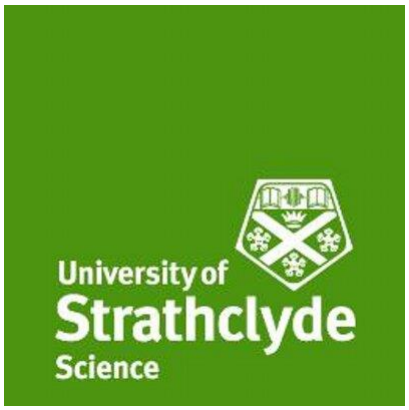

Real world outcomes with systemic anti-cancer treatments for advanced melanoma: experience from the West of Scotland 2010-2018

Julie Anne Clarke

A thesis presented in fulfilment of the requirements for the degree of Master of Philosophy

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The University of Strathclyde, Glasgow

Copyright declaration

Signed: Julie Clarke

Date: 7.12.20

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List of publications and presentations

Clarke J, Laskey J, Crearie C, Bennie M, Waterston A. New Treatments for advanced (unresectable or metastatic) melanoma: What do they mean for patients? Real world experience from NHS Greater Glasgow and Clyde. Abstract. *Journal of Oncology Pharmacy Practice*. 2017;23(8_suppl):1-70. doi:10.1177/1078155217729776 Poster and presentation

Clarke J, Laskey J, Crearie C, Waterston A, Bennie M. Comparing clinical trials populations to real world patients in the West Of Scotland – experience in treatments for advanced (unresectable or metastatic) melanoma. Poster presentation at EuroDURG 2017

Clarke J, Laskey J, Crearie C, Waterston A, Bennie M. Treatments for advanced melanoma: How does real world experience compare to clinical trials? Poster presentation at PHE Cancer Services, Data and Outcomes Conference 2018

Laskey J, Clarke J, Baillie K, Semple Y, Wu O, Crearie C, Jones R, Waterston A, Mueller T, Pan J, Bennie M. Cancer Medicines Outcomes Programme (CMOP): Better use of existing data to understand outcomes in a local population. Poster presentation at NCRI 2018.

Laskey J, Baillie K, Clarke J, Crearie C, Dunlop E, Kurdi A, Mueller T, Wu O, Bennie M. Real world data – can routinely captured health care data be used to determine outcomes of SACT? Experience from the Cancer Medicines Outcomes Programme. 2020. Poster abstract from British Oncology Pharmacy Association (BOPA) 23rd Annual Symposium.

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Abbreviations

A&A	Ayrshire and Arran
AE	Adverse Event(s)
AJCC	American Joint Committee on Cancer
BCC	Basal Cell Carcinoma
CEL	Chief Executive Letter
CEPAS	Chemotherapy Electronic Prescribing and Administration System (Chemocare®)
CHI	Community Health Index
CI	Confidence Interval
CIO	Cancer Information Officer
CMO	Chief Medical Officer
CNS	Central Nervous System
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-Lymphocyte-associated Antigen- 4
DAB	Dabrafenib monotherapy
DT	Dabrafenib with trametinib
DTIC	Dacarbazine
ECOG	Eastern Cooperative Oncology Group
ECS	Extra Capsular Spread
EMA	European Medicines Agency
ERL	Electronic Record Linkage
FDA	Food and Drug Administration
FU	Follow Up
FV	Forth Valley
GGC	Greater Glasgow and Clyde
HTA	Health Technology Assessment
ICD10	International Statistical Classification of Diseases and Related Health Problems, 10th revision
ICDO	International Classification of Diseases for Oncology
IL-2	Interleukin-2
IN	Ipilimumab with nivolumab
IPI	Ipilimumab
IPLR	Individual Patient Level Data Retrieval
irRECIST	Immune related Response Evaluation Criteria in Solid Tumours
ISD	Information Services Division
LDH	Lactate Dehydrogenase
MA	Marketing Authorisation
MAPK	Mitogen Activated Protein Kinase
MDT	Multi-disciplinary Team
MHRA	Medicines and Healthcare products Regulatory Agency
NA	Not Applicable
NE	Not Estimable
NHS	National Health Service
NHSCR	National Health Service Central Register
NICE	National Institute for Health and Care Excellence
NIVO	Nivolumab monotherapy

NR	Not Recorded
NRS	National Records of Scotland
NSS	National Services Scotland
OPCS-4	Office of Population Censuses and Surveys procedural codes, 4th revision
OTC	Over the counter
OS	Overall Survival
PACE	Patient and Clinician Engagement
PBPP	Public Benefit and Privacy Panel
PD-1	Programmed cell Death protein - 1
PD-L1/2	Programmed cell Death Ligand 1 / 2
PEM	Pembrolizumab
PET	Positron Emission Tomography
PFS	Progression Free Survival
PIS	Prescribing Information System
PS	Performance Status
Q2W	Every 2 weeks
Q3W	Every 3 weeks
QALY	Quality Adjusted Life Year
QoL	Quality of Life
RECIST	Response Evaluation Criteria in Solid Tumours
RWD	Real World Data
RWE	Real World Evidence
SACT	Systemic Anti-Cancer Therapy
SCC	Squamous Cell Carcinoma
SCI	Scottish Care Information
SG	Scottish Government
SIMD	Scottish Index of Multiple Deprivation
SMC	Scottish Medicines Consortium
SMR	Scottish Morbidity Record
SMR00	Scottish Morbidity Record Outpatient Attendance
SMR01	Scottish Morbidity Record General Acute Inpatient and Daycase Attendance
SMR06	Scottish Cancer Registry
SPC	Summary of Product Characteristics
TNF-α	Tumour Necrosis Factor – alpha
UK	United Kingdom
ULN	Upper Limit of Normal
USA	United States of America
UV	Ultra Violet
VEM	Vemurafenib
VPN	Virtual Private Network
WHO	World Health Organisation
WoS	West of Scotland
WoSCAN	West of Scotland Cancer Network

Thesis abstract

Background:

Ipilimumab was the first systemic anti-cancer therapy (SACT) to show survival benefit in clinical trials for advanced (unresectable or metastatic) melanoma. (Hodi et al. 2010) Vemurafenib, dabrafenib with trametinib, pembrolizumab and nivolumab followed but it is recognised that clinical trial findings are not always representative of real world practice (Donia et al. 2017). It was proposed that electronic record linkage (ERL) of routinely captured healthcare data with SACT prescriptions would generate real world data (RWD) to supplement clinical trial results for treatment decision making.

Methods:

Patients starting SACT for advanced melanoma between 1.11.10 and 31.12.17 in the West of Scotland were identified and followed up until 31.3.18. Prescribing records from the Chemotherapy Electronic Prescribing and Administration System (CEPAS) were linked with routinely captured healthcare data including the Scottish Cancer Registry, anonymised then accessed in the NHSGGC Safe Haven. Multivariable Cox regression models estimated impact of patient baseline characteristics and SACT on OS. ERL methodology was validated using results from individual patient case notes (IPLR).

Results:

Median OS varied from 18.5 months (95%CI 14.4-not estimable) for ipilimumab with nivolumab to 5.6 months (4.5-7.3) with dabrafenib. Dabrafenib with trametinib (HR 0.42, p=0.0014) and ipilimumab with nivolumab (HR 0.50, p=0.0352) had a positive impact on OS compared to ipilimumab monotherapy. Baseline characteristics including LDH levels above the upper limit of normal; ECOG performance status ≥2 and mucosal melanomas had a negative impact on OS.

Data availability differences between ERL and IPLR (some laboratory results and disease characteristics) did not have a statistically significant impact on the hazard ratios for each SACT, except dabrafenib, in the multivariable Cox model.

Conclusion:

Our RWD showed reduced median OS compared to the pivotal clinical trials but it included patients often excluded from clinical trials. ERL is a valid method for obtaining real world outcomes.

1. Introduction

This thesis describes the study of systemic anti-cancer treatments (SACT) used by patients with advanced (unresectable or metastatic) melanoma in the West of Scotland from 2010 to 2017 using routinely collected healthcare data. This introductory chapter explains the drug development process; describing how medicines move from the laboratory to clinical use and explaining where real world data (RWD) may be of benefit. The second part of this chapter describes the epidemiology and pathophysiology of melanoma, a type of skin cancer, with a focus on advanced (unresectable or metastatic) melanoma which is the therapeutic area of interest for this thesis. Advanced (unresectable or metastatic) melanoma may also be referred to as stage 4 melanoma which means the cancer has spread beyond the primary site and treatment is given with a palliative rather than curative intent.

1.1 **Drug Development**

1.1.1 Drug Development Process

Drug development is a complex process starting with identification of a compound, often by methodical testing or computational modelling of novel compounds against a specific target or a serendipitous discovery. (Torjesen 2015) *In vitro* and *in vivo* testing follows this to determine if the compound is likely to be safe for human use and effective in desired therapeutic area(s). In addition tests may be carried out at this stage to determine if the compound may be manufactured at scale in a suitable formulation for delivery. If it is thought that the compound may become a successful medication then the pharmaceutical company may make an application to the relevant regulatory body for approval to carry out early phase clinical trials. (Torjesen 2015) In the United Kingdom (UK) this is the Medicines and Healthcare products Regulatory Agency (MHRA) and in the United States of America (USA) it is the Food and Drug Administration (FDA). Figure 1 provides information on the phases of clinical trials for cancer medicines.

TRIAL PHASE	SUBJECTS / SETTING	PURPOSE OF TRIAL PHASE
Pre-clinical / Phase 0	Laboratory Computational models Animal tests 	Identify drug has intended therapeutic action
Following successful pre-clinical testing an application may be submitted to regulatory authorities for permission to test in humans		
Phase I	Small numbers (10-30) of humans 	Test for safety issues and potential activity.
Phase II	Larger patient numbers with cancer of interest 	Determine drug has efficacy in intended cancer(s). May include dose finding work.
Phase III	Increasing patient numbers 	Compare drug to standard to care. Identify further adverse effects.
Marketing authorisation may be granted if evidence from earlier stages of clinical trials demonstrates positive benefit-harm ratio.		
Phase IV	Real world use 	Assess further adverse effects and long term effects of drug

Figure 1. Phases of drug development in cancer medicines

Randomised controlled trials (Phase II and III) provide a robust, controlled method for assessing the intended and unintended effects of new drugs. Patient selection for clinical trials often follows strict inclusion and exclusion criteria and trials are carried out in controlled conditions, with close follow up and monitoring. This makes it easier to attribute any effects to the drug under investigation but does not always replicate conditions in the real world or routine clinical practice which the medicine may ultimately be used. In Europe pharmaceutical companies may make a single centralised marketing authorisation (MA) application to the European Medicines Agency (EMA) for cancer medicines, rather than multiple applications for individual countries. (Torjesen 2015) Following MA approval the medicine may legally be prescribed although countries with a publicly funded health service, such as the National Health Service (NHS) in the UK, often require a health technology assessment (HTA) to be carried out to further assess the clinical and cost effectiveness before a medicine will be funded by the public health service.

1.1.2 Health Technology Assessment

The World Health Organisation (WHO) defines HTA as "the systematic evaluation of properties, effects, and/or impacts of health technology. It covers both the direct, intended and indirect, unintended consequences of technologies and interventions". It is a multidisciplinary process that is used to inform policy and decision making in health care, identifying health interventions that produce the greatest gain and offer value for money. (World Health Organisation 2018)

In Scotland medicines are only routinely available on NHS prescription if accepted for use by the Scottish Medicines Consortium (SMC), the HTA body in Scotland. (Scottish Medicines Consortium 2020a) The HTA process starts with pharmaceutical companies submitting evidence generated from published clinical trials, pre-clinical data from company files and pricing details which may adjust the cost-effectiveness analysis of the medicine. Due to the timing of this stage in the drug life cycle it is rare for drug companies to include real world data (RWD) in this submission. This evidence is reviewed by the SMC committee, which comprises clinicians, representatives of the pharmaceutical industry, NHS senior management and the public, with support from health economists. A decision is then made on whether or not the medicine is accepted for use in NHS Scotland. The National Institute for Health and Care Excellence (NICE) carries out a similar role for NHS England and All Wales Medicines Strategy Group for NHS Wales.

An economic tool called the Quality Adjusted Life Year (QALY) is widely used to help those assessing healthcare to take a consistent approach to comparing the value of different medicines to facilitate fair and transparent decisions. This is combined with the cost of the medicine to generate a ratio of cost per QALY. NICE sets a threshold of £20000-£30000/ QALY but there is no specific limit set by SMC. (Rothwell 2017) A higher cost per QALY may be accepted in circumstances such as medicines used at the end of life (used to treat a condition that leads to end of life within three years on currently available treatments); orphan medicines for very rare conditions (affecting fewer than 2500 people in a population of 5 million people); ultra-orphan medicines (affecting a maximum of 1 in 50000 people). (Scottish Medicines Consortium 2020b) Patient and Clinician Engagement (PACE) meetings were introduced to SMC processes in 2014, for end of life, orphan and ultra-orphan medicines. These meetings may be requested by pharmaceutical companies, when making a submission to the SMC, and provide an opportunity for patient groups and

clinicians to describe the added benefits of the medicine including impact on quality of life (QoL), which may not be captured in the data provided by the pharmaceutical company. (Scottish Medicines Consortium 2020c)

A review of the changes made in 2014 was carried out by Dr Brian Montgomery in 2016. (Scottish Government 2016) The report acknowledged that access to new medicines had improved with the introduction of PACE meetings but there is an on-going challenge balancing the introduction of new medicines with the finite resources of the NHS. Some of the report recommendations included enabling SMC to decide to "recommend medicines for use subject to on-going evaluation and future reassessment" and developing methods for collecting outcome measurements in relation to treatment with medicines. (Scottish Government 2016)

1.1.3 Post Marketing Authorisation and Real World Evidence

It is recognised that patients participating in oncology clinical trials may not be fully representative of the population in which the medicine is ultimately used. (Donia et al. 2017) Patients who receive the medicine as part of routine clinical practice may have additional co-morbidities, which would have excluded them from the clinical trial. In cancer medicine trials factors, such as poorer Eastern Cooperative Oncology Group performance status (ECOG PS) or presence of brain metastases, which may affect outcomes with treatment, can mean patients are excluded from clinical trials but these restrictions may not apply once the medicine is licensed. Utilising the medicine in a wider population, not fully represented in the clinical trial, may mean that previously seen clinical benefits are not replicated. Use in a wider patient cohort may also expose previously unidentified adverse events (AEs). This information may be collected as part of a phase IV post marketing clinical trial, safety study or expanded access programme managed by the pharmaceutical company. Alternatively pharmacovigilance activities, such as the Yellow Card Scheme run by the MHRA in the UK, may gather reports from patients and prescribers regarding potential AEs from medicines. (Yellow Card Scheme 2018) Data gathered in either of these ways may be used to modify marketing authorisations or even lead to withdrawal of the medicine from the market if necessary.

1.2 **Melanoma**

1.2.1 Epidemiology

Melanoma, the least common form of skin cancer, accounts for 90% of the mortality associated with skin cancer. The global incidence of melanoma in 2015 was 351 880 cases (95% CI 281 633–445 036), with 59 782 global deaths (95% CI 47 602–72 671) being linked to the disease. (Karimkhani et al. 2017) In Scotland, malignant melanoma of skin was the sixth most common cancer, with 1226 cases diagnosed in 2017. (Information Services Division 2019) Melanoma incidence is known to vary by latitude and altitude worldwide due to the effect of population pigmentation and sun exposure patterns. It is rare for the disease to be identified in African and Asian populations with darker skin pigmentations but a moderate to high incidence is reported in white populations such as those in Australia, New Zealand, the UK and Scandinavia. Differences in gender, age and location can also affect global trends in incidence and mortality. Males are more likely to develop melanoma in Australia and the white US population than females but this is reversed in Northern Europe. (Garbe, Leiter 2009; Garbe et al. 2016; Margaret, Alisa 2000; Whiteman et al. 2016)

Globally, melanoma incidence continues to rise although the increasing trend is stabilising and even potentially decreasing in areas such as Australia where mass media campaigns have been spreading a safe sun message since the early 1980s. (Whiteman et al. 2016) Mortality rates have also stabilised partly due to earlier detection. (Garbe, Leiter 2009; Nikolaou, Stratigos 2014) Furthermore, the development of new treatments for advanced (unresectable or metastatic) melanoma is also contributing to improving mortality and it is the use of these newer treatments in routine clinical practice which will be a focus of this thesis.

1.2.2 Pathophysiology and Risk Factors

Melanoma is a tumour arising from melanocytic cells most commonly found in the skin, although ocular sites, meninges and mucous membranes may also be involved. (Garbe et al. 2016) It should be noted that melanoma incidence figures reported earlier include cutaneous melanomas only, which are identified using International Classification of Diseases, 10th edition (ICD10) codes C43. Ocular and mucosal melanomas are not routinely included when melanoma incidence is reported in cancer statistics but these rarer types of

melanoma are included here for completeness as the treatment for advanced (unresectable or metastatic) is not affected by the primary melanoma site.

In 2000, Hanahan and Weinberg published their initial, seminal paper describing six hallmarks of cancer cells providing a framework to understand the diversity of neoplastic cells and identifying targets for rational drug design. This paper was reviewed and the six original hallmarks expanded, in 2011, to include two enabling characteristics and two additional hallmark capabilities which enable tumour growth through proliferative mechanisms or evasion of cell death, and metastatic dissemination. (Hanahan, Weinberg 2011)

Evading immune destruction is an emerging hallmark targeted by immunotherapies involved in the treatment of advanced melanoma. It is generally thought that the immune system plays a part in identifying and destroying cancerous cells in the body therefore it is hypothesised that cancer cells have developed a mechanism for avoiding this process and so developing into solid tumours. (Hanahan, Weinberg 2011) This theory is supported by the increased risk of cancer development in immunocompromised patients. (Disis 2014)

Immunotherapy encompasses a number of licensed and developing treatments, from cytokines such as tumour necrosis factor (TNF-α) which may directly suppress tumour growth, whilst others, such as interleukin-2 (IL-2), stimulate anti-tumour response by promoting growth and activation of T cells and natural killer (NK) cells. The potential benefits of treatments that work via these mechanisms are often limited by toxicities. Other immunotherapy approaches may involve cancer vaccines (not available for use in the NHS in Scotland) and adoptive T-cell therapy however it is immune checkpoint inhibitors that are presently the most commonly used immunotherapies in advanced (unresectable or metastatic) melanoma. (Disis 2014)

Cytotoxic T-lymphocyte-associated antigen- 4 (CTLA-4) and programmed cell death-1 protein (PD-1) are two checkpoint inhibitors that have been successfully targeted by treatments for advanced (unresectable or metastatic) melanoma. CTLA-4 is expressed on activated T cells and regulates the amplitude of early T cell activation. Binding of B7-1 (CD80) and B7-2 (CD86) molecules on antigen presenting cells to CTLA-4 sends inhibitory signals to prevent further activation of T-cells. (Disis 2014; Buchbinder, Hodi 2015; Pardoll 2012)

PD-1 has a role in limiting the activity of T cells in peripheral tissues. In addition to expression on activated T cells, PD-1 has also been detected on regulatory T cells, B cells, NK cells and dendritic cells. Under physiological conditions PD-1 may interact with either of its two ligands, PD-L1 or PD-L2, to lower the immune system by suppressing T cell function. Blocking this interaction, with inhibitors of either the receptor (PD-1) or the ligands (PD-L1 or PD-L2) boosts the immune response to tackle cancerous cells. (Pardoll 2012; Li et al 2016) As the mechanism by which PD-1 inhibitors work is different to CTLA-4 inhibitors clinical trials investigating the combination of checkpoint inhibitors are on-going, with one combination available for use in Scotland since 2017.

Melanoma may develop due to a number of complex interactions between environmental and genetic factors. Some of the molecular changes that enable melanoma cell growth and provide a survival advantage also provide a target for drug development. Mutations that may provide suitable targets for further development of treatments for advanced melanoma include CDNK2A deletions and PTEN disruption leading to PI3 kinase/AKT activation. (Hodis et al. 2012; Miller, Mihm 2006) Mutations that are targets for medicines in use in routine clinical practice or in clinical trials in 2018 include:

BRAF - This was first identified as an oncogene by Davies et al as part of the cancer genome project in 2002. (Davies et al. 2002) Around 50% of melanoma cases have a mutation in this proto-oncogene which encodes a serine/threonine protein kinase as part of the RAS-RAF-MEK-ERK kinase pathway. An activating mutation enables BRAF to become self-sufficient, bypassing the usual processes that control cell growth, leading to uncontrolled cell proliferation and tumour development. (Flaherty, McArthur 2010; Inamdar et al. 2010) It is hypothesised that this mutation plays a part in melanocytic neoplasm formation rather than carcinogenesis as this mutation is also present in benign cells.

c-KIT – This mutation is more common in acral lentiginous melanoma, which is a subtype of melanoma more commonly found on the palms and soles of the black, Asian/Pacific islanders than the white population. Point mutations or gene duplications of c-KIT, which encodes a tyrosine kinase transmembrane receptor, may alter melanocyte proliferation and contribute to tumour genesis. This pathway is being explored in phase II and III clinical trials.

MC1R – Melanocortin 1 receptor (MC1R) acts as a G-protein coupled receptor in melanocytes and has a key role in determining skin pigmentation, one of the main risk factors for developing melanoma, as several allelic variants of this gene are associated with red hair and fair skin phenotypes.

Ultraviolet (UV) radiation exposure is known to have an important role in the development of DNA mutations that contribute to melanoma tumour genesis with melanoma tumour samples demonstrating one of the highest rates of base rate mutations in solid tumours. (Liu Y, Sheikh 2014; Ikehata, Ono 2011) Exposure to UV rays is one of the most modifiable risk factors for development of melanoma.

Additional risk factors for developing melanoma include family history of melanoma, multiple benign or atypical nevi and genetic susceptibility as detailed above. Modifiable environmental risk factors include immunosuppression and exposure to UV rays. (Miller, Mihm 2006; Rastrelli et al. 2014)

1.2.3 Diagnosis and Staging

About 90% of melanomas are diagnosed as primary tumours without any evidence of metastasis, with a 10 year survival rate of 75-85%. Clinicians use ABCDE (A – asymmetry; B – irregular border; C – colour; D – diameter >6mm; E – elevated surface) criteria to identify suspicious lesions. Further investigations with dermoscopy or biopsy may also be carried out. (Garbe et al. 2016) There are four main subtypes of cutaneous melanoma:

Superficial Spreading Melanoma –accounting for approximately 70% of melanoma diagnoses. This type of melanoma often starts as a macule, evolving into a plaque with multiple colours and irregular outline. As this tends to be associated with areas of intermittent sun exposure it is commonly found on the back of legs in women and backs in men.

Nodular Melanoma – accounts for approximately 5% of melanoma diagnoses. As suggested by the name this type of melanoma is often a black-brown exophytic nodule with an aggressive vertical growth phase. This melanoma is more common in males and tends to be found on the trunk or limbs of patients in their fifth or sixth decade.

Lentigo maligna melanoma –accounts for up to 15% of melanomas and is predominantly found on the head and neck of older people, associated with areas of chronic sun exposure.

This may be a large, flat tumour with a variety of colours and it may arise from a lentigo maligna (melanoma in situ).

Acral lentiginous melanoma – accounts for approximately 5% of cases in white people but is the melanoma most commonly found in Asian, Hispanic and African patients. Areas that this melanoma affects are palms of hands and soles of feet with a female predominance.

In addition to cutaneous melanomas patients may also present with ocular or mucosal melanomas or metastatic melanoma with an unknown primary site.

Cutaneous melanomas are often biopsied and the following histological factors may be recorded for staging purposes: Vertical tumour thickness (Breslow's depth); Presence or absence of ulceration; Mitotic rate (number of mitosis/mm^2). The American Joint Committee on Cancer (AJCC) 7th Edition on staging of melanoma is used for classification purposes in this thesis and is summarised in table 1. (Balch et al. 2009) The newer 8th edition of classification was introduced in January 2018.

Table 1. Staging of cutaneous melanoma (Adapted from AJCC 7th edition).

Stage	Primary Tumour thickness (T)	Regional Lymph Node Metastases (N)	Distant Metastases (M)
0	*In situ* tumour	None	None
I	≤1.0mm, ± ulceration or mitotic rate ≥1/ mm^2 OR 1.01–2.00mm, no ulceration	None	None
II	1.01–4.0mm ± ulceration OR >4.0mm ± ulceration	None	None
III	Any thickness ± ulceration	Micrometastases[1] OR Up to three macrometastases[2] OR None but satellite and/or in-transit metastases OR Four or more macrometastases[2] or matted nodes or in transit/satellite metastases with metastatic nodes	None
IV*	Any thickness ± ulceration	Any nodes	Distant metastases

Micrometastases[1] are diagnosed after sentinel lymph node biopsy and completion lymphadenectomy (if performed); Macrometastases[2] are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or when nodal metastasis exhibits gross extracapsular spread.

*** Stage IV melanoma** may be further subdivided by site of distant metastases and lactate dehydrogenase (LDH) levels:

M1a – Skin, subcutaneous tissue or lymph nodes, LDH within normal limits

M1b – Lungs, LDH within normal limits

M1c – All other visceral metastases with LDH within normal limits OR any distant metastasis with raised LDH

1.2.4 Treatments for early stage disease (stages I-III)

Surgical excision is the main treatment for melanoma, particularly cutaneous melanoma. Excisional biopsies are preferred to provide an optimal specimen for pathological diagnosis and evaluation of optimal excision margins for any residual tumour. Due to the position of lentigo maligna melanoma on the face and neck, surgical resection with suitable margins may be challenging and lead to unsatisfactory cosmetic results. In this case, imiquimod cream (immune response modifier) may be considered. Following successful removal of the tumour patients will be advised how to check their own skin for recurrence or development of metastases and may be followed up for a set time period with imaging requested as necessary. Surgery and/or radiotherapy may also be used for mucosal and ocular melanomas.

Adjuvant treatments for melanoma have been accepted for use in Scotland by the SMC, with nivolumab the first to be accepted for use in December 2018, after the study period had ended. (Scottish Medicines Consortium 2018) Adjuvant treatment, which utilises medicines already accepted for use in advanced melanoma patients, may be offered to patients with resected Stage III/IV melanomas to reduce the risk of recurrence. These medicines will not be discussed further in the adjuvant setting.

1.2.5 Treatments for advanced (unresectable or metastatic) disease

The proportion of patients with melanoma who develop metastases is unknown although it is generally considered to be small. Patients who are diagnosed at a more advanced primary stage have an increased risk of metastasis or disease recurrence. Patients presenting with metastatic disease have a median overall survival (OS) of only 6-9 months, without treatment. (Garbe et al. 2016) Estimated 5 year survival for patients with advanced (unresectable or metastatic) disease varies from 9-28% (Svedman et al. 2016)

1.2.5.1 *Treatment options prior to 2010*

Dacarbazine (DTIC) had been the standard treatment for melanoma for a number of years, although complete responses were rare and usually of short duration. Dacarbazine and temozolomide are both pro-drugs of the alkylating agent 5-(3-methyltriazen-1-yl)imidazole-4-carboximide. Temozolomide can penetrate the blood-brain barrier and hence was used, and continues to be used as a last treatment option, in patients with brain metastases. As

with DTIC, responses are rare and use is often limited by toxicity. A phase III study, reported in 2000, demonstrated a median OS of 7.7 months with temozolomide compared to 6.4 months with dacarbazine (hazard ratio (HR) 1.18, 95% confidence interval (CI) 0.92-1.52). A complete response was identified in 3% of patients in both groups and the duration of this response was not fully reported but is generally thought to be short. (Middleton et al. 2000; Jilaveanu et al. 2009)

Other treatments historically used for advanced melanoma include platinum analogues, taxanes and vinca alkaloids. (Jilaveanu et al. 2009) Radiotherapy is not usually considered for primary treatment of advanced disease but may be used for palliation of symptoms that are causing patient's distress.

1.2.5.2 *Treatment options since 2010*

Immunotherapy with checkpoint inhibitors

Immune checkpoint inhibitors act by enhancing the body's immune system as described previously (chapter 1.2.2). Ipilimumab (CTLA-4 inhibitor) was the first checkpoint inhibitor to be marketed for advanced melanoma, as it was used in the first clinical trial to demonstrate a survival benefit in medications for advanced melanoma. (Hodi et al. 2010) This was followed by successful clinical trials of PD-1 inhibitors, nivolumab and pembrolizumab along with the combination of nivolumab and ipilimumab summarised in Table 2. (Larkin et al. 2015; Robert et al. 2015)

Table 2. Summary of phase 3 trials of immunotherapy treatments for use in patients with advanced (unresectable or metastatic) melanoma

	Ipilimumab (Hodi et al. 2010)	**Checkmate 067 (Wolchok 2013; Larkin et al. 2015; Postow et al. 2015; Wolchok 2017)**	**Keynote 006 (Robert et al. 2015; Schachter et al. 2017)**
Phase 3 trial summary	Randomised trial: **ipilimumab (IPI)** 3mg/kg Q3W for 4 doses plus gp100 vs. IPI monotherapy vs. gp100 monotherapy 3:1:1 treatment ratio	Randomised trial (stratified): **nivolumab (NIV)** 1mg/kg Q3W **plus ipilimumab** 3mg/kg Q3W for 4 doses then NIV 3mg/kg Q2W vs. NIV monotherapy 3mg/kg Q2W vs. IPI monotherapy 3mg/kg Q3W for 4 doses 1:1:1 treatment ratio	Randomised trial (stratified): **pembrolizumab (PEM)** 10mg/kg Q2W vs. PEM 10mg/kg Q3W vs. 4 doses of IPI 3mg/kg Q3W 1:1:1 treatment ratio
No. of patients	676 worldwide with previously treated advanced melanoma	945 worldwide with previously untreated advanced melanoma	834 worldwide with advanced melanoma.

	Ipilimumab (Hodi et al. 2010)	Checkmate 067 (Wolchok 2013; Larkin et al. 2015; Postow et al. 2015; Wolchok 2017)	Keynote 006 (Robert et al. 2015; Schachter et al. 2017)
Time period	Sep 2004 – Aug 2008	Jul 2013 – Mar 2014	Sep 2013 – Mar 2014
Exclusion criteria	ocular melanoma; active CNS metastases	ocular melanoma; active CNS metastases; PS ≥2	previous immunotherapy; ocular melanoma; active CNS metastases
Patient baseline characteristics			
Study arm	**Ipilimumab monotherapy**	**Nivolumab with ipilimumab**	**Pembrolizumab every 3 weeks**
age (years)	median 56.8	mean 59	median 63
gender (% male)	59	66	63
% ECOG PS 0-1	99	>99	100
% M1c	73	58	68
% LDH>ULN	39	63	35
% CNS metastases	11	No information	No information
% BRAF mutant	No information	32	35
% no previous treatment	No information	100	67
Follow up details	Up to 55 months. Eligible patients could receive further treatment	Minimum 36 months for living patients. Subsequent therapy administered to 32% NIV-IPI pts and 46% NIV pts Update after minimum 60 months follow up	Median 22.9 months At data cut-off 3rd Dec 2015, 19% Q2W and 14% Q3W on-going treatment with 40% Q2W and 39% Q3W receiving further therapies
Median OS	IPI plus gp 100 10.0 months (95%CI 8.5-11.5); IPI mono. 10.1 months (8.0-13.8) No significant difference between IPI containing groups	Not reached in NIV-IPI pts, 3 year OS rate 58%, HR vs. IPI 0.55 (95%CI 0.45-0.69), p<0.001; 5 year update OS rate: NIV-IPI 52% (95% CI 46-57); NIV 44% (39-50), HR not reported NB – trial not powered to determine OS difference between NIV-IPI and NIV alone	Not yet reached. 24 month OS rates in Q2W & Q3W 55% (95%CI 49-61); HR 0.68 (0.53-0.87); p=0.0009
Additional Outcomes	Immune related adverse events at CTCAE any grade in approximately 60% of IPI patients	Grade 3/4 CTCAE in 59% NIV-IPI patients and 21% NIV patients	Median PFS Q2W 5.6 months (range 3.4-8.2), Q3W 4.1 months (2.9-7.2) ; ORR Q2W is 37% (95%CI 31-43), Q3W 36% (30-42); Duration of response Q2W NR (range 1.8->22.8); Q3W NR (>2.0->22.8); Grade 3 / 4 CTCAE Q2W & Q3W 17%

Key: IPI = ipilimumab; NIV = nivolumab; PEM = pembrolizumab; CNS = central nervous system; RCT = randomised controlled study; Q2W = every 2 weeks; Q3W = every 3 weeks; PS = performance status (Eastern Cooperative Oncology Group); LDH = lactate dehydrogenase level; ULN = upper limit of normal; OS = overall survival; PFS = progression free survival; ORR = overall response rate; 95%CI = 95% confidence intervals; CTCAE = common terminology criteria for adverse events; NR = not reached

These pivotal trials showed that all immunotherapies had a survival benefit for patients and whilst nivolumab with ipilimumab appears to show the longest survival, there are differences between the patients in each trial which means that the results should not be directly compared. Results from the trials also suggest that both ipilimumab monotherapy and combination immunotherapy with nivolumab and ipilimumab are more toxic than pembrolizumab monotherapy, Grade 3 or 4 common terminology criteria for adverse events (CTCAE) were reported in almost 60% of patients compared to 17% in the respective trials.

Alongside these key clinical trials, there have been a number of other trials looking at other aspects of immunotherapy treatments. Robert *et al* published results, in 2011, of a phase III trial comparing ipilimumab (10mg/kg every 3 weeks for 4 cycles) plus dacarbazine (850mg/m^2 every 3 weeks until week 22) to dacarbazine alone in patients with previously untreated melanoma. Exclusion criteria was broadly similar to the Hodi *et al* trial already described and median OS with ipilimumab plus dacarbazine was 11.2 months (95%CI 9.4-13.6), which is similar to the results of the earlier trial and further evidence of the benefit of ipilimumab in advanced (unresectable or metastatic) melanoma. (Robert et al. 2011; Hodi et al. 2010) A phase II trial (Keynote – 002) compared pembrolizumab (2mg/kg or 10mg/kg every 3 weeks) to investigator choice of chemotherapy in patients who had progressed following treatment with ipilimumab. The results from this dose comparison trial suggested there was no significant difference in terms of OS between either pembrolizumab dose as 2 year survival rates were 35.9% for 2mg/kg and 38.2% for 10mg/kg, supporting the licenced dose of 2mg/kg every 3 weeks. (Ribas et al. 2015)

Published results from expanded access schemes in the UK, Spain and Italy provide information on the use of ipilimumab in the real world, with a wider range of patients exposed to the drug and varying results reported, depending on the cohort. In the UK 193 patients (8% with uveal melanoma) with previously treated melanoma had a median OS of 6.1 months, although this varied from 2.9 months – 13.2 months depending on baseline patient characteristics. (Ahmad et al. 2015; Ascierto et al. 2014; Guglieri-Lopez et al. 2016)

Another retrospective chart review study involving 371 patients from Australia, Germany, Italy and Spain starting ipilimumab between September 2010 and April 2012 showed 66% of patients received ipilimumab as a second line treatment and had a one year survival rate of 46%(95%CI 40-51%). (Mohr et al. 2017) A Japanese study by Tsutsumida et al looked at

sequential use of ipilimumab and nivolumab in 68 patients reported a median OS of 7.0 months from start of ipilimumab treatment. (Tsutsumida et al. 2019)

In 2019 RWD published by Arheden *et al* reported median OS of 27.9 months (95% CI 19.8-36.0) in 116 Swedish patients receiving any PD-1 inhibitor for advanced melanoma followed up for a minimum of 6 months. (Arheden et al. 2019) This is similar to results from Liu *et al* in the US who followed up 532 patients, who received pembrolizumab as a first, second or third line treatment, for a median of 12.9 months and reported median OS of 21.8 months (95% CI 16.8-29.1). (Liu et al. 2019)

Targeted Treatments

BRAF inhibitors were the first medicines developed to target the RAS-RAF-MEK-ERK kinase pathway, which is central to cell proliferation in many cancers, in patients who are BRAF mutant.

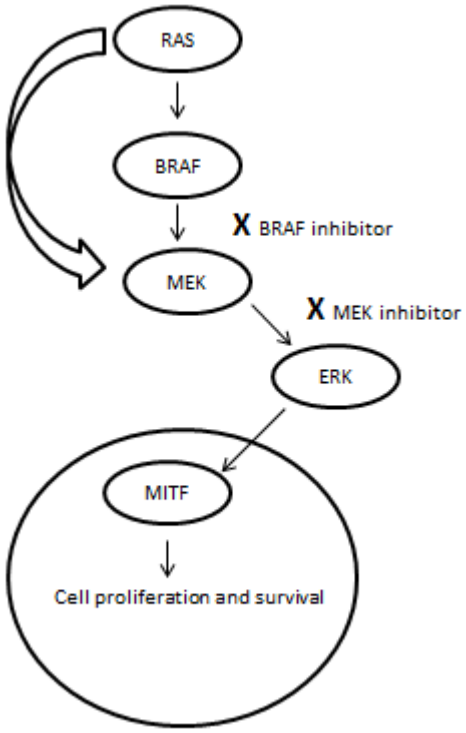


Figure 2. RAS-RAF-MEK-ERK kinase pathway showing how BRAF and MEK inhibitors may reduce cell proliferation. Adapted from Wellbrock, Hurlstone 2010.

Clinical and pre-clinical data suggested that resistance could develop to BRAF inhibition, leading to disease progression (after approximately 12 months). Combining BRAF inhibitors with MEK inhibitors enhances inhibition of the RAS-RAF-MEK-ERK kinase pathway leading to

better outcomes and combination BRAF and MEK inhibition is now the most common targeted treatment option. (Trunzer et al. 2013; Amann et al. 2017)

The first BRAF inhibitor to the UK market was vemurafenib followed by dabrafenib with clinical trials involving companion MEK inhibitors, cobimetinib and trametinib, following at a later date. Key details of the pivotal trials are included in Table 3.

Table 3. Comparison of clinical trials of targeted treatments for use in patients with advanced (unresectable or metastatic) melanoma.

	BRIM 3 **(Chapman et al. 2011; McArthur et al. 2014)**	BREAK 3 **(Hauschild et al. 2012; 2013)**	Combi – d **(Long et al. 2014; 2015; 2017)**
Phase 3 trial summary	Randomised trial: **vemurafenib** (960mg BD) vs. dacarbazine (1000mg/m^2) in patients with previously untreated metastatic melanoma 1:1 treatment ratio	Open label trial: **dabrafenib** (150mg BD) vs. dacarbazine (1000mg/m^2) in patients with previously untreated metastatic melanoma 3:1 treatment ratio	Randomised trial: **dabrafenib** (150mg BD) and **trametinib** (2mg OD) vs. dabrafenib and placebo in patients with previously untreated metastatic melanoma 1:1 treatment ratio
No. of patients	675 worldwide	250 worldwide	423 worldwide
Time period	Jan-Dec 2010	Dec 2010- Sep 2011	May 2012- Nov 2012
Patient details			
Treatment arm	Vemurafenib	Dabrafenib	Dabrafenib with trametinib
median age (years)	56	53	55
% male	59%	60%	53%
% PS 0-1	100	>99	100
%M1c	66	66	67
Median follow up	12.5 months;	15.2 months	not reported
Primary Outcomes	Median OS 13.6 (95%CI 12.0-15.2) months vs. 9.7 (7.9-12.8) months; HR 0.7 (0.57-0.87), p=0.0008 Median PFS 6.9 (6.1-7.0) months vs. 1.6 (1.6-2.1) months	Median PFS 6.9 months (95% CI not reported) in dabrafenib group vs. 2.7 months; HR 0.37 (95% CI 0.23-0.57), p-value not reported	3 year PFS was 22% for combination arm vs. 12% in monotherapy; HR 0.71 (95%CI 0.57-0.88)
Additional outcomes	19% vemurafenib patients had CTCAE grade 3-4 SCC; 10% keratocanthomas	Median OS 18.2 (16.6- not estimable) months vs. 15.6 (12.7- not estimable) 4% dabrafenib patients had CTCAE grade ≥3 SCC/keratocanthomas (not reported separately) ; 3% pyrexia	Median OS 25.1 (19.2- not estimable)months vs. 18.7 (15.2-23.7) months 1% combination patients had CTCAE grade ≥3 SCC compared to 5% in monotherapy arm
Key: BD = twice daily; OD = once daily; PS = performance status (Eastern Cooperative Oncology Group); OS = overall survival; PFS = progression free survival; 95%CI = 95% confidence intervals; CTCAE = common terminology criteria for adverse events; SCC = squamous cell carcinoma			

The longest median OS was reported in clinical trials with combination BRAF and MEK inhibitors rather than monotherapy arms as expected due to the additional inhibition of the RAS-RAF-MEK-ERK kinase pathway described earlier. This is also demonstrated in the co-BRIM trial which compared vemurafenib in combination with cobimetinib to vemurafenib monotherapy but this combination has never been submitted to the SMC for review and so cannot be prescribed for NHS patients in Scotland. The results of targeted SACT trials demonstrated a lower incidence of severe adverse events when compared to immunotherapy trials.

When this thesis study was designed (2018) dabrafenib in combination with trametinib was the only targeted combination accepted for use in Scotland. In July 2018 the European Medicines Agency (EMA) recommended that encorafenib alongside the companion MEK inhibitor binimetinib was granted a marketing authorisation by the European Commission and accepted for use in Scotland by the SMC in February 2020. (Scottish Medicines Consortium 2020d)

1.2.6 Clinical practice in NHS Greater Glasgow and Clyde since 2010

Figure 2 shows when immunotherapies and targeted treatments were licensed in the UK for advanced (unresectable or metastatic) melanoma. The medicines above the line have been accepted for use in Scotland by the SMC, some with restrictions, and may therefore be prescribed by clinicians for NHS patients in Glasgow. Those below the line are licensed for use in the United Kingdom (UK) but have not been submitted to the SMC for use in Scotland.

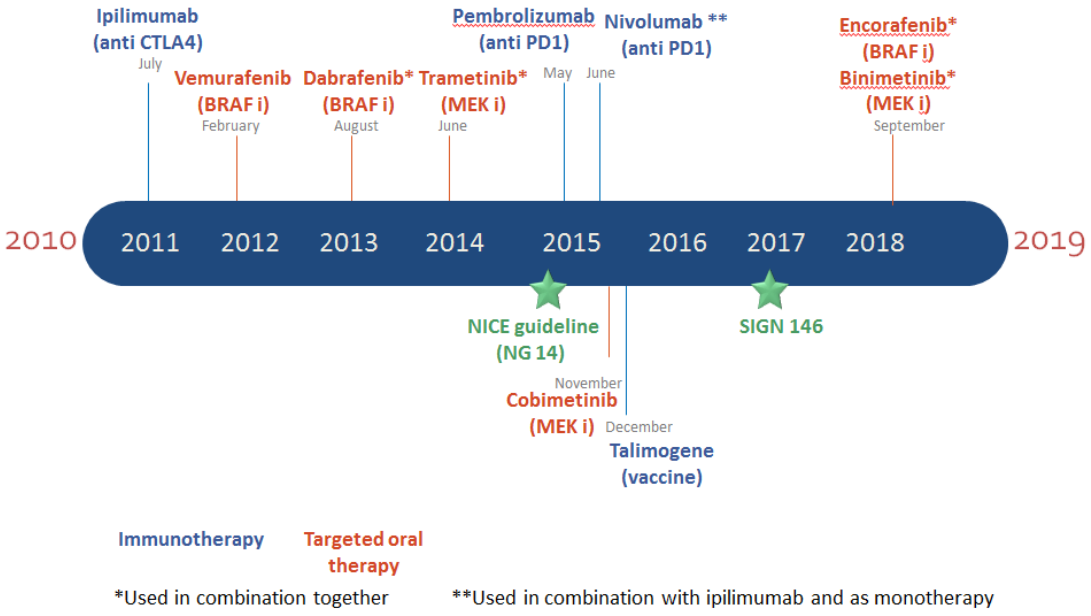


Figure 3. Treatments available in the UK for advanced (unresectable or metastatic) melanoma since 2010.

Treatment and prescribing decisions made by patients and clinicians should follow clinical management guidelines which should be in accordance with SMC advice and may consider practical aspects such as time needed for infusions or frequency of patient monitoring. These guidelines are reviewed regularly as new information becomes available. When this study was designed in 2018, dabrafenib and trametinib could only be prescribed as a first line treatment, to patients who had a BRAF mutation; combination nivolumab and ipilimumab was also restricted to treatment in the first line whilst pembrolizumab could be administered following any SACT, except ipilimumab. Ipilimumab could be prescribed for patients who received any prior SACT. (Scottish Medicines Consortium 2013; Scottish Medicines Consortium 2014; Scottish Medicines Consortium 2015a; Scottish Medicines Consortium 2015b; Scottish Medicines Consortium 2016a; Scottish Medicines Consortium 2016b; Scottish Medicines Consortium 2016c) This meant that, in the West of Scotland in 2018, patients with advanced (unresectable or metastatic) melanoma had two or three main options for treatment depending on their BRAF status. Those who were BRAF mutant could receive first line targeted SACT with dabrafenib and trametinib with pembrolizumab as a second line treatment option, or consideration of an individualised patient request to get permission to use the combination of ipilimumab with nivolumab in the second line. Both immunotherapy treatments could also be considered as first line therapy with consideration of an individualised patient request to get permission to use dabrafenib with

trametinib in the second line. Patients who were BRAF wildtype could consider either combination (ipilimumab with nivolumab) or single agent immunotherapy. Pembrolizumab had been the PD1 checkpoint inhibitor of choice due to the dosing intervals which were every 3 weeks instead of nivolumab which was administered fortnightly. Whilst there had not been a study to compare the difference in benefit between single or combination immunotherapy the results of the clinical trials in table 2 suggested that whilst there potentially was a survival benefit with the combination immunotherapy this was offset with the increased incidence of severe adverse events which needed careful consideration by patients and clinicians.

Published real world evidence (RWE) from routine clinical practice to support treatment decisions has increased but was initially limited to expanded access programmes with vemurafenib or ipilimumab (first medicines to market) or general survival analysis comparing OS of patients with advanced (unresectable or metastatic) melanoma before and after the introduction of the newer treatments described in this chapter. (Middleton et al. 2016; Polkowska et al. 2017; Forschner et al. 2017) Other RWE described earlier relates to specific SACT only i.e. only targeted treatments or immunotherapy, and does not compare outcomes with different types of SACT in a single cohort. Therefore there is a need for studies of SACT use in routine clinical practice, to better understand the impact of varied treatment regimens in the management of patients with advanced (unresectable or metastatic) melanoma. Most of the real world studies described in this chapter used data either from patient medical records or specialist databases. Collecting data from patient medical records is a labour intensive, time consuming process; developing a more efficient process to collect and analyse data from routine clinical practice would facilitate RWE generation in a standardised method and enable patients and clinicians to make better informed treatment decisions.

2. Study Rationale

2.1 **Study Rationale**

The literature review in the introduction revealed a lack of real world evidence for treatments for advanced (unresectable or metastatic) melanoma and consequently patients and clinicians are making treatment decisions based on results published from clinical trials supplemented with clinical experience. However, it is increasingly recognised that clinical trials are not fully representative of the real world population as less than 10% of all oncology patients participate in clinical trials. (Murthy et al 2004) Patients with brain metastases, ocular or mucosal melanomas, poor performance status or laboratory values such as albumin levels or haemoglobin out with normal ranges are typically excluded from advanced melanoma clinical trials but not from treatment in the real world. Generating information and evidence about how these patients may respond to treatments in routine clinical practice enables patients and clinicians to make better informed treatment decisions.

The NHS in Scotland is a publicly-funded healthcare system used universally by the Scottish population. Funding comes from the Scottish Government and it is important that this funding is used appropriately to provide high quality care for all and maximise value for money. The introduction of new, often expensive, systemic anti-cancer treatments (SACT) to clinical practice in the NHS in Scotland is subject to a positive appraisal from the SMC. Applications are submitted by pharmaceutical companies and carefully evaluated for evidence of patient benefit and effective use of limited NHS resources. (Scottish Medicines Consortium 2018)

Evaluating real world effectiveness and safety of medicines in Scotland, including SACT, is facilitated by having a unique identification number called the Community Health Index (CHI) for all Scottish residents, enabling population studies to be carried out. This CHI is included in records each time a person interacts with the NHS. (Scottish Government 2015) This enables longitudinal follow-up of patients as their data from multiple sources, such as prescriptions, mortality and hospital records, can be linked and interrogated to answer research questions. It was envisaged that electronic record linkage (ERL), by CHI, of routinely collected data could be an alternative method to gather intelligence on the real world outcomes of medicines instead of the more traditional, time consuming, review of patient case notes at an individual patient level (IPLR). The NHS in Scotland comprises of 14

different, regional Health Boards which are grouped into three different regional cancer networks (South East Cancer Network; North Cancer Alliance; West of Scotland Cancer Network). These linked groups of health professionals and organisations from primary, secondary and tertiary care, work in a co-ordinated manner to support equitable provision of high quality clinically effective services. Advanced (unresectable or metastatic) melanoma is relatively rare with a limited number of clinicians treating these patients. As a result of this all patients from the West of Scotland Cancer Network (comprising NHS health boards Ayrshire and Arran; Forth Valley; Greater Glasgow and Clyde and Lanarkshire) are treated by clinicians at the Beatson West of Scotland Cancer Centre in Glasgow, providing a discrete population to investigate medicine use in routine clinical practice.

2.2 **Research Questions**

What are the clinical outcomes (intended and unintended) for patients in the West of Scotland receiving SACT for advanced (unresectable or metastatic) melanoma?

Can CHI linked, routinely collected, data be used to robustly identify, describe and determine the clinical outcomes of SACT in advanced (unresectable or metastatic) melanoma?

2.3 Aims and Objectives

The main aims of the study were:

1. To determine the clinical outcomes of patients receiving SACT for advanced (unresectable or metastatic) melanoma in the West of Scotland.
2. To test the validity of utilising electronic record linkage (ERL) of routinely captured data in evaluating clinical outcomes of SACT (immunotherapy and targeted treatments) for advanced (unresectable or metastatic) melanoma

The objectives were:

- Identify a cohort of patients with advanced (unresectable or metastatic) melanoma who received the SACT of interest
- Describe the baseline characteristics of the patient cohort
- Determine outcomes of SACT including: median overall survival (OS); incidence of toxicities; duration of treatment; time to subsequent treatments
- Identify patient factors associated with OS
- Compare the results generated from electronic record linkage (ERL) with results generated from individual patient level review (IPLR).

3. Method and Data Sources

3.1 Study Design

This was a longitudinal, retrospective cohort study of patients who were prescribed SACT for advanced (unresectable or metastatic) melanoma identified from the Chemotherapy Electronic Prescribing and Administration System (CEPAS) from November 2010 to December 2017. The study had two phases: Phase 1 was electronic record linkage (ERL), by CHI number, of routinely collected healthcare data in the Robertson Centre Safe Haven; Phase 2 was analysis of data collected from individual patient case notes (IPLR) to validate the results generated from ERL. (Figure 3)

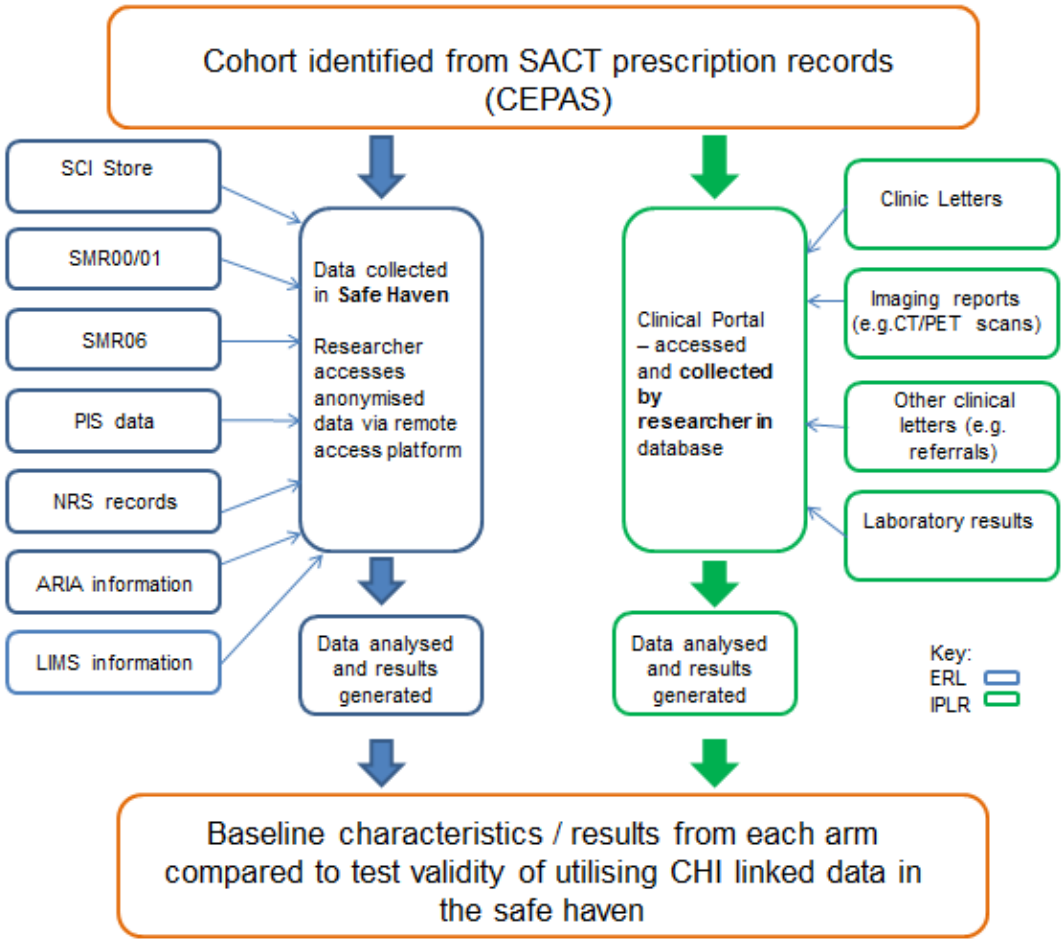


Figure 4. Study design summary

3.2 Data Sources

3.2.1 Robertson Centre Safe Haven

Five safe havens were established in Scotland to enable rapid access to high quality health data for research purposes. Safe Havens are a secure location in which patient data, from multiple sources, can be linked using individual Community Health Index (CHI) numbers: a unique 10-digit number used to identify individuals consistently across health services in Scotland. The CHI number contains personal, identifiable information (date of birth and gender) and use of an individual's CHI number is mandatory on all clinical communications facilitating the linkage of patient information from multiple sources. (Scottish Government, 2013)

Once data is linked it is anonymised before being made available to researcher via a secure virtual private network (VPN) connection. In order to ensure patients cannot be identified inadvertently results where n is less than five cannot be reported. The data sources utilised by the safe haven for this study are described in more detail in this section (3.2).

3.2.2 Chemocare® - Chemotherapy Electronic Prescribing and Administration System (CEPAS)

This data source was used for both ERL and IPLR. Chemotherapy Electronic Prescribing and Administration System (CEPAS) records SACT prescribed and administered to patients in WoSCAN. It has been used in NHS GGC since 2007 with data relating to SACT prescriptions reliably available from 2010.

In line with CEL 30 (Scottish Government 2012), CEPAS helps to facilitate safe SACT prescribing. All prescriptions for SACT are written electronically with CEPAS providing a disease tree structure to ensure that SACT regimens are allocated to specific tumour types; treatment intents and lines of therapy are also used, when necessary, to facilitate prescribing. The records are stored in a single place which provides information that may be utilised for audit and research purposes. This enabled all SACT prescribed for advanced (unresectable or metastatic) melanoma to be identified for the study.

Patients are prescribed treatments assigned to a specific diagnosis i.e. advanced melanoma, with patient demographics such as age, weight recorded at every cycle. Recording of

Eastern Cooperative Oncology Group performance status (ECOG PS) has been mandatory since July 2015 and gives an indication as to the fitness of patients for treatment. (Oken et al. 1982) For each prescribed cycle, date of treatment and any dose adjustments or delays should be recorded along with reasons for these changes. A limited number of supportive medications such as cyclizine for nausea/vomiting or loperamide for diarrhoea may also be prescribed on CEPAS.

A recognised limitation of this data source is the inability to determine if an authorised treatment had definitely been administered. For the purposes of this study it was assumed that all authorised prescriptions were administered to patients.

Information from CEPAS was expected to be equally available in the safe haven and data collected by the researcher. It was used to estimate Body Mass Index (BMI) for patients; identify ECOG PS at index date and provide information about total number of SACT given (Tables 4 & 5). Data from this source was also used to determine duration of treatment and incidence of treatment modifications as a surrogate measure for adverse events (Tables 7 & 8).

3.2.3 Scottish Morbidity Records (SMR)

This data source was used for ERL only. The Information Services Division (ISD) is a part of NHS Scotland which provides health information, intelligence and statistical services to support the NHS in planning and decision making to facilitate quality improvement. ISD gathers data from hospital inpatient and outpatient attendances, utilising CHI numbers, in a number of different datasets, two of which were used for this study:

SMR00 – Outpatient Attendance

SMR01 – General Acute Inpatient and Daycase Attendance

For SMR00 and SMR01 clinical coding staff extract information from patient discharge letters and other clinical documents and use appropriate codes from the UK and internationally recognised clinical coding schemes, International Classification of Diseases, 10th edition (ICD10) and Office of Population Censuses and Surveys procedural codes, 4th revision (OPCS-4), to record activity in a standardised manner. This is recorded at an individual patient level, alongside other information such as demographic details and treatment locations. This information is utilised in routine national reports such as those of

acute hospital activity but it is also available for research, such as this project, subject to required permissions and anonymisation in a safe haven. (Information Services Division Scotland 2010)

There are variations in the completeness of these data at both different timeframes and between different health boards but the current data completeness, estimated for the quarter ending 31st March 2018 are: 98% for SMR00 (new attendances) and 93% for SMR01 (Information Services Division Scotland 2018)

Information from both SMR00 and SMR01 was used to determine the Charlson comorbidity index, (Quan 2011; Charlson et al. 1987) an indicator of patients' co-morbidities prior to starting SACT. SMR01 was also interrogated to gain information on emergency hospitalisations of patients receiving SACT as potential surrogate measure for severe adverse events (Table 7).

3.2.4 Scottish Cancer Registry (SMR06)

This data source was used for ERL only. ISD collects data for the Scottish Cancer Registry (SMR06). This dataset records details of all new cases of cancer in Scottish residents including primary malignant and haematopoietic neoplasms; carcinoma in situ and benign brain and spinal cord tumours. (Information Services Division Scotland 2010). The registry was first started in 1958 and collected personal, demographic and diagnostic information (histology, behaviour, histological confirmation) but a new, electronic cancer recording system was introduced in 1997. This system enabled further information on tumour stage to be collected for some cancers (breast, cervical and colorectal) alongside details about tumour grade and treatment information. (Information Services Division Scotland 2018). Details of other contributing factors may also be recorded; this included details of Breslow thickness for melanomas. SMR06 also uses the internationally recognised clinical coding schemes, ICD10 and International Classification of Diseases for Oncology 3rd edition (ICD O) to identify cancer types. C43 is used for cutaneous melanomas but other codes may be used for ocular and mucosal melanomas. Specific details about the use of ICD10 and ICD O codes to determine cancer site are included in Appendix 1.

The incidence date is recorded as the earliest date the cancer has been suspected and may pre date any relevant pathology or radiological investigations. Information about suspected cases is linked using probability matching and a provisional cancer registration record is

created. Cancer Information Officers (CIOs) use the electronic source data on the registration system along with local hospital systems, case notes and primary care records, to determine if the provisional registration should be verified. (Scottish Public Health Observatory 2018) A limitation with data captured from this source was that the information provided related to the initial cancer diagnosis for each patient but it had limited information about the metastatic diagnosis or disease pathway, unless the patient was initially diagnosed with metastatic disease.

National cancer statistics are produced by ISD by linking information from SMR06 with other datasets such as National Records of Scotland (NRS), described in section 3.2.5. The rate of completeness for SMR06 for 2017 was 90%. (Information Services Division Scotland 2017)

Data from SMR06 were used in this study to: determine the primary site of melanoma and to calculate the time from primary diagnosis to index SACT (Table 5).

3.2.5 National Records of Scotland

This data source was used for ERL only. National Records of Scotland (NRS) is the government department responsible for the registration of life events such as births, deaths and marriages along with the census of Scotland's population every 10 years. The civil registration system, which covers every regular resident of Scotland, provides information to the National Health Service Central Register (NHSCR) utilising the Community Health Index and so can be linked to other CHI records, including those originating from NHS services. (National Records of Scotland 2019)

3.2.6 Prescribing Information System (PIS)

This data source was used for ERL only. The Prescribing Information System (PIS) is the definitive data source for information relating to primary care prescriptions in Scotland. It includes data about the medication prescribed and dispensed alongside information about the prescriber and dispenser but does not include indication for medication.

Although prescribing data is available from 1993, CHI coverage has only been deemed sufficient to enable linkage of prescriptions at an individual patient level since April 2009. The CHI capture rate for this source, showing the availability of patient level data, is almost 100% for both prescribed and dispensed items. Data is thought to have a high level of

completeness because prescriptions need to be submitted for reimbursement purposes. (Alvarez-Madrazo et al. 2016)

As PIS data does not include information on the specific indication for each medicine i.e. ramipril for hypertension or heart failure it can only be used to provide an indication of co-morbidities for patients' prior to starting SACT. It was also used to estimate incidence of a limited number of AEs with SACT. Further details are provided in chapter 3.4.2.2.

3.2.7 Laboratory Information Management System (molecular pathology)

This data source was used for ERL only. The West of Scotland laboratory Genetics Department has assayed melanoma samples for BRAF codon 600 mutations since January 2013, with the results collected in a local database. Staff working in the department submitted an extract from the database to the Robertson Centre safe haven to facilitate identification of BRAF status for the patients in the study cohort.

3.2.8 ARIA®

This data source was used for both ERL and IPLR. ARIA® is a radiotherapy management system from which information about planned radiotherapy treatments was gathered. This included date(s) of treatment alongside treatment intention. It was limited to details of planned radiotherapy only and does not provide full details of actual treatment given but as this project was not looking at the impact of radiotherapy this was sufficient for baseline characterisation of patients.

3.2.9 Clinical Portal®

This data source was used for IPLR only. Clinical Portal® is a web based application that presents patient clinical data i.e. past medical history and diagnosis information, from multiple sources such as blood test results; radiology reports; letters (e.g. outpatient; discharge and referral letters) and molecular pathology information relating to BRAF status. Members of the healthcare team working in NHS GGC are able to access information about patients via Clinical Portal®, depending on role-based permissions.

This source was used to record baseline patient and tumour characteristics for the validation phase of the study. Limitations with this source include potential misinformation

due to typographical errors; transcription errors; missing letters e.g. when letters are unavailable or patients receive additional treatment in other settings (alternative health boards or private sector). Discrepancies and queries arising from data collected from this source were discussed with the clinical team to gain consensus where possible or if necessary items were noted as 'not recorded'. Patients' paper case notes were not checked.

3.3 Study cohort and Setting

The study was conducted in WoSCAN, which includes four health boards: NHS Ayrshire and Arran; NHS Forth Valley; NHS Greater Glasgow and Clyde and NHS Lanarkshire. WoSCAN serves a population of approximately 2.5 million patients, almost half the population of Scotland (46.5%). (WoSCAN 2017) Patients with advanced (unresectable or metastatic) melanoma residing in any of the four constituent health boards of WoSCAN and who received treatment at the Beatson West of Scotland Cancer Centre in Glasgow were eligible for inclusion in the study subject to the following criteria:

Inclusion Criteria:

Patients diagnosed with advanced (unresectable or metastatic) melanoma and commenced on at least one of the following treatments after 1st November 2010 and before 31st December 2017:

Targeted treatments:	Vemurafenib Dabrafenib +/- trametinib
Immunotherapy:	Ipilimumab+/- nivolumab Pembrolizumab

Prescription details, including doses and supportive medicines routinely supplied as part of the SACT regimens are included in Appendix 2.

Exclusion criteria:

- Treatment administered as part of an investigational clinical trial where the active treatment cannot be identified
- Patients under 18 years of age at index date
- Patients from health boards out with WoSCAN
- Treatment started after 31st December 2017

Patients were followed up from their first SACT (index date) to the end of the study period (31st March 2018), ensuring all patients had at least 3 months follow up (Figure 5).

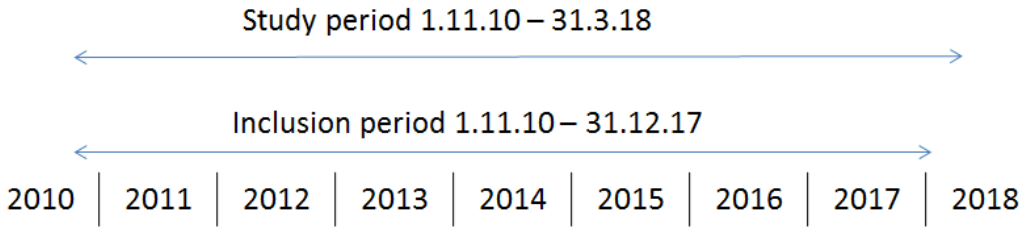


Figure 5. Study timeline

3.4 Study Outcomes and Analysis Plan

The primary clinical outcome measure of the study was overall survival (OS), stratified by patients' index SACT treatment. Additional secondary outcome measures were evaluated to enhance the information available to patients and clinicians when making treatment decisions and included: time to next SACT treatment (proposed proxy measure of progression free survival) and incidence of adverse events.

3.4.1 Overall Survival

Overall survival (OS) was estimated using Kaplan-Meier methodology and defined as the time from first (index) SACT prescription date (exposure) until date of death, or end of study period whichever happened first. This was estimated for the whole cohort and was stratified by the initial SACT (index SACT) prescribed for each patient.

Median OS and one-year landmark survival rate with 95% confidence intervals was reported for the total cohort as well as for the index SACT prescribed. Median follow up time for the cohort was calculated in two ways:

- Descriptive measure using median total observation time (time from first SACT date to death or end of follow up time)
- Reverse Kaplan-Meier estimate of potential follow up time had the patient not died (event of interest is reversed to survival). (Schemper, Smith 1996)

3.4.1.1 *Study covariates*

Kaplan-Meier methodology was used to estimate median OS of each SACT but there were a number of patient (Table 4) and treatment (Table 5) characteristics which may have affected SACT choice and OS. Data regarding potential confounders was collected at the index date to enable exploration of potential risk factors for OS. Basic demographic information, such as age, gender and deprivation status using the Scottish Index of Multiple Deprivation (SIMD), ranging from 1 (most deprived) to 5 (most affluent) (Scottish Government 2020) was captured alongside lactate dehydrogenase (LDH) levels and neutrophil to lymphocyte ratio (NLR) score. LDH levels above the upper limit of normal (ULN) are recognised as a poor prognostic factor (Diem et al. 2016). NLR score is a marker of systemic inflammation that has demonstrated prognostic value in pancreatic and breast cancers but has not been reported in advanced (unresectable or metastatic) melanoma however it was calculated for inclusion in analysis to explore whether or not this translates to melanoma. (Guthrie et al. 2013; Walsh et al. 2005)

It is often hypothesised that patients with multiple co-morbidities, or those who are less fit, may not have the same benefit with cancer treatments as fitter patients. For the purposes of this study, co-morbidities, estimated using the Charlson score, (Quan et al. 2011) and number of distinct medicines dispensed for a patient in the year prior to starting treatment, was also included. Eastern Co-operative Oncology Group Performance Status (ECOG PS), valued from 0 (fully active) to 5 (dead), was also included, where available, as it is a subjective measurement of each patient's fitness for treatment. (Oken et al. 1982)

Body-mass index (BMI), calculated from each patient's height and weight, was also included since a recent study has suggested that BMI may have an impact on OS, with patients who are overweight or obese appearing to have a better prognosis than those who have a BMI within normal range. (McQuade 2018)

Table 4. Study cohort details: patient specific factors captured for analysis

Co-variate	Data manipulation / calculations	Categories
Eastern Cooperative Oncology Group Performance Status (ECOG PS)	Extracted from CEPAS records on, or prior to, index date Recording was made mandatory in July 2015	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 Not recorded
Lactate Dehydrogenase levels (LDH levels)	Taken from blood sample closest to, but up to 28 days prior to, index date	Normal range= 80-240 Units/Litre; Above upper limit of normal (ULN) = >240 Units/Litre Not recorded
Neutrophil to Lymphocyte Score (NLR score)	Calculated from neutrophil and lymphocyte count closest to, but up to 28 days prior to, index date.	Neutrophil: lymphocyte ratio ≥5 = 1 Neutrophil: lymphocyte ratio <5 = 0 Unable to determine
Co-morbidities – **1. Charlson Score** **2. No. of medicines prescribed in primary care prior to SACT**	1. Calculated from data in SMR00 and SMR01 2. Number of PIS prescriptions for distinct medicines each patient has received in prescriptions in the calendar year prior to index date.	1. Grouped as: 0; 1; 2; 3+; Unable to determine 2. Grouped as: 0-4 medicines; 5-9; 10-14; 15-19; more than 20
Body Mass Index (BMI)	Calculated at index date: BMI = $\frac{(\text{height (m)})^2}{\text{weight (kg)}}$	18-<25 (normal); <18 (underweight); 25-29.9 (overweight); ≥30 (obese) Unable to determine
Scottish Index of Multiple Deprivation (SIMD)	Extracted directly from the Safe Haven based on patients' postcode	1; 2; 3; 4; 5; Not recorded

Along with patient factors, a number of tumour and treatment factors were also included such as primary melanoma site; time from initial diagnosis; BRAF status; total number of SACT received and whether or not patients switched from the index SACT to a subsequent SACT (Table 5).

The Scottish Cancer Registry (SMR06) captures information on all new cases of cancer in Scotland; some patients may have more than one entry in this registry. If a patient has metastatic disease at the time of their diagnosis then this information may be recorded but information about recurrence or patients who develop metastatic disease at any time after the primary diagnosis is not routinely captured. It is generally thought that patients with non-cutaneous (i.e. mucosal and ocular) melanomas have an inferior prognosis to

cutaneous melanomas (Kuk et al. 2016) and these groups are often excluded from clinical trials. Site of primary melanoma was deduced from SMR06 for ERL, utilising ICD 10 and ICD O codes (Appendix 1). Time from initial diagnosis to start of SACT was calculated and grouped accordingly to enable this to be explored. Developing metastatic disease shortly after initial diagnosis might suggest that a patient has a more aggressive disease than patients who develop metastases after a number of years.

Treatment specific information included the total number of SACT the patient received for advanced (unresectable or metastatic) melanoma and information about whether or not a patient had received a subsequent SACT following index SACT. Patients may switch to a subsequent SACT due to disease progression or intolerable AEs but it was not possible to gather information regarding the reason for switching SACT.

Information obtained from IPLR, but not available from ERL, included presence or absence of brain metastases at index date, with the presence of active brain metastases reported to be a poor prognostic factor, (Vosoughi et al. 2018) and M classification (as per AJCC 7th Edition), an indicator of severity of melanoma (Table 1).

Table 5. Study cohort details: tumour and treatment specific factors captured for analysis

Co-variate	Data manipulation / calculations	Categories
Melanoma site	Utilised ICD 10 and ICD O codes linked to first recorded diagnosis in SMR06 (Appendix 1)	Cutaneous Ocular Mucosal Unknown primary No information - patients with no information in SMR06
BRAF status	Obtained from molecular pathology information requested specifically for this project	Mutant Wildtype Not information available
Time from initial diagnosis	Calculated, where possible, from first melanoma diagnosis date in SMR06 and first SACT date.	Less than 1year 1-3 years 3-5 years 5-10 years More than 10 years Unable to determine
Total number of SACT treatments received for advanced melanoma	Included dacarbazine, temozolomide and clinical trials. Excluded SACT for other cancers and radiotherapy	1 2 3+
Treatment switch		Y – patients who received a subsequent SACT for advanced melanoma after index SACT N – no further SACT

3.4.1.2 *Analysis*

Cox Proportional Hazard models were used to estimate the effect of each index SACT on OS. The first step was to estimate the unadjusted hazard ratios for survival for the patient and tumour covariates described in tables 4 and 5 to identify factors that might have an impact on OS. The baseline characteristics were also compared between index SACT to identify any significant differences between them that might influence OS and should be included in the regression model.

In order to fit the best regression model, with index SACT as the exposure, each covariate that had a p-value<0.05 in the univariate analysis, alongside a priori confounders (age; gender; LDH levels and melanoma site) identified from the literature search, were added to the adjusted multivariable Cox regression model to examine the effect each potential confounder had on the exposure. Any variables that were missing for more than 10% of patients in the univariate analysis were not included in the multivariate Cox-regression model.

The effect of regimen choice on treatment switching was explored further with an interacted model to determine changes to hazard ratios for patients who received a subsequent SACT.

3.4.2 Secondary clinical outcomes

In order to maximise the information available when patients and clinicians are making treatment decisions, this study also evaluated outcomes regarding SACT duration, time to next SACT and adverse events (AE) with SACT for all exposures to SACT, not just the initial SACT.

3.4.2.1 *Duration of SACT*

Clinical trials often report progression-free survival (PFS) for SACT when data regarding overall survival is not mature enough. It was not possible to report this with ERL as imaging reports are not available in the safe haven. Duration of SACT and time to next SACT were proposed as potential surrogate measures for PFS as all SACT included in this study, with the exception of ipilimumab which is given for four cycles only, may be prescribed until

progressive disease. Patients may, however, also stop SACT if they experience intolerable AEs but unfortunately reason for stopping or switching SACT is not routinely recorded.

Table 6. Determining duration of treatment and time to next treatment as a surrogate measure for progression free survival

Outcome	Method
Duration of SACT therapy	1. Total number of cycles of SACT given 2. Estimated (in months) using Kaplan-Meier method. For targeted treatments Event: finished treatment/ death Censor: end of study (31/03/2018) Start: first appointment date (for specific SACT) Stop: last appointment date + duration of last cycle, date of death, date of switching SACT or 31/03/2018 whichever comes first. If duration of last cycle was blank, assume it was 28 days for targeted treatments For immunotherapy Event: finished treatment/ death Censor: end of study (31/03/2018) Start: first appointment date Stop: last appointment date
Time to next treatment (months)	This was only reported for patients who progressed to subsequent SACT treatment. It was calculated from index date (for specific SACT) to the start date of the second SACT

3.4.2.2 *Adverse events (AEs)*

Information about frequency and severity of AEs is often captured during clinical trials but whilst assessment of AEs is a key part of clinical consultations with patients, this information is not captured in a format that can be assessed using ERL. Nor is it systematically recorded in electronic patient case notes. In order to attempt to capture information about incidence of AEs in real world practice, surrogate measures were used. Dose reductions are indicated for targeted SACT (vemurafenib, dabrafenib and trametinib) when patients report AEs. (Roche Products Limited 2016; Novartis Pharmaceuticals UK Ltd 2016a; 2016b) Delays to treatment are indicated for patients who develop AEs whilst receiving immunotherapy (ipilimumab with or without nivolumab or pembrolizumab) instead of dose reductions. (Bristol-Myers Squibb Pharmaceutical Limited 2016; 2017; Merck Sharp & Dohme Limited 2017) The occurrence of either dose reductions or delays was explored as a potential indication of incidence of general, non-specific AEs. Incidence of emergency hospital admissions was included as a potential measure of severe AEs. Patients

who receive immunotherapy may experience AEs at any time, even after treatment has been discontinued, (Postow et al. 2018) but AEs experienced by patients prescribed targeted treatments should find these resolve once treatment has been discontinued. For this reason, the timeframe for emergency hospital admissions was limited to time on treatment for targeted treatments but any time after index date for immunotherapy (Table 7).

Table 7. Determining dose modifications and emergency hospital admissions as surrogate measures for adverse events.

Indicator of Adverse Event	**Method**
Dose reductions - applicable to targeted treatments only	Outcome measure: The number and percentage of patients who received any dose reduction.
Treatment delays - applicable to immunotherapy only	No definition of treatment delay was identified in the literature and hence, following discussion with clinicians, an arbitrary cut off of more than 25 days for treatments given every 3 weeks and 18 days for treatments given fortnightly was used to allow for delays due to public holidays. Outcome measure: The number and percentage of patients who received a dose delay.
Emergency hospital admissions	Use SMR01 data to identify number of patients with an emergency admission to hospital. Limited to time on SACT for targeted treatments and any time after index date for patients who received immunotherapy Report median time to hospital admission from index date Identify most common reasons for admission using ICD 10 codes (must be experienced by ≥5 patients to allow results to be reported from Safe Haven)

In addition to capturing information on non-specific AEs this study explored the possibility of capturing information regarding the incidence of some of the most common AEs that were experienced in the pivotal clinical trials i.e. nausea and vomiting or rash. (Hodi et al. 2010; Chapman et al. 2011; Long et al. 2014; Larkin et al. 2015; Robert et al. 2015) This was explored by identifying new prescriptions on CEPAS, after SACT started, for supportive medications such as antiemetics. Prescriptions on CEPAS are generally written during clinical consultations, when patients are pre-assessed for treatment. During these consultations patients are assessed for AEs and prescribed supportive medicines if necessary, although it should be noted that the indication for supportive medicines is not routinely captured via CEPAS. There is no information available regarding indication for medicines in PIS either but it is recognised that AEs such as hypophysitis, hypothyroidism

and hepatitis, may require long-term immunosuppressant medication or hormone replacement to be prescribed in primary care (via PIS). These AEs are more commonly associated with immunotherapy than targeted treatments and may occur even after treatment has been discontinued. (Hodi et al. 2010; Larkin et al. 2015; Robert et al. 2015; Postow et al. 2018) (Table 8)

Table 8. Methods used to capture information on specific adverse events.

Specific Adverse Event	Method
Nausea/vomiting	New prescriptions for anti-emetics (cyclizine, prochlorperazine, metoclopramide) on CEPAS. Metoclopramide with dabrafenib was excluded as this is given routinely
Itch/rash	New prescriptions for antihistamines (cetirizine, loratidine, chlorpheniramine) and topical steroids (hydrocortisone cream) on CEPAS.
Hypothyroidism	New prescriptions for levothyroxine tablets identified on PIS at any time after index date
Hypophysitis	New prescriptions for hydrocortisone tablets identified on PIS at any time after index date
Autoimmune events	New prescriptions for oral immunosuppressants (mycophenolate, ciclosporin, sirolimus) identified on PIS at any time after index date

3.4.3 Data validation

The second aim of this study was to validate the ability of ERL to robustly determine outcomes of SACT for advanced melanoma. Baseline demographics and treatment outcomes determined via ERL were compared to IPLR by conducting Chi square tests for categorical variables (if counts were less than five, Fisher exact tests were applied instead), and two-sample t-tests for continuous variables (with transformation for variables with skewed distribution). An adjustment for multiple testing – using the Benjamini-Hochberg false discovery rate procedure – was applied to all comparison tests.

It was possible to collect additional tumour characteristics from IPLR (Table 9). The impact of these additional variables on OS was estimated in an expanded multivariable Cox model to enable comparison with the final ERL generated model. In order to fully evaluate the differences between the ERL and IPLR, two multivariate IPLR Cox-regression models were generated: one using variables available in the safe haven and the other with the additional variables only available via IPLR.

Table 9. Disease specific factors only available from individual patient level records

Factor	Data manipulation / calculations	Categories
Disease stage (as per AJCC 7th edition)	Determined using scan results available in clinical portal up to 3 months pre or 2 weeks post first SACT date and LDH levels prior to index SACT.	**M0** = no distant metastases (mets) **M1a** = Mets to skin, subcutaneous tissue, or distant lymph nodes with normal serum LDH **M1b** = Mets to lung and normal LDH **M1c** = Mets to all other visceral sites and normal LDH or distant mets to any site and elevated LDH
Presence of brain metastases	Taken from scans available in clinical portal up to 3 months pre or 2 weeks post first SACT date	Yes; No; Not scanned

Baseline factors that were found to be statistically significantly different between ERL and IPLR were examined to determine potential reasons for these differences and to consider the clinical impact of these findings. A rule of thumb is that if there is a change of more than 10% in hazard ratios for each SACT then the confounders are important. This is described and discussed further in the results and discussion.

The methods used for secondary clinical outcomes in ERL were not validated using IPLR. SACT duration and incidence of dose modifications were determined using CEPAS data which was equally available via both ERL and IPLR. Information about incidence of AEs could not be reliably captured via IPLR. Patients may report AEs in a number of ways: tiredness could be reported during a clinic appointment but may not be recorded in the letter dictated by the clinician after the appointment; AEs may also be reported to other healthcare providers such as GPs or community pharmacists, the records of which were not routinely available in outpatient appointments. For this reason the study used only surrogate measures described in 3.4.2.2 to capture limited information about AEs.

3.5 **Ethics, Approval and Governance**

It is imperative that ethical considerations and good information governance principles are followed whilst undertaking any form of research. In Scotland, applications for the use of NHS data from more than one health board are addressed to the Public Benefit and Privacy Panel (PBPP). An application was made and approved, with permission granted to access NHS Scotland originated data for purposes other than direct patient care (from both safe haven and through review of individual patient case notes), Reference 1617-0371

(Appendix 3). Separate ethical consent was not required as this project utilises data from administrative systems, which does not require expressed patient consent.

NHSGGC board information governance processes were applied in data handling, collection and storage to protect patient identifiable data for the individual case note review phase of the study. Data were stored on an NHS desktop computer in a password protected folder located within the main NHS staff server and were anonymised before analysis was conducted.

All analyses were performed using R software, version 3.3.3.

4. Results

This chapter presents the results obtained from the study. The baseline characteristics of the cohort and information relating to treatment patterns are presented followed by primary and secondary outcomes. The chapter finishes with results of the data validation work.

4.1 Study Cohort

A total of 362 patients were identified as starting treatment for advanced melanoma between 2010-2017 from the CEPAS prescriptions. The 362 patients received 556 SACT courses for advanced (unresectable or metastatic) melanoma. This included the SACT of interest for this study and other SACT such as dacarbazine, temozolomide and clinical trials (included in total number of SACT given). At censor date (31st March 2018) 249 patients were deceased. Of those that were alive (n=113): 48 patients were alive on treatment and 65 remained alive off treatment.

The median observed follow up time for the study cohort was 7.8 months (IQR 4.0-17.4). Estimated median follow up time, using reverse Kaplan-Meier methodology, was 27.7 months (95% CI 24.3-31.4).

Overall, 49% (n=176) of patients were female; median age was 64 years (IQR 51-75) and almost 80% (n=289) had an ECOG performance status of 0-1 (Table 10). Lactate dehydrogenase levels were raised in almost 40% (n=143) of patients and almost 30% (n=104) of patients had a neutrophil to lymphocyte ratio score of 1. The majority (n=217, 60%) of patients had a Charlson score (indicative of co-morbidities) of 0 although only 84 patients (23%) took fewer than 5 medicines prior to starting SACT. Over 50% (n=198) of patients were overweight or obese. Patients were spread evenly across SIMD categories.

Table 10. Baseline demographics of patients, in the West of Scotland, starting systemic anti-cancer treatments for advanced melanoma between 2010 and 2017 (n=362)

Characteristic		N (%)
Age	Median (IQR)	64 years (51-75)
Gender	Male	186 (51.4)
	Female	176 (48.6)
ECOG performance status	0	184 (50.8)
	1	105 (29)
	2+	42 (11.6)
	Not recorded	31 (8.6)
Lactate dehydrogenase level	Within normal limits	181 (50)
	Above ULN	143 (39.5)
	Not recorded	38 (10.5)
NLR Score	0	241 (66.6)
	1	104 (28.7)
	Unable to determine	17 (4.7)
Charlson score	0	217 (59.9)
	1	52 (14.4)
	2	62 (17.1)
	3+	30 (8.3)
	Unable to determine	*
Number of medicines taken in the 12 months prior to starting SACT	0-4	84 (23.2)
	5-9	106 (29.3)
	10-14	92 (25.4)
	15-19	46 (12.7)
	>19	34 (9.4)
Body Mass Index	Normal range	86 (23.8)
	Underweight	*
	Overweight	109 (30.1)
	Obese	89 (24.6)
	Unable to determine	73 (20.2)
Scottish Index of Multiple Deprivation (SIMD)	1	78 (21.5)
	2	75 (20.7)
	3	66 (18.2)
	4	65 (18)
	5	77 (21.3)
	Not reported	*

KEY: IQR = interquartile range; ECOG PS= Eastern Cooperative Oncology Group Performance Status; ULN = upper limit of normal; NLR = neutrophil-lymphocyte ratio; SACT = systemic anti-cancer treatment; *= n<5

The majority of patients had a cutaneous primary melanoma (n=274, 76%) and over 50% (n=196) started index SACT less than 3 years after the primary diagnosis. BRAF status could not be identified for almost 40% (n=142) of patients. Almost 60% (n=215) of patients received only one SACT whilst less than 30% of patients switched to a subsequent SACT after index SACT. (Table 11)

Table 11. Disease and treatment factors of patients, in the West of Scotland, starting systemic anti-cancer treatments for advanced melanoma between 2010 and 2017 (n=362)

Characteristic		N (%)
Primary melanoma site	Cutaneous	274 (75.7)
	Mucosal	25 (6.9)
	Ocular	22 (6.1)
	Unknown	28 (7.7)
	No information available	13 (3.6)
BRAF status	Wildtype	144 (39.8)
	Mutant	76 (21)
	No information available	142 (39.2)
Time from primary diagnosis to index date	Less than 1 year	86 (23.8)
	1-3 years	110 (30.4)
	3-5 years	52 (14.4)
	5-10 years	62 (17.1)
	More than 10 years	39 (10.8)
	Unable to determine	13 (3.6)
Total number of SACT given for advanced melanoma (includes chemotherapy and clinical trials)	1	215 (59.4)
	2	109 (30.1)
	3+	38 (10.5)
Treatment switch	No	261 (72.1)
	Yes	101 (27.9)

Different SACT regimens were available at different times; ipilimumab and vemurafenib the first to be used in WoSCAN, with ipilimumab the most commonly prescribed SACT overall (n=100, 28%). There was an increasing trend in patient numbers over the years, from 16 patients (4%) in 2010-11 (merged due to low patient numbers) to 83 patients (23%) in 2017 (Figure 5).

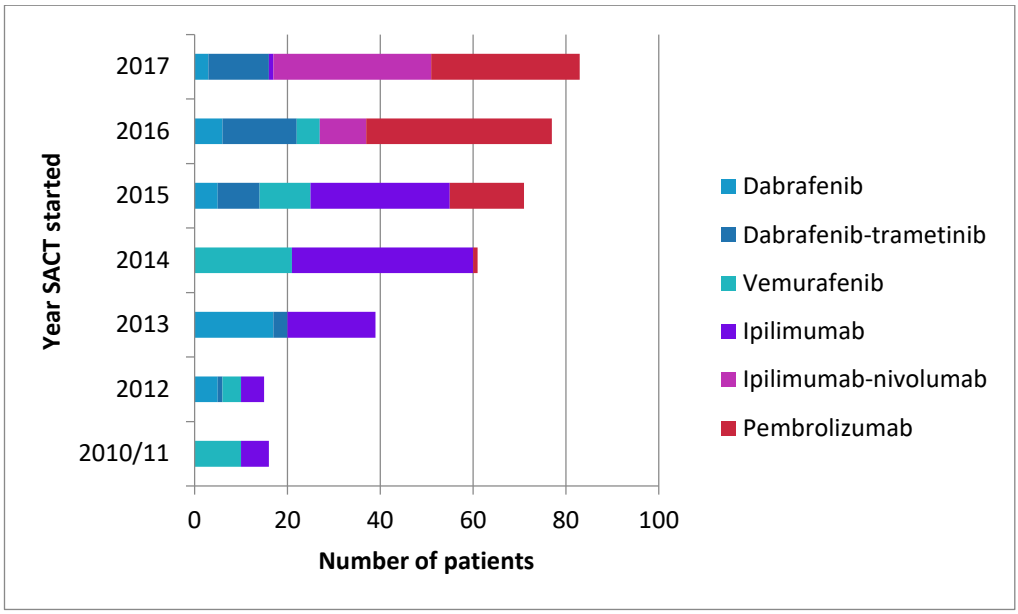


Figure 6. Bar chart showing SACT prescriptions for patients in the West of Scotland starting treatment between 2010 -2017 (n=362)

4.2 **Overall Survival**

Median OS from first SACT date for all patients was 9.4 months (95% CI 8.0 - 11.6). The landmark survival were: one year survival 44.2% (39.2-49.9); two year survival 29.3% (24.6-35.1); three year survival 23.7% (19.0-29.6)

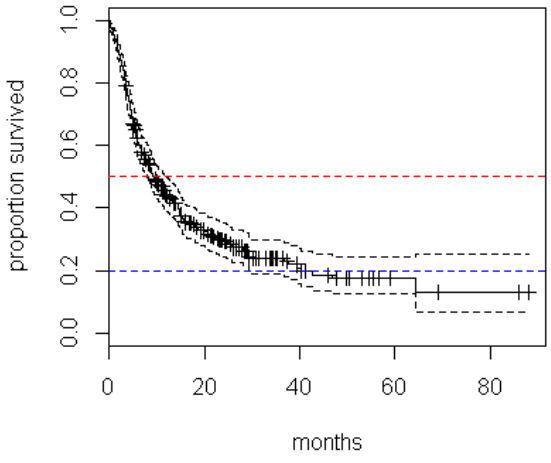


Figure 7. Kaplan-Meier curve showing overall survival for the study cohort from index SACT date

Ipilimumab was the first SACT licensed for use in advanced melanoma followed by vemurafenib. Both these regimens had the highest proportion of patients receiving further SACT. Median overall survival was longest for ipilimumab with nivolumab but the upper limits of the confidence intervals were not reached (Table 12).

Table 12. Overall survival for the study cohort (n=362) stratified by the index SACT

SACT	n	deaths	Median OS in months (95%CI)	n (%) patients progressing to subsequent SACT	One year survival %
Ipilimumab monotherapy	100	80	6.3 (4.9-10.3)	30 (30)	35.7 (27.4-46.5)
Pembrolizumab	89	56	8.0 (4.8-15.5)	17 (19)	46.4 (37.0-58.2)
Ipilimumab with nivolumab	44	12	18.5 (14.4-NR)	7 (16)	79.2 (68.0-92.3)
Vemurafenib	51	42	13.0 (9.9-18.0)	29 (57)	51.0 (39.0-66.7)
Dabrafenib	36	33	5.6 (4.5-7.3)	8 (22)	22.2 (12.1-40.9)
Dabrafenib with trametinib	42	26	11.5 (9.4-23.0)	11 (26)	48.8 (35.3-67.5)

KEY: OS = overall survival; CI=confidence intervals; SACT = systemic anti-cancer treatment; NR = not reached

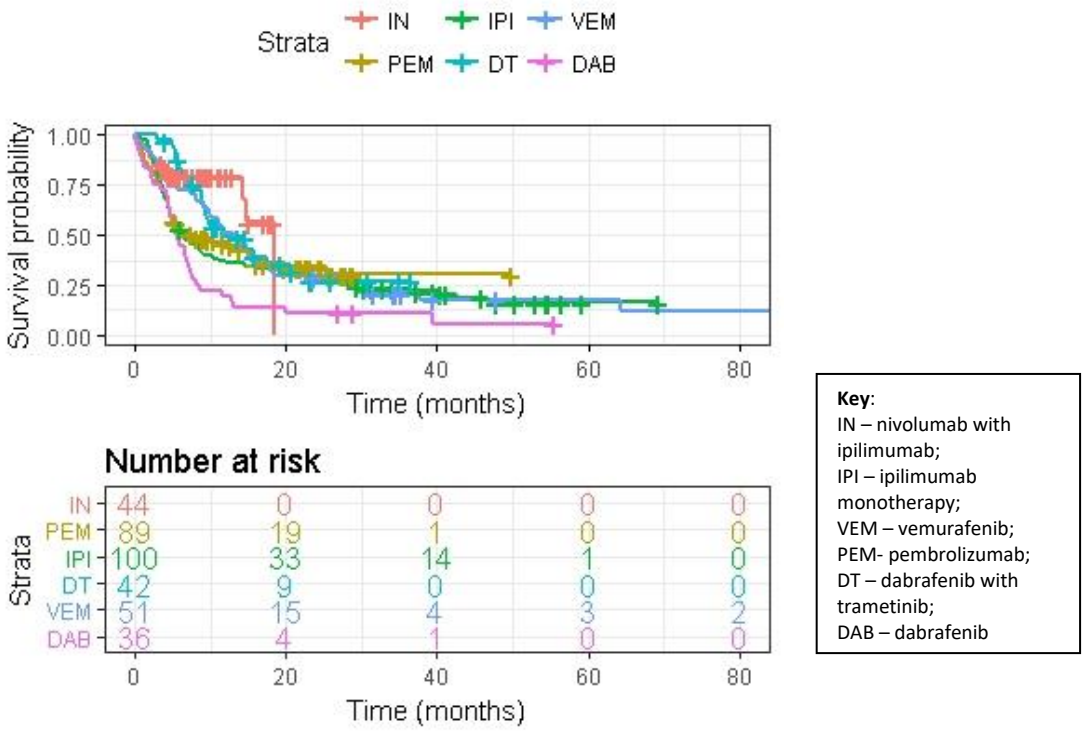


Figure 8. Kaplan-Meier survival curves showing overall survival for the index SACT for the study cohort (n=362)

The impact of each of the study variables on OS were evaluated using univariate Cox-regression analysis (Appendix 4). The results from the univariate analyses indicated a significant association between OS and initial SACT choice: all regimens, except for dabrafenib monotherapy, showed an improvement in OS when compared to ipilimumab monotherapy. LDH levels above the upper limit of normal; NLR score equal to 1; poor PS (1+) at baseline and an increasing number of medicines prior to starting SACT were all associated with poorer survival. BMI above the normal range and increasing number of SACT given were associated with improved survival. Age; gender; site of melanoma; time from melanoma diagnosis to first SACT date; year SACT started; Charlson score and DEPCAT did not have a statistically significant impact on OS. Chi square and fisher exact tests were used to identify statistically significant differences between baseline characteristics for each SACT to identify any other variables that could be considered for inclusion in the multivariable analysis. Those that were found to be statistically significantly different are included in Table 13. There were statistically significant differences in the performance status between SACT types: patients prescribed ipilimumab with nivolumab had better ECOG PS than those prescribed pembrolizumab whilst there were more patients with unknown BMI in the targeted treatments (vemurafenib, dabrafenib and trametinib). As shown in figure 5 there were significant differences in the year SACT started and more patients receiving ipilimumab and vemurafenib switched to further SACT than in the other regimens.

Table 13. Statistically significant differences in baseline characteristics for patients at index SACT for advanced melanoma in the West of Scotland from 2010-2017 (n=362)

SACT		IPI	PEM	IN	VEM	DAB	DT	Comparison p-value
N		100	89	44	51	36	42	
Median Age (IQR) in years		65 (52.8-74)	77 (67-83)	58 (49.8-64.3)	57 (48.5-66)	59.5 (48-69.8)	57 (45-68.5)	
Variable		**% patients with each variable**						
ECOG PS	0	55	37.1	84.1	60.8	25	45.2	0.0005
	1	26	51.7	13.6	23.5	16.7	21.4	
	2+	1	11.2	2.3	7.8	44.4	23.8	
	Unknown	18	0	0	7.8	13.9	9.5	
Body Mass Index	Normal range	33	31.5	29.5	7.8	8.3	11.9	0.0005
	Underweight	0	1.1	4.5	0	2.8	2.4	
	Overweight	34	38.2	29.5	19.6	16.7	28.6	
	Obese	33	29.2	36.4	5.9	11.1	16.7	
	Unknown	0	0	0	66.7	61.1	40.5	
Primary site	Cutaneous	68	68.5	65.9	86.3	94.4	90.5	0.003
	Mucosal	13	6.7	11.4	2	0	0	
	Ocular	10	10.1	6.8	0	0	0	
	Unknown (known)	8	9	9.1	9.8	2.8	4.8	
	No SMR06 information	1	5.6	6.8	2	2.8	4.8	
LDH levels	Within normal limits	59	52.8	63.6	37.3	27.8	42.9	0.001
	Above ULN	31	42.7	36.4	41.2	61.1	35.7	
	Unknown	10	4.5	0	21.6	11.1	21.4	

SACT		IPI	PEM	IN	VEM	DAB	DT	Comparison p-value
NLR Score	0	70	74.2	77.3	56.9	50	57.1	0.0005
	1	28	25.8	22.7	31.4	41.7	28.6	
	Unknown	2	0	0	11.8	8.3	14.3	
Line of treatment	1	40	100	100	94.1	94.4	97.6	0.0005
	2+	60	0	0	5.9	5.6	2.4	
Total number of SACT given	1	27	83.1	90.9	43.1	72.2	71.4	0.0005
	2	49	15.7	9.1	33.3	27.8	28.6	
	3+	24	1.1	0	23.5	0	0	
Patient had subsequent SACT	No	60	85.4	90.9	45.1	83.3	73.8	0.0005
	Yes	40	14.6	9.1	54.9	16.7	26.2	
BRAF status	Wildtype	32.0	93.3	65.9	0.0	0.0	0.0	0.0005
	Mutant	3.0	1.1	29.5	23.5	36.1	81.0	
	Unknown	65.0	5.6	4.5	76.5	63.9	19.0	

KEY: SACT=systemic anticancer treatment; IPI=ipilimumab monotherapy; PEM=pembrolizumab; IN=ipilimumab with nivolumab; VEM=vemurafenib monotherapy; DAB= dabrafenib monotherapy; DT=dabrafenib with trametinib; ECOG PS=eastern cooperative oncology group performance status; LDH=lactate dehydrogenase; NLR=neutrophil to lymphocyte ratio; ULN=upper limit of normal

The multivariable Cox-regression model included a priori factors (gender, age and primary melanoma site) along with those variables that were significantly associated with OS in the univariate analysis (Appendix 4). Ipilimumab was used as the comparator as it had the most number of patients and is currently used in clinical practice as a second line treatment. The results from the multivariate analysis indicated a statistically significant association between OS and type of the initial SACT treatment (p=0.0012) (Table 14). Dabrafenib with trametinib (HR=0.42, 95%CI: 0.25-0.71) and ipilimumab with nivolumab (HR=0.50, 95%CI: 0.26-0.95) were shown to have statistically significantly positive impact on OS when compared to ipilimumab monotherapy. Patients who switched to subsequent SACT had an improved OS compared to those who did not (HR 0.53, 95%CI 0.39-0.73).

Patients with mucosal melanoma had a statistically significantly poorer OS compared to those with cutaneous melanoma (HR 1.86, 95% CI 1.14-3.02). Other factors associated with poorer OS were: LDH levels above the upper limit of normal (HR 1.72, 95% CI 1.28-2.31); NLR score equal to 1 (HR 2.17, 95%CI 1.61-2.94) and ECOG PS equal to 2 or higher (HR 2.28, 95% CI 1.41-3.68).

Table 14. Association of baseline characteristics with overall survival using multivariable cox-proportional hazards models

Variable		Adjusted HR (95% CI)	p-value	Global p-value
Gender	Male	1		
	Female	0.92 (0.7-1.21)	0.5407	
Age		1 (0.99-1.01)	0.6061	
Regimen	Ipilimumab	1		0.0012
	Pembrolizumab	0.86 (0.59-1.27)	0.4611	
	Ipilimumab with nivolumab	0.50 (0.26-0.95)	0.0352	
	Vemurafenib	0.93 (0.61-1.42)	0.7359	
	Dabrafenib	1.14 (0.71-1.83)	0.5954	
	Dabrafenib with trametinib	0.42 (0.25-0.71)	0.0014	
LDH level	Within normal range	1		0.0004
	Above ULN	1.72 (1.28-2.31)	0.0003	
	Unknown	1.93 (1.21-3.09)	0.0057	
NLR Score	0	1		0.0000
	1	2.17 (1.61-2.94)	0.0000	
	Unknown	1.53 (0.81-2.92)	0.1920	
ECOG PS	0	1		0.0104
	1	1.31 (0.94-1.84)	0.1154	
	2+	2.28 (1.41-3.68)	0.0007	
	Unknown	1.31 (0.81-2.12)	0.2759	
Primary site	Cutaneous	1		0.0213
	Mucosal	1.86 (1.14-3.02)	0.0122	
	Ocular	1.67 (0.97-2.90)	0.0658	
	Unknown	0.67 (0.39-1.14)	0.1378	
	No information in SMR06	1.10 (0.53-2.29)	0.7954	
Treatment switch?	No	1		
	Yes	0.53 (0.39-0.73)	0.0001	
Number of medicines prior to starting SACT	0-4	1		0.7089*
	5-9	0.90 (0.61-1.32)	0.5790	
	10-14	1.07 (072-1.60)	0.7395	
	15-19	0.93 (0.57-1.50)	0.7558	
	20 or more	1.21 (0.73-2.00)	0.4586	

KEY: HR = hazard ratio; CI=confidence interval; LDH = lactate dehydrogenase; NLR = neutrophil: lymphocyte ratio; ECOG PS = Eastern Cooperative Oncology Group Performance Status; SACT = systemic anti-cancer treatment; *ordered p-value

The effect of regimen choice on treatment switching was explored further with an interacted model comparing patients who progressed to subsequent SACT to those who

received ipilimumab and did not receive subsequent SACT. The results demonstrated that all patients who progressed to subsequent SACT had improved OS compared to those who did not. The patients who received either vemurafenib or dabrafenib monotherapy alone had poorer OS than those who only received ipilimumab whilst patients who received only dabrafenib with trametinib, pembrolizumab or ipilimumab with nivolumab and did not receive subsequent SACT still had improved OS compared to ipilimumab monotherapy (Table 15).

Table 15. Interacted hazard ratios for patients who progress to subsequent SACT

SACT regimen	No subsequent SACT	Progressed to subsequent SACT
Ipilimumab	1.00 (reference)	0.32
Pembrolizumab	0.63	0.58
Ipilimumab with nivolumab	0.35	0.13
Vemurafenib	1.17	0.37
Dabrafenib	1.31	0.45
Dabrafenib with trametinib	0.44	0.52

4.3 Secondary Clinical Outcomes

The secondary clinical outcome analysis included all SACT episodes and was not adjusted for confounding factors. As some patients received more than one SACT for advanced (unresectable or metastatic) melanoma there were 448 SACT episodes for this analysis.

4.3.1 Duration of treatment

SACT for advanced (unresectable or metastatic) melanoma is administered in cycles of varying length and all regimens, except ipilimumab which has a fixed course length of four cycles, may continue until disease progression or the patient suffers unmanageable toxicities. Duration of treatment was reported as both number of cycles prescribed and estimated using the Kaplan-Meier method (Table 16).

Dabrafenib with trametinib had the longest median duration of treatment, with the estimated duration of 11.1 months (95%CI 8.3-16.0) similar to the median OS (11.5 months (95%CI 9.4-23.0), Table 16). Ipilimumab with nivolumab and pembrolizumab both have similar duration of treatments (2.2 and 2.9 months), which is shorter than the estimated median OS for both treatments (18.5 months and 8.0 months respectively, Table 12).

Table 16. Summary of SACT duration for all prescribed courses in the West of Scotland from 2010-2017 (n=448)

SACT	N	Number (%) of patients who have stopped treatment	Estimated median duration of treatment in months (95% CI)	Median number cycles given (IQR)
Ipilimumab	127	127 (100)	2.1 (2.1-2.1)	4 (3-4)
Pembrolizumab	118	107 (90.7)	2.9 (2.3-4.1)	5 (3-12)
Ipilimumab with nivolumab	53	41 (77.4)	2.2 (1.5-4.6)	3.5 (2-8)
Vemurafenib	52	50 (96.2)	6.2 (4-7.8)	6.5 (2-9.2)
Dabrafenib	42	41 (97.6)	3.5 (3.1-4.6)	4 (3-6)
Dabrafenib with trametinib	56	41 (73.2)	11.1 (8.3-16)	10 (6-17.2)
KEY: SACT = systemic anti-cancer treatment; CI = confidence intervals; IQR = interquartile range				

Table 17 shows the proportion of patients who progressed to further SACT and the median time from the index SACT to the first date of the subsequent SACT, as a potential surrogate measure for PFS. There were 101 patients who received 138 courses of subsequent SACT (including clinical trials, dacarbazine and temozolomide). More than 50% of vemurafenib patients progressed onto further SACT with the median time for this to occur recorded as 8.1 (95% CI 6.5-10.9) months. A much smaller proportion of patients progressed to further treatment following ipilimumab with nivolumab with a median time to next treatment of 4.4 months (95% CI 3.0-not reached) followed by pembrolizumab with 18% of patients progressing to further SACT after a median of 5.5 months.

Table 17. Median time to subsequent SACT for all patients progressing to further treatment (n=138)

Regimen	N	No. (%) pts progressing to subsequent SACT	Median time to next SACT in months (95% CI)
Ipilimumab	127	36 (28)	8 (6.4-11.3)
Pembrolizumab	118	21 (18)	5.5 (4.1-14.6)
Ipilimumab with nivolumab	53	7 (13)	4.4 (3.0-NE)
Vemurafenib	52	29 (56)	8.1 (6.5-10.9)
Dabrafenib	42	12 (29)	4.4 (3.6-NE)
Dabrafenib with trametinib	56	14 (25)	6.3 (5.5-24.7)
Key: SACT = systemic anti-cancer treatment; CI= confidence intervals; NE= not estimable			

4.3.2 Adverse events

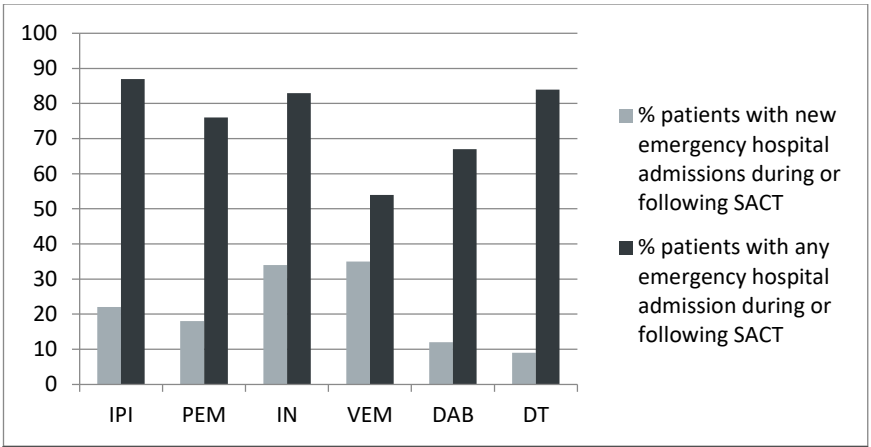
As discussed in 3.4.2.2 information about dose modifications was used to provide an indication of frequency of AEs which can be useful when patients and clinicians are making treatment decisions. The dosing schedules for targeted treatments (vemurafenib, dabrafenib and trametinib) permit dose reductions to mediate for AEs. For immunotherapy (ipilimumab, nivolumab and pembrolizumab) dose delays are used to manage AEs, with treatment restarted at the standard dose once the AE has resolved; dose reductions are not permitted. Table 18 summarises the dose modifications experienced with each treatment to enable comparison between each regimen. Vemurafenib and ipilimumab with nivolumab have the highest proportion of dose modifications overall with ipilimumab and dabrafenib monotherapy having the least. Most dose modifications happen near the start of treatment at cycle 2 or 3 although pembrolizumab is slightly later with the median cycle for dose modifications being cycle 4. Patients who only received one cycle of SACT and therefore could not have had any dose modifications were also recorded for completeness.

Table 18. Proportion of patients receiving dose modifications with each SACT regimen (n=448)

Regimen	N	Total no. cycles given	No. (%) pts with 1 cycle only	No. (%) pts with any dose modification	Median cycle for first modification (range)
Ipilimumab	127	418	14 (11)	36 (28)	3 (2-5)
Pembrolizumab	118	1129	15 (13)	53 (45)	4 (2-32)
Ipilimumab with nivolumab	53	352	8 (15)	33 (63)	3 (2-8)
Vemurafenib	52	514	10 (19)	33 (64)	2 (1-17)
Dabrafenib	42	247	8 (19)	9 (21)	2 (1-22)
Dabrafenib with trametinib	56	721	*	21 (38)	3 (1-19)
Key: *= n<5					

It was proposed that emergency hospital admissions following initiation of treatment might indicate severe adverse events. There were 247 (68%) patients with emergency admissions to hospital prior to starting SACT with any regimen and 296 (82%) patients with at least one emergency admission to hospital after starting SACT. Figure 8 shows the proportion of patients who had a first emergency hospital admission following initiation of SACT, alongside the proportion of patients who had any emergency hospital admission. Over 30% of patients receiving ipilimumab with nivolumab or vemurafenib had a new emergency

hospital admission after starting SACT but less than 10% of dabrafenib with trametinib patients did.



Key: IPI – ipilimumab monotherapy; PEM- pembrolizumab; IN – nivolumab with ipilimumab; VEM – vemurafenib; DAB – dabrafenib monotherapy; DT – dabrafenib with trametinib

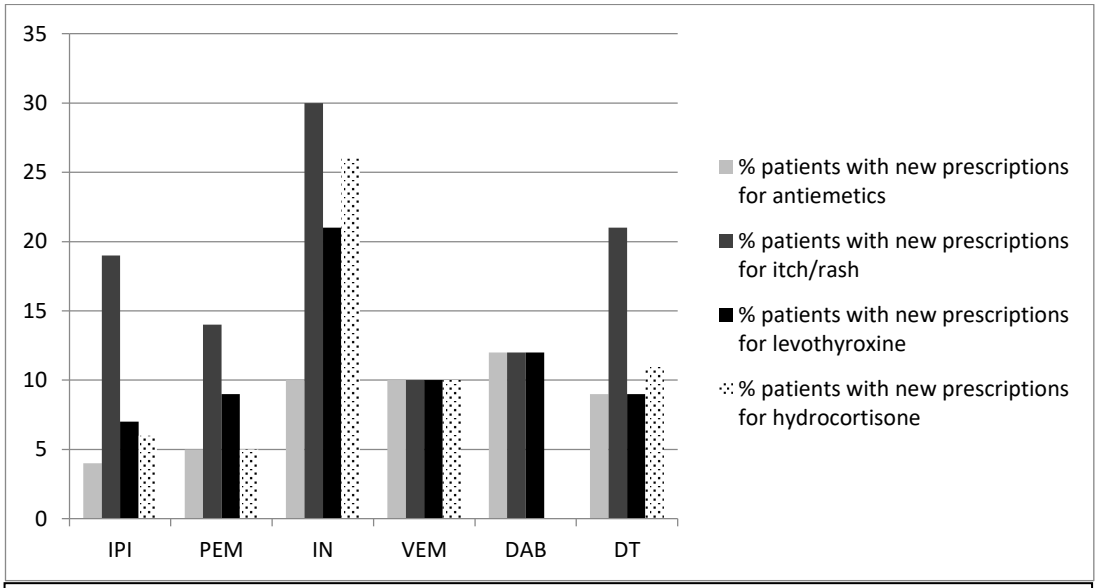
Figure 8. Bar chart showing number of patients with emergency hospital admissions during or following SACT

The median time to first emergency hospital admission after starting SACT varied from 0.5 months with vemurafenib to 3.5 months for patients receiving dabrafenib with trametinib. There were a large number of emergency hospital admissions occurring after starting SACT for a wide range of reasons but it was only possible to extract reasons for admission if more than 5 patients were identified with this condition in the Safe Haven (Table 19). Colitis was most commonly reported with ipilimumab containing regimens whilst sepsis or respiratory infections were reported in 51.8% (n=29) of patients receiving dabrafenib with trametinib.

Table 19. Median time to first emergency hospital admissions after starting SACT with most commonly reported reasons for admission (n=448)

SACT	N	Median time to first emergency hospital admission in months (IQR)	Adverse events occurring in 5 or more patients N (%)		
			Colitis	Sepsis/ Infection	Chest pain/ Anaemia
Ipilimumab	127	1.9 (1.1-4.5)	7 (5.5)	13 (10.2)	8(6.3)
Pembrolizumab	118	2.3 (0.5-4.9)		7 (5.9)	5 (4.2)
Ipilimumab with nivolumab	53	1.0 (0.4-2.0)	11 (20.8)		
Vemurafenib	52	0.5 (0.3-3.6)			
Dabrafenib	42	1.5 (0.6-2.2)			
Dabrafenib with trametinib	56	3.5 (1.1-6.8)		29 (51.8)	

The most commonly reported AEs in clinical trials varied slightly between SACT with AEs such as fatigue or high temperatures (dabrafenib/vemurafenib only) unable to be identified using ERL. Antiemetics were prescribed for 5 or fewer patients with each SACT meaning the bar chart shows the maximum possible percentage of patients prescribed antiemetics. A higher proportion of patients received prescriptions for either antihistamines or topical steroids, presumed to be prescribed for itch or rash than antiemetics. New prescriptions for itch/rash, levothyroxine and hydrocortisone were most common for patients who received ipilimumab with nivolumab (30%; 21% and 26% patients respectively). (Figure 9)



Key: IPI – ipilimumab monotherapy; PEM- pembrolizumab; IN – nivolumab with ipilimumab; VEM – vemurafenib; DAB – dabrafenib monotherapy; DT – dabrafenib with trametinib;

Figure 9. Bar chart showing percentage of patients prescribed supportive medicines, presumed to be for treatment of adverse events with SACT

4.4 **Data Validation**

4.4.1 Baseline characteristics

The first stage of data validation was to compare the baseline characteristics identified from ERL and IPLR. Chi squared tests and fisher tests (for counts less than five) were carried out to check for statistically significant differences between the two sets (Table 21). Tumour baseline factors that could only be captured from case note review: AJCC M-Stage; presence of brain metastases were also presented for information. Data only available utilising ERL was Charlson score and number of medicines prescribed for each patient in the 12 months prior to starting SACT (Table 10).

The main differences in the data sources are between primary disease site, BRAF status, NLR score and time from primary diagnosis to initial SACT appointment. There were 13 patients with no information in SMR06 meaning that primary disease site could not be determined for those patients. Slightly more patients were classed as cutaneous primary in the ERL method compared to the IPLR and there were smaller patient numbers in the other sites (ocular; mucosal and unknown primary site). There were more patients for whom an NLR score could not be determined (n=17) via ERL than IPLR.

For other variables: number of patients who are alive; Scottish Index of Multiple Deprivation; LDH levels at baseline; total number of SACT given, there were some numeric differences but none of these were shown to be statistically significant.

Table 20. Comparison of baseline factors available from electronic record linkage and individual patient level data for the cohort (n=362).

Co-variate		ERL n=362	IPLR n=362	Comparison test p-value
Primary disease site – n (%)	Cutaneous	274 (75.7)	267 (73.8)	0.0012
	Mucosal	25 (6.9)	34 (9.4)	
	Ocular	22 (6.1)	24 (6.6)	
	Unknown	28 (7.7)	37 (10.2)	
	No information	13 (3.6)		
Metastasis stage	M0 – M1b	Data not Available	111 (30.7)	NA
	M1c		243 (67.1)	
	Unable to determine		8 (2.2)	
Brain metastases	Yes	Data not Available	63 (17.4)	NA
	No		143 (39.5)	
	Not scanned or unknown		156 (43.1)	
BRAF status	Mutant	144 (39.8)	152 (41.9)	<0.001
	Wildtype	76 (21)	201 (55.4)	
	Unknown	142 (39.2)	9 (2.5)	
Lactate dehydrogenase level	ULN or less	181 (50.0)	181 (50.0)	0.3959
	Above ULN	143 (39.5)	153 (42.1)	
	Unknown	38 (10.5)	28 (7.7)	
Total No. of treatments given for melanoma (all SACT)	1	219 (60.5)	214 (59.1)	0.9258
	2	106 (29.3)	110 (30.4)	
	3+	37 (10.2)	38 (10.5)	
Neutrophil-Lymphocyte Ratio Score	0	241 (66.6)	251 (69.3)	0.0154
	1	104 (28.7)	107 (29.6)	
	Unknown	17 (4.7)	*	
Scottish Index of Multiple Deprivation	1	78 (21.5)	75 (20.7)	0.9714
	2	75 (20.7)	76 (20.9)	
	3	66 (18.2)	67 (18.5)	
	4	65 (18)	64 (17.6)	
	5	77 (21.3)	77 (21.2)	
	Unknown	*	*	
Time from initial melanoma diagnosis to first prescription date	Less than 1 year	86 (23.8)	96 (26.5)	0.0350
	1-3 years	110 (30.4)	112 (30.9)	
	3-5 years	52 (14.4)	54 (14.9)	
	5 – 10years	62 (17.1)	58 (16)	
	10+ years	39 (10.8)	41 (11.3)	
	unknown	13 (3.6)	*	
Line of initial treatment	1st	297 (81.8)	297 (81.8)	1
	2nd or higher	66 (18.2)	66 (18.2)	
Vital status	Alive	114	115 (31.7)	1
	Deceased	249	248 (68.3)	

KEY: ERL=Electronic record linkage; IPLR=Individual patient level records; SACT = systemic anti-cancer treatment

4.4.2 Overall survival

Median OS was estimated using the Kaplan-Meier method for IPLR for the whole cohort and individual SACT regimens, as per ERL, and the results were the same (see Table 12 and Figure 5).

A univariate analysis was carried out on the IPLR dataset to determine what baseline characteristics may impact OS (Appendix 5). The results were similar to those generated from the safe haven data although the additional IPLR variables: presence of brain metastases and increasing severity of disease (M1c compared to M0-M1b) both had statistically significant negative impact on OS.

The multivariate model shown in table 21 used the same variables that were included in the multivariate model from ERL, although the number of medicines prescribed prior to starting SACT was not available via IPLR. Similarly to table 14, this model shows that age and gender have no statistically significant impact on OS and there was a significant association between OS and type of the initial SACT treatment (p=0.0095). Dabrafenib with trametinib was the only regimen shown to have statistically significant, positive impact on OS (HR 0.43, 95%CI 0.26-0.74) compared to ipilimumab monotherapy.

Patients with mucosal melanoma had a poorer OS compared to those with cutaneous melanoma (HR 1.75, 95% CI 1.12-2.73). Other factors associated with poorer OS were: LDH levels above the upper limit of normal (HR 1.66, 95% CI 1.24-2.20); ECOG PS equal to 2 or higher (HR 2.46, 95% CI 1.54-3.95) and NLR score equal to 1 (HR 1.91, 95%CI 1.43-2.56). Patients who switched treatments had an improved OS compared to those who did not (HR 0.62, 95%CI 0.45-0.86). In general the hazard ratios and results were similar to the hazard ratios generated in the multivariable model from the ERL data (Table 14).

Table 21. Multivariable model utilising individual patient level data co-variates, closest to electronic record linkage model, to determine impact of baseline characteristics on OS.

Variable		Adjusted HR (95% CI)	p-value	Global p-value
Gender	Male	1		
	Female	0.86 (0.66-1.12)	0.2565	
Age		1 (0.99-1.01)	0.5053	
Regimen	Ipilimumab	1		0.0095
	Pembrolizumab	0.87 (0.6-1.28)	0.4894	
	Ipilimumab with nivolumab	0.54 (0.29-1.02)	0.0586	
	Vemurafenib	0.86 (0.57-1.3)	0.4808	
	Dabrafenib	0.95 (0.58-1.56)	0.8548	
	Dabrafenib with trametinib	0.43 (0.26-0.74)	0.0019	
LDH level	Within normal range	1		0.0008
	Above ULN	1.66 (1.24-2.2)	0.0007	
	Unknown	1.98 (1.22-3.22)	0.0060	
NLR Score	0	1		0.0001
	1	1.91 (1.43-2.56)	0.0000	
	Unknown	1.38 (0.73-2.6)	0.3205	
ECOG PS	0	1		0.0033
	1	1.36 (0.97-1.9)	0.0727	
	2+	2.46 (1.54-3.95)	0.0002	
	Unknown	1.24 (0.76-2.02)	0.3827	
Primary site	Cutaneous	1		0.0341
	Mucosal	1.75 (1.12-2.73)	0.0145	
	Ocular	1.38 (0.8-2.38)	0.2502	
	Unknown	0.78 (0.5-1.23)	0.2827	
	No information	NA		
Treatment switcher	No	1		
	Yes	0.62 (0.45-0.86)	0.0036	

KEY: HR=hazard ratio; CI=confidence interval; LDH=lactate dehydrogenase; ULN=Upper Limit of Normal; NLR=neutrophil: lymphocyte ratio; ECOG PS=Eastern Cooperative Oncology Group Performance Status; SACT = systemic anti-cancer treatment;

The multivariable Cox-regression model with the additional variables available via IPLR demonstrated once again that age and gender have no significant impact on OS; dabrafenib with trametinib is statistically significantly better than ipilimumab monotherapy (HR= 0.38, 95% CI: 0.22-0.66). Mucosal melanomas have poorer OS compared to cutaneous melanomas (HR=1.89, 95%CI: 1.21-2.98). Poorer ECOG PS (HR=2.46, 95%CI: 1.54-3.95) and NLR score equal to one (HR=1.82, 95%CI: 1.35-2.46) continue to have a negative impact on

OS. LDH levels at baseline continue to show a statistically significant negative impact on OS, although interestingly, this is greatest in patients with unknown levels (HR= 2.09, 95%CI: 1.27-3.43). Patients who switch and receive further SACT have an improved OS (HR=0.6, 95%CI: 0.43-0.83) (Table 22).

The additional variables also show a statistically significant impact on OS: patients with more severe disease (M1c) have a poorer OS (HR=1.68, 95%CI: 1.18-2.4) whilst those without brain metastases at baseline do better (HR=0.66, 95%CI: 0.45-0.97) (Table 22).

Table 22. Multivariable model showing adjusted hazard ratios using all variables that are available using individual patient case note data

Variables		HR (95% CI)	p-value	Global p-value
Gender	Male	1		
	Female	0.85 (0.65-1.11	0.2292	
Age		1 (0.99-1.01)	0.8715	
Regimen	Ipilimumab	1		0.0034
	Pembrolizumab	0.85 (0.58-1.25)	0.4156	
	Ipilimumab with nivolumab	0.54 (0.29-1.02)	0.0584	
	Vemurafenib	0.96 (0.63-1.46)	0.8418	
	Dabrafenib	0.79 (0.47-1.32)	0.3748	
	Dabrafenib with trametinib	0.38 (0.22-0.66)	0.0005	
LDH level	Within normal range	1		0.0132
	Above ULN	1.31 (0.96-1.80)	0.0856	
	Unknown	2.09 (1.27-3.43)	0.0033	
NLR Score	0	1		0.0005
	1	1.82 (1.35-2.46)	0.0001	
	Unknown	1.77 (0.62-5.07)	0.2871	
ECOG PS	0	1		0.0096
	1	1.32 (0.94-1.84)	0.1047	
	2+	2.3 (1.42-3.72)	0.0007	
	Unknown	1.19 (0.73-1.94)	0.4819	
Primary site	Cutaneous	1		0.0355
	Mucosal	1.89 (1.21-2.98)	0.0056	
	Ocular	1.31 (0.76-2.28)	0.3353	
	Unknown	0.86 (0.55-1.36)	0.528	
Treatment switch	No	1		
	Yes	0.6 (0.43-0.83)	0.0020	
M status	M0-M1b	1		0.0140
	M1c	1.68 (1.18-2.4)	0.0044	
	Unknown	1.16 (0.48-2.84)	0.7414	
Brain metastases	Yes	1		
	No or unknown	0.66 (0.45-0.97)	0.0325	

KEY: HR=hazard ratio; CI=confidence interval; LDH=lactate dehydrogenase; ULN=Upper limit of normal; NLR=neutrophil: lymphocyte ratio; ECOG PS=Eastern Cooperative Oncology Group Performance Status; SACT=systemic anti-cancer treatment

Table 23 summarises the hazard ratios for each SACT type from the final multivariable models to facilitate comparison between the data collection methods ability to determine the impact of SACT on OS. In addition to the final multivariable models shown in Tables 14,

21 and 22, a fourth multivariable model was run using ERL data but without "Number of medicines prior to starting SACT", as this variable was not available in IPLR. This table shows that hazard ratios for each SACT in the different models were broadly similar. Dabrafenib monotherapy showed the biggest change in hazard ratios between models from 1.14 (95%CI 0.71-1.83) in ERL models to 0.95 (0.58-1.56) and 0.79 (0.47-1.32) in the IPLR models; none were statistically significant. In all the models dabrafenib with trametinib showed improved OS compared to ipilimumab alone. Ipilimumab with nivolumab showed an improvement in OS but this was only statistically significant in the ERL models. The baseline characteristics of each SACT via IPLR methods are reported in Appendix 6 and showed that over 40% of patients who received dabrafenib monotherapy had brain metastases and 86% of them were AJCC stage M1c (i.e. the most severe stage).

Table 23. Summary of adjusted hazard ratios from multivariable models showing impact of each systemic anti-cancer treatment on overall survival

SACT	Final ERL multivariable model (Table 14)	ERL closest to IPLR	Final IPLR multivariable model (Table 21)	IPLR multivariable model with additional variables (Table 22)
Ipilimumab	1	1	1	1
Pembrolizumab	0.86 (0.59-1.27)	0.85 (0.58-1.24)	0.87 (0.60-1.28)	0.85 (0.58-1.25)
Ipilimumab with Nivolumab	0.50 (0.26-0.95)	0.49 (0.26-0.92)	0.54 (0.29-1.02)	0.54 (0.29-1.02)
Vemurafenib	0.93 (0.61-1.42)	0.93 (0.61-1.41)	0.86 (0.57-1.30)	0.96 (0.63-1.46)
Dabrafenib	1.14 (0.71-1.83)	1.14 (0.71-1.83)	0.95 (0.58-1.56)	0.79 (0.47-1.32)
Dabrafenib with Trametinib	0.42 (0.25-0.71)	0.42 (0.25-0.71)	0.43 (0.26-0.74)	0.38 (0.22-0.66)

5. Discussion

5.1 Summary of Key Findings

The aim of this retrospective, observational cohort study was to determine the clinical outcomes of patients receiving SACT for advanced (unresectable or metastatic) melanoma in the West of Scotland between 2010 and 2017. Furthermore, to test the validity of using electronic record linkage (ERL) of routinely collected healthcare data to determine these clinical outcomes by comparing the results to those generated from individual patient level records (IPLR).

5.1.1 Overall Survival

The median OS for the whole cohort was estimated at 9.4 months (95% CI 8.0-11.6) which is disappointing when untreated patients with advanced (unresectable or metastatic) melanoma generally have a life expectancy of 6-9 months (Garbe et al. 2016). However median OS varied for each SACT and the Kaplan-Meier curve (Figure 6) showed that 23.7% (95% CI 19.0-29.6) of patients were still alive at 3 years which suggests that some patients have a durable response to SACT. The longest observed OS in this study was 18.5 months (95%CI 14.4-not estimable) with ipilimumab with nivolumab whilst dabrafenib monotherapy had the shortest at 5.6 months (95%CI 4.5-7.3) but there were a number of differences in the baseline characteristics of patients receiving each SACT (Table 13). A multivariable analysis (Table 14) adjusted for the differences in the baseline characteristics and the results showed that both dabrafenib with trametinib (HR 0.42 (95%CI 0.25-0.71), p-value 0.0014) and ipilimumab with nivolumab (HR 0.50 (95%CI 0.26-0.95), p-value 0.0352) improved OS compared to ipilimumab alone. This was expected as ipilimumab monotherapy is no longer used as standard of care for patients with advanced (unresectable or metastatic) melanoma, it has been relegated to a second, or third line treatment for patients who progress on other SACT. It was used as the reference in the multivariable analysis due to highest patient numbers in this group, driven by the fact that ipilimumab was the first SACT available for prescription in this cohort.

A number of baseline characteristics showed an impact on OS in the adjusted model (Table 14). Non cutaneous primary site (mucosal and ocular melanomas), LDH levels above the upper limit of normal, poorer ECOG PS were already identified in the literature as having a negative impact on OS (Yde et al. 2018; Diem et al. 2016) and the results of our study support this. NLR score has been utilised as a prognostic marker in other tumour types,

with scores of 1 suggesting a poorer outcome. (Guthrie et al. 2013; Walsh et al. 2005) This appears to be replicated in this study suggesting that determining this score at baseline may give an indication of prognosis when patients and clinicians are having treatment discussions. Patients who switch to a second line of SACT appear to have improved OS but this is subject to immortal time bias. (Levesque et al. 2010) The results are affected because some patients died before switching to a second line SACT, which means that this outcome could not occur. The results do not enable comment on whether patients are living longer because they receive more than one SACT or if patients receive multiple SACT because they live longer. For example, ipilimumab was the first SACT available in this study but only as a second line treatment, this meant patients initially receiving ipilimumab had to be fit enough to receive at least two SACT for advanced (unresectable or metastatic) melanoma which may have skewed the initial population selection.

Whilst OS is a key measure when reporting outcomes of medicines in clinical trials, it is useful for patients and clinicians to have additional treatment information to aid decision making discussions. For some patients the potential increase in OS may be negated by the increased risk of adverse events that could negatively impact on quality of life (QoL). (Shrestha et al. 2019) This is evident in this study when the baseline characteristics for patients receiving ipilimumab with nivolumab are compared to those receiving pembrolizumab. The results of Checkmate 067 (three arms: ipilimumab with nivolumab; nivolumab monotherapy and ipilimumab monotherapy) showed an increased survival for the combination immunotherapy compared to both monotherapy arms (52%; 44%; 26% respectively) but CTCAE grade 3 or 4, including colitis and hepatitis, were recorded in 59% of patients receiving the combination compared to only 21% of patients receiving nivolumab monotherapy. (Larkin et al. 2015; Wolchok 2017) Similarly, only 13% of patients receiving pembrolizumab monotherapy in Keynote 006 reported CTCAE grade 3 or 4. The patients in our study who received pembrolizumab tended to be older (median age 77 years), with a poorer ECOG PS (37% PS 0) whilst those who received ipilimumab with nivolumab were younger (median age 58 years) and fitter (84% ECOG PS 0). It was therefore useful to investigate secondary outcomes to determine if similar patterns occurred in real world practice.

5.1.2 Secondary clinical outcomes

There were two main types of secondary clinical outcomes reported in this study. Treatment duration and time to next treatment were recorded as potential surrogate measures for PFS whilst a number of surrogate measures were used to capture information on incidence of adverse events, which may impact QoL.

5.1.2.1 *Treatment pathways*

The differences shown in median OS (ranging from 6.3-18.5 months) reported with each immunotherapy was not reflected in the median duration of treatment: median duration of any immunotherapy treatment was less than 3 months (Table 16) and less than 30% of patients received subsequent SACT (Table 17). This shows that duration of immunotherapy treatment may not be a surrogate measure for PFS although it does suggest that immunotherapy may continue to have a beneficial effect even after treatment has stopped. (Postow M et al. 2015)

In contrast dabrafenib with trametinib had a median duration of treatment of 11.1 (95%CI 8.3-16.0) months, median OS was 11.5 (95%CI 9.4-23.0) months and only 25% patients received subsequent SACT, suggesting that the majority of patients remained on treatment until death. Dabrafenib monotherapy has similar results: median duration of treatment 3.5 months (95%CI 3.1-4.6) with median OS 5.6 months (95%CI 4.5-7.3). More than 50% of vemurafenib patients received subsequent treatment and median OS of 13 (95%CI 9.9-18.0) months is much longer than the median duration of treatment at 6.2 (95%CI 4.0-7.8) months. There is no information available about the reason for switching vemurafenib: it may be due to disease progression but may also indicate that patients experienced AEs and required an alternative SACT. These results all suggest that duration of treatment is not a useful surrogate measure for PFS, and alternatives should be considered.

Time to next treatment, for patients who received a subsequent SACT, was hypothesised at the start of this study as another surrogate measure for PFS. The results showed that the median time to next treatment was at least 4 months for every SACT (Table 17). This should be expected as most patients would be imaged 3-4 months after starting to determine if the tumour was responding to treatment. In clinical trials, response rates and PFS are obtained using imaging reported to RECIST (Response Evaluation Criteria in Solid Tumours) or irRECIST criteria, with all lesions measured routinely to enable objective reporting of

disease response or progression. This detailed report does not always happen in clinical practice in Scotland and imaging reports are not available in the Safe Haven. This means that there was no reliable way of reporting PFS in this study and thus other measures should be considered as surrogate measures for PFS.

5.1.2.2 *Adverse events*

Patients participating in clinical trials are monitored closely with AEs clearly documented as per CTCAE criteria and reported in the clinical trial publications. The pivotal trials reported adverse events at any grade occurring in 73-99% of patients, (Hodi et al. 2010; Chapman et al. 2011; Long et al. 2014; Larkin et al. 2015; Robert et al. 2015) with more severe adverse events (CTCAE Grade 3+) ranging from 10% of patients receiving pembrolizumab to 59% of patients receiving nivolumab with ipilimumab. In clinical practice patients who experience AEs with SACT may have their dose reduced or a delay to treatment in order to manage adverse events at any CTCAE grade. (Bristol-Myers Squibb Pharmaceutical Limited 2016; 2017; Merck Sharp & Dohme Limited 2017; Roche Products Limited 2016; Novartis Pharmaceuticals UK Ltd 2016a; 2016b) Our results showed that over 60% of patients taking either nivolumab with ipilimumab or vemurafenib had a dose modification suggesting that these treatments were more toxic than the other SACT included in this study. This pattern is repeated with the number of patient who have a new emergency hospital admission after SACT initiation, but not when total number of patients with emergency admissions is included (Figure 8).

It was hypothesised that emergency hospital admissions might indicate the proportion of patients with more severe, CTCAE grade 3 or 4. Over 50% of patients receiving any SACT required an emergency hospital admission after start of SACT which, with the exception of vemurafenib, was more than the percentage of patients requiring a dose modification with each SACT. This is the reverse of what was expected from clinical trial results which suggest that whilst most patients suffer minor AEs, a smaller proportion reported CTCAE grade 3+. The inability to capture fatigue using the data available in the Safe Haven, one of the most common AEs reported in clinical trials (Hodi et al. 2010; Chapman et al. 2011; Long et al. 2014; Larkin et al. 2015; Robert et al. 2015) may be affecting our results. Another reason for this could be that patients stopped treatment after hospitalisation rather than having a dose modification. Table 19 showed that 62 (17%) patients had emergency hospital

admissions for sepsis; chest pain or anaemia; including admissions such as these, which may not be due to SACT, may have artificially inflated the numbers of patients with emergency admissions. The most common reasons for admission were identified using ICD10 codes, however most codes were used fewer than five times which meant the information could not be extracted from the Safe Haven, due to Safe Haven regulations. It was not possible to determine whether or not all emergency admissions were related to SACT exposure limiting our ability to accurately interpret these data.

Data regarding prescriptions for supportive medications to manage AEs were extracted from both CEPAS and PIS (primary care) but it should be noted there is no data available regarding the indication for these prescriptions and so assumptions have been made. Figure 9 showed that new prescriptions for supportive medicines were most common with ipilimumab with nivolumab suggesting, once again, that more AEs occur with this SACT. The results also showed that itch or rash was one of the most commonly experienced AE, requiring supportive medications, overall. Nausea and vomiting is also a commonly reported AE in clinical trials, with 43% of vemurafenib patients reporting this in the clinical trial. (Chapman et al. 2011) Patients in our cohort received prophylactic antiemetics with their first cycle of targeted treatment, which may explain the lower numbers for prescriptions shown in our results.

The results from this chapter reinforce the evidence from clinical trials that ipilimumab with nivolumab is associated with the highest number of AEs, particularly colitis and endocrine disorders such as hypophysitis and hypothyroidism, when compared to other SACT for advanced (unresectable or metastatic) melanoma. Additional information regarding indications for prescriptions and/ or patient co-morbidities may enable the results from the data to be interpreted with a higher degree of confidence.

5.1.3 Data Validation

The second aim of this study was to validate the use of ERL as an appropriate alternative robust method for determining outcomes of SACT. This required the baseline characteristics and results obtained from ERL to be compared to the baseline characteristics and results obtained from IPLR.

There was a high level of consistency in the baseline characteristics identified in both ERL and IPLR: median age; gender; ECOG PS; BMI; index SACT and line of initial treatment were

identical reflecting that this information came from CEPAS data which was equally available in both methods. Minor variations shown in SIMD category and vital status may be due to differences in the source used to capture this information. Observed differences in laboratory tests, required for calculation of NLR score; LDH levels and BRAF status may be because the researcher was able to access information from a wider variety of sources e.g. laboratory results from outside NHS GGC which could not be accessed in the Safe Haven.

Primary disease site and time from diagnosis both relied on data from SMR06 (Scottish Cancer Registry) but there were 13 (3.6%) patients who did not have an entry relating to melanoma in this data source, which would explain why there are statistically significant differences in these characteristics. Identification of primary melanoma site was also hampered by the ICD10 codes. C43 is the code for cutaneous melanomas but there is no specific code for ocular or mucosal melanomas, these are more likely to be coded by the primary site in which the melanoma occurs i.e. C69.3 malignant neoplasm of the choroid which may contribute to the differences in primary site. Data showing the presence or absence of brain metastases and AJCC staging at baseline, recognised prognostic indicators, (Schadendorf et al. 2018) were not available in the Safe Haven.

In order to complete the validation of ERL methodology it was necessary to examine the impact of the differences on baseline characteristics on the estimated outcomes of SACT by comparing the multivariable models obtained with each method (Table 23). With the exception of dabrafenib monotherapy, the differences in the hazard ratios for survival with each SACT generated in the multivariable models were less than 10% which was deemed an acceptable limit for change. There was a similar pattern with HR in each model: dabrafenib with trametinib showed a statistically significant improvement in OS compared to ipilimumab monotherapy; ipilimumab with nivolumab showed a statistically significant improvement in OS in ERL models but the results in IPLR models HR 0.54 (95%CI 0.29-1.02) did not show statistical significance as the confidence intervals just crossed 1; no other SACT showed a statistically significant difference in OS. The largest change in HR was shown in dabrafenib monotherapy. Appendix 6 shows that over 40% of patients who received dabrafenib monotherapy had brain metastases and 86% were staged as M1c which may account for this. The IPLR multivariable model that included the additional variables of M stage and information on brain metastases (Table 22) showed that both these factors had a

statistically significant impact on OS which has been previously reported in the literature. (Schadendorf et al. 2018)

Data validation was not carried out for the secondary clinical outcomes as information about hospital admissions was only captured via ERL. Dose reduction and delay results were generated from the CEPAS data which was equally available for both ERL and IPLR and so no differences would be expected. Given the limitations with data interpretation this an area for future work.

5.2 Comparison with literature

Our cohort included patients with PS ≥ 2 [n=42(11.6%)]; brain metastases [n=63(17.4%)] and non-cutaneous melanomas [n=95(26.2%)] treated in routine clinical conditions. These are recognised as poor prognostic factors, supported by the results of the multivariable models (Tables 14 & 22), and patients with these characteristics are often excluded from clinical trials. With the exception of Keynote 006 (pembrolizumab trial, Robert et al. 2015) the median age of patients participating in clinical trials was less than 60 years old; the median age of our cohort was 65 years. This may provide some explanation for the shorter OS reported in our study compared to the pivotal trials.

Since this study was designed there have been a number of publications reporting real world outcomes with SACT for advanced melanoma in routine care. In 2019, an observational study by Liu et al in the US reported median OS with pembrolizumab of 21.8 months, after a median of 4.9 months treatment, (Liu et al. 2019) which is much longer than the median OS of 8.0 months (95%CI 4.8-15.5) experienced in our cohort after a median duration of treatment of 2.9 months (2.3-4.1). The cohort for Liu *et al.* included only cutaneous melanomas as well as those who may have had unresectable stage III disease which may be a reason for the better outcomes in the study compared to our cohort which included patients with non-cutaneous melanomas. Other US studies report response rate rather than median OS and are limited to BRAF mutant patients only therefore direct comparison would require a subset analysis of a small proportion of our cohort (19.9%, n=72). (Luke et al. 2019)

Arheden *et al* who carried out a retrospective study of PD1 inhibitor monotherapy (either nivolumab or pembrolizumab) for 116 patients with advanced melanoma between 2015 and 2017 reported a median OS of 27.9 months (95% CI, 19.8–36.0) after a median follow

up of 17 months. (Arheden et al. 2019) The longer OS in this Swedish group may be due to a number of factors including; younger patients cohort (median age 66 years vs. 77 years in our cohort); patients having less severe disease than those included in our cohort: 50% M0-M1b in Swedish group, whilst only 25.2% of patients in our cohort had the least severe disease, although the Swedish study used AJCC 8th edition staging whilst our study used AJCC 7th edition (Appendix 6).

A Japanese study reported the outcomes of 68 patients who had received sequential nivolumab followed by ipilimumab or vice versa; most patients switched treatment due to progressive disease (n=55, 81%). (Tsutsumida et al. 2019) Median OS from the start of ipilimumab is reported as 7.0 months which is similar to the median OS reported in our cohort but the majority of patients (n=61, 90%) in the Tsutsumida study had prior exposure to nivolumab. Given that most of the patients received ipilimumab due to progression with nivolumab it is unclear whether OS reported is due to ipilimumab alone or if the prior nivolumab exposure is also having an effect.

Work from Australia by Dearden *et al*, investigating real world outcomes for 152 patients receiving ipilimumab in combination with nivolumab, found an estimated median OS ranging from 3.6 months in patients with previous BRAF/MEK treatment to 14.2 months in patients who were treatment naïve which is shorter than the median OS of 18.5 months (95%CI 14.4-not estimable) in our study. Almost 90% of the patients in Australia had an AJCC 8th edition stage of M1c or d i.e. more severe disease and 55% had raised LDH levels (Dearden et al. 2018) whilst our study had only 60% M1c stage and 35% with raised LDH levels (Appendix 6) which may explain why the results for our cohort are slightly better although it should be noted that the upper confidence intervals for OS in both the Dearden study and our cohort have not yet been reached which could affect the comparison.

Donia *et al* extracted information from the Danish Metastatic Melanoma Database (DAMMED) to study immunotherapy, showing how OS has improved with the introduction of new SACT from 2012-2016. Their results showed OS of 16.5 months in “trial-like” patients in 2012 to not yet reached in “trial-like” patients in 2016. In “trial-excluded” patients OS improved from 4.2 months in 2012 to 6.9 months in 2016. Utilising the DAMMED database meant that the researchers were able to clearly identify the patients who would not have been eligible for clinical trials using seven specific criteria: ECOG PS≥2; active brain metastases or leptomeningeal disease; serious or uncontrolled medical

conditions; autoimmune diseases; previous malignancies in the 3 years prior to treatment; immunosuppressive medications; unmeasurable disease. (Donia et al. 2019) It was not possible for this to be replicated with the information available about our patients from ERL because information about disease severity and scan results was not available in the safe haven. Information about co-morbidities is also limited, restricting our study to top level findings for now. Similar top level findings have been reported using the German Central Malignant Melanoma Registry which reported an improvement in OS with three year OS increasing from 18% in 2011 to 37% in 2014 (Forschner et al. 2017) but again limited baseline characteristics mean comparison with our cohort is not possible.

In Poland, Polkowska *et al* reported an improvement in OS with the introduction of ipilimumab, vemurafenib and dabrafenib monotherapy, between January 2012 and October 2016, to treat malignant melanoma in place of dacarbazine. Data were extracted from the National Health Fund in Poland, which reportedly collects reimbursement data and holds some medical records. For the 686 patients who received vemurafenib as a first line treatment median OS was reported as 9.9 months (95%CI 8.9-11.0) whilst 432 patients who received second line ipilimumab demonstrated a median OS of 5.9 months (95%CI 5.6-8.4). (Polkowska et al. 2017) The benefit of increased patient numbers in this Polish study, likely leads to narrower confidence intervals when reporting OS but the missing baseline characteristic information makes it difficult to make any comparisons to our cohort.

It should be noted that none of the real world studies described in this chapter used routinely collected healthcare data as in the ERL phase of this study. Data were either obtained from melanoma specific registries, funded by governments or pharmaceutical industry or through a more typical case note review, similar to the IPLR phase of this study. To date only one study (abstract form) has been identified that uses routinely collected health care data, carried out by Corrie *et al* in 2020. This team used information from routine Public Health England data sources to report the outcomes of immunotherapy on patients with metastatic melanoma between 2014 and 2018. Three year survival was reported for ipilimumab ((32% (95%CI 28-35), n=724); pembrolizumab ((40% (95%CI 37-43), n=1174)) and for ipilimumab in combination with nivolumab ((56% (95%CI 49-62), n=372)). Three year survival was not reported separately for our immunotherapy cohort; it is not estimable for the patients who received ipilimumab with nivolumab but the Kaplan-Meier curve in figure 7 suggests that the three year survival in our cohort is slightly less than in the

Corrie study. It is approximately 20% for patients receiving ipilimumab and 30% in those receiving pembrolizumab. Similar to our study, the smallest number of patients received nivolumab with ipilimumab. Corrie *et al* also showed that patients who received ipilimumab with nivolumab had higher rates of emergency hospital admission than those who received single agent immunotherapy (37% vs. 17-24% within 30 days of first SACT and 55% vs. 29-40% within 30 days of last SACT date). (Corrie et al. 2020) The lower rate of emergency admissions compared to emergency hospital admissions in our study may be due to different timeframes used. Adverse events may occur at any time after a patient has received immunotherapy which is why there was no time limit on hospital admissions for our cohort but Corrie et al did not record hospital admissions more than 30 days after the end of treatment.

This pattern of improvement in OS with time is shown when the results of our study are compared to the results of a local audit (poster) following the introduction of ipilimumab in the second line setting. OS for patients treated in the Beatson WoSCC showed a median OS of 4.4 months following the initial introduction of ipilimumab. (Spiliopoulou et al. 2014) Whilst the median OS of 9.6 months for our cohort is still what might be expected in advanced melanoma patients without treatment, the plateau in the Kaplan-Meier curve shows that approximately 20% patients remained alive 3.5 years after starting SACT. (Figure 6)

5.3 Strengths and limitations

Real world data allows patients and clinicians to access more realistic information about treatment outcomes with routine clinical use in addition to the results obtained from the carefully constructed confines of a randomised controlled trial. One strength is that this is currently the only study that reports outcomes of the most commonly used SACT (both targeted and immunotherapy) for advanced melanoma which provides useful information for clinical decision making. The study inclusion period from 1st November 2010 until 31st December 2017, with follow up until the 31st March 2018, was used in order to capture as many patients as possible, which is a strength of the study, but it did mean that follow up time was limited to just over 3 months for a small number of patients. As a result of that, some of the data is immature with wide confidence intervals around median OS and there is an imbalance in the follow up times. This imbalance also occurs in the number of patients

receiving each SACT due to the different availability throughout the study period and in the baseline characteristics of patients receiving each SACT, which can be a limitation of retrospective, observational cohort studies. In clinical trials patients are often stratified to ensure patient numbers and baseline characteristics are evenly spread across each arm to ensure that any differences in results are due to the treatment alone and not any confounding factors. Reporting baseline characteristics for each SACT enabled these differences to be examined and a multivariable model was developed to enable the impact of SACT on OS to be determined.

An additional objective of the study was to capture information on adverse events with SACT. It was anticipated that having access to coded data from hospital admissions (SMR01) would be strength of this study and allow identification of serious adverse events in a replicable, methodical manner to facilitate comparison between each SACT. Unfortunately this was complicated by the large number of emergency hospital admissions recorded for each patient and the variety of ICD10 codes that were recorded as reasons for admission. Most of the individual ICD10 codes applied to fewer than 5 patients, which meant that this information could not be released from the Safe Haven and is a limitation of the study. Neither PIS nor CEPAS prescriptions have the indication attached to them which means that assumptions were made that the prescriptions were for adverse events. Assumptions were also made that information about dose reductions and dose delays were also due to adverse events. None of these methods enabled causation of adverse events to be reliably confirmed limiting the usefulness of this information.

A strength of using routinely captured data for ERL is that it facilitated objective data capture, limiting the need for interpretation of information from clinical letters and so reduces the likelihood of researcher bias. It was also anticipated that ERL would be a time efficient method compared to IPLR. However this study was limited by challenges gaining access to ERL, for a number of reasons including technical issues with data access and information governance procedures. Having worked through these issues further work should be less challenging although the lag time for completeness for some of the datasets used in ERL will be a persistent limitation.

This study, by comparing both the baseline characteristics and the results obtained from ERL with IPLR, has enabled a comprehensive validation of the ERL methodology which is a strength. It has shown that ERL is a useful method to report outcomes of SACT use in

routine clinical practice. The data gaps, such as melanoma disease stage and sites of metastases, that have been identified were shown to have a minimal impact on the hazard ratios for individual SACT. Moving forward it should therefore be possible to replicate this work, or extend the cohort using ERL without the additional validation step using IPLR.

5.4 **Further work**

This study has generated a number of interesting findings but clinical questions still remain. One example of this is the optimal sequencing of targeted treatment and immunotherapy in patients who are BRAF mutant. There was only a small number of patients who received both targeted and immunotherapy in our study (n=36, 10%) which means that any results generated are unlikely to have a statistical and clinical significance. Extending the time period for the study to patients starting SACT up to 31st December 2019, with follow up until 30th June 2020 would increase patient numbers receiving each SACT and provide more time for data to mature, potentially enabling this question to be answered. In addition to this accessing a larger cohort, with longer follow up, would enable the multivariable analysis to be adjusted and re-run, to facilitate comparison between SACT used first line (ipilimumab with nivolumab; pembrolizumab and dabrafenib with trametinib) and it might enable information to be captured about long term survivors of SACT: is there a difference in SACT with immunotherapy compared to targeted treatments? How long did the long term survivors remain on SACT? Another option to increase patient numbers would be to include patients from outside the West of Scotland. This would enable SACT patterns and baseline characteristics of patients across Scotland to be reported. The impact of any differences in both baseline characteristics of patients and SACT patterns could then be explored, with regional sub group analysis if necessary. It is important to ensure that as these clinical questions are answered we consider how best to share the results of the study, alongside any new findings, with the wider clinical community and general public.

The Glasgow Safe Haven at the Robertson Centre was the source for ERL for this study but there were challenges accessing all the required data. Further work may be carried out to explore the scope of other Safe Havens in Scotland or services such as the Scottish Cancer Registry and Intelligence Service (SCRIS) to link data and determine outcomes of SACT. The IPLR data that has been collected for this study could be used to validate the data available

via SCRIS by comparing two matched cohorts. If this is successful then the SCRIS platform could be used to extend the cohort.

Work is needed to address the data gaps identified in this study including: missing BRAF status and information about disease severity at index date (M stage; presence of brain metastases) within ERL. Whilst these factors did not have an impact on the hazard ratios for SACT the results did show that that these factors did have an impact on survival and so can be useful for clinicians to contextualise results. The addition of some of these factors to a wider cohort would also enable sub analysis of discrete patient groups, i.e. those who are BRAF mutant, to be carried out. Engaging with clinical teams to determine the optimal method for recording this information is critical: local teams could adjust documentation to enable BRAF status and primary disease site to be more reliably captured prospectively which would be very beneficial if this study was extended. Improving access to imaging reports in ERL, which would facilitate identification of metastatic sites, is a vast undertaking outwith the scope of future work for this project.

This study explored the ability of ERL to generate objective, reproducible information regarding the incidence of adverse events with SACT. It was not possible to validate these results because it would have been very time consuming to examine every discharge letter and primary care prescription that a patient may have received during the study period. Analysis of a subset of patients i.e. those who received pembrolizumab alone, using both ERL and IPLR may be useful to gain a better understanding of how hospital admissions and new medications link to occurrence of AEs. For example if a patient had a new dermatology outpatient appointment followed by a prescription for a topical steroid and a dose reduction to dabrafenib this might indicate an adverse skin reaction, which may be reported in patient case notes. If this validation was successful then it may be possible to extend the cohort. This might enable identification of a wider range of adverse events particularly using ICD10 codes from SMR01 as the limitations reporting numbers less than five may be overcome.

The complexities of treating patients in routine clinical practice, outside the measured confines of a clinical trial, can be difficult to manage when analysing data, patients receive multiple SACT and do not always follow standard treatment pathways. Our results showed that 60% (n=219) of patients received only one SACT which means that 40% (n=143) had more than one SACT; statistical analysis with multiple treatments can be challenging and

results should be interpreted cautiously. It may be possible to carry out further work to explore options for alternative analyses of impact of multiple SACT, i.e. sequential use of immunotherapy, on outcomes, particularly if patient numbers increased. Limiting the analysis to only those patients who had received one SACT would have had a detrimental impact on cohort numbers and generated results that would not apply to all the patients encountered in clinical practice.

6. Conclusion

The results of this study showed that OS with SACT for patients with advanced melanoma in the West of Scotland was poorer than the results of the pivotal trials would suggest. Despite numerical differences in the survival for each SACT ranging from 6 -18 months, the adjusted multivariable model showed that dabrafenib with trametinib and ipilimumab with nivolumab had a survival advantage over ipilimumab. The West of Scotland population included patients with: ECOG PS ≥2; brain metastases and non-cutaneous melanomas; shown to have a negative impact on survival and who are typically excluded from clinical trials. Lactate dehydrogenase levels above the upper limit of normal and NLR score of 1 were also shown to have a negative impact on survival.

Treatment specific information including duration of treatment and dose modifications, as a surrogate measure for adverse events, was also captured. There were clear differences in treatment duration between targeted treatments and immunotherapy with most patients prescribed immunotherapy for less than 3 months but targeted treatments were generally prescribed for a longer period than this. This suggests that even a short course of immunotherapy may have an impact on survival whilst most patients take targeted treatments until progression.

The validation work showed that the additional variables available from IPLR (brain metastases and M status) had an impact on OS but only one hazard ratio for SACT changed by more than 10% - dabrafenib monotherapy. Consequently, ERL in Scotland could be considered as a valid method for determining outcomes, both intended and unintended, of SACT in local populations. This is in agreement with work published by colleagues investigating outcomes of treatments for metastatic castrate resistant prostate cancer using ERL. (Baillie et al. 2020)

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Appendices

Appendix 1 – ICD codes used to identify primary melanoma site

ICD 10 codes	Site of malignant neoplasm	Melanoma information
C43	Malignant melanoma of skin	Cutaneous
C69.3/ 69.4/ 69.6/ 69.9	Eye and adnexa	Ocular
C05.1	Soft Palate	Mucosal
C06.1	Vestibule of mouth	
C12	Piriform sinus	
C21	Anus and anal canal	
C30	Nasal cavity and middle ear	
C31	Accessory sinuses	
C32	Larynx	
C51	Vulva	
C52	Vagina	
C77	Secondary and unspecified neoplasm of lymph nodes	Unknown primary if no other ICD10 codes were recorded for patients
C78	Secondary of respiratory and digestive organs	
C79	Secondary of other unspecified sites	
C80	No site specification	

ICD O codes	Preferred terms
87203	melanoma in situ
87206	metastatic melanoma
87213	nodular melanoma
87233	regressing malignant melanoma
87303	amelanocytic melanoma
87403	malignant melanoma in junctional naevus
87423	lentigo maligna melanoma
87433	superficial spreading melanoma
87443	acral melanoma
87463	mucosal lentiginous melanoma
87703	malignant spitz tumour
87723	spindle cell melanoma

Appendix 2 – Dosing information for SACT of interest

Drug	Dose information	Supportive medicines on cycle 1	Modifications
Dabrafenib	150mg BD PO	Metoclopramide 10mg TID PRN nausea Loperamide 4mg initially then 2mg after each loose motion PRN	100mg BD 75mg BD
Trametinib	2mg OD PO	as dabrafenib	1.5mg OD 1.0mg OD
Ipilimumab	3mg/kg Q3W for 4 doses IV	Nil	Delay to allow resolution of AE
Nivolumab	1mg/kg Q3W (when administered with ipilimumab) then 1mg/kg Q2W IV*	Nil	Delay to allow resolution of AE
Pembrolizumab	2mg/kg Q3W IV*	Nil	Delay to allow resolution of AE
Vemurafenib	960mg BD PO	Metoclopramide 10mg TID PRN nausea	720mg BD 480mg BD
KEY: BD=twice daily; PO=oral; TID=three times daily; PRN=when required; OD=once daily; Q3W=every 3 weeks; IV=intravenously; AE=adverse events; Q2W=every 2 weeks; *both nivolumab and pembrolizumab have had changes to licensed doses since this study was completed			

Appendix 3 – Public Benefit and Privacy Panel confirmation

Public Benefit and Privacy Panel for Health and Social Care
nss.PBPP@nhs.net
www.informationgovernance.scot.nhs.uk

NHS SCOTLAND

Professor Marion Bennie
Strathclyde Institute of Pharmacy and Biomedical Sciences,
161 Cathedral Street,
Glasgow
G4 0RE

Date: 1st June 2018
Your Ref:
Our Ref: 1617-0371

Dear Professor Bennie,

Re Application: Cancer Medicines Outcomes Programme (CMOP)
Version: 20180530 PBPP CMOP melanoma v2 conditions met

Further to your conditional approval issued by the Public Benefit and Privacy Panel for Health and Social Care on 30th May 2018, I am writing to confirm that all conditions applied to the approval have now been satisfied. Your application and supporting documents have undergone proportionate governance review and have now been approved in full.

This approval is given to process data as specified in the approved application form, and is limited to this. Approval is valid for the period specified until 31st January 2020. You are required to notify the Panel Manager of any proposed changes to your proposal, e.g. purpose or method of processing, data or data variables being processed, study cohorts, individuals accessing and processing data, timescales, technology/infrastructure.

On conclusion of your proposal, as part of NHS Scotland Governance and monitoring we will require you to complete an End of Project reporting form to demonstrate that you have complied with the obligations outlined e.g. data destruction or submission of references for publications of findings.

I would take this opportunity to remind you of the declaration you have made in your application form committing you to undertakings in respect of information governance, confidentiality and data protection.

Requests for access to NHS Scotland data as part of this approved application should be supported by evidencing a copy of your approval letter and application form to the relevant local board contacts/data providers.

Please note that summary information about your application and its approval, including the title and nature of your proposal, will be published on the panel website (www.informationgovernance.scot.nhs.uk).

I hope that your proposal progresses well.

Yours sincerely,
Marian

Dr Marian Aldhous
Panel Manager
NHS Scotland Public Benefit and Privacy Panel for Health and Social Care
Email: nss.PBPP@nhs.net

Appendix 4 – ERL univariate analysis

Co-variate	level	N	no. of events	Median OS in months (95% CI)	HR (95% CI)	p value	overall p-value
SACT	Ipilimumab	100	80	6.3 (4.9-10.3)	1 (-)		0.0019
	Pembrolizumab	89	56	8 (4.8-15.5)	0.94 (0.66-1.32)	0.7036	
	Ipilimumab with nivolumab	44	12	18.5 (14.4-NA)	0.45 (0.24-0.83)	0.0107	
	Vemurafenib	51	42	13 (9.9-18)	0.87 (0.6-1.26)	0.4554	
	Dabrafenib	36	33	5.6 (4.5-7.3)	1.61 (1.07-2.42)	0.0232	
	Dabrafenib with trametinib	42	26	11.5 (9.4-23)	0.7 (0.45-1.1)	0.1229	
Gender	Male	186	129	8.9 (6.5-11.5)	1 (-)		
	Female	176	120	10.3 (8.2-14.8)	0.85 (0.66-1.09)	0.2097	
ECOG Performance Status	0	184	106	17.5 (14.4-23.8)	1 (-)		<0.001
	1	105	80	6.5 (4.9-9.4)	1.87 (1.39-2.5)	0	
	2+	42	37	4.7 (2.3-7.9)	3.31 (2.26-4.85)	0	
	unknown	31	26	6.6 (4.4-20.6)	1.65 (1.07-2.55)	0.0239	
No. medicines prescribed on PIS pre index date	less than 5	84	48	16.3 (9.4-36.8)	1 (-)		0.0269
	5 to 9	106	68	11.3 (8.5-20.6)	1.22 (0.85-1.77)	0.2847	
	10 to 14	92	70	7.6 (4.9-9.9)	1.68 (1.16-2.43)	0.0058	
	15 to 19	46	35	6.5 (4.4-15.4)	1.6 (1.03-2.47)	0.0359	
	20 or more	34	28	6.7 (4.9-14.4)	1.72 (1.08-2.75)	0.0222	
BMI	normal range	86	64	5.6 (4.4-9.1)	1 (-)		0.0237
	obese	89	52	13 (7.6-29.2)	0.58 (0.4-0.83)	0.0033	
	overweight	109	71	14.4 (8.8-20)	0.63 (0.45-0.88)	0.007	
	underweight	5	*	7.6 (4-NA)	1.05 (0.38-2.88)	0.9288	
	unknown	73	58	9.9 (6.9-13.8)	0.79 (0.55-1.13)	0.1922	

Co-variate	level	N	no. of events	Median OS in months (95% CI)	HR (95% CI)	p value	overall p-value
Charlson Score	0	217	142	9.6 (8-14.5)	1 (-)		0.2525
	1	52	38	6.4 (3.9-12.8)	1.34 (0.94-1.92)	0.1076	
	2	62	49	8.9 (5.6-14.7)	1.25 (0.9-1.73)	0.1749	
	3+	30	19	13.8 (8.5-NA)	0.92 (0.57-1.48)	0.7238	
SIMD	1	78	59	7.1 (5.7-10.2)	1 (-)		0.188
	2	75	55	8.8 (5.6-13.5)	0.91 (0.63-1.32)	0.6181	
	3	66	42	9.9 (5.9-22.5)	0.78 (0.52-1.15)	0.2096	
	4	65	44	13 (6.6-20.6)	0.75 (0.51-1.11)	0.15	
	5	77	49	13.3 (8.6-29.2)	0.68 (0.47-0.99)	0.0464	
	unknown	*	*	NA (NA-NA)	0 (0-Inf)	0.9927	
Primary melanoma site	Cutaneous	274	188	9.9 (8.7-13.8)	1 (-)		0.1676
	Mucosal	25	21	4.8 (3.8-14.4)	1.59 (1.01-2.51)	0.0431	
	Ocular	22	16	5.1 (3.7-NA)	1.42 (0.85-2.37)	0.1761	
	Unknown primary	28	16	10.2 (5.6-NA)	0.78 (0.47-1.3)	0.3434	
	No information	13	8	13.5 (3-NA)	1 (0.49-2.04)	0.994	
LDH levels	Normal range	181	99	18 (12.4-29.2)	1 (-)		<0.001
	Above upper limit of normal	143	117	5.9 (4.8-8.1)	2.29 (1.75-3)	0	
	unknown	38	33	6 (4.6-9.4)	2.37 (1.59-3.52)	0	
NLR Score	0	241	146	14.8 (11.6-20)	1 (-)		<0.001
	1	104	88	3.8 (3.3-5.6)	2.58 (1.98-3.37)	0	
	unknown	17	15	7.9 (6.6-15.4)	1.83 (1.07-3.12)	0.0267	

Co-variate	level	N	no. of events	Median OS in months (95% CI)	HR (95% CI)	p value	overall p-value
Breslow thickness of primary (mm)	0-1	22	15	7.9 (4.5-NA)	1 (-)		0.7318
	1-2	43	33	9.4 (7.6-14.9)	1.04 (0.56-1.92)	0.8965	
	2-4	73	51	8.8 (5.6-13.8)	1.02 (0.57-1.81)	0.9589	
	>4	88	59	11.1 (6.6-18.5)	0.91 (0.51-1.6)	0.7333	
	Unrecorded	30	20	14.9 (11.1-29.9)	0.74 (0.38-1.44)	0.3759	
Time from diagnosis	1-3 years	110	76	8 (5.6-11.1)	1 (-)		0.8177
	3-5 years	52	36	12.8 (8.1-25.4)	0.82 (0.55-1.22)	0.3246	
	5-10 years	62	47	9.8 (8.2-23)	0.86 (0.6-1.24)	0.4118	
	less than 1 year	86	58	10.3 (6-16)	0.87 (0.62-1.23)	0.4329	
	more than 10 years	39	24	13 (6.7-NA)	0.74 (0.47-1.17)	0.1922	
	unknown	13	8	13.5 (3-NA)	0.86 (0.41-1.78)	0.6787	
Melanoma subtype	acral	15	11	10.5 (3.4-NA)	1 (-)		0.8904
	lentigo Maligna Melanoma	16	9	14.6 (4.5-NA)	0.76 (0.31-1.83)	0.5391	
	melanoma (unspecified)	98	70	8.1 (5.6-14.4)	0.98 (0.52-1.85)	0.951	
	Nodular	72	50	9.4 (7.4-18.5)	0.93 (0.48-1.78)	0.8208	
	other	12	6	25.8 (3.4-NA)	0.65 (0.24-1.77)	0.4034	
	Superficial Spreading MM	89	64	8.8 (6-11.5)	0.99 (0.52-1.89)	0.9855	
Line of treatment	1	296	195	9.6 (8.2-13)	1 (-)		
	2+	66	54	7.3 (5.8-20.6)	1.03 (0.76-1.4)	0.8589	
Total no. of treatments	1	215	138	7.4 (5.6-9.9)	1 (-)		0.0018
	2	109	84	9.2 (7.3-13)	0.91 (0.7-1.2)	0.5088	
	3+	38	27	25.2 (20.6-46.7)	0.49 (0.32-0.75)	0.001	

Co-variate	level	N	no. of events	Median OS in months (95% CI)	HR (95% CI)	p value	overall p-value
Year SACT started	2010/11	16	14	12.3 (5.6-64.3)	1 (-)		0.5549
	2012	15	14	6.6 (4.9-11.1)	1.54 (0.73-3.24)	0.2565	
	2013	39	33	7.3 (4.9-11.6)	1.28 (0.68-2.41)	0.4465	
	2014	61	52	11.1 (4.9-18.4)	1.12 (0.62-2.04)	0.7046	
	2015	71	51	8.9 (5.9-13.8)	1.04 (0.57-1.91)	0.8862	
	2016	77	50	14.5 (8.1-18.5)	0.89 (0.49-1.64)	0.7169	
	2017	83	35	9.6 (7.4-NA)	0.94 (0.5-1.78)	0.852	
Did patient switch SACT?	No	261	179	6.3 (5.3-8.1)	1 (-)		
	Yes	101	70	18 (14.5-24.7)	0.55 (0.42-0.73)	0	
Did patient receive radiotherapy (at any time)?	No	234	150	8.9 (6.7-12.4)	1 (-)		
	Yes	128	99	11.1 (7.9-14.4)	1.13 (0.87-1.45)	0.3619	
BRAF status	Wildtype	144	88	12.4 (6.1-18.5)	1 (-)		0.0061
	Mutant	76	41	13.8 (9.4-37.7)	0.75 (0.51-1.08)	0.1214	
	unknown	142	120	7.4 (5.6-9.8)	1.29 (0.98-1.7)	0.0735	
KEY: SACT=systemic anticancer treatment; ECOG PS=eastern cooperative oncology group performance status; LDH=lactate dehydrogenase; NLR=neutrophil to lymphocyte ratio; ULN=upper limit of normal							

Appendix 5 – IPLR univariate analysis

Co-variate	level	N	No. of events	Median OS in months (95%CI)	HR (95%CI)	p-value
Gender	M	186	129	8.9 (6.5-11.5)	1 (-)	
	F	176	119	11.2 (8.7-14.9)	0.84 (0.65-1.07)	0.1627
ECOG performance status	0	184	106	17.5 (14.4-23.8)	1 (-)	
	1	105	80	6.5 (4.9-9.4)	1.89 (1.41-2.54)	0
	2+	42	37	4.7 (2.3-7.9)	3.44 (2.34-5.05)	0
Primary melanoma site	cutaneous	267	181	10.5 (8.7-13.8)	1 (-)	
	mucosal	34	29	4.8 (3.8-10.3)	1.7 (1.15-2.52)	0.0084
	ocular	24	16	5.4 (4.3-NE)	1.28 (0.77-2.14)	0.3453
	unknown	37	22	11.1 (5.7-NE)	0.87 (0.56-1.35)	0.5261
LDH VALUE	ULN or less	181	99	18 (13-25.8)	1 (-)	
	above ULN	153	125	6 (4.8-8.1)	2.22 (1.7-2.89)	0
NLR Score	0	251	153	14.7 (11.5-18.5)	1 (-)	
	1	107	91	4.3 (3.4-6)	2.46 (1.9-3.2)	0
Scottish Index of Multiple Deprivation	1	75	56	7.6 (5.7-11.6)	1 (-)	
	2	76	55	9.1 (6-14.4)	0.95 (0.65-1.38)	0.7847
	3	67	43	9.9 (5.9-22.5)	0.84 (0.56-1.24)	0.3783
	4	64	43	14.4 (6.6-20.6)	0.78 (0.53-1.16)	0.2265
	5	77	50	10.5 (8.2-28.1)	0.75 (0.51-1.1)	0.141

Co-variate	level	N	No. of events	Median OS in months (95%CI)	HR (95%CI)	p-value
Time from diagnosis to index SACT	less than 1 year	96	64	8.8 (5.7-15.4)	1 (-)	
	1-3 years	112	77	8 (5.5-11.1)	1.06 (0.76-1.48)	0.7274
	3-5 years	54	36	11.2 (8.5-29.2)	0.84 (0.56-1.26)	0.394
	5-10 years	58	44	11.5 (8.8-23)	0.93 (0.64-1.37)	0.7236
	10+ years	41	26	13.3 (7.1-NE)	0.79 (0.5-1.25)	0.3215
Line of Treatment	1	296	194	9.8 (8.6-13)	1 (-)	
	2	63	51	8.5 (6-20.6)	1 (0.73-1.37)	0.9907
	3	3	3	3.8 (3.3-NE)	3.4 (1.08-10.73)	0.0364
Total no. of SACT	1	214	138	7.1 (5.3-9.4)	1 (-)	
	2	110	84	9.4 (8-13.3)	0.87 (0.66-1.14)	0.3232
	3+	38	26	25.8 (20.9-46.7)	0.46 (0.3-0.71)	<0.0001
SACT	Ipilimumab	100	80	6.3 (4.9-10.3)	1 (-)	
	Pembrolizumab	89	56	8 (4.8-15.5)	0.93 (0.66-1.31)	0.6802
	Ipilimumab with nivolumab	44	12	18.5 (14.4-NE)	0.45 (0.24-0.82)	0.0098
	Vemurafenib	51	42	13 (9.9-18)	0.87 (0.6-1.27)	0.4673
	Dabrafenib	36	32	5.6 (4.5-7.6)	1.45 (0.96-2.18)	0.0786
	Dabrafenib with trametinib	42	26	11.5 (9.4-23)	0.7 (0.45-1.09)	0.1172
Year SACT started	2010/11	16	14	12.3 (5.6-64.3)	1 (-)	
	2012	15	13	6.6 (4.9-40.3)	1.24 (0.58-2.65)	0.5701
	2013	39	33	7.3 (4.9-11.6)	1.27 (0.67-2.38)	0.462
	2014	61	52	11.1 (4.9-18.4)	1.11 (0.61-2.02)	0.725
	2015	71	51	8.9 (5.9-13.8)	1.03 (0.57-1.88)	0.9133
	2016	77	50	14.5 (8.1-18.5)	0.88 (0.48-1.61)	0.6881
	2017	83	35	9.6 (7.4-NE)	0.93 (0.49-1.75)	0.8127

Co-variate	level	N	No. of events	Median OS in months (95%CI)	HR (95%CI)	p-value
BRAF status	Wildtype	201	137	8 (5.6-13.5)	1 (-)	
	Mutant	152	102	11.5 (9.2-14.9)	0.82 (0.64-1.06)	0.1384
	unknown	9	9	5.8 (4.5-NE)	1.68 (0.86-3.3)	0.1316
Brain mets at index date	N or unknown	299	196	11.5 (9.2-14.9)	1 (-)	
	Y	63	52	4.9 (3.9-7.3)	1.95 (1.43-2.66)	0
M stage at index date	M0-M1b	111	56	20.9 (14.8-36.8)	1 (-)	
	M1c	243	186	6.2 (5.4-8.7)	2.31 (1.71-3.12)	0
	unknown	8	6	6.7 (3.0-NE)	1.59 (0.68-3.72)	0.2886
Body Mass Index	normal range	86	64	5.6 (4.4-9.1)	1 (-)	
	underweight	5	4	7.6 (4.0-NE)	1.04 (0.38-2.86)	0.9357
	overweight	109	71	14.4 (8.8-20)	0.64 (0.45-0.89)	0.009
	obese	89	52	13 (7.6-29.2)	0.59 (0.41-0.85)	0.0048
Did pt switch SACT?	No	260	179	6.6 (5.6-8.6)	1 (-)	
	Yes	102	69	18.4 (14.5-24.7)	0.56 (0.43-0.75)	<0.0001
KEY: SACT=systemic anticancer treatment; ECOG PS=eastern cooperative oncology group performance status; LDH=lactate dehydrogenase; NLR=neutrophil to lymphocyte ratio; ULN=upper limit of normal; pt=patient						

Appendix 6 - IPLR baseline factors differences by index SACT

		Ipilimumab	Pembrolizumab	Ipilimumab with nivolumab	Vemurafenib	Dabrafenib	Dabrafenib with trametinib	Comparison p-value
	n	100	89	44	51	36	42	
Gender	M	50.0	53.9	52.3	56.9	44.4	47.6	0.8672
	F	50.0	46.1	47.7	43.1	55.6	52.4	
Age	median (IQR)	65 (52.8-74)	77 (67-83)	58 (49.8-64.3)	57 (48.5-67.5)	59.5 (48-69.8)	57 (45-68.5)	
	Range	28-86	22-91	28-77	34-85	26-90	33-92	
Follow Up in months	median	6.1	6.2	6.7	13	5.6	10.1	
	IQR	3.6-26.4	3.4-16.1	4.4-11.0	5.6-28.7	3.2-9.4	7.2-17.1	
	Range	0.7-69.2	0.3-49.8	0.6-18.5	0.4-88.1	0.1-65.5	3.1-36.4	
	mean	15.9	10.6	8	18.8	10.8	13.2	
Reverse Kaplan-Meier FU	median	45.9	21.5	8.9	39.5	55.3	23.2	
	95%CI	39.3-54.6	19.7-25.5	6.6-11.1	34.4-na	28.7-NA	15.8-NA	
ECOG PS	0	55.0	37.1	84.1	60.8	25.0	45.2	0.0000
	1	26.0	51.7	13.6	23.5	16.7	21.4	
	2+	1.0	11.2	2.3	7.8	44.4	23.8	
	Unknown	18.0	0.0		7.8	13.9	9.5	
Primary site	cutaneous	60.0	68.5	65.9	90.2	91.7	90.5	0.0000
	mucosal	20.0	7.9	13.6	2.0	0.0	0.0	
	ocular	10.0	12.4	6.8	0.0	0.0	0.0	
	unknown	10.0	11.2	13.6	7.8	8.3	9.5	
LDH	ULN or less	59.0	52.8	63.6	35.3	27.8	45.2	0.0023
	above ULN	33.0	42.7	36.4	47.1	63.9	45.2	
	Unknown	8.0	4.5	0.0	17.6	8.3	9.5	

		Ipilimumab	Pembrolizumab	Ipilimumab with nivolumab	Vemurafenib	Dabrafenib	Dabrafenib with trametinib	Comparison p-value
NLR Score	0	74.0	74.2	77.3	62.7	50.0	64.3	0.0588*
	1	25.0	25.8	22.7	35.3	44.4	35.7	
	Unknown	1.0	0.0	0.0	2.0	5.6	0.0	
SIMD	1	22.0	21.3	18.2	19.6	25.0	16.7	0.9523
	2	22.0	18.0	15.9	25.5	22.2	23.8	
	3	15.0	18.0	22.7	21.6	16.7	21.4	
	4	20.0	14.6	18.2	17.6	13.9	21.4	
	5	19.0	28.1	25.0	15.7	22.2	14.3	
	Unknown	2.0	0.0	0.0	0.0	0.0	2.4	
Time from diagnosis to index SACT	less than 1 year	23.0	34.8	36.4	19.6	19.4	21.4	0.0618
	1-3 years	28.0	34.8	27.3	41.2	38.9	14.3	
	3-5 years	20.0	10.1	13.6	13.7	11.1	19.0	
	5-10 years	21.0	10.1	13.6	9.8	11.1	31.0	
	10+ years	7.0	10.1	9.1	15.7	19.4	14.3	
	Unknown	1.0	0.0	0.0	0.0	0.0	0.0	
Line of treatment	1	40.0	100.0	100.0	94.1	94.4	97.6	0.0000
	2+	60.0	0.0	0.0	5.9	5.6	2.4	
Year treatment started	2010/11	6.0	0.0	0.0	19.6	0.0	0.0	0.0000
	2012	5.0	0.0	0.0	7.8	13.9	2.4	
	2013	19.0	0.0	0.0	0.0	47.2	7.1	
	2014	39.0	1.1	0.0	41.2	0.0	0.0	
	2015	30.0	18.0	0.0	21.6	13.9	21.4	
	2016	0.0	44.9	22.7	9.8	16.7	38.1	
	2017	1.0	36.0	77.3	0.0	8.3	31.0	

		Ipilimumab	Pembrolizumab	Ipilimumab with nivolumab	Vemurafenib	Dabrafenib	Dabrafenib with trametinib	Comparison p-value
BRAF Status	Wildtype	85.0	97.8	65.9	0.0	0.0	0.0	0.0000
	Mutant	6.0	2.2	34.1	100.0	100.0	100.0	
	unknown	9.0	0.0	0.0	0.0	0.0	0.0	
Brain metastases	No or unknown	91.0	86.5	81.8	88.2	58.3	69.0	0.0001
	Yes	9.0	13.5	18.2	11.8	41.7	31.0	
M status	M0-M1b	31.0	25.8	40.9	37.3	13.9	35.7	0.0139*
	M1c	63.0	74.2	59.1	58.8	86.1	64.3	
	unknown	6.0	0.0	0.0	3.9	0.0	0.0	
BMI	Normal Range	33.0	31.5	29.5	7.8	8.3	11.9	0.0000
	Underweight	0.0	1.1	4.5	0.0	2.8	2.4	
	Overweight	34.0	38.2	29.5	19.6	16.7	28.6	
	Obese	33.0	29.2	36.4	5.9	11.1	16.7	
	Unknown	0.0	0.0	0.0	66.7	61.1	40.5	
Further SACT	No	70.0	80.9	84.1	43.1	77.8	73.8	0.0000
	Yes	30.0	19.1	15.9	56.9	22.2	26.2	

KEY: SACT=systemic anticancer treatment; IQR=interquartile range; FU=follow-up; CI=confidence intervals; ECOG PS=Eastern Cooperative Oncology Group Performance Status; LDH=lactate dehydrogenase; ULN=upper limit of normal; NLR=neutrophil-lymphocyte ratio; SIMD=Scottish Index of Multiple Deprivation; BMI=body mass index; *=no longer significant when adjusted for multiple using Benjamini Hofberg

Appendix 7 – R code used in analysis

```
setwd("S:/Julie")
library(survival)
library(reshape2)
library(plyr)
library(ggplot2)
library(survminer)
options(max.print=1000000)

##CHECK PATIENTS FOR EXCLUSION CRITERIA (U18).NEED TO DETERMINE 1ST APPT DATE FOR TX OF INTEREST AND THEN CHECK AGE AT THIS POINT
##summarise demographic data
chi_database_deaths <- read.csv("Z:/chi_database_deaths.csv", stringsAsFactors=FALSE)
WoS_Melanoma_Chemocare <- read.csv("Z:/WoS_Melanoma_Chemocare.csv", stringsAsFactors=FALSE)
DEMOG<-chi_database_deaths[,c("SafeHavenID", "DATE_OF_DEATH", "PRIMARY_CAUSE_OF_DEATH", "DATE_OF_BIRTH", "SEX",
"simd2012_sc_quintile")]
str(DEMOG)
DEMOG$DOD<-as.Date(as.character(DEMOG$DATE_OF_DEATH), format="%Y%m%d")
DEMOG$DOD[DEMOG$DOD> as.Date("2018-03-31")] <-NA ##EXCLUDE DOD AFTER CENSOR DATE
DEMOG$DOB<-as.Date(as.character(DEMOG$DATE_OF_BIRTH), format="%Y%m%d")
DEMOG$SEX<-as.factor(DEMOG$SEX)
DEMOG$simd2012_sc_quintile<-as.factor(DEMOG$simd2012_sc_quintile)
DEMOG$PRIMARY_CAUSE_OF_DEATH<-as.factor(DEMOG$PRIMARY_CAUSE_OF_DEATH)

##identify index date
C<-WoS_Melanoma_Chemocare
appt<-colsplit(C$APPT_DATE," ",names =c("d", "t"))
C$apdate<-appt$d
C$apdate<-as.Date(C$apdate, format="%Y-%m-%d")
str(C)
```

```
C$DIAGNOSIS<-as.factor(C$DIAGNOSIS)
C$REGIME<-as.factor(C$REGIME)

MM<-subset(C, C$DIAGNOSIS %in% c("Malignant Melanoma - Metastatic", "Malignant Melanoma"))
MM$REG<-NA
MM$REG[MM$REGIME %in% c("BRIM 3 ARM A", "SK31 RO5185426", "SK44 VEMURAFINIB", "VEMURAFENIB")] <- "VEM"
MM$REG[MM$REGIME %in% c ("BRIM 3 ARM B", "DACARBAZINE")] <- "CD"
MM$REG[MM$REGIME %in% c ("TEMOZ. MELANOMA","TEMOZOL200mg/m2")] <- "CT"
MM$REG[MM$REGIME %in% c ("PAC/CARB AUC 5", "PAC/CARB AUC 6")] <- "CO"
MM$REG[MM$REGIME %in% "DABRAFENIB"] <- "DAB"
MM$REG[MM$REGIME %in% c ("DABRA+TRAMETINIB", "DABRAF+TRAMETIN" ,"SK36 DABRA+TRAM")] <- "DT"
MM$REG[MM$REGIME %in% c("IPILIMUMAB", "SK33 IPILIMUMAB", "SK39 IPILIMUMAB")] <- "IPI"
MM$REG[MM$REGIME %in% c ("MK-3475", "PEMBROLIZUMAB" ,"PEMBROLIZUMAB EX","SK39 MK-3475 Q2W")] <- "PEM"
MM$REG[MM$REGIME %in% c("NIVO + IPILUM", "NIVOLUMAB+IPILIM", "SK51 NIVO/IPILIM")] <- "IN"
MM$REG[MM$REGIME %in% c("NIVOLUMAB 3MG/KG", "NIVOLUMAB SKIN", "SK51 NIVOLUMAB")] <- "NI"
MM$REG[MM$REGIME %in% c("SK46 NIVOLUMAB")] <- "NIVO"
MM$REG[MM$REGIME %in% c("SK27 DACAR/E7080", "SK27 DACARBAZINE", "SK27 E7080")] <- "TSK27"
MM$REG[MM$REGIME %in% c("SK30 DOC-MEK")] <- "TSK30"
MM$REG[MM$REGIME %in% c("SK38 GO28141")] <- "TSK38"
MM$REG[MM$REGIME %in% c("SK28 E7080")] <- "TSK28"
MM$REG[MM$REGIME %in% c("SK34 PACLITAXEL", "SK34 PAZOP+PACLI")] <- "TSK34"
MM$REG[MM$REGIME %in% c("SK41 CYCLES 1+2")] <- "TSK41"
MM$REG[MM$REGIME %in% c("SK43 SUMIT COMBO")] <- "TSK43"
MM$REG[MM$REGIME %in% c("SK48 SELUMETINIB" )] <- "TSK48"
MM$REG[MM$REGIME %in% c("SK49 DURV/TREMEL", "SK49 DURVALUMAB", "SK49 IMCGP100" )] <- "TSK49"
MM$REG[MM$REGIME %in% "ZOLEDRONIC ACID"]<-"ZOLE"
MM$REG[MM$REGIME %in% "AVAST-M TRIAL"]<-"AVASTM"
#MM contains all treatments for melanoma and all pts (none excluded yet)

MM1<-MM[, c("SafeHavenID", "CYCLE", "REG", "apdate")]
```

```
str(MM1)
MM1$CYCLE<-as.factor(MM1$CYCLE)
MM1$REG<-as.factor(MM1$REG)
MM2<-subset(MM1, MM1$REG %in% c("VEM", "DAB", "DT", "IN","NI", "IPI", "PEM", "NIVO"))
MM3<-MM2[order(MM2$SafeHavenID, MM2$apdate),]
MM3<-MM3[! duplicated(MM3[ ,c("SafeHavenID", "REG")]), ]
table(MM3$REG)


##rename courses if pts have DT/IN to avoid double counting
D<-subset(MM3, MM3$REG =="DAB")
DT<-subset(MM3, MM3$REG=="DT")
Dtid<-intersect(D$SafeHavenID,DT$SafeHavenID)##id pts getting both DT DAB
save(Dtid, file = "Dtid.Rda")
MM3$REG[MM3$REG == "DAB" & MM3$SafeHavenID %in%Dtid ]<-"DT" ##rename DAB-DT reg

IN<-subset(MM3, MM3$REG =="IN")
NI<-subset(MM3, MM3$REG=="NI")
INid<-intersect(IN$SafeHavenID,NI$SafeHavenID)##id pts getting both IN NI
save(INid, file = "INid.Rda")
MM3$REG[MM3$REG == "NI" & MM3$SafeHavenID %in%INid ]<-"IN" ##rename IN reg

MM4<-MM3[order(MM3$SafeHavenID, MM3$apdate),]
MM4<-MM4[!duplicated(MM4[ ,c("REG", "SafeHavenID")]),] ##summary of tx of interest only including 2018 tx

##add counter to treatments of interest
MM4$counter<-sequence(rle(as.character(MM4$SafeHavenID))$lengths)
MM4$counter<-as.factor(MM4$counter)
MM5<-subset(MM4, MM4$counter =="1") ##this is index date for all patients
```

```
##calculate age at index date - to id patient(s) for exclusion (U18)
DEMOG<-merge (DEMOG, MM5, by ="SafeHavenID" ,all=TRUE)
str(DEMOG)
DEMOG1<-DEMOG[,c("SafeHavenID", "SEX", "DOD", "DOB", "REG", "apdate")]
DEMOG1$AGE<-as.numeric(DEMOG1$apdate-DEMOG1$DOB)
DEMOG1$AGEY<-floor(DEMOG1$AGE/365.25) ##round down to get age in years

##id patients to exclude (U18)
exid<-unique(DEMOG1$SafeHavenID[DEMOG1$AGEY<18])

MMex<-MM[!MM$SafeHavenID %in% exid,] # EXCLUDE PTS AND TX
MMex<-MMex[!MMex$REG =="ZOLE",] #this is not active melanoma treatment
MMex<-MMex[!MMex$REG == "AVASTM",] #this is an adjuvant trial

DEMOG2<-DEMOG1[!DEMOG1$SafeHavenID %in% exid,]
##exclude nivo patient(s) due to low numbers
nid<-unique(DEMOG2$SafeHavenID[DEMOG2$REG =="NIVO"])
DEMOG2<-DEMOG2[!DEMOG2$SafeHavenID %in% nid,]
DEMOG2$DEATH<-ifelse(is.na(DEMOG2$DOD), 0, 1)
DEMOG2$end <- DEMOG2$DOD
DEMOG2$end[is.na(DEMOG2$DOD)]<-as.Date("2018-03-31")
DEMOG2$TIME<-as.numeric(DEMOG2$end-DEMOG2$apdate)

##INDEX SET FOR ONGOING USE containing first appt date only
INDEX<-DEMOG2[,c("SafeHavenID", "apdate","REG")]
### save dataset
save(INDEX, file = "INDEX.Rda")

##UTILISE SMR06 DATA TO DETERMINE MELANOMA SITE AND INITIAL DIAGNOSIS DATE
```

```
SMR06 <- read.csv("Z:/SMR06.csv", stringsAsFactors=FALSE)
z<-SMR06
length(unique(z$SafeHavenID))
table(z$ICD10S_CANCER_SITE)
z$breslow<-cut(z$MELANOMA_SKIN_BRESLOW_SIZE, breaks=c(0,1.00,2.00,4.00,41,100)) ##>41 is unknown
z<-z[,c("SafeHavenID", "INCIDENCE_DATE", "ICD10S_CANCER_SITE","breslow", "TYPE_ICDO3")]
str(z)
z$INCIDENCE_DATE<-as.Date(as.character(z$INCIDENCE_DATE), format="%Y%m%d")
z$ICD10S_CANCER_SITE<-as.factor(z$ICD10S_CANCER_SITE)
z$TYPE_ICDO3<-as.factor(z$TYPE_ICDO3)
z<-merge(z, DEMOG2[,c("SafeHavenID", "apdate")], by="SafeHavenID")

table(z$ICD10S_CANCER_SITE)

z$site<-NA
z$site[z$ICD10S_CANCER_SITE %in% c("C430", "C431", "C432", "C433", "C434", "C435", "C436", "C437", "C439")] <- "CUT"
z$site[z$ICD10S_CANCER_SITE %in%
c("D020","D033","D035","D036","D037","D042","D044","D045","D046","D047","D069","D071","D075","D320","D414","D464","D472","D473" )] <-
"INSITU"
z$site[z$ICD10S_CANCER_SITE %in% c("C693","C694","C696","C699")]<-"OCULAR"
z$site[z$ICD10S_CANCER_SITE %in% c("C051","C061","C12X","C300","C310","C319")]<-"MUCOSAL"
z$site[z$ICD10S_CANCER_SITE %in% c("C169","C180","C185","C186","C187","C19X","C20X")]<-"CRC"
z$site[z$ICD10S_CANCER_SITE %in% c("C440", "C441", "C442","C443","C444","C445","C446","C447","C449")]<-"NONMEL"
z$site[z$ICD10S_CANCER_SITE %in% c("C504","C508","C509")]<-"BREAST"
z$site[z$ICD10S_CANCER_SITE %in% c("C511","C519")]<-"VULVA"
z$site[z$ICD10S_CANCER_SITE %in% "C52X"]<-"VAG"
z$site[z$ICD10S_CANCER_SITE %in% c("C539","C541","C56X")]<-"GYNAE"
z$site[z$ICD10S_CANCER_SITE %in% "C579"]<-"UNSPEC FEM GEN"
z$site[z$ICD10S_CANCER_SITE %in% "C61X"]<-"PROSTATE"
z$site[z$ICD10S_CANCER_SITE %in% "C600"]<-"FORESKIN"
```

```
z$site[z$ICD10S_CANCER_SITE %in% c("C64X","C670")]<-"KID/BLAD"
z$site[z$ICD10S_CANCER_SITE %in% c("C774","C778","C780","C792","C793","C798")]<-"SECONDARY"
z$site[z$ICD10S_CANCER_SITE %in% "C73X"]<-"THYROID"
z$site[z$ICD10S_CANCER_SITE %in% c("C829","C830","C921")]<-"HAEM"
z$site[z$ICD10S_CANCER_SITE %in% c("C809","C80X", "C800")]<-"UNKNOWN PRIMARY"
z$site[z$ICD10S_CANCER_SITE %in% "C320"]<-"GLOTTIS"
z$site[z$ICD10S_CANCER_SITE %in% c("C210","C211","C218")]<-"ANUS"
z$site[z$ICD10S_CANCER_SITE %in% "C341"]<-"LUNG"
z$site<-as.factor(z$site)
table(z$site)


##subset sites of potential interest
z1<-subset(z, z$site %in% c("CUT", "OCULAR", "MUCOSAL", "SECONDARY","FORESKIN", "UNKNOWN PRIMARY","UNSPEC FEM GEN",  "ANUS", "VAG",
"VULVA"))
length(unique(z1$SafeHavenID))
table(z1$TYPE_ICDO3)
z1$meltype<-NA
z1$meltype[z1$TYPE_ICDO3 %in% c("87203","87206")]<-"mel"
z1$meltype[z1$TYPE_ICDO3 %in% c("87233","87303","87403","87463","87703","87723")]<-"other"
z1$meltype[z1$TYPE_ICDO3 %in% "87213"]<-"nodular"
z1$meltype[z1$TYPE_ICDO3 %in% "87423"]<-"lentigo MM"
z1$meltype[z1$TYPE_ICDO3 %in% "87433"]<-"SSM"
z1$meltype[z1$TYPE_ICDO3 %in% "87443"]<-"acral"
z1$meltype[z1$TYPE_ICDO3 %in% "87213"]<-"nodular"
#check for diagnoses after first appointment
z2<-subset(z1,z1$INCIDENCE_DATE <z1$apdate)
##relabel to have just M, CUT, UNKN, OC AND 2
z2$site2<-NA
z2$site2[z2$site %in% c("VAG", "VULVA","MUCOSAL","ANUS")]<-"M"
```

```
z2$site2[z2$site %in% c("CUT","FORESKIN", "UNSPEC FEM GEN")]<-"C"
z2$site2[z2$site =="OCULAR"]<-"O"
z2$site2[z2$site =="SECONDARY"]<-"2"
z2$site2[z2$site =="UNKNOWN PRIMARY"]<-"U"
table(z2$site2)

##check if pts with secondary ca have any other sites
secondary<-unique(z2$SafeHavenID[z2$site2=="2"])
check<-subset(z,z$SafeHavenID %in% secondary) ##leave as 2dary ca

##id patients with more than 1 SMR06 entry of interest relating to melanoma
id<-unique(subset(z2, duplicated(SafeHavenID))$SafeHavenID)

z3<-subset(z2, SafeHavenID %in% id==FALSE) ##pts with 1 SMR06 entry of interest for baseline
z4<-subset(z2, SafeHavenID %in% id) ##pts with 1+ SMR06 entry of interest for baseline
length(unique(z4$SafeHavenID))

z5<-z4[order(z4$SafeHavenID, z4$INCIDENCE_DATE),] ##use first entry in SMR06 for diagnosis and diagnosis date
z5<-z5[!duplicated(z5$SafeHavenID),]
z6<-rbind(z3,z5)
z7<-z6[,c("SafeHavenID", "INCIDENCE_DATE","site2", "breslow", "meltype")] ##this can be merged with baseline info
z7$meltype<-as.factor(z7$meltype)
##merge DEMOG2 with SMR06 summary to get baseline chars and then calc OS from initial treatment (SMR06 file)
b<-merge(DEMOG2,z7, by = "SafeHavenID", all=TRUE)

##addSIMD info
b<-merge(b, (chi_database_deaths[,c("SafeHavenID", "simd2012_sc_quintile")]), by = "SafeHavenID")

b$REG<-factor(b$REG, levels = c("IPI", "VEM", "DAB", "DT", "PEM", "IN"))
b$site2<- factor(b$site2, levels =c("C", "M","O", "2", "U"))
```

```
b$simd2012_sc_quintile<-as.factor(b$simd2012_sc_quintile)
b$tfd<-as.numeric(b$apdate-b$INCIDENCE_DATE) #calculate time from diagnosis to first treatment
b$tfd<-cut(b$tfd, breaks = c(0,365,1065,1795,3650,20000))
table(b$tfd)
levels(b$tfd)[1]<-"less than 1 year"
levels(b$tfd)[2]<-"1-3 years"
levels(b$tfd)[3]<-"3-5 years"
levels(b$tfd)[4]<-"5-10 years"
levels(b$tfd)[5]<-"more than 10 years"

base<-b[,c("SafeHavenID","SEX","end","REG","apdate","AGEY","DEATH","tfd","site2","TIME", "simd2012_sc_quintile", "breslow","meltype")]
summary(base)

##IDENTIFY BASELINE BLOODS TO ADD TO BASELINE TABLE
INDEX$CUTOFF<-as.Date(INDEX$apdate-28)
SCI_Store <- read.csv("Z:/SCI_Store.csv", stringsAsFactors=FALSE)

BIOCHEM<-subset(SCI_Store, SCI_Store$DISCIPLINE =="Biochemistry")
HAEM<-subset(SCI_Store, SCI_Store$DISCIPLINE =="Haematology")

#get baseline LDH
ldh<-subset(BIOCHEM, BIOCHEM$CLINICALCODEVALUELOCAL =="LDH")
ldh<-ldh[,c("SafeHavenID","SAMPLEDATE","QUANTITYVALUE","QUANTITYUNIT","RANGEHIGHVALUE","RANGELOWVALUE","RANGEUNIT")]
LDHBASE<-merge(INDEX, ldh, by="SafeHavenID")
str(LDHBASE)
LDHBASE$SAMPLEDATE<-as.Date(LDHBASE$SAMPLEDATE, format = "%Y-%m-%d")
LDHBASE1<-subset(LDHBASE, LDHBASE$SAMPLEDATE>=LDHBASE$CUTOFF & LDHBASE$SAMPLEDATE<=LDHBASE$apdate)

LDHBASE2<-subset(LDHBASE1, !LDHBASE1$QUANTITYVALUE =="0")
LDHBASE2<-LDHBASE2[order(-LDHBASE2$SafeHavenID, LDHBASE2$SAMPLEDATE, decreasing = TRUE),]##ORDER BY NEWEST DATE FIRST
```

```
LDHBASE3<-LDHBASE2[!duplicated(LDHBASE2$SafeHavenID),]
LDH<-LDHBASE3[,c("SafeHavenID","SAMPLEDATE","QUANTITYVALUE")]
LDH<-rename(LDH, c("SAMPLEDATE"= "LDHDATE", "QUANTITYVALUE"="LDH"))
str(LDH)
LDH$CUT<-cut(LDH$LDH, breaks = c(0,240, 6000))

##get baseline NLR - neut and  lymph should be available from same blood sample

n<-subset(HAEM, HAEM$CLINICALCODEVALUELOCAL %in% c("NE", "NEUT", "NEU"))
n<-n[,c("SafeHavenID","SAMPLEDATE","QUANTITYVALUE","QUANTITYUNIT","RANGEHIGHVALUE","RANGELOWVALUE","RANGEUNIT")]
str(n)
n$SAMPLEDATE<-as.Date(n$SAMPLEDATE, format="%Y-%m-%d")
n<-rename(n,  c("QUANTITYVALUE"="N"))
NBASE<-merge(INDEX, n, by="SafeHavenID", all=TRUE)
N1<-subset(NBASE, NBASE$SAMPLEDATE>=NBASE$CUTOFF & NBASE$SAMPLEDATE<=NBASE$apdate)

N2<-N1[,c("SafeHavenID","SAMPLEDATE","N")]
N2<-N2[order(-N2$SafeHavenID, N2$SAMPLEDATE, decreasing = TRUE),]
N3<-N2[!duplicated(N2$SafeHavenID),]

ly<-subset(HAEM, HAEM$CLINICALCODEVALUELOCAL %in% c("LY","LYABS","LYM","LYMPH"))
ly<-ly[,c("SafeHavenID","SAMPLEDATE","QUANTITYVALUE","QUANTITYUNIT","RANGEHIGHVALUE","RANGELOWVALUE","RANGEUNIT")]
str(ly)
ly$SAMPLEDATE<-as.Date(ly$SAMPLEDATE, format="%Y-%m-%d")
ly<-rename(ly, c("QUANTITYVALUE"="LY"))
LYBASE<-merge(INDEX, ly, by="SafeHavenID", all=TRUE)
LY1<-subset(LYBASE, LYBASE$SAMPLEDATE>=LYBASE$CUTOFF & LYBASE$SAMPLEDATE<=LYBASE$apdate)
LY2<-LY1[,c("SafeHavenID","SAMPLEDATE","LY")]
LY2<-LY2[order(-LY2$SafeHavenID, LY2$SAMPLEDATE, decreasing = TRUE),]
LY3<-LY2[!duplicated(LY2$SafeHavenID),]
```

```
NL<-merge(N3,LY3, c("SafeHavenID", "SAMPLEDATE"), all=TRUE)
NL$NLRSCORE<-as.numeric(NL$N/NL$LY)
NL$NLR<-ifelse(NL$NLRSCORE>=5,1,0)
NLR<-NL[,c("SafeHavenID", "NLR","SAMPLEDATE")]
NLR<-rename(NLR, c("SAMPLEDATE"= "NLRDATE"))
NLR$NLR<-as.factor(NLR$NLR)

base<-merge(base,LDH, by="SafeHavenID", all=TRUE)
base<-merge(base,NLR, by="SafeHavenID", all=TRUE)

##SUMMARISE TOTAL NO OF TX GIVEN FOR BASELINE TABLE; determine BMI/PS too - this doesn't account for treatment interruptions

MMex1<-MMex[, c("SafeHavenID", "CYCLE", "REG", "DRUGNAME", "apdate", "PS.DIAGNOSIS","PS.CYCLE", "DURATION","SAHEIGHT","SAWEIGHT")]

MMex1$REG[MMex1$REG == "DAB" & MMex1$SafeHavenID %in%Dtid ]<-"DT" ##rename DAB-DT reg
MMex1$REG[MMex1$REG == "NI" & MMex1$SafeHavenID %in%INid ]<-"IN" ##rename reg

MMex2<-MMex1[order(MMex1$SafeHavenID, MMex1$apdate),]
MMex2<-MMex2[! duplicated(MMex2[ ,c("SafeHavenID", "REG")]), ]
table(MMex2$REG)
MMex2$PS<-NA
MMex2$PS<- MMex2$PS.CYCLE
MMex2$PS[is.na(MMex2$PS)]<-MMex2$PS.DIAGNOSIS[is.na(MMex2$PS)]
MMex2$BMI<-NA
MMex2$BMI<-round(as.numeric(MMex2$SAWEIGHT/(MMex2$SAHEIGHT*MMex2$SAHEIGHT)),1)


##add tx line column -still includes 2018 tx
MMex2$txline<-sequence(rle(as.character(MMex2$SafeHavenID))$lengths)
```

```
MMex2$txline<-as.factor(MMex2$txline)
MMex2 <- rename(MMex2, c("apdate" = "txstart"))
table(MMex2$txline)
MMSTART<-MMex2[,c("SafeHavenID", "REG", "txstart", "txline", "PS","BMI")]
str(MMSTART)

MMSTART$PS<-as.factor(MMSTART$PS)
##find end date for each treatment and last cycle no. Need to count actual no of cycles separately
MMex4 <- MMex1[order(-MMex1$SafeHavenID, MMex1$apdate, decreasing = TRUE),]
MMex5 <- MMex4[! duplicated(MMex4[ ,c("SafeHavenID", "REG")]), ]
MMex5 <- MMex5[order(MMex5$SafeHavenID, MMex5$apdate),]
MMex5 <- rename(MMex5, c("apdate" = "txend", "CYCLE" = "last.cycle.no"))
MMEND<-MMex5[,c("SafeHavenID", "REG", "txend", "DURATION", "last.cycle.no")]

MMD <- merge(MMSTART, MMEND, c("SafeHavenID", "REG"))
MMD <- MMD[order(MMD$SafeHavenID, MMD$txstart),]

##count total no.tx including those started in 2018
number<-ddply(MMD, .(SafeHavenID), function(x){length(unique(x$REG))})
str(number)
number$no.tx<-as.factor(number$V1)
no.tx<-number[,c("SafeHavenID", "no.tx")]
summary(no.tx)

##add flag to pts who switch tx
switch<-merge(MMD, no.tx, by="SafeHavenID", all=TRUE)

switch$switchflag<-NA
switch$txline<-as.numeric(switch$txline)
switch$no.tx<-as.numeric(switch$no.tx)
```

```
switch$switchflag[switch$no.tx>switch$txline]<-"Y"
switch$switchflag[switch$no.tx==switch$txline]<-"N"
table(switch$switchflag, switch$REG, useNA = "ifany")
save(switch, file = "all.tx.summary.Rda")

switch<-subset(switch, switch$REG %in% c("DAB","DT","IN","IPI","NIVO","PEM","VEM"))
s<-switch[,c("SafeHavenID","switchflag", "no.tx")] ##REG not included as it's already in INDEX
s<-s[!duplicated(s[,"SafeHavenID"]),]
s<-s[!s$SafeHavenID %in% nid,]
INDEXS<-merge(INDEX, s, by="SafeHavenID")
save(INDEXS, file = "INDEXS.Rda")


##ADD TOTAL NO OF TX TO BASELINE TABLE
base<-merge(base,s,by="SafeHavenID", all=TRUE)
table(base$switchflag, base$REG)

##add PS to base
b<-merge(base,MMSTART,c("SafeHavenID", "REG"))
b$year<-as.numeric(format(b$apdate, "%Y"))

##add no. of drugs pre tx (drug count) to baseline table
PIS <- read.csv("Z:/PIS.csv", stringsAsFactors=FALSE)
str(PIS)
length(unique(PIS$SafeHavenID))

f<-PIS[,c("SafeHavenID","DispDate","PIApprovedName","PIDrugFormulation",     "PIItemStrengthUOM","PIBNFChapterCode",     "PIBNFSectionCode",
"PIBNFSubSectionCode","PIBNFParagraphCode", "PIBNFItemDescription")]
f1<-merge(f,INDEX, by="SafeHavenID", all=TRUE)
str(f1)
```

```
f1$DispDate<-as.Date(as.character(f1$DispDate), format = "%Y%m%d")
f1$CUTOFF<-f1$apdate-365
fpre<-subset(f1, f1$DispDate<f1$apdate & f1$DispDate>f1$CUTOFF)
length(unique(fpre$SafeHavenID)) ##355
fpre1<-fpre[!duplicated(fpre[,c("SafeHavenID", "PIApprovedName")]),]
table(fpre1$PIBNFChapterCode, useNA = "ifany")
fpre2<-subset(fpre1, !fpre1$PIBNFChapterCode %in% c("14","19","20","21","22","23","NA")) ##exclude vaccines; dressings etc

dcount<-aggregate (PIApprovedName ~SafeHavenID, data=fpre2, FUN=length)
dcount <- rename(dcount,c("PIApprovedName" = "drugcount"))
table(dcount$drugcount)
summary(dcount)

fpre3<-subset(fpre2, !fpre2$PIBNFSectionCode %in% c("1103", "1307", "1308","1311","1312","1501"))
dcount<-aggregate (PIApprovedName ~SafeHavenID, data=fpre3, FUN=length)
dcount <- rename(dcount,c("PIApprovedName" = "drugcount"))
table(dcount$drugcount, exclude = NULL)
length(unique(dcount$SafeHavenID))#353

##merge to baseline
b<-merge(b,dcount, by="SafeHavenID", all=TRUE)
table(b$drugcount, useNA = "ifany")
b$drugcount[is.na(b$drugcount)]<-0
b$drugcount<-as.numeric(b$drugcount)
b$dgroup<- cut(b$drugcount, breaks = c(-1,4,9,14,19,50))
table(b$dgroup, useNA = "ifany") ##assume all NA are 0 and include in 0-4 group
levels(b$dgroup)[1]<-"less than 5"
levels(b$dgroup)[2]<-"5 to 9"
levels(b$dgroup)[3]<-"10 to 14"
levels(b$dgroup)[4]<-"15 to 19"
```

```
levels(b$dgroup)[5]<-"20 or more"
##add groupings for table publication
table(b$PS)
levels(b$PS)[3:4]<-"2+"
table(b$no.tx)
b$no.tx<-as.factor(b$no.tx)
levels(b$no.tx)[3:5]<-"3+"
b$BMIGP<-cut(b$BMI, breaks = c(0,18.40,24.90,29.90,50.00))
summary(b$BMI)
table(b$BMIGP, exclude = NULL)
levels(b$BMIGP)[1]<-"underweight"
levels(b$BMIGP)[2]<-"normal range"
levels(b$BMIGP)[3]<-"overweight"
levels(b$BMIGP)[4]<-"obese"
table(b$BMIGP, exclude = NULL)
b$BMIGP<-factor(b$BMIGP, levels = c("normal range", "underweight","overweight", "obese"))

##add charlson score
smr01 <- read.csv("Z:/SMR01.csv", stringsAsFactors=FALSE)
length(unique(smr01$SafeHavenID))#364
smr011 <- subset(smr01, !SafeHavenID %in% exid)
dim(b)#363

z <-
smr011[,c("SafeHavenID","ADMISSION_DATE","MAIN_CONDITION","OTHER_CONDITION_1","OTHER_CONDITION_2","OTHER_CONDITION_3","OTHE
R_CONDITION_4","OTHER_CONDITION_5")]
length(unique(z$SafeHavenID))#363
names(z)[2] <- "Date"
z$ICD10 <- NA
```

```
z2 <- read.csv("Z:/SMR06.csv", stringsAsFactors=FALSE)
#names(z2)
z2 <-z2[,c("SafeHavenID","INCIDENCE_DATE","ICD10S_CANCER_SITE")]

dim(z2)#522
z2 <- cbind.data.frame(z2[,1:2], NA,NA,NA,NA,NA,NA,z2[,3])
names(z2)<-names(z)
z <- rbind(z,z2)
dim(z)#7759
z$Date <- as.Date(as.character(z$Date), format="%Y%m%d")


z <- merge(b[,c("SafeHavenID","apdate")],z)

z <- subset( z, Date < apdate)
length(unique(z$SafeHavenID))#361


ex.list <- c("C430", "C431", "C432", "C433", "C434", "C435", "C436", "C437", "C439","C693","C694","C696","C699",
          "C051","C061","C12X","C300","C310","C319","C511","C519","C52X","C774","C778","C780","C792","C793","C798",
          "C809","C80X", "C800", "C320", "C210","C211","C218")
ex.list2 <- c("C77", "C78", "C79", "C80","C43")

diag.list <- c("MAIN_CONDITION", paste("OTHER_CONDITION_",1:5,sep=""),"ICD10")
for(i in 1:length(diag.list)){
  if(i==1) cancer.list.smr01 <- subset(z, substr(z[,diag.list[i]],1,1)=="C")[,diag.list[i]] else
    cancer.list.smr01 <- c(cancer.list.smr01,subset(z, substr(z[,diag.list[i]],1,1)=="C")[,diag.list[i]])}
cancer.list.smr01 <- unique(cancer.list.smr01)
length(cancer.list.smr01)#57
```

```
for(i in 1:length(diag.list)){
  z[,diag.list[i]] <- ifelse(substr(z[,diag.list[i]],1,4) %in%ex.list, NA, z[,diag.list[i]])}

for(i in 1:length(diag.list)){
  z[,diag.list[i]] <- ifelse(substr(z[,diag.list[i]],1,3) %in%ex.list2, NA, z[,diag.list[i]])}

for(i in 1:length(diag.list)){
  z[,diag.list[i]] <- ifelse((substr(z[,diag.list[i]],1,1) =="C") & (z$apdate-z$Date>365*5), NA, z[,diag.list[i]])}

#head(subset(z,substr(z[,diag.list[i]],1,1) =="C" & (z$apdate-z$ADMISSION_DATE>365*5)))


source("U:\\code for Julie\\charlson function for melanoma.r")

charlson.score <- fun.charlson(z, diag.list = diag.list)

dim(charlson.score)#361

z <- merge(b, charlson.score,all.x=TRUE)
dim(z)#363

table(z$charlson,exclude=NULL)
class(z$charlson)
z$charlson<-as.factor(z$charlson)
levels(z$charlson)[4:7]<-"3+"

##add RT summary info
RT <- read.csv("Z:/09_Aria_Melanoma.csv", stringsAsFactors=FALSE)
str(RT)
```

```
RT$FirstTreatmentDate<-as.Date(RT$FirstTreatmentDate, format = "%d/%m/%Y")
RT$LastTreatmentDate<-as.Date(RT$LastTreatmentDate, format = "%d/%m/%Y")
RT$Course.DIAG<-as.factor(RT$Course.DIAG)
RT$ISD.Tumour.Group<-as.factor(RT$ISD.Tumour.Group)
RT$Primary.Diag<-as.factor(RT$Primary.Diag)
RT$Secondary.Diag<-as.factor(RT$Secondary.Diag)

RT1<-subset(RT, !RT$FirstTreatmentDate>= "2018-01-01")

RTTEST<-RT1[,c("SafeHavenID","CourseId","FirstTreatmentDate","Course.DIAG","Primary.Diag")]
RTTEST<-merge(RTTEST, INDEX, by="SafeHavenID", all=TRUE)
RTTEST$RTFLAG<-ifelse(is.na(RTTEST$CourseId),0,1)
RTTEST$DIFF<-as.numeric(RTTEST$FirstTreatmentDate-RTTEST$apdate)
PRE<-subset(RTTEST,RTTEST$DIFF<0)
POST<-subset(RTTEST,RTTEST$DIFF>0 )
RTID<-intersect(PRE$SafeHavenID,POST$SafeHavenID)

##SUMMARY RT INFO; NB SOME RT MAY NOT RELATE TO MELANOMA
RTTEST$RTINFO<-"NORT"
RTTEST$RTINFO[RTTEST$DIFF<0]<-"RTPRETX"
RTTEST$RTINFO[RTTEST$DIFF>0]<-"RTPOSTTXSTART"
RTTEST$RTINFO[RTTEST$SafeHavenID %in% RTID]<-"RTPREANDPOSTTX"
RTTEST1<-RTTEST[order(RTTEST$SafeHavenID, -RTTEST$CourseId),]
RTTEST2<-RTTEST1[!duplicated(RTTEST1[,c("SafeHavenID")]),]
RTSUM<-RTTEST2[,c("SafeHavenID","CourseId", "RTFLAG","RTINFO")]

RTB<-merge(z, RTSUM, by="SafeHavenID")
RTB$RTINFO<-as.factor(RTB$RTINFO)
RTB$RTFLAG<-as.factor(RTB$RTFLAG)
b<-RTB
```

```
##add BRAF info
BRAF<-read.csv("Z:/01_Extract_BRAF_Melanoma.csv", stringsAsFactors=FALSE)
str(BRAF)
BRAF$Result<-as.factor(BRAF$Result)
BRAF$SafeHavenID<-as.factor(BRAF$SafeHavenID)
BRAF<-BRAF[!BRAF$SafeHavenID %in% exid,]
BRAF$MUTATION<-NA
BRAF$MUTATION[BRAF$Result %in% c("BRAF sequence variant p.(Leu597Ser) detected (see interpretation).","BRAF sequence variant p.(Lys601Glu) detected (see interpretation).","BRAF sequence variant p.(Val600Arg) detected.","BRAF sequence variant p.(Val600Glu) detected (see interpretation).","BRAF sequence variant p.(Val600Glu) detected.","BRAF sequence variant p.(Val600Lys) detected.","BRAF sequence variant p.Val600Glu detected.")]<-"M"
BRAF$MUTATION[BRAF$Result %in% c("No sequence variant detected in codon 600 of the BRAF gene (see interpretation).","No sequence variant detected in codon 600 of the BRAF gene.")]<-"WT"
M<-subset(BRAF, BRAF$MUTATION =="M")
WT<-subset(BRAF, BRAF$MUTATION=="WT")
Mid<-intersect(M$SafeHavenID,WT$SafeHavenID)##id pts WITH BRAF WT AND M
BRAF$MUTATION[BRAF$MUTATION == "WT" & BRAF$SafeHavenID %in%Mid ]<-"M" ##make all M if pts have any BRAF mutation
BRAF<-BRAF[!duplicated(BRAF[,c("SafeHavenID")]),]
BRAF<-BRAF[,c("SafeHavenID","MUTATION")]
test<-merge(b, BRAF, by="SafeHavenID", all=TRUE)
b<-test

##calcuate OS
OS<-Surv(b$TIME/30.4, b$DEATH)
summary(survfit(OS~1, b))
survfit(OS~1, b)
##follow up
summary(b$TIME/30.4)
##reverse KM for follow up
```

```
b$event2<-ifelse(b$DEATH==0,1,0)
FU<-Surv(b$TIME/30.4, b$event2)
summary(survfit(FU~1, b))
survfit(FU~1, b)
survfit(FU~REG,b)

##PREPARE VARIABLES FOR UNIVARIATE ANALYSIS
b$REG<-factor(b$REG, levels = c("IPI","PEM","IN","DT","DAB","VEM")) ##THIS ENABLE COMPARISON TO CURRENT GOLD STANDARD OF TX BUT FINAL MODEL COMPARES TO IPI
##MERGE SECONDARY MELANOMAS (UNKNOWN PRIMARY WITH KNOWN UNKNOWNS)
b$site3<-b$site2
table(b$site3, exclude=NULL)
levels(b$site3)[4]<-"U"
##MERGE YEARS TO AID ANALYSIS
b$year<-as.factor(b$year)
table(b$year)
levels(b$year)[1:2]<-"2010/11"
##MERGE TX LINE
b$txline2<-b$txline
table(b$txline2)
levels(b$txline2)[2:3]<-"2+"
##ENSURE NO. MEDS IS IN CORRECT ORDER
table(b$dgroup,exclude=NULL)
b$switchflag<-as.factor(b$switchflag)
b$MUTATION<-as.factor(b$MUTATION)
##CLEAN FINAL DATAFRAME
b=droplevels(b)

save(b, file = "baseline char.Rda")
```

```
##TABLE BASELINE CHARACTERISTICS
z.t <- data.frame(var="SEX", as.data.frame(table(b$SEX)))
z.t <- rbind(z.t,data.frame(var="PS", as.data.frame(table(b$PS,exclude=NULL))))
z.t <- rbind(z.t,data.frame(var="No. meds pre tx", as.data.frame(table(b$dgroup, exclude=NULL))))
z.t <- rbind(z.t,data.frame(var="BMI", as.data.frame(table(b$BMIGP, exclude=NULL))))
z.t <- rbind(z.t,data.frame(var="Charlson score", as.data.frame(table(b$charlson, exclude=NULL))))
z.t<- rbind(z.t, data.frame(var="Vital status", as.data.frame(table(b$DEATH, exclude=NULL))))
z.t <- rbind(z.t,data.frame(var="DEPCAT", as.data.frame(table(b$simd2012_sc_quintile, exclude =NULL))))
z.t <- rbind(z.t,data.frame(var="Melanoma site", as.data.frame(table(b$site2, exclude=NULL))))
z.t <- rbind(z.t,data.frame(var="Melanoma site2", as.data.frame(table(b$site3, exclude=NULL))))
z.t <- rbind(z.t,data.frame(var="LDH level", as.data.frame(table(b$CUT,exclude=NULL))))
z.t <- rbind(z.t,data.frame(var="NLR Score", as.data.frame(table(b$NLR,exclude=NULL))))
z.t<-rbind(z.t,data.frame(var="breslow", as.data.frame(table(b$breslow, exclude=NULL))))
z.t <- rbind(z.t,data.frame(var="Time from diagnosis", as.data.frame(table(b$tfd,exclude=NULL ))))
z.t<-rbind(z.t,data.frame(var="MEL.TYPE", as.data.frame(table(b$meltype, exclude=NULL))))
z.t <- rbind(z.t,data.frame(var="Line of treatment", as.data.frame(table(b$txline2,exclude=NULL))))
z.t <- rbind(z.t,data.frame(var="Total no. of SACT tx.", as.data.frame(table(b$no.tx, exclude=NULL))))
z.t <- rbind(z.t,data.frame(var="1st Regimen", as.data.frame(table(b$REG))))
z.t <- rbind(z.t,data.frame(var="year 1st tx started", as.data.frame(table(b$year))))
z.t<-rbind(z.t,data.frame(var="tx switch", as.data.frame(table(b$switchflag, exclude=NULL))))
z.t<-rbind(z.t,data.frame(var="RT", as.data.frame(table(b$RTFLAG, exclude=NULL))))
z.t<-rbind(z.t,data.frame(var="RTinfo", as.data.frame(table(b$RTINFO, exclude=NULL))))
z.t<-rbind(z.t,data.frame(var="BRAF", as.data.frame(table(b$MUTATION, exclude=NULL))))
z.t$p <- round(z.t$Freq/nrow(b)*100,1) ##CHANGE FREQ TO % (1DP)
z.t$Fp<-paste(z.t$Freq,"(",z.t$p,")",sep = "")
##add age summary
summary(b$AGEY)

##make NA variables known to include in analysis
table(b$simd2012_sc_quintile, exclude = NULL)
```

```
b$simd2012_sc_quintile<-as.character(b$simd2012_sc_quintile)
b[is.na(b$simd2012_sc_quintile),"simd2012_sc_quintile"] <- "unknown"
b$simd2012_sc_quintile<-as.factor(b$simd2012_sc_quintile)
table(b$CUT, exclude = NULL)
b$CUT<-as.character(b$CUT)
b[is.na(b$CUT),"CUT"]<-"unknown"
b$CUT<-as.factor(b$CUT)
table(b$NLR, exclude = NULL)
b$NLR<-as.character(b$NLR)
b[is.na(b$NLR),"NLR"]<-"unknown"
b$NLR<-as.factor(b$NLR)
table(b$PS, exclude = NULL)
b$PS<-as.character(b$PS)
b[is.na(b$PS),"PS"]<-"unknown"
b$PS<-as.factor(b$PS)
table(b$dgroup, exclude = NULL)
b$dgroup<-as.character(b$dgroup)
b[is.na(b$dgroup),"dgroup"]<-"unknown"
b$dgroup<-as.factor(b$dgroup)
b$dgroup<-factor(b$dgroup, levels = c("less than 5","5 to 9","10 to 14","15 to 19","20 or more"))
table(b$BMIGP, exclude = NULL)
b$BMIGP<-as.character(b$BMIGP)
b[is.na(b$BMIGP),"BMIGP"]<-"unknown"
b$BMIGP<-as.factor(b$BMIGP)
table(b$site3, exclude=NULL)
b$site3<-as.character(b$site3)
b[is.na(b$site3),"site3"]<-"unknown"
b$site3<-as.factor(b$site3)
table(b$tfd,useNA="ifany")
b$tfd<-as.character(b$tfd)
```

```
b[is.na(b$tfd),"tfd"]<-"unknown"
b$tfd<-as.factor(b$tfd)
table(b$breslow, useNA = "ifany")
b$breslow<-as.factor(b$breslow)
levels(b$breslow)[5]<-"unknown"
b$breslow<-as.character(b$breslow)
b[is.na(b$breslow),"breslow"]<-"unknown"
b$breslow<-as.factor(b$breslow)
table(b$MUTATION, useNA = "ifany")
b$MUTATION<-as.character(b$MUTATION)
b[is.na(b$MUTATION),"MUTATION"]<-"unknown"
b$MUTATION<-as.factor(b$MUTATION)
b$MUTATION<-factor(b$MUTATION, levels = c("WT","M","unknown"))
b$REG<-factor(b$REG, levels = c("IPI","PEM","IN","DT","DAB","VEM"))
b.MV<-b
save(b.MV, file = "b.MV.Rda")
table(b.MV$REG)

##UNIVARIATE ANALYSIS
z.var<-c("REG","SEX","PS","dgroup","BMIGP","charlson","simd2012_sc_quintile","site3","CUT","NLR","breslow","tfd","meltype","txline2","no.tx",
"year","switchflag","RTFLAG","MUTATION")

for(i in 1:length(z.var)){
  z.cox<-coxph(OS~get(z.var[i]),b)
  z.cox<-summary(z.cox)
  sf<-summary(survfit(OS~get(z.var[i]),b))
  z.r<-cbind.data.frame(var=z.var[i],level=levels(b[,z.var[i]]),                                                                    number=sf$n,
death=sf$table[,"events"],medianSurv=sf$table[,"median"],medianSurvLow=sf$table[,"0.95LCL"],medianSurvUpper=sf$table[,"0.95UCL"],
HR=c(1,round(z.cox$conf.int[,"exp(coef)"],2)),
```

```
                HRlower=c("",round(z.cox$conf.int[,"lower .95"],2)), HRupper=c("",round(z.cox$conf.int[,"upper .95"],2)),
p=c("",round(z.cox$coefficients[,"Pr(>|z|)"],4)), poverall=round(as.numeric(z.cox$logtest[3]),4))
 if(i==1)
   z.rr<-z.r else
    z.rr<-rbind.data.frame(z.rr,z.r)}

##generate survival curves
plot(survfit(OS~1, data=b),mark.time=TRUE, xscale=1, main= "Overall Survival (from initial treatment)", xlab="months", ylab = "proportion survived")
abline(h=0.5, col="red", lty=2)
abline(h=0.2, col="blue",lty=2)
##OS curve without title
plot(survfit(OS~1, data=b),mark.time=TRUE, xscale=1, xlab="months", ylab = "proportion survived")
abline(h=0.5, col="red", lty=2)
abline(h=0.2, col="blue",lty=2)

##KM curves for regimen
plot(survfit(OS~REG,data=b),mark.time = TRUE,xscale = 1, main ="OS (by initial treatment)",xlab="months",ylab="proportion survived",col=1:7)
legend("topright",levels(b$REG),lty=1,col = 1:6,cex=0.8)
abline(h=0.5, col="red", lty=2)
abline(h=0.2, col="blue",lty=2)
plot(survfit(OS~REG,data=b),mark.time = TRUE,xscale = 1, main ="OS (by initial treatment)",xlab="months",ylab="proportion survived",col=1:7)
legend("topright",c("Ipilimumab/nivolumab","Pembrolizumab","Ipilimumab","Dabrafenib/trametinib","Vemurafenib","Dabrafenib"),lty=1,col =
1:6,cex=0.8)
abline(h=0.5, col="red", lty=2)
##km without title
plot(survfit(OS~REG,data=b),mark.time = TRUE,xscale = 1,xlab="months",ylab="proportion survived",col=1:6)
legend("topright",levels(b$REG),lty=1,col = 1:6,cex=0.8)
abline(h=0.5, col="red", lty=2)
abline(h=0.2, col="blue",lty=2)
```

```
##KM curves with no. at risk
fit<-survfit(OS~1, b)
ggsurvplot(fit, data = b, title= "OS (full cohort)", size=0.8, palette = "black", conf.int = FALSE, pval=FALSE,legend="none",
        xlab="Time in months", risk.table=TRUE, risk.table.height=0.25, ggtheme=theme_bw())
ggsurvplot(fit, data = b, size=0.8, palette = "black", conf.int = FALSE, pval=FALSE,legend="none",
        xlab="Time in months", risk.table=TRUE, risk.table.height=0.25, ggtheme=theme_bw())
fit2<-survfit(OS~REG,b)
fit2<-survfit(OS~REG,data = b)
ggsurvplot(fit2, data=b, title="OS by REG",size=1, palette = "colour",conf.int = FALSE, pval=FALSE,xlab="Time (months)",
        risk.table = TRUE, risk.table.col = "strata",legend.labs = levels(b["REG"]),risk.table.height=0.25, ggtheme = theme_bw())
ggsurvplot(fit2, data=b, size=1, palette = "colour",conf.int = FALSE, pval=FALSE,xlab="Time (months)",
        risk.table = TRUE, risk.table.col = "strata",legend.labs = levels(b["REG"]),risk.table.height=0.25, ggtheme = theme_bw())
ggsurvplot(fit2, data=b, size=1, palette = "colour",conf.int = FALSE, pval=FALSE,xlab="Time (months)",
        risk.table = TRUE, risk.table.col = "strata",legend.labs = levels(b["REG"]),risk.table.height=0.4, ggtheme = theme_bw())
##compare baseline char between REG types

chisq.test(table(b$SEX,b$REG))
fisher.test(table(b$PS,b$REG, useNA = "ifany"),simulate.p.value=TRUE)##SIGNIF
fisher.test(table(b$dgroup, b$REG),simulate.p.value=TRUE)##SIGNIF
fisher.test(table(b$BMIGP,b$REG, useNA = "ifany"),simulate.p.value=TRUE)##signif
fisher.test(table(b$charlson,b$REG, useNA = "ifany"),simulate.p.value = TRUE)
fisher.test(table(b$simd2012_sc_quintile,b$REG, useNA = "ifany"),simulate.p.value = TRUE)
fisher.test(table(b$site3,b$REG, useNA = "ifany"),simulate.p.value = TRUE)##signif
fisher.test(table(b$CUT,b$REG, useNA = "ifany"),simulate.p.value = TRUE)##signif
fisher.test(table(b$NLR,b$REG, useNA = "ifany"),simulate.p.value = TRUE)##signif
fisher.test(table(b$breslow,b$REG, useNA = "ifany"),simulate.p.value = TRUE)##signif
fisher.test(table(b$tfd,b$REG, useNA = "ifany"), simulate.p.value=TRUE) ##SIGNIF
fisher.test(table(b$meltype,b$REG, useNA = "ifany"), simulate.p.value=TRUE)
fisher.test(table(b$txline2,b$REG, useNA = "ifany"), simulate.p.value=TRUE) ##signif
fisher.test(table(b$no.tx,b$REG, useNA = "ifany"), simulate.p.value=TRUE)##signif
```

```
fisher.test(table(b$year,b$REG, useNA = "ifany"), simulate.p.value=TRUE)##signif
fisher.test(table(b$switchflag,b$REG, useNA = "ifany"), simulate.p.value=TRUE)##signif
fisher.test(table(b$RTFLAG,b$REG, useNA = "ifany"), simulate.p.value=TRUE)##signif
fisher.test(table(b$DEATH,b$REG, useNA = "ifany"), simulate.p.value=TRUE)##signif
fisher.test(table(b$MUTATION,b$REG, useNA = "ifany"), simulate.p.value = TRUE) ##signif

##subset regimens to determine age and follow up for each REG
ipi<-subset(b, b$REG=="IPI")
P<-subset(b, b$REG=="PEM")
IN<-subset(b, b$REG=="IN")
V<-subset(b, b$REG=="VEM")
D<-subset(b, b$REG=="DAB")
DT<-subset(b, b$REG=="DT")
summary(ipi$TIME/30.4)
summary(P$TIME/30.4)
summary(IN$TIME/30.4)
summary(V$TIME/30.4)
summary(D$TIME/30.4)
summary(DT$TIME/30.4)
summary(ipi$AGEY)
summary(P$AGEY)
summary(IN$AGEY)
summary(V$AGEY)
summary(D$AGEY)
summary(DT$AGEY)

##final MV model
survdiff(OS~REG+SEX+AGEY+site3+CUT+NLR+PS+switchflag+ordered(dgroup), b.MV)
summary(survdiff(OS~REG+SEX+AGEY+site3+CUT+NLR+PS+switchflag+ordered(dgroup), b.MV))
v.cox<-coxph(OS~REG+SEX+AGEY+site3+CUT+NLR+PS+switchflag+ordered(dgroup), b.MV)
```

```
summary(v.cox)
drop1(v.cox,test="Chisq")
##run unordered to get HR
v.cox<-coxph(OS~REG+SEX+AGEY+site3+CUT+NLR+PS+switchflag+dgroup, b.MV)
summary(v.cox)

##final MV model - no dgroup to match non safe haven data
v.cox<-coxph(OS~REG+SEX+AGEY+site3+CUT+NLR+PS+switchflag, b.MV)
summary(v.cox)
drop1(v.cox,test="Chisq")
```

Treatment summary R code

```
load("C:/Users/jclarke-cmopcgm/Documents/MMDEX18.Rda")
load("S:/Julie/all.tx.summary.Rda") ##called switch
##summarise tx info for patients - USE MMDEX18 FROM BASELINE CHAR
MMDEX18<-switch
table(MMDEX18$DURATION)
MMDEX18$DURATION[MMDEX18$DURATION %in% c("1 month", "1 MONTH","1/12" , "28 days", "28 dAYS", "28 Days", "28 DAYS", "28dys", "28d", "28D", "28days", "28DAYs", "30 days", "4 weeks", "4 WEEKS" ,"4 wks", "4w", "4WEEKS", "4WKS", "cont (28D)", "cont 28 da", "cont(28D)", "cont28day", "28 dys", "28DAYS", "29 days", "4W")]<-"28"
MMDEX18$DURATION[MMDEX18$DURATION %in% c("1 week", "1 WEEK", "1 weeks", "7 days", "7 Days", "7 DAYS", "7D", "7days",  "cont (7D)", "cont(07D)", "5-7 Days")]<-"7"
MMDEX18$DURATION[MMDEX18$DURATION %in% c("14", "14 D", "14 days", "14 DAYS", "14D", "14DAYs", "2 weeks", "2 WEEKS" ,"cont (14D)", "cont(14D)", "14DAYS", "DAYS 1-14", "2/52")]<-"14"
MMDEX18$DURATION[MMDEX18$DURATION %in% c("21", "21 days", "21 Days", "21 DAYS", "21DYS", "21D", "21DAYs", "3WEEKS" ,"3w", "3WKS", "3 weeks", "3 WEEKS", "3 WK", "3 WKS", "3W", "cont (21D)", "cont (21D)", "21 DYS", "21DAYS", "Cont (21D)", "cont(21D)", "cont(23D)")]<-"21"
```

```
MMDEX18$DURATION[MMDEX18$DURATION%in% c("1 Bottle", "1 BOTTLE", "1 BOX", "1 pack", "1 Pack", "1 PACK", "1 TUBE", "1OP" ,"MDU", "STAT", "TO LEGS" )]<-"MDU"
MMDEX18$DURATION[MMDEX18$DURATION %in% c("2 days", "2 DAYS", "3-5 Days", "3-5 DAYS", "3 days", "3 Days", "3 DAYs", "3 DAYS","3D","3d" ,"5", "5 D", "5 days", "5 Days", "5 DAYS", "5DAY", "5DAYS", "Days 1-5", "Days 1 - 5", "5d")]<-"5d"
MMDEX18$DURATION[MMDEX18$DURATION%in% c("33 Days", "35 DAYS", "35d", "35DAYS", "5 weeks","5 WEEKS","cont (35D)", "cont (5WK)", "cont(35D)")]<-"35"
MMDEX18$DURATION[MMDEX18$DURATION%in% c("prn 28 d", "PRN 35days", "PRN 5 WEEK", "prn itch", "PRN ITCH", "5 days+PRN")]<-"PRN"
MMDEX18$DURATION[MMDEX18$DURATION %in% c("10 days", "10 DAYS", "8 days", "8 Days", "cont (9D)")]<-"10d"
MMDEX18$DURATION[MMDEX18$DURATION %in% c("4 doses", "6 doses", "TDS", "See note", "IND")]<-"OTHER"
MMDEX18$DURATION[MMDEX18$DURATION %in% c("6 weeks")]<-"42"
MMDEX18$DURATION[MMDEX18$DURATION%in% c("7 WEEKS")]<-"49"
MMDEX18$DURATION[MMDEX18$DURATION %in% c("Cont (12W)")]<-"84"
MMDEX18$DURATION[MMDEX18$DURATION%in% c("10d", "5d", "MDU", "OTHER", "PRN","", "CONT", "CONTINUE")]<-"0"

MMDEX18$DURATION[MMDEX18$DURATION == "0" & MMDEX18$REG %in% c("DAB","DT","VEM")]<-"28" ##ASSUME THAT DT/VEM IS 28 DAYS UNLESS OTHER INFO IS AVAILABLE
table(MMDEX18$DURATION, MMDEX18$REG, exclude=NULL)
MMDEX18$DURATION<-as.numeric(MMDEX18$DURATION)

##summarise data to 1 line per cycle per patient per treatment
MMex10 <- MMex1[order(MMex1$SafeHavenID, MMex1$apdate),]
MMex10 <- MMex10[! duplicated(MMex10[ ,c("SafeHavenID", "REG","apdate")]), ]

ccount<-aggregate (CYCLE ~SafeHavenID + REG, data=MMex10, FUN=length)
ccount <- rename(ccount,c("CYCLE" = "cyclecount")) ##this includes tx started in 2018 as well as cycles given in 2018

MMDEX18T<-merge(MMDEX18, ccount, c("SafeHavenID", "REG")) ##ENSURE ALL TX INCLUDED NOT JUST THOSE OF INTEREST
MMDEX18T$esttxend<- as.Date(MMDEX18T$txend+MMDEX18T$DURATION)
##replace estimated tx end date if IV tx
MMDEX18T$esttxend[MMDEX18T$REG %in% c("IPI","PEM","IN","NIVO")]<-NA
```

```
MMDEX18T$esttxend[is.na(MMDEX18T$esttxend)]<-(MMDEX18T$txend)[is.na(MMDEX18T$esttxend)]
##ADD DOD TO THIS TO ENABLE EST TX END TO BE ADJUSTED IF PTS RIP
DOD<-DEMOG2[,c("SafeHavenID", "end", "DEATH")]
MMDEX18T<-merge(MMDEX18T, DOD, by = "SafeHavenID", all=TRUE)
##replace est tx end date if DOD before est tx end
MMDEX18T$esttxend[MMDEX18T$esttxend>MMDEX18T$end]<-MMDEX18T$end[MMDEX18T$esttxend>MMDEX18$end]

MMDEX18T<-MMDEX18T[order(MMDEX18T$SafeHavenID, MMDEX18T$txstart),]# put tx in start date orded to enable time to next treatment to be
calc

MMDEX18T$LASTEND<-c(NA, as.character(MMDEX18T$esttxend[1:nrow(MMDEX18T)-1])) ##CHECK IF TX OVERLAP
MMDEX18T[MMDEX18T$txline==1, "LASTEND"]<-NA
MMDEX18T$LASTEND<-as.Date(MMDEX18T$LASTEND, format = "%Y-%m-%d")
MMDEX18T$TTNT<-as.numeric(MMDEX18T$txstart-MMDEX18T$LASTEND)##this is time from end of 1st treatment
table(MMDEX18T$TTNT<0)
id=subset(MMDEX18T, TTNT<0)$SafeHavenID
subset(MMDEX18T, SafeHavenID%in%id)
MMDEX18T$TTNT2 <- MMDEX18T$TTNT
MMDEX18T[which((MMDEX18T$REG %in% c("DAB","DT","VEM")==FALSE) & (as.numeric(MMDEX18T$no.tx)>1))+1,"TTNT2"] <- 0
MMDEX18T[which(MMDEX18T$TTNT2< -28),"TTNT2"]<- 0
MMDEX18T$adjtxend <- MMDEX18T$esttxend
MMDEX18T[which(MMDEX18T$TTNT2<0)-1,"adjtxend"] <- MMDEX18T[which(MMDEX18T$TTNT2<0),"txstart"]
##ADD CENSOR DATE FOR DURATIONS BEYOND 31/3/2018
MMDEX18T$adjtxend[MMDEX18T$adjtxend>"2018-03-31"]<-"2018-03-31"

##NEED TO LINK TIME TO NEXT TREATMENT WITH FIRST TX, NOT 2ND TX
MMDEX18T$NEXTSTART<-c(as.character(MMDEX18T$txstart[1:nrow(MMDEX18T)+1])) ##CHECK IF TX OVERLAP
MMDEX18T[MMDEX18T$no.tx==1, "NEXTSTART"]<-NA
MMDEX18T[MMDEX18T$no.tx==MMDEX18T$txline, "NEXTSTART"]<-NA
MMDEX18T$NEXTSTART<-as.Date(MMDEX18T$NEXTSTART, format = "%Y-%m-%d")
```

```
MMDEX18T$TTNTFROM1<-as.numeric(MMDEX18T$NEXTSTART-MMDEX18T$adjtxend)

id2 <- MMDEX18T[which(MMDEX18T$TTNT2<0), "SafeHavenID"]
id <- id[id%in%id2==FALSE]
MMDEX18T$complexpt <- ifelse(MMDEX18T$SafeHavenID%in%id , 1, 0)
##ADD A CONDITION TO MAKE NON COMPLAEX IF PT IS COMPLEX DUE TO TRIAL/CHEMO/ANOTHER REASON

MMDEX18T$TXFLAG<-ifelse((MMDEX18T$adjtxend>="2018-03-03" & MMDEX18T$DEATH=="0"), 0, 1)
MMDEX18T$TDUR<-as.numeric(MMDEX18T$adjtxend-MMDEX18T$txstart)
##redo ttnt from start of first treatment to start of next treatment
MMDEX18T$TTNT1TO2<-as.numeric(MMDEX18T$NEXTSTART-MMDEX18T$txstart)

TXSUM<-MMDEX18T[, c("SafeHavenID","REG","txstart","adjtxend","TDUR","TXFLAG","TTNTFROM1","txline","no.tx","cyclecount","PS", "TTNT1TO2")]
TXSUM1<-subset(TXSUM, TXSUM$REG %in% c("IPI","VEM","DT","DAB","IN","PEM"))
table(TXSUM1$REG,TXSUM1$cyclecount==1)
table(TXSUM1$REG, TXSUM1$no.tx ==1)
table(TXSUM1$TXFLAG, TXSUM1$txline)
dim(TXSUM1)
on.tx<-TXSUM[which(TXSUM$TXFLAG==0),"SafeHavenID"]
table(TXSUM$REG,TXSUM$TXFLAG)
TXSUMD<-merge(TXSUM1,DOD, by="SafeHavenID")

b$on.tx.flag<-NA
b$on.tx.flag[b$SafeHavenID %in% on.tx]<-"on.tx"
b$on.tx.flag[!b$SafeHavenID %in% on.tx]<-"off.tx"
table(b$on.tx.flag, b$DEATH)
##nb some of these patients may be on chemo/trials
alive.off.tx<-b[which(b$on.tx.flag=="off.tx" & b$DEATH==0),"SafeHavenID"]
alive<-subset(TXSUM, TXSUM$SafeHavenID %in% alive.off.tx)
table(alive$REG,alive$no.tx)
```

```
##SUMMARISE TREATMENT DURATION
DUR<-Surv(TXSUM1$TDUR/30.4, TXSUM1$TXFLAG)
summary(survfit(DUR~REG, TXSUM1))
survfit(DUR~REG, TXSUM1)

##summaryTTNT from start of first tx to start of 2nd tx
summary(TXSUM1$TTNT1TO2[TXSUM1$REG =="VEM"], na.rm = TRUE)
summary(TXSUM1$TTNT1TO2[TXSUM1$REG =="IPI"], na.rm = TRUE)
summary(TXSUM1$TTNT1TO2[TXSUM1$REG =="DAB"], na.rm = TRUE)
summary(TXSUM1$TTNT1TO2[TXSUM1$REG =="DT"], na.rm = TRUE)
summary(TXSUM1$TTNT1TO2[TXSUM1$REG =="PEM"], na.rm = TRUE)
summary(TXSUM1$TTNT1TO2[TXSUM1$REG =="IN"], na.rm = TRUE)

##median time to next treatment
z.ttnt1to2 <- aggregate(TXSUM1$TTNT1TO2, list(TXSUM1$REG), summary)
str(z.ttnt1to2)
z.tttnt1to2 <- data.frame(reg=z.ttnt1to2$Group.1, median=z.ttnt1to2$x[,3], q1=round(z.ttnt1to2$x[,2],1), q3=round(z.ttnt1to2$x[,5],1),
min=round(z.ttnt1to2$x[,1],1), max=round(z.ttnt1to2$x[,6],1), not.app=round(z.ttnt1to2$x[,7],1))
##KM estimate of time to next treatment
TXSUM1$TTNTFLAG<-ifelse(is.na(TXSUM1$TTNTFROM1),0,1)
ttnt<-Surv(TXSUM1$TTNT1TO2, TXSUM1$TTNTFLAG)
summary(survfit(ttnt~REG, TXSUM1))
survfit(ttnt~REG, TXSUM1)

##median no of cycles per tx
z.t <- aggregate(MMDEX18T$cyclecount, list(MMDEX18T$REG), summary)
str(z.t)
z.tt <- data.frame(reg=z.t$Group.1, median=z.t$x[,3], q1=round(z.t$x[,2],1), q3=round(z.t$x[,5],1))
z.ttt <- data.frame(reg=z.t$Group.1, median=z.t$x[,3], q1=round(z.t$x[,2],1), q3=round(z.t$x[,5],1), low=round(z.t$x[,1],1), high=round(z.t$x[,6],1))
z.tt$medianiqr <- paste(z.tt$median,"(",z.tt$q1,"-",z.tt$q3,")",sep="")
```

```
str(TXSUM)
TXSUM$complexpt<-as.factor(TXSUM$complexpt)
TXSUM$TXFLAG<-as.factor(TXSUM$TXFLAG)
TXSUM$CYCLECOUNTF<-as.factor(TXSUM$cyclecount)
TXSUM$txline<-as.factor(TXSUM$txline)
TXSUM$no.tx<-as.factor(TXSUM$no.tx)

TXIPI<-subset(TXSUM1, TXSUM1$REG =="IPI")
summary(TXIPI)
sum(TXIPI$cyclecount)##418

TXVEM<-subset(TXSUM1, TXSUM1$REG =="VEM")
summary(TXVEM)
sum(TXVEM$cyclecount)##517

TXDAB<-subset(TXSUM1, TXSUM1$REG =="DAB")
summary(TXDAB)
sum(TXDAB$cyclecount)##247

TXDT<-subset(TXSUM1, TXSUM1$REG =="DT")
summary(TXDT)
sum(TXDT$cyclecount)##722
table(TXDT$CYCLECOUNTF)

TXIN<-subset(TXSUM1, TXSUM1$REG =="IN")
summary(TXIN) ##352
sum(TXIN$cyclecount)

TXPEM<-subset(TXSUM1, TXSUM1$REG =="PEM")
```

```
summary(TXPEM)
sum(TXPEM$cyclecount)##1129


##work out index dates for toxicity work
TXIM<-subset(TXSUM, REG %in% c("IPI", "PEM", "IN", "NIVO"))
TXT<-subset(TXSUM, REG %in% c("DT", "DAB", "VEM"))
TXIM1<-TXIM[order(TXIM$SafeHavenID, TXIM$txstart),]
TXIM1<-TXIM1[!duplicated(TXIM1[,c("SafeHavenID")]),]
TXIMINDEX<-TXIM1[,c("SafeHavenID", "txstart", "REG")]
save(TXIMINDEX, file = "TXIMINDEX.Rda")

table(TXIMINDEX$REG)
TXT1<-TXT[order(TXT$SafeHavenID, TXT$txstart),]
TXTINDEX<-TXT1[,c("SafeHavenID","txstart", "adjtxend", "REG")]
save(TXTINDEX, file = "TXTINDEX.Rda")

immuno<-unique(TXIMINDEX$SafeHavenID)
BRAF<-unique(TXTINDEX$SafeHavenID)
both<-intersect(immuno, BRAF) #id pts getting both IMMUNO AND TARGETED TX


##look for treatment delays in immunotherapy
table(MM$DRUGNAME)
z1 <- subset(MM, DRUGNAME %in% c( "IPILIMUMAB", "IPILIMUMAB (BLINDED)"))
table(z1$REGIME)
z1<-subset(z1, REGIME %in% c("IPILIMUMAB","SK33 IPILIMUMAB", "SK39 IPILIMUMAB"))
z1 <- z1[,c("SafeHavenID","apdate", "CYCLE")] ##need to exclude treatments started in 2018 (1 pt)
str(z1)
z1 <- z1[order(z1$SafeHavenID, z1$apdate),]
```

```
z1$lasttrt <- c(NA, as.character(z1$apdate[1:(nrow(z1)-1)]))
z1$lasttrt <- as.Date(z1$lasttrt)
z1$seq <- sequence(rle(as.character(z1$SafeHavenID))$lengths)
z1[z1$seq==1, "lasttrt"] <- NA
z1$diff <- as.numeric(z1$apdate-z1$lasttrt)
z1$trtdelay <- ifelse(z1$diff>=25,1,0)
z1[is.na(z1$trtdelay),"trtdelay"] <- 0
z.agg <- aggregate(z1$trtdelay,list(z1$SafeHavenID),sum)
names(z.agg) <- c("SafeHavenID","n_trtdelay")
z.agg$regime2 <- "IPI"
z.agg$trtdelay <- ifelse(z.agg$n_trtdelay>0,1,0)


zz <- subset(z1, trtdelay==1)
z.agg2 <- aggregate(zz$seq,list(zz$SafeHavenID),min)
names(z.agg2) <- c("SafeHavenID","cycle_1st_trtdelay")
z.agg <- merge(z.agg,z.agg2,all.x=TRUE)
dim(z.agg)
zz1 <- z.agg
summary(zz1)
length(unique(zz1$SafeHavenID))


z1 <- subset(MM, DRUGNAME %in% c( "PEMBROLIZUMAB", "MK-3475"))
table(z1$REGIME)
z1 <- z1[,c("SafeHavenID","apdate", "CYCLE", "REGIME")] ##q2w trial
str(z1)
z1 <- z1[order(z1$SafeHavenID, z1$apdate),]
z1$lasttrt <- c(NA, as.character(z1$apdate[1:(nrow(z1)-1)]))
z1$lasttrt <- as.Date(z1$lasttrt)
```

```
z1$seq <- sequence(rle(as.character(z1$SafeHavenID))$lengths)
z1[z1$seq==1, "lasttrt"] <- NA
z1$diff <- as.numeric(z1$apdate-z1$lasttrt)
z1$trtdelay <- ifelse(z1$diff>=25,1,0)
z1[is.na(z1$trtdelay),"trtdelay"] <- 0
z.agg <- aggregate(z1$trtdelay,list(z1$SafeHavenID),sum)
names(z.agg) <- c("SafeHavenID","n_trtdelay")
z.agg$regime2 <- "PEM"
z.agg$trtdelay <- ifelse(z.agg$n_trtdelay>0,1,0)


zz <- subset(z1, trtdelay==1)
z.agg2 <- aggregate(zz$seq,list(zz$SafeHavenID),min)
names(z.agg2) <- c("SafeHavenID","cycle_1st_trtdelay")
z.agg <- merge(z.agg,z.agg2,all.x=TRUE)
dim(z.agg)
zz1 <- z.agg
summary(zz1)


##treatment delays with ipi-nivo
 ##rename IN reg
MM$REG[MM$REGIME %in% c("NIVO + IPILUM","NIVOLUMAB 3MG/KG","NIVOLUMAB SKIN","NIVOLUMAB+IPILIM","SK51 NIVO/IPILIM","SK51
NIVOLUMAB") & MM$SafeHavenID %in% INid]<-"IN"
z1 <- subset(MM, REG %in% c( "IN"))
table(z1$DRUGNAME)
z2<-subset(z1, DRUGNAME %in% c("IPILIMUMAB","NIVOLUMAB"))
z2 <- z2[,c("SafeHavenID","apdate", "CYCLE", "REGIME","DRUGNAME")]
str(z2)
summary(z2)
```

```
z2 <- z2[order(z2$SafeHavenID, z2$apdate),]
z3<-z2[!duplicated(z2[,c("REGIME","SafeHavenID", "CYCLE")]),]
z3$lasttrt <- c(NA, as.character(z3$apdate[1:(nrow(z3)-1)]))
z3$lasttrt <- as.Date(z3$lasttrt)
z3$seq <- sequence(rle(as.character(z3$SafeHavenID))$lengths)
z3[z3$seq==1, "lasttrt"] <- NA
z3$diff <- as.numeric(z3$apdate-z3$lasttrt)
z3$trtdelay[z3$REGIME %in% c("NIVO + IPILUM","NIVOLUMAB+IPILIM","SK51 NIVO/IPILIM")]<-ifelse(z3$diff>=25,1,0)[z3$REGIME %in% c("NIVO + IPILUM","NIVOLUMAB+IPILIM","SK51 NIVO/IPILIM")]
z3$trtdelay[z3$REGIME %in% c("NIVOLUMAB 3MG/KG","NIVOLUMAB SKIN", "SK51 NIVOLUMAB")]<-ifelse(z3$diff>=18,1,0)[z3$REGIME %in% c("NIVOLUMAB 3MG/KG","NIVOLUMAB SKIN", "SK51 NIVOLUMAB")]
z3[is.na(z3$trtdelay),"trtdelay"] <- 0

z.agg <- aggregate(z3$trtdelay,list(z3$SafeHavenID),sum)
names(z.agg) <- c("SafeHavenID","n_trtdelay")
z.agg$regime2 <- "IN"
z.agg$trtdelay <- ifelse(z.agg$n_trtdelay>0,1,0)




##hospital admissions by tx
TXINFO<-TXSUM1[, c("SafeHavenID","REG","txstart","adjtxend", "txline","no.tx","complexpt")]
smr011$ADMISSION_DATE<-as.Date(as.character(smr011$ADMISSION_DATE), format = "%Y%m%d")
SMR1<-
smr011[,c("SafeHavenID","ADMISSION_DATE","DISCHARGE_DATE","LOCATION","SPECIALTY","SIGNIFICANT_FACILITY","MANAGEMENT_OF_PATIENT"
,"ADMISSION_TYPE","MAIN_CONDITION","OTHER_CONDITION_1", "Main_op_A","CIS_MARKER")]
length(unique(SMR1$SafeHavenID))
```

```
SMR1<-SMR1[!SMR1$SafeHavenID%in% nid,]
SMR1em<-subset(SMR1, !SMR1$ADMISSION_TYPE %in% c("10","11","18","19"))

I<-TXINFO[TXINFO$REG=="IPI",]
I<-I[!I$txstart>"2018-01-01",]
SMR1i<-merge(SMR1em, I, by="SafeHavenID")
length(unique(SMR1i$SafeHavenID))
SMR1i$ADMTIME<-NA
SMR1i$ADMTIME[SMR1i$ADMISSION_DATE<SMR1i$txstart]<-"PRETX"
SMR1i$ADMTIME[SMR1i$ADMISSION_DATE>SMR1i$txstart & SMR1i$ADMISSION_DATE<SMR1i$adjtxend]<-"ONTX"
SMR1i$ADMTIME[SMR1i$ADMISSION_DATE>SMR1i$adjtxend]<-"POSTTX"
table(SMR1i$ADMTIME)
SMR1i.post<-subset(SMR1i, SMR1i$ADMTIME %in% c("ONTX","POSTTX"))
length(unique(SMR1i.post$SafeHavenID))
table(SMR1i.post$MAIN_CONDITION)
SMR1i.post<-SMR1i.post[order(SMR1i.post$SafeHavenID, SMR1i.post$ADMISSION_DATE),]
SMR1i.post$counter<-sequence(rle(as.character(SMR1i.post$SafeHavenID))$lengths)
SMR1i.post$counter<-as.factor(SMR1i.post$counter)
##number of emergency admission
number1<-ddply(SMR1i.post, .(SafeHavenID), function(x){length(unique(x$ADMISSION_DATE))})
number1$no.ADM<-as.factor(number1$V1)
no.ADM<-number1[,c("SafeHavenID", "no.ADM")]
summary(no.ADM)
table(no.ADM$no.ADM)
SMR1i.post<-merge(SMR1i.post,no.ADM, by="SafeHavenID")

SMR1i.post$time<-as.numeric(SMR1i.post$ADMISSION_DATE-SMR1i.post$txstart)
summary(SMR1i.post$time/30.4)

SMR1i.post1<-SMR1i.post[SMR1i.post$counter=="1",]
```

```
summary(SMR1i.post1$time/30.4)


IPIN<-TXINFO[TXINFO$REG=="IN",]
IPIN<-IPIN[!IPIN$txstart>"2018-01-01",]
SMR1IN<-merge(SMR1em, IPIN, by="SafeHavenID")
length(unique(SMR1IN$SafeHavenID))
SMR1IN$ADMTIME<-NA
SMR1IN$ADMTIME[SMR1IN$ADMISSION_DATE<SMR1IN$txstart]<-"PRETX"
SMR1IN$ADMTIME[SMR1IN$ADMISSION_DATE>SMR1IN$txstart & SMR1IN$ADMISSION_DATE<SMR1IN$adjtxend]<-"ONTX"
SMR1IN$ADMTIME[SMR1IN$ADMISSION_DATE>SMR1IN$adjtxend]<-"POSTTX"
table(SMR1IN$ADMTIME)
SMR1IN.post<-subset(SMR1IN, SMR1IN$ADMTIME %in% c("ONTX","POSTTX"))
length(unique(SMR1IN.post$SafeHavenID))
table(SMR1IN.post$MAIN_CONDITION)
SMR1IN.post<-SMR1IN.post[order(SMR1IN.post$SafeHavenID, SMR1IN.post$ADMISSION_DATE),]
SMR1IN.post$counter<-sequence(rle(as.character(SMR1IN.post$SafeHavenID))$lengths)

##number of emergency admission
number1<-ddply(SMR1IN.post, .(SafeHavenID), function(x){length(unique(x$ADMISSION_DATE))})
number1$no.ADM<-as.factor(number1$V1)
no.ADM<-number1[,c("SafeHavenID", "no.ADM")]
summary(no.ADM)
table(no.ADM$no.ADM)
SMR1IN.post<-merge(SMR1IN.post,no.ADM, by="SafeHavenID")

SMR1IN.post$time<-as.numeric(SMR1IN.post$ADMISSION_DATE-SMR1IN.post$txstart)
summary(SMR1IN.post$time/30.4)

SMR1IN.post1<-SMR1IN.post[SMR1IN.post$counter=="1",]
```

```
summary(SMR1IN.post1$time/30.4)


P<-TXINFO[TXINFO$REG=="PEM",]
P<-P[!P$txstart>"2018-01-01",]
SMR1P<-merge(SMR1em, P, by="SafeHavenID")
length(unique(SMR1P$SafeHavenID))
SMR1P$ADMTIME<-NA
SMR1P$ADMTIME[SMR1P$ADMISSION_DATE<SMR1P$txstart]<-"PRETX"
SMR1P$ADMTIME[SMR1P$ADMISSION_DATE>SMR1P$txstart & SMR1P$ADMISSION_DATE<SMR1P$adjtxend]<-"ONTX"
SMR1P$ADMTIME[SMR1P$ADMISSION_DATE>SMR1P$adjtxend]<-"POSTTX"
table(SMR1P$ADMTIME)
SMR1P.post<-subset(SMR1P, SMR1P$ADMTIME %in% c("ONTX","POSTTX"))
length(unique(SMR1P.post$SafeHavenID))
table(SMR1P.post$MAIN_CONDITION)
SMR1P.post<-SMR1P.post[order(SMR1P.post$SafeHavenID, SMR1P.post$ADMISSION_DATE),]
SMR1P.post$counter<-sequence(rle(as.character(SMR1P.post$SafeHavenID))$lengths)

##number of emergency admission
number1<-ddply(SMR1P.post, .(SafeHavenID), function(x){length(unique(x$ADMISSION_DATE))})
number1$no.ADM<-as.factor(number1$V1)
no.ADM<-number1[,c("SafeHavenID", "no.ADM")]
summary(no.ADM)
table(no.ADM$no.ADM)
SMR1P.post<-merge(SMR1P.post,no.ADM, by="SafeHavenID")

SMR1P.post$time<-as.numeric(SMR1P.post$ADMISSION_DATE-SMR1P.post$txstart)
summary(SMR1P.post$time/30.4)

SMR1P.post1<-SMR1P.post[SMR1P.post$counter=="1",]
```

```
summary(SMR1P.post1$time/30.4)


D<-TXINFO[TXINFO$REG=="DAB",]
D<-D[!D$txstart>"2018-01-01",]
SMR1D<-merge(SMR1em, D, by="SafeHavenID")
length(unique(SMR1D$SafeHavenID))
SMR1D$ADMTIME<-NA
SMR1D$ADMTIME[SMR1D$ADMISSION_DATE<SMR1D$txstart]<-"PRETX"
SMR1D$ADMTIME[SMR1D$ADMISSION_DATE>SMR1D$txstart & SMR1D$ADMISSION_DATE<SMR1D$adjtxend]<-"ONTX"
SMR1D$ADMTIME[SMR1D$ADMISSION_DATE>SMR1D$adjtxend]<-"POSTTX"
table(SMR1D$ADMTIME)
SMR1D.post<-subset(SMR1D, SMR1D$ADMTIME %in% c("ONTX","POSTTX"))
length(unique(SMR1D.post$SafeHavenID))
SMR1D.ON<-subset(SMR1D, SMR1D$ADMTIME %in% c("ONTX"))
length(unique(SMR1D.ON$SafeHavenID))
table(SMR1D.post$MAIN_CONDITION)
table(SMR1D.ON$MAIN_CONDITION)
SMR1D.post<-SMR1D.post[order(SMR1D.post$SafeHavenID, SMR1D.post$ADMISSION_DATE),]
SMR1D.post$counter<-sequence(rle(as.character(SMR1D.post$SafeHavenID))$lengths)

##number of emergency admission
number1<-ddply(SMR1D.post, .(SafeHavenID), function(x){length(unique(x$ADMISSION_DATE))})
number1$no.ADM<-as.factor(number1$V1)
no.ADM<-number1[,c("SafeHavenID", "no.ADM")]
summary(no.ADM)
table(no.ADM$no.ADM)
SMR1D.post<-merge(SMR1D.post,no.ADM, by="SafeHavenID")

SMR1D.post$time<-as.numeric(SMR1D.post$ADMISSION_DATE-SMR1D.post$txstart)
```

```
summary(SMR1D.post$time)

SMR1D.ON<-SMR1D.ON[order(SMR1D.ON$SafeHavenID, SMR1D.ON$ADMISSION_DATE),]
SMR1D.ON$counter<-sequence(rle(as.character(SMR1D.ON$SafeHavenID))$lengths)

##number of emergency admission
number1<-ddply(SMR1D.ON, .(SafeHavenID), function(x){length(unique(x$ADMISSION_DATE))})
number1$no.ADM<-as.factor(number1$V1)
no.ADM<-number1[,c("SafeHavenID", "no.ADM")]
summary(no.ADM)
table(no.ADM$no.ADM)
SMR1D.ON<-merge(SMR1D.ON,no.ADM, by="SafeHavenID")

SMR1D.ON$time<-as.numeric(SMR1D.ON$ADMISSION_DATE-SMR1D.ON$txstart)
summary(SMR1D.ON$time)

SMR1D.ON1<-SMR1D.ON[SMR1D.ON$counter=="1",]
summary(SMR1D.ON1$time)


DT<-TXINFO[TXINFO$REG=="DT",]
DT<-DT[!DT$txstart>"2018-01-01",]
SMR1DT<-merge(SMR1em, DT, by="SafeHavenID")
length(unique(SMR1DT$SafeHavenID))
SMR1DT$ADMTIME<-NA
SMR1DT$ADMTIME[SMR1DT$ADMISSION_DATE<SMR1DT$txstart]<-"PRETX"
SMR1DT$ADMTIME[SMR1DT$ADMISSION_DATE>SMR1DT$txstart & SMR1DT$ADMISSION_DATE<SMR1DT$adjtxend]<-"ONTX"
SMR1DT$ADMTIME[SMR1DT$ADMISSION_DATE>SMR1DT$adjtxend]<-"POSTTX"
table(SMR1DT$ADMTIME)
SMR1DT.post<-subset(SMR1DT, SMR1DT$ADMTIME %in% c("ONTX","POSTTX"))
```

```
length(unique(SMR1DT.post$SafeHavenID))
SMR1DT.ON<-subset(SMR1DT, SMR1DT$ADMTIME %in% c("ONTX"))
length(unique(SMR1DT.ON$SafeHavenID))
table(SMR1DT.post$MAIN_CONDITION)
table(SMR1DT.ON$MAIN_CONDITION)
SMR1DT.post<-SMR1DT.post[order(SMR1DT.post$SafeHavenID, SMR1DT.post$ADMISSION_DATE),]
SMR1DT.post$counter<-sequence(rle(as.character(SMR1DT.post$SafeHavenID))$lengths)

##number of emergency admission
number1<-ddply(SMR1DT.post, .(SafeHavenID), function(x){length(unique(x$ADMISSION_DATE))})
number1$no.ADM<-as.factor(number1$V1)
no.ADM<-number1[,c("SafeHavenID", "no.ADM")]
summary(no.ADM)
table(no.ADM$no.ADM)
SMR1DT.post<-merge(SMR1DT.post,no.ADM, by="SafeHavenID")

SMR1DT.post$time<-as.numeric(SMR1DT.post$ADMISSION_DATE-SMR1DT.post$txstart)
summary(SMR1DT.post$time)

SMR1DT.ON<-SMR1DT.ON[order(SMR1DT.ON$SafeHavenID, SMR1DT.ON$ADMISSION_DATE),]
SMR1DT.ON$counter<-sequence(rle(as.character(SMR1DT.ON$SafeHavenID))$lengths)

##number of emergency admission
number1<-ddply(SMR1DT.ON, .(SafeHavenID), function(x){length(unique(x$ADMISSION_DATE))})
number1$no.ADM<-as.factor(number1$V1)
no.ADM<-number1[,c("SafeHavenID", "no.ADM")]
summary(no.ADM)
table(no.ADM$no.ADM)
SMR1DT.ON<-merge(SMR1DT.ON,no.ADM, by="SafeHavenID", all = TRUE)
```

```
SMR1DT.ON$time<-as.numeric(SMR1DT.ON$ADMISSION_DATE-SMR1DT.ON$txstart)
summary(SMR1DT.ON$time/30.4)

SMR1DT.ON1<-SMR1DT.ON[SMR1DT.ON$counter=="1",]
summary(SMR1DT.ON1$time/30.4)

V<-TXINFO[TXINFO$REG=="VEM",]
V<-V[!V$txstart>"2018-01-01",]
SMR1V<-merge(SMR1em, V, by="SafeHavenID")
length(unique(SMR1V$SafeHavenID))
SMR1V$ADMTIME<-NA
SMR1V$ADMTIME[SMR1V$ADMISSION_DATE<SMR1V$txstart]<-"PRETX"
SMR1V$ADMTIME[SMR1V$ADMISSION_DATE>SMR1V$txstart & SMR1V$ADMISSION_DATE<SMR1V$adjtxend]<-"ONTX"
SMR1V$ADMTIME[SMR1V$ADMISSION_DATE>SMR1V$adjtxend]<-"POSTTX"
table(SMR1V$ADMTIME)
SMR1V.post<-subset(SMR1V, SMR1V$ADMTIME %in% c("ONTX","POSTTX"))
length(unique(SMR1V.post$SafeHavenID))
SMR1V.ON<-subset(SMR1V, SMR1V$ADMTIME %in% c("ONTX"))
length(unique(SMR1V.ON$SafeHavenID))
table(SMR1V.post$MAIN_CONDITION)
table(SMR1V.ON$MAIN_CONDITION)
SMR1V.post<-SMR1V.post[order(SMR1V.post$SafeHavenID, SMR1V.post$ADMISSION_DATE),]
SMR1V.post$counter<-sequence(rle(as.character(SMR1V.post$SafeHavenID))$lengths)

##number of emergency admission
number1<-ddply(SMR1V.post, .(SafeHavenID), function(x){length(unique(x$ADMISSION_DATE))})
number1$no.ADM<-as.factor(number1$V1)
no.ADM<-number1[,c("SafeHavenID", "no.ADM")]
summary(no.ADM)
table(no.ADM$no.ADM)
```

```
SMR1V.post<-merge(SMR1V.post,no.ADM, by="SafeHavenID")

SMR1V.post$time<-as.numeric(SMR1V.post$ADMISSION_DATE-SMR1V.post$txstart)
summary(SMR1V.post$time)

SMR1V.ON<-SMR1V.ON[order(SMR1V.ON$SafeHavenID, SMR1V.ON$ADMISSION_DATE),]
SMR1V.ON$counter<-sequence(rle(as.character(SMR1V.ON$SafeHavenID))$lengths)

##number of emergency admission
number1<-ddply(SMR1V.ON, .(SafeHavenID), function(x){length(unique(x$ADMISSION_DATE))})
number1$no.ADM<-as.factor(number1$V1)
no.ADM<-number1[,c("SafeHavenID", "no.ADM")]
summary(no.ADM)
table(no.ADM$no.ADM)
SMR1V.ON<-merge(SMR1V.ON,no.ADM, by="SafeHavenID")

SMR1V.ON$time<-as.numeric(SMR1V.ON$ADMISSION_DATE-SMR1V.ON$txstart)
summary(SMR1V.ON$time)

SMR1V.ON1<-SMR1V.ON[SMR1V.ON$counter=="1",]
summary(SMR1V.ON1$time/30.4)
```