipilimumab; NIVO – Nivolumab; NIVOIPI – Nivolumab plus ipilimumab; PEM – Pembrolizumab; VEM – Vemurafenib

3.4.4. Kaplan-Meier estimates and survival curves

3.4.4.1. Total cohort

The KM estimates display the OS probability calculated for the study cohort. For the entire cohort of all 350 adult patients with advanced melanoma included in the study, the median OS was 10 months (95% CI: 9–12 months) as shown in Table 3.5. Notwithstanding being below the 1-year mark, median OS appears to be slightly higher but still comparable to results in the previous decade [3]. Figure 3.3 shows the KM curve

for the entire cohort, showing the median OS and the number of patients at risk at six-month intervals.

Table 3.5 – Summary of KM estimates at baseline for the total study cohort

N	Events	Median OS (months)	0.95 LCL	0.95 UCL
350	237	10	9	12

Abbreviations: LCL – Lower confidence level; N – Number of patients; OS – Overall survival; UCL – Upper confidence level

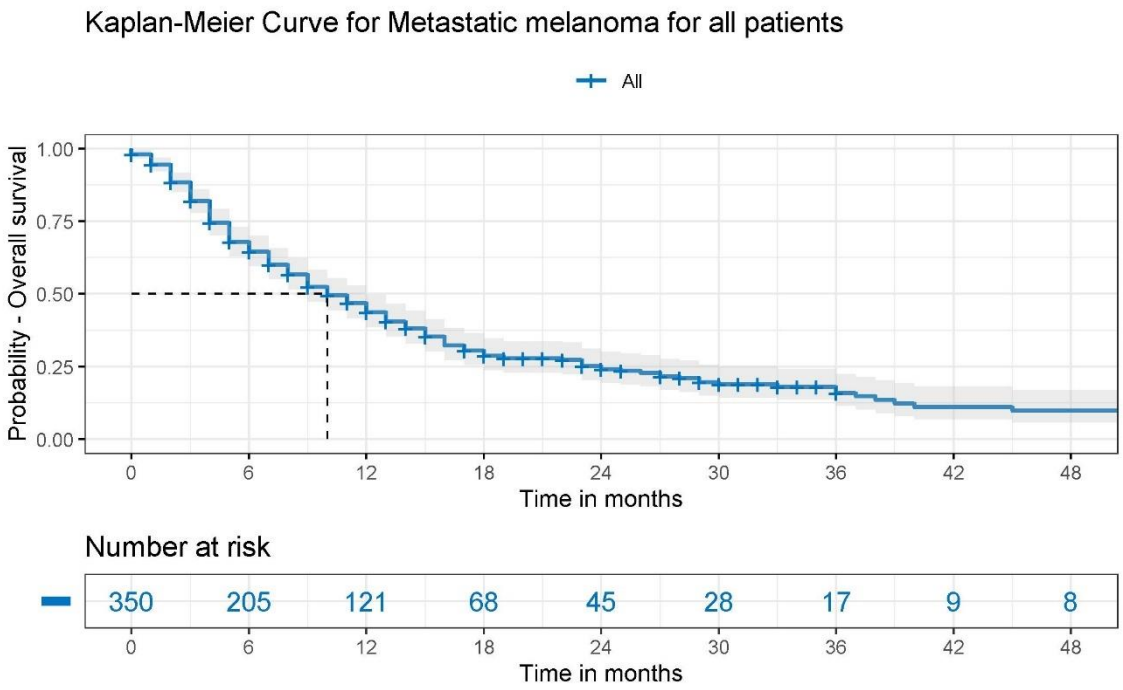

Figure 3.3 – Survival probability for total cohort of advanced melanoma patients

3.4.4.2. Univariable analysis by gender

The estimates for the study cohort according to gender are described in Table 3.6. The KM estimates revealed a median OS of 11 months (95% CI: 9−14 months) and 10 months (95% CI: 8−13 months), for female and male patients, respectively. Although females appear to have a slightly higher median OS, there were no statistically significant differences in survival between the two groups (p-value = 0.62). Figure 3.4 shows the KM curve for the stratified cohort by gender, showing the median OS and the number of patients at risk in three timepoints.

Table 3.6 – Summary of KM estimates at baseline for OS by gender

Gender	N	Events	Median OS (months)	0.95 LCL	0.95 UCL
Male	179	121	10	8	13
Female	171	116	11	9	14

Abbreviations: N – Number of patients; LCL – Lower confidence level; OS – Overall survival; UCL – Upper confidence level

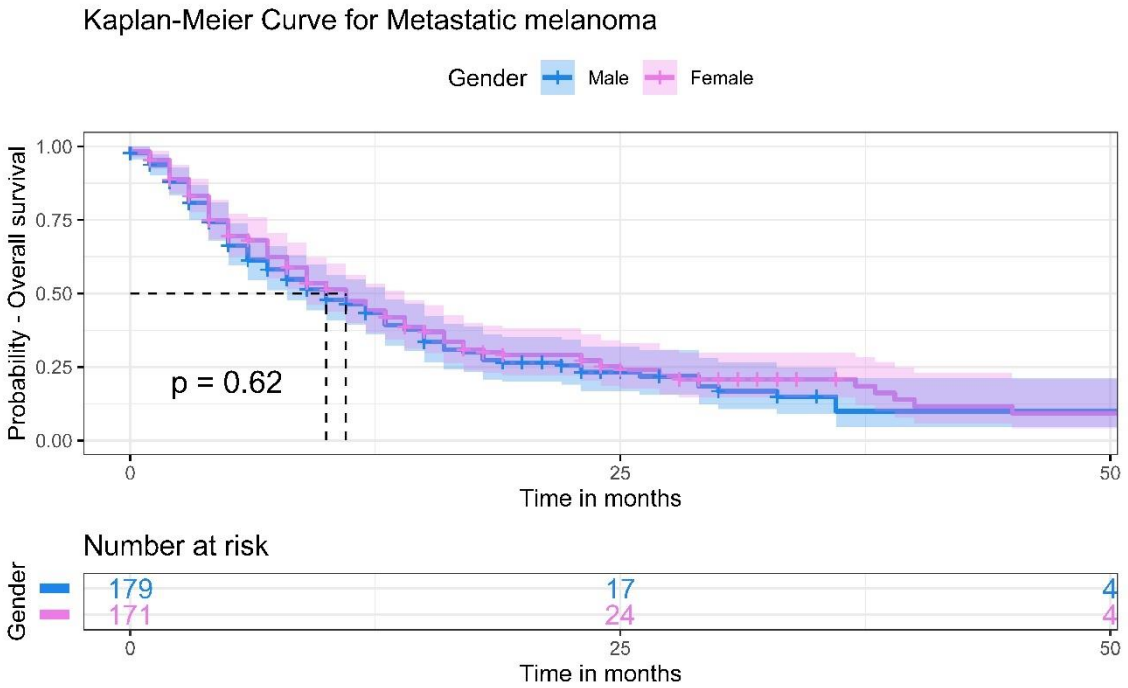

Figure 3.4 – Survival probability for advanced melanoma patients by gender

3.4.4.3. Univariable analysis by age group

Patients were categorised into three age groups: “under 50 years”, “50 to 65 years”, and “over 65 years”. KM survival estimates for these age groups are presented in Table 3.7. The median OS for patients under 50 years was 11 months (95% CI: 7–18 months), and for those aged 50 to 65 years, it was 12 months. Patients over 65 years had the lowest median OS at 8 months (95% CI: 7–12 months).

Figure 3.5 illustrates the survival probability curves stratified by age groups. Despite the observed differences in median OS among the age groups, these differences were not statistically significant (p = 0.088). This suggests that while there is a trend towards shorter survival in older patients, the variation in survival outcomes across

different age groups does not reach statistical significance, indicating that age alone may not be a definitive predictor of OS in advanced melanoma patients.

Table 3.7 – Summary of KM estimates at baseline for overall survival by age groups

Age group	N	Events	Median OS (months)	0.95 LCL	0.95 UCL
Under 50	81	55	11	7	18
From 50 to 65	107	72	12	10	15
Over 65	162	110	8	7	12

Abbreviations: N – Number of patients; LCL – Lower confidence level; OS – Overall survival; UCL – Upper confidence level

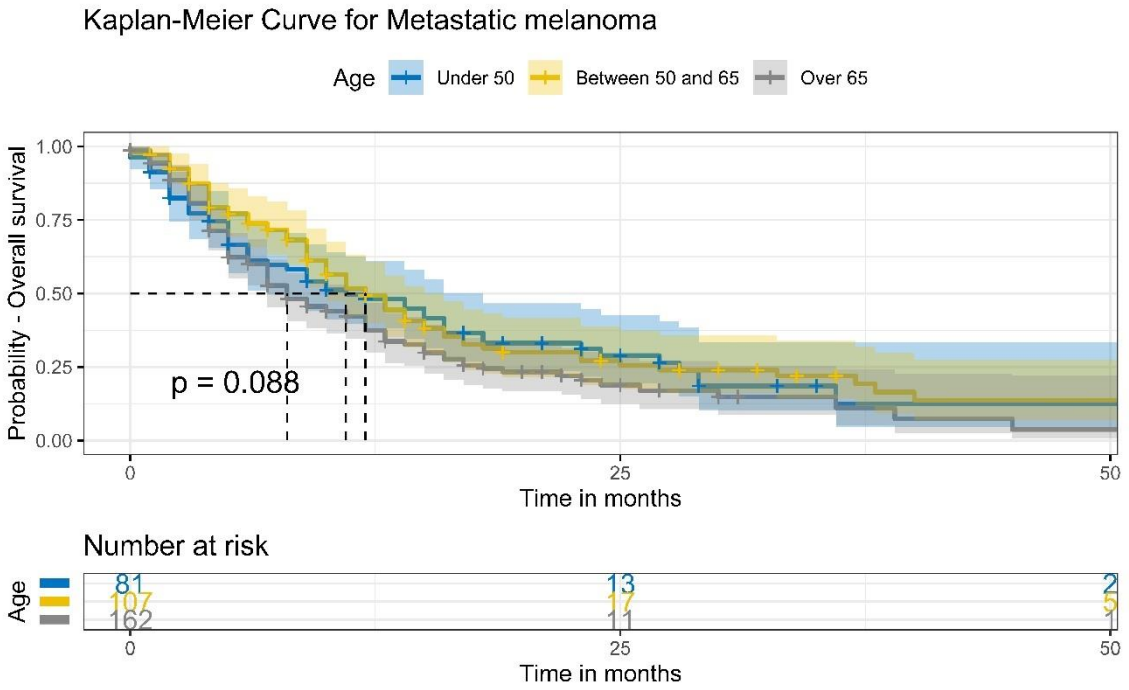

Figure 3.5 – Survival probability for advanced melanoma patients by age groups

3.4.4.4. Univariable analysis by BRAF gene status

The BRAF gene plays an important role in patients diagnosed with melanoma and, therefore, this gene status has implications in the choice of treatment. Patients that have a *BRAF* mutation can be treated with targeted drugs that were developed to target the BRAF gene whilst patients that have no mutation (*BRAF*-wild-type) cannot receive

this type of therapy. Thus, categorisation to calculate KM estimates and understand the possible differences in survival were based on *BRAF* status and are displayed in Table 3.8.

It appears that patients with no mutation verified (*BRAF*-wild-type) have a lower probability of survival in comparison with those with a BRAF gene mutation as KM estimates shown. The median OS was 9 months (95% CI: 5−15 months) and 11 months (95% CI: 9−13 months), respectively for the *BRAF*-wild-type and *BRAF*-mutant.

The figure below (Figure 3.6) displays a KM curve for survival probability by BRAF gene status. Regardless of the 2 months difference in median OS survival between the two gene categories, this difference appears not to be statistically significant as the result of the log-rank test showed a p-value of 0.16.

Table 3.8 – Summary of KM estimates at baseline for overall survival by BRAF gene status

BRAF status	N	Events	Median OS (months)	0.95 LCL	0.95 UCL
Wild-type	137	82	9	5	15
Mutation	139	94	11	9	13

Abbreviations: LCL – Lower confidence level; N – Number of patients; OS – Overall survival; UCL – Upper confidence level

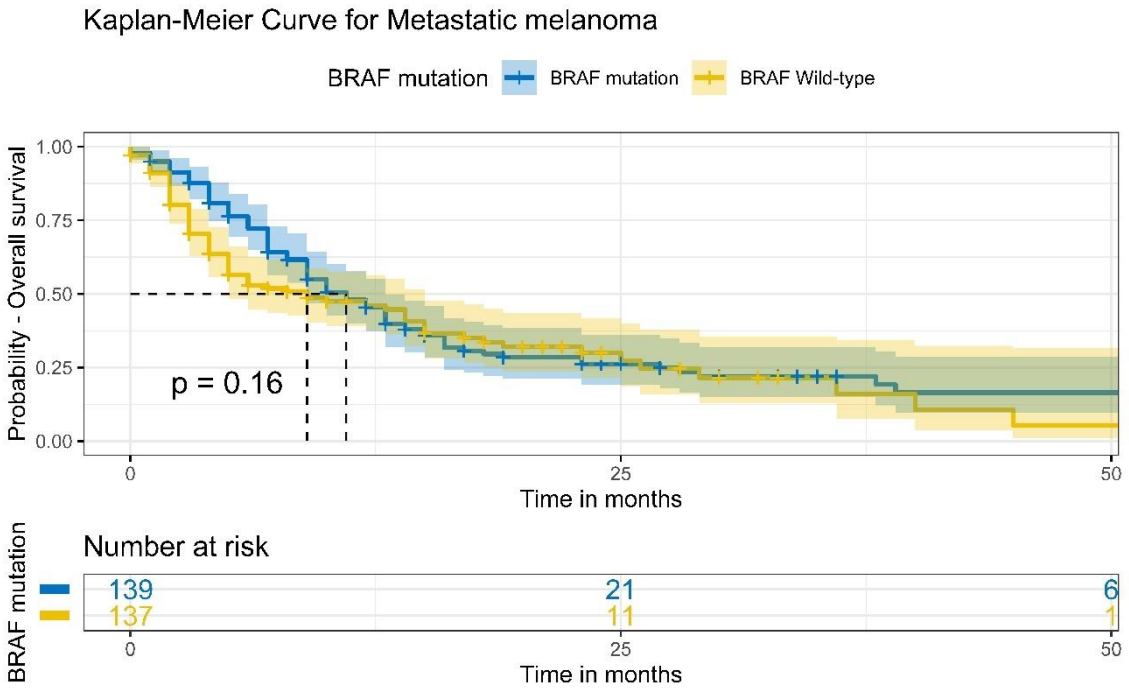

Figure 3.6 – Survival probability for advanced melanoma patients by BRAF gene status

3.4.4.5. Univariable analysis by drug treatment

The analysis of overall survival by initial drug treatment for advanced melanoma reveals distinct variations in median OS across the different therapies. The KM estimates provide insight into the survival outcomes associated with each treatment regimen as summarised in Table 3.9.

Among the drugs analysed, the chemotherapy drug treatments in this analysis, dacarbazine and temozolomide, showed distinct outcomes, with dacarbazine providing the highest median OS of 15.6 months (95% CI: 11.8−23.0 months) and temozolomide yielding a median OS of 9.8 months (95% CI: 6.3−NA months).

Regarding ICI treatments, ipilimumab had the lowest median OS of all drugs analysed with a median OS 5.0 months (95% CI: 3.5−9.2 months), indicating less favourable survival outcomes for patients receiving ipilimumab as monotherapy. Similarly, patients treated with pembrolizumab monotherapy had a median OS of 7.3 months (95% CI: 4.6−14.7 months). The combination of nivolumab plus ipilimumab demonstrated the highest median OS within the ICI treatments, with a median OS of 14.4 months (95% CI: 10.0−NA months), suggesting a significant survival benefit in comparison to monotherapy with either agent alone.

This was followed closely by vemurafenib, a *BRAF* inhibitor, which exhibited a median OS of 12.6 months (95% CI: 9.2−16.0 months). Patients treated with dabrafenib plus trametinib, a combination of a *BRAF* and MEK inhibitors, also showed relatively favourable outcomes with a median OS of 11.5 months (95% CI: 8.8−17.5 months). Monotherapy with dabrafenib exhibited the lowest median OS for targeted therapy drugs, with a median OS of 5.7 months (95% CI: 4.1−8.6 months), roughly half of the median OS for the combination strategy of both *BRAF* and MEK inhibitors, dabrafenib plus trametinib. Figure 3.7 presents the KM curves for survival probability by initial drug treatment, offering a visual representation of the differences in survival across these treatment groups. The differences in survival between drug treatments demonstrated to be statistically significant as a result of the log-rank test with a p-value of 0.029.

Table 3.9 – Summary of KM estimates at baseline for overall survival by drug treatment

Treatment	N	Events	Median OS (months)	0.95 LCL	0.95 UCL
Ipilimumab	34	27	5.0	3.5	9.2
Nivolumab plus ipilimumab	44	13	14.4	10.0	NA
Pembrolizumab	86	54	7.3	4.6	14.7
Dabrafenib	34	28	5.7	4.1	8.6
Dabrafenib plus trametinib	42	31	11.5	8.8	17.5
Vemurafenib	44	39	12.6	9.2	16.0
Dacarbazine	51	41	15.6	11.8	23.0
Temozolomide	7	6	9.8	6.3	NA
Other	8	7	14.5	7.8	NA

Notes: The '*Other*' category includes treatments that were under study in clinical trials or considered as adjuvant treatment. **Abbreviations:** LCL – Lower confidence level; N – Number of patients; OS – Overall survival; UCL – Upper confidence level

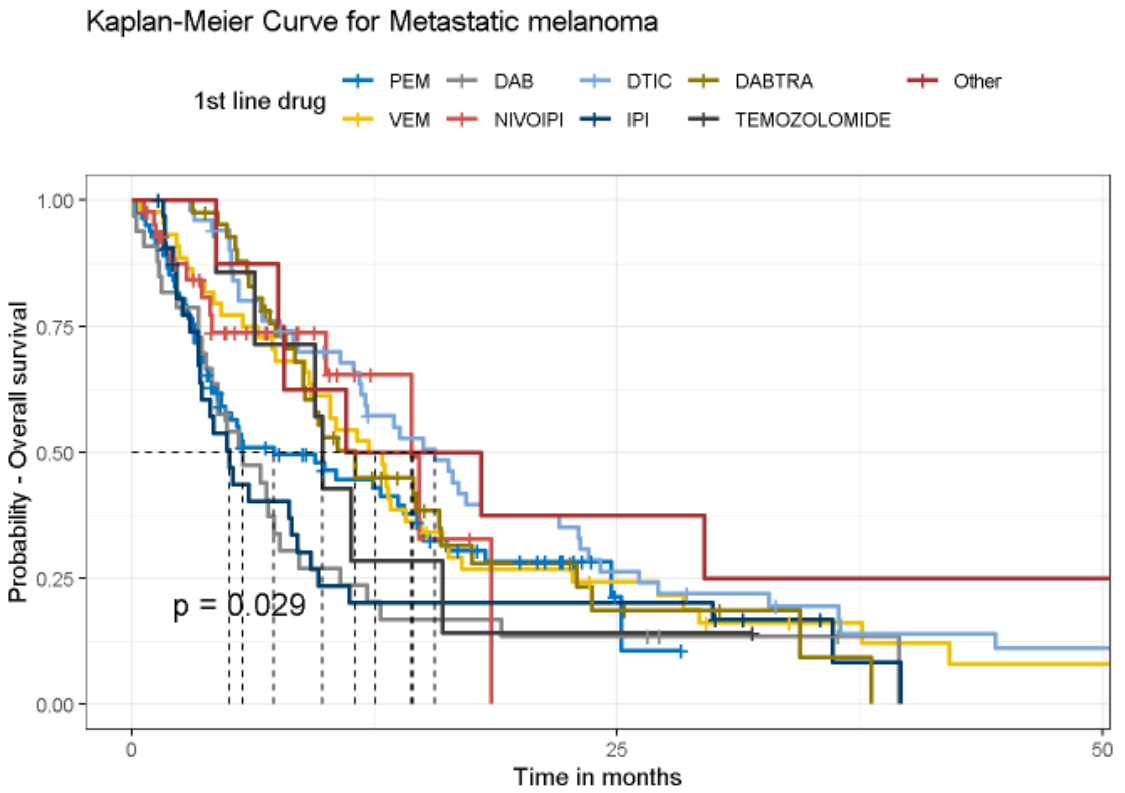

Figure 3.7 –Survival probability for advanced melanoma patients by drug treatment at baseline

Notes: The '*Other*' category includes treatments that were under study in clinical trials or considered as adjuvant treatment. **Abbreviations:** DAB – Dabrafenib; DABTRA – Dabrafenib plus trametinib; DTIC – Dacarbazine; IPI – Ipilimumab; NIVOIPI – Nivolumab plus ipilimumab; PEM – Pembrolizumab; VEM – Vemurafenib

3.4.4.6. Univariable analysis by type of therapy

The type of therapy administered to patients with advanced melanoma is a critical factor influencing OS outcomes. The KM estimates for different therapy types at baseline is shown in Table 3.10. Patients who received chemotherapy had the highest median OS of 13.8 months (95% CI: 11.4−18.0 months), followed closely by those treated with targeted therapy, who exhibited a median OS of 9.8 months (95% CI: 8.4−12.8 months). Immunotherapy was associated with a median OS of 8.5 months (95% CI: 5.2−12.8 months).

Figure 3.8 presents the KM curves for survival probability by therapy type, offering a visual representation of the differences in survival across these groups. Despite the observed variation in median OS, with chemotherapy showing a longer survival duration compared to targeted therapy and immunotherapy, these differences were not statistically significant. The log-rank test returned a p-value of 0.069, indicating that the survival differences between the type of therapy groups do not reach the threshold for statistical significance.

Table 3.10 – Summary of KM estimates at baseline for overall survival by type of therapy

Therapy type	N	Events	Median OS (months)	0.95 LCL	0.95 UCL
Immunotherapy	165	94	8.5	5.2	12.8
Targeted therapy	119	98	9.8	8.4	12.8
Chemotherapy	58	47	13.8	11.4	18.0
Other	8	7	14.5	7.8	NA

Notes: The '*Other*' category includes treatments that were under study in clinical trials or considered as adjuvant treatment. **Abbreviations:** LCL – Lower confidence level; N – Number of patients; OS – Overall survival; UCL – Upper confidence level

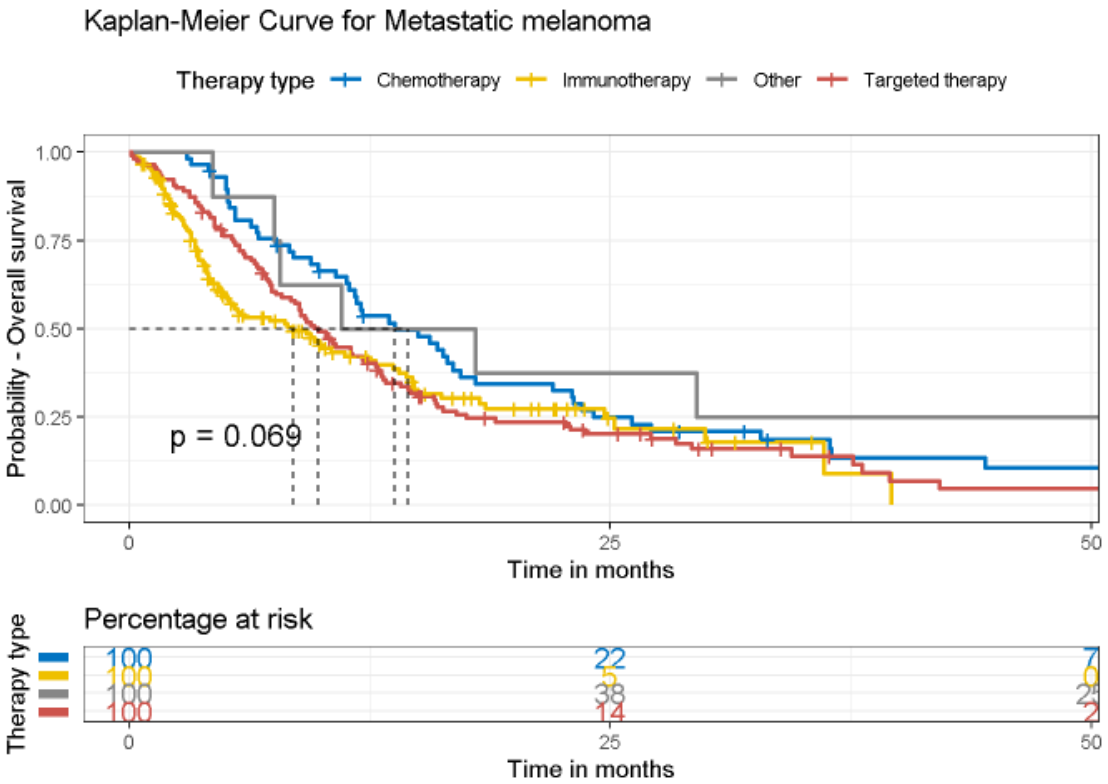

Figure 3.8 – Survival probability for advanced melanoma patients by type of therapy at baseline

Notes: The '*Other*' category includes treatments that were under study in clinical trials or considered as adjuvant treatment

3.4.4.7. Univariable analysis by ECOG Performance Status

The ECOG Performance Score is a prognostic factor in patients diagnosed with advanced melanoma that revealed differences in the probability of survival between groups [120]. A difference in survival between patients with lower ECOG PS scores and higher ECOG PS scores is evident when analysing the OS of this cohort according to levels at baseline. A patient's health condition, thus lower grades for ECOG PS are preferred as the higher ECOG PS the higher the risk of a patient's health condition being associated with increased comorbidities. The KM estimates for ECOG PS are shown in the table below (Table 3.11). Higher levels are related to different degrees of physical limitation. Patients with a PS equal to 0 at the start of treatment appear to have a higher survival probability in comparison with higher ECOG PS scores. These patients had a median OS

of 16 months (95% CI: 13−18 months) whilst the median OS was 6 months (95% CI: 5−9 months) and 4.5 months (95% CI: 2−8 months) for patients with a ECOG PS grade 1 and 2+ at baseline, respectively. The visual representation of the survival curves is provided in Figure 3.9 alongside the result for the log-rank test between the three ECOG PS groups. The p-value that resulted from the log-rank test reveals a statistically significant difference in survival between ECOG PS groups. It is also noticeable that there were no patients at risk after 15 months and 35 months for patients with ECOG PS 2+ and ECOG PS 1, respectively, as patient had died or lost to follow-up during that period. Patients with an ECOG PS score equal to 0 at baseline were able to reach the 40-month mark.

Table 3.11 – Summary of KM estimates at baseline for overall survival by ECOG Performance Status

Category	N	Events	Median OS (months)	0.95 LCL	0.95 UCL
ECOG PS 0	185	109	16.0	13	18
ECOG PS 1	88	65	6.0	5	9
ECOG PS 2+	40	35	4.5	2	8

Abbreviations: N – Number of patients; LCL – Lower confidence level; OS – Overall survival; UCL – Upper confidence level

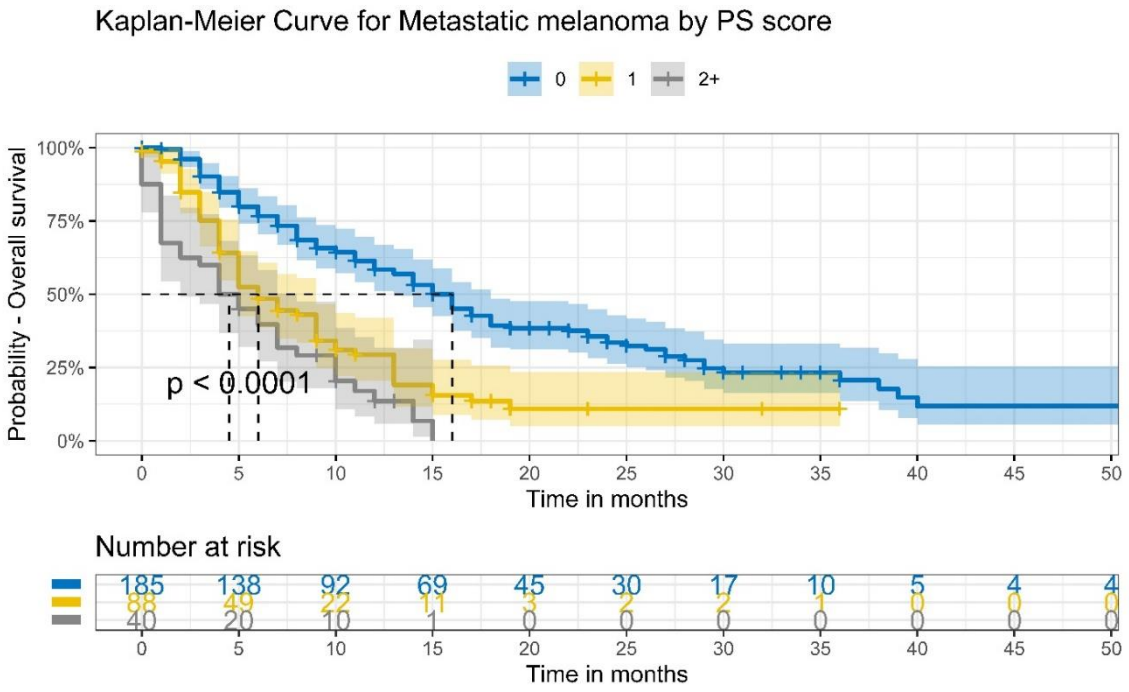

Figure 3.9 – Survival probability for advanced melanoma patients by ECOG PS

Abbreviation: ECOG PS – Eastern Cooperative Oncology Group Performance Status

3.4.4.8. Univariable analysis by LDH level

The KM estimates for LDH blood level revealed a median OS of 12 months (95% CI: 11−15 months) and 4 months (95% CI: 3−5 months) for patients with normal and high level of LDH, respectively (Table 3.12). Thus, patients within the normal range live on average, three-fold longer than those with LDH levels above the upper limit at baseline. A total of 175 patients with a LDH considered normal died during follow-up period whilst for LDH high group 51 patients had passed away during the same time, which represents 64.10% and 82.25%, respectively, of the baseline population in each group at the start of follow-up. The survival curves for the two groups are displayed in Figure 3.10 along with the result for the log-rank test which revealed a statistically significant difference (p-value < 0.0001) in survival between normal and high LDH level at baseline.

Table 3.12 – Summary of KM estimates at baseline for overall survival by LDH blood level

LDH group	N	Events	Median OS (months)	0.95 LCL	0.95 UCL
Normal	273	175	12	11	15
High	62	51	4	3	5

Abbreviations: N – Number of patients; LCL – Lower confidence level; OS – Overall survival; UCL – Upper confidence level

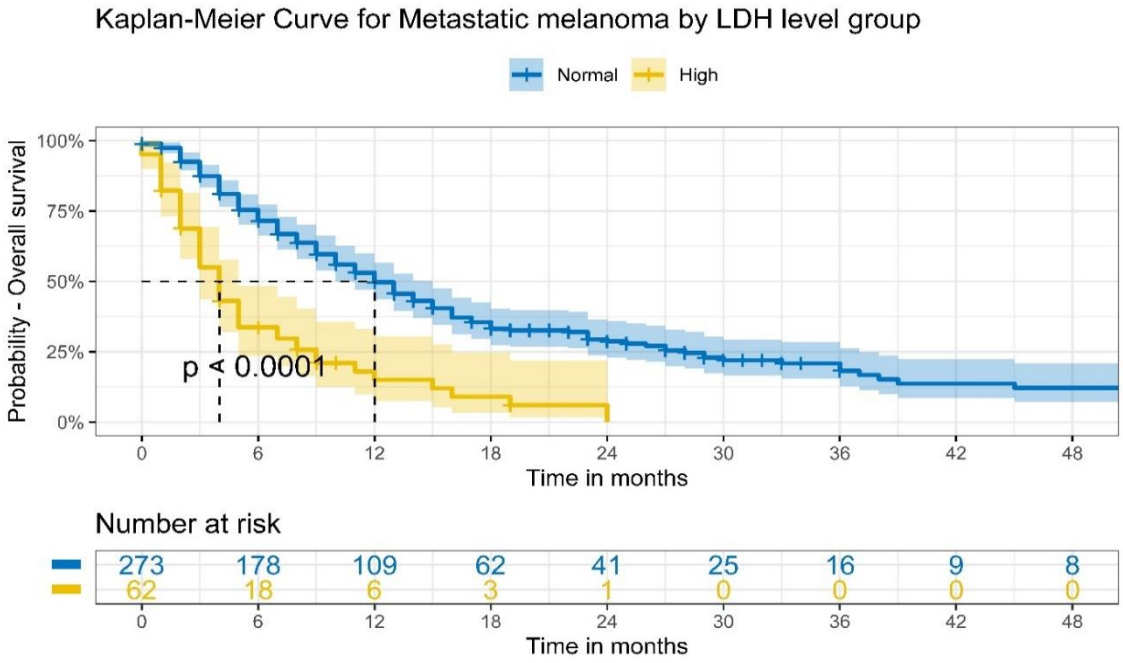

Figure 3.10 – Survival probability for advanced melanoma patients by LDH group level

Abbreviation: LDH – Lactate dehydrogenase

3.4.4.9. Univariable analysis by BMI category

Furthermore, KM estimates were calculated to assess differences in survival for BMI at baseline by groups, based on WHO standards which are represented in Table 1.1. Interestingly, as presented in Table 3.13 patients within higher BMI groups, overweight and obese, appear to have a higher survival probability in comparison with patients with a considerate normal weight. Correspondingly, patients considered overweighted have the highest median OS corresponding to 16 months (95% CI: 13−23 months), whilst the remaining groups similar median OS. The median OS for these groups is 10 months (95% CI: 8−Not reached [NR]), 9 months (95% CI: 7−12 months) and 11 months (95% CI: 8−15 months) for underweight, normal and obese, respectively. Despite BMI being typically a prognostic factor for several diseases including cancer, associated with decreasing the chances of survival with higher levels of BMI, research about the link between melanoma and BMI revealed that patients with higher levels of BMI appear to have better results in terms of survival [8], [9]. Similar results were achieved with this study and can be visualised in Figure 3.11.

Table 3.13 – Summary of KM estimates at baseline for overall survival by BMI category

BMI category	N	Events	Median OS (months)	0.95 LCL	0.95 UCL
Underweight	13	10	10	8	NA
Normal	112	87	9	7	12
Overweight	112	63	16	13	23
Obese	87	51	11	8	15

Notes: BMI groups are based on the categories provided by the World Health Organization. **Abbreviations:** BMI – Body-mass index; LCL – Lower confidence level; N – Number of patients; NA – Not applicable; OS – Overall survival; UCL – Upper confidence level

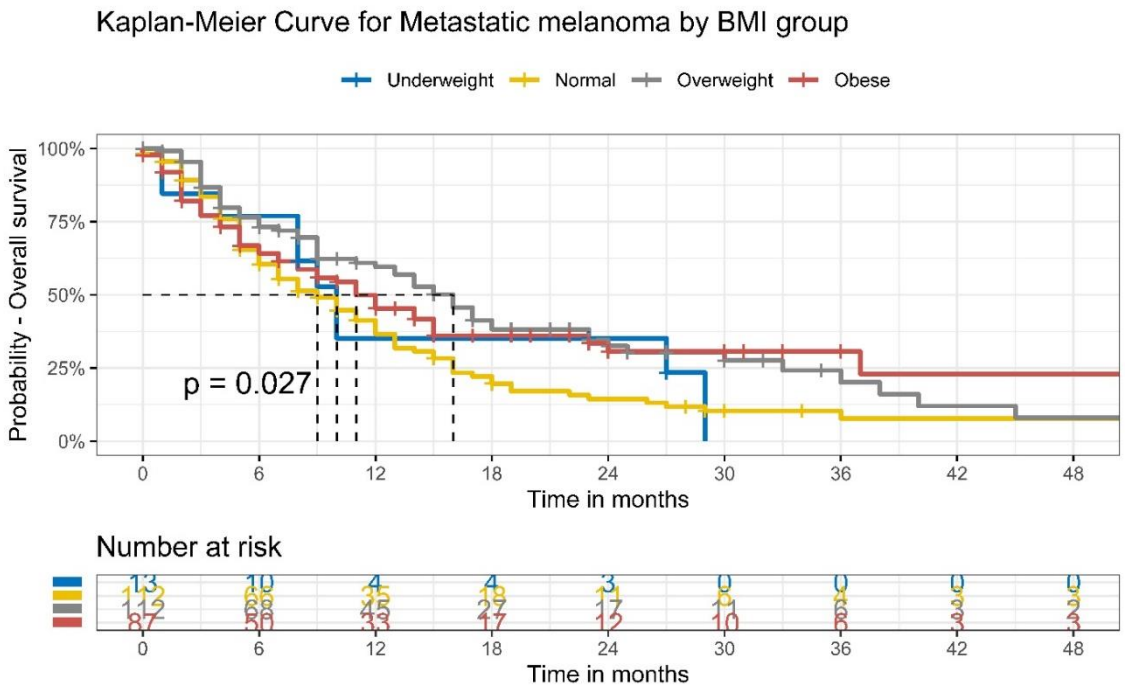

Figure 3.11 – Survival probability for advanced melanoma patients by BMI group
Abbreviations: BMI – Body-mass index

3.4.5. Cox proportional-hazards model

3.4.5.1. Univariable Cox proportional-hazards model

The analysis of univariable Cox PH models for advanced melanoma patients provides valuable insights into the impact of various covariates on survival outcomes. The covariates examined include age, gender, SIMD quintile, ECOG PS, BRAF status, BMI, and LDH. Each variable was analysed individually to determine their influence on survival, with the results presented in terms of HRs and their corresponding 95% confidence intervals, along with p-values resulting from the log-rank tests to assess statistical significance (Table 3.14).

Age, as a continuous variable, exhibited a HR over 1 (HR: 1.009 [95% CI: 1–1.018]). This suggests a slight increase in the risk of death with each additional year of age. However, the p-value of 0.0431 indicates that this result is statistically significant, implying that age alone may be a strong predictor of survival in this cohort.

Regarding gender, female patients had a HR of 0.914 (95% CI: 0.712–1.175) suggesting a potential reduction in the risk of death compared to male patients. Nevertheless, this association was not statistically significant (p-value = 0.485), indicating that gender may not play a substantial role in influencing survival outcomes in this patient population.

The SIMD was categorised into five levels, with the most deprived category serving as the reference (SIMD 1). The HRs for SIMD 2 to SIMD 5 ranged from 0.709 to 0.866. Despite these variations and the HRs below 1, which would suggest a risk reduction in comparison with SIMD 1, none of the results reached statistical significance, as evidenced by p-values exceeding the conventional threshold for significance (p-value > 0.05). This suggests that socioeconomic status, as measured by SIMD, may not have a pronounced impact on survival in advanced melanoma patients.

ECOG PS was evaluated as a categorical variable across three levels, ECOG PS 0, ECOG PS 1, and ECOG PS 2+, with the first group used as reference. The analysis revealed a trend of increasing HR with higher ECOG PS scores. Specifically, an ECOG PS of 1 was associated with a HR of 2.152 (95% CI: 1.655−3.062) compared to the reference ECOG PS of 0. Furthermore, ECOG PS 2+ exhibited a HR three times higher than the reference group (HR: 3.721 [95% CI: 2.497−5.544]). Both results demonstrated a highly statistically significance, with p-values less than 0.01. These findings underscore the critical importance of functional status in predicting survival outcomes, with worse ECOG Performance Status being strongly associated with increased mortality risk.

As to *BRAF* status, the comparison between '*BRAF*-mutant' (reference group) versus '*BRAF*-wild-type', yielded a HR of 1.295 (95% CI: 0.970–1.729). Although this suggests a potential reduction in risk for patients with the mutant type, the result was not statistically significant (p-value = 0.079). Therefore, *BRAF* status alone may not be a decisive factor in determining survival in this cohort. However, this result must be carefully interpreted as *BRAF* status might influence the choice of treatment as mentioned in section 1.2.

Additionally, BMI was found to be a protective factor, with higher BMI associated with a lower risk of death. The HR for BMI was 0.952 (95% CI: 0.926–0.979), and this result was statistically significant (p-value < 0.001). This indicates that higher BMI may confer a survival advantage in advanced melanoma patients.

Lastly, blood level of LDH was significantly associated with increased risk of death in the univariable analysis. The HR for LDH was above 1 (HR: 1.001 [95% CI: 1.001–1.002]), with a highly significant p-value (p-value < 0.001). Elevated LDH levels are indicative of higher tumour burden and more aggressive disease, which likely explains the observed association with poorer survival outcomes.

In conclusion, the univariable Cox PH models highlighted the significant impact of ECOG PS and LDH on survival in advanced melanoma patients. While other variables such as age, gender, SIMD quintile, *BRAF* status, and BMI did not show statistically significant associations, the findings emphasise the importance of functional status and tumour burden in predicting survival outcomes in this patient population. These results provide a foundation for further research and potential interventions aimed at improving survival in advanced melanoma.

Table 3.14 – Summary results of seven univariable Cox proportional-hazard models for continuous and categorical variables

Variable	Category	Hazard ratio (95% CI)	p-value
Age		1.009190 (1−1.018)	0.0431*
Gender	Male	Reference	-
	Female	0.91450 (0.7116−1.175)	0.485
SIMD quintile	1	Reference	-
	2	0.8656 (0.5962−1.257)	0.4480
	3	0.7469 (0.4943−1.129)	0.1660
	4	0.7700 (0.5169−1.147)	0.1987
	5	0.7092 (0.4844−1.038)	0.0773
***BRAF* status**	Mutant	Reference	-
	Wild-type	1.2951 (0.9701−1.729)	0.0794
BMI		0.95214 (0.9257−0.9793)	0.000632*
ECOG PS	0	Reference	-
	1	2.2516 (1.655−3.062)	2.31e-07*
	2+	3.7209 (2.497−5.544)	1.06e-10*
LDH		1.0012611 (1.001−1.002)	1.1e-11*

Notes: The table displays the results of seven univariable Cox PH models. *Considered as being statistically significant with a p-value below 0.05. **Abbreviations:** BMI – Body-mass index; BRAF – B-Raf oncogene; CI – Confidence interval; ECOG PS – Eastern Cooperative Oncology Group Performance Status; LDH – Lactate dehydrogenase; SIMD – Scottish Index of Multiple Deprivation

3.4.5.2. Multivariable Cox proportional-hazards model

After assessing the results from the multiple univariable Cox PH models (Table 3.14), the categorical variables of SIMD, gender, ECOG PS and *BRAF* status, and the continuous variables of age (continuous variable), BMI (continuous variable), LDH (continuous variable), were fitted in a multivariable Cox PH model with survival as the outcome of interest.

Figure 3.12 displays the HR and consequent influence of each covariate on survival. Results shown in the forest plot revealed that only LDH and ECOG PS had a significant impact on survival according to results from log-rank tests. The hazard ratio of ECOG PS 1 was approximately two-fold in comparison with the HR from the reference group, ECOG PS 0 (HR: 2.11 [95% CI: 1.28−3.5]). In addition, the HR for patients with a ECOG PS 2+ was over six times the HR for the reference group, ECOG PS 0 (HR: 6.19 [95% CI: 3.24−11.8]).

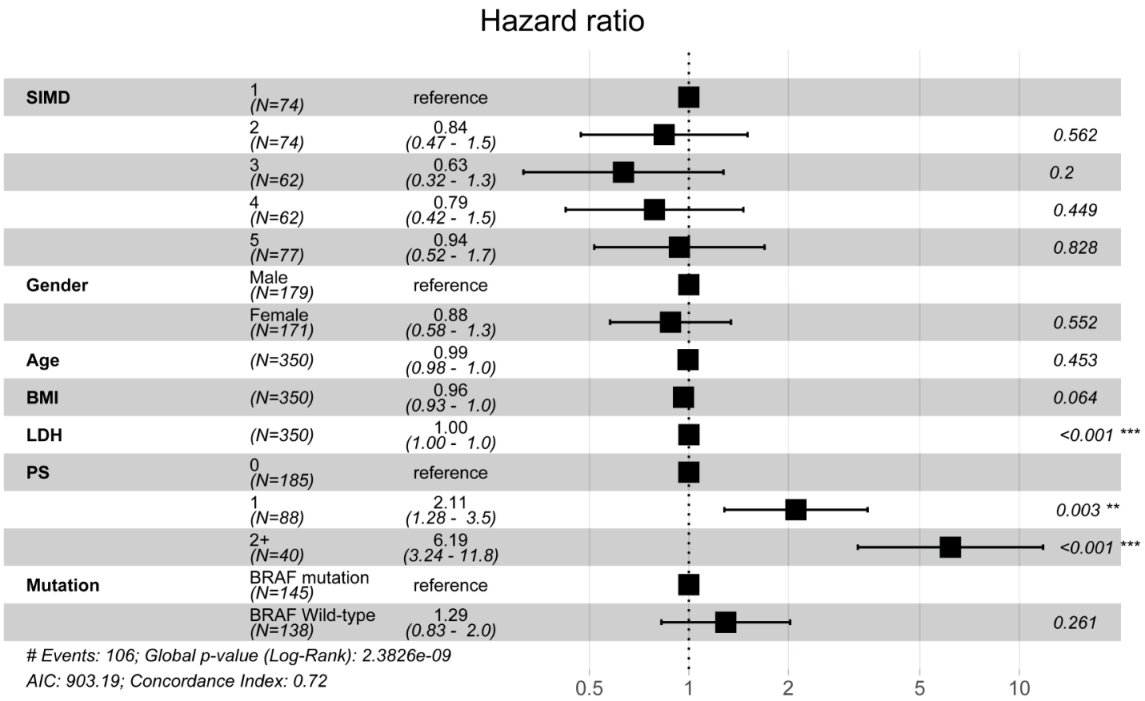

Figure 3.12 – Forest plot for multivariable Cox Proportional-Hazards model

Notes: The figure illustrates the hazard ratios according to each covariate fitted in the model. Results for log-rank test are displayed on the right-hand side. **Abbreviations:** AIC – Akaike information criterion; BRAF – B-Raf proto-oncogene; BMI – Body-mass index; PS – Eastern Cooperative Oncology Group Performance Status; LDH – Lactate dehydrogenase; SIMD – Scottish Index of Multiple Deprivation

3.4.5.3. Time-dependency adjusted Cox PH models

Patient survival is not exclusively dependent on patient and treatment characteristics at the start of treatment (baseline). During the course of treatment, patients' parameters (e.g., clinical, biochemical), or treatment-related changes may affect survival outcomes. If a patient changes the type of anti-cancer therapy during their treatment course, then one cannot be solely responsible for survival probability. Therefore, time-dependent adjusted Cox PH models were developed to assess this possibility.

To assess the impact of treatment on survival, the data was manipulated to account for patients with more than one observation, and therefore allowing the implementation of time-dependent covariates, thereby avoiding the pitfalls of immortal-time bias. Immortal-time bias occurs when a period of follow-up during which the event of interest (e.g., death) could not occur is incorrectly attributed to a particular treatment, leading to an overestimation of the treatment's effectiveness. To mitigate the immortal-time bias, a time-dependency adjusted Cox PH model was employed, where type of treatment was treated as a time-dependent variable. This approach allowed the model to capture the dynamic nature of treatment administration, fitting each therapy type those patients received over time rather than attributing survival solely to the first-line treatment. Consequently, the model provided a more accurate estimate of survival outcomes based on the entire treatment pathway, reflecting the real-world clinical scenario where patients often undergo multiple lines of therapy.

Similarly, a time-dependency adjusted Cox PH model with BMI as a time-dependent covariate was explored. This modification made it possible for this model to more realistically represent how variations in a patient's BMI may affect survival results. Rather than depending on a single baseline BMI measurement, the model addressed the complex impacts of BMI on patient prognosis by treating BMI as a variable that may change over time.

3.4.5.3.1. Univariable time-dependency adjusted Cox PH model for type of therapy

A time-dependency adjusted Cox PH model with therapy type as a time-dependent covariate was fitted to the data. This model used chemotherapy as the reference group, and it demonstrated differences in survival depending on the type of therapy administered. In comparison with the reference group, targeted therapy had a HR of 0.22 with a confidence interval between 0.07 and 0.63. The log-rank test revealed a statistically significant difference in survival. Regarding immunotherapy, the HR was 1.64 with a wide confidence interval ranging from 0.85 to 3.15. However, in comparison with the reference group, immunotherapy patients did not show a statistically significant difference in terms of survival. These results are displayed in Table 3.15.

Table 3.15 – Results of adjusted Cox model for time-dependency with the type of therapy

	Category	N	Hazard ratio (95% CI)	Standard error	p-value
Type of therapy	Chemotherapy	71	Reference	Reference	Reference
	Immunotherapy	103	1.53 (0.617−3.80)	0.33	0.14
	Targeted therapy	55	0.21 (0.07−0.91)	0.54	0.005*

Notes: *Considered as being statistically significant with a p-value below 0.05. **Abbreviations:** N – Number of patients; CI – Confidence interval

3.4.5.3.2. Multivariable time-dependency adjusted Cox PH model with for type of therapy as a time-dependency covariate

A Cox PH model was fitted to the data including all variables of interest (age, gender, SIMD quintile, BMI, LDH and ECOG PS) and time-dependency covariate for therapy type administered to each patient. The BRAF gene mutation status was removed from this analysis due to the inclusion of type of therapy covariate. Targeted therapy

can only be administered to patients with a mutation in the BRAF gene causing an interference in the model. The HR, confidence intervals and corresponding result for log-rank test (p-value) of each covariate can be observed in Figure 3.13.

The estimated HRs for targeted therapy and immunotherapy in comparison with the reference group (chemotherapy) were 0.21 (95% CI: 0.07−0.91) and 1.53 (95% CI: 0.617−3.80), respectively, but only targeted therapy revealed a statistically significant difference in survival in comparison with chemotherapy as a first-line treatment.

Additionally, the hazard ratios from SIMD 2 to SIMD 5 were all below 1 (HR: 0.51, 0.33, 0.41 and 0.28, respectively) suggesting a positive impact on survival in comparison with the reference group (SIMD 1). However, these differences in survival probability were not statistically significant. Patients included in an ECOG PS 1 had a lower survival probability with a HR of 2.58 (95% CI: 1.073−6.19) in comparison with the reference group (ECOG PS 0), being this difference statistically significant. Patients with a Performance Score of two or higher at baseline also shown a higher HR in comparison with the reference group but no statistically significant difference was noted from the log-rank test (HR: 3.30 [95% CI: 0.338−32.18]).

In terms of gender, female patients had a survival probability 28% higher than male patients but this survival difference was not statistically significant (HR: 0.78 [95% CI: 0.361−1.42]). The remaining covariates (age, BMI and LDH) were fitted as continuous numerical covariates but none were statistically significant in terms of survival.

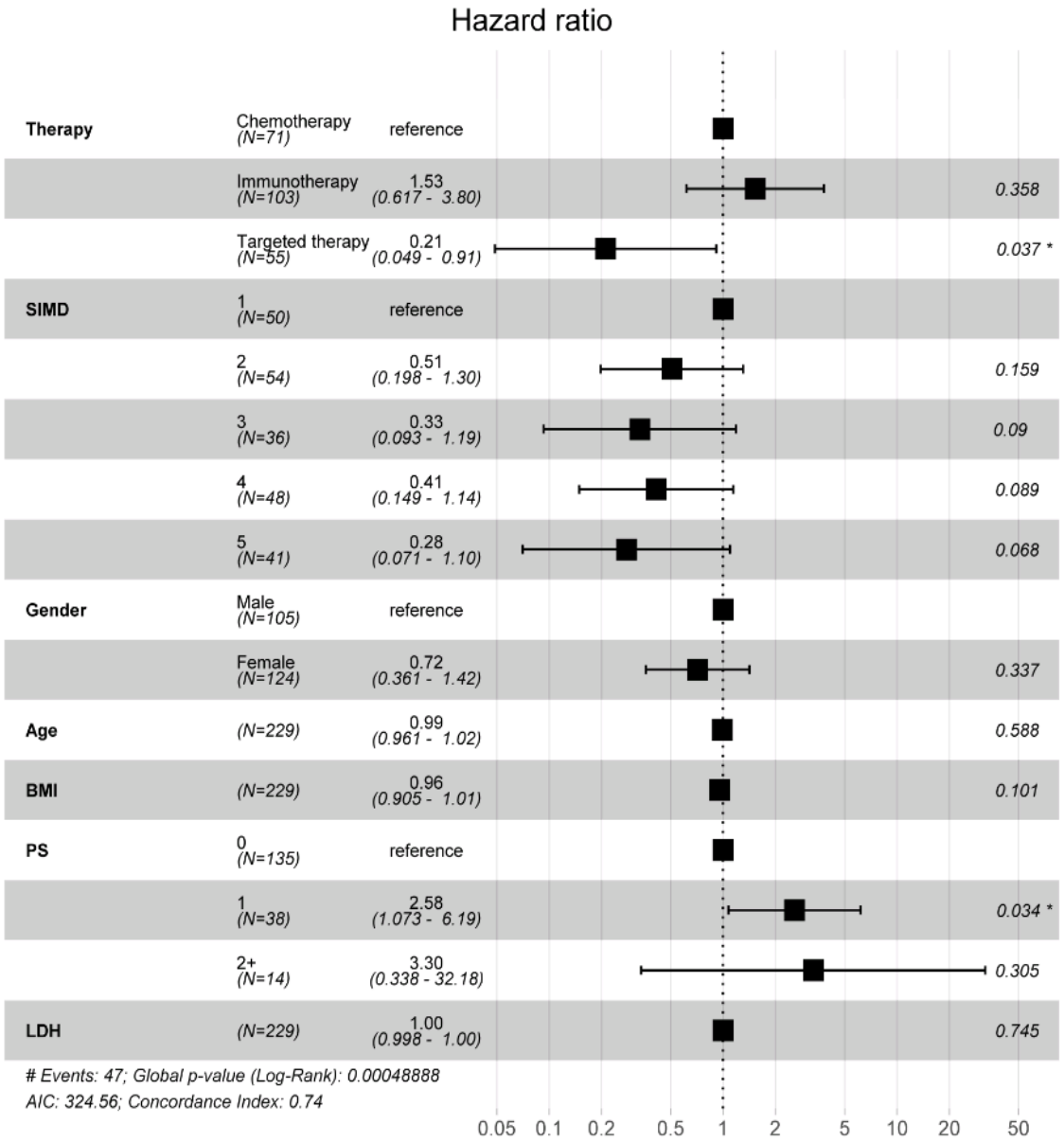

Figure 3.13 – Forest plot for the multivariable time-dependency adjusted Cox model for therapy switches

Notes: The figure illustrates the hazard ratios according to each covariate fitted in the model. Results for log-rank test are displayed on the right-hand side. Immunotherapy includes ipilimumab, nivolumab, pembrolizumab, and ipilimumab plus nivolumab; Targeted therapy includes dabrafenib, dabrafenib plus trametinib, and vemurafenib. *Considered as being statistically significant with a p-value below 0.05. Chemotherapy includes dacarbazine and temozolomide. **Abbreviation:** AIC – Akaike information criterion; BMI – Body-mass index; LDH – Lactate dehydrogenase; PS – Eastern Cooperative Oncology Group Performance Status; SIMD – Scottish Index of Multiple Deprivation

3.4.5.3.3. Univariable time-dependency adjusted Cox PH model for BMI

At the time of each appointment date for cancer treatment, weight and height were registered for each patient allowing to calculate BMI as a continuous variable. Thus, the influence of BMI over time in survival probability was investigated. This analysis shown a HR of 0.94 with a confidence interval between 0.92 and 0.97, associating BMI over time with a lower probability of death (Table 3.16). The log-rank test demonstrated a statistically significant difference in terms of survival.

Table 3.16 – Summary results of univariable time-dependency adjusted Cox PH model for BMI

	Hazard ratio (95% CI)	Standard error	p-value
BMI (kg/m^2)	0.94 (0.92-0.97)	0.01421	1.87×10^{-5}*

Notes: *Considered as being statistically significant with a p-value below 0.05. **Abbreviations:** BMI – Body-mass index; CI – Confidence interval

3.4.5.3.4. Multivariable time-dependency adjusted Cox PH model with for BMI as a time-dependency covariate

In continuation of the survival analysis, a multivariable time-dependency adjusted Cox PH model was developed to incorporate key prognostic factors alongside relevant patient characteristics. The model included age, gender, SIMD quintile, LDH, and ECOG PS as time-fixed covariates, with BMI incorporated as a time-dependent covariate. This approach was supported by recognition of variables such as LDH and ECOG PS being as prognostic factors in melanoma, reflecting the disease's biological aggressiveness as well as the patients' general health as previously mentioned in section 3.3.4.

BMI as a time-dependent covariate in the multivariable time-dependent Cox model shown an estimated HR below 1 (HR: 0.96 [95% CI: 0.93−1.0]) which translates into a lower risk of death for each BMI level. The difference in survival between BMI

levels is statistically significant as demonstrated by result from the log-rank test (p-value = 0.026).

In terms of therapy types, both targeted therapy and immunotherapy shown a lower HRs in comparison with the reference group, chemotherapy. Targeted therapy and immunotherapy showed hazard ratios of 0.75 (95% CI: 0.48−1.2), and 0.76 (95% CI: 0.45−1.3), respectively. However, the survival differences between chemotherapy and the two compared treatments (targeted therapy and immunotherapy) were not statistically significant.

Regarding other covariates in the model, patients with high levels of LDH had a HR of HR 2.46 (95% CI: 1.57−3.9) in comparison with those with normal levels. Those with higher Performance Status of 1 and 2+ had hazard ratios of 1.6 (95% CI: 1.16−2.7), and 4.91 (95% CI: 2.61−9.2), respectively, in comparison with the reference group (ECOG PS 0). Both LDH and ECOG PS covariates were statistically significant in terms of survival following in line with the results from previous models in this study.

The results of this analysis are visually represented in the forest plot shown in Figure 3.14, which illustrates the relative impact of each covariate on survival outcomes within the cohort.

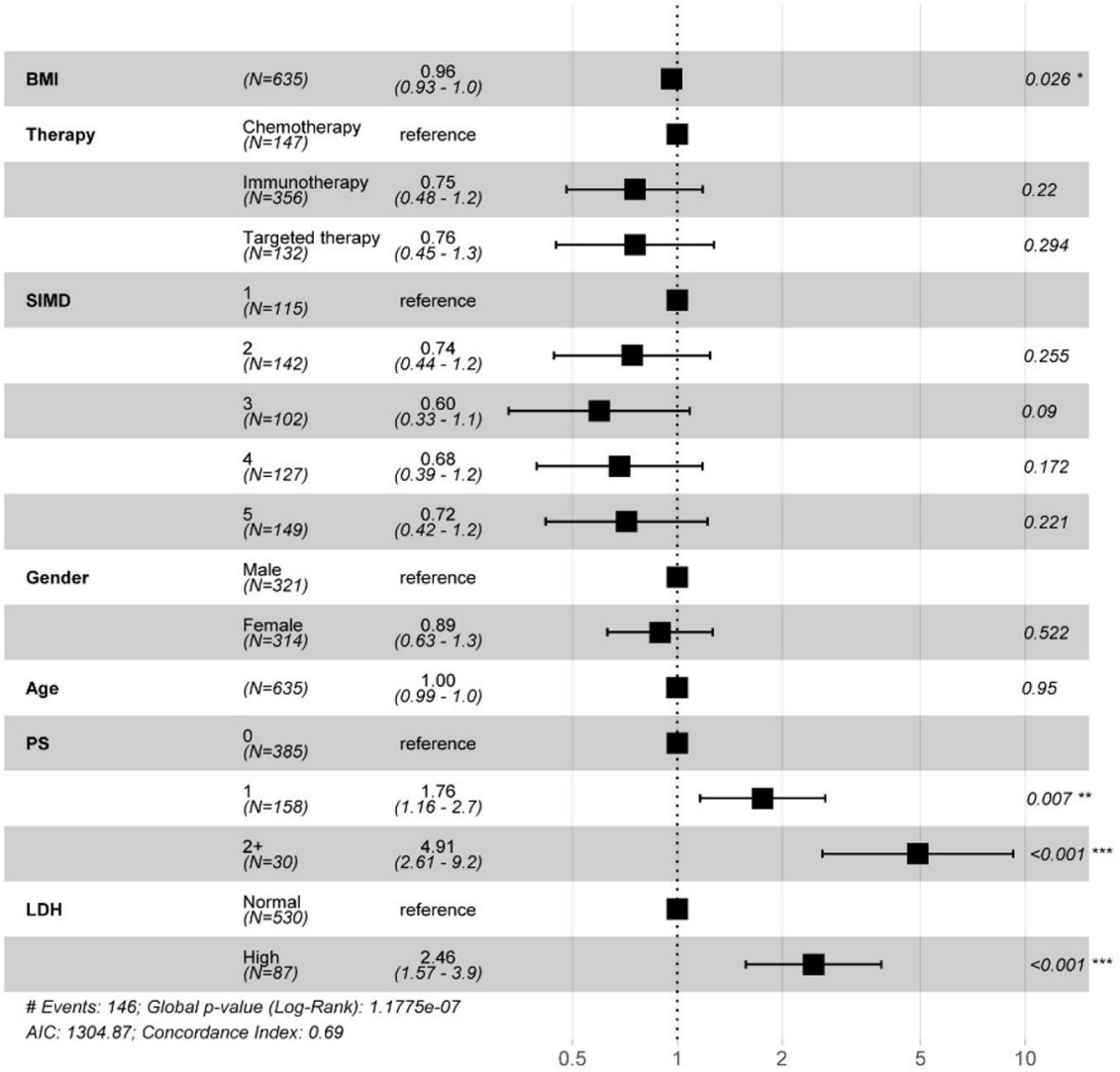

Figure 3.14 – Forest plot of survival model with BMI as a time-dependent covariate

Notes: BMI is included as a time-dependent covariate in a multivariable Cox regression model. The remaining covariates included in the model are time-fixed at baseline; *Considered as being statistically significant with a p-value below 0.05. Chemotherapy includes dacarbazine and temozolomide; Immunotherapy includes ipilimumab, nivolumab, pembrolizumab and nivolumab plus ipilimumab; Targeted therapy includes dabrafenib, dabrafenib plus trametinib, and vemurafenib. **Abbreviations**: BMI – Body-mass index; LDH – Lactate dehydrogenase; PS – ECOG Performance Status; SIMD – Scottish Index of Multiple Deprivation

3.5. Discussion

The primary aim of this chapter was to evaluate the influence of various clinical and demographic variables on the probability of survival among advanced melanoma patients within a real-world cohort from the Greater Glasgow and Clyde region. This study sought to analyse these factors and identify key patient characteristics that could be associated with survival outcomes, providing insights into the effectiveness of SACT and how these findings compare with those from clinical trials.

The demographic profile of the patient cohort, which had a median age of 64 years, ranging from 22 to 92 years, and nearly equal gender distribution (51.1% male, 48.9% female), reflects the broader epidemiological trends observed in melanoma [128]. The even distribution of socioeconomic status, as measured by the SIMD quintile, underscores the diverse nature of the population, which may influence treatment access and outcomes. This diversity is particularly relevant when comparing real-world data to results from RCTs, which often have more homogeneous patient populations.

The analysis of OS by initial drug treatment for advanced melanoma in this real-world cohort reveals distinct variations across different therapies, highlighting both the strengths and limitations of these treatments when applied outside of a controlled clinical trial setting. Chemotherapy with dacarbazine demonstrated a median OS of 15.6 months (95% CI: 11.8−23.0 months) in this cohort, which is higher than the median OS reported in earlier clinical trials such as CheckMate 066 [129]. In this trial, the efficacy of nivolumab was compared with dacarbazine which showed a median OS of 11.2 months (95% CI, 9.6-13.0 months), significantly lower than the median OS of nivolumab in this trial (37.5 months) [129]. This discrepancy could be attributed to patient selection, supportive care advancements, or subsequent lines of therapy in the real-world setting.

ICI treatments presented varying outcomes. Ipilimumab monotherapy exhibited the lowest median OS of 5.0 months (95% CI: 3.5−9.2 months), which is about half the than the approximately 10 months reported in pivotal trials [11]. Pembrolizumab showed a median OS of 7.3 months (95% CI: 4.6−14.7 months), which is lower than the median OS reported in the follow-up of the KEYNOTE-006 trial, where pembrolizumab

demonstrated a median OS of 32.7 months [130]. The combination of nivolumab plus ipilimumab displayed the highest median OS among ICI treatments in this cohort, with a median OS of 14.4 months (95% CI: 10.0−NA months). However, the median OS for the combination of nivolumab plus ipilimumab in this real-world setting was about five times lower than the median OS reported in the results of CheckMate 067 trial of 72.1 months [131].

Targeted therapies also demonstrated distinct survival outcomes in the real-world population in comparison with results from clinical trials. Vemurafenib showed a median OS of 12.6 months (95% CI: 9.2−16.0 months), which aligns closely with the results from the BRIM-3 trial, where vemurafenib demonstrated a median OS of approximately 13.6 months (95% CI: 12.0–15.4 months) [132]. The therapy combination of dabrafenib plus trametinib exhibited a median OS of 11.5 months (95% CI: 8.8−17.5 months), below half the median OS observed in the COMBI-v trial results, where this combination showed a median OS of 25.9 months (95% CI: 22.6−31.5 months). Monotherapy with dabrafenib, however, had a lower median OS of 5.7 months (95% CI: 4.1−8.6 months) than the combination of *BRAF* and MEK inhibitors, dabrafenib plus trametinib, further emphasising the superior efficacy of combination therapy over monotherapy in *BRAF*-mutant patients similarly to the outcomes observed from clinical trials.

The discrepancies between median OS in this study and the median OS reported in clinical trials for ICI and targeted therapy regimens may reflect the challenges of achieving trial-level outcomes in a real-world setting, where in patient characteristics such as a higher burden of disease or comorbidities, poorer ECOG PS, or other complicating factors that contribute to inferior survival outcomes. The observed differences in median OS when comparing real-world data with clinical trial outcomes highlight the complexity of replicating clinical trial efficacy into clinical effectiveness in real-world practice. These changes are likely a reflection of the broader patient heterogeneity and treatment pathways encountered in real-world practice. The findings in this study highlight the need for ongoing research to optimise treatment strategies in real-world settings, in order to ensure that advanced melanoma patients receive the most effective therapies.

The multivariable Cox PH regression analysis highlighted LDH levels and ECOG Performance Status as the most significant predictors of OS. Results regarding the blood

level of LDH revealed that survival difference was statistically significant as a result of the log-rank test (p-value < 0.001). Also, patients with a higher ECOG PS at baseline had a lower survival probability when compared to the reference group (ECOG PS 0). Thus, patients with an ECOG PS equal to 1 and patients with a ECOG PS equal to 2 or higher had a risk of death two-fold and six-fold higher, respectively (HR for ECOG PS 1: 2.11 [95% CI: 1.28−3.5]; HR for ECOG PS 2+: 6.19 [95% CI: 3.24−11.8]). Thus, ECOG Performance Status can be considered as prognostic factor in this cohort as stated in previous studies [133]. The significant association of these factors with survival in this study's cohort aligns with the well-established understanding that elevated LDH level is indicative of tumour burden and that a higher ECOG PS reflects worse physical functioning and disease progression. These findings are consistent with prior research which have demonstrated the prognostic value of LDH and ECOG PS in melanoma patients [133], [134], [135].

Additionally, the findings of this analysis align with several key observations reported in the real-world evidence retrospective study by Clarke *et al.* (2023), which identified LDH and ECOG Performance Status as key prognostic factors, underscoring their critical role in predicting outcomes for advanced melanoma patients [136]. The findings from Clarke *et al.* (2023) analysis demonstrated that elevated LDH levels were strongly associated with poorer survival, aligning with our findings that indicate LDH as a significant predictor of mortality [136]. Similarly, ECOG Performance Status was highlighted in both studies as a crucial determinant of survival, with poorer ECOG PS scores correlating with significantly higher risks of death [136]. This consistency across studies reinforces the importance of these biomarkers in the clinical management of advanced melanoma, suggesting that they should be considered essential components of any prognostic model or therapeutic decision-making process for this patient population.

However, other covariates in the model, such as gender and *BRAF* status, did not show statistically significant differences in survival, despite trends suggesting potential associations. For instance, female patients exhibited a hazard ratio below 1 (HR: 0.88), indicating a survival advantage, which has been observed in other studies [137]. Therefore, female patients had a 22% higher likelihood of survival in comparison with male patients. However, the wide confidence interval of the HR for female patients (95%

CI: 0.58−1.3) cross the threshold between favourable and unfavourable towards survival which suggests a high degree of uncertainty, indicating that the observed survival benefit may be arbitrary. As a result, the statistical comparison between the groups is influenced by this imprecision, making it difficult to draw conclusions about the survival benefit. Hence, the wide confidence interval underscores the need for further research with larger sample sizes or additional studies to narrow the confidence interval and provide more reliable estimates.

The analysis of *BRAF* status revealed a similar non-statistically significant regarding patient survival. Despite patients with *BRAF*-wild-type having 29% increased risk of death, this hazard was not statistically significant and presented a wide confidence interval (HR: 1.29 [95% CI: 0.83−2.0]). Although *BRAF* mutation status is a critical factor in determining treatment strategies, its prognostic value in terms of survival is unclear.

The subsequent analysis pursued the influence of observations over time with the time-adjusted Cox PH models. Results from the multivariable time-dependency adjusted Cox PH model with BMI as a time-dependent covariate indicated a hazard ratio below 1 for BMI, indicating a higher survival probability as observed in Figure 3.14 (HR: 0.96 [95% CI: 0.93−1.0]). Hence, for each additional value in the BMI scale was associated with a decreased mortality risk of 4%. This decreased risk of mortality was deemed statistically significant as result from the log-rank test (p-value = 0.026). The findings in this study are in line with recent findings regarding the correlation between BMI and mortality risk in melanoma. Recent studies on the impact of BMI and obesity on survival suggest that obesity in with metastatic melanoma patients is associated with improved outcomes such as PFS and OS [138], [139], [140]. Additionally, it is advisable to proceed with caution when interpreting BMI measurements, as changes in BMI might have been affected by disease progression or treatment-emergent adverse events. Rather of directly affecting survival, BMI may serve as a proxy or confounding factor for other variables.

The type of treatment was also studied as time-dependent covariable in time-dependency adjusted Cox PH models. Therefore, each therapy type includes patients that had the type of therapy mentioned but had changed during cancer treatment to one of the remaining types of therapy. The multivariable Cox PH model developed included type of therapy as a time-dependency covariate and remaining covariates of

interest as time-fixed covariates as previously mentioned. The estimated hazard ratios for type of therapy demonstrated that targeted therapy was the most effective first-line treatment after adjustment for time-dependency. A HR of 0.21 (95% CI: 0.049−0.91) indicates that patients that started treatment with targeted therapy had a survival probability 79% higher than the reference group, patients who started treatment under chemotherapy. The scenario was different regarding immunotherapy. Patient who started treatment with immunotherapy and changed during course of treatment, had a HR of 1.53 which suggested an increased risk of death by 53% in comparison with patients who started treatment with chemotherapy. However, survival difference between patients who started with immunotherapy (and received further subsequent treatment) and those who started with chemotherapy (and received further subsequent treatment) appears not to be statistically significant as demonstrated by the result of the log-rank test (p-value = 0.358). Additionally, confidence intervals were wide and over threshold between beneficial and detrimental in terms of survival (95% CI: 0.617−3.80) which could influence the statistical comparison.

Several limitations of this analysis should be acknowledged. First, the observational nature of the study and the reliance on real-world data introduce potential biases, such as confounding and selection bias. The wide confidence intervals observed in several analyses further underscore the need for caution in interpreting these results and suggest that larger, more comprehensive studies are necessary to confirm these findings.

The findings from this chapter have several implications for the broader thesis and the field of melanoma research. The identification of LDH and ECOG Performance Status as key prognostic factors reaffirms their importance in clinical decision-making and underscores the need for their routine assessment in advanced melanoma patients. The observed association between BMI and improved survival, although suggests that further research is needed to elucidate the underlying mechanisms and to explore the potential role of BMI as a prognostic factor or treatment modifier. Additionally, the differential survival benefits observed with targeted therapy versus immunotherapy highlight the importance of personalised treatment approaches and the need for ongoing research to optimise treatment strategies in real-world settings.

In conclusion, this chapter's findings contribute to the existing body of knowledge on advanced melanoma and provide a foundation for further research. The results underscore the complexity of survival outcomes in advanced melanoma and the importance of considering multiple factors, including demographic, clinical, and treatment-related variables, in both research and clinical practice. These findings will inform the subsequent sections of the thesis, particularly in addressing the research questions related to survival outcomes and treatment efficacy in advanced melanoma. Moving forward, it will be essential to integrate these insights into the broader context of melanoma research and to continue exploring the factors that influence survival in this challenging and heterogeneous disease.

Chapter 4 Multi-state model of advanced melanoma patients

4.1. Introduction

In this chapter a multi-state transition model was developed to analyse OS in advanced (unresectable or metastatic) melanoma using real-world evidence from Scottish patients. This approach provides framework to explore the progression of patients through different lines of therapy and their subsequent survival outcomes. The overarching objective of this chapter is to evaluate how therapy changes between immunotherapy and targeted therapy influence survival outcomes and time spent in each treatment state. To achieve this objective, this chapter addresses the following research questions:

1. How can a multi-state model be developed to accurately represent the OS of advanced melanoma patients using real-world evidence data?
2. How do therapy changes impact the survival outcomes of advanced melanoma patients receiving SACT?
3. What are the sojourn times (length of stay) and transition probabilities between health states defined by lines of therapy, specifically for immunotherapy and targeted therapy?

To address these research questions, a multi-state model was developed using parametric hazard functions, with health states based on the line of therapy (first- and second-line therapy), and death as an absorbing state. The cohort consisted of advanced melanoma patients, including those who underwent therapy changes during SACT.

A multi-state can either encompass or deviate from the Markov property, depending on the model's intention and timescale. A multi-state Markov model describes a process in which individual transitions between a series of health states over continuous time, assuming that the hazard function depends solely on the time elapsed since entering the current state (referred to as '*clock-forward*') [141]. The Markov

property implies that the future trajectory of a process depends only on its current state, not on the sequence of prior states. Only '*clock-forward*' models can be considered Markov models; a '*clock-reset'* multi-state model cannot hold the Markov property since the timescale depends only on the history since reaching the current state [141].

A MSM allows for a framework to analyse complex processes where patients transition between multiple health states over time. The rationale for choosing this approach lies in its ability to capture the dynamic progression of disease and treatment pathways, which are often oversimplified in traditional survival analysis. While methods such as the Cox PH model focus on time-to-event analysis for a single endpoint (i.e., OS, PFS, time to discontinuation of treatment), multi-state models account for intermediate events, transitions between states, and the associated probabilities. This allows for a better understanding of patient trajectories throughout their course of treatment, such as how long patients remain in specific health states, the factors influencing transitions, and the overall impact of treatment strategies on survival outcomes. For example, in the context of advanced melanoma, a multi-state model can simultaneously examine the time spent in first-line therapy, transitions to subsequent therapies, and the eventual outcome of death.

The use of multi-state modelling provides insights beyond the analyses conducted in previous chapter (see Chapter 3), which used Cox PH models to examine OS. While the Cox PH model was developed in identifying factors associated with OS and assessing proportional hazards, it does not account for the intermediate transitions or sojourn times that occur during the course of treatment. By capturing the complexity of disease progression, multi-state modelling fills this gap, facilitating an integrated analysis of survival, transitions between treatments, and the time patients spend in distinct health states. This method is well-suited for real-world settings where patients often switch therapies due to disease progression or adverse effects, offering valuable insights into the effects of treatment pathways on patient outcomes.

In summary, the overarching objective of this chapter was to understand how real-world advanced melanoma patients experienced therapy changes and how these transitions impacted their survival and time spent in each health state. By employing a multi-state Markov model, this analysis intended to provide a framework for examining patient outcomes, sojourn times, and transition probabilities in a real-world setting.

4.2. Aims and objectives

The general aim of the work in this chapter was to develop a multi-state transition model for OS analysis on advanced (unresectable or metastatic) melanoma using real-world evidence from Scottish patients. Thus, the aims and objectives of this chapter were:

- Develop a multi-state model for OS in advanced melanoma patients;
- Investigate how therapy changes impact the survival of advanced melanoma patients;
- Explore the sojourn times and transition probabilities associated with the lines of treatment for immunotherapy and targeted therapy.

4.3. Methods

4.3.1. Data

The data used in this chapter was collected, anonymised, and stored by the University of Glasgow's SafeHaven as previously mentioned in 0. Patients were included in this analysis if treated with first-line immunotherapy or targeted therapy drugs. Patients who had chemotherapy or other therapies not classified as ICIs or targeted therapy as first-line treatment were excluded. An initial analysis including all three therapy types (i.e., chemotherapy, immunotherapy, and targeted therapy) was conducted. However, due to the small cohort numbers and the resulting increase in the number of health states required to accommodate an additional treatment pathway, the results from that analysis could not be reliably reported. For this reason, the presented analysis focused exclusively on patients treated with immunotherapy or targeted therapy. Thus, from the initial cohort of 350 patients (see 0) a total of 127 were excluded due to these criteria. The final model was developed using data from 284 patients who received first-line targeted therapy or immunotherapy for advanced melanoma.

4.3.2. Multi-state model framework

The multi-state model developed represents a hazard function based on the time elapsed since entering the initial state, defined as the first appointment of immunotherapy or targeted therapy for the treatment of advanced melanoma [141]. The multi-state model was specifically designed to account for changes in therapy type during the course of SACT, incorporating health states for second-line immunotherapy after first-line targeted therapy and second-line targeted therapy after first-line immunotherapy. Given the need to capture these transitions, a continuous time Markov multi-state model was deemed the most appropriate approach.

The model was fitted using maximum likelihood estimation, with observations recorded as exact transition times between states. Health states were classified based upon the sequence and type of SACT received [141]. The structure of the model comprised five health states: the two initial states were defined as the either first-line immunotherapy or first-line targeted therapy; transient states were defined as the second-line targeted therapy after first-line immunotherapy and second-line targeted therapy after first-line immunotherapy; and death was an absorbing state (see Figure 4.1). This framework allowed the inclusion of patients who switched therapy types, providing a detailed representation of treatment pathways and associated outcomes. The states and their description are listed below:

- **State 1:** First-line immunotherapy
- **State 2:** First-line targeted therapy
- **State 3:** Second-line targeted therapy after first-line immunotherapy
- **State 4:** Second-line immunotherapy after first-line targeted therapy
- **State 5:** Death

There were six transitions allowed in this model, which represented a therapy change to the remaining type of therapy available. The possible transitions between states in this model are the following:

- **Transition 1:** First-line immunotherapy → Second-line targeted therapy (after first-line immunotherapy)

- **Transition 2:** First-line immunotherapy → Death
- **Transition 3:** First-line targeted therapy → Second-line immunotherapy (after first-line targeted therapy)
- **Transition 4:** First-line targeted therapy → Death
- **Transition 5:** Second-line targeted therapy (after first-line immunotherapy) → Death
- **Transition 6:** Second-line immunotherapy (after first-line targeted therapy) → Death

The visual representation of the model is displayed in Figure 4.1. All analyses in this study were conducted in the R programming language using RStudio® as the primary software environment. The model was developed using the *msm* package [142]. The data collected represented patients' appointments allowing to extract the exact transition times between health states (see 0).

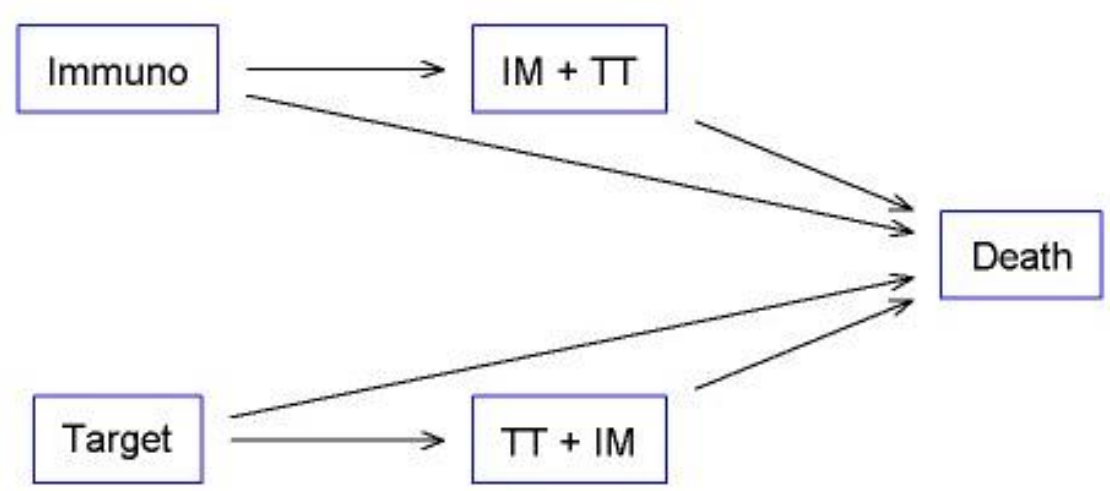

Figure 4.1 – Five-state multi-state model structure for possible transitions between immunotherapy, targeted therapy and death as an absorbing state

Abbreviations: IM + TT – First-line immunotherapy followed by second-line targeted therapy; TT + IM – First-line targeted therapy followed by second-line immunotherapy

4.3.3. Analysis and outcomes

The primary outcomes assessed in this study included OS, transition probabilities between health states, sojourn times (time spent in each health state), and hazard ratios for covariates. A continuous time Markov multi-state model was implemented using the

msm package in R to analyse the transitions between health states for patients with advanced melanoma undergoing SACT with immunotherapy and targeted therapy [142].

4.3.3.1. Transition probabilities

Transition probabilities describe the likelihood of a patient moving from one health state to another within a specified timeframe [142]. These probabilities were derived from the estimated transition intensity matrix (Q), which represents the instantaneous transition rates between states. Transition probabilities were calculated using matrix exponentiation of Q:

$$P(t) = Exp(tQ)$$

where $P(t)$ is the transition probability matrix for a given time t [142]. These probabilities provide insight into how likely patients are to progress between lines of therapy or reach the absorbing state (death) over time.

4.3.3.2. Censoring

Censoring from patients lost to follow-up or did not experience transitions within the study period, was addressed using likelihood-based methods built into the *msm* package [142].

4.3.3.3. Covariate selection

The covariates included in the model were selected based on their clinical relevance to advanced melanoma progression and treatment response, as discussed in section 3.3.4. Thus, the covariates defining LDH, ECOG PS, and BMI were incorporated into the model. LDH serves as a critical biomarker for tumour burden and disease progression in melanoma patients. Elevated LDH levels have been consistently associated with poorer prognosis and reduced OS, therefore making high LDH negative prognostic factor in metastatic melanoma [143]. ECOG Performance Status is recognised measure of a patient's functional status. An ECOG PS of 1 or higher has been linked to

an increased risk of death in metastatic melanoma patients, underscoring its prognostic significance [143]. Lastly, Body-mass index (BMI) is a known factor influencing treatment outcomes in cancer patients. Research indicates that higher BMI may be associated with improved survival rates in metastatic melanoma patients, as previously mentioned in section 0 [8], [9].

These covariates were incorporated into the model in order to account for variability in transition intensities due to patient characteristics. For instance, the model examined how baseline LDH levels, ECOG PS, and BMI influenced the likelihood of switching therapies or reaching the absorbing state (death). Thus, the inclusion of these variables in the model helped to mitigate potential confounding, such as variations in the patient's baseline characteristics. Nonetheless, residual confounding due to unmeasured factors remains a consideration in real-world data analyses.

4.3.3.4. Model assumptions

The continuous time Markov multi-state model relies on several key assumptions, which were critically evaluated to ensure their validity and understand their potential impact on results. Firstly, the Markov property assumes that the future state of a process depends only on the present state, not on the sequence of prior states. This was implemented by using a 'clock-forward' timescale, where transition intensities were modelled as a function of time since entering the current state (see section 4.3.3.1). While this assumption simplifies modelling, it may not fully reflect real-world scenarios where prior treatments influence future transitions. For instance, a patient's response to second-line therapy may depend on both the type and duration of first-line therapy.

Additionally, the model assumes that transition intensities are constant over time within a given state and are only influenced by covariates. While reasonable in clinical contexts, time-varying effects (e.g., treatment efficacy declining over time) may violate this assumption. Also, the inclusion of an absorbing state (death) implies no possibility of returning to other health states once this state was reached.

Violations of these assumptions could introduce bias to the analysis. For example, if transition rates vary over time, the assumption of constant intensities could underestimate the cumulative effect of time-dependent processes. Similarly, if prior

therapy strongly influences future transitions, the Markov property may lead to oversimplified results.

Nevertheless, a multi-state Markov model provides a framework for capturing disease progression and treatment pathways. This model offers a comprehensive assessment of advanced melanoma treatment in real-world settings, enabling insights into how therapy sequences and baseline characteristics, such as LDH, ECOG PS, and BMI, impact patient outcomes beyond what is achievable with simpler survival models.

4.4. Results

4.4.1. Sojourn time

One outcome of this model was the sojourn time, represented in Table 4.1 by the estimated mean sojourn times in each transient state. This means the amount of time spent in each disease state before moving on to the next one, excluding the absorbent state (death) [142]. It was estimated that patients under first-line immunotherapy remained in this state for over half a year (6.25 months) while those who started with first-line targeted therapy stayed for in this state for approximately nine months. Additionally, it was estimated that patients who started with first-line immunotherapy and received follow-up treatment with targeted therapy as a second-line treatment stayed in this state for an amount of time close to two months (2.10 months); and patients who received first-line targeted therapy and in a second-line treatment were treated with immunotherapy stayed in this state for a period close to five months (4.94 months).

Table 4.1 – Summary of estimated sojourn times for intermediate health states of the multi-state model

Health state	Estimates (months)	Standard error	Lower limit	Upper limit
IM	6.25	0.638	5.116	7.63
TT	8.80	0.898	7.201	10.74
IM + TT	2.10	2.100	0.296	14.91
TT + IM	4.94	1.030	3.282	7.43

Abbreviations: IM – First-line immunotherapy; TT – First-line Targeted therapy; IM + TT – Second-line targeted therapy administered after first-line immunotherapy; time in this state reflects only the targeted therapy phase; TT + IM – Second-line immunotherapy administered after first-line targeted therapy; time in this state reflects only the immunotherapy phase

4.4.2. Parametric survival curves

An important use of the multi-state model is to predict the survival probability. Figure 4.2 shows a plot with four lines representing the four transient states (states 1 to 4) with the associated survival probability. The survival probability for each state was obtained directly from the transition probability matrix, producing a plot of the expected probability of survival against time from each transient states. In this context, survival is defined as not entering the final absorbing state.

The curves are based on the parametric form assumed by the *msm* package, which models sojourn times using exponential distributions under the assumption of constant transition intensities. In this study, no alternative parametric distributions were compared. The exponential model was considered the most appropriate approach in this setting as it provides a parsimonious representation of the data and is the natural choice within the Markov framework employed in this analysis. Nonetheless, it should be acknowledged that this modelling choice imposes limitations. In particular, the exponential distribution assumes a constant hazard which may not fully reflect the clinical reality of advanced melanoma treatments. Future research with a larger dataset could extend this work by formally comparing alternative parametric distributions using Akaike Information Criterion (AIC) or Bayesian Information Criterion (BIC), and assessing their fit relative to empirical survival functions.

For the survival plot, it is possible to visualise a clear distinction between states 1 and 2, first-line treatments, and states 3 and 4, second-line treatments. This plot shows

a higher survival probability for patients treated with a first-line immunotherapy and first-line targeted therapy, with the highest survival probability observed in the latest. Using the 10 months as a landmark, the survival probability for state 1 and 2 were over 0.2 and 0.4, respectively.

On the other hand, patients who had a follow-up treatment with a second-line therapy had a lower survival probability in comparison with the first-line therapies, with patients in the third state, second-line targeted therapy after first-line immunotherapy, having the lowest survival probability. For patients in this transient state, the survival probability diminishes very quickly to around 0.1 in the first five months after starting second-line targeted therapy.

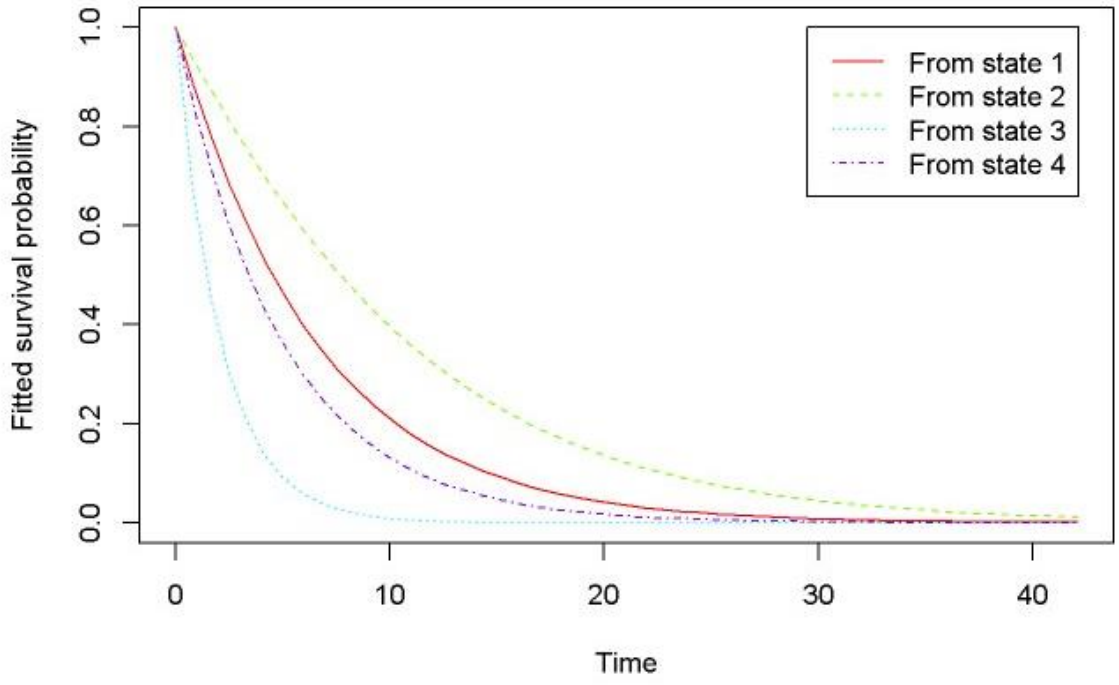

Figure 4.2 – Parametric survival curves stratified by health state

Notes: Time is expressed in months. State 1 – First-line immunotherapy; State 2 – First-line targeted therapy; State 3 – Second-line targeted therapy following first-line immunotherapy; State 4 – Second-line immunotherapy following first-line targeted therapy

4.4.3. Next state probability

From this model it was extracted a matrix with the next state probability and results are displayed in Table 4.2. This matrix revealed that patients that started on immunotherapy as a first-line treatment (state 1) had a transition probability of 8.3%

(95% CI: 4.3−14.3%) and 91.7% (95% CI: 85.7−95.7%) to receive second-line targeted therapy and death, respectively. Regarding patients being cared with first-line targeted therapy, these patients had a transition probabilities of 31.2% (95% CI: 23.0−41.4.3%) and 68.7% (95% CI: 58.7−77.0%) for receiving a second-line immunotherapy and dying, respectively. Furthermore, patients who under states 3 and 4 (first-line immunotherapy followed by second-line targeted therapy; and first-line targeted therapy followed by second-line immunotherapy) had a probability of death equal to 1 since there is only one absorbing state (death) and no other available transitions.

Table 4.2 – Next state probability for the multi-state model

	Probability (95% CI)		
	State 3 (IM + TT)	State 4 (TT + IM)	State 5 (Death)
State 1 (IM)	0.08333 (0.04323, 0.1430)	0	0.91667 (0.85695, 0.9568)
State 2 (TT)	0	0.31250 (0.23006, 0.4134)	0.68750 (0.58659, 0.7699)
State 3 (IM + TT)	0	0	1 (1.000, 1.000)
State 4 (TT + IM)	0	0	1 (1.000, 1.000)
State 5 (Death)	0	0	1 (1.000, 1.000)

Abbreviations: CI – Confidence interval; IM – First-line immunotherapy; TT – First-line targeted therapy; IM + TT – First-line immunotherapy followed by second-line targeted therapy; TT + IM – First-line targeted therapy followed by second-line immunotherapy

4.4.4. Transition probability matrix

It is possible to extract the transition probability matrix for this model. Through this matrix, it is possible to assess the probability of transitioning between the allowed states during a certain timeline. For the purpose of this analysis, a timeframe of 5 years was chosen with a yearly increment from therapy initiation. Thus, Table 4.3 to Table 4.7 displayed the matrices for the first to fifth years, respectively.

At a starting point, 1 year after treatment start, it is observed that the probability of remaining in the first-line treatment was 14.7% and 25.6% and the probability of these patients dying was 84.7% and 67.7% for immunotherapy and targeted therapy,

respectively. Regarding transitions to intermediates states of a second-line therapy, the probabilities of this event were 0.6% and 6.7%. From the second year onwards until the fifth year, there is a decrease in the probabilities of transitioning from the first-line treatment states (state 1 and 2) to the second-line treatment states (states 3 and 4), and the likelihood of moving to the absorbing state (death) naturally increases.

The probability of transitioning from the first-line therapy states (states 1 and 2) to the second-line treatment states (states 3 and 4) decreases from the first year to the fifth year, while the probability of going to the absorbing state (death) naturally increases.

Table 4.3 – Transition probability matrix for a time interval of 1 year

	IM	TT	IM + TT	TT + IM	Death
IM	0.147	0	0.00604	0	0.847
TT	0	0.256	0	0.0670	0.677
IM + TT	0	0	0.00330	0	0.997
TT + IM	0	0	0	0.0881	0.912
Death	0	0	0	0	1

Abbreviations: IM – First-line immunotherapy; IM + TT – First-line immunotherapy followed by second-line targeted therapy; TT – First-line targeted therapy; TT + IM – First-line targeted therapy followed by second-line immunotherapy

Table 4.4 – Transition probability matrix for a time interval of 2 years

	IM	TT	IM + TT	TT + IM	Death
IM	0.0215	0	0.000906	0	0.978
TT	0	0.0653	0	0.02303	0.912
IM + TT	0	0	0.0000109	0	1.000
TT + IM	0	0	0	0.00776	0.992
Death	0	0	0	0	1

Abbreviations: IM – First-line immunotherapy; IM + TT – First-line immunotherapy followed by second-line targeted therapy; TT – First-line targeted therapy; TT + IM – First-line targeted therapy followed by second-line immunotherapy

Table 4.5 – Transition probability matrix for a time interval of 3 years

	IM	TT	IM + TT	TT + IM	Death
IM	0.00315	0	0.000133	0	0.997
TT	0	0.0167	0	0.006407	0.977
IM + TT	0	0	0.000000036	0	1
TT + IM	0	0	0	0.000683	0.999
Death	0	0	0	0	1

Abbreviations: IM – First-line immunotherapy; IM + TT – First-line immunotherapy followed by second-line targeted therapy; TT – First-line targeted therapy; TT + IM – First-line targeted therapy followed by second-line immunotherapy

Table 4.6 – Transition probability matrix for a time interval of 4 years

	IM	TT	IM + TT	TT + IM	Death
IM	0.000461	0	0.0000195	0	1
TT	0	0.00427	0	0.00168311	0.994
IM + TT	0	0	0.000000000118	0	1
TT + IM	0	0	0	0.0000602	1
Death	0	0	0	0	1

Abbreviations: IM – First-line immunotherapy; IM + TT – First-line immunotherapy followed by second-line targeted therapy; TT – First-line targeted therapy; TT + IM – First-line targeted therapy followed by second-line immunotherapy

Table 4.7 – Transition probability matrix for a time interval of 5 years

	IM	TT	IM + TT	TT + IM	Death
IM	0.0000676	0	0.00000285	0	1
TT	0	0.00109	0	0.000434	0.998
IM + TT	0	0	0.00000000000039	0	1
TT + IM	0	0	0	0.00000530	1
Death	0	0	0	0	1

Abbreviations: IM – First-line immunotherapy; IM + TT – First-line immunotherapy followed by second-line targeted therapy; TT – First-line targeted therapy; TT + IM – First-line targeted therapy followed by second-line immunotherapy

4.4.5. Covariate influence on transition rates

In order to understand the influence of certain covariates in the HRs for the health state transitions, new multi-state models that included one covariate at the time were tested, thus investigating the covariates of interest included in Cox models from previous chapters (see sections 3.3.4 and 3.4.5). The covariates included in this analysis were LDH, ECOG Performance Status, and BMI. The HRs for each of the possible transitions between health states are displayed from Table 4.8 to Table 4.10.

4.4.5.1. LDH

Regarding LDH (Table 4.8), it is possible to notice that this covariate resulted in a small decrease of the HR (0.998) for the first allowed transition (first-line immunotherapy to second-line targeted therapy). There were small increments in the HR (1.001) for the second, fourth, and sixth transitions (first-line immunotherapy to

death; first-line targeted therapy to death; second-line immunotherapy to death). Moreover, the results for transitions 4 and 6 (first-line targeted therapy to second-line immunotherapy; second-line targeted therapy to death) demonstrated a HR of 1.0.

Table 4.8 – Hazard ratios for LDH on the multi-state model transitions

Transition number	Transitions	Hazard ratio
T1	IM → IM + TT	0.998
T2	IM → Death	1.001
T3	TT → TT + IM	1.000
T4	TT → Death	1.001
T5	IM + TT → Death	1.000
T6	TT + IM → Death	1.001

Abbreviations: IM – First-line immunotherapy; IM + TT – First-line immunotherapy followed by second-line targeted therapy; T1 – First transition; T2 – Second transition; T3 – Third transition; T4 – Fourth transition; T5 – Fifth transition; T6 – Sixth transition; TT – First-line targeted therapy; TT + IM – First-line targeted therapy followed by second-line immunotherapy

4.4.5.2. ECOG Performance Status

After the inclusion of ECOG PS in the multi-state model, the HRs for the transitions were extracted. This is a categorical variable which included three groups: ECOG PS 0, ECOG PS 1 and ECOG PS 2+. For the analysis purposes, ECOG PS 0 was set to be the baseline. Thus, the hazard ratios for each transition for ECOG PS 1 and ECOG PS 2+ in comparison with the baseline are displayed in Table 4.9.

Overall, there was a general increase in the hazard ratios for both groups, with this being generally higher for patients with an ECOG PS 2+. Regarding the first transition (first-line immunotherapy to second-line targeted therapy), the extracted HRs for both groups were extremely low (0.000000421, 0.00000334). Additionally, the highest HRs extracted were for the sixth health state transition (T6) which represents the transition from second-line targeted therapy to death. The hazard ratios for T6 were 2.81 and 4.92 for ECOG PS 1, and ECOG PS 2+, respectively. Moreover, the results for transition 5 (first-line immunotherapy to second-line targeted therapy) demonstrated a hazard ratio of 1.0.

Table 4.9 – Hazard ratios for ECOG PS on the multi-state model transitions

		Hazard ratio	
Transition number	**Transitions**	**ECOG PS 1**	**ECOG PS 2+**
T1	IM → IM + TT	0.000000421	0.00000334
T2	IM → Death	1.68	3.03
T3	TT → TT + IM	1.31	2.25
T4	TT → Death	1.30	2.06
T5	IM + TT → Death	1.00	1.00
T6	TT + IM → Death	2.81	4.92

Abbreviations: ECOG PS 1 – Eastern Cooperative Oncology Group Performance Status 1; ECOG PS 2+ – Eastern Cooperative Oncology Group Performance Status 2 or higher; IM – First-line immunotherapy; IM + TT – First-line immunotherapy followed by second-line targeted therapy; T1 – First transition; T2 – Second transition; T3 – Third transition; T4 – Fourth transition; T5 – Fifth transition; T6 – Sixth transition; TT – First-line targeted therapy; TT + IM – First-line targeted therapy followed by second-line immunotherapy

4.4.5.3. BMI

Regarding BMI (Table 4.10), it is possible to notice that this predictor resulted in an increased HR for patients transitioning to a second-line treatment (first-line immunotherapy followed by second-line targeted therapy; first-line targeted therapy followed by second-line immunotherapy), and from a second-line immunotherapy to death. Moreover, in cases of transitions from a first-line immunotherapy and first-line targeted therapy to the death state, BMI showed a hazard ratio decrease of 1.6% and 3.3%, respectively.

Table 4.10 – Hazard ratios for BMI on the multi-state model transitions

Transition number	Transitions	Hazard ratio
T1	IM → IM + TT	1.088
T2	IM → Death	0.984
T3	TT → TT + IM	1.051
T4	TT → Death	0.967
T5	IM + TT → Death	1.000
T6	TT + IM → Death	1.083

Abbreviations: BMI – Body-mass index; IM – First-line immunotherapy; IM + TT – First-line immunotherapy followed by second-line targeted therapy; T1 – First transition; T2 – Second transition; T3 – Third transition; T4 – Fourth transition; T5 – Fifth transition; T6 – Sixth transition; TT – First-line targeted therapy; TT + IM – First-line targeted therapy followed by second-line immunotherapy

4.4.6. Model assessment

In order to assess the goodness-of-fit for this multi-state model, the values for observed and expected values were plotted in a line plot in Figure 4.3. For this assessment, the observed and expected values were calculated at monthly (30-day) intervals up to 5 years after the initiation of the first-line treatment. The visual predictive check in Figure 4.3 demonstrates a good fit by the multi-state model to the observed data. From this plot, it possible to observe an exponential increase in prevalence in the death state from the start of treatments while the prevalence of patients in health states 1 and 2 (first-line immunotherapy and first-line targeted therapy) decreases overtime. It is also visible in this plot an increase in prevalence of patients in the health state 4 (second-line immunotherapy after first-line targeted therapy) which is capture by the model as well.

The goodness-of-fit can also serve as an indicator of the model's alignment with observed data and validates the success of the underlying Markov assumption.

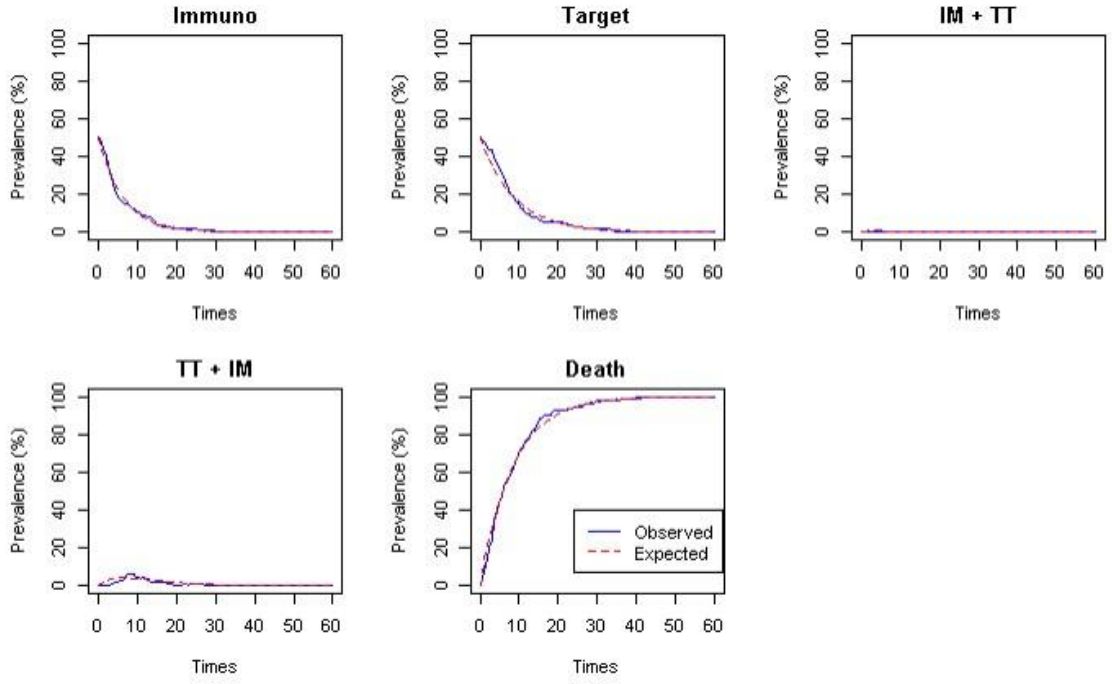

Figure 4.3 – Plotted observed vs expected percentage of patients by health state over 5-year period.

Notes: Blue solid line – Observed values; Red dashed line – Expected values. **Abbreviations:** Immuno – First-line immunotherapy; Target – First-line targeted therapy; IM + TT – First-line immunotherapy followed by second-line targeted therapy; TT + IM – First-line targeted therapy followed by second-line immunotherapy

4.5. Discussion

The implementation of multi-state models in the study of advanced melanoma patients using real-world evidence provides several distinctive advantages. Firstly, a significant advantage is the flexibility of a multi-state model which allows the evaluation of survival and other health outcomes based on the entire journey of cancer treatment rather than merely the initial health state or first-line. This approach can accommodate the evolving nature of the disease through progression or therapeutic interventions. Consequently, it provides a more comprehensive understanding of a patient's anti-cancer treatment, complementing conventional survival analyses. Moreover, it is worth noting that the application of multi-state models to the context of advanced melanoma is still relatively underexplored, specifically the application of these methods to real-world patients.

The examination of sojourn time yields valuable insights into the dynamics of advanced melanoma treatment. Notably, the mean sojourn time was observed to be higher for patients receiving first-line targeted therapy compared to those on first-line immunotherapy, with durations of 8.8 and 6.25 months, respectively. This distinction suggests that patients undergoing targeted therapy tend to spend a longer period in this treatment phase before transitioning to other transient states, such as a second-line treatment or death. When assessing the mean sojourn times in the context of second-line treatments, a higher duration was noted for second-line immunotherapy (State 4) in comparison to second-line targeted therapy (State 5), with respective times of 4.94 and 2.10 months. This result needs to be interpreted with caution due to the standard error of 2.1 months and the wide confidence interval of second-line targeted therapy (95% CI: 0.296−14.91 months). The variability in the confidence interval demonstrates the need for further investigation, potentially using a larger sample size in order to gain a more precise understanding of the duration of the second-line targeted therapy.

The parametric survival curves included in this analysis provided an insight into the survival probabilities associated with different treatment sequences. Firstly, we observed higher survival probabilities for first-line therapies in comparison to second-line therapies. The resort to second-line therapy suggests a failure of first-line therapy. This could be due to treatment factors such as the onset of adverse events, toxicity

effects, intolerances, or disease progression that led to the aggravation of the patient's condition, which can explain the lower survival probabilities upon starting second-line therapy. However, the reasoning behind the changes to second-line therapy is unclear due to the lack of evidence.

At the landmark of 10 months, a difference in survival probability becomes evident. Patients starting with first-line targeted therapy exhibit a higher probability of survival compared to those receiving first-line immunotherapy, with probabilities of 40% and 20%, respectively. Moreover, when comparing the survival probabilities associated with second-line treatments in states 3 and 4, an interesting pattern emerges. Patients who receive second-line immunotherapy following first-line targeted therapy exhibit higher survival probabilities than those receiving second-line targeted therapy after first-line immunotherapy. Looking at a 6-month landmark, patients in states 3 and 4 had survival probabilities of approximately 35% and 10%, respectively. This discrepancy may be attributed to the distinct mechanisms of action and the onset of therapeutic effects associated with these therapy types. The quick onset and mechanism of action of targeted therapy could be complemented by the long-term therapeutic effects of immunotherapy, resulting in the observed survival advantage for patients in health state 4, following a second-line immunotherapy after a first-line targeted therapy [144].

Results from the multi-state model also highlight variations in the probabilities of transitioning between treatment states. Notably, there is a higher probability of patients transitioning from first-line targeted therapy to second-line immunotherapy compared to patients transitioning from first-line immunotherapy to second-line targeted therapy, with probabilities of 31% and 8%, respectively. This contrast may be attributed to the BRAF gene status of the disease. Patients commencing with first-line targeted therapy are inherently *BRAF*-mutant, rendering immunotherapy a feasible alternative should targeted therapy prove ineffective. In contrast, patients who initiate anti-cancer treatment with first-line immunotherapy may not be eligible for second-line targeted therapy if they lack the mutation in the BRAF gene, therefore considered *BRAF*-wild-type.

The impact of the variables, such as LDH, ECOG PS and BMI, on changes in health states and how those changes affect treatment outcomes and the HR for those changes, were clarified by the study of these covariates. Regarding the influence of LDH in the

transition rates, a decrease in the HR for the first transition, from first-line immunotherapy to second-line targeted therapy suggests that patients transitioning to second-line targeted therapy from an initial immunotherapy regimen may experience a slightly reduced risk of transitioning to a second-line targeted therapy after initial treatment with immunotherapy. Inversely, the results indicated increments in the HRs for the second, fourth and sixth transitions, suggesting that LDH negatively impacts survival which goes accordingly to results from previous studies classifying LDH as a prognostic factor. The evaluation of hazard ratios for the ECOG PS in relation to transition rates revealed a general increase in HR for patients with ECOG PS 1 and ECOG PS 2+ in comparison to patients with a baseline ECOG PS equal to 0. This outcome underscores that the patients with higher ECOG PS scores, indicative of poorer general health, have an associated elevated risk of transitioning to a second-line treatment and a decreased probability of survival. This risk is elevated even higher when the comparison lies between baseline and patients with an ECOG PS of 2 or higher. Additionally, it is notable that during the first transition the HR for both ECOG PS groups (ECOG PS 1 and ECOG PS 2+) was extremely low. This exceptionally low HR suggests a low probability of patients with ECOG PS scores higher than 0 transitioning to second-line targeted therapy. Furthermore, it is worth mentioning that among patients with a ECOG PS of 2 or higher, a trend emerges with generally higher hazard ratios in contrast to patients with a ECOG PS equal to 1. This observation underscores that higher ECOG PS levels are associated with an augmented risk of transitioning to a second-line treatment or death. Given that the ECOG Performance Status serves as a measure of a patient's overall health and functional well-being, these results align logically with the principle that individuals with poorer health, as reflected by a higher ECOG PS score, are more susceptible to increased risks in the context of treatment transitions and survival outcomes. The analysis regarding the impact of BMI on the transition hazard ratio revealed decreases in HR of 1.6% and 3.3% for transition 2 (from first-line immunotherapy to death) and transition 4 (from first-line targeted therapy to death), respectively. This result suggests that patients with a higher BMI may experience a reduced risk of death, which could indicate a possible survival benefit from increased BMI levels. The potential influence of BMI on the survival outcomes of advanced

melanoma patients in the context of immunotherapy and targeted therapy demands further investigation [139].

Targeted therapy focuses on specific molecular targets within cancer cells, while immunotherapy aims to enhance the body's immune response against cancer. The study suggests that combining these two treatment approaches may lead to improved outcomes in advanced melanoma patients. The findings from this study suggests that the mechanism of action and the rapid onset of therapeutic effects associated with targeted therapy may confer an advantage during the early stages of treatment. The significance of the synergy between both therapy types lies in the potentially for enhanced treatment efficacy and the possibility of overcoming resistance to individual therapies for advanced melanoma patients with a mutation in the *BRAF* gene. Further research is needed to explore the mechanisms underlying this synergy and to identify the patient populations that would benefit the most from this combined approach [46], [144].

This study comes with its limitations such as its small sample size which poses challenges regarding the generalisability of the findings to broader populations. Additionally, information regarding disease progression, surgical interventions, and/or the location of metastasis were absent. These factors could significantly influence patient outcomes and treatment decisions, restricting the depth and comprehensiveness of the analysis. The most prominent limitation lies in the absence of data regarding the reasons behind therapy changes. During the course of treatment, patients might suffer immune-related adverse events due to treatment, which can lead to pausing the treatment or searching for an alternative therapy. The details of why patients transition between different treatment types remain unclear, making it challenging to offer comprehensive insights into the motivations behind these therapeutic decisions. In summary, the small cohort size, the scarcity of data, and the unavailability of pertinent information concerning surgeries, disease progression, and the reasoning behind therapy changes represent substantial challenges. These limitations increase the need for better data collection and linkage for more comprehensive datasets, which can provide a more robust understanding of the experiences and treatment outcomes of advanced melanoma patients in a real-world setting.

In conclusion, this approach has demonstrated advantages in the analysis of advanced melanoma patients in a real-world setting, along with limitations. Despite the limitations, the results in this chapter explain the complex relationship between treatment pathways and their impact on advanced melanoma patient outcomes, while also highlighting opportunities for further research. By acknowledging the potential therapeutic synergy between targeted therapy and immunotherapy, the insights from this study aim to contribute to the ongoing efforts to optimise treatment strategies and enhance the prognosis of advanced melanoma patients.

Chapter 5 Health economic evaluation of advanced melanoma patients with progressive disease in real-world practice

5.1. Introduction

This chapter focuses on building a health economic evaluation for estimating the cost-effectiveness of drug interventions with immunotherapy and targeted therapy in real-world advanced melanoma patients. The analysis in this chapter examines patients who started anti-cancer treatment with first-line immunotherapy or first-line targeted therapy. During the course of treatment, patients could continue treatment with the first treatment option or change to the other treatment type as a second-line therapy (i.e., patients treated with first-line immunotherapy that changed to second-line targeted therapy; and patients who received first-line targeted therapy that changed to second-line immunotherapy).

The main objective of this chapter is to provide further insight into the treatment sequence for patients with advanced melanoma by comparing the cost-effectiveness of different SACT strategies using real-world evidence. In particular, this chapter seeks to address how real-world treatment patterns, survival outcomes, and treatment sequencing influence economic value within the NHS context.

Therefore, this chapter addresses the following research questions:

1. How can a fast, efficient, and adaptable multi-state cost-effectiveness model be developed in R to facilitate health economic evaluations?
2. What is the cost-effectiveness of first-line immunotherapy compared to first-line targeted therapy for patients with advanced melanoma in a real-world practice from the UK NHS perspective?

3. How do first- and second-line treatments (immunotherapy or targeted therapy) influence QALYs for advanced melanoma patients?

To address these questions, this chapter builds upon the clinical results and survival analyses presented in Chapter 3 and Chapter 4 which established the foundation for this health economic analysis by describing the clinical results and survival rates linked to different treatment choices for advanced melanoma. Conducting a health economic evaluation for advanced melanoma treatment in a real-world setting can help healthcare providers and policymakers make informed decisions about resource allocation, ensuring that patients receive the most effective and efficient care.

A multi-state Markov model was developed using data from real-world advanced melanoma patients (see 0) and supplemented by literature-derived values to simulate disease progression and estimate health and economic outcomes. This methodological approach builds directly on the multi-state modelling outlined in Chapter 4 and adapts them for the purpose of a health economic evaluation. The aim was to create an efficient and adaptable framework to perform cost-effectiveness analyses, suitable for application to other therapeutic areas or treatment contexts.

The analyses carried out in this chapter are based on the established economic evaluation methodologies and HTAs, including those submitted for NICE appraisal [73]. As previously described in section 1.6.1, the NICE technology appraisals (TA) are systematic assessments of the characteristics, outcomes, and/or implications of health technology. These appraisals, conducted upon the introduction of a new treatment or intervention, are based on the information and outcomes provided by the submitter. The social, economic, organisational, and ethical aspects of a health intervention or health technology are assessed in a multidisciplinary process. Thus, the objective of these TAs is to provide evidence about the benefits of novel treatments and interventions in order to influence healthcare policy and decision-making. Accordingly, the TAs that were submitted for NICE appraisal comprise thorough assessments of the clinical efficacy, cost-effectiveness, and overall effects of immunotherapy and targeted therapy for advanced melanoma. These evaluations are essential for deciding whether novel treatments should be suggested for use in the NHS.

For the purpose of making decisions based on a formal assessment of costs and effects, assessments such as NICE HTAs rely on cost-effectiveness analysis. Therefore,

this chapter aims to understand the cost-effectiveness of advanced melanoma therapies in clinical practice through the use of real-world evidence and publicly available literature. By doing so, it seeks to provide a comprehensive evaluation that can inform clinical and policy decisions, ultimately improving patient outcomes and resource utilisation.

5.2. Aims and objectives

The general aim of the work in this chapter is to conduct a health economic assessment and evaluate the cost-effectiveness of recent SACT with immunotherapy and targeted therapy drugs for advanced (unresectable or metastatic) melanoma using real-world evidence from Scottish patients. Thus, the objectives of this chapter were:

- Develop an efficient, fast and adaptable multi-state cost-effectiveness model in R to facilitate health economic evaluations;
- Determine the cost-effectiveness of immunotherapy and targeted therapy treatments in real-world setting;
- Investigate the influence of first and second-line treatments (immunotherapy or targeted therapy) in QALYs.

5.3. Methods

The modelling and analysis in this chapter used the *hesim* package for R that facilitates parameterisation, simulation and analysis of economic models [145]. This package supports various model types including ICTSTMs and partitioned survival models. These encompass both Markov (time-homogeneous and time-inhomogeneous) and semi-Markov processes. Compared with the *mstate* package, which primarily focuses on multi-state survival analysis and transition probability estimation, *hesim* provides a more comprehensive framework for integrating these statistical analyses directly with economic evaluation components, such as costs and utilities. The modular design of the *hesim* package allows the combination of separate submodels for disease

progression, costs, and health-related utilities, offering greater flexibility for cost-effectiveness modelling [145].

Furthermore, a probabilistic sensitivity analysis (PSA) was conducted on the economic model to evaluate its uncertainty. Using a simulation with a thousand samples for the PSA, the uncertainty around the parameters from the statistical models is propagated throughout the economic model [146]. Thus, a cost-effectiveness analysis was performed after creating the health economic model. The previous topics will be further elaborated in the sections below as section 5.3.1 describes the methodological approach and section 5.3.2 provides an overview of the model structures and its key components. A detailed explanation of the sensitivity analysis is presented in section 5.3.3, outlining how the probabilistic approach was employed to assess uncertainty. Results of the cost-effectiveness analysis are presented in section 5.4, while section 5.5 discusses the implications of these findings within a broader context.

All analyses in this study were conducted in the R programming language using RStudio® as the primary software environment.

5.3.1. Methodological approach

5.3.1.1. Individual continuous time state transition model

An ICTSTM encompassing a Markovian process (i.e., '*clock-forward*'), as previously described in Chapter 4, was developed using IPD as these models can be parameterised when continuously observed patient-level data is available [145]. An ICTSTM simulates individual trajectories between health states through random number generation. Those trajectories are simulated for multiple patients and the expected costs and QALYs are computed by averaging across the simulated patients [145].

The target population for the model simulation contains of a heterogeneous population of 1,000 patients, which is large enough to ensure that averages across patients in the individual simulation are reasonably stable [145]. As IPD and multi-state data were available, it was possible to know the exact transition times for each

transition. Thus, an ICTSTM was used to parameterise all possible transitions in a state transition model while accounting for censoring [147].

5.3.1.2. Treatment sequencing modelling

A multi-state transition model (Figure 5.1) was developed to describe the treatment sequences, the associated costs, and health outcomes. The multi-state transition model was defined by three mutually exclusive health states and three health state transitions.

Health states

- State 1 – Progression-free;
- State 2 – Progression;
- State 3 – Death.

Health state transitions

- Transition 1 – Progression-free → Progression;
- Transition 2 – Progression-free → Death;
- Transition 3 – Progression → Death.

At the start of advanced melanoma treatment, all patients enter the model in the progression-free state (State 1). Assumptions were made for the second health state in order to classify the patients entering a disease progression health state (State 2). Therefore, a state of disease progression was assumed to represent a health state in which, during the course of treatment, a patient had changed to a different therapy regimen than the initial treatment assigned to that patient, either immunotherapy or targeted therapy. When a patient had a type of therapy change, it was assumed that the purpose of this modification to a different SACT type was due to the lack of efficacy of the initial treatment and with the intention of providing the patient with the best option to treat their health condition. Thus, type of therapy changes was assumed to be a result of disease progression. However, this assumption overlooks therapy changes occurring due to other clinical considerations, such as adverse events or treatment-related toxicities, without evidence of disease progression. As such, this assumption may lead to a potential overestimation of progression events within the model.

Furthermore, only certain changes in therapy could be considered as changes due to progression as part of common clinical practice. Patients who changed from immunotherapy regimens (nivolumab, ipilimumab, and pembrolizumab) to targeted therapy regimens (dabrafenib, dabrafenib plus trametinib, and vemurafenib) and from targeted therapy regimens to immunotherapy regimens. Additionally, patients who started their anti-cancer treatment with an immunotherapy regimen and switched to a different immunotherapy regimen were also considered to have progressive disease. Changes between targeted therapy drugs are more likely to arise due to the occurrence of adverse events during treatment, thus not considered as disease progression in this model [148].

An illustration of the multi-state transition model is displayed in Figure 5.1.

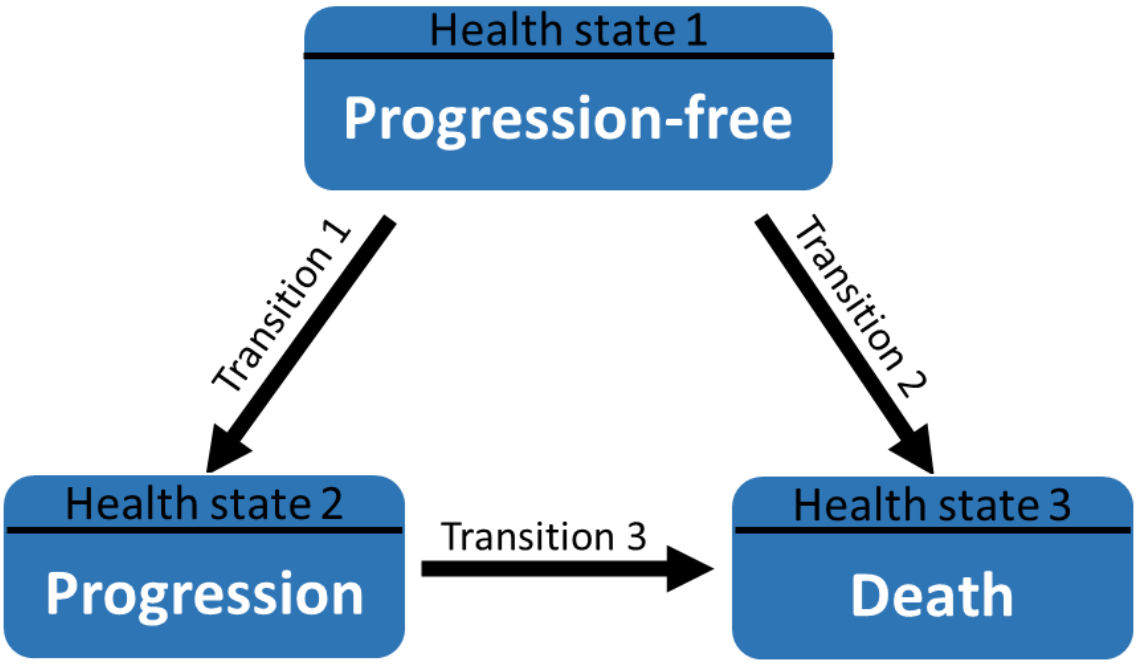

Figure 5.1 – Three-state transition model for health states of progression-free and progressive disease

Notes: The model represents three health states including one absorbing state (death). There are only three possible transitions between health states (Transition 1 - Progression-free to progression; Transition 2 - Progression-free to death; Transition 3 - Progression to death)

5.3.1.3. Health state transitions

Health state transition probabilities were informed by PFS and OS from real-world IPD (see 0). Transition probabilities for each health state were estimated using a parametric multi-state modelling approach with different parametric functions fitted to each individual transition. For the parameterisation of the three health state transitions in the multi-state model, five parametric distributions were evaluated: (1) Weibull, (2) exponential, (3) Gompertz, (4) log-logistic, and (5) log-normal [147]. The distribution choice was based on goodness-of-fit (assessed by mean squared error and visual assessment) and AIC statistics for each distribution [147], [149].

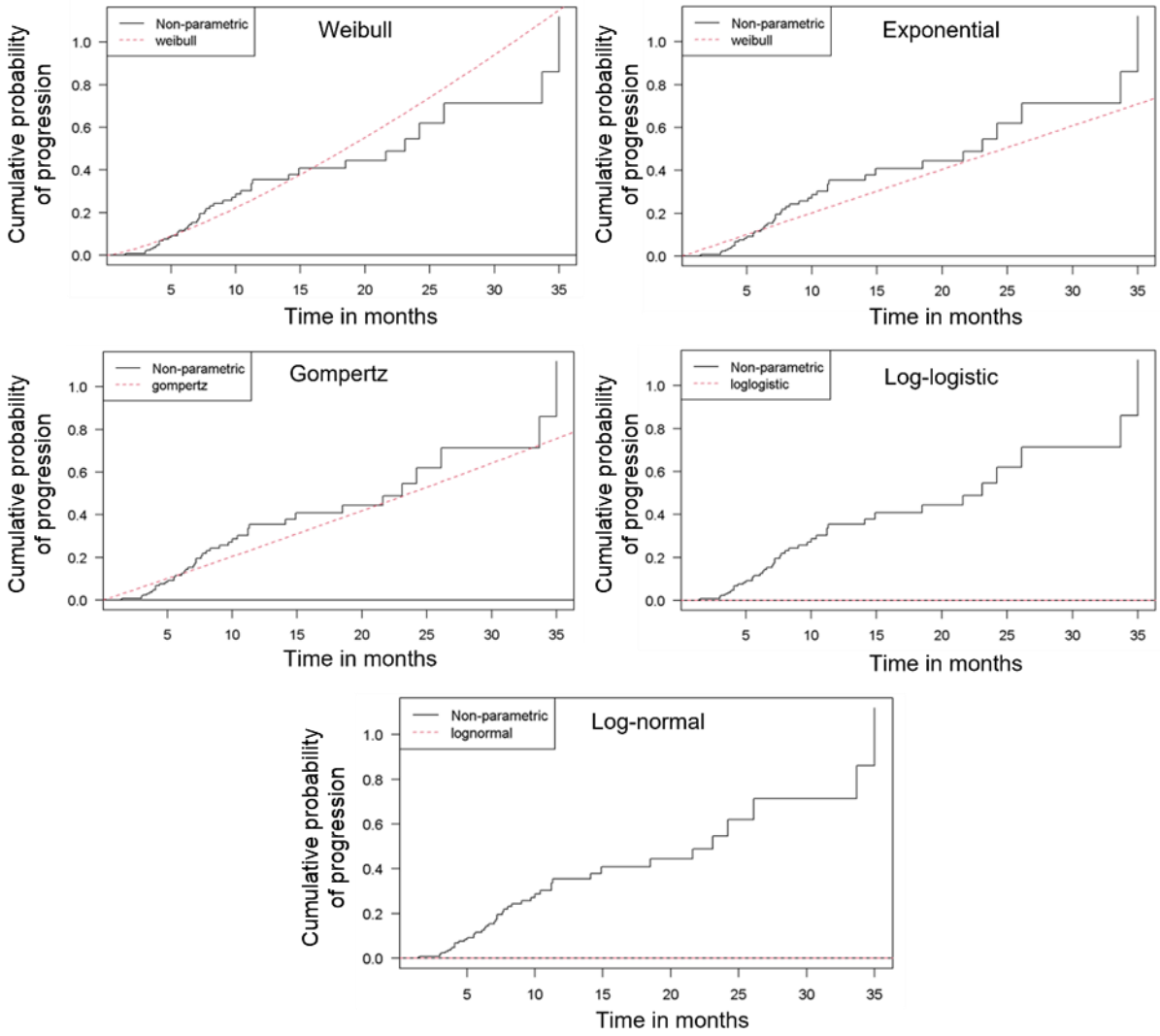

Figure 5.2 – Parametric and non-parametric distribution plots for the first transition (T1)

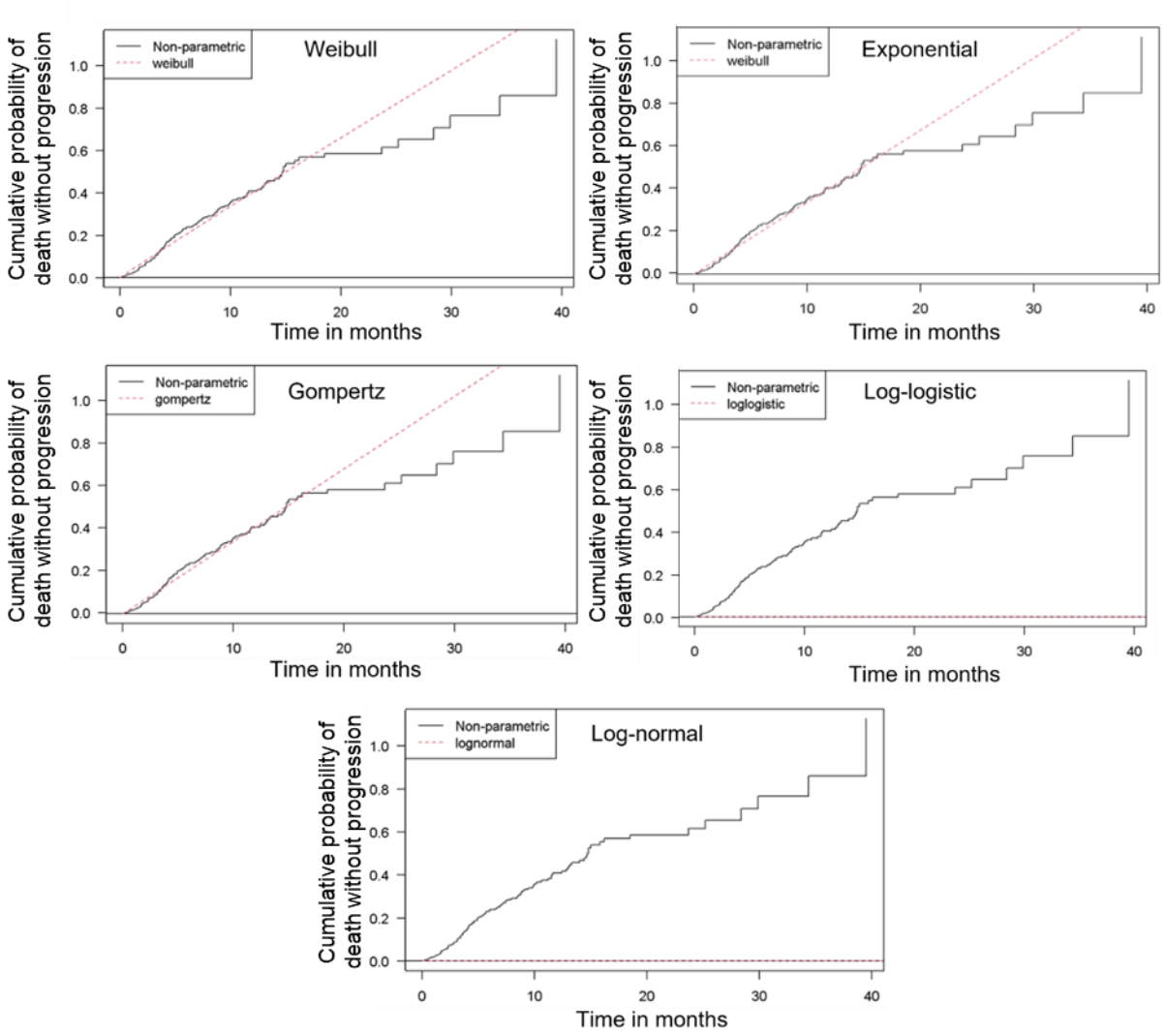

Figure 5.3 – Parametric and non-parametric distribution plots for the second transition (T2)

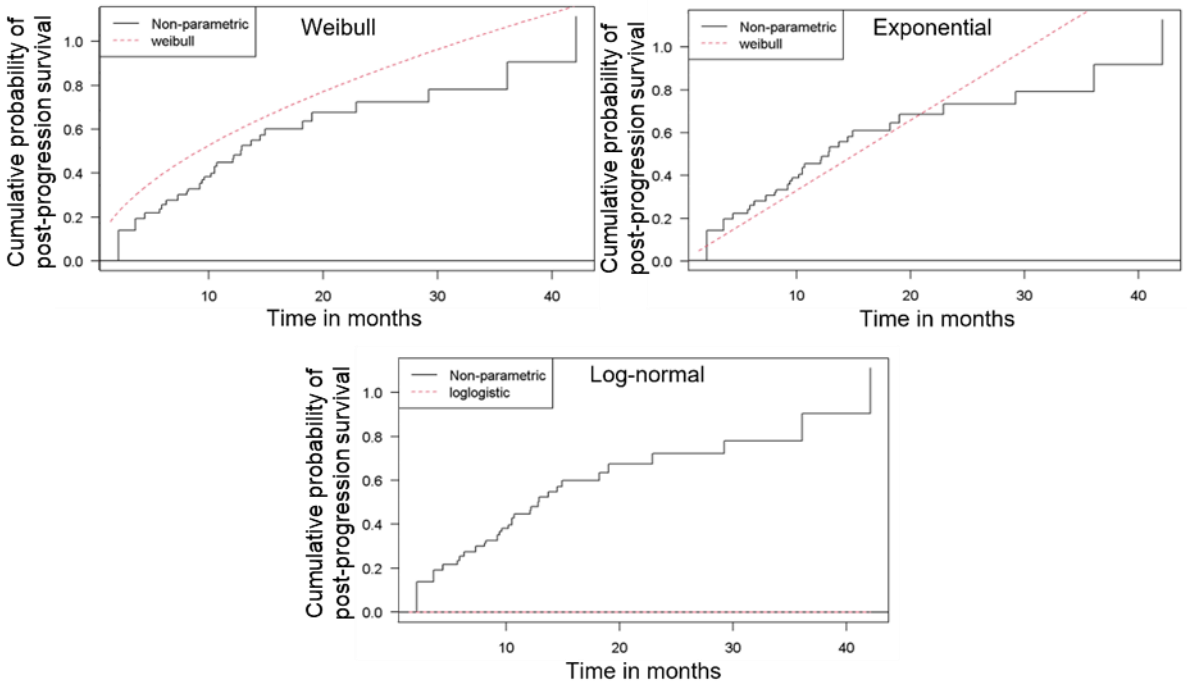

Figure 5.4 – Parametric and non-parametric distribution plots for the third transition (T3)

Regarding patients transitioning from progression-free to progression (T1) and from progression-free to death (T2), the comparison of the visual representation of the distribution curves between parametric and non-parametric distributions revealed a poor fit for the log-logistic and log-normal distributions and a good fit for the remaining distributions (Figure 5.2 and Figure 5.3). Only three distributions were tested for the third transition (T3) due to limited data availability. The Weibull and exponential distributions demonstrated a good fit, while the log-normal distribution revealed similar behaviour as a non-parametric distribution (Figure 5.4).

Since the visual assessment for the first and second transitions (T1 and T2) did not reveal a significant difference between the Weibull and exponential distributions, the choice as based on the distributions presented the lowest AIC statistic for each transition (Table 5.1). Therefore, the Weibull and exponential distributions were chosen for the first and second transitions, respectively.

The third transition (T3) is a transition from an intermediate state and the hazard rate does not depend on time since entry into this health state. Thus, despite the

similarities between Weibull and exponential distributions' results for this transition, the distribution chosen was the exponential distribution.

In summary, the distributions chosen for the transition model were Weibull for the first transition (progression-free to progression) and exponential for the second (progression-free to death) and third transitions (progression to death) for all treatment strategies. The AIC scores for each all distribution tested and per transition are displayed in Table 5.1.

Table 5.1 – AIC scores for parametric distributions per health state transition

	AIC		
Distribution	**First transition (T1)**	**Second transition (T2)**	**Third transition (T3)**
Weibull	443.3	1048.4	193.5
Exponential	447.3	1046.7	193.5
Gompertz	449.2	1048.7	-
Log-logistic	431.3	1033.2	195.5
Log-normal	431.8	1036.5	-

Abbreviation: AIC – Akaike Information Criterion

5.3.2. Model structure

5.3.2.1. Patient population

As stated in 0, the data originated from patient healthcare in the region of Greater Glasgow and Clyde. The data was collected, anonymised, and stored by the University of Glasgow's SafeHaven.

Due to the limited amount of data available, only patients treated with immunotherapy or targeted therapy drugs were included in this analysis. The assumptions for disease progression (as described in section 5.3.1.2) would not hold for patients treated with chemotherapy, hence patients treated with chemotherapy were removed from the final cohort.

5.3.2.2. Intervention and comparators

The selection of the intervention and comparators for this health economic evaluation was based on the treatments currently available in real-world clinical practice for advanced melanoma. The primary intervention, ipilimumab, was chosen due to its historical significance as the first ICI treatment to receive regulatory approval for advanced melanoma, as previously mentioned in section 1.5.

Intervention

- Ipilimumab

Comparators

- *Immune checkpoint inhibitors:*
  - Nivolumab plus ipilimumab
  - Pembrolizumab
- *Targeted therapy:*
  - Dabrafenib
  - Dabrafenib plus trametinib
  - Vemurafenib

5.3.2.3. Utility estimation

Utilities, also known as health state preference values, are numerical representations of the quality of life associated with different health states. These values are ranging from 0.0 to 1.0, where 0.0 represents the worst possible health state (often equated with death) and 1.0 represents perfect health [150]. Utility measurement is on an interval scale with the "anchors" of 0 and 1, so that a change in health from 0.2 to 0.3 is similar to a shift from 0.8 to 0.9. These changes are deemed to be the same regardless of the part of the scale being analysed [150].

Utilities are integral to health economic evaluations because they allow for the comparison of the effectiveness of different healthcare interventions on a common scale. One of the most common applications of utilities is in the calculation of QALYs. QALYs combine both the quantity and quality of life into a single measure, making it easier to compare the health outcomes of different interventions. QALYs account for

different health states over time, weighted by their utility scores and are calculated by multiplying the duration in a health state by the associated utility score. For example, 10 years in a health state with a utility of 0.6 equals six QALYs. For example, one year of life in perfect health is equivalent to 1 QALY, while one year of life in a health state valued at 0.5 utility would be equivalent to 0.5 QALYs [150].

NICE recommends the use of QALYs as a measure of health benefit, enabling a standardised approach for comparing economic evaluations across different healthcare areas [150]. Thus, this health economic evaluation included utility values for progression-free and progression health states. These utilities were derived from a cross-sectional study conducted in the United Kingdom and Australia to obtain the mean utilities for advanced melanoma clinical response states (Table 5.2) [151]. The utilities for patients in the progression-free and progressive disease health states were 0.77 and 0.59, respectively, with a standard error of 0.02 for both utility values [151]. Utility values are assumed to follow a beta distribution, which can be parameterised through their means and standard error [145].

Table 5.2 – Mean utilities per health state for advanced melanoma patients in the UK

State	Utility value (SE)	Distribution
Progression-free	0.77 (0.02)	Beta (β)
Progressive disease	0.59 (0.02)	Beta (β)

Abbreviation: SE – Standard error

5.3.2.4. Outcome measures

Consistent with NICE requirements, health outcomes are expressed as QALYs and applied a discount rate of 3.5% per year, same as in the costs [152].

Outcomes from the PSA are expressed as total QALYs, incremental QALYs, incremental costs, incremental net monetary benefit (NMB), and ICUR. The ICUR represents the ratio of the difference in costs (incremental costs) to the difference in health outcomes (incremental QALYs) between two competing interventions. It is calculated using the formula:

$$ICUR = \frac{Incremental\ costs}{Incremental\ QALYs}$$

The ICUR is a central measure in cost-effectiveness analysis, providing insight into whether the additional cost of one treatment compared to another is justified by the additional health benefit it provides [153], [154].

Results from the PSA are presented through several visual and analytical tools:

- **Cost-effectiveness plane**: A graphical representation of the uncertainty around the cost-effectiveness estimate. It plots incremental costs against incremental QALYs for each simulation, providing insight into the distribution of cost-effectiveness outcomes across the four quadrants of the plane (see Figure 5.5) [154].
- **Cost-effectiveness acceptability curve**: This curve shows the probability of an intervention being cost-effective across a range of WTP thresholds. The cost-effectiveness acceptability curve is derived by plotting the proportion of PSA iterations in which the intervention is cost-effective against varying WTP thresholds. A cost-effectiveness acceptability curve illustrates the likelihood that an intervention is cost-effective at different WTP values [155].
- **Cost-effectiveness frontier**: The cost-effectiveness frontier identifies the optimal treatment strategies at different WTP thresholds by plotting the most cost-effective options that maximise health benefits while considering costs, highlighting the intervention with the greatest NMB at each threshold [154].
- **Expected value of perfect information**: This metric quantifies the value of eliminating all uncertainty in the decision-making process. It is obtained by calculating the difference between the expected NMB when perfect information is available and the expected NMB under current uncertainty [156]. The expected value of perfect information helps assess whether additional research to reduce uncertainty is economically justified [156].

These tools provide a comprehensive understanding of cost-effectiveness by capturing uncertainty, supporting decision-making under varying WTP thresholds, and identifying areas where further research could add value.

5.3.2.5. Costs

5.3.2.5.1. Drug costs

The individual drug acquisitions costs were obtained from the data publicly available through NICE [157], [158], [159], [160], [161], [162]. The model used monthly costs as the schedule of administering varies by drug treatment.

The acquisition costs for SACT drugs included in the model are described in Table 5.3 [73], [163]. Also, the model follows the NICE guidelines on discounting, which states that a discount rate of 3.5% per year should be used for costs [152]. The dose for ipilimumab and the combination of nivolumab plus ipilimumab are administered based on the patient's body weight. An average body weight of 70 kg was assumed for the calculations for dose and respective cost, following the same guidance as the health technology appraisal submitted to NICE [163].

Table 5.3 – Acquisition costs per drug intervention per dose and monthly cost

Drug	Costs	Monthly cost
Ipilimumab [157]	£3,750 for 50 mg £15,000 for 200 mg	£26,790
Nivolumab [158]	£439 per 4ml vial (40 mg) £1,097 per 10 ml vial (100 mg)	£28,050
Pembrolizumab [159]	£1,315 per 50 mg vial	£9,390
Dabrafenib [160]	£1,400 per 75 mg capsules pack (28 capsules per pack)	£6,000
Trametinib [161]	£1,120 per pack of 2 mg tablets (7 tablets per pack)	£10,800
Vemurafenib [162]	£1,750 for 1 pack of 56 × 240 mg tablets (1 week's supply)	£7,500

Notes: Costs exclude VAT and originate from company's submission. These costs may vary in different settings because of negotiated procurement discounts

The IPD was sourced from a real-world cohort of advanced melanoma patients in a specific clinical setting (see 0), but it did not include data on other costs of healthcare resource utilisation, such as adverse event management costs, hospitalisation, supportive care, or terminal care. Thus, the cost analysis in this study was limited to drug

acquisition costs, as the dataset used only included information on drug use. Costs in this analysis were included as pound sterling (GBP) as it is the official currency of the United Kingdom.

At the time of conducting the analysis in this chapter, the IPD did not contain information on adverse events, hospitalisation rates, or other healthcare resource utilisation costs. To provide contextual insight into broader healthcare resource use, real-world and retrospective studies were reviewed. Among patients receiving immunotherapy, pembrolizumab was associated with lower hospitalisation rates compared to the nivolumab plus ipilimumab, with adjusted mean hospitalisations per patient per month of 0.016 for pembrolizumab versus 0.020 for the combination, and a significantly lower odds of hospitalisation (OR = 0.55; 95% CI: 0.31–0.97) [164]. Additionally, a US-based study by Qian *et al.* (2023) found that ipilimumab monotherapy and combination of nivolumab plus ipilimumab were linked to significantly higher monthly hospitalisations and inpatient bed days than pembrolizumab alone [165]. In contrast, targeted therapies appear to incur a heavier inpatient burden. A multicentre analysis of systemic therapies from 2016–2020 revealed that both combination ICIs and BRAF/MEK regimens were associated with increased inpatient hospital days compared to nivolumab monotherapy [107].

Real-world evidence indicates significant differences in the incidence of grade ≥3 immune-related adverse events (irAEs) across various treatment regimens for advanced melanoma, which in turn can influence healthcare resource utilisation. For pembrolizumab monotherapy, the incidence of grade ≥3 irAEs is generally lower, with rates ranging from approximately 9% to 15% [166]. In contrast, nivolumab plus ipilimumab combination therapy is associated with higher rates of severe irAEs in comparison with pembrolizumab, with real-world studies reporting incidences between 50% and 60% [167]. These elevated rates of severe irAEs often necessitate increased supportive care and more frequent hospital visits. Regarding targeted therapy, real-world data suggest that approximately 14.5% of patients treated with a combination therapy of dabrafenib plus trametinib experience grade ≥3 treatment-related adverse events [168]. The elevated rates of severe irAEs often necessitate increased supportive care and more frequent hospital visits, while the variations in adverse event profiles contribute to differences in healthcare resource utilisation across treatment strategies.

In summary, pembrolizumab monotherapy tend to result in fewer hospitalisations, shorter inpatient stays, and lower rates of severe adverse events compared with combination immunotherapy regimens such as nivolumab plus ipilimumab. Targeted therapies, including *BRAF*/MEK inhibitor combinations, are associated with higher rates of severe adverse events and increased resource use, including hospital visits and monitoring. These patterns provide important context for understanding the broader economic and healthcare implications of different treatment strategies.

While it is now recognised that additional cost inputs, such as rates of adverse events, hospitalisations, or supportive care, are commonly sourced from published literature in economic evaluations, revising and rerunning the analysis to incorporate such inputs at this stage is no longer feasible. This is due to the completion of the modelling phase, time constraints, and the extensive recalibration and validation that would be required to integrate these new data sources without compromising methodological rigour. Retrospective adjustments could risk introducing inconsistencies or deviations from the initial design framework.

5.3.2.5.2. Willingness-to-pay threshold

The WTP threshold for evaluating the cost-effectiveness of healthcare interventions was defined as £30,000. In NICE appraisals, the WTP threshold typically ranges between £20,000 and £30,000 per QALY gained [73]. Interventions that deliver additional QALYs at a cost below this threshold are considered cost-effective and likely to be accepted into clinical practice by the NHS [73]. Conversely, interventions that exceed this threshold may considered as not being cost-effective unless additional justifications, such as significant unmet needs or innovative mechanisms of action, are presented [73].

In this study, the £30,000 WTP threshold was used to interpret the results of the health economic evaluation by determining whether a treatment strategy offers sufficient value for its cost. The WTP of £30,000 was applied in the analysis in the following tools:

- **Cost-effectiveness plane**: On this scatterplot (Figure 5.9), the slope of the WTP threshold line represents the cost per QALY boundary. Strategies falling below the line are considered cost-effective compared to the comparator, while those above the line are not (see Figure 5.5).
- **Incremental cost-utility ratios**: ICURs were calculated as the ratio of the incremental cost to the incremental QALYs gained for each treatment strategy. If the ICUR for a treatment strategy was below £30,000, it was deemed cost-effective. Likewise, treatments with an ICUR over this threshold were interpreted as providing less value for money.
- **Cost-effectiveness acceptability curves**: The cost-effectiveness acceptability curves demonstrate the probability of each treatment strategy being cost-effective at varying WTP thresholds (see Figure 5.10). At the defined threshold (£30,000), the curve indicates the probability that a given treatment represents the optimal choice in terms of cost-effectiveness.

5.3.2.6. Time horizon, perspective, and discounting

NICE guidelines recommend that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or clinical outcomes between the technologies or interventions being compared [154]. Thus, a lifetime horizon of 100 years was considered adequate to reflect lifetime costs and effects.

The model is parameterised from a healthcare system payer perspective, considering direct healthcare costs and effects. In particular, the health economic evaluation in this chapter uses the perspective of the NHS UK, in line with the reference case recommended by NICE for technology appraisals [169].

Costs and health effects were discounted at an annual rate of 3.5% in line with current NICE recommendations [152].

5.3.3. Sensitivity analysis

Decisions informed by health economic evaluations and CEA are subject to uncertainty [145], [170]. The parameters are sources of uncertainty in an economic model, thus a PSA was conducted to assess the robustness of cost-effectiveness estimates.

PSA, which simulates the model for each sampled parameter set and randomly selects the model parameters from appropriate probability distributions, is commonly used to quantify parameter uncertainty in health economic evaluations [171]. This approach allows to assess the impact of parameter uncertainty on the model outputs, providing a more comprehensive understanding of the potential outcomes and their likelihoods [172].

The number of iterations for the PSA in order to ensure a robust exploration of the uncertainty surrounding the results, a total of 1,000 iterations was specified for the PSA.

5.3.4. Cost-effectiveness analysis

To perform a cost-effectiveness analysis, the simulated costs and QALYs were summarised to obtain the health economic model outcomes as previously described in section 5.3.2.4. The ICUR, cost-effectiveness plane, cost-effectiveness acceptability curves, cost-effectiveness acceptability frontier, and expected value of perfect information were estimated in this analysis.

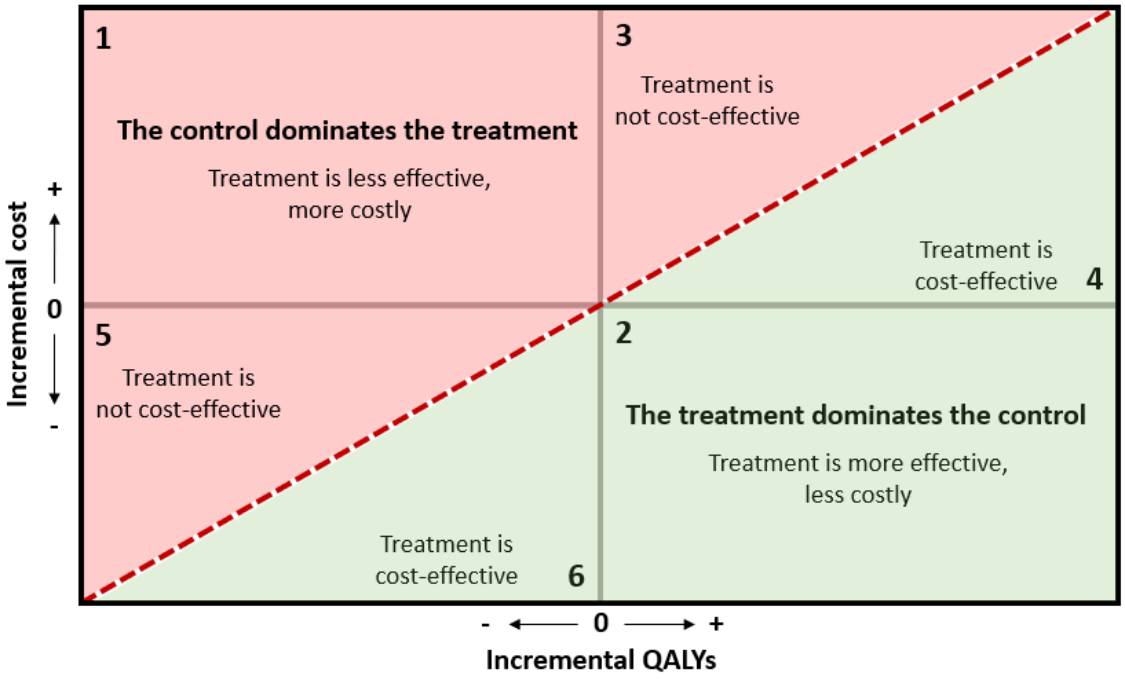

Figure 5.5 – Visual inference aid for the interpretation of cost-effectiveness planes

Notes: The dashed red line represents the willingness-to-pay threshold. A treatment or intervention that is in red zone is not considered cost-effective in comparison with the comparator(s); a treatment or intervention that is in green zone is considered cost-effective in comparison with the comparator(s). **Abbreviation:** QALYs – Quality-adjusted life years

In order to help the analysis, Figure 5.5 can be used as a template to aid the interpretation of the cost-effectiveness acceptability curves. The dashed red line represents the WTP threshold chosen for the analysis. The treatment or intervention in study is compared with a comparator(s). If the new treatment or intervention falls in the red zone, it is not considered to be cost-effective in comparison with the comparator(s). On the other hand, if the new treatment or intervention falls in the green zone, then it is considered to be cost-effective in comparison with the comparator(s). Furthermore, a treatment in study that in the first quadrant (Figure 5.5) is dominated by the comparator(s) treatment. This means that the treatment in study is considered more costly and less effective than the comparator(s) treatment(s). The inverse occurs in second quadrant (Figure 5.5). A treatment that falls in this quadrant dominates the comparator(s) treatment(s), meaning that the treatment in study is less costly and more effective than the comparator(s) treatment(s).

5.4. Results

5.4.1. Patient population

The total cohort for the health economic analysis included 284 advanced melanoma patients who received first-line immunotherapy or targeted therapy. Patient characteristics and prognostic factors at baseline are described in Table 5.4. Population in this study had a median age of 66 years at the time of first entry. Regarding gender, the cohort included 147 (51.8%) male patients and 137 (48.2%) female patients. The SIMD appears to be evenly distributed along with the five ranks. The percentage range varies between 16.6% to 23.2% from SIMD 1 to SIMD 5.

All patients had *BRAF* status information, with 141 (49.7%) patients being *BRAF*-wild-type and 143 (50.3%) considered as *BRAF*-mutant advanced melanoma patients. Thus, about half of the cohort had a mutation in the *BRAF* gene which aligns with results from the literature [21].

Regarding BMI groups, the cohort as evenly distributed between patient groups. A total of 61 patients (21.5%) had a normal BMI while 75 (26.4%) were considered as obese. Also, 68 patients (23.9%) did not have information regarding BMI at the time of entry.

The median value for LDH at the date of first treatment was 216 U/L and the values ranged between 83 to 5869 U/L. Most patients (76.4%) presented an LDH level considered normal and almost half of the patients (141 patients, 49.7%) had registered an ECOG PS of grade 0 at the time of initial treatment, which indicates that these patients were fully active at the start of treatment.

Table 5.4 – Descriptive statistics of demographic and prognostic factors for advanced melanoma patients at baseline

Variable	Category	N
Age (years)	Median (IQR)	66 (51-76)
Gender	Male	147 (51.8 %)
	Female	137 (48.2 %)
SIMD quintile	1	62 (21.8 %)
	2	57 (20.1 %)
	3	52 (18.3 %)
	4	47 (16.6 %)
	5	66 (23.2 %)
BMI	Normal	61 (21.5 %)
	Overweight	80 (28.2 %)
	Obese	75 (26.4 %)
	NA	68 (23.9 %)
LDH in units per litre (U/L)	Median (IQR) [Range]	216 (175-313) [83-5869]
LDH group	Normal	217 (76.4 %)
	High	67 (23.6 %)
ECOG PS	0	141 (49.7 %)
	1	79 (27.8 %)
	2+	44 (15.5 %)
	NA	20 (7.0 %)
BRAF gene status	Wild-type	141 (49.7 %)
	Mutation	143 (50.3 %)

Abbreviations: BMI – Body-mass index; BRAF - proto-oncogene B-Raf; LDH – Lactate dehydrogenase; ECOG PS – Eastern Cooperative Oncology Group Performance Status; IQR – Interquartile range; NA – Not applicable; SD – Standard deviation; SIMD – Scottish Index of Multiple Deprivation

Table 5.5 displays the descriptive statistics for drug treatments which shows that most patients started treatment with first-line immunotherapy (57.8%) while the remaining patients had first-line targeted therapy (42.2%). Pembrolizumab was administered to approximately a third of patients (86 patients; 30.3%), followed by nivolumab plus ipilimumab (15.5%), and vemurafenib (15.5%).

Regarding survival, a total of 193 patients died (68.0 %) and 91 patients (32.0 %) were still alive at the end of follow-up.

Table 5.5 – Descriptive statistics for drug treatment at baseline, therapy type at baseline and outcome for patient cohort included in the health economic evaluation

	Category	N (%)
Drug (first-line)	Dabrafenib	34 (12.0 %)
	Dabrafenib plus trametinib	42 (14.7 %)
	Ipilimumab	34 (12.0 %)
	Nivolumab plus ipilimumab	44 (15.5 %)
	Pembrolizumab	86 (30.3 %)
	Vemurafenib	44 (15.5 %)
Type of therapy (first-line)	Immunotherapy	164 (57.8 %)
	Targeted therapy	120 (42.2 %)
Status at end of follow-up	Alive	91 (32.0 %)
	Dead	193 (68.0 %)

5.4.2. Probabilistic sensitivity analysis

Decision uncertainty often arises from the inherent uncertainty of model parameters, which can be systematically quantified through a PSA. The PSA constitutes a vital step in the validation and robustness assessment of the health economic model and involves the random sampling of model parameters from their respective probability distributions, followed by the simulation of the model for each set of sampled parameters [171]. The significance of PSA lies in its capability to account for the uncertainty associated with the parameters integrated within the economic model, encompassing health state transitions, costs, and utilities [145], [146]. Using a probabilistic approach, a set of 1000 samples was generated, representing a distinct combination of parameter values drawn from their respective probability distributions, thereby enhancing the robustness and reliability of the model's predictions [145], [173]. The scope of uncertainty surrounding the model's parameters was expanded through the PSA samples, thereby acquiring a more comprehensive understanding of the potential outcomes that may occur.

When PSA is combined with individual-level simulation, the computational requirements can become significant, requiring substantial time to execute [174]. Despite the additional computation time required to run the PSA, the detailed insights

gained are invaluable as they provide a deeper understanding of the potential variability and uncertainty in the model's outcomes.

The exploration of the parameters' uncertainty allowed to capture a wide range of potential scenarios and their corresponding economic implications. Consequently, the outcomes of the PSA facilitated a more comprehensive evaluation of the model's performance and allowed for a more reliable assessment of its implications in real-world applications. This exploration of parameter uncertainty ensures that decision-makers are better equipped to assess the reliability and validity of the economic model.

Trajectories through the multi-state model were simulated with patients assumed to live to a maximum age of 100 as described in section **Error! Reference source not found.**. Figure 5.6 plots the transition probability across the PSA samples. This helps to demonstrate the simulated trajectories for patients between mutually exclusive health states by initial treatment strategy.

Figure 5.6 shows a tendency for the patients treated with first-line immunotherapy regimens (ipilimumab, pembrolizumab, and nivolumab plus ipilimumab) to progress, whereas patients treated with first-line targeted therapy drugs have higher transition rates towards the death state earlier in comparison with the immunotherapy regimens.

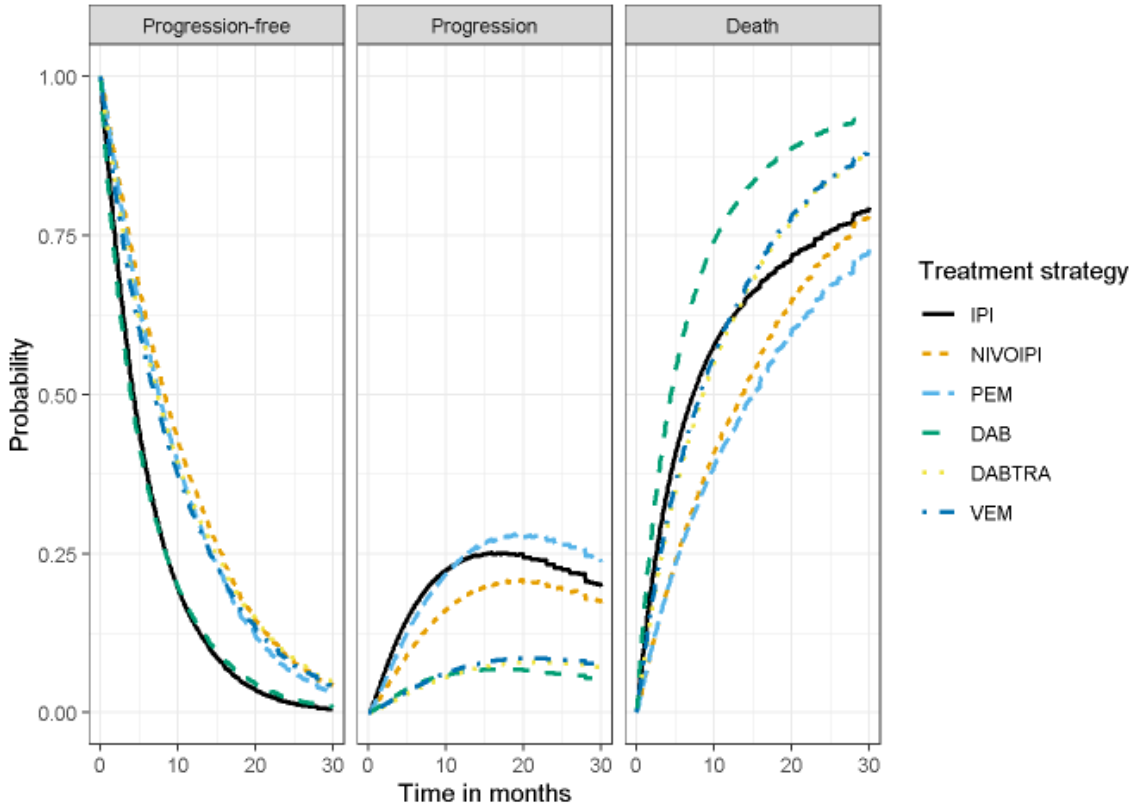

Figure 5.6 – Mean simulated state occupancy probabilities by drug treatment from the probabilistic sensitivity analysis

Abbreviations: DAB – Dabrafenib; DABTRA – Dabrafenib + trametinib; IPI – Ipilimumab; NIVOIPI – Nivolumab + ipilimumab; PEM – Pembrolizumab; VEM – Vemurafenib

The bar plots in Figure 5.7 and Figure 5.8 represent the QALYs stratified by each treatment strategy after running the simulation for PSA with the economic model previously described. This is a visual representation of mean QALYs per drug treatment across the simulated samples, colour-coded per health state (progression and progression-free). It is possible to observe from Figure 5.7 and Figure 5.8 that the immunotherapy drugs pembrolizumab and the combination of nivolumab plus ipilimumab yielded the highest mean QALYs within the within the progression-free health state among the immunotherapy strategies. Similarly, the targeted therapy regimens of vemurafenib and the combination of dabrafenib plus trametinib showed the highest mean QALYs within the progression-free health state among the targeted therapy strategies. Ipilimumab monotherapy and dabrafenib monotherapy were the treatment strategies with the lower mean QALYs from their distinct therapy classes, immunotherapy and targeted therapy, respectively.

Throughout progression, all treatments strategies demonstrate lower QALYs in comparison with QALYs from the progression-free state. During progression, immunotherapy drugs revealed higher mean QALYs in comparison with targeted therapies.

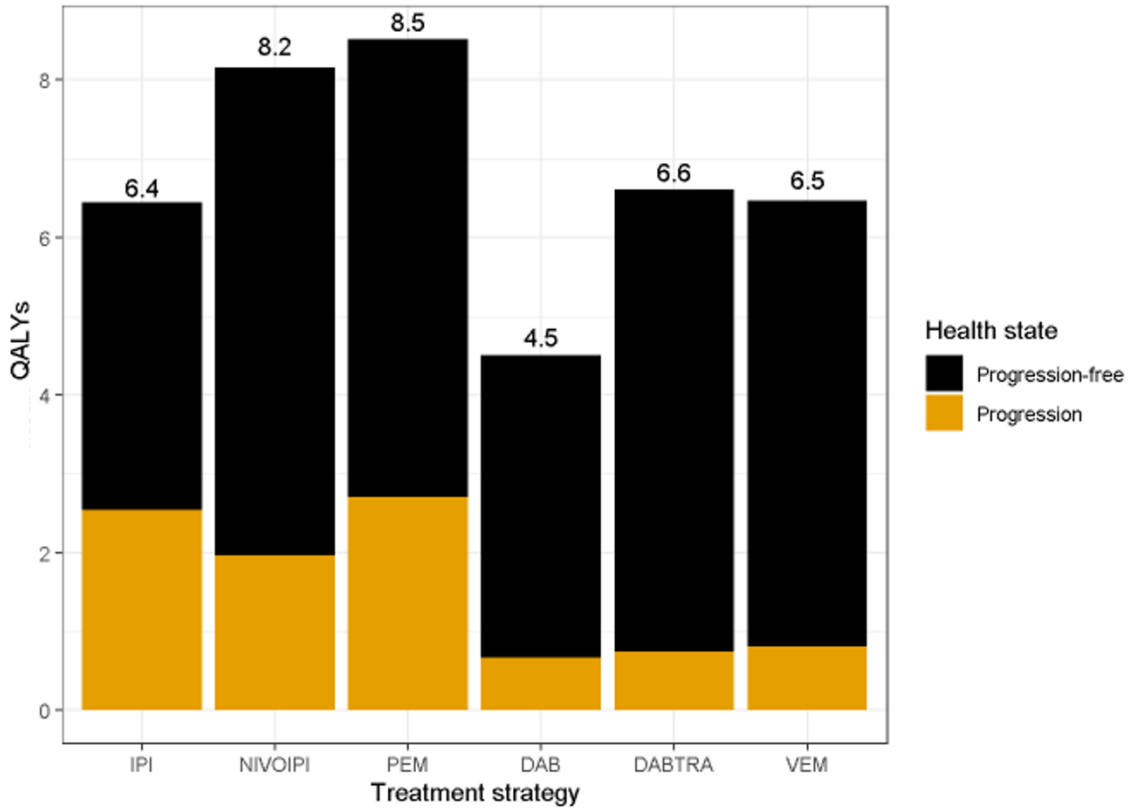

Figure 5.7 – Stacked barplot with QALYs by health state from simulated samples stratified by treatment strategies

Abbreviations: DAB – Dabrafenib; DABTRA – Dabrafenib plus trametinib; NIVOIPI – Nivolumab plus ipilimumab; PEM – Pembrolizumab; QALYs – Quality-adjusted Life Years; VEM – Vemurafenib

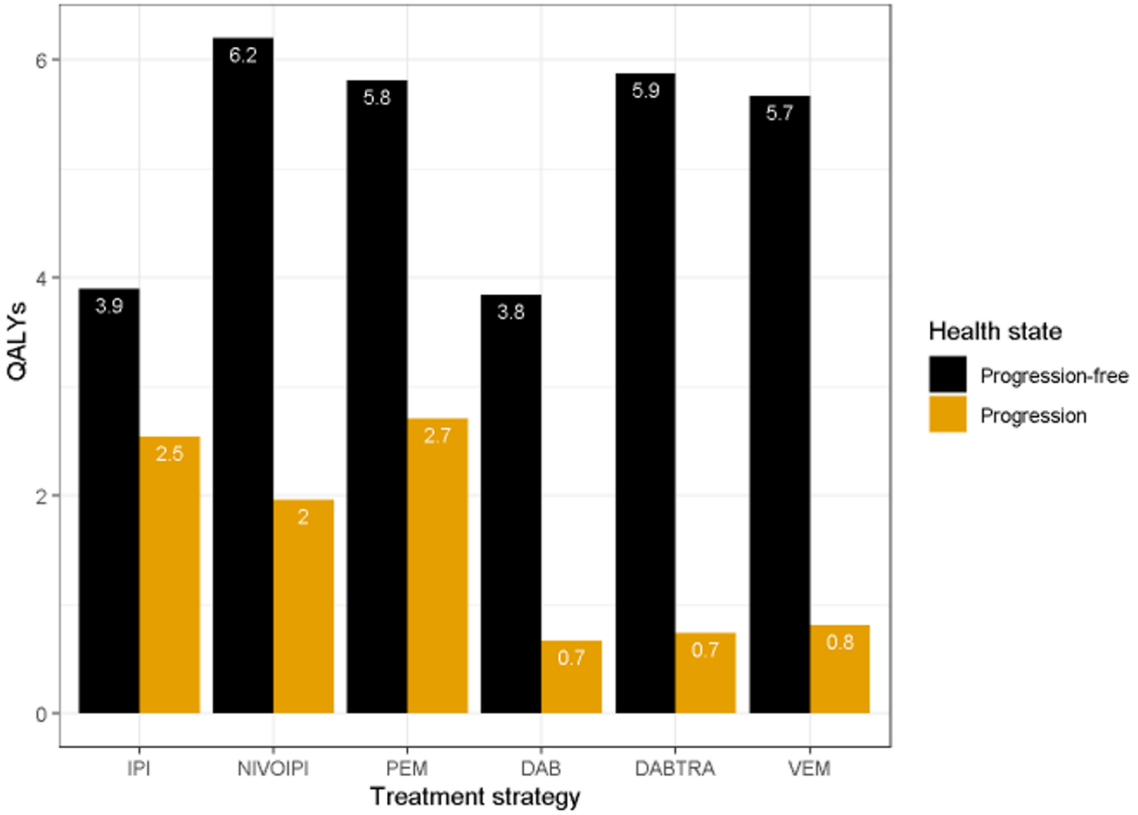

Figure 5.8 – Barplot with QALYs by health state from simulated samples stratified by treatment strategies

Abbreviations: DAB – Dabrafenib; DABTRA – Dabrafenib plus trametinib; NIVOIPI – Nivolumab plus ipilimumab; PEM – Pembrolizumab; QALYs – Quality-adjusted Life Years; VEM – Vemurafenib

The results presented in

Table **5.6** summarise the total QALYs and total costs associated to each treatment strategy. Pembrolizumab offered the highest QALYs (8.51), followed by nivolumab plus ipilimumab (8.16), and dabrafenib plus trametinib (6.61).

Regarding the total costs, the lowest costs were linked to the targeted therapy treatments with dabrafenib presenting the lowest total cost (£36,712) while the combination of nivolumab plus ipilimumab presented the highest total cost (£319,010).

Table 5.6 – Summary results of total QALYs and total costs per treatment strategy

Outcome	Total QALYs (95% CI)	Total costs in £ (95% CI)
IPI	6.44 (4.53; 8.17)	251,045 (173,153; 322,094)
NIVOIPI	8.16 (5.88; 10.49)	319,010 (225,117; 417,738)
PEM	8.51 (6.96; 10.00)	113,894 (90,386; 135,657)
DAB	4.51 (2.90; 6.66)	36,712 (23,249; 55,583)
DABTRA	6.61 (4.70; 8.75)	95,907 (66,305; 129,191)
VEM	6.47 (4.34; 8.87)	65,429 (43,707; 89,806)

Abbreviations: CI – Confidence interval; DAB – Dabrafenib; DABTRA – Dabrafenib plus trametinib; NIVOIPI – Nivolumab plus ipilimumab; PEM – Pembrolizumab; QALYs – Quality-adjusted Life Years; VEM – Vemurafenib

5.4.2.1. Pairwise comparison and incremental cost-utility ratio

In this analysis, ipilimumab was chosen as the intervention for the remaining drug treatments. The reason for this is that, from this drug pool, ipilimumab was the first to be approved as a first-line treatment for advanced melanoma. Table 5.7 represents a summary of the analysis, including 95% confidence intervals computed using the quantiles from the PSA samples.

Regarding the incremental QALYs, immunotherapy regimens, nivolumab plus ipilimumab and pembrolizumab, and the targeted therapy combination of dabrafenib plus trametinib, incremental gains were shown in comparison with ipilimumab alone. The remaining targeted therapy drugs, dabrafenib and vemurafenib, showed a decrease in QALYs in comparison with ipilimumab.

Concerning the incremental costs, the gain of 1.72 QALYs from nivolumab plus ipilimumab is associated with an increase in cost of £67,724. The remaining drugs in the study revealed a decrease in costs when compared to ipilimumab. Lastly, pembrolizumab and dabrafenib plus trametinib dominate ipilimumab, according to ICUR.

Table 5.7 – Summary table for pairwise comparison by incremental QALYs, incremental costs, incremental NMB, and ICUR

Outcome	NIVOIPI	PEM	DAB	DABTRA	VEM
Incremental QALYs (95% CI)	1.72 (-0.91-4.24)	2.09 (0.39-3.87)	-2.01 (-4.58-1.17)	0.13 (-2.74−3.52)	-0.04 (-2.89−3.49)
Incremental costs (95% CI)	67,724 (-45,547-175,468)	-137,198 (-202,926; -64,957)	-215,294 (-288,595; -126,556)	-156,184 (-240,611; -61,114)	-186,719 (-262,685; -97,722)
Incremental NMB (95% CI)	-16,203 (-52,175-19,522)	199,784 (156,415; 238,102)	155,006 (117,110; 200,045)	159,973 (127,107; 198,623)	185,596 (144,474; 233,591)
ICUR	39,435	Dominates	107,134	Dominates	4,990,802

Abbreviations: CI – Confidence interval; DAB – Dabrafenib; DABTRA – Dabrafenib plus trametinib; ICUR – Incremental cost-utility ratio; NIVOIPI – Nivolumab plus ipilimumab; NMB – Net monetary benefit; PEM – Pembrolizumab; QALYs – Quality-adjusted Life Years; VEM – Vemurafenib

5.4.2.2. Cost-effectiveness plane

A scatterplot where each point is a particular draw from the PSA samples generated the cost-effectiveness plane represented in Figure 5.9. This plot shows the pairwise comparison of the incremental effectiveness in QALYs of a treatment strategy against the incremental cost of that drug in relation to a comparator. In this analysis, ipilimumab is the chosen comparator. The dashed line represents the WTP threshold.

Among the five treatment strategies analysed versus the ipilimumab (see section 5.3.2.2), the combination of nivolumab plus ipilimumab is the only option where some PSA samples cross the threshold slope. The majority of these samples are dispersed in the second quadrant of the cost-effectiveness plane, indicating that this combination is associated with higher effectiveness, but higher costs compared to ipilimumab. This suggests that, depending on the WTP threshold, nivolumab plus ipilimumab may be considered a cost-effective option.

In contrast, the remaining treatment strategies — including pembrolizumab, dabrafenib, dabrafenib plus trametinib, and vemurafenib — are positioned below the WTP threshold set to £30,000. Their PSA samples are mostly distributed across the third and fourth quadrants. This distribution suggests that these treatments are associated with either lower costs but reduced effectiveness (third quadrant) or both lower costs and higher effectiveness (fourth quadrant) compared to ipilimumab. These results highlight that these strategies, while less expensive than the comparator, may not meet the criteria for cost-effectiveness under the WTP threshold.

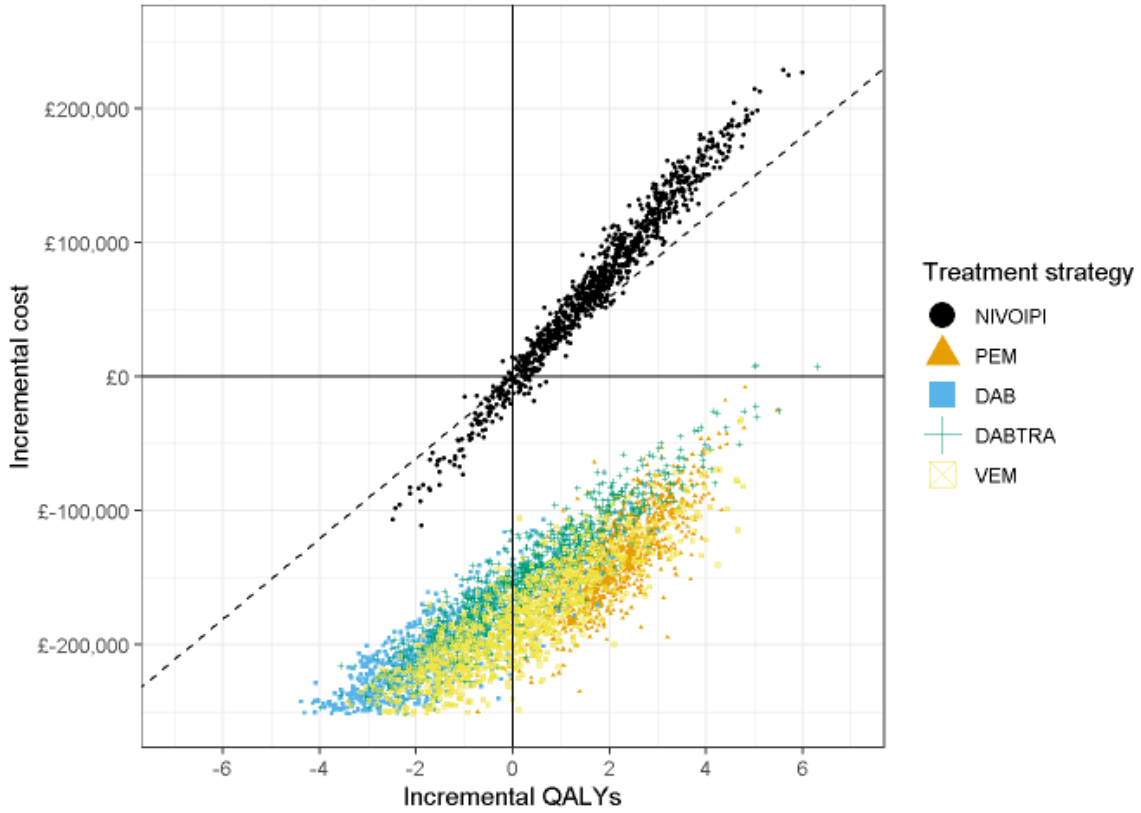

Figure 5.9 – Cost-effectiveness plane for pairwise comparison between ipilimumab (intervention) and comparators

Abbreviations: DAB – Dabrafenib; DABTRA – Dabrafenib plus trametinib; NIVOIPI – Nivolumab plus ipilimumab; PEM – Pembrolizumab; QALYs – Quality-adjusted life years; VEM – Vemurafenib

5.4.2.3. Cost-effectiveness acceptability curves

The cost-effectiveness acceptability curve was generated based on simultaneous comparisons of the six treatment strategies. With the cost-effectiveness curves, it is possible to evaluate which treatment strategy would be most cost-effective given the budget available to finance that treatment. The cost-effectiveness acceptability curve allows to visually evaluate how the probability for each treatment varies along the WTP threshold and the variance of probabilities between drug treatments.

At lower WTP thresholds, dabrafenib performed as the most cost-effective treatment strategy. However, as the WTP threshold approaches approximately £14,000 per QALY, a shift occurred, and vemurafenib became the most cost-effective strategy, reflecting its improved balance of costs and health outcomes in this range. Beyond

£22,000 per QALY, the probability of pembrolizumab being the most cost-effective treatment surpassed all previous strategies and appeared as the optimal choice at higher WTP thresholds.

In contrast, treatments such as ipilimumab, nivolumab plus ipilimumab, and dabrafenib plus trametinib did not emerge as the most cost-effective options at any WTP threshold considered in the analysis. This finding suggests that these therapies, while clinically effective, are associated with either higher costs or insufficient incremental health benefits compared to other comparators.

The observed transitions between dabrafenib, vemurafenib, and pembrolizumab as the most cost-effective options illustrate how the cost-effectiveness of treatments is sensitive to WTP thresholds.

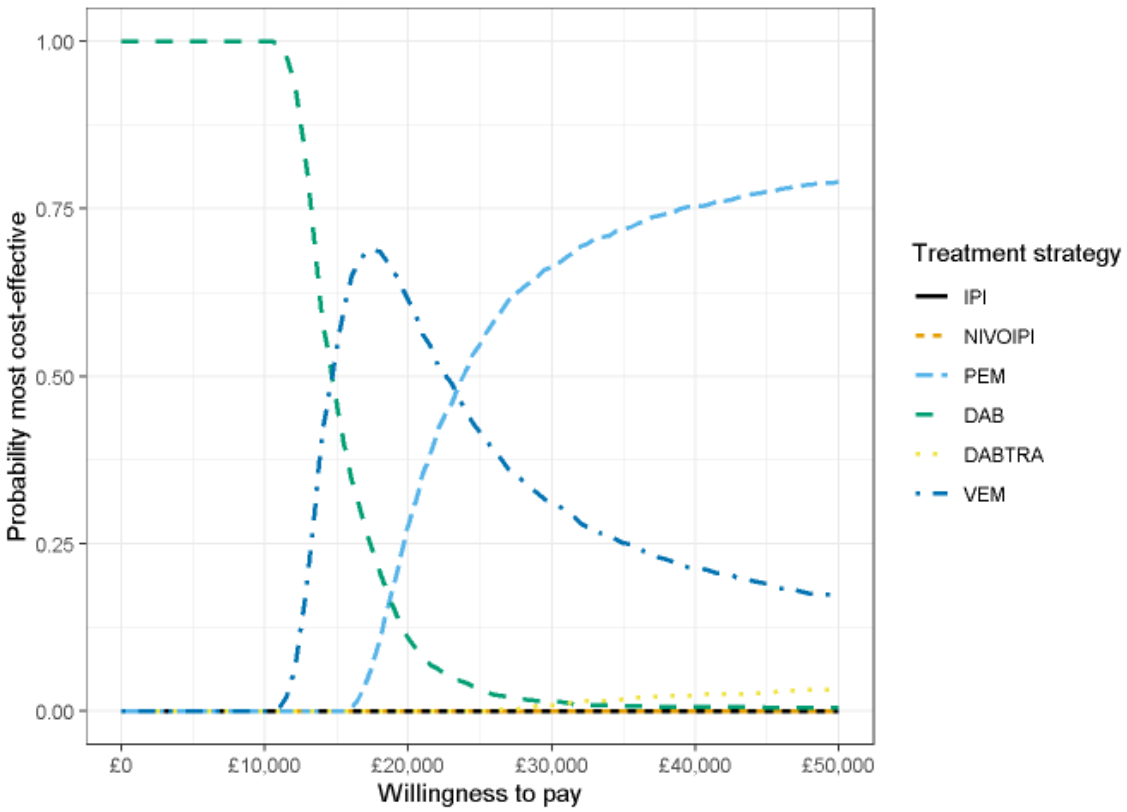

Figure 5.10 – Cost-effectiveness acceptability curves of the intervention and treatment comparators over a willingness-to-pay threshold of £50,000

Abbreviations: DAB – Dabrafenib; DABTRA – Dabrafenib plus trametinib; IPI – Ipilimumab; NIVOIPI – Nivolumab plus ipilimumab; PEM – Pembrolizumab; VEM – Vemurafenib

5.4.2.4. Cost-effectiveness frontier

The cost-effectiveness frontier plots the probability that the optimal treatment strategy is cost-effective based on the treatment with the highest expected NMB for each WTP value. Thus, the cost-effectiveness frontier only shows the optimal treatment across intervals of the WTP axis.

Figure 5.11 illustrates the cost-effectiveness frontier which identifies the optimal treatment strategy across varying WTP thresholds. Initially, dabrafenib emerges as the most cost-effective option at lower WTP thresholds, remaining the preferred strategy up to approximately £14,000 per QALY. At this point, a shift occurs, and vemurafenib becomes the optimal treatment strategy, indicating its greater NMB in the mid-range WTP thresholds. Subsequently, another transition in the optimal strategy is observed between £22,000 and £23,000 per QALY, where pembrolizumab takes precedence as the most cost-effective treatment option.

These changes in the optimal strategy reflect the varying cost-effectiveness profiles of the treatments as the WTP threshold increases. At lower thresholds, dabrafenib's relatively low cost makes it the preferred option despite potentially lower QALY gains. As the WTP threshold rises, the higher cost of vemurafenib is justified by its incremental health benefits, overtaking dabrafenib in terms of NMB. Finally, at higher WTP thresholds, pembrolizumab—characterised by significant health benefits—becomes the most cost-effective strategy, despite its higher associated costs.

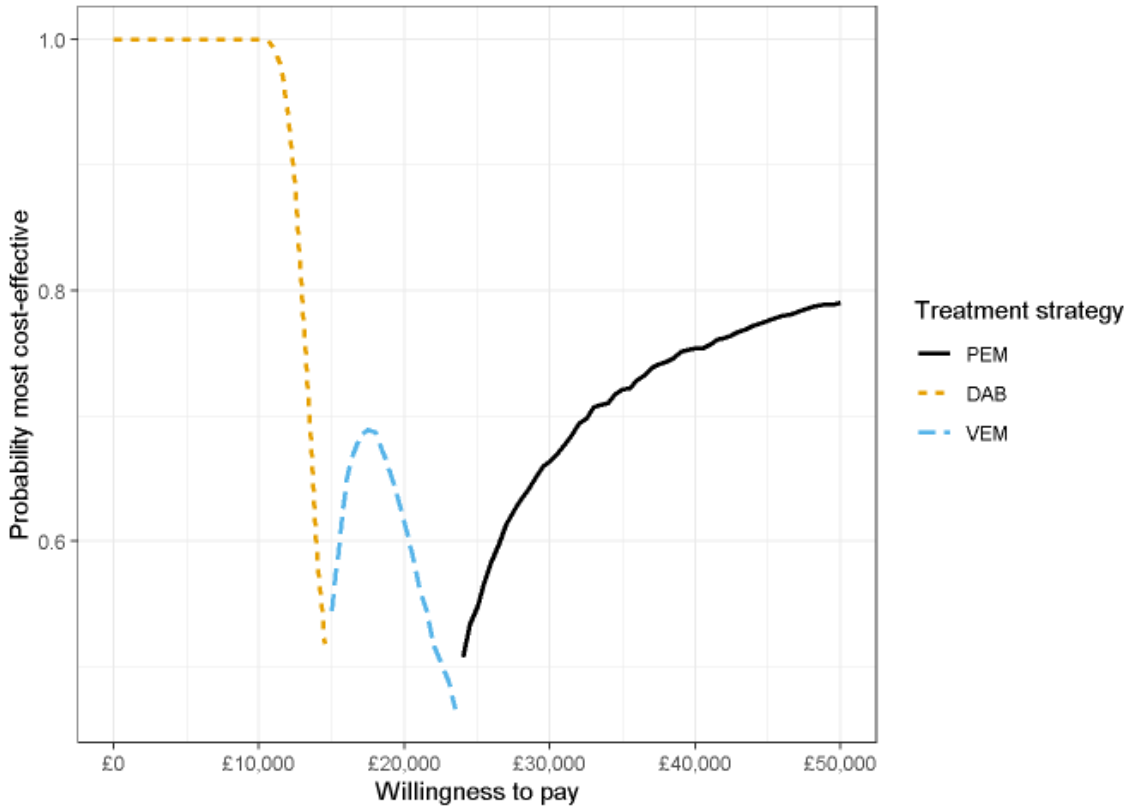

Figure 5.11 – Cost-effectiveness frontier over a willingness-to-pay threshold of £50,000

Abbreviations: DAB – Dabrafenib; PEM – Pembrolizumab; VEM – Vemurafenib

5.4.2.5. Expected value of perfect information

The expected value of perfect information can be mathematically defined as the difference between the maximum values of expected NMBs given the current and perfect information. It calculates the NMB for the optimal treatment strategy for each random draw of the parameters and compares that to the NMB for the treatment strategy that is optimal when averaging across all parameters [145].

Hence, the peaks in the expected value of perfect information curve represent the WTP values where the optimal strategy changes. Figure 5.12 shows the resulting expected value of perfect information for this analysis. In this plot, there are two visible peaks around £15,000 and a second peak between £22,000 and £25,000, which represent two changes in the optimal treatment sequence across a WTP threshold of £50,000.

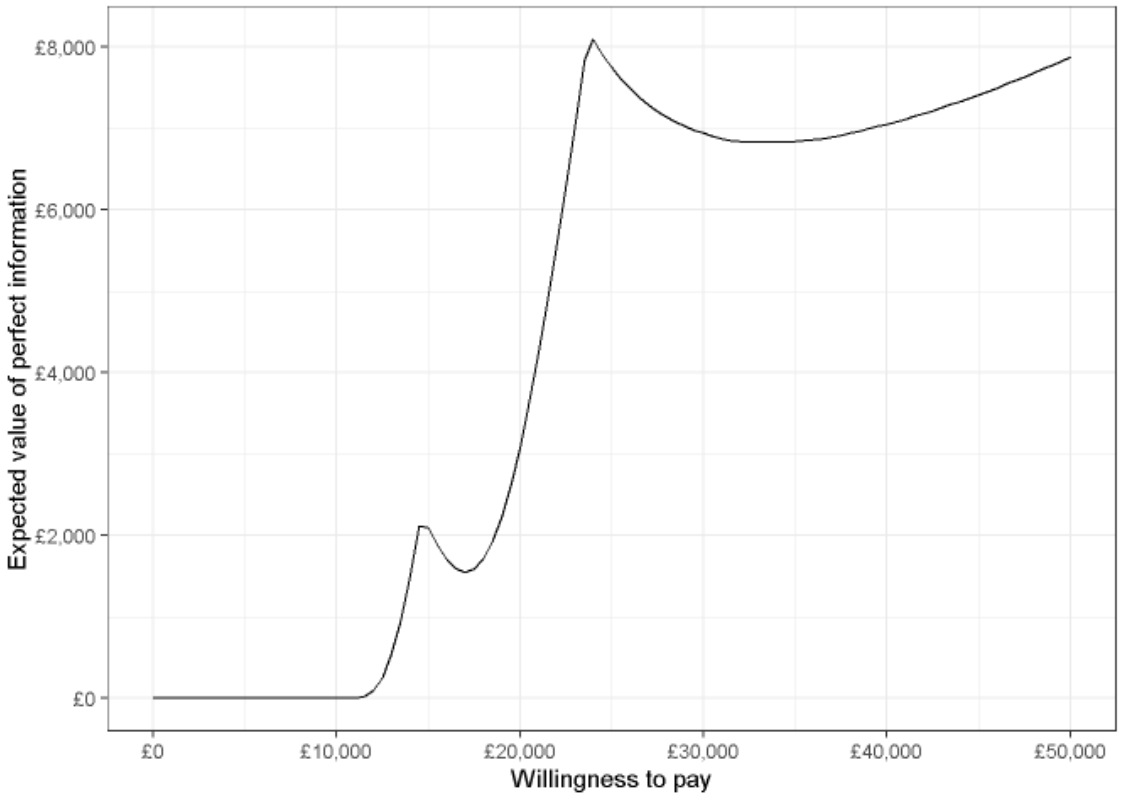

Figure 5.12 – Expected value of perfect information for the cost-effectiveness analysis of all comparators over a willingness-to-pay threshold of £50,000

5.5. Discussion

Every drug treatment used in a real-world setting has been approved for both its clinical efficacy and cost-effectiveness before it becomes available to be used in clinical practice. Clinical efficacy and cost-effectiveness are used in HTA to evaluate the potential applicability of a drug to a certain disease or health condition beyond clinical trials. However, this assessment is usually a reflection of outcomes from clinical trials and might not reflect what happens in a heterogeneous cohort that usually includes patients that would not fulfil the clinical trials' inclusion criteria in a real-world setting. It is important to build on the knowledge gathered from clinical trials and improve healthcare practise and the decision-making process based on the outcomes shown from real-world evidence. The synergy between the two will provide the foundation for future patients to be treated in the best way possible. With the increasing availability of

IPD, retrospective studies such as this one can provide knowledge on how well drugs are working after clinical trials and if the conditions demonstrated are still valid.

The results from this economic model reveal that despite variations in clinical efficacy, the cost-effectiveness ranking can change with alterations in the WTP threshold. Interventions with a cost per QALY ratio of below £30,000 are generally considered a cost-effective use of NHS resources [73]. In accordance with the findings in this study, at a WTP threshold of £30,000, pembrolizumab appears to be the immunotherapy drug with the highest probability of being cost-effective, while vemurafenib occupies a similar position regarding targeted therapy options. This is consistent with the results observed in the cost-effectiveness acceptability curve and the cost-effectiveness acceptability frontier, where pembrolizumab consistently exhibits the highest probability of being cost-effective at this specific WTP threshold. Beyond that threshold, pembrolizumab remains the treatment option most likely to be considered cost-effective.

Additionally, immunotherapy options (ipilimumab, nivolumab plus ipilimumab, and pembrolizumab) exhibit higher QALYs in the progression state compared to targeted therapy drugs, with ranges of 2.0 to 2.7 and 0.7 to 0.8, respectively. This discrepancy suggests that after progression, patients tend to respond more favourably to immunotherapy drugs, potentially attributed to the enduring effects of these treatments, while targeted therapy drugs may assume a more aggressive position.

The health economic evaluation and economic model in this analysis are not without limitations. Firstly, the analysis presented in this chapter lacks a base case. The omission of a base case in this analysis aligns with the overall objective of the model which was to create an accessible, efficient, and adaptable framework for cost-effectiveness analysis. By using R, rather than Excel, this model streamlines computational efficiency and avoids the more resource-intensive processes often associated with traditional cost-effectiveness models. The emphasis on PSA rather than a single deterministic base case provides a thorough examination of the uncertainty and variability in the model parameters. Nevertheless, this analysis offers a robust understanding of the potential range of outcomes. The PSA, with its 1000 iterations, explores a wide range of parameter values, effectively covering multiple potential scenarios and ensuring that the analysis captures the full spectrum of possible outcomes

in the economic model. This approach aligns closely with the complexities and uncertainties inherent in real-world healthcare decisions, providing a flexible and adaptable framework for decision-making.

Additionally, due to limited information regarding post-chemotherapy progression, patients who were treated at any point with chemotherapy were excluded from the model, thus not allowing for the inclusion and comparison of chemotherapy with the six SACT included in this health economic evaluation.

Furthermore, another limitation of the analysis conducted is this chapter was the incorporation of only drug acquisition costs in the economic model, omitting potential variations in other possible costs such as hospital admission and adverse event management costs, among others as the analysis in this chapter relied solely on real-world IPD for advanced melanoma patients to evaluate the cost-effectiveness of immunotherapy and targeted therapy (see section 5.3.2.5).

Synthesising data from various reliable sources or meta-analysis to populate health economic models is standard practice. These evaluations include direct costs, such as drug acquisition, administration, and monitoring, as well as indirect costs, including healthcare resource utilisation (e.g., hospitalisations, adverse event management, and supportive or terminal care) which can be sourced from real-world evidence and literature-based estimates. The integrative approach of combining real-world evidence with literature-based information aims to create a comprehensive evaluation that reflects both controlled clinical trial conditions and real-world variability. In standard practice, health economic evaluations often synthesise data from several sources, including clinical trial data for efficacy, safety, and adverse event rates; observational studies for long-term outcomes; published literature for cost estimates and utility values; and national datasets or registries for hospitalisation rates and other healthcare resource use. However, a limitation of integrative approach is the potential inconsistency when combining data from diverse sources, particularly if there are differences in study populations, healthcare settings, or time periods [175].

Despite the limitations in this study, the use of real-world IPD provides a robust foundation for assessing cost-effectiveness based on clinical practice in the region of Greater Glasgow and Clyde. The methodology used in this study was purposefully centred on real-world IPD. This decision reflects a methodological commitment to

maintaining the study consistency, as well as a focus on capturing the actual treatment strategy patterns observed in this cohort of advanced melanoma patients (see 0). The methodological approach in this analysis aimed to guarantee that all cost inputs, treatment patterns, and outcomes are derived from the same population and healthcare setting. However, it is acknowledged that utility values were sourced from published literature due to the absence of routinely collected utility data within the available IPD. While this introduces an external element into the model, the selected utility values were based on studies with comparable patient populations and disease stages, supporting their relevance to the analysis. Overall, this approach minimises the risk of bias or inconsistency that may arise when combining literature-derived data with real-world observations, as patient characteristics and treatment paradigms often differ across datasets. For example, adverse event rates reported in clinical trials may not reflect real-world occurrences due to the controlled nature of trials and strict inclusion criteria.

Furthermore, the data used to conduct the analysis in this chapter captured treatment pathways and outcomes experienced by advanced melanoma patients in routine clinical practice. This includes variability in treatment adherence and patient characteristics that are not always reflected in literature-based inputs. Thus, a model based solely on real-world IPD ensures greater transparency and reproducibility, as all inputs are derived from a single, well-defined dataset. This approach minimises the use of assumptions and reduces uncertainty, which can arise when relying on literature-based estimates with varying levels of quality and applicability.

In conclusion, the health economic model and its subsequent economic analysis contribute to the understanding of current treatment strategies used in real-world clinical practise for treating advanced melanoma. The decision to rely solely on real-world IPD reflects a methodological approach aimed at ensuring consistency, transparency, and relevance to the study population (see 0). While the omission of literature-based estimates for broader costs is acknowledged as a limitation, this approach provides a robust foundation for real-world evidence-based decision-making in the cost-effectiveness evaluation of advanced melanoma treatments. Furthermore, the economic evaluation in this analysis provided insights into the cost-effectiveness of various SACT strategies for advanced melanoma in a real-world setting. The findings

reported can help decision-makers choose therapies and allocate resources in a way that optimises patient outcomes while taking related costs into account. Nonetheless, it is crucial to acknowledge the assumptions and limitations inherent in this analysis, and further research and data collection are necessary to refine the model and enhance its accuracy. Future studies can address this limitation by integrating additional cost components using data from complementary sources.

Chapter 6 Conclusions and further research

6.1. Conclusions

Current treatment of advanced melanoma focuses on the novel treatments such as ICIs and targeted therapy drugs that have been developed over the past decade. More treatments and treatment strategies are still being developed and analysed through clinical trials. These pivotal trials provide the clinical evidence for treatments safety and efficacy, while real-world evidence has the potential clarify how well these treatments are being tolerated and can provide a specific insight in real-world setting outcomes. Real-world evidence can be used to further enhance our understanding of advanced melanoma treatment sequences and outcomes. Therefore, the overarching aim of this thesis was to use Scottish real-world evidence to characterise survival outcomes, treatment sequencing, and the cost-effectiveness of systemic anti-cancer therapies for advanced melanoma.

Chapter 3 addressed the research question: "*What are the real-world survival outcomes and prognostic factors for patients with advanced melanoma treated with immunotherapy and/or targeted therapy in Scotland?*". This analysis was concerning patient characteristics, OS, and prognostic factors in an advanced melanoma cohort using real-world evidence. The baseline characteristics of this cohort including age, sex distribution, socioeconomic status (i.e., SIMD), and *BRAF* status were broadly consistent with epidemiological patterns reported in UK and European melanoma populations, supporting the external validity of the dataset [5], [136]. The findings in this analysis revealed that median OS improved in comparison with results from the past decade. While assessing the multivariable Cox survival model, results were consistent with prior studies, further reinforcing the significance of covariates such as LDH and ECOG Performance Status as statistically significant prognostic factors impacting survival outcomes. These findings align with prior clinical and epidemiological literature and

further reinforce the relevance of established prognostic factors such as LDH and ECOG Performance Status in predicting survival outcomes in advanced melanoma.

Intriguingly, when analysing the univariable and multivariable time-dependency adjusted Cox models for BMI, and contrary to conventional perceptions in other cancer studies, the findings from the Cox PH models suggest a potential positive correlation between higher levels of BMI and improved survival outcomes in metastatic melanoma patients. The results are consistent with the 'obesity paradox' reported in recent studies (McQuade *et al.*, (2015); Smith *et al.*, (2020); and Zepeda-Najar *et al.* (2021)) showing comparable trends, challenging notions of the impact of BMI on the prognosis of advanced melanoma [138], [139], [140].

The application of time-dependent Cox PH models revealed insightful associations between therapy types and survival outcomes in the context of advanced melanoma treatment. The univariable Cox model incorporating therapy type as a time-dependency covariate revealed statistically significant differences in survival probabilities among patients receiving targeted therapy. Specifically, patients administered targeted therapy exhibited a 78% higher survival probability in comparison to those treated solely with chemotherapy. Contrarywise, the immunotherapy outcomes did not reach statistical significance. Still, further research should be done given the larger confidence intervals and higher HR. Building on the previous model, the subsequent multivariable Cox model which included therapy type as a time-dependent covariate reaffirmed the efficacy of targeted therapy after adjustments for time-dependency and additional covariates.

In Chapter 4 addressed the research question: *"How treatment transitions between immunotherapy and targeted therapy influence survival outcomes in routine clinical practice?"* through a multi-state Markov model for advanced melanoma patients. This model was developed to consider patients who underwent therapy changes between targeted therapy and immunotherapy in order to study the effects of these modifications in a practical context on patient survival. The application of the multi-state model with real-world data for patients with advanced melanoma offers benefits in understanding the complexities of the therapy process, allowing for the accommodation of multiple health states in order to assess survival outcomes. However, the application of multi-state models to real-world metastatic melanoma patients is still underexplored. The sojourn time in these findings revealed that patients on first-line

targeted therapy exhibited a longer duration within this phase compared to first-line immunotherapy, suggesting prolonged stability before transitioning to another type of therapy. Additionally, the discrepancies in the mean sojourn times between second-line immunotherapy and second-line targeted therapy require further research due to wide confidence intervals, highlighting the need for larger sample sizes to validate these durations more accurately.

The parametric survival curves provided critical information regarding the treatment sequence survival probabilities. The higher survival probabilities associated with first-line therapies in contrast to second-line treatments underscore the failure of initial therapies, potentially due to adverse events or disease progression. Moreover, the advantageous survival probabilities for second-line immunotherapy following first-line targeted therapy highlight potential synergies between the two treatment types, possibly enhancing treatment efficacy.

Examining the transitions between treatment states revealed distinct probabilities, with higher transition probabilities from first-line targeted therapy to second-line immunotherapy. However, the contrast between both probabilities may be explained by a patient's BRAF gene status since patients with *BRAF* mutations typically receive targeted therapy as a first-line of therapy, whereas patients who are BRAF-wild-type can only receive immunotherapy treatments, reducing the number of patients eligible for second-line targeted therapy.

In Chapter 5 addressed the research question: "*What is the cost-effectiveness of first-line immunotherapy versus first-line targeted therapy using real-world survival and treatment patterns?*". By building on the previous multi-state model information, a health economic evaluation of advanced melanoma patients treated with either immunotherapy or targeted therapy as a first-line treatment was conducted. In this study, patients who switched type of therapy for a second-line treatment were assumed to have progressed disease. Thus, the model included progression-free, progression and death as health states. The integration of real-world evidence alongside clinical trials data is essential in informing healthcare practices and decision-making processes.

Randomised clinical trials, while fundamental in drug approval, may not fully represent outcomes in diverse patient populations present in real-world settings. Retrospective studies, like the one conducted herein, offer insights into treatment

efficacy and cost-effectiveness beyond controlled clinical trial settings. Thus, real-world evidence is imperative to optimise treatment strategies and enhance patient care outcomes in broader patient cohorts.

The health economic model unveiled critical aspects influencing treatment strategies for advanced melanoma within the NHS framework. Notably, changes in WTP thresholds demonstrated shifts in the cost-effectiveness rankings across different treatment alternatives. Pembrolizumab and vemurafenib emerged as potential cost-effective options at a WTP threshold of £30,000, aligning with established NHS benchmarks. Immunotherapy drugs showed higher QALYs post-progression when compared to targeted therapy drugs, potentially reflecting sustained immunotherapy effects. Furthermore, the model's stability in the face of varied treatment costs within a 20% range underscores its robustness, supporting consistent conclusions and reliable decision-making guidance within this cost bracket. However, the exclusive consideration of drug acquisition costs, excluding potential additional costs such as hospitalisation, staff, and side effect treatments poses limitations in evaluating the economic impact comprehensively. The health economic model in this study provides crucial insight into advance melanoma treatment strategies in a real-world setting, aiding decision-makers in future health assessments and optimising treatment selection to maximise patient outcomes while considering the associated costs.

In conclusion, as novel treatments for advanced melanoma are being researched and developed, the range of available alternatives is beginning to expand. The optimal course of treatment or sequence of treatments to prescribe to patients in order to achieve the best possible outcome is still not fully understood. Retrospective studies using real-world evidence can provide a realistic awareness of treatment outcomes outside a controlled setting of clinical trials, contributing to a comprehensive analysis surrounding treatment outcomes and patient care.

6.1.1. Strengths and limitations

The work presented in this thesis has several strengths as it uses individual-level real-world data that covers a defined Scottish population which allowed the evaluation

of treatment effectiveness, treatment sequencing, and cost-effectiveness in real-world clinical practice rather than under the controlled conditions of randomised trials.

Additionally, the integration of different methodological approaches including survival analysis, time-dependent Cox models, multi-state modelling, and health economic evaluation, provides a comprehensive assessment of clinical and economic outcomes across the treatment pathway in real-world practice. The use of time-dependent and multi-state transition models allowed a more realistic representation of changing therapies and disease progression than traditional static approaches. Few real-world melanoma studies have combined these methods within a single analytical framework, particularly using IPD rather than aggregate estimates.

Finally, the development of a flexible, R-based multi-state cost-effectiveness model demonstrates the feasibility of conducting reproducible economic evaluations using real-world data. This approach aligns with emerging HTA interest in adaptive modelling frameworks that can be updated as new data become available.

Nevertheless, this study is not without limitations as previously state throughout this thesis. The cohort size in the multi-state analyses was based on a small cohort (N=284) which limited precision, producing wide confidence intervals for some sojourn and transition estimates. However, this sample size was comparable with other real-world sequencing studies such as Hu *et al.* (2023) which included 161 patients, but substantially smaller than national registry analyses [176]. Another limitation lies in the absence of data regarding the reasons behind therapy changes. In practice, patients may discontinue or switch therapy due to different reasons such as toxicity, immune-related adverse events, lack of response, or personal preferences. Without information on the motivations for these transitions, it is challenging to offer comprehensive insights into treatment decision-making. Moreover, the health economic model included drug acquisition costs exclusively, and omitted other costs such as hospitalisation admissions, outpatient visits, monitoring costs, management of treatment-related adverse event, other resource uses. This understates the true health service costs and restricts the interpretation of the ICURs.

6.1.2. Study assumptions

The assumptions taken to conduct the analyses presented in this thesis should be considered when interpreting the results. Initially, to reduce the uncertainty regarding *BRAF* status, '*BRAF*-mutant' status was inferred for patients receiving targeted therapy without a recorded laboratory confirmation. While clinically reasonable, misclassification could bias treatment comparisons and inflate apparent mutation prevalence. If a subset of those patients were in fact '*BRAF*-wild-type' due to, for example, prescribing errors or off-label treatment, the prevalence of *BRAF* mutations would be overestimated and effect estimates comparing treatment effects conditional on mutation could be biased. A set of sensitivity analyses could be performed in order to reduce uncertainty around this assumption: treating imputed *BRAF* mutation cases as missing by excluding them from stratified analyses; conduct a multiple imputation of *BRAF* status; or investigating the results stratified by confirmed or imputed *BRAF* mutation.

In order to quantify progression in Chapter 5, a change in therapy type for a second-line was treated as evidence of disease progression as previously described in section 5.3.1.2. However, treatment switches can occur for toxicity, patient preference, or logistical reasons, not only disease progression. Misclassifying such treatment changes as disease progression will overestimate progression rates, shorten estimated time spent in a progression-free state, and potentially bias survival and cost estimates. In the health economic evaluation the costs and QALYs assigned to 'Progressed disease' health state would be misallocated. The direction of bias depends on whether non-progression switches associate with better or worse prognosis than true progression. Additionally, for the analysis in Chapter 5, utility values were sourced from published literature rather than directly measured within the study cohort as such was this information was not available. Although these values were drawn from studies with comparable disease stages and treatment contexts, differences in patient-reported outcomes between trial populations and real-world patients may result in overestimation of QALYs if real-world quality of life is lower due to comorbidities or treatment burden.

Furthermore, only drug acquisition costs were included in this economic analysis as previously stated. This led to the exclusion of other costing variables such as irAE management costs, hospitalisations, and monitoring, which can change ICURs. The conclusion that a regimen is cost-effective at a given WTP threshold may not hold if all resource use costs are included. The exclusion of non-drug costs is likely to bias ICUR estimates downward, as total costs are underestimated. Immunotherapy regimens are associated with immune-related adverse events that may require prolonged hospitalisation, specialist management, and long-term follow-up, whereas targeted therapies are often associated with different toxicity profiles that may need alternative patterns of resource use. If these additional costs were incorporated, the absolute costs of both treatment strategies would increase. However, the direction and magnitude of bias in the ICURs would depend on the relative intensity and duration of downstream resource utilisation associated with each therapy. Alternative modelling approaches could have mitigated this limitation, including the incorporation of literature-based estimates for adverse event costs, hospitalisation rates, and end-of-life care.

6.1.3. Implications for policy and clinical decision-making

Notwithstanding the limitations of this thesis, the findings have important implications for health technology assessment and decision-making within the SMC and similar organisations. RCTs remain the cornerstone of drug approval, but their selective inclusion criteria mean that trial populations often differ from the broader, more heterogeneous population encountered in routine NHS practice. The use of real-world data can provide complementary insights by showing how treatments perform under everyday clinical conditions, where comorbidities, variations in treatment adherence, and service delivery constraints play a critical role. By offering a more accurate picture of survival outcomes, treatment sequencing, and resource utilisation, real-world evidence can help SMC contextualise trial findings when making reimbursement and guideline decisions.

The economic analyses presented in this thesis highlight the relevance of real-world data to local resource planning. Estimates of treatment duration, treatment sequencing patterns, and survival outcomes derived from Scottish practice can be used to anticipate NHS costs more accurately than sole reliance on trial data. This allows decision-makers to assess not only whether a drug is likely to be cost-effective under national thresholds. Real-world data-based economic evaluations are likely to be most informative during the post-marketing and early adoption phases of a drug's lifecycle, when uncertainty around long-term effectiveness, treatment sequencing, and real-world resource use remains high. At this stage, these health economic evaluations can complement trial evidence by informing reassessments, conditional reimbursement decisions, and potential updates to clinical guidance. By incorporating such context-specific data into their deliberations, SMC can provide guidance that is both clinically relevant and economically sustainable.

In summary, the work undertaken in this thesis demonstrates how real-world evidence can support SMC at multiple stages of an intervention lifecycle as it can complement trial findings and reduce uncertainty about external validity. The systematic use of real-world data in HTAs would strengthen the evidence base for oncology decision-making, leading to treatment recommendations that are more representative of actual clinical practice and more responsive to the needs of NHS Scotland.

6.2. Further research

The primary challenge lies in overcoming the data limitations in the current study. The small cohort size, limited granularity in the data, and absence of detailed information concerning the reasons behind therapy changes prevent a comprehensive understanding of certain treatment decisions. Enhancing data collection methodologies could provide supplementary insights into the reasoning behind therapeutic transitions, facilitating the analysis of treatment pathways and survival outcomes.

The correlation between higher BMI classifications and improved survival probabilities is an intriguing subject for future research. This correlation presents an

opportunity for in-depth exploration in order to understand the mechanisms and potential impacts on treatment responses. Despite the recent studies conducted on this subject, retrospective analyses with real-world evidence could uncover valuable insights into the link between BMI and survival in metastatic melanoma patients, specifically in the Scottish and UK populations [138], [139].

Also, further research should delve into refining the multi-state Markov model for treatment sequencing. Extending the multi-state model to incorporate more treatments is a promising way to investigate a broader range of treatment sequences, especially considering the survival and therapeutic advantages of treating advanced melanoma with immunotherapy and targeted therapy regimens. Incorporating various treatment regimens into the model, would allow an evaluation of alternative therapeutic pathways, potentially uncovering more effective treatment strategies for advanced melanoma patients.

Furthermore, extending the health economic model by including other costs, such as hospitalisation, adverse event costs, indirect costs, and other healthcare-related services, will strengthen its robustness. This expanded model could provide a more comprehensive assessment of the economic implications of different treatment options, offering clearer insights into the overall economic burden associated with advanced melanoma treatments.

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Appendix 1 – Sample R code

Appendix 1.1 – Data manipulation

```
knitr::opts_chunk$set(echo = TRUE)
library(tidyr)
library(readr)
library(dplyr)
library(lubridate) #dates
library(ggplot2)
library(gmodels)
setwd("S:/Pedro")
```

Load data, summary and structure

```
WoS_Melanoma_Chemocare <- read.csv("Z:/WoS_Melanoma_Chemocare.csv", header = TRUE, st
ringsAsFactors = FALSE)
chi_database_deaths <- read.csv("Z:/chi_database_deaths.csv", header = TRUE, stringsA
sFactors=FALSE)
BRAF <- read.csv("Z:/01_Extract_BRAF_Melanoma.csv", header = TRUE, stringsAsFactors=F
ALSE)
deaths <- read.csv("Z:/Deaths.csv", header = TRUE, stringsAsFactors = FALSE)

summary(WoS_Melanoma_Chemocare)
str(WoS_Melanoma_Chemocare)

summary(chi_database_deaths)
str(chi_database_deaths)
```

Creating the demographics subset

Change format of DATE_OF_DEATH, DATE_OF_BIRTH, simd2012_sc_quintile, GENRE and PRIMARY_CAUSE_OF_DEATH

```
demographics <- chi_database_deaths %>%
  select(SafeHavenID, DATE_OF_BIRTH, SEX, simd2012_sc_quintile) %>%
  mutate(DATE_OF_BIRTH = ymd(DATE_OF_BIRTH),
         GENDER = factor(SEX, labels = c("Male", "Female")), # Labels: 1 = M; 2 = F
         simd2012_sc_quintile = as.factor(simd2012_sc_quintile))

deaths <- deaths %>%
  arrange(SafeHavenID) %>%
  select(SafeHavenID, DOD, CODDESC) %>%
  rename(DATE_OF_DEATH = DOD) %>%
  mutate(DATE_OF_DEATH = ymd(DATE_OF_DEATH),
         CODDESC = as.factor(CODDESC))

summary(demographics) # DoD - 115 NA's
str(demographics) # Check the changes in the structure

summary(deaths)
str(deaths) # Check the changes in the structure
```

Manipulation of BRAF dataset (0 - No mutation; 1 - Mutation)

```
table(BRAF$Result)

BRAF <- BRAF %>%
  arrange(SafeHavenID, Report.Date) %>%
  mutate(MUTATION = case_when(Result %in% c("No sequence variant detected in codon 60
0 of the BRAF gene.",
```

```
                                              "No sequence variant detected in codon 60
0 of the BRAF gene (see interpretation).",
                                              "Analysis failed.") ~ 0,
                                  TRUE ~ 1)) %>%
  mutate(MUTATION = factor(MUTATION, levels = c(0, 1), labels = c("BRAF Wild-type", "
BRAF mutation"))) %>%
  group_by(SafeHavenID) %>%
  filter(!duplicated(SafeHavenID)) %>%
  select(SafeHavenID, MUTATION) %>%
  ungroup()

unique(BRAF$SafeHavenID)
str(BRAF)
table(BRAF$MUTATION, exclude = NULL)
```

Create subset for metastatic melanoma

Change date format and index

```
Metastatic_Melanoma <- WoS_Melanoma_Chemocare %>%
  filter(DIAGNOSIS == c("Malignant Melanoma", "Malignant Melanoma - Metastatic")) %>%
  mutate(APPT_DATE = as.Date(APPT_DATE, format = "%Y-%m-%d"),
         DIAGNOSIS = as.factor(DIAGNOSIS),
         REGIME = as.factor(REGIME),
         CYCLE = as.factor(CYCLE)) %>%
  arrange(SafeHavenID, APPT_DATE)

table(WoS_Melanoma_Chemocare$DIAGNOSIS, exclude = NULL)

# Time period (first and last appointment date)
min(WoS_Melanoma_Chemocare$APPT_DATE, exclude = NULL); max(WoS_Melanoma_Chemocare$APP
T_DATE, exclude = NULL);

table(Metastatic_Melanoma$DIAGNOSIS, exclude = NULL)
n_distinct(Metastatic_Melanoma$SafeHavenID) # Total of 351 patients diagnosed
str(Metastatic_Melanoma)
```

Create Melanoma1 - Only metastatic melanoma patients with SACT

New variables “DRUG” and “TYPE”

```
summary(Metastatic_Melanoma$REGIME)

Melanoma1 <- Metastatic_Melanoma %>%
  mutate(DRUG = case_when(REGIME %in% c("BRIM 3 ARM A", "SK31 RO5185426", "SK44 VEMUR
AFINIB",
                                        "VEMURAFENIB", "SK38 GO28141") ~ "VEM",
                          REGIME %in% "DABRAFENIB" ~ "DAB",
                          REGIME %in% c("DABRA+TRAMETINIB", "DABRAF+TRAMETIN","SK36 D
ABRA+TRAM") ~ "DABTRA",
                          REGIME %in% c("IPILIMUMAB", "SK33 IPILIMUMAB", "SK39 IPILIM
UMAB") ~ "IPI",
                          REGIME %in% c("MK-3475", "PEMBROLIZUMAB","PEMBROLIZUMAB EX"
,"SK39 MK-3475 Q2W") ~ "PEM",
                          REGIME %in% c("NIVO + IPILUM", "NIVOLUMAB+IPILIM", "SK51 NI
VO/IPILIM") ~ "NIVOIPI",
                          REGIME %in% c("NIVOLUMAB 3MG/KG", "NIVOLUMAB SKIN", "SK51 N
IVOLUMAB", "SK46 NIVOLUMAB") ~ "NIVO",
                          REGIME %in% c("BRIM 3 ARM B", "DACARBAZINE", "SK27 DACAR/E7
080",
                                        "SK27 DACARBAZINE", "SK27 E7080") ~ "DTIC",
                          REGIME %in% c("TEMOZ. MELANOMA", "TEMOZOL200mg/m2") ~ "TEMO
ZOLOMIDE",
                          TRUE ~ "Other"),
         TYPE = case_when(DRUG %in% c("VEM", "DAB", "DABTRA", "LENVATINIB") ~ "Target
ed therapy",
                          DRUG %in% c("IPI", "PEM", "NIVOIPI", "NIVO") ~ "Immunothera
```

```
py",
                          DRUG %in% c("TEMOZOLOMIDE", "DTIC", "PAC+CARBO") ~ "Chemoth
erapy",
                          TRUE ~ "Other")) %>%
  mutate(DRUG = as.factor(DRUG),
         TYPE = as.factor(TYPE))

str(Melanoma1)
table(Melanoma1$DRUG, exclude = NULL); table(Melanoma1$TYPE, exclude = NULL)
```

Duration of treatment (New variable in Days)

```
# Fix the duration of treatment
unique(Melanoma1$DURATION) # Check unique values for DURATION

Melanoma1 <- Melanoma1 %>%
  mutate(DUR_DAYS = case_when(DURATION %in% c("PRN", "1 BOTTLE", "1 Pack", "1 PACK",
"1 BOX", "1 TUBE") ~ 0,
                              DURATION %in% c("2 DAYS") ~ 2,
                              DURATION %in% c("3 days", "3 DAYS", "3D", "3 Days") ~ 3
,
                              DURATION %in% c("5 days", "5 days+PRN", "Days 1 - 5",
                                              "5 DAYS", "5", "5 D", "5DAY", "5DAYS",
"3-5 Days") ~ 5,
                              DURATION %in% c("7 DAYS", "7 days", "1 weeks", "1 week"
,
                                              "cont (7D)", "7D", "1 WEEK", "5-7 Days"
, "cont(07D)") ~ 7,
                              DURATION %in% c("8 days") ~ 8,
                              DURATION %in% c("cont (9D)") ~ 9,
                              DURATION %in% c("14 DAYS", "14DAYS", "14D", "2 WEEKS",
"cont(14D)",
                                              "cont (14D)", "2 weeks", "14 days", "14
", "14 D") ~ 14,
                              DURATION %in% c("cont (17D)") ~ 17,
                              DURATION %in% c("3 WEEKS", "3 weeks","3W", "21 DAYS", "
3 WK", "3 WKS", "3WKS",
                                              "21DAYS", "3WEEKS", "cont (21D)","cont(
21D)", "21",
                                              "21 days", "21 DYS", "21D", "Cont (21D)
", "21 Days") ~ 21,
                              DURATION %in% c("cont(23D)") ~ 23,
                              DURATION %in% c("cont(28D)", "cont (28D)", "4 WEEKS", "
4WKS", "4 weeks", "4WEEKS",
                                              "4W", "4 wks", "28 DAYS", "28 Days", "2
8 days", "28days", "28 dys",
                                              "prn 28 d", "cont28day", "cont 28 da",
"28D") ~ 28,
                              DURATION %in% c("29 days") ~ 29,
                              DURATION %in% c("1 MONTH", "1 month") ~ 30,
                              DURATION %in% c("5 WEEKS", "cont (35D)", "cont (5WK)",
"PRN 35days", "35 DAYS") ~ 35,
                              DURATION %in% c("6 weeks") ~ 42,
                              DURATION %in% c("7 WEEKS") ~ 49,
                              DURATION %in% c("Cont (12W)") ~ 84,
                              TRUE ~ NA_real_))

table(Melanoma1$DUR_DAYS, exclude = NULL)
str(Melanoma1)
```

Create Melanoma2

Join demographics + create AGE variable (remove patients under 18) + Age grouping

```
Melanoma2 <- Melanoma1 %>%
  left_join(BRAF, by = "SafeHavenID") %>%
  left_join(demographics, by = "SafeHavenID") %>%
```

```
  left_join(deaths, by = "SafeHavenID") %>%
  mutate(AGE = floor(as.numeric(difftime(APPT_DATE, DATE_OF_BIRTH, units = "days")/36
5.25))) %>%
  filter(!AGE < 18) %>%
# Remove patients under 18 years
  mutate(AGE_group = case_when(AGE <= 49         ~ "Under 50",
# Create age grouping
                               AGE %in% c(50:65) ~ "Between 50 and 65",
                               AGE >= 66         ~ "Over 65")) %>%
  mutate(AGE_group = factor(AGE_group,
                            levels = c("Under 50", "Between 50 and 65", "Over 65")))

table(Melanoma2$MUTATION, exclude = NULL)

dim(Melanoma2)
str(Melanoma2)
n_distinct(Melanoma2$SafeHavenID) # Total number of patients - 350
```

Fix BRAF NA's

```
# If a patient is under BRAF inhibitor (Targeted therapy), should be BRAF mutant
braf_mutate <- Melanoma2 %>%
  filter(is.na(MUTATION)) %>%
  select(SafeHavenID, MUTATION, REGIME, TYPE) %>%
  group_by(SafeHavenID) %>%
  filter(TYPE == "Targeted therapy") %>%
  filter(!duplicated(SafeHavenID))

table(braf_mutate$MUTATION, exclude = NULL) # Check values are NA
n_distinct(braf_mutate$SafeHavenID) # 69 patients

x <- intersect(Melanoma2$SafeHavenID, braf_mutate$SafeHavenID)
x

Melanoma2 <- Melanoma2 %>%
  mutate(MUTATION = case_when(SafeHavenID %in% x ~ "BRAF mutation",
                              TRUE ~ as.character(MUTATION))) %>%
  mutate(MUTATION = as.factor(MUTATION))

## Check number of mutations
Melanoma2 %>% filter(!duplicated(SafeHavenID)) %>% group_by(MUTATION) %>% summarise(c
ount = n())
str(Melanoma2)
```

Create Melanoma3

CENS (event is death) + FUTIME (follow-up time in months)

```
Melanoma3 <- Melanoma2 %>%
  arrange(SafeHavenID, APPT_DATE) %>%
  group_by(SafeHavenID) %>%
  mutate(CENS = case_when(DATE_OF_DEATH %in% NA ~ 0, # Creating CENS variable (0 - Al
ive; 1 - Event)
                          TRUE ~ 1)) %>%
  mutate(FUTIME = case_when(CENS == 1 ~ as.numeric(difftime(DATE_OF_DEATH, min(APPT_D
ATE), units = "days")),
                            CENS == 0 ~ as.numeric(difftime(max(APPT_DATE), min(APPT_
DATE), units = "days")))) %>%
  # Convert follow-up time to months
  mutate(FUTIME = round(FUTIME/30.417, digit = 1)) %>%
  mutate(TIME = as.numeric(difftime(APPT_DATE, min(APPT_DATE), units = "days"))) %>%
  # Convert time to months
  mutate(TIME = round(TIME/30.417, digit = 1)) %>%
  # Remove patients with only one observation (FUTIME = 0)
  filter(FUTIME!= 0) %>%
  ungroup()
```

```
n_distinct(Melanoma3$SafeHavenID) # Total number of patients - 346

summary(Melanoma3$FUTIME) # FUTIME cannot be 0
```

ORDER - New variable for the order of treatments

```
line_treatment <- Melanoma3 %>% # Final table with lines of treatment (1 to 5)
  select(SafeHavenID, APPT_DATE, REGIME, DRUG, APPT_DATE) %>%
  arrange(SafeHavenID, APPT_DATE) %>%
  group_by(SafeHavenID) %>%
  filter(!duplicated(DRUG)) %>%
  group_by(SafeHavenID) %>%
  mutate(ORDER = order(APPT_DATE)) %>%
  ungroup()

n_distinct(line_treatment$SafeHavenID) # Total number of patients - 346

# Line of treatment table
CrossTable(line_treatment$DRUG, line_treatment$ORDER, dnn = c("Drug", "Order"),
           prop.t = FALSE, prop.chisq = FALSE, prop.c = FALSE) # Percentage by row (G
enre)

# Join the new variable (ORDER) to Melanoma subset
Melanoma3 <- line_treatment %>%
  select(SafeHavenID, DRUG, ORDER) %>%
  left_join(Melanoma3, by = c("SafeHavenID", "DRUG"))

n_distinct(Melanoma3$SafeHavenID) # Total number of patients - 346
str(Melanoma3)
```

Create subsets with only patients with treatment switches

Melanoma_switch_drug: 2+ drugs

```
# Patients that had more than 1 treatment
# Switched between TT and/OR IM
Melanoma_2drugs <- Melanoma3 %>%
  arrange(SafeHavenID, APPT_DATE) %>%
  group_by(SafeHavenID) %>%
  transmute(n_treatment = n_distinct(DRUG)) %>%
  filter(row_number() == 1, n_treatment >= 2) %>%
  ungroup()

n_distinct(Melanoma_2drugs$SafeHavenID) # 180 patients had at least 2 different drugs

# Merge melanoma patients with 2+ drugs with the original melanoma dataset (all colum
ns)
Melanoma_switch_drug <- Melanoma3 %>%
  right_join(Melanoma_2drugs, by = "SafeHavenID") %>%
  select(-n_treatment) %>%
  arrange(SafeHavenID, APPT_DATE)

n_distinct(Melanoma_switch_drug$SafeHavenID) # Check the SafeHavenID for the 180 pati
ents

str(Melanoma_switch_drug)
table(Melanoma3$MUTATION, exclude = NULL)
table(Melanoma_switch_drug$MUTATION, exclude = NULL)

# Save dataset for treatment switches!
save(Melanoma_switch_drug, file = "Melanoma_switch_drug.Rda")
```

Melanoma_switch_type: 2+ types of therapy

```
# Patients that had different therapies (Chemotherapy, targeted therapy, immunotherap
y or other)
Melanoma_2types <- Melanoma3 %>%
  arrange(SafeHavenID, APPT_DATE) %>%
  group_by(SafeHavenID) %>%
  transmute(n_type = n_distinct(TYPE)) %>%
  filter(row_number() == 1, n_type >= 2) %>%
  ungroup()

n_distinct(Melanoma_2types$SafeHavenID) # 121 patients switched therapy

# Merge melanoma patients with 2 types of treatment with the original melanoma datase
t (all columns)
Melanoma_switch_type <- Melanoma3 %>%
  right_join(Melanoma_2types, by = "SafeHavenID") %>%
  select(-n_type) %>%
  arrange(SafeHavenID, APPT_DATE)

n_distinct(Melanoma_switch_type$SafeHavenID) # Check the SafeHavenID for the 121 pati
ents

str(Melanoma_switch_type)
table(Melanoma3$MUTATION, exclude = NULL)
table(Melanoma_switch_type$MUTATION, exclude = NULL)

# Save dataset for treatment switches!
save(Melanoma_switch_type, file = "Melanoma_switch_type.Rda")
```

Create subset only with patients with monotherapy

```
# Patients that had only 1 treatment type (IT or TT)
# Use anti_join to remove Melanoma_2types patients from the bigger subset (Melanoma3)
Melanoma_monotherapy <- Melanoma3 %>%
  anti_join(Melanoma_switch_type, by = "SafeHavenID") %>%
  arrange(SafeHavenID, APPT_DATE)

n_distinct(Melanoma_monotherapy$SafeHavenID) # Check the SafeHavenID for the 229 pati
ents
intersect(Melanoma_monotherapy$SafeHavenID, Melanoma_switch_type$SafeHavenID) # No in
tersection - Different patients

str(Melanoma_monotherapy)
table(Melanoma_monotherapy$MUTATION, exclude = NULL)

# Save dataset for patients WITHOUT treatment switches!
save(Melanoma_monotherapy, file = "Melanoma_monotherapy.Rda")
```

Create Melanoma4 - Same as Melanoma3 but with one more variable

New variable - Patients that switched therapies (SWITCH)

New variable - Total number of SACT treatments (N_SACT)

```
# Create variable SWITCH
n_distinct(setdiff(Melanoma_monotherapy$SafeHavenID, Melanoma_switch_drug$SafeHavenID
)) # 170 patients: No drug switch nor type switch
n_distinct(intersect(Melanoma_monotherapy$SafeHavenID, Melanoma_switch_drug$SafeHaven
ID)) # 59 patients: Drug switch, no type switch
n_distinct(intersect(Melanoma_switch_type$SafeHavenID, Melanoma_switch_drug$SafeHaven
ID)) # 121 patients: Drug switch AND type switch

# 170 patients: No drug switch nor type switch
x <- setdiff(Melanoma_monotherapy$SafeHavenID, Melanoma_switch_drug$SafeHavenID)
# 59 patients: Drug switch, no type switch
y <- intersect(Melanoma_monotherapy$SafeHavenID, Melanoma_switch_drug$SafeHavenID)
# 121 patients: Drug switch AND type switch
z <- intersect(Melanoma_switch_type$SafeHavenID, Melanoma_switch_drug$SafeHavenID)
```

```
# 180 patients: Switchers
w <- Melanoma_switch_drug %>% select(SafeHavenID) %>% filter(!duplicated(SafeHavenID)
)

Melanoma4 <- Melanoma3 %>%
  mutate(SWITCH = case_when(SafeHavenID %in% x ~ 1,
                            SafeHavenID %in% y ~ 2,
                            SafeHavenID %in% z ~ 3)) %>%
  mutate(SWITCH = factor(SWITCH, levels = c(1,2,3), labels = c("No switch", "Switch d
rug only", "Switch drug AND type")))

# Create variable N_SACT: Compile 3, 4 and 5 SACT treatments into category "3+"
Melanoma4 %<>%
  group_by(SafeHavenID) %>%
  mutate(N_SACT = case_when(max(ORDER) %in% 1 ~ 1,
                            max(ORDER) %in% 2 ~ 2,
                            max(ORDER) %in% c(3,4,5) ~ 3)) %>%
  mutate(N_SACT = factor(N_SACT, levels = c(1,2,3), labels = c("1","2","3+"))) %>%
  ungroup()

# Check intersections (same number of patients)
n_distinct(Melanoma4$SafeHavenID) # 350 patients
n_distinct(intersect(Melanoma4$SafeHavenID, Melanoma_switch_type$SafeHavenID)) # 121
patients - Correct
n_distinct(intersect(Melanoma4$SafeHavenID, Melanoma_monotherapy$SafeHavenID)) # 229
patients - Correct
```

Add new variables:

```
## BMI at baseline:
Malignant_Melanoma_final <- Melanoma4 %>%
  arrange(SafeHavenID, APPT_DATE) %>%
  mutate(BMI = case_when(SAWEIGHT %in% 0 ~ NA_real_,
                                 is.numeric(SAWEIGHT) ~ round(SAWEIGHT/(SAHEIGHT*SAH
EIGHT), 0))) %>%
  mutate(BMI_group = case_when(BMI <= 24.9              ~ "Normal",
                               BMI >= 25 & BMI <= 29.9  ~ "Overweight",
                               BMI >= 30                ~ "Obese",
                               TRUE                     ~ NA_character_)) %>%
  mutate(BMI_group = factor(BMI_group, levels = c("Normal", "Overweight", "Obese")))
%>%
  ungroup()

# Relevel BMI_group - Normal should be the reference
Malignant_Melanoma_final$BMI_group <- relevel(Malignant_Melanoma_final$BMI_group, ref
= "Normal")

table(Malignant_Melanoma_final$BMI_group, exclude = NULL) # Check the grouping is wor
king



## PS Score
Malignant_Melanoma_final <- Malignant_Melanoma_final %>%
  mutate(PS = case_when(is.na(PS.DIAGNOSIS) ~ PS.CYCLE,
                        is.na(PS.CYCLE) ~ PS.DIAGNOSIS,
                        TRUE ~ NA_integer_)) %>%
  select(-c(PS.DIAGNOSIS, PS.CYCLE)) %>%
  mutate(PS = case_when(PS %in% 0 ~ 0,
                        PS %in% 1 ~ 1,
                        PS %in% c(2,3) ~ 2)) %>%       # Group PS = "2+"
  mutate(PS = factor(PS, levels = c(0,1,2), labels = c("0","1","2+")))

str(Malignant_Melanoma_final) # Check new PS variable
```

Biomarkers

```
# Load SCI from hard drive
SCI <- read.csv("Z:/SCI_Store.csv", header = TRUE, stringsAsFactors=FALSE)

# Check structure
str(SCI)
```

LDH

```
LDH <- SCI %>%
  semi_join(Malignant_Melanoma_final, by = "SafeHavenID") %>%                  # Keep
only patients that appear on the final subset
  filter(CLINICALCODEDESCRIPTION %in% c("Lactate Dehydrogenas", "LDH")) %>%   # Filte
r for LDH observations
  arrange(SafeHavenID, SAMPLEDATE) %>%
  select(SafeHavenID, QUANTITYVALUE) %>%
  rename(LDH = QUANTITYVALUE) %>%
  filter(LDH!= 0,
 !duplicated(SafeHavenID))                                                    # Keep only the
first observation (baseline)

# Check 0 were erased from LDH
summary(LDH)

Malignant_Melanoma_final <- Malignant_Melanoma_final %>%
  left_join(LDH, by = "SafeHavenID") %>%
  mutate(LDH_group = case_when(LDH <= 333 ~ "Normal",
                               LDH >= 334 ~ "High")) %>%
  mutate(LDH_group = factor(LDH_group, levels = c("Normal", "High"))) %>%
  ungroup()
```

C-Reactive Protein

```
CRP <- SCI %>%
  filter(CLINICALCODEDESCRIPTION %in% c("C-reactive Protein", "C-Reactive Protein(0-5
Normal)",
                                        "C Reactive Protein", "Serum C reactive prote
in level")) %>%
  arrange(SafeHavenID, desc(SAMPLEDATE)) %>%
  select(SafeHavenID, QUANTITYVALUE, QUANTITYUNIT) %>%
  rename(CRP = QUANTITYVALUE,
         CRP_Unit = QUANTITYUNIT) %>%
  filter(!duplicated(SafeHavenID))

Malignant_Melanoma_final <- Malignant_Melanoma_final %>%
  left_join(CRP, by = "SafeHavenID")

summary(Malignant_Melanoma_final$CRP)
```

NOTE: There are duplicated dates because some patients had more than one drug in the same appointment date (treatment adverse events)

```
Malignant_Melanoma_final <- Malignant_Melanoma_final %>%
  group_by(SafeHavenID, APPT_DATE) %>%
  filter(!duplicated(SafeHavenID)) %>%
  ungroup()
```

Find patients with NIVOIPI + NIVO and DAB + DABTRA

```
# NIVOIPI
NIVOIPI <- Malignant_Melanoma_final %>%
  select(SafeHavenID, APPT_DATE, CENS, FUTIME, TYPE, DRUG) %>%
  group_by(SafeHavenID) %>%
  filter(!duplicated(DRUG)) %>%
  select(SafeHavenID, APPT_DATE, DRUG) %>%
  group_by(SafeHavenID) %>%
  filter(DRUG %in% c("NIVOIPI", "NIVO")) %>%
  mutate(ORDER = order(APPT_DATE)) %>%
```

```
  filter(ORDER == 2 & DRUG == "NIVO")

NIVOIPI_NIVO_ID <- NIVOIPI$SafeHavenID

Malignant_Melanoma_final <- Malignant_Melanoma_final %>%
  group_by(SafeHavenID) %>%
  mutate(DRUG = as.character(DRUG)) %>%
  mutate(DRUG = case_when(SafeHavenID %in% NIVOIPI_NIVO_ID & DRUG == "NIVO" ~ "NIVOIP
I",
                          TRUE ~ DRUG)) %>%
  # Convert DRUG back to factor
  mutate(DRUG = as.factor(DRUG))

# DAB
DAB <- Malignant_Melanoma_final %>%
  select(SafeHavenID, APPT_DATE, CENS, FUTIME, TYPE, DRUG) %>%
  group_by(SafeHavenID) %>%
  filter(!duplicated(DRUG)) %>%
  select(SafeHavenID, APPT_DATE, DRUG) %>%
  group_by(SafeHavenID) %>%
  filter(DRUG %in% c("DAB", "DABTRA")) %>%
  mutate(ORDER = order(APPT_DATE)) %>%
  filter(ORDER == 2 & DRUG == "DABTRA")

DAB_DABTRA_ID <- DAB$SafeHavenID

Malignant_Melanoma_final <- Malignant_Melanoma_final %>%
  group_by(SafeHavenID) %>%
  mutate(DRUG = as.character(DRUG)) %>%
  mutate(DRUG = case_when(SafeHavenID %in% DAB_DABTRA_ID & DRUG == "DAB" ~ "DABTRA",
                          TRUE ~ DRUG)) %>%
  # Convert DRUG back to factor
  mutate(DRUG = as.factor(DRUG))
```

Fix ORDER

```
ORDER <- Malignant_Melanoma_final %>%
  select(SafeHavenID, APPT_DATE, DRUG) %>%
  arrange(SafeHavenID, APPT_DATE) %>%
  group_by(SafeHavenID) %>%
  filter(!duplicated(DRUG)) %>%
  mutate(ORDER = order(APPT_DATE)) %>%
  select(-APPT_DATE)

# Join the new variable (ORDER) to Melanoma subset
Malignant_Melanoma_final <- Malignant_Melanoma_final %>%
  select(-ORDER) %>%
  right_join(ORDER, by = c("SafeHavenID", "DRUG")) %>%
  relocate(SafeHavenID, DRUG, ORDER)

# Remove NIVO patients
NIVO <- Malignant_Melanoma_final %>%
  filter(DRUG == "NIVO" & ORDER == 1) %>%
  filter(!duplicated(SafeHavenID))
NIVO_ID <- NIVO$SafeHavenID

# Final dataset
Malignant_Melanoma_final <- Malignant_Melanoma_final %>%
  filter(SafeHavenID!= NIVO_ID)
```

Save latest subset: Malignant melanoma final

```
# Number of patients
n_distinct(Malignant_Melanoma_final$SafeHavenID) # 345 patients
```

```
# Save subset
save(Malignant_Melanoma_final, file = "Malignant_Melanoma_final.Rda")
```

Appendix 1.2 – Descriptive statistics

Summary statistics - Malignant_Melanoma_final

```
length(unique(Malignant_Melanoma_final$SafeHavenID)) # Total patients - 345 patients
table(Malignant_Melanoma_final$DRUG, exclude = NULL)

# First and last date of first appointment (cohort timeline)
substr(min(Malignant_Melanoma_final$APPT_DATE), 0, 4)
substr(max(Malignant_Melanoma_final$APPT_DATE), 0, 4)
```

Subsets

```
# MM_no_duplicates - Only the first observation by patients
MM_no_duplicates <- Malignant_Melanoma_final %>%
  group_by(SafeHavenID) %>%
  arrange(SafeHavenID, APPT_DATE) %>%
  filter(!duplicated(SafeHavenID))
```

Descriptive statistics - MM_no_duplicates

```
# Number of patients
n_patients <- n_distinct(MM_no_duplicates$SafeHavenID) # 346 patients

# Numerical covariates
# Age
hist(MM_no_duplicates$AGE)

# LDH
hist(MM_no_duplicates$LDH)
# BMI
hist(MM_no_duplicates$BMI)

# Age
median(MM_no_duplicates$AGE)
quantile(MM_no_duplicates$AGE, 0.25); quantile(MM_no_duplicates$AGE, 0.75)

# LDH
summary(MM_no_duplicates$LDH)
sd(MM_no_duplicates$LDH, na.rm = TRUE)

# CRP
summary(MM_no_duplicates$CRP)
sd(MM_no_duplicates$CRP, na.rm = TRUE)

# Gender
MM_no_duplicates %>%
  group_by(GENDER) %>%
  summarise(count = n(),
            percentage = count*100/n_patients)

# SIMD
MM_no_duplicates %>%
  group_by(simd2012_sc_quintile) %>%
  summarise(count = n(),
            percentage = count*100/n_patients)

# DRUG
MM_no_duplicates %>%
  group_by(DRUG) %>%
  summarise(count = n(),
```

```
            percentage = count*100/n_patients)

# TYPE
MM_no_duplicates %>%
  group_by(TYPE) %>%
  summarise(count = n(),
            percentage = count*100/n_patients)

# BRAF
MM_no_duplicates %>%
  group_by(MUTATION) %>%
  summarise(count = n(),
            percentage = count*100/n_patients)

# PS Score
MM_no_duplicates %>%
  group_by(PS) %>%
  summarise(count = n(),
            percentage = count*100/n_patients)

# LDH_group
MM_no_duplicates %>%
  group_by(LDH_group) %>%
  summarise(count = n(),
            percentage = count*100/n_patients)

# BMI_group
MM_no_duplicates %>%
  group_by(BMI_group) %>%
  summarise(count = n(),
            percentage = count*100/n_patients)

# CENS
MM_no_duplicates %>%
  group_by(CENS) %>%
  summarise(count = n(),
            percentage = count*100/n_patients)

# SWITCH
MM_no_duplicates %>%
  group_by(SWITCH) %>%
  summarise(count = n(),
            percentage = count*100/n_patients)
```

Summary for first treatment

```
# Summary table for 1st line treatment
library(survival)
fitmodel_DRUG <- survfit(Surv(FUTIME, CENS) ~ DRUG, data = MM_no_duplicates)
print(fitmodel_DRUG)

# Summary table for 1st line TYPE
fitmodel_TYPE <- survfit(Surv(FUTIME, CENS) ~ TYPE, data = MM_no_duplicates)
print(fitmodel_TYPE)
```

ORDER - New variable for the order of treatments

```
line_treatment <- Malignant_Melanoma_final %>% # Final table with lines of treatment
(1 to 5)
  select(SafeHavenID, APPT_DATE, REGIME, DRUG, APPT_DATE, TYPE) %>%
  arrange(SafeHavenID, APPT_DATE) %>%
  group_by(SafeHavenID) %>%
  filter(!duplicated(DRUG)) %>%
  group_by(SafeHavenID) %>%
  mutate(ORDER = order(APPT_DATE)) %>%
  ungroup()
```

```
n_distinct(line_treatment$SafeHavenID) # Total number of patients - 345

# Line of treatment table
CrossTable(line_treatment$DRUG, line_treatment$ORDER, dnn = c("Drug", "Order"),
           prop.t = FALSE, prop.chisq = FALSE, prop.c = FALSE) # Percentage by row (G
enre)

# Line of treatment table - TYPE
CrossTable(line_treatment$TYPE, line_treatment$ORDER, dnn = c("Type", "Order"),
           prop.t = FALSE, prop.chisq = FALSE, prop.c = FALSE) # Percentage by row (T
YPE)
```

Demographics' summary

```
library(purrr)

# Table for first treatment
(drug_table <- MM_no_duplicates %>%
  # Choose demographic variables
  select(SafeHavenID, TYPE, DRUG, AGE, GENDER, simd2012_sc_quintile, BMI_group, LDH_g
roup, PS, MUTATION) %>%
  split(.$TYPE) %>%
  map(summary))

# Table by GENDER
(gender_table <- MM_no_duplicates %>%
  # Choose demographic variables
  select(SafeHavenID, TYPE, DRUG, AGE, GENDER, simd2012_sc_quintile, BMI_group, LDH_g
roup, PS, MUTATION) %>%
  split(.$GENDER) %>%
  map(summary))
```

Appendix 1.3 – Survival analysis (Sankey Plots)

My dataset – Type of therapy changes

```
z <- Melanoma_switch_type %>%
  select(SafeHavenID, TYPE, APPT_DATE) %>%
  arrange(SafeHavenID, APPT_DATE) %>%
  group_by(SafeHavenID, TYPE) %>%
  filter(!duplicated(SafeHavenID),
         TYPE!= "Other") %>%
  select(-APPT_DATE) %>%
  ungroup()

n_distinct(z$SafeHavenID)
dim(z)

z <- z %>%
  group_by(SafeHavenID) %>%
  mutate(from = TYPE,
         to = lead(TYPE)) %>%
  filter(!is.na(to))

z$counter <- sequence(rle(as.character(z$SafeHavenID))$length)

links <- aggregate(z$SafeHavenID, list(z$from, z$to), length)
names(links) <- c("source", "target", "value")

# Create nodes
nodes <- data.frame(name = c(as.character(links$source), as.character(links$target))
%>%
                    unique())

links$IDsource <- match(links$source, nodes$name)-1
links$IDtarget <- match(links$target, nodes$name)-1
nodes$group <- as.factor(c("type_0", "type_1", "type_2"))

my_color <- 'd3.scaleOrdinal().domain(["Chemotherapy", "Targeted therapy", "Immunothe
rapy"]).range(["red", "blue", "green"])'

(p <- sankeyNetwork(Links = links, Nodes = nodes, Source = "IDsource", Target = "IDta
rget",
                    Value = "value", NodeID = "name", NodeGroup = "group",
                    sinksRight = FALSE, fontSize = 20, nodeWidth = 30, colourScale =
my_color))

library(htmlwidgets)
saveWidget(p, file = paste0(getwd(), "/sankeyTreatmentPathway - Type of therapy.html"
))
```

My dataset - Drug changes

```
x <- Melanoma_switch_drug %>%
  select(SafeHavenID, TYPE, DRUG, APPT_DATE) %>%
  filter(TYPE!= "Other") %>%
  arrange(SafeHavenID, APPT_DATE) %>%
  group_by(SafeHavenID, DRUG) %>%
  filter(!duplicated(SafeHavenID)) %>%
  select(-c(TYPE, APPT_DATE)) %>%
  ungroup()
```

```
n_distinct(x$SafeHavenID)
dim(x)

x <- x %>%
  group_by(SafeHavenID) %>%
  mutate(from = DRUG,
         to = lead(DRUG)) %>%
  filter(!is.na(to))

x$counter <- sequence(rle(as.character(x$SafeHavenID))$length)

links <- aggregate(x$SafeHavenID, list(x$from, x$to), length)
names(links) <- c("source", "target", "value")

links <- aggregate(x$SafeHavenID, list(x$from, x$to), length)
names(links) <- c("source", "target", "value")

# Create nodes
nodes <- data.frame(name = c(as.character(links$source), as.character(links$target))
%>%
                      unique())

links$IDsource <- match(links$source, nodes$name)-1
links$IDtarget <- match(links$target, nodes$name)-1
nodes$group <- as.factor(c("type_0", "type_1", "type_2", "type_3", "type_4",
                           "type_5", "type_6", "type_7", "type_8"))

my_color <- 'd3.scaleOrdinal().domain(["DABTRA", "DTIC", "NIVO", "NIVOIPI", "TEMOZOLO
MIDE", "VEM", "DAB", "IPI", "PEM"]).range(["red", "blue", "orange", "yellow", "cyan",
"green", "magenta", "pink", "gold"])'

(p <- sankeyNetwork(Links = links, Nodes = nodes, Source = "IDsource", Target = "IDta
rget",
                    Value = "value", NodeID = "name", NodeGroup = "group",
                    sinksRight = FALSE, fontSize = 20, nodeWidth = 30, colourScale = m
y_color))

library(htmlwidgets)
saveWidget(p, file = paste0(getwd(), "/sankeyTreatmentPathway - Drug treatment.html")
)
```

Appendix 1.4 – Survival analysis (KM Plots)

Subsets

```
# MM_no_duplicates - Only the first observation by patients
MM_no_duplicates <- Malignant_Melanoma_final %>%
  arrange(SafeHavenID, APPT_DATE) %>%
  group_by(SafeHavenID) %>%
  filter(!duplicated(SafeHavenID))
```

Survival analysis - ALL patients

Only CENS and FUTIME

```
fit_all <- survfit(Surv(FUTIME, CENS) ~ 1, data = MM_no_duplicates)
print(fit_all)

# KM Plot - Survival curve
(KM_all <- ggsurvplot(fit_all, data = MM_no_duplicates,
                      xlab = "Time in months",
                      ylab = "Probability - Overall survival",
                      xlim = c(0, 48),
                      title = "Kaplan-Meier Curve for Metastatic melanoma",
                      legend.title = "All patients",
                      surv.median.line = "hv",                # Add median line
                      size = 1,                               # change line size
                      palette = "jco",                        # custom color palettes
                      conf.int = TRUE,                        # Add confidence interv
al
                      pval = TRUE,                            # Add p-value
                      risk.table = "absolute",                # Add risk table (absol
ute number + %)
                      risk.table.y.text.col = TRUE,           # Colour risk table tex
t annotations
                      risk.table.y.text = FALSE,              # F - Shows bars instea
d of names in text annotations
                      risk.table.col = "strata",              # Risk table color by g
roups
                      risk.table.height = 0.25,               # Useful to change when
you have multiple groups
                      ggtheme = theme_bw()))                  # Change ggplot2 theme

ggsave("KM - All.jpg", plot = print(KM_all))
```

KM - Fit by gender

```
fit_GENDER <- survfit(Surv(FUTIME, CENS) ~ GENDER, data = MM_no_duplicates)
print(fit_GENDER)

names(fit_GENDER$strata) <- gsub("GENDER=", "", names(fit_GENDER$strata)) # Removes t
he name from top label

# KM Plot - Survival curve
(KM_GENDER <- ggsurvplot(fit_GENDER, data = MM_no_duplicates,
                         xlab = "Time in months",
                         ylab = "Probability - Overall survival",
                         xlim = c(0, 48),
                         title = "Kaplan-Meier Curve for Metastatic melanoma",
                         legend.title = "Gender",
                         legend.labs = c("Male", "Female"),      # Change legend labe
ls
```

```
                         surv.median.line = "hv",                # Add median line
                         size = 1,                               # change line size
                         linetype = "strata",
                         palette = c("dodgerblue2", "orchid2"),  # custom color palet
tes
                         conf.int = TRUE,                        # Add confidence int
erval
                         pval = TRUE,                            # Add p-value
                         risk.table = "percentage",              # Add risk table (ab
solute number + %)
                         risk.table.y.text.col = TRUE,           # Colour risk table
text annotations
                         risk.table.y.text = FALSE,              # F - Shows bars ins
tead of names in text annotations
                         risk.table.col = "strata",              # Risk table color b
y groups
                         risk.table.height = 0.25,               # Useful to change w
hen you have multiple groups
                         ncensor.plot = FALSE,                   # Plot the number of
censored at time t
                         ncensor.plot.height = 0.25,
                         ggtheme = theme_bw()))                  # Change ggplot2 the
me

ggsave("KM - Gender.jpg", plot = print(KM_GENDER), dpi = 2000)


# Compare survival curves - Log-rank test
surv_diff_GENDER <- survdiff(Surv(FUTIME, CENS) ~ GENDER, data = MM_no_duplicates)
surv_diff_GENDER # Not significant (p = 0.6)


######################################## Other plots ###################################
####################
# Survival plot - Cumulative events
(GENDER_event <- ggsurvplot(fit_GENDER, data = MM_no_duplicates,
                            xlab = "Time in months",
                            ylab = "Cumulative events",
                            xlim = c(0, 48),
                            legend.title = "Gender",
                            legend.labs = c("Male", "Female"),      # Change legend l
abels
                            size = 1,                               # change line siz
e
                            linetype = "strata",
                            palette = c("dodgerblue2", "orchid2"),  # custom color pa
lettes
                            fun = "event",                          # Function - cumu
lative events
                            ggtheme = theme_bw()))                  # Change ggplot2
theme

# Survival plot - Cumulative hazard
(GENDER_cumhaz <- ggsurvplot(fit_GENDER, data = MM_no_duplicates,
                             xlab = "Time in months",
                             ylab = "Cumulative hazard",
                             xlim = c(0, 48),
                             legend.title = "Gender",
                             legend.labs = c("Male", "Female"),      # Change legend
labels
                             size = 1,                               # change line si
ze
                             linetype = "strata",
                             palette = c("dodgerblue2", "orchid2"),  # custom color p
alettes
```

```
                            fun = "cumhaz",                          # Function - cum
ulative hazards
                            ggtheme = theme_bw()))                   # Change ggplot2
theme

# Survival plot - Survival probability
(GENDER_pct <- ggsurvplot(fit_GENDER, data = MM_no_duplicates,
                          xlab = "Time in months",
                          ylab = "Survival probability in percentage",
                          xlim = c(0, 48),
                          legend.title = "Gender",
                          legend.labs = c("Male", "Female"),      # Change legend lab
els
                          size = 1,                               # change line size
                          linetype = "strata",
                          palette = c("dodgerblue2", "orchid2"),  # custom color pale
ttes
                          fun = "pct",                            # Function - % surv
prob
                          ggtheme = theme_bw()))                  # Change ggplot2 th
eme

# Save plots
ggsave("Survival plot - Gender (cumulative events).jpg", plot = print(GENDER_event),
dpi = 2000)
ggsave("Survival plot - Gender (cumulative hazards).jpg", plot = print(GENDER_cumhaz)
, dpi = 2000)
ggsave("Survival plot - Gender (Survival probability in %).jpg", plot = print(GENDER_
pct), dpi = 2000)
```

KM - Fit by age

```
fit_AGE <- survfit(Surv(FUTIME, CENS) ~ AGE_group, data = MM_no_duplicates)
print(fit_AGE)

names(fit_AGE$strata) <- gsub("AGE_group=", "", names(fit_AGE$strata)) # Removes the
name from top label

(KM_AGE <- ggsurvplot(fit_AGE, data = MM_no_duplicates,
                      xlab = "Time in months",
                      ylab = "Probability - Overall survival",
                      xlim = c(0, 48),
                      title = "Kaplan-Meier Curve for Metastatic melanoma",
                      legend.title = "Age",
                      surv.median.line = "hv",                # Add median line
                      size = 1,                               # change line size
                      palette = "jco",                        # custom color palettes
                      conf.int = TRUE,                        # Add confidence interv
al
                      pval = TRUE,                            # Add p-value
                      risk.table = "percentage",              # Add risk table (absol
ute number + %)
                      risk.table.y.text.col = TRUE,           # Colour risk table tex
t annotations
                      risk.table.y.text = FALSE,              # F - Shows bars instea
d of names in text annotations
                      risk.table.col = "strata",              # Risk table color by g
roups
                      risk.table.height = 0.25,               # Useful to change when
you have multiple groups
                      ncensor.plot = FALSE,                   # Plot the number of ce
nsored at time t
                      ncensor.plot.height = 0.25,
                      ggtheme = theme_bw()))                  # Change ggplot2 theme

ggsave("KM - Age groups.jpg", plot = print(KM_AGE), dpi = 2000)
```

```
# Compare survival curves - Log-rank test
surv_diff_AGE <- survdiff(Surv(FUTIME, CENS) ~ AGE_group, data = MM_no_duplicates)
surv_diff_AGE # Not significant (p = 0.6)


######################################## Other plots ###################################
####################
# Cumulative events
(AGE_event <- ggsurvplot(fit_AGE, data = MM_no_duplicates,
                         xlab = "Time in months",
                         ylab = "Cumulative events",
                         legend.title = "Age",
                         size = 1,                                # change line size
                         linetype = "strata",
                         palette = "jco",                         # custom color palet
tes
                         fun = "event",                           # Function - cumulat
ive events
                         ggtheme = theme_bw()))                   # Change ggplot2 the
me

# Cumulative hazard
(AGE_cumhaz <- ggsurvplot(fit_AGE, data = MM_no_duplicates,
                          xlab = "Time in months",
                          ylab = "Cumulative hazard",
                          legend.title = "Age",
                          size = 1,                                # change line size
                          linetype = "strata",
                          palette = "jco",                         # custom color pale
ttes
                          fun = "cumhaz",                          # Function - cumula
tive hazard
                          ggtheme = theme_bw()))                   # Change ggplot2 th
eme

# Survival probability (%)
(AGE_pct <- ggsurvplot(fit_AGE, data = MM_no_duplicates,
                       xlab = "Time in months",
                       ylab = "Survival probability in percentage",
                       legend.title = "Age",
                       size = 1,                                # change line size
                       linetype = "strata",
                       palette = "jco",                         # custom color palette
s
                       fun = "pct",                             # Function - % surv pr
ob
                       ggtheme = theme_bw()))                   # Change ggplot2 theme

# Save plots
ggsave("Survival plot - Age (cumulative events).jpg", plot = print(AGE_event), dpi =
2000)
ggsave("Survival plot - Age (cumulative hazards).jpg", plot = print(AGE_cumhaz), dpi
= 2000)
ggsave("Survival plot - Age (Survival probability in %).jpg", plot = print(AGE_pct),
dpi = 2000)
```

KM - Fit by BRAF status

```
fit_BRAF <- survfit(Surv(FUTIME, CENS) ~ MUTATION, data = MM_no_duplicates)
print(fit_BRAF)

names(fit_BRAF$strata) <- gsub("MUTATION=", "", names(fit_BRAF$strata)) # Removes the
name from top label
```

```
(KM_BRAF <- ggsurvplot(fit_BRAF, data = MM_no_duplicates,
                       xlab = "Time in months",
                       ylab = "Probability - Overall survival",
                       xlim = c(0, 48),
                       title = "Kaplan-Meier Curve for Metastatic melanoma",
                       legend.title = "BRAF status",
                       surv.median.line = "hv",                # Add median line
                       size = 1,                               # change line size
                       palette = "jco",                        # custom color palette
s
                       conf.int = TRUE,                        # Add confidence inter
val
                       pval = TRUE,                            # Add p-value
                       risk.table = "percentage",              # Add risk table (abso
lute number + %)
                       risk.table.y.text.col = TRUE,           # Colour risk table te
xt annotations
                       risk.table.y.text = FALSE,              # F - Shows bars inste
ad of names in text annotations
                       risk.table.col = "strata",              # Risk table color by
groups
                       risk.table.height = 0.25,               # Useful to change whe
n you have multiple groups
                       ncensor.plot = FALSE,                   # Plot the number of c
ensored at time t
                       ncensor.plot.height = 0.25,
                       ggtheme = theme_bw()))                  # Change ggplot2 theme

# Save KM plot
ggsave("KM - BRAF status.jpg", plot = print(KM_BRAF), dpi = 2000)



# Compare survival curves - Log-rank test
surv_diff_BRAF <- survdiff(Surv(FUTIME, CENS) ~ MUTATION, data = MM_no_duplicates)
surv_diff_BRAF # Highly significant (p = 0.05)



######################################## Other plots ###################################
####################
# Cumulative events
(BRAF_event <- ggsurvplot(fit_BRAF, data = MM_no_duplicates,
                          xlab = "Time in months",
                          ylab = "Cumulative events",
                          legend.title = "BRAF status",
                          size = 1,                                  # change line size
                          linetype = "strata",
                          palette = "jco",                           # custom color pale
ttes
                          fun = "event",                             # Function - cumula
tive events
                          ggtheme = theme_bw()))                     # Change ggplot2 th
eme

# Cumulative hazard
(BRAF_cumhaz <- ggsurvplot(fit_BRAF, data = MM_no_duplicates,
                           xlab = "Time in months",
                           ylab = "Cumulative hazard",
                           legend.title = "BRAF status",
                           size = 1,                                  # change line size
                           linetype = "strata",
                           palette = "jco",                           # custom color pal
ettes
                           fun = "cumhaz",                            # Function - cumul
```

```
ative hazard
                          ggtheme = theme_bw()))                 # Change ggplot2 t
heme

# Survival probability (%)
(BRAF_pct <- ggsurvplot(fit_BRAF, data = MM_no_duplicates,
                        xlab = "Time in months",
                        ylab = "Survival probability in percentage",
                        legend.title = "BRAF status",
                        size = 1,                                # change line size
                        linetype = "strata",
                        palette = "jco",                         # custom color palett
es
                        fun = "pct",                             # Function - % surv p
rob
                        ggtheme = theme_bw()))                   # Change ggplot2 them
e

# Save plots
ggsave("Survival plot - BRAF status (cumulative events).jpg", plot = print(BRAF_event
), dpi = 2000)
ggsave("Survival plot - BRAF status (cumulative hazards).jpg", plot = print(BRAF_cumh
az), dpi = 2000)
ggsave("Survival plot - BRAF status (Survival probability in %).jpg", plot = print(BR
AF_pct), dpi = 2000)
```

KM - Fit by initial drug

```
fit_DRUG <- survfit(Surv(FUTIME, CENS) ~ DRUG, data = MM_no_duplicates)
print(fit_DRUG)

names(fit_DRUG$strata) <- gsub("DRUG=", "", names(fit_DRUG$strata)) # Removes the nam
e from top label

(KM_DRUG <- ggsurvplot(fit_DRUG, data = MM_no_duplicates,
                       xlab = "Time in months",
                       ylab = "Probability - Overall survival",
                       xlim = c(0, 48),
                       title = "Kaplan-Meier Curve for Metastatic melanoma",
                       legend.title = "1st line drug",
                       surv.median.line = "hv",                  # Add median line
                       size = 1,                                 # change line size
                       palette = "jco",                          # custom color palette
s
                       conf.int = FALSE,                         # Add confidence inter
val
                       pval = TRUE,                              # Add p-value
                       risk.table = "percentage",                # Add risk table (abso
lute number + %)
                       risk.table.y.text.col = TRUE,             # Colour risk table te
xt annotations
                       risk.table.y.text = FALSE,                # F - Shows bars inste
ad of names in text annotations
                       risk.table.col = "strata",                # Risk table color by
groups
                       risk.table.height = 0.25,                 # Useful to change whe
n you have multiple groups
                       ncensor.plot = FALSE,                     # Plot the number of c
ensored at time t
                       ncensor.plot.height = 0.25,
                       ggtheme = theme_bw()))                    # Change ggplot2 theme



# Save KM plot
ggsave("KM - Inital drug treatment.jpg", plot = print(KM_DRUG), dpi = 2000)
```

```
# Compare survival curves - Log-rank test
surv_diff_DRUG <- survdiff(Surv(FUTIME, CENS) ~ DRUG, data = MM_no_duplicates)
surv_diff_DRUG  # Not significant (p = 0.13)


######################################## Other plots ###################################
####################
# Cumulative events
(DRUG_event <- ggsurvplot(fit_DRUG, data = MM_no_duplicates,
                          xlab = "Time in months",
                          ylab = "Cumulative events",
                          legend.title = "1st line drug",
                          size = 1,                                  # change line size
                          linetype = "strata",
                          palette = "jco",                           # custom color pale
ttes
                          fun = "event",                             # Function - cumula
tive events
                          ggtheme = theme_bw()))                     # Change ggplot2 th
eme

# Cumulative hazard
(DRUG_cumhaz <- ggsurvplot(fit_DRUG, data = MM_no_duplicates,
                           xlab = "Time in months",
                           ylab = "Cumulative hazard",
                           legend.title = "1st line drug",
                           size = 1,                                  # change line size
                           linetype = "strata",
                           palette = "jco",                           # custom color pal
ettes
                           fun = "cumhaz",                            # Function - cumul
ative hazard
                           ggtheme = theme_bw()))                     # Change ggplot2 t
heme

# Survival probability (%)
(DRUG_pct <- ggsurvplot(fit_DRUG, data = MM_no_duplicates,
                        xlab = "Time in months",
                        ylab = "Survival probability in percentage",
                        legend.title = "1st line drug",
                        size = 1,                                  # change line size
                        linetype = "strata",
                        palette = "jco",                           # custom color palett
es
                        fun = "pct",                               # Function - % surv p
rob
                        ggtheme = theme_bw()))                     # Change ggplot2 them
e

# Save plots
ggsave("Survival plot - Drugs (cumulative events).jpg", plot = print(BRAF_event), dpi
= 2000)
ggsave("Survival plot - Drugs (cumulative hazards).jpg", plot = print(BRAF_cumhaz), d
pi = 2000)
ggsave("Survival plot - Drugs (Survival probability in %).jpg", plot = print(BRAF_pct
), dpi = 2000)
```

KM - Fit by initial TYPE

```
fit_TYPE <- survfit(Surv(FUTIME, CENS) ~ TYPE, data = MM_no_duplicates)
print(fit_TYPE)

names(fit_TYPE$strata) <- gsub("TYPE=", "", names(fit_TYPE$strata)) # Removes the nam
```

```
e from top label

# KM Plot - Survival curve
(KM_TYPE <- ggsurvplot(fit_TYPE, data = MM_no_duplicates,
                       xlab = "Time in months",
                       ylab = "Probability - Overall survival",
                       xlim = c(0, 48),
                       title = "Kaplan-Meier Curve for Metastatic melanoma",
                       legend.title = "Therapy type",
                       surv.median.line = "hv",                # Add median line
                       size = 1,                               # change line size
                       palette = "jco",                        # custom color palette
s
                       conf.int = FALSE,                       # Add confidence inter
val
                       pval = TRUE,                            # Add p-value
                       risk.table = "percentage",              # Add risk table (abso
lute number + %)
                       risk.table.y.text.col = TRUE,           # Colour risk table te
xt annotations
                       risk.table.y.text = FALSE,              # F - Shows bars inste
ad of names in text annotations
                       risk.table.col = "strata",              # Risk table color by
groups
                       risk.table.height = 0.25,               # Useful to change whe
n you have multiple groups
                       ncensor.plot = FALSE,                   # Plot the number of c
ensored at time t
                       ncensor.plot.height = 0.25,
                       ggtheme = theme_bw()))                  # Change ggplot2 theme



# Save KM plot
ggsave("KM - Type of treatment.jpg", plot = print(KM_TYPE), dpi = 2000)



# Compare survival curves - Log-rank test
surv_diff_TYPE <- survdiff(Surv(FUTIME, CENS) ~ TYPE, data = MM_no_duplicates)
surv_diff_TYPE # Not significant (p = 0.5)
```

KM - Fit by LDH

```
fit_LDH <- survfit(Surv(FUTIME, CENS) ~ LDH_group, data = MM_no_duplicates)
print(fit_LDH)

#          n    events   median   0.95LCL  0.95UCL
# Normal  273    175       12       11       15
# High     62     51        4        3        5

names(fit_LDH$strata) <- gsub("LDH_group=", "", names(fit_LDH$strata)) # Removes the
name from top label

# KM Plot - Survival curve
(KM_LDH <- ggsurvplot(fit_LDH, data = MM_no_duplicates,
                      xlab = "Time in months",
                      xlim = c(0, 48),
                      ylab = "Probability - Overall survival",
                      title = "Kaplan-Meier Curve for Metastatic melanoma",
                      legend.title = "LDH level",
                      surv.median.line = "hv",                # Add median line
                      size = 1,                               # change line size
                      palette = "jco",                        # custom color palettes
                      conf.int = TRUE,                        # Add confidence interv
al
                      pval = TRUE,                            # Add p-value
```

```
                      risk.table = "percentage",              # Add risk table (absol
ute number + %)
                      risk.table.y.text.col = TRUE,           # Colour risk table tex
t annotations
                      risk.table.y.text = FALSE,              # F - Shows bars instea
d of names in text annotations
                      risk.table.col = "strata",              # Risk table color by g
roups
                      risk.table.height = 0.25,               # Useful to change when
you have multiple groups
                      ncensor.plot = FALSE,                   # Plot the number of ce
nsored at time t
                      ncensor.plot.height = 0.25,
                      ggtheme = theme_bw()))                  # Change ggplot2 theme


# Save KM plot
ggsave("KM - LDH.jpg", plot = print(KM_LDH), dpi = 2000)

# Compare survival curves LDH_group - Log-rank test
surv_diff_LDH_group <- survdiff(Surv(FUTIME, CENS) ~ LDH_group, data = MM_no_duplicat
es)
surv_diff_LDH_group # Highly significant (p = 1e-13)


######################################### Other plots ###################################
###################
# Cumulative events
(LDH_event <- ggsurvplot(fit_LDH, data = MM_no_duplicates,
                         xlab = "Time in months",
                         ylab = "Cumulative events",
                         legend.title = "LDH level",
                         size = 1,                                 # change line size
                         linetype = "strata",
                         palette = "jco",                          # custom color palet
tes
                         fun = "event",                            # Function - cumulat
ive events
                         ggtheme = theme_bw()))                    # Change ggplot2 the
me

# Cumulative hazard
(LDH_cumhaz <- ggsurvplot(fit_LDH, data = MM_no_duplicates,
                          xlab = "Time in months",
                          ylab = "Cumulative hazard",
                          legend.title = "LDH level",
                          size = 1,                                 # change line size
                          linetype = "strata",
                          palette = "jco",                          # custom color pale
ttes
                          fun = "cumhaz",                           # Function - cumula
tive hazard
                          ggtheme = theme_bw()))                    # Change ggplot2 th
eme

# Survival probability (%)
(LDH_pct <- ggsurvplot(fit_LDH, data = MM_no_duplicates,
                       xlab = "Time in months",
                       ylab = "Survival probability in percentage",
                       legend.title = "LDH level",
                       size = 1,                                 # change line size
                       linetype = "strata",
                       palette = "jco",                          # custom color palette
s
```

```
                       fun = "pct",                              # Function - % surv pr
ob
                       ggtheme = theme_bw()))                    # Change ggplot2 theme



# Save plots
ggsave("Survival plot - LDH group (cumulative events).jpg", plot = print(LDH_event),
dpi = 2000)
ggsave("Survival plot - LDH group (cumulative hazards).jpg", plot = print(LDH_cumhaz)
, dpi = 2000)
ggsave("Survival plot - LDH group (Survival probability in %).jpg", plot = print(LDH_
pct), dpi = 2000)
```

Survival for PS Score

```
fit_PS <- survfit(Surv(FUTIME, CENS) ~ PS, data = MM_no_duplicates)
print(fit_PS)

names(fit_PS$strata) <- gsub("PS=", "", names(fit_PS$strata)) # Removes the name from
top label

# KM Plot - Survival curve
(KM_PS <- ggsurvplot(fit_PS, data = MM_no_duplicates,
                     xlab = "Time in months",
                     xlim = c(0, 48),
                     ylab = "Probability - Overall survival",
                     title = "Kaplan-Meier Curve for Metastatic melanoma",
                     legend.title = "ECOG PS Score",
                     surv.median.line = "hv",                  # Add median line
                     size = 1,                                 # change line size
                     palette = "jco",                          # custom color palettes
                     conf.int = TRUE,                          # Add confidence interv
al
                     pval = TRUE,                              # Add p-value
                     risk.table = "percentage",                # Add risk table (absol
ute number + %)
                     risk.table.y.text.col = TRUE,             # Colour risk table tex
t annotations
                     risk.table.y.text = FALSE,                # F - Shows bars instea
d of names in text annotations
                     risk.table.col = "strata",                # Risk table color by g
roups
                     risk.table.height = 0.25,                 # Useful to change when
you have multiple groups
                     ncensor.plot = FALSE,                     # Plot the number of ce
nsored at time t
                     ncensor.plot.height = 0.25,
                     ggtheme = theme_bw()))                    # Change ggplot2 theme

# Save KM plot
ggsave("KM - PS.jpg", plot = print(KM_PS), dpi = 2000)

surv_diff_PS <- survdiff(Surv(FUTIME, CENS) ~ PS, data = MM_no_duplicates)
surv_diff_PS # Significant difference (p = 4e-10)



######################################## Other plots ################################
###################
# Cumulative events
(PS_event <- ggsurvplot(fit_PS, data = MM_no_duplicates,
                        xlab = "Time in months",
                        ylab = "Cumulative events",
                        legend.title = "ECOG PS Score",
                        size = 1,                                  # change line size
                        linetype = "strata",
```

```
                        palette = "jco",                          # custom color palett
es
                        fun = "event",                            # Function - cumulati
ve events
                        ggtheme = theme_bw()))                    # Change ggplot2 them
e

# Cumulative hazard
(PS_cumhaz <- ggsurvplot(fit_PS, data = MM_no_duplicates,
                         xlab = "Time in months",
                         ylab = "Cumulative hazard",
                         legend.title = "ECOG PS Score",
                         size = 1,                                 # change line size
                         linetype = "strata",
                         palette = "jco",                          # custom color palet
tes
                         fun = "cumhaz",                           # Function - cumulat
ive hazard
                         ggtheme = theme_bw()))                    # Change ggplot2 the
me

# Survival probability (%)
(PS_pct <- ggsurvplot(fit_PS, data = MM_no_duplicates,
                      xlab = "Time in months",
                      ylab = "Survival probability in percentage",
                      legend.title = "ECOG PS Score",
                      size = 1,                                 # change line size
                      linetype = "strata",
                      palette = "jco",                          # custom color palettes
                      fun = "pct",                              # Function - % surv pro
b
                      ggtheme = theme_bw()))                    # Change ggplot2 theme



# Save plots
ggsave("Survival plot - PS (cumulative events).jpg", plot = print(PS_event), dpi = 20
00)
ggsave("Survival plot - PS (cumulative hazards).jpg", plot = print(PS_cumhaz), dpi =
2000)
ggsave("Survival plot - PS (Survival probability in %).jpg", plot = print(PS_pct), dp
i = 2000)
```

Survival for LDH + PS Score (6 groups)

```
fit_LDH_PS <- survfit(Surv(FUTIME, CENS) ~ PS + LDH_group, data = MM_no_duplicates)
print(fit_LDH_PS)

# KM Plot - Survival curve
(KM_LDH_PS <- ggsurvplot(fit_LDH_PS, data = MM_no_duplicates,
                         xlab = "Time in months",
                         ylab = "Probability - Overall survival",
                         xlim = c(0, 48),
                         title = "Kaplan-Meier Curve for Metastatic melanoma",
                         legend.title = "PS and LDH group",
                         surv.median.line = "hv",                 # Add median line
                         size = 1,                                # change line size
                         color = "PS",
                         linetype = "LDH_group",
                         pallete = "Darjeeling1",                 # custom color palet
tes
                         conf.int = FALSE,                        # Add confidence int
erval
                         pval = TRUE,                             # Add p-value
                         pval.coord = c(50, 0.9),
                         risk.table = "percentage",               # Add risk table (ab
solute number + %)
```

```
                        risk.table.y.text.col = FALSE,          # Colour risk table
text annotations
                        risk.table.y.text = TRUE,               # F - Shows bars ins
tead of names in text annotations
                        risk.table.height = 0.30,               # Useful to change w
hen you have multiple groups
                        ncensor.plot = FALSE,                   # Plot the number of
censored at time t
                        ncensor.plot.height = 0.25,
                        tables.theme = theme_cleantable(),
                        ggtheme = theme_bw()))

# Save KM plot
ggsave("KM - LDH with PS.jpg", plot = print(KM_LDH_PS), dpi = 2500)

surv_diff_LDH_PS <- survdiff(Surv(FUTIME, CENS) ~ LDH_group + PS, data = MM_no_duplic
ates)
surv_diff_LDH_PS # Significant difference (p = <2e-16)



######################################## Other plots ################################
####################
# Cumulative events
(LDH_PS_event <- ggsurvplot(fit_LDH_PS, data = MM_no_duplicates,
                            xlab = "Time in months",
                            ylab = "Cumulative events",
                            legend.title = "PS and LDH group",
                            size = 1,                                  # change line siz
e
                            linetype = "strata",
                            palette = "jco",                           # custom color pa
lettes
                            fun = "event",                             # Function - cumu
lative events
                            ggtheme = theme_bw()))                     # Change ggplot2
theme

# Cumulative hazard
(LDH_PS_cumhaz <- ggsurvplot(fit_LDH_PS, data = MM_no_duplicates,
                             xlab = "Time in months",
                             ylab = "Cumulative hazard",
                             legend.title = "PS and LDH group",
                             size = 1,                                  # change line si
ze
                             linetype = "strata",
                             palette = "jco",                           # custom color p
alettes
                             fun = "cumhaz",                            # Function - cum
ulative hazard
                             ggtheme = theme_bw()))                     # Change ggplot2
theme

# Survival probability (%)
(LDH_PS_pct <- ggsurvplot(fit_LDH_PS, data = MM_no_duplicates,
                          xlab = "Time in months",
                          ylab = "Survival probability in percentage",
                          legend.title = "PS and LDH group",
                          size = 1,                                 # change line size
                          linetype = "strata",
                          palette = "jco",                          # custom color pale
ttes
                          fun = "pct",                              # Function - % surv
prob
                          ggtheme = theme_bw()))                    # Change ggplot2 th
eme
```

```
# Save plots
ggsave("Survival plot - PS and LDH group (cumulative events).jpg", plot = print(LDH_PS_event), dpi = 2000)
ggsave("Survival plot - PS and LDH group (cumulative hazards).jpg", plot = print(LDH_PS_cumhaz), dpi = 2000)
ggsave("Survival plot - PS and LDH group (Survival probability in %).jpg", plot = print(LDH_PS_pct), dpi = 2000)
```

Survival for BMI_group

```
fit_BMI_group <- survfit(Surv(FUTIME, CENS) ~ BMI_group, data = MM_no_duplicates)
print(fit_BMI_group)

names(fit_BMI_group$strata) <- gsub("BMI_group=", "", names(fit_BMI_group$strata)) # Removes the name from top label

# KM Plot - Survival curve (BMI_group)
(KM_BMI_group <- ggsurvplot(fit_BMI_group, data = MM_no_duplicates,
                            xlab = "Time in months",
                            xlim = c(0, 48),
                            ylab = "Probability - Overall survival",
                            title = "Kaplan-Meier Curve for Metastatic melanoma",
                            legend.title = "BMI group",
                            surv.median.line = "hv",                # Add median line
                            size = 1,                               # change line size
                            palette = "jco",                        # custom color palettes
                            conf.int = FALSE,                       # Add confidence interval
                            pval = TRUE,                            # Add p-value
                            risk.table = "percentage",              # Add risk table (absolute number + %)
                            risk.table.y.text.col = TRUE,           # Colour risk table text annotations
                            risk.table.y.text = FALSE,              # F - Shows bars instead of names in text annotations
                            risk.table.col = "strata",              # Risk table color by groups
                            risk.table.height = 0.25,               # Useful to change when you have multiple groups
                            ncensor.plot = FALSE,                   # Plot the number of censored at time t
                            ncensor.plot.height = 0.25,
                            ggtheme = theme_bw()))                  # Change ggplot2 theme


# Save KM plot
ggsave("KM - BMI group.jpg", plot = print(KM_BMI_group), dpi = 2000)

surv_diff_BMI <- survdiff(Surv(FUTIME, CENS) ~ BMI_group, data = MM_no_duplicates)
surv_diff_BMI # Significant (p = 0.02)


######################################## Other plots ##################################################
# Cumulative events
(BMI_group_event <- ggsurvplot(fit_BMI_group, data = MM_no_duplicates,
                               xlab = "Time in months",
                               ylab = "Cumulative events",
                               legend.title = "BMI group",
                               size = 1,                                # change line size
```

```
                              linetype = "strata",
                              palette = "jco",                          # custom color
palettes
                              fun = "event",                            # Function - c
umulative events
                              ggtheme = theme_bw()))                    # Change ggplo
t2 theme

# Cumulative hazard
(BMI_group_cumhaz <- ggsurvplot(fit_BMI_group, data = MM_no_duplicates,
                               xlab = "Time in months",
                               ylab = "Cumulative hazard",
                               legend.title = "BMI group",
                               size = 1,                                 # change line
size
                               linetype = "strata",
                               palette = "jco",                          # custom colo
r palettes
                               fun = "cumhaz",                           # Function -
cumulative hazard
                               ggtheme = theme_bw()))                    # Change ggpl
ot2 theme

# Survival probability (%)
(BMI_group_pct <- ggsurvplot(fit_BMI_group, data = MM_no_duplicates,
                             xlab = "Time in months",
                             ylab = "Survival probability in percentage",
                             legend.title = "BMI group",
                             size = 1,                                 # change line si
ze
                             linetype = "strata",
                             palette = "jco",                          # custom color p
alettes
                             fun = "pct",                              # Function - % s
urv prob
                             ggtheme = theme_bw()))                    # Change ggplot2
theme

# Save plots
ggsave("Survival plot - BMI group (cumulative events).jpg", plot = print(BMI_group_ev
ent), dpi = 2000)
ggsave("Survival plot - BMI group (cumulative hazards).jpg", plot = print(BMI_group_c
umhaz), dpi = 2000)
ggsave("Survival plot - BMI group (Survival probability in %).jpg", plot = print(BMI_
group_pct), dpi = 2000)
```

Appendix 1.5 – Survival analysis (Cox models)

Subsets

```
# MM_no_duplicates - Only the first observation by patients
MM_no_duplicates <- Malignant_Melanoma_final %>%
  arrange(SafeHavenID, APPT_DATE) %>%
  group_by(SafeHavenID) %>%
  filter(!duplicated(SafeHavenID)) %>%
  # Change variable names for ggforest (HR)
  rename(SIMD = simd2012_sc_quintile,
         Gender = GENDER,
         Age = AGE,
         Mutation = MUTATION) %>%
  ungroup()

# Convert to data frame
MM_no_duplicates <- as.data.frame(MM_no_duplicates)
```

Cox Proportional-hazards model

Age

```
cox_AGE <- coxph(Surv(FUTIME, CENS) ~ Age, data = MM_no_duplicates)
summary(cox_AGE)
tidy(cox_AGE, exponentiate = TRUE)



# Check linearity using:
## Martingale residuals
ggcoxdiagnostics(cox_AGE, type = "martingale", linear.predictions = FALSE, ggtheme =
theme_bw())

## Deviance residuals
ggcoxdiagnostics(cox_AGE, type = "deviance", linear.predictions = FALSE, ggtheme = th
eme_bw())

# Test PH assumption:
cox_AGE_PH <- cox.zph(cox_AGE)
cox_AGE_PH                          # PH assumption MET - p-value > 0.05
ggcoxzph(cox_AGE_PH)                # PH assumption MET - Slope similar to 0 (flat
curve)

# Prediction
lp <- augment(cox_AGE, data = MM_no_duplicates)
risks <- augment(cox_AGE, data = MM_no_duplicates, type.predict = "risk")
expected <- augment(cox_AGE, data = MM_no_duplicates, type.predict = "expected")

# Martingale residuals - Test assumption that AGE has a linear relationship with the
outcome
ggcoxfunctional(Surv(FUTIME, CENS) ~ Age + log(Age) + sqrt(Age), data = MM_no_duplica
tes)
```

Gender

```
cox_Gender <- coxph(Surv(FUTIME, CENS) ~ Gender, data = MM_no_duplicates)
summary(cox_Gender)
tidy(cox_Gender, exponentiate = TRUE)

# Test PH assumption:
```

```
cox_Gender_PH <- cox.zph(cox_Gender)
cox_Gender_PH                              # PH assumption MET - p-value > 0.05
ggcoxzph(cox_Gender_PH)                    # PH assumption MET - Slope similar to 0 (fl
at curve)
```

SIMD

```
cox_SIMD <- coxph(Surv(FUTIME, CENS) ~ SIMD, data = MM_no_duplicates)
summary(cox_SIMD)
tidy(cox_SIMD, exponentiate = TRUE)

# Test PH assumption:
cox_SIMD_PH <- cox.zph(cox_SIMD)
cox_SIMD_PH                               # PH assumption MET - p-value > 0.05
ggcoxzph(cox_SIMD_PH)                     # PH assumption MET - Slope similar to 0 (flat
curve)
```

Mutation

```
cox_Mutation <- coxph(Surv(FUTIME, CENS) ~ Mutation, data = MM_no_duplicates)
summary(cox_Mutation)
tidy(cox_Mutation, exponentiate = TRUE)

# Test PH assumption:
cox_Mutation_PH <- cox.zph(cox_Mutation)
cox_Mutation_PH                             # PH assumption MET - p-value > 0.05
ggcoxzph(cox_Mutation_PH)                   # PH assumption MET - Slope similar to 0 (
flat curve)
```

BMI

```
cox_BMI <- coxph(Surv(FUTIME, CENS) ~ BMI, data = MM_no_duplicates)
summary(cox_BMI)
tidy(cox_BMI, exponentiate = TRUE)

# Test PH assumption:
cox_BMI_PH <- cox.zph(cox_BMI)
cox_BMI_PH                                # PH assumption MET - p-value > 0.05
ggcoxzph(cox_BMI_PH)                      # PH assumption MET - Slope similar to 0 (flat
curve)
```

PS

```
cox_PS <- coxph(Surv(FUTIME, CENS) ~ PS, data = MM_no_duplicates)
summary(cox_PS)
tidy(cox_PS, exponentiate = TRUE)

# Test PH assumption:
cox_PS_PH <- cox.zph(cox_PS)
cox_PS_PH                                # PH assumption MET - p-value > 0.05
ggcoxzph(cox_PS_PH)                      # PH assumption MET - Slope similar to 0 (flat c
urve)
```

LDH

```
cox_LDH <- coxph(Surv(FUTIME, CENS) ~ LDH, data = MM_no_duplicates)
summary(cox_LDH)
tidy(cox_LDH, exponentiate = TRUE)

# Test PH assumption:
cox_LDH_PH <- cox.zph(cox_LDH)
cox_LDH_PH                                # PH assumption NOT MET
ggcoxzph(cox_LDH_PH)                      # PH assumption NOT MET
```

Cox Model - Multiple univariable analysis

```
# ALL
cox_model <- coxph(Surv(FUTIME, CENS) ~ SIMD + Gender + Age + BMI + LDH + PS + Mutati
on,
```

```
                  data = MM_no_duplicates)
summary(cox_model)
tidy(cox_model, exponentiate = TRUE)
glance(cox_model)
extractAIC(cox_model)

# Check linearity using:
## Martingale residuals
ggcoxdiagnostics(cox_model, type = "martingale", ox.scale = "linear.predictions", ggt
heme = theme_bw())

## Deviance residuals
ggcoxdiagnostics(cox_model, type = "deviance", linear.predictions = FALSE, ggtheme =
theme_bw())

# Test PH assumption:
cox_final_PH <- cox.zph(cox_model)
cox_final_PH                          # PH assumption MET - p-value > 0.05
plot(cox_final_PH)                    # PH assumption MET - Slope similar to 0 (fla
t curve)

# Save ggforest plot
(HR <- ggforest(cox_model,
                refLabel = "Reference",
                noDigits = 2))
ggsave("Multivariable Cox model - Hazard ratio.jpg", plot = print(HR), dpi = 2000)

##############################################################################################
#####################################################
# Test interaction term: LDH_group*PS
cox_interaction <- coxph(Surv(FUTIME, CENS) ~ LDH + PS + LDH*PS, data = MM_no_duplica
tes)
summary(cox_interaction) # Not significant difference
```

BMI changing over time - Time-dependent covariate (TDC)

```
# Add BMI variable and BMI_group categorical variable
BMI <- Malignant_Melanoma_final %>%
  select(SafeHavenID, APPT_DATE, FUTIME, CENS, BMI, BMI_group) %>%
  group_by(SafeHavenID, APPT_DATE) %>%
  filter(!duplicated(APPT_DATE)) %>%
  filter(BMI_group!= "Underweight")

BMI_short <- BMI %>%
  arrange(SafeHavenID, APPT_DATE) %>%
  group_by(SafeHavenID, BMI) %>%
  filter(!duplicated(SafeHavenID)) %>%
  group_by(SafeHavenID) %>%
  mutate(diff = APPT_DATE - first(APPT_DATE))

BMI_overtime <- BMI_short %>%
  mutate(ORDER = order(SafeHavenID)) %>%  # create ORDER variable for BMI (to be spli
t afterwards)
  select(-APPT_DATE, -BMI_group, -BMI) %>%
  arrange(SafeHavenID, ORDER) %>%
  spread(ORDER, diff) %>%
  rename("time1" = "1", "time2" = "2", "time3" = "3",
         "time4" = "4", "time5" = "5", "time6" = "6",
         "time7" = "7", "time8" = "8", "time9" = "9")

# Set the range
BMI_tdc <- tmerge(data1 = BMI_overtime, data2 = BMI_overtime,
                  id = SafeHavenID, tstop = FUTIME, death = event(FUTIME, CENS))

# Incorporate BMI as a time-dependent variable based on the measurement date
```

```
BMI_tdc_2 <- tmerge(data1 = BMI_tdc, data2 = BMI_short,
                    id = SafeHavenID, BMI_tdc = tdc(diff, BMI))

BMI_tdc_2 <- BMI_tdc_2 %>% select(c(-2:-12))

# Cox model - BMI_tdc
BMI_tdc_model <- coxph(Surv(tstart, tstop, death) ~ BMI_tdc, data = BMI_tdc_2)
summary(BMI_tdc_model)

# Test PH assumption
Cox_BMI_PH <- cox.zph(BMI_tdc_model)
Cox_BMI_PH                                  # PH assumption MET - p-value > 0.05
ggcoxzph(Cox_BMI_PH)                        # PH assumption MET - Slope curve is fla
t (near 0)

ggforest(BMI_tdc_model)
```

Treatment SWITCHES over time - Time-dependent covariate (TDC)

```
Switches <- Malignant_Melanoma_final %>%
  select(SafeHavenID, APPT_DATE, DRUG, TYPE, REGIME, FUTIME, CENS) %>%
  mutate(CIT  = factor(TYPE),
         CHEMO  = as.factor(case_when(TYPE %in% "Chemotherapy" ~ 1,
                                      TRUE ~ 0)),
         IMMUNO = as.factor(case_when(TYPE %in% "Immunotherapy" ~ 1,
                                      TRUE ~ 0)),
         TARGET = as.factor(case_when(TYPE %in% "Targeted therapy" ~ 1,
                                      TRUE ~ 0))) %>%
  group_by(SafeHavenID) %>%
  filter(CIT %in% c("Chemotherapy", "Immunotherapy", "Targeted therapy")) %>%
  droplevels()

Switches$CIT <- relevel(Switches$CIT, ref = 3) # Ref = 3 is the third group (Targeted
therapy)
str(Switches$CIT) # Check that ref has changed + "Other" were removed

#### TDC TYPE OF THERAPY ####
Switches_short <- Switches %>%
  arrange(SafeHavenID, APPT_DATE) %>%
  group_by(SafeHavenID, TYPE) %>%
  filter(!duplicated(SafeHavenID)) %>%
  group_by(SafeHavenID) %>%
  filter(n() > 1) %>%
  mutate(diff = APPT_DATE - first(APPT_DATE))

Switches_overtime <- Switches_short %>%
  mutate(ORDER = order(SafeHavenID)) %>%  # create ORDER variable for TYPE (to be spl
itted afterwards)
  select(-APPT_DATE, -DRUG, -REGIME, -TYPE, -CIT, -CHEMO, -IMMUNO, -TARGET) %>%
  arrange(SafeHavenID, ORDER) %>%
  spread(ORDER, diff) %>%
  rename("time1" = "1", "time2" = "2", "time3" = "3")

# Step 1 - Set the range
switches_tdc <- tmerge(data1 = Switches_overtime, data2 = Switches_overtime,
                       id = SafeHavenID, tstop = FUTIME, death = event(FUTIME, CENS))

# Step 2 - Incorporate changes as a time-dependent variable based on the measurement
date
switches_tdc_2 <- tmerge(data1 = switches_tdc, data2 = Switches_short, id = SafeHaven
ID,
                         CIT_tdc  = tdc(diff, CIT),
                         chemo_tdc   = tdc(diff, CHEMO),
                         immuno_tdc  = tdc(diff, IMMUNO),
                         target_tdc  = tdc(diff, TARGET))
```

```
switches_tdc_2 <- switches_tdc_2 %>% select(c(-2:-6))

# Cox model - CIT_tdc
switches_tdc_model <- coxph(Surv(tstart, tstop, death) ~ CIT_tdc, data = switches_tdc
_2)
summary(switches_tdc_model)

# Test PH assumption
Cox_join_PH <- cox.zph(switches_tdc_model)
Cox_join_PH                                  # PH assumption MET - p-value > 0.05
ggcoxzph(Cox_join_PH)                        # PH assumption MET - Slope curve is fl
at (near 0)

(HR <- ggforest(switches_tdc_model))
```

Join Malignant_Melanoma_final to switch_tdc - Fit TDC + other variables

```
# Add standard Cox model covariates to switches_tdc subset
Joint <- Malignant_Melanoma_final %>%
  group_by(SafeHavenID) %>%
  filter(!duplicated(SafeHavenID)) %>%
  select(SafeHavenID, simd2012_sc_quintile, GENDER, AGE, BMI, PS, LDH, MUTATION) %>%
  right_join(switches_tdc_2, by = "SafeHavenID") %>%
  # Change variable names for ggforest (HR)
  rename(Therapy = CIT_tdc,
         SIMD = simd2012_sc_quintile,
         Gender = GENDER,
         Age = AGE) %>%
  ungroup()

# Cox model - Therapy_tdc
joint_model <- coxph(Surv(tstart, tstop, death) ~ Therapy + SIMD + Gender + Age + BMI
+ PS + LDH,
                     data = as.data.frame(Joint))
summary(joint_model)

# Test PH assumption
Cox_joint_PH <- cox.zph(joint_model)
Cox_joint_PH                                  # PH assumption MET - p-value > 0.05
ggcoxzph(Cox_joint_PH)                        # PH assumption MET - Slope curve is f
lat (near 0)

(HR <- ggforest(joint_model))
ggsave("Time-dependency adjusted Cox model - Hazard ratio.jpg", plot = print(HR), dpi
= 1000)
```

Select Cox model by AIC

```
# Create outcome variable
MM <- within(Malignant_Melanoma_final, {
  survival.vector    <- Surv(FUTIME, CENS)
})

# Create vectors for outcome and predictors
outcome    <- c("survival.vector")
predictors <- c("AGE", "GENDER", "simd2012_sc_quintile", "MUTATION", "PS", "LDH", "BM
I")
dataset    <- MM

# The lines belows should not need modification,
## Create list of models
list_of_models <- lapply(seq_along((predictors)), function(n) {

  left_hand_side <- outcome
```

```
  rigt_hand_side <- apply(X = combn(predictors, n), MARGIN = 2, paste, collapse = " +
")

  paste(left_hand_side, rigt_hand_side, sep = " ~ ")
})

## Convert to a vector
vector_of_models <- unlist(list_of_models)

## Fit coxph to all models
list_of_fits <- lapply(vector_of_models, function(x) {

  formula    <- as.formula(x)
  fit        <- coxph(formula, data = dataset)
  result_AIC <- extractAIC(fit)

  data.frame(num_predictors = result_AIC[1],
             AIC            = result_AIC[2],
             model          = x)
})

## Collapse to a data frame
result <- do.call(rbind, list_of_fits) %>%
  arrange((AIC))
print(result)

# BEST MODEL (Lowest AIC with fewer covariates)
best_cox_model <- coxph(Surv(FUTIME, CENS) ~ Mutation + BMI + PS + LDH, data = MM_no_
duplicates)
summary(best_cox_model)
tidy(best_cox_model, exponentiate = TRUE)
glance(best_cox_model)
```

Appendix 1.6 – Time-dependent Cox models

Analysis for time-dependent covariates

TIME is time before switching to another treatment type

```
# MM has max follow-up time (SWITCH_TIME) by each patient (total 346 patients)
Melanoma_tdc_type <- Malignant_Melanoma_final %>%
  group_by(SafeHavenID, TYPE) %>%
  filter(row_number() == 1) %>%
  group_by(SafeHavenID) %>%
  mutate(SWITCH_TIME = as.numeric(difftime(max(APPT_DATE), min(APPT_DATE)))) %>%
  group_by(SafeHavenID) %>%
  filter(!duplicated(SafeHavenID)) %>%
  ungroup()

time_dependent_type <- tmerge(data1 = Melanoma_tdc_type,
                              data2 = Melanoma_tdc_type,
                              id = SafeHavenID,
                              death = event(FUTIME, CENS),
                              SWITCH_TDC = tdc(SWITCH_TIME))

# Cox model with SWITCH_TDC (Time-dependent covariate)
y <- coxph(Surv(time = tstart, time2 = tstop, event = death) ~ SWITCH_TDC + cluster(S
afeHavenID), data = time_dependent_type)
summary(y) # p-value = Significant

# Test PH assumption
Cox_SWITCH_PH <- cox.zph(y)
Cox_SWITCH_PH                           # PH assumption MET - p-value > 0.05
ggcoxzph(Cox_SWITCH_PH)                 # PH assumption MET - Slope curve is flat (n
ear 0)
```

Analysis for time-dependent covariates

TIME is time before switching to another drug

```
colnames(Malignant_Melanoma_final)
summary(Malignant_Melanoma_final$FUTIME)

# MM has max follow-up time (SWITCH_TIME) by each patient (total 346 patients)
Melanoma_tdc_drug <- Malignant_Melanoma_final %>%
  select(SafeHavenID, APPT_DATE, DRUG, FUTIME, CENS, SWITCH) %>%
  group_by(SafeHavenID, DRUG) %>%
  filter(row_number() == 1) %>%
  group_by(SafeHavenID) %>%
  mutate(SWITCH_TIME = as.numeric(difftime(max(APPT_DATE), min(APPT_DATE)))) %>%
  group_by(SafeHavenID) %>%
  filter(!duplicated(SafeHavenID)) %>%
  ungroup()

time_dependent_drug <- tmerge(data1 = Melanoma_tdc_drug,
                              data2 = Melanoma_tdc_drug,
                              id = SafeHavenID,
                              death = event(FUTIME, CENS),
                              SWITCH_TDC = tdc(SWITCH_TIME))

# Cox model with SWITCH_TDC (Time-dependent covariate)
x <- coxph(Surv(time = tstart, time2 = tstop, event = death) ~ SWITCH_TDC, data = tim
e_dependent_drug)
summary(x) # p-value = Significant
```

```
# Test PH assumption
Cox_SWITCH_PH <- cox.zph(x)
Cox_SWITCH_PH                              # PH assumption MET - p-value > 0.05
ggcoxzph(Cox_SWITCH_PH)                    # PH assumption MET - Slope curve is flat (0
)
```

Time-to-event with multiple events

```
cgd0 <- Melanoma_switch_drug %>%
  select(SafeHavenID, APPT_DATE, DRUG, FUTIME, CENS, ORDER) %>%
  arrange(SafeHavenID, APPT_DATE) %>%
  group_by(SafeHavenID, DRUG) %>%
  filter(!duplicated(SafeHavenID)) %>%
  group_by(SafeHavenID) %>%
  mutate(diff = APPT_DATE - lag(APPT_DATE, default = first(APPT_DATE))) %>%
  select(-APPT_DATE, -DRUG) %>%
  group_by(SafeHavenID) %>%
  arrange(SafeHavenID, ORDER) %>%
  spread(ORDER, diff) %>%
  rename("time1" = "1",
         "time2" = "2",
         "time3" = "3",
         "time4" = "4",
         "time5" = "5")

dim(cgd0)

newcgd <- tmerge(data1 = cgd0, data2 = cgd0,
                 id = SafeHavenID, tstop = FUTIME, death = event(FUTIME, CENS),
                 Switch = event(time1), Switch = event(time2),
                 Switch = event(time3), Switch = event(time4),
                 Switch = event(time5))

newcgd_start_stop <- newcgd %>%
  select(c(-4:-8))

# Cox model - Multiple switch events
multiple_switch_model <- coxph(Surv(tstart, tstop, death) ~ Switch, data = newcgd_sta
rt_stop)
summary(multiple_switch_model)

# Test PH assumption
Cox_SWITCH_PH <- cox.zph(multiple_switch_model)
Cox_SWITCH_PH                                  # PH assumption MET - p-value > 0.05
ggcoxzph(Cox_SWITCH_PH)                        # PH assumption MET - Slope curve is
flat (near 0)
```

BMI Time-dependency

```
# Add BMI variable and BMI_group categorical variable
BMI <- Malignant_Melanoma_final %>%
  select(SafeHavenID, APPT_DATE, FUTIME, CENS, BMI, BMI_group) %>%
  group_by(SafeHavenID, APPT_DATE) %>%
  filter(!duplicated(APPT_DATE)) %>%
  filter(!is.na(BMI)) %>%
  filter(BMI_group!= "Underweight")

BMI_short <- BMI %>%
  arrange(SafeHavenID, APPT_DATE) %>%
  group_by(SafeHavenID, BMI) %>%
  filter(!duplicated(SafeHavenID)) %>%
  group_by(SafeHavenID) %>%
  mutate(diff = APPT_DATE - lag(APPT_DATE, default = first(APPT_DATE)))

BMI_overtime <- BMI_short %>%
```

```
  mutate(ORDER = order(SafeHavenID)) %>%  # create ORDER variable for BMI (to be spli
tted afterwards)
  select(-APPT_DATE, -BMI_group, -BMI) %>%
  arrange(SafeHavenID, ORDER) %>%
  spread(ORDER, diff) %>%
  rename("time1" = "1", "time2" = "2", "time3" = "3",
         "time4" = "4", "time5" = "5", "time6" = "6",
         "time7" = "7", "time8" = "8", "time9" = "9")

# Set the range
BMI_tdc <- tmerge(data1 = BMI_overtime, data2 = BMI_overtime,
                  id = SafeHavenID, tstop = FUTIME, death = event(FUTIME, CENS))

# Incorporate BMI as a time-dependent variable based on the measurement date
BMI_tdc_2 <- tmerge(data1 = BMI_tdc, data2 = BMI_short,
                    id = SafeHavenID, BMI_tdc = tdc(diff, BMI))

BMI_tdc_2 <- BMI_tdc_2 %>% select(c(-4:-12))

# Cox model - BMI_tdc
BMI_tdc_model <- coxph(Surv(tstart, tstop, death) ~ BMI_tdc, data = BMI_tdc_2)
summary(BMI_tdc_model)

# Test PH assumption
Cox_BMI_PH <- cox.zph(BMI_tdc_model)
Cox_BMI_PH                                    # PH assumption MET - p-value > 0.05
ggcoxzph(Cox_BMI_PH)                          # PH assumption MET - Slope curve is fla
t (near 0)
```

Appendix 1.7 – Time-dependency adjusted Cox model for BMI

Subsets

```
# MM_no_duplicates - Only the first observation by patients
MM_no_duplicates <- Malignant_Melanoma_final %>%
  arrange(SafeHavenID, APPT_DATE) %>%
  group_by(SafeHavenID) %>%
  filter(!duplicated(SafeHavenID)) %>%
  # Change variable names for ggforest (HR)
  rename(SIMD = simd2012_sc_quintile,
         Gender = GENDER,
         Age = AGE,
         Mutation = MUTATION) %>%
  ungroup()

# Get final cohort - Excluding criteria
MM_no_duplicates_BMI <- MM_no_duplicates %>%
  group_by(SafeHavenID) %>%
  # remove "Underweight"" patients
  filter(!BMI_group %in% "Underweight") %>%
  # Exclude adjuvant treatment patients (8 patients)
  filter(TYPE!= "Other") %>%
  # remove patients with only one obs (follow-up time of 0)
  filter(FUTIME!= 0) %>%
  # remove NA
  filter(!is.na(BMI)) %>%
  droplevels() %>%
  ungroup()

MM_no_duplicates_BMI <- as.data.frame(MM_no_duplicates_BMI)
```

Check BMI distribution

```
MM_incomplete_BMI <- MM_no_duplicates %>%
  select(SafeHavenID, APPT_DATE, TYPE, FUTIME, BMI, BMI_group) %>%
  group_by(SafeHavenID) %>%
  filter(!duplicated(SafeHavenID)) %>%
  filter(is.na(BMI)) %>%
  droplevels()

# Check type of therapy at baseline - Only TT patients
table(MM_incomplete_BMI$TYPE)

BMI_NA <- MM_incomplete_BMI$SafeHavenID

MM_BMI_NA <- Malignant_Melanoma_final %>%
  select(SafeHavenID, APPT_DATE, TYPE, FUTIME, BMI, BMI_group) %>%
  group_by(SafeHavenID) %>%
  filter(SafeHavenID %in% BMI_NA)
```

Descriptive statistics - MM_no_duplicates

```
# Number of patients
n_patients <- n_distinct(MM_no_duplicates_BMI$SafeHavenID) # 259 patients

# BMI
hist(MM_no_duplicates_BMI$BMI)

# FUTIME
```

```
summary(MM_no_duplicates_BMI$FUTIME)

# TYPE
MM_no_duplicates_BMI %>%
  group_by(TYPE) %>%
  summarise(count = n(),
            percentage = count*100/n_patients)

# BMI_group
MM_no_duplicates_BMI %>%
  group_by(BMI_group) %>%
  summarise(count = n(),
            percentage = count*100/n_patients)

# CENS
MM_no_duplicates_BMI %>%
  group_by(CENS) %>%
  summarise(count = n(),
            percentage = count*100/n_patients)
```

Survival analysis

```
fit_all <- survfit(Surv(FUTIME, CENS) ~ 1, data = MM_no_duplicates_BMI)
print(fit_all)

# KM Plot - Survival curve
(KM_all <- ggsurvplot(fit_all, data = MM_no_duplicates_BMI,
                      xlab = "Time in months",
                      ylab = "Probability - Overall survival",
                      xlim = c(0, 48),
                      title = "Kaplan-Meier Curve for Metastatic melanoma",
                      legend.title = "All patients",
                      surv.median.line = "hv",                # Add median line
                      size = 1,                               # change line size
                      palette = "jco",                        # custom color palettes
                      conf.int = TRUE,                        # Add confidence interv
al
                      pval = TRUE,                            # Add p-value
                      risk.table = "absolute",                # Add risk table (absol
ute number + %)
                      risk.table.y.text.col = TRUE,           # Colour risk table tex
t annotations
                      risk.table.y.text = FALSE,              # F - Shows bars instea
d of names in text annotations
                      risk.table.col = "strata",              # Risk table color by g
roups
                      risk.table.height = 0.25,               # Useful to change when
you have multiple groups
                      ggtheme = theme_bw()))                  # Change ggplot2 theme

ggsave("KM - BMI patients (266).jpg", plot = print(KM_all))
```

Survival for BMI_group

```
fit_BMI_group <- survfit(Surv(FUTIME, CENS) ~ BMI_group, data = MM_no_duplicates_BMI)
print(fit_BMI_group)

names(fit_BMI_group$strata) <- gsub("BMI_group=", "", names(fit_BMI_group$strata)) #
Removes the name from top label

# KM Plot - Survival curve (BMI_group)
(KM_BMI_group <- ggsurvplot(fit_BMI_group, data = MM_no_duplicates,
                            xlab = "Time in months",
                            xlim = c(0, 48),
                            ylab = "Probability - Overall survival",
                            title = "Kaplan-Meier Curve for Metastatic melanoma",
```

```
                           legend.title = "BMI Category",
                           surv.median.line = "hv",                # Add median line
                           size = 1,                               # change line siz
e
                           palette = "jco",                        # custom color pa
lettes
                           conf.int = FALSE,                       # Add confidence
interval
                           pval = TRUE,                            # Add p-value
                           risk.table = "absolute",                # Add risk table
(absolute number + %)
                           risk.table.y.text.col = TRUE,           # Colour risk tab
le text annotations
                           risk.table.y.text = FALSE,              # F - Shows bars
instead of names in text annotations
                           risk.table.col = "strata",              # Risk table colo
r by groups
                           risk.table.height = 0.25,               # Useful to chang
e when you have multiple groups
                           ncensor.plot = FALSE,                   # Plot the number
of censored at time t
                           ncensor.plot.height = 0.25,
                           ggtheme = theme_bw()))                  # Change ggplot2
theme



# Save KM plot
ggsave("KM - BMI groups.jpg", plot = print(KM_BMI_group), dpi = 2000)

surv_diff_BMI <- survdiff(Surv(FUTIME, CENS) ~ BMI_group, data = MM_no_duplicates_BMI
)
surv_diff_BMI # Significant (p = 0.02)
```

Cox Proportional-hazards model - BMI (STANDARD)

```
cox_BMI <- coxph(Surv(FUTIME, CENS) ~ BMI, data = MM_no_duplicates_BMI)
summary(cox_BMI)
tidy(cox_BMI, exponentiate = TRUE)

# Test PH assumption:
cox_BMI_PH <- cox.zph(cox_BMI)
cox_BMI_PH                          # PH assumption MET - p-value > 0.05
ggcoxzph(cox_BMI_PH)                # PH assumption MET - Slope similar to 0 (flat
curve)
```

Cox Model - Multiple univariable analysis

```
##### ALL ##########################################################################
#####################################################
cox_model <- coxph(Surv(FUTIME, CENS) ~ BMI + TYPE + SIMD + Gender + Age + LDH + PS +
Mutation,
                   data = MM_no_duplicates_BMI)
summary(cox_model)
tidy(cox_model, exponentiate = TRUE)
glance(cox_model)
extractAIC(cox_model)

# Check linearity using:
## Martingale residuals
ggcoxdiagnostics(cox_model, type = "martingale", ox.scale = "linear.predictions", ggt
heme = theme_bw())

## Deviance residuals
ggcoxdiagnostics(cox_model, type = "deviance", linear.predictions = FALSE, ggtheme =
theme_bw())
```

```
# Test PH assumption:
cox_final_PH <- cox.zph(cox_model)
cox_final_PH                              # PH assumption MET- p-value > 0.05
plot(cox_final_PH)                        # PH assumption MET - Slope similar to 0 (fla
t curve)
ggforest(cox_model)

# Save ggforest plot
(HR <- ggforest(cox_model,
                refLabel = "Reference",
                noDigits = 2))
ggsave("BOPA - Multivariable Cox model - Hazard ratio.jpg", plot = print(HR), dpi = 2
000)

##############################################################################################
#####################################################
# Test interaction term: LDH_group*PS
cox_interaction <- coxph(Surv(FUTIME, CENS) ~ LDH + PS + LDH*PS, data = MM_no_duplica
tes)
summary(cox_interaction) # Not significant difference
```

BMI changing over time - Time-dependent covariate (TDC)

```
cohort_BMI <- MM_no_duplicates_BMI$SafeHavenID

# Add BMI variable and BMI_group categorical variable
BMI <- Malignant_Melanoma_final %>%
  select(SafeHavenID, APPT_DATE, FUTIME, CENS, BMI, BMI_group) %>%
  group_by(SafeHavenID, APPT_DATE) %>%
  filter(SafeHavenID %in% cohort_BMI) %>%
  ungroup()

BMI_short <- BMI %>%
  arrange(SafeHavenID, APPT_DATE) %>%
  group_by(SafeHavenID, BMI) %>%
  filter(!duplicated(SafeHavenID)) %>%
  group_by(SafeHavenID) %>%
  mutate(diff = APPT_DATE - first(APPT_DATE)) %>%
  mutate(diff = round(diff/30.417, digit = 1)) %>%
  ungroup()

BMI_overtime <- BMI_short %>%
  group_by(SafeHavenID) %>%
  mutate(ORDER = order(SafeHavenID)) %>%  # create ORDER variable for BMI (to be spli
t afterwards)
  select(-APPT_DATE, -BMI_group, -BMI) %>%
  arrange(SafeHavenID, ORDER) %>%
  spread(ORDER, diff) %>%
  rename("time1" = "1", "time2" = "2", "time3" = "3",
         "time4" = "4", "time5" = "5", "time6" = "6",
         "time7" = "7", "time8" = "8", "time9" = "9") %>%
  ungroup()

# Set the range
BMI_tdc <- tmerge(data1 = BMI_overtime, data2 = BMI_overtime,
                  id = SafeHavenID, tstop = FUTIME, death = event(FUTIME, CENS))

# Incorporate BMI as a time-dependent variable based on the measurement date
BMI_tdc_2 <- tmerge(data1 = BMI_tdc, data2 = BMI_short,
                    id = SafeHavenID, BMI_tdc = tdc(diff, BMI))

BMI_tdc_2 <- BMI_tdc_2 %>% select(c(-2:-12))

# Cox model - BMI_tdc
BMI_tdc_model <- coxph(Surv(tstart, tstop, death) ~ BMI_tdc, data = BMI_tdc_2)
```

```
summary(BMI_tdc_model)

# Test PH assumption
Cox_BMI_PH <- cox.zph(BMI_tdc_model)
Cox_BMI_PH                                    # PH assumption MET - p-value > 0.05
ggcoxzph(Cox_BMI_PH)                          # PH assumption MET - Slope curve is fla
t (near 0)

ggforest(BMI_tdc_model)
```

Join Malignant_Melanoma_final to switch_tdc - Fit BMI_TDC + other variables

```
# Add standard Cox model covariates to switches_tdc subset
Joint <- Malignant_Melanoma_final %>%
  group_by(SafeHavenID) %>%
  filter(!duplicated(SafeHavenID)) %>%
  select(SafeHavenID, simd2012_sc_quintile, TYPE, GENDER, AGE, BMI, PS, LDH_group, MU
TATION) %>%
  right_join(BMI_tdc_2, by = "SafeHavenID") %>%
  # Change variable names for ggforest (HR)
  rename(Therapy = TYPE,
         SIMD = simd2012_sc_quintile,
         Gender = GENDER,
         Age = AGE,
         LDH = LDH_group) %>%
  droplevels() %>%
  ungroup()

# Cox model - BMI_tdc
joint_model <- coxph(Surv(tstart, tstop, death) ~ BMI + Therapy + SIMD + Gender + Age
+ PS + LDH,
                     data = as.data.frame(Joint))
summary(joint_model)

# Test PH assumption
Cox_joint_PH <- cox.zph(joint_model)
Cox_joint_PH                                    # PH assumption MET - p-value > 0.05
ggcoxzph(Cox_joint_PH)                          # PH assumption MET - Slope curve is f
lat (near 0)

(HR <- ggforest(joint_model))
ggsave("BOPA - Time-dependency adjusted Cox model - Hazard ratio.jpg", plot = print(H
R), dpi = 1000)
```

Appendix 1.8 – Multi-state Markov model

```
states <- c("Immuno", "Target", "Chemo",
            "IM + CH", "IM + TT",
            "TT + CH", "TT + IM",
            "CH + IM", "CH + TT",
            "IM + CH + TT", "IM + TT + CH",
            "TT + CH + IM", "TT + IM + CH",
            "CH + IM + TT", "CH + TT + IM",
            "Death", "Censoring")

tmat <- matrix(0L, 17, 17,
               dimnames = list(states, states))

# Immunotherapy pathways
tmat[1,4] <- tmat[1,5] <- tmat[1,16] <- tmat[1,17] <- 1
tmat[4,10] <- tmat[4,16] <- tmat[4,17] <- 1
tmat[5,11] <- tmat[5,16] <- tmat[5,17] <- 1
tmat[10,16] <- tmat[11,16] <- tmat[11,17] <- 1
# Targeted therapy pathways
tmat[2,6] <- tmat[2,7] <- tmat[2,16] <- tmat[2,17] <- 1
tmat[6,12] <- tmat[6,16] <- tmat[6,17] <- 1
tmat[7,13] <- tmat[7,16] <- tmat[7,17] <- 1
tmat[12,16] <- tmat[13,16] <- tmat[13,17] <- 1
# Chemotherapy pathways
tmat[3,8] <- tmat[3,9] <- tmat[3,16] <- tmat[3,17] <- 1
tmat[8,14] <- tmat[8,16] <- tmat[8,17] <- 1
tmat[9,15] <- tmat[9,16] <- tmat[9,17] <- 1
tmat[14,16] <- tmat[15,16] <- tmat[15,17] <- 1

# Check
tmat

# Create figure for the model
statefig(c(3, 6, 6, 2), tmat,
         bcol = "blue")

# Check states table
statetable.msm(STATE, SafeHavenID, data = MM_4)

# Transition matrix
tmat <- matrix(0L, 15, 15,
               dimnames = list(from = 1:15, to = 1:15))

# Immunotherapy pathways
tmat[1,4] <- tmat[1,5] <- tmat[1,14] <- tmat[1,15] <- 1
tmat[4,14] <- tmat[4,15] <- 1
tmat[5,14] <- tmat[5,15] <- 1
# Targeted therapy pathways
tmat[2,6] <- tmat[2,7] <- tmat[2,14] <- tmat[2,15] <-1
tmat[6,10] <- tmat[6,14] <- tmat[6,15] <- 1
tmat[7,11] <- tmat[7,14] <- tmat[7,15] <- 1
tmat[10,14] <- tmat[10,15] <- 1
tmat[11,14] <- tmat[11,15] <- 1
# Chemotherapy pathways
tmat[3,8] <- tmat[3,9] <- tmat[3,14] <- tmat[3,15] <- 1
tmat[8,12] <- tmat[8,14] <- tmat[8,15] <- 1
tmat[9,13] <- tmat[9,14] <- tmat[9,15] <- 1
```

```
tmat[12,14] <- tmat[12,14] <- tmat[12,15] <- 1
tmat[13,14] <- tmat[13,15] <- 1

# Check
tmat

# Crude estimate of transition rates
qmat1 <- crudeinits.msm(STATE ~ DIFF, subject = SafeHavenID, data = MM_4, qmatrix = t
mat)

# Fit the model
model <- msm(STATE ~ DIFF, subject = SafeHavenID, data = MM_4,
             qmatrix = qmat1, exacttimes = TRUE)

# Show results from the model
model
## Mean time for each state before moving
sojourn.msm(model)
## Plots parametric survival curves stratified by state
plot(model)
## Create transition probability matrix for a time interval (t)
pmatrix.msm(model, 12)    # 1 year
pmatrix.msm(model, 12*2)  # 2 years
pmatrix.msm(model, 12*3)  # 3 years
pmatrix.msm(model, 12*4)  # 4 years
pmatrix.msm(model, 12*5)  # 5 years

options(digits = 3)
prevalence.msm(model, times = seq(0, 54, 2))
plot.prevalence.msm(model, mintime = 0, maxtime = 54,
                    xlab = "Time in months")

# First - Save the transition intensity matrix from the first model
qmat2 <- qmatrix.msm(model)$estimate

# Fit the model
model_final <- msm(STATE ~ DIFF, subject = SafeHavenID, data = MM_4,
                   qmatrix = qmat1, exacttimes = TRUE,
                   covariates = ~ LDH_group)

# Print model
model_final

# Extract separate intensity matrices
qmatrix.msm(model_final, covariates = list(LDH_group = "Normal"))
qmatrix.msm(model_final, covariates = list(LDH_group = "High"))
# Categorical variables -> See the result for the baseline category
qmatrix.msm(model_final, covariates = 0)

# HR and CI for allowed transitions
hazard.msm(model_final)

states <- c("Immuno", "Target",
            "IM + TT", "TT + IM",
            "Death")

tmat <- matrix(0L, 5, 5,
               dimnames = list(states, states))

# Immunotherapy pathways
tmat[1,3] <- tmat[2,4] <- 1
tmat[1,5] <- tmat[2,5] <- tmat[3,5] <- tmat[4,5] <- 1

# Check
```

```
tmat

# Create figure for the model
statefig(c(2, 2, 1), tmat,
         bcol = "blue")

# Check states table
statetable.msm(STATE, SafeHavenID, data = MM_4)

# Crude estimate of transition rates
qmat1 <- crudeinits.msm(STATE ~ DIFF, subject = SafeHavenID, data = MM_4, qmatrix = t
mat)

# Fit the model
model <- msm(STATE ~ DIFF, subject = SafeHavenID, data = MM_4,
             qmatrix = qmat1, exacttimes = TRUE)

# Show results from the model
model
## Mean time for each state before moving
sojourn.msm(model)
## Plots parametric survival curves stratified by state
plot(model)
## Create transition probability matrix for a time interval (t)
pmatrix.msm(model, 12)  # 1 year
pmatrix.msm(model, 12*2)  # 2 years
pmatrix.msm(model, 12*3)  # 3 years
pmatrix.msm(model, 12*4)  # 4 years
pmatrix.msm(model, 12*5)  # 5 years

# Fit the model
model_LDH <- msm(STATE ~ DIFF, subject = SafeHavenID, data = MM_4,
                 qmatrix = qmat1, exacttimes = TRUE,
                 covariates = ~ LDH)

# Print model
model_LDH

# Extract separate intensity matrices
qmatrix.msm(model_LDH)

# HR and CI for allowed transitions
hazard.msm(model_LDH)

# Fit the model
model_PS <- msm(STATE ~ DIFF, subject = SafeHavenID, data = MM_4,
                qmatrix = qmat1, exacttimes = TRUE,
                covariates = ~ PS)

# Print model
model_PS

# Extract separate intensity matrices
qmatrix.msm(model_PS, covariates = list(PS = "2+"))
# Categorical variables -> See the result for the baseline category
qmatrix.msm(model_PS, covariates = 0)

# HR and CI for allowed transitions
hazard.msm(model_PS)
```

BRAF

```
# Fit the model
model_BRAF <- msm(STATE ~ DIFF, subject = SafeHavenID, data = MM_4,
                  qmatrix = qmat1, exacttimes = TRUE,
```

```
                  covariates = ~ MUTATION)

# Print model
model_BRAF

# Extract separate intensity matrices
qmatrix.msm(model_BRAF)
# HR and CI for allowed transitions
hazard.msm(model_BRAF)

# Fit the model
model_BMI <- msm(STATE ~ DIFF, subject = SafeHavenID, data = MM_4,
                 qmatrix = qmat1, exacttimes = TRUE,
                 covariates = ~ BMI)

# Print model
model_BMI

# Extract separate intensity matrices
qmatrix.msm(model_BMI)
# HR and CI for allowed transitions
hazard.msm(model_BMI)

# Calculate observed and expected numbers and percentage until 1 year (30 day interva
l)
x <- prevalence.msm(model, times = seq(0, 54, 1))

# Plot observed vs expected values
plot.prevalence.msm(model, mintime = 0, maxtime = 54) # Number of deaths is underesti
mated (5 year period)
```

Appendix 1.9 – Health economic evaluation for advanced melanoma patients with progressive disease

```
states <- c("Immuno", "Target",
            "Progression",
            "Death")

tmat <- matrix(0L, 4, 4,
               dimnames = list(states, states))

# Immunotherapy pathways
tmat[1,3] <- tmat[1,4] <- 1
# Targeted therapy pathways
tmat[2,3] <- tmat[2,4] <- 1
# PD pathways
tmat[3,4] <- 1

# Check
tmat

# Create figure for the model
statefig(c(2, 1, 1), tmat,
         bcol = "blue")

DOD <- Malignant_Melanoma_final %>%
  select(SafeHavenID, DATE_OF_DEATH) %>%
  group_by(SafeHavenID) %>%
  filter(!is.na(DATE_OF_DEATH)) %>%
  filter(!duplicated(SafeHavenID)) %>%
  rename("DATE" = "DATE_OF_DEATH") %>%
  ungroup()

MM <- Malignant_Melanoma_final %>%
  select(SafeHavenID, APPT_DATE, DATE_OF_DEATH, TYPE, MUTATION, DRUG, ORDER, 34:42, 4
5:51) %>%
  rename("DATE" = "APPT_DATE")

# Remove patients where TYPE is "Chemotherapy" (Adjuvant treatments)
TYPE_Chemo <- MM %>%
  group_by(SafeHavenID) %>%
  filter(TYPE == "Chemotherapy") %>%
  filter(!duplicated(SafeHavenID)) %>%
  ungroup()

ID_TYPE_Chemo <- TYPE_Chemo$SafeHavenID # 74 patients

# Remove patients where TYPE is "Other" (Adjuvant treatments)
TYPE_Other <- MM %>%
  group_by(SafeHavenID) %>%
  filter(TYPE == "Other") %>%
  filter(!duplicated(SafeHavenID)) %>%
  ungroup()
```

```
ID_TYPE_Other <- TYPE_Other$SafeHavenID # 15 patients

# Patients with ORDER 3 or higher
ORDER_3 <- MM %>%
  select(SafeHavenID, DATE, ORDER) %>%
  group_by(SafeHavenID) %>%
  filter(ORDER %in% c(3, 4, 5)) %>%
  filter(!duplicated(SafeHavenID))

ID_ORDER_3 <- ORDER_3$SafeHavenID # 36 patients

# Remove patients: Chemo; Other; Order 3 or higher
MM <- MM %>%
  # Remove patients
  filter(!SafeHavenID %in% c(ID_TYPE_Chemo, ID_TYPE_Other, ID_ORDER_3)) %>%
  droplevels()

# Check total number of patients
n_distinct(MM$SafeHavenID) # 256 patients

# Remove duplicates and check order
MM_1 <- MM %>%
  select(SafeHavenID, DATE, TYPE, DRUG, MUTATION, CENS, ORDER) %>%
  group_by(SafeHavenID) %>%
  filter(!duplicated(DRUG))

# Line of treatment table
library(gmodels)
CrossTable(MM_1$DRUG, MM_1$ORDER, dnn = c("Drug", "Order"),
           prop.t = FALSE, prop.chisq = FALSE, prop.c = FALSE) # Percentage by row

# Create PD covariate
STATES <- MM_1 %>%
  mutate(PROGRESSION = case_when(# Changes from TT to IM
                                 lag(DRUG == "DAB") & DRUG %in% "IPI"        & ORDER =
= 2 ~ 1,
                                 lag(DRUG == "DAB") & DRUG %in% "NIVO"       & ORDER =
= 2 ~ 1,
                                 lag(DRUG == "DAB") & DRUG %in% "PEM"        & ORDER =
= 2 ~ 1,
                                 lag(DRUG == "DAB") & DRUG %in% "NIVOIPI"    & ORDER =
= 2 ~ 1,
                                 lag(DRUG == "DABTRA") & DRUG %in% "IPI"     & ORDER =
= 2 ~ 1,
                                 lag(DRUG == "DABTRA") & DRUG %in% "NIVO"    & ORDER =
= 2 ~ 1,
                                 lag(DRUG == "DABTRA") & DRUG %in% "PEM"     & ORDER =
= 2 ~ 1,
                                 lag(DRUG == "DABTRA") & DRUG %in% "NIVOIPI" & ORDER =
= 2 ~ 1,
                                 lag(DRUG == "VEM") & DRUG %in% "IPI"        & ORDER =
= 2 ~ 1,
                                 lag(DRUG == "VEM") & DRUG %in% "NIVO"       & ORDER =
= 2 ~ 1,
                                 lag(DRUG == "VEM") & DRUG %in% "PEM"        & ORDER =
= 2 ~ 1,
                                 lag(DRUG == "VEM") & DRUG %in% "NIVOIPI"    & ORDER =
= 2 ~ 1,
                                 # Changes from IM to TT
                                 lag(DRUG == "IPI") & DRUG %in% "DAB"        & ORDER =
= 2 ~ 1,
                                 lag(DRUG == "IPI") & DRUG %in% "DABTRA"     & ORDER =
= 2 ~ 1,
                                 lag(DRUG == "IPI") & DRUG %in% "VEM"        & ORDER =
= 2 ~ 1,
```

```
                                lag(DRUG == "NIVO") & DRUG %in% "DAB"       & ORDER =
= 2 ~ 1,
                                lag(DRUG == "NIVO") & DRUG %in% "DABTRA"    & ORDER =
= 2 ~ 1,
                                lag(DRUG == "NIVO") & DRUG %in% "VEM"       & ORDER =
= 2 ~ 1,
                                lag(DRUG == "NIVOIPI") & DRUG %in% "DAB"    & ORDER =
= 2 ~ 1,
                                lag(DRUG == "NIVOIPI") & DRUG %in% "DABTRA" & ORDER =
= 2 ~ 1,
                                lag(DRUG == "NIVOIPI") & DRUG %in% "VEM"    & ORDER =
= 2 ~ 1,
                                lag(DRUG == "PEM") & DRUG %in% "DAB"        & ORDER =
= 2 ~ 1,
                                lag(DRUG == "PEM") & DRUG %in% "DABTRA"     & ORDER =
= 2 ~ 1,
                                lag(DRUG == "PEM") & DRUG %in% "VEM"        & ORDER =
= 2 ~ 1,
                                # Changes from IM to IM
                                lag(DRUG == "IPI") & DRUG %in% "NIVO"     & ORDER ==
2 ~ 1,
                                lag(DRUG == "IPI") & DRUG %in% "NIVOIPI"  & ORDER ==
2 ~ 1,
                                lag(DRUG == "IPI") & DRUG %in% "PEM"      & ORDER ==
2 ~ 1,
                                lag(DRUG == "NIVO") & DRUG %in% "IPI"     & ORDER ==
2 ~ 1,
                                lag(DRUG == "NIVO") & DRUG %in% "NIVOIPI" & ORDER ==
2 ~ 1,
                                lag(DRUG == "NIVO") & DRUG %in% "PEM"     & ORDER ==
2 ~ 1,
                                lag(DRUG == "NIVOIPI") & DRUG %in% "IPI"  & ORDER ==
2 ~ 1,
                                lag(DRUG == "NIVOIPI") & DRUG %in% "NIVO" & ORDER ==
2 ~ 1,
                                lag(DRUG == "NIVOIPI") & DRUG %in% "PEM"  & ORDER ==
2 ~ 1,
                                lag(DRUG == "PEM") & DRUG %in% "IPI"      & ORDER ==
2 ~ 1,
                                lag(DRUG == "PEM") & DRUG %in% "NIVO"     & ORDER ==
2 ~ 1,
                                lag(DRUG == "PEM") & DRUG %in% "NIVOIPI"  & ORDER ==
2 ~ 1,
                                TRUE ~ 0)) %>%
  mutate(PROGRESSION = as.factor(PROGRESSION)) %>%
  mutate(STATE = case_when(TYPE == "Immunotherapy"    & ORDER == 1 ~ 1,
                           TYPE == "Targeted therapy" & ORDER == 1 ~ 2,
                           PROGRESSION == 1 ~ 3)) %>%
  # Fill NA's with initial STATE because the change is not considered progression
  fill(STATE,.direction = "down") %>%
  mutate(STATE = as.integer(STATE)) %>%
  select(-ORDER, -CENS) %>%
  ungroup()

# Check STATES
table(STATES$STATE, exclude = NULL) # 46 patients progressed
# Check progression
table(STATES$PROGRESSION, exclude = NULL)
# Check STATES
table(STATES$STATE, exclude = NULL)

# BRAF wild-type
MM_5_BRAF_WILD <- MM_5 %>%
  filter(MUTATION == "BRAF Wild-type")

# BRAF mutant
```

```
MM_5_BRAF_MUTANT <- MM_5 %>%
  filter(MUTATION == "BRAF mutation")

# Full cohort
save(MM_5, file = "CEA - MSM Markov model dataset.rda")

# BRAF wild-type
save(MM_5_BRAF_WILD, file = "CEA - MSM Markov model dataset (BRAF wild-type).rda")

# BRAF mutant
save(MM_5_BRAF_MUTANT, file = "CEA - MSM Markov model dataset (BRAF mutant).rda")



# Fit multi-state model

tmat <- transMat(list(c(2,3), 3, c()),
                 names = c("Progression-free", "Progression", "Death"))
tmat

# Create transition matrix with death split into two states
tmat2 <- transMat(x = list(c(2, 4), c(3), c(), c()),
                  names=c("Progression-free", "Progression", "Death after progression
", "Death without progression"))
tmat2

# Different drugs for STATES
MM_5 <- MM_5 %>%
  mutate(STATE = case_when(DRUG == "IPI"     ~ 1,
                           DRUG == "NIVOIPI" ~ 2,
                           DRUG == "PEM"     ~ 3,
                           DRUG == "DAB"     ~ 4,
                           DRUG == "DABTRA"  ~ 5,
                           DRUG == "VEM"     ~ 6))

# Create dataset that can be used for multi-state modelling
covs <- c("STATE", "PROG_TIME", "GENDER", "AGE", "MUTATION", "PS", "simd2012_sc_quint
ile")
msmcancer <- msprep(time = c(NA, "PROG_TIME", "FUTIME"),
                    status = c(NA, "PROG", "CENS"),
                    data = MM_5, trans = tmat, keep = covs)

# Changes in format of the last dataset
msmcancer_2 <- msmcancer %>%
  rename(strategy_id = STATE,
         age = AGE,
         gender = GENDER,
         mutation = MUTATION,
         ps = PS,
         simd = simd2012_sc_quintile)

msmcancer_2 <- data.frame(msmcancer_2)

# Create subsets specific to each transition
msmcancer_trans1 <- subset(msmcancer_2, trans==1)
msmcancer_trans2 <- subset(msmcancer_2, trans==2)
msmcancer_trans3 <- subset(msmcancer_2, trans==3)



# Build a Cox Markov model including time in previous state as a covariate
CoxMarkov <- coxph(Surv(Tstart, Tstop, status) ~ strategy_id + PROG_TIME,
                   data = msmcancer_trans3, method = "breslow")
```

```
summary(CoxMarkov) # Markov assumption holds; PROG_TIME Not statistically significant



library(eha)
# Fit Cox regression
fit_cr  <- coxreg(Surv(Tstart, Tstop, status) ~ strategy_id, data = msmcancer_2)
fit_cr; plot(fit_cr)

# Fit Cox regression for each transition
fit_cr_1  <- coxreg(Surv(Tstart, Tstop, status) ~ strategy_id, data = msmcancer_trans
1)
fit_cr_2  <- coxreg(Surv(Tstart, Tstop, status) ~ strategy_id, data = msmcancer_trans
2)
fit_cr_3  <- coxreg(Surv(Tstart, Tstop, status) ~ strategy_id, data = msmcancer_trans
3)



# Transition 1

# Weibull
(wei_trans1  <- phreg(Surv(Tstart, Tstop, status) ~ strategy_id,
                      dist = "weibull", data = msmcancer_trans1))
check.dist(fit_cr_1, wei_trans1)
aic <- -2*wei_trans1$loglik[2]+2*nrow(wei_trans1$var); aic
# Exponential
(exp_trans1  <- phreg(Surv(Tstart, Tstop, status) ~ strategy_id,
                      dist = "weibull", shape = 1, data = msmcancer_trans1))
check.dist(fit_cr_1, exp_trans1)
aic <- -2*exp_trans1$loglik[2]+2*nrow(exp_trans1$var); aic
# Gompertz
(gom_trans1  <- phreg(Surv(Tstart, Tstop, status) ~ strategy_id,
                      dist = "gompertz", data = msmcancer_trans1))
check.dist(fit_cr_1, gom_trans1)
aic <- -2*gom_trans1$loglik[2]+2*nrow(gom_trans1$var); aic
# Loglogistic
(logl_trans1 <- phreg(Surv(Tstart, Tstop, status) ~ strategy_id,
                      dist = "loglogistic", data = msmcancer_trans1))
check.dist(fit_cr_1, logl_trans1)
aic <- -2*logl_trans1$loglik[2]+2*nrow(logl_trans1$var); aic
# Lognormal
(logn_trans1 <- phreg(Surv(Tstart, Tstop, status) ~ strategy_id,
                      dist = "lognormal", data = msmcancer_trans1))
check.dist(fit_cr_1, logn_trans1)
aic <- -2*logn_trans1$loglik[2]+2*nrow(logn_trans1$var); aic



# Transition 2

# Weibull
(wei_trans2  <- phreg(Surv(Tstart, Tstop, status) ~ strategy_id,
                      dist = "weibull", data = msmcancer_trans2))
check.dist(fit_cr_2, wei_trans2)
aic <- -2*wei_trans2$loglik[2]+2*nrow(wei_trans2$var); aic
# Exponential
(exp_trans2  <- phreg(Surv(Tstart, Tstop, status) ~ strategy_id,
                      dist = "weibull", shape = 1, data = msmcancer_trans2))
check.dist(fit_cr_2, exp_trans2)
aic <- -2*exp_trans2$loglik[2]+2*nrow(exp_trans2$var); aic
# Gompertz
(gom_trans2  <- phreg(Surv(Tstart, Tstop, status) ~ strategy_id,
                      dist = "gompertz", data = msmcancer_trans2))
check.dist(fit_cr_2, gom_trans2)
```

```
aic <- -2*gom_trans2$loglik[2]+2*nrow(gom_trans2$var); aic
# Loglogistic
(logl_trans2 <- phreg(Surv(Tstart, Tstop, status) ~ strategy_id,
                      dist = "loglogistic", data = msmcancer_trans2))
check.dist(fit_cr_2, logl_trans2)
aic <- -2*logl_trans2$loglik[2]+2*nrow(logl_trans2$var); aic
# Lognormal
(logn_trans2 <- phreg(Surv(Tstart, Tstop, status) ~ strategy_id,
                      dist = "lognormal", data = msmcancer_trans2))
check.dist(fit_cr_2, logn_trans2)
aic <- -2*logn_trans2$loglik[2]+2*nrow(logn_trans2$var); aic



# Transition 3

# Weibull
(wei_trans3  <- phreg(Surv(Tstart, Tstop, status) ~ strategy_id,
                      dist = "weibull", data = msmcancer_trans3))
check.dist(fit_cr_3, wei_trans3)
aic <- -2*wei_trans3$loglik[2]+2*nrow(wei_trans3$var); aic
# Exponential
(exp_trans3  <- phreg(Surv(Tstart, Tstop, status) ~ strategy_id,
                      dist = "weibull", shape = 1, data = msmcancer_trans3))
check.dist(fit_cr_3, exp_trans3)
aic <- -2*exp_trans3$loglik[2]+2*nrow(exp_trans3$var); aic
# Gompertz
#(gom_trans3  <- phreg(Surv(Tstart, Tstop, status) ~ strategy_id,
#                      dist = "gompertz", data = msmcancer_trans3))
#check.dist(fit_cr_3, gom_trans3)
#aic <- -2*gom_trans3$loglik[2]+2*nrow(gom_trans3$var); aic
# Loglogistic
(logl_trans3 <- phreg(Surv(Tstart, Tstop, status) ~ strategy_id,
                      dist = "loglogistic", data = msmcancer_trans3))
check.dist(fit_cr_3, logl_trans3)
aic <- -2*logl_trans3$loglik[2]+2*nrow(logl_trans3$var); aic
# Lognormal
(logn_trans3 <- phreg(Surv(Tstart, Tstop, status) ~ strategy_id,
                      dist = "lognormal", data = msmcancer_trans3))
#check.dist(fit_cr_3, logn_trans3)
#aic <- -2*logn_trans3$loglik[2]+2*nrow(logn_trans3$var); aic

# Utilities table - Use beta distribution
## Add utility means and standard error
utility_tbl <- stateval_tbl(data.table(state_id = c(1, 2),
                                       mean = c(0.77, 0.59),
                                       se = 0.02),
                            dist = "beta")

print(utility_tbl)

# Costs table
costs <- data.table(c("IPI", "NIVOIPI", "PEM", "DAB", "DABTRA", "VEM"),
                    c(3*70, (3*70)*2, 200, 300, 300+2, 960)) # body weight (70kg); we
ekly cost

DRUG_RATES <- MM_5 %>%
  group_by(DRUG) %>%
  summarize(RATE = round(n()/262, digits = 2))

costs_2 <- costs %>%
  rename(DRUG    = V1,
         DOSE_MG = V2) %>%
  right_join(DRUG_RATES) %>%
  # Cost per cycle
```

```
  mutate(COST_CYCLE = case_when(DRUG == "IPI"     ~ 18750, # Every 3 weeks
                                DRUG == "NIVOIPI" ~ 19628, # Every 3 weeks
                                DRUG == "PEM"     ~ 6575,  # Every 3 weeks
                                DRUG == "DAB"     ~ (1400/28)*4, # Every day
                                DRUG == "DABTRA"  ~ ((1400/28)*4) + (4800/30), # Ever
y day
                                DRUG == "VEM"     ~ 250)) %>%
  mutate(COST_CYCLE = round(COST_CYCLE, digits = 0)) %>%
  # Cost per week
  mutate(COST_WEEK = case_when(DRUG == "IPI"     ~ 18750/3, # Every 3 weeks (divide b
y 3)
                               DRUG == "NIVOIPI" ~ 19628/3, # Every 3 weeks (divide b
y 3)
                               DRUG == "PEM"     ~ 6575/3,  # Every 3 weeks (divide b
y 3)
                               DRUG == "DAB"     ~ (1400/28)*4*7, # Every day (times
7)
                               DRUG == "DABTRA"  ~ ((1400/28)*4*7) + ((4800/30)*7), #
Every day (times 7)
                               DRUG == "VEM"     ~ 1750)) %>%
  mutate(COST_WEEK = round(COST_WEEK, digits = 0)) %>%
  # Cost per day
  mutate(COST_DAY = round((COST_WEEK/7), digits = 0)) %>%
  # Cost per month
  mutate(COST_MONTH = COST_DAY * 30) %>%
  mutate(COST_RATE = RATE*COST_MONTH) %>%
  mutate(TYPE = case_when(DRUG %in% c("IPI", "NIVOIPI", "PEM") ~ as.character("Immuno
therapy"),
                          DRUG %in% c("DAB", "DABTRA", "VEM") ~ as.character("Targete
d therapy"))) %>%
  group_by(TYPE) %>%
  mutate(TYPE_COST = round(sum(COST_RATE[1:3])/3, digits = 0))

## Drug 1-month cycle cost
drug_tbl <- stateval_tbl(data.table(strategy_id = c(1:6),
                                    strategy_name = c("IPI", "NIVOIPI", "PEM", "DAB",
"DABTRA", "VEM"),
                                    est = costs_2$COST_MONTH),
                         dist = "fixed")
## Medical cost
med_tbl <- stateval_tbl(data.table(strategy_id = states$state_id,
                                   mean = c(1000, 1600),
                                   se = c(10.9, 14.1)),
                        dist = "gamma")
print(drug_tbl)
print(med_tbl)



# Simulation

# 1000 samples of the parameters for the probabilistic sensitivity analysis (PSA)
n_samples <- 1000

# Disease model
transmod_data <- expand(hesim_dat, by = c("strategies", "patients", "transitions"))
head(transmod_data)

# Transition model
transmod_cf <- create_IndivCtstmTrans(wei_fits_cf, transmod_data,
                                      trans_mat = tmat, n = n_samples,
                                      uncertainty = "normal",
                                      clock = "forward",
                                      start_age = patients$age)
# Utility
utility_mod <- create_StateVals(utility_tbl, n = n_samples, hesim_data = hesim_dat)
```

```
# Costs
drug_cost_mod <- create_StateVals(drug_tbl, n = n_samples, hesim_data = hesim_dat)
med_cost_mod <- create_StateVals(med_tbl, n = n_samples, hesim_data = hesim_dat)
cost_mods <- list(Drug = drug_cost_mod)

# Combining the disease progression, cost and utility models
econmod_cf <- IndivCtstm$new(trans_model = transmod_cf,
                             utility_model = utility_mod,
                             cost_models = cost_mods)
# Simulating outcomes

# Disease progression
ptm <- proc.time() # Start running time
econmod_cf$sim_disease(max_age = 100) # Patients assumed to live a max of 100 years
proc.time() - ptm  # Return running time
head(econmod_cf$disprog_)

# State occupancy probabilities
econmod_cf$sim_stateprobs(t = seq(0, 30, 1/12))
head(econmod_cf$stateprobs_)

autoplot(econmod_cf$stateprobs_, labels = labs, ci = FALSE)

# Compare state probabilities between the competing treatment strategies
## Function to create state probability "dataset" for plotting
summarize_stprobs <- function(stateprobs) {
  x <- stateprobs[,.(prob_mean = mean(prob)),
                  by = c("strategy_id", "state_id", "t")]
  set_labels(x, labels = labs, new_names = c("strategy_name", "state_name"))
}

# Plot of state probabilities
stprobs_cf <- summarize_stprobs(econmod_cf$stateprobs_)
ggplot(stprobs_cf, aes(x = t, y = prob_mean, col = strategy_name)) +
  geom_line(aes(linetype = strategy_name,
                colour = strategy_name), size = 1) +
  facet_wrap(~state_name) +
  scale_color_manual(values = cb_palette) +
  xlab("Time in months") + ylab("Probability") +
  labs(linetype = "Treatment strategy",
       colour = "Treatment strategy") +
  theme_bw()



# Simulate costs and QALYs

econmod_cf$sim_qalys(dr = c(0, 0.035)) # No discount rate and 3.5% discount rate
head(econmod_cf$qalys_)

# Compute means across PSA samples by treatment strategy and health state
qalys_summary <- econmod_cf$qalys_[,.(mean = mean(qalys)),
                                   by = c("strategy_id", "state_id", "dr")]
set_labels(qalys_summary, labels = labs,
           new_names = c("strategy_name", "state_name"))

## Stacked barplot
totals <- qalys_summary[dr == 0.035] %>%
  group_by(strategy_name) %>%
  summarise(total = sum(round(mean, digits = 1)))

ggplot(qalys_summary[dr == 0.035],
       aes(x = strategy_name, y = mean, fill = state_name)) +
```

```
  geom_bar(binwidth = 0.5, stat = "identity") +
  geom_text(aes(strategy_name, total, label = total, fill = NULL),
            vjust = -0.5, data = totals) +
  scale_fill_discrete(name = "") +
  scale_fill_manual(values = cb_palette) +
  xlab("Treatment strategy") + ylab("Mean QALYs") +
  labs(fill = "Health state") +
  theme_bw()

## Barplot
ggplot(qalys_summary[dr == 0.035],
       aes(x = strategy_name, y = mean, fill = state_name)) +
  geom_bar(stat = "identity", position = position_dodge()) +
  geom_text(aes(label = round(mean, digits = 1)), size = 3,
            vjust = 1.5, colour = "white",
            position = position_dodge(0.9)) +
  scale_fill_discrete(name = "") +
  scale_fill_manual(values = cb_palette) +
  xlab("Treatment strategy") + ylab("Mean QALYs") +
  labs(fill = "Health state") +
  theme_bw()

# Costs are computed the same way as QALYS but by category
econmod_cf$sim_costs(dr = 0.035) # Discount rate of 3.5%
head(econmod_cf$costs_)



# Decision analysis

ce_sim_ictstm <- econmod_cf$summarize()
format(summary(ce_sim_ictstm, labels = labs))

# Save cost-effectiveness simulation
save(ce_sim_ictstm, file = "Markov cohort ce_sim_ictstm.rda")

wtp <- seq(0, 50000, 500) # Willingness to pay

cea_out <- cea(ce_sim_ictstm, k = wtp, dr_qalys = 0.035, dr_costs = 0.035)
cea_pw_out <- cea_pw(ce_sim_ictstm, k = wtp, comparator = 1,
                     dr_qalys = 0.035, dr_costs = 0.035)

# Incremental cost-effectiveness ratio (ICER)
format(icer(cea_pw_out, k = 30000))
plot_ceac(cea_pw_out, labels = labs)

library(scales)
ggplot(cea_out$mce[best == 1],
       aes(x = k, y = prob, col = factor(strategy_id))) +
  geom_line() +
  xlab("Willingness to pay") +
  ylab("Probability mostt cost-effective") +
  scale_x_continuous(breaks = seq(0, 50000, 5000), labels = scales::dollar) +
  theme(legend.position = "bottom") +
  scale_colour_discrete(name = "Strategy") +
  theme_bw()

# Cost-effectiveness plane
head(cea_pw_out$delta)
plot_ceplane(cea_pw_out, k = 30000, labels = labs) +
  theme_bw()

# Cost-effectiveness curves (CEAC)
plot_ceac(cea_out, labels = labs) +
```

```
  theme_bw()

# Cost-effectiveness acceptability frontier (CEAF)
plot_ceaf(cea_out, labels = labs) +
  theme_bw()

# Value for perfect information
plot_evpi(cea_out) +
  theme_bw()



# Custom plots
# Cost-effectiveness plane
strategy_factor <- function(x) {
  factor(x, levels = 1:6, labels = c("IPI", "NIVOIPI", "PEM", "DAB", "DABTRA", "VEM")
)
}

format_pound <- function(x) {
  paste0("£", formatC(x, format = "d", big.mark = ","))
}

ylim <- max(cea_pw_out$delta[, ic]) * 1.1
xlim <- ceiling(max(cea_pw_out$delta[, ie]) * 1.1)
ggplot(cea_pw_out$delta,
       aes(x = ie, y = ic)) +
  geom_jitter(aes(shape = strategy_factor(strategy_id),
                  colour = strategy_factor(strategy_id)), size = 0.5) +
  xlab("Incremental QALYs") +
  ylab("Incremental cost") +
  scale_y_continuous(limits = c(-ylim, ylim),
                     labels = format_pound) +
  scale_x_continuous(limits = c(-xlim, xlim), breaks = seq(-6, 6, 2)) +
  theme(legend.position = "bottom") +
  scale_colour_manual(values = cb_palette) +
  geom_abline(slope = 30000, linetype = "dashed") +
  geom_hline(yintercept = 0) +
  geom_vline(xintercept = 0) +
  labs(shape = "Treatment strategy",
       colour = "Treatment strategy") +
  guides(colour = guide_legend(override.aes = list(size = 5))) +
  theme_bw()



# Cost-effectiveness acceptability curves (CEAC)
ggplot(cea_out$mce,
       aes(x = k, y = prob, col = strategy_factor(strategy_id))) +
  geom_line(aes(linetype = strategy_factor(strategy_id),
                colour = strategy_factor(strategy_id)), size = 1) +
  xlab("Willingness to pay") +
  ylab("Probability most cost-effective") +
  scale_x_continuous(breaks = seq(0, max(wtp), length.out = 6),
                     label = format_pound) +
  theme(legend.position = "bottom") +
  scale_colour_manual(values = cb_palette) +
  labs(linetype = "Treatment strategy",
       colour = "Treatment strategy") +
  theme_bw()



# Cost-effectiveness acceptability frontier (CEAF)
ggplot(cea_out$mce[best == 1],
       aes(x = k, y = prob, col = strategy_factor(strategy_id))) +
```

```
  geom_line(aes(linetype = strategy_factor(strategy_id),
                colour = strategy_factor(strategy_id)), size = 1) +
  xlab("Willingness to pay") +
  ylab("Probability most cost-effective") +
  scale_x_continuous(breaks = seq(0, max(wtp), length.out = 6),
                     label = format_pound) +
  theme(legend.position = "bottom") +
  scale_colour_manual(values = cb_palette) +
  labs(linetype = "Treatment strategy",
       colour = "Treatment strategy") +
  theme_bw()


# Value for perfect information
plot_evpi(cea_out) +
  scale_y_continuous(label = format_pound) +
  scale_x_continuous(label = format_pound) +
  theme_bw()


wtp <- seq(0, 100000, 1000) # Willingness to pay
cea_out <- cea(ce_sim_ictstm, k = wtp, dr_qalys = 0.035, dr_costs = 0.035)
cea_pw_out <- cea_pw(ce_sim_ictstm, k = wtp, comparator = 1,
                     dr_qalys = 0.035, dr_costs = 0.035)

# Incremental cost-effectiveness ratio (ICER)
format(icer(cea_pw_out, k = 100000))



# Cost-effectiveness plane
strategy_factor <- function(x) {
  factor(x, levels = 1:6, labels = c("IPI", "NIVOIPI", "PEM", "DAB", "DABTRA", "VEM")
)
}

format_pound <- function(x) {
  paste0("£", formatC(x, format = "d", big.mark = ","))
}

ylim <- max(cea_pw_out$delta[, ic]) * 1.1
xlim <- ceiling(max(cea_pw_out$delta[, ie]) * 1.1)
ggplot(cea_pw_out$delta,
       aes(x = ie, y = ic)) +
  geom_jitter(aes(shape = strategy_factor(strategy_id),
                  colour = strategy_factor(strategy_id)), size = 0.5) +
  xlab("Incremental QALYs") +
  ylab("Incremental cost") +
  scale_y_continuous(limits = c(-ylim, ylim),
                     labels = format_pound) +
  scale_x_continuous(limits = c(-xlim, xlim), breaks = seq(-6, 6, 2)) +
  theme(legend.position = "bottom") +
  scale_colour_manual(values = cb_palette) +
  geom_abline(slope = 100000, linetype = "dashed") +
  geom_hline(yintercept = 0) +
  geom_vline(xintercept = 0) +
  labs(shape = "Treatment strategy",
       colour = "Treatment strategy") +
  guides(colour = guide_legend(override.aes = list(size = 5))) +
  theme_bw()



# Cost-effectiveness acceptability curves (CEAC)
ggplot(cea_out$mce,
       aes(x = k, y = prob, col = strategy_factor(strategy_id))) +
```

```
  geom_line(aes(linetype = strategy_factor(strategy_id),
                colour = strategy_factor(strategy_id)), size = 1) +
  xlab("Willingness to pay") +
  ylab("Probability most cost-effective") +
  scale_x_continuous(breaks = seq(0, max(wtp), length.out = 6),
                     label = format_pound) +
  theme(legend.position = "bottom") +
  scale_colour_manual(values = cb_palette) +
  labs(linetype = "Treatment strategy",
       colour = "Treatment strategy") +
  theme_bw()


# Cost-effectiveness acceptability frontier (CEAF)
ggplot(cea_out$mce[best == 1],
       aes(x = k, y = prob, col = strategy_factor(strategy_id))) +
  geom_line(aes(linetype = strategy_factor(strategy_id),
                colour = strategy_factor(strategy_id)), size = 1) +
  xlab("Willingness to pay") +
  ylab("Probability most cost-effective") +
  scale_x_continuous(breaks = seq(0, max(wtp), length.out = 6),
                     label = format_pound) +
  theme(legend.position = "bottom") +
  scale_colour_manual(values = cb_palette) +
  labs(linetype = "Treatment strategy",
       colour = "Treatment strategy") +
  theme_bw()


# Value for perfect information
plot_evpi(cea_out) +
  scale_y_continuous(label = format_pound) +
  scale_x_continuous(label = format_pound) +
  theme_bw()
```

Appendix 2 – CHEERS 2022 checklist

Section/topic	Item no	Guidance for reporting	Reported in section
Title			
Title	1	Identify the study as an economic evaluation and specify the interventions being compared.	5.1
Abstract			
Abstract	2	Provide a structured summary that highlights context, key methods, results, and alternative analyses.	5.1, 5.3
Introduction			
Background and objectives	3	Give the context for the study, the study question, and its practical relevance for decision-making in policy or practice.	5.1, 5.2
Methods			
Health economic analysis plan	4	Indicate whether a health economic analysis plan was developed and where available.	–
Study population	5	Describe characteristics of the study population (such as age range, demographics, socioeconomic, or clinical characteristics).	5.3.2.1
Setting and location	6	Provide relevant contextual information that may influence findings.	5.1
Comparators	7	Describe the interventions or strategies being compared and why chosen.	5.3.2.2
Perspective	8	State the perspective(s) adopted by the study and why chosen.	5.3.2.6
Time horizon	9	State the time horizon for the study and why appropriate.	**Error! Reference source not found.**
Discount rate	10	Report the discount rate(s) and reason chosen.	**Error! Reference source not found.**

Selection of outcomes	11	Describe what outcomes were used as the measure(s) of benefit(s) and harm(s).	5.3.2.4
Measurement of outcomes	12	Describe how outcomes used to capture benefit(s) and harm(s) were measured.	5.3.2.4
Valuation of outcomes	13	Describe the population and methods used to measure and value outcomes.	5.3.2.4
Measurement and valuation of resources and costs	14	Describe how costs were valued.	5.3.2.5
Currency, price date, and conversion	15	Report the dates of the estimated resource quantities and unit costs, plus the currency and year of conversion.	5.3.2.5
Rationale and description of model	16	If modelling is used, describe in detail and why used. Report if the model is publicly available and where it can be accessed.	5.3.2
Analytics and assumptions	17	Describe any methods for analysing or statistically transforming data, any extrapolation methods, and approaches for validating any model used.	5.3.2
Characterising heterogeneity	18	Describe any methods used for estimating how the results of the study vary for subgroups.	–
Characterising distributional effects	19	Describe how impacts are distributed across different individuals or adjustments made to reflect priority populations.	–
Characterising uncertainty	20	Describe methods to characterise any sources of uncertainty in the analysis.	5.3.3
Approach to engagement with patients and others affected by the study	21	Describe any approaches to engage patients or service recipients, the general public, communities, or stakeholders (such as clinicians or payers) in the design of the study.	–
Results			
Study parameters	22	Report all analytic inputs (such as values, ranges, references) including uncertainty or distributional assumptions.	5.3.2
Summary of main results	23	Report the mean values for the main categories of costs and outcomes of	5.4

		interest and summarise them in the most appropriate overall measure.	
Effect of uncertainty	24	Describe how uncertainty about analytic judgements, inputs, or projections affect findings. Report the effect of choice of discount rate and time horizon, if applicable.	5.5
Effect of engagement with patients and others affected by the study	25	Report on any difference patient/service recipient, general public, community, or stakeholder involvement made to the approach or findings of the study.	–
Discussion			
Study findings, limitations, generalisability, and current knowledge	26	Report key findings, limitations, ethical or equity considerations not captured, and how these could affect patients, policy, or practice.	5.5
Other relevant information			
Source of funding	27	Describe how the study was funded and any role of the funder in the identification, design, conduct, and reporting of the analysis.	–
Conflicts of interest	28	Report authors conflicts of interest according to journal or International Committee of Medical Journal Editors requirements.	–

Abbreviations: CHEERS – Consolidated Health Economic Evaluation Reporting Standards