Real-world effectiveness of systemic anticancer therapy for advanced melanoma in the West of Scotland from 2010-18

Aim:

Assess real-world effectiveness of systemic anticancer therapy (SACT) in advanced (unresectable or metastatic) melanoma (MM).

Methods:

Retrospective cohort study linking routine healthcare data with SACT prescriptions for patients starting immunotherapy or targeted treatments between 1.11.2010-31.12.2017 in the West of Scotland.

Results:

Among 362 patients identified, median overall survival (mOS) varied between 18.5 months (95% Confidence Interval (CI) 14.4-not estimable) for ipilimumab/nivolumab combination and 5.6 months (95%CI 4.5-7.3) with dabrafenib, but there were differences in characteristics of each regimen cohort. Raised LDH levels and ECOG performance status ≥2 negatively impacted OS.

Conclusion:

Our patients had a shorter mOS than pivotal trials. This was expected given that our real-world cohort includes patients with poorer prognostic indicators typically excluded from trials.

Keywords: metastatic melanoma; immunotherapy; targeted treatment; real world data; routine clinical practice

Introduction

Outcomes for patients with advanced (unresectable or metastatic) melanoma (MM) changed dramatically in 2010 with the introduction of ipilimumab, a CTLA4 checkpoint inhibitor – the first systemic anticancer treatment (SACT) to show a survival benefit in clinical trials for patients with MM, with a median overall survival (mOS) of 10.1 months (95% Confidence Interval (CI) 8.0-13.8) [1]. Prior to this, no SACT had shown a survival benefit in clinical trials, and patients with distant metastases had a median survival of 6-9 months [2]. Ipilimumab was accepted for use in Scotland in 2013, initially restricted to patients who had received prior therapy such as dacarbazine; however, following a resubmission, it became available for any line of treatment [3,4]. Further successful clinical trials with targeted treatments (vemurafenib, dabrafenib and trametinib) and additional immunotherapies (pembrolizumab and nivolumab) have followed; for example, results of the clinical trial for ipilimumab in combination with nivolumab in 2021 demonstrated overall 6.5-year survival rates of 49% (95% CI 44-55) [5].

It is increasingly recognised that participants in clinical trials may not be representative of the patients who receive treatments in routine clinical practice [6-8], which may mean that the results from clinical trials are not always replicable in routine clinical practice, and should, instead, be considered a surrogate measure for survival in the real-world [9]. In addition to the potentially highly selective populations (hence the issues with external validity), the control arms of clinical trials may not represent clinical practice at the time of publication due to the time elapsed during clinical trial design and recruitment, whilst the follow up period of the study may not be sufficient to enable mature outcomes to be captured. This has an impact on health technology assessments (HTA), which utilise information from clinical trials to assess the clinical and cost-

effectiveness of treatments. Publicly funded healthcare systems such as the National Health Service (NHS) in the UK, which provides universal access to healthcare that is free at the point of delivery, have a duty to ensure efficient use of resources for population health benefit. Real world, observational data, therefore, may be used to enhance HTA processes, as detailed in the Montgomery Review of the Scottish Medicine Consortium (SMC); NICE technology appraisals; and the Heads of Medicines Agencies – European Medicines Agency Joint Big Data Taskforce [10-12].

This study was undertaken as part of the Cancer Medicines Outcomes Programme (CMOP), funded by the Scottish Government in 2016 as part of the "Beating Cancer: Ambition and Action" Cancer Plan [13]. The primary aim was to determine the clinical outcomes of patients receiving SACT for MM in the West of Scotland, using electronic record linkage (ERL) of routinely captured administrative healthcare data. A secondary aim was to test the validity of using ERL as opposed to using patient case notes, the most commonly used method, to evaluate outcomes of SACT in routine practice within the Scottish context. Using routinely captured administrative healthcare data to determine SACT outcomes, as described by Baillie et al., can provide an alternative, more efficient route to collecting RWD than patient case notes or disease-specific prospective registries [8].

Material and Methods

Study Design and Population

This retrospective cohort study was conducted within the West of Scotland Cancer Network (WoSCAN), which serves almost half the population of Scotland (approximately 2.5 million patients) [14] and includes patients from the following four out of the 14 health boards in Scotland: NHS Ayrshire and Arran; NHS Forth Valley;

NHS Greater Glasgow and Clyde; and NHS Lanarkshire. The cohort was identified using the Chemotherapy Electronic Prescribing and Administration System (CEPAS), which contains records of all SACT prescribed within WoSCAN.

Inclusion criteria

Patients who started any of the following medicines (referred to as index SACT), in any line of therapy, for MM, including cutaneous, ocular and mucosal melanoma, between 1st November 2010 and 31st December 2017, with a study end of 31st March 2018:

Any immunotherapy, including: ipilimumab; pembrolizumab monotherapy; and ipilimumab in combination with nivolumab

Any targeted treatments, including: vemurafenib; dabrafenib monotherapy; and dabrafenib in combination with trametinib

Exclusion criteria

Patients who: were under 18 years of age; had participated in clinical trials for MM where the treatment could not be identified; or with incomplete SACT records (e.g. patients who had started SACT outside WoSCAN). Medicines that were not accepted for use in Scotland by the SMC.

Data Collection

Each patient in Scotland has a unique identifier, the Community Health Index (CHI) number, which is used on all NHS records and correspondence, including SACT prescriptions [15]. The CHI number was used to link SACT prescribing records from CEPAS in a secure environment to a number of routine administrative healthcare databases [16]. SACT prescribing records were used to identify the cohort for the study; determine median age at start of treatment; line of treatment; and provide SACT

information, including duration of treatment. The Scottish Cancer Registry (SMR06) was used to capture disease related information such as primary site of diagnosis using International Classification of Diseases 10th edition (ICD10) and International Classification of Diseases for Oncology (ICDO) codes whilst information from the molecular pathology laboratory information management system was used to determine BRAF status of the tumour. Information about patients' comorbidities was captured in two ways. The first used the Scottish Morbidity Records for outpatient attendances (SMR00) and general/acute inpatient and day case admissions (SMR01) to calculate Charlson score [17] and the second used the Prescribing Information System (PIS), which records information on all primary care prescriptions prescribed and dispensed in Scotland, to evaluate the number of medications prescribed in the calendar year prior to treatment start as a proxy for comorbidities [18]. Baseline blood results (reported up to 28 days prior to index SACT) were extracted from the Scottish Care Information Store and mortality data from the National Records of Scotland were used to estimate overall survival (OS). Data were also captured from individual patient level records (IPLR) by the researcher (JC) to provide quality assurance for ERL. Additional information available through IPLR meant it was possible to record the baseline tumour stage as per AJCC 7th edition [19] and if brain metastases were present or absent at start of SACT. Information about staging and prescence or absence of brain metastases were not available for ERL. Unfortunately, imaging reports were not available in a standardised form in either ERL or IPLR and so it was not possible to accurately report response rate or progression-free survival (PFS).

Study outcomes and statistical analysis

The primary outcome measure of OS was estimated using the Kaplan Meier

methodology from first index SACT date until death or censor date of 31st March 2018 for patients who remained alive at this time, whichever occurred first. It should be noted that patients were not censored if switching to a subsequent SACT for MM; however we have adjusted for this in the multivariable analysis. One year survival rates were also estimated for each index SACT. Median follow up time was estimated using the Kaplan Meier estimate of potential time for follow up [20]. Univariable analyses were carried out to determine the independent impact of variables on OS, followed by multivariable Cox regression to adjust for confounding. A priori selected variables (age, sex, primary site of melanoma), in addition to variables found to be statistically significant (p value<0.05) in the univariable analyses, were included in the multivariable model. Variables were also reported for each SACT individually to explore differences in the baseline characteristics of patients receiving each SACT. Any variables which were found to be statistically significant were also included in the multivariable model, excluding those that had more than 10% missing values. Subgroup analyses estimated mOS for patients with cutaneous melanomas and those receiving first line SACT.

All systemic treatment options, including clinical trials and chemotherapy, for MM were included to: describe previous and subsequent treatment information; count total SACT administered to patients; and determine line of treatment. Duration of treatment was calculated, for each index SACT, as the time between first and last treatment dates; for oral SACT this duration also included the duration of final supply with adjustments for patients who switched SACT or died.

To test the validity of ERL to determine outcomes with SACT the survival analysis was repeated with data captured via IPLR. Statistical analyses were carried out using R Studio version 3.3.3 [21].

Ethical Approval

A Public Benefit Privacy Panel application (Reference 1617-0371) was approved to access the information. No further ethics approval was required, as the study used routinely collected data and had no influence on the SACT received by each patient. The study was carried out in accordance with ethical and information governance guidelines.

Results

Overall, 362 patients were identified as starting SACT for MM during the study period, of which 176 (48.6%) were female and 215 (59.4%) received one SACT only. No patients received nivolumab monotherapy Figure 1 shows how the patient numbers and index SACT choice changed from 2010 to 2017; mOS for patients who started SACT between 2010-2014 was 8.5 months (95% CI 6.0-11.2) which increased slightly for patients starting SACT between 2015-2017 to 10.5 months (95% CI 8.1-14.7).

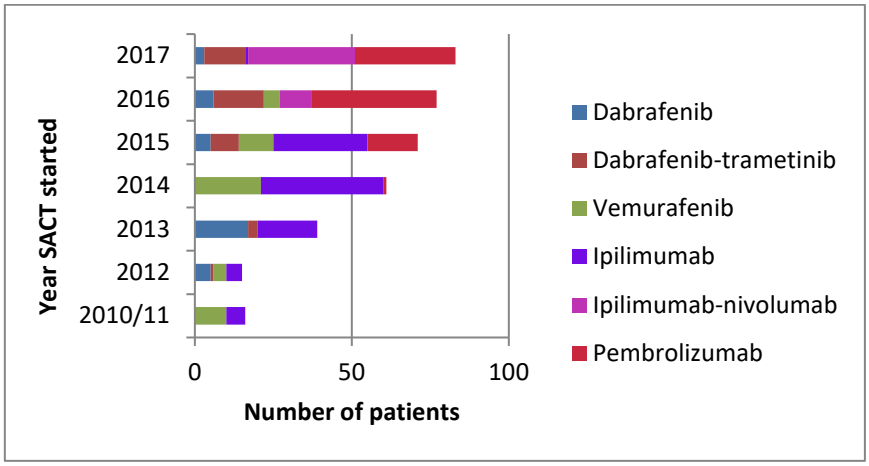


Figure 1. Index SACT prescriptions for patients in the West of Scotland starting treatment between 2010 -2017 (n=362)

Baseline characteristics for the cohort captured via ERL are shown in tables 1 and 2; with a summary of results in table 1 and a description of characteristics which differed by SACT, including proportion of patients with cutaneous melanomas, is shown in table 2. At the censor date (31st March 2018), 249 (69%) patients had died; 45 (12%) patients were alive and receiving SACT; 68 (19%) were alive and not receiving SACT.

Table 1. Baseline characteristics of patients at index systemic anti-cancer treatment given for advanced melanoma to patients in the West of Scotland between 2010-2017 (full cohort n=362; cutaneous patients only n= 274)

Variable		**N (%) full cohort (n=362)**	**N (%) cutaneous (n=274)**
Median Age (IQR) years		64 (51-75)	65 (50-75)
ECOG PS	**0**	184 (50.8)	140 (51.1)
	1	105 (29)	77 (28.1)
	2+	42 (11.6)	34 (12.4)
	Unknown	31 (8.6)	23 (8.4)
Primary melanoma site	**Cutaneous**	274 (75.7)	274 (100.0)
	Mucosal	25 (6.9)	
	Ocular	22 (6.1)	
	Unknown (known)	28 (7.7)	
	No SMR06 information	13 (3.6)	
LDH levels	**Within normal limits**	181 (50)	136 (49.6)
	Above ULN	143 (39.5)	108 (39.4)
	Unknown	38 (10.5)	30 (10.9)
NLR score	**0**	241 (66.6)	185 (67.5)
	1	104 (28.7)	74 (27.0)
	Unknown	17 (4.7)	15 (5.5)
Line of treatment	**First line SACT**	297 (81.8)	231 (84.3)
	Second or subsequent line SACT	66 (18.2)	43 (15.7)
BRAF status	**Wildtype**	144 (39.8)	98 (35.8)
	Mutant	76 (21)	66 (24.1)
	Unknown	142 (39.2)	110 (40.1)

Key: IQR=interquartile range; ECOG PS=Eastern Cooperative Oncology Group Performance Status; SMR06=Scottish Cancer registry; LDH=lactate dehydrogenase; ULN=upper limit of normal; NLR score=neutrophil-lymphocyte ratio; SACT=systemic anti-cancer therapy

Table 2. Comparison of characteristics for patients by index SACT for advanced melanoma in the West of Scotland from 2010-2017 (n=362)

SACT		**Ipilimumab**	**Pembrolizumab**	**Ipilimumab-nivolumab**	**Vemurafenib**	**Dabrafenib**	**Dabrafenib -trametinib**	**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**						
ECOG PS	**0**	55.0	37.1	84.1	60.8	25	45.2	0.0005
	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	0.0	7.8	13.9	9.5	
Body Mass Index	**Normal range**	33.0	31.5	29.5	7.8	8.3	11.9	0.0005*
	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	
Primary site	**Cutaneous**	68.0	68.5	65.9	86.3	94.4	90.5	0.003

	Mucosal	13.0	6.7	11.4	2.0	0.0	0.0	
	Ocular	10.0	10.1	6.8	0	0	0	
	Unknown (known)	8.0	9.0	9.1	9.8	2.8	4.8	
	No SMR06 information	1.0	5.6	6.8	2.0	2.8	4.8	
LDH levels	**Within normal limits**	59.0	52.8	63.6	37.3	27.8	42.9	0.001
	Above ULN	31.0	42.7	36.4	41.2	61.1	35.7	
	Unknown	10.0	4.5	0.0	21.6	11.1	21.4	
NLR Score	**0**	70.0	74.2	77.3	56.9	50.0	57.1	0.0005
	1	28.0	25.8	22.7	31.4	41.7	28.6	
	Unknown	2.0	0.0	0.0	11.8	8.3	14.3	
Line of treatment	**1**	40.0	100.0	100.0	94.1	94.4	97.6	0.0005
	2+	60.0	0.0	0.0	5.9	5.6	2.4	
Total number of SACT given	**1**	27.0	83.1	90.9	43.1	72.2	71.4	0.0005
	2	49.0	15.7	9.1	33.3	27.8	28.6	
	3+	24.0	1.1	0.0	23.5	0.0	0.0	

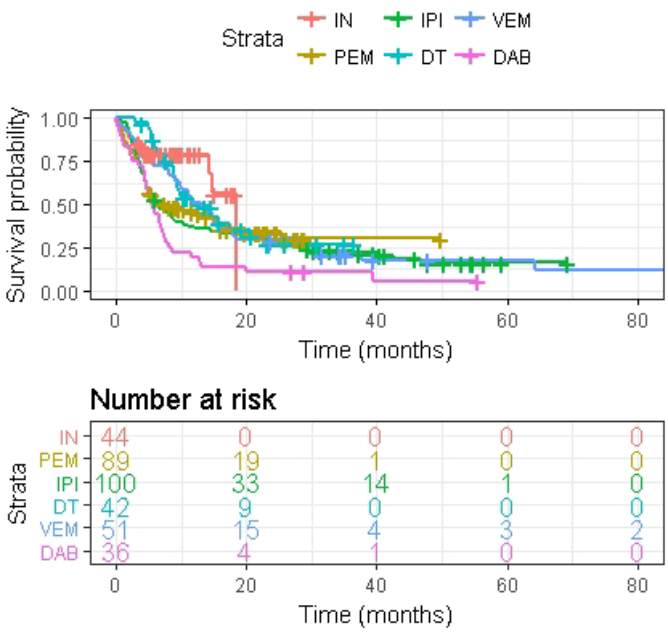
Patient had subsequent SACT	**No**	69.0	82.0	86.4	43.1	77.8	73.8	0.0005
	Yes	31.0	18.0	13.6	56.9	22.2	26.2	
BRAF status	**Wildtype**	32.0	93.3	65.9	0.0	0.0	0.0	0.0005
	Mutant	3.0	1.1	29.5	23.5	36.1	81.0	
	Unknown	65.0	5.6	4.5	76.5	63.9	19.0	
KEY: SACT=systemic anticancer treatment; ECOG PS=eastern cooperative oncology group performance status; SMR06 = Scottish Cancer Registry; LDH=lactate dehydrogenase; NLR=neutrophil to lymphocyte ratio; ULN=upper limit of normal *=not significant once adjusted for Benjamini Hofberg								

After a reverse Kaplan-Meier (KM) estimated follow-up of 27.7 months (95% CI 24.6-32.9), mOS for the whole cohort was 9.4 months (95% CI 8.0-11.6), however this varied significantly between treatments. Median OS with each index SACT is shown in table 3 together with duration of SACT and reverse KM follow-up. The KM curves for each index SACT are shown in figure 2. Ipilimumab in combination with nivolumab was associated with the longest mOS of 18.5 months (95% CI 14.4-not reached), with only 6 patients (16%) receiving subsequent targeted therapies; vemurafenib monotherapy had the longest mOS of the targeted treatments at 13.0 months (95% CI 9.9-18.0) but the median duration of treatment was 6.2 months (IQR 2.2-9.2) and 29 patients (57%) received subsequent SACT, the majority (n=22, 76%) with immunotherapy.

Table 3. Overall survival and treatment duration for patients receiving systemic anti-cancer treatment for all advanced melanoma in the West of Scotland (n=362) and cutaneous melanomas (n=274).

Index SACT		**n**	**deaths**	**Follow up time in months (95% CI)**	**Median OS in months (95%CI)**	**One year survival % (95%CI)**	**Median SACT duration in months (IQR)**
Ipilimumab monotherapy	**All patients**	100	80	45.9 (39.3-54.6)	6.3 (4.9-10.3)	35.7 (27.4-46.5)	2.1 (1.4-2.1)
	Cutaneous melanoma	68	54	45.9 (37.2-NA)	7.5 (5.0-20.9)	40.8 (30.5-54.4)	
Pembrolizumab	**All patients**	89	56	21.5 (19.7-25.5)	8.0 (4.8-15.5)	46.4 (37.0-58.2)	2.9 (1.4-8.0)
	Cutaneous melanoma	61	38	21.5 (17.1-27.7)	10.5 (4.8-25.4)	48.2 (36.9-62.8)	
Ipilimumab with nivolumab	**All patients**	44	12	8.9 (6.6-11.1)	18.5 (14.4-NR)	79.2 (68.0-92.3)	2.2 (1.3-4.8)

	Cutaneous melanoma	29	4	8.9 (5.9-11.1)	18.5 (NA-NA)	89.5 (79.0-100.0)	
Vemurafenib	**All patients**	51	42	39.5 (34.4-NA)	13.0 (9.9-18.0)	51.0 (39.0-66.7)	6.2 (2.2-9.2)
	Cutaneous melanoma	44	36	35.1 (34.2-NA)	13.1 (9.2-18.0)	52.3 (39.4-69.3)	
Dabrafenib	**All patients**	36	33	42.0 (26.7 – NA)	5.6 (4.5-7.3)	22.2 (12.1-40.9)	3.5 (1.7-4.9)
	Cutaneous melanoma	34	31	42.0 (26.7-NA)	5.8 (4.6-7.6)	20.6 (10.6-39.8)	
Dabrafenib with trametinib	**All patients**	42	26	23.2 (15.8-NA)	11.5 (9.4-23.0)	48.8 (35.3-67.5)	8.9 (5.7-14.5)
	Cutaneous melanoma	38	25	23.4 (15.8-NA)	11.5 (9.4-20.6)	46.8 (32.9-66.6)	
KEY: OS = overall survival; CI=confidence intervals; SACT = systemic anti-cancer treatment; IQR=interquartile range; NA = not available							



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

Figure 2. . Kaplan-Meier survival curves showing overall survival for the index SACT for the study cohort (n=362)

In the univariable analyses (appendix 1), baseline characteristics with a statistically significant negative impact on OS were: baseline LDH above the upper limit of normal; NLR score =1; poorer ECOG performance status; and primary disease site, with mucosal melanomas having a poorer outcome than cutaneous melanomas. These characteristics were also found to differ between patients receiving each SACT regimen (table 2). An increasing number of medicines prescribed in primary care prior to starting SACT was associated with poorer survival in the univariable analysis. These variables were subsequently included in the multivariable Cox regression analysis (table 4). In the multivariable model (ERL) regimen choice had a statistically significant impact on OS (global p-value=0.0012); ipilimumab in combination with nivolumab (HR 0.50 (95% CI 0.26-0.95)) and dabrafenib in combination with trametinib (HR 0.42 (95% CI 0.25-0.71)) being associated with improved OS compared to ipilimumab monotherapy. With the exception of number of medicines prescribed in primary care prior to starting index SACT, all the variables continued to show a statistically significant impact on OS.

The analysis was repeated withdata obtained from IPLR (appendix 2 and 3), and the final IPLR multivariable Cox-regression model generated similar results (table 4), although only dabrafenib with trametinib showed a statistically significant survival benefit compared to ipilimumab (HR 0.38 (95%CI 0.22-0.66)). AJCC stage M1c compared to M0-M1b (HR 1.68 (95%CI 1.18-2.40)) had poorer survival, and patients with no known brain metastases (HR 0.66 (95%CI 0.45-0.97)) had improved survival. These variables were only available for analysis in IPLR.

Table 4. Comparison of hazard ratios for patients receiving systemic anti-cancer treatment for advanced melanoma in the West of Scotland estimated using both electronically linked data and individual patient records.

		ERL multivariable Cox regression model			IPLR multivariable Cox regression model		
Variable		**Adjusted HR (95% CI)**	**p-value**	**Global p-value**	**Adjusted HR (95% CI)**	**p-value**	**Global p-value**
Gender	**Male**	1		0.5407	1		0.174
	Female	0.92 (0.7-1.21)	0.5407		0.83 (0.64-1.09)	0.174	
Age*		1 (0.99-1.01)	0.6061	NA	1 (0.99-1.01)	0.6709	NA
Regimen	**Ipilimumab**	1		0.0012	1		0.003
	Pembrolizumab	0.86 (0.59-1.27)	0.4611		0.85 (0.58-1.25)	0.4156	
	Ipilimumab with nivolumab	0.50 (0.26-0.95)	0.0352		0.54 (0.29-1.02)	0.0584	
	Vemurafenib	0.93 (0.61-1.42)	0.7359		0.96 (0.63-1.46)	0.8418	
	Dabrafenib	1.14 (0.71-1.83)	0.5954		0.79 (0.47-1.32)	0.3748	
	Dabrafenib with trametinib	0.42 (0.25-0.71)	0.0014		0.38 (0.22-0.66)	0.0005	
LDH level	**Within normal range**	1		0.0004	1		0.0132

	Above ULN	1.72 (1.28-2.31)	0.0003		1.35 (0.99-1.85)	0.0549	
	Unknown	1.93 (1.21-3.09)	0.0057		2.24 (1.37-3.66)	0.0013	
NLR Score	**0**	1		<0.0001	1		0.0005
	1	2.17 (1.61-2.94)	<0.0001		1.92 (1.43-2.58)	<0.0001	
	Unknown	1.53 (0.81-2.92)	0.1920		2.02 (0.71-5.77)	0.1901	
ECOG PS	**0**	1		0.0104	1		0.0096
	1	1.31 (0.94-1.84)	0.1154		1.47 (1.06-2.03)	0.0214	
	2+	2.28 (1.41-3.68)	0.0007		2.38 (1.46-3.86)	0.0005	
	Unknown	1.31 (0.81-2.12)	0.2759		1.26 (0.78-2.05)	0.3483	
Primary site	**Cutaneous**	1		0.0213	1		0.0355
	Mucosal	1.86 (1.14-3.02)	0.0122		2.08 (1.33-3.26)	0.0013	
	Ocular	1.67 (0.97-2.90)	0.0658		1.32 (0.76-2.29)	0.3257	
	Unknown	0.67 (0.39-1.14)	0.1378		0.91 (0.58-1.44)	0.6909	
	No information in SMR06	1.10 (0.53-2.29)	0.7954		NA		
Treatment switch?**	**No**	1		0.0001	1		0.002
	Yes	0.53 (0.39-0.73)	0.0001		0.6 (0.43-0.83)	0.002	
	0-4	1			Not available		

Number of medicines prescribed in primary care prior to starting SACT	**5-9**	0.90 (0.61-1.32)	0.5790	0.7089** *			
	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				
AJCC stage (7th edition)	**M0-M1b**	Not available			1		0.014
	M1c				1.65 (1.16-2.35)	0.0057	
	unknown				1.04 (0.43-2.52)	0.9308	
Brain metastases at baseline	**None or unknown**	Not available			1		NA
	Present				1.47 (1.01-2.16)	0.047	

KEY: ERL = electronic record linkage; IPLR= individual patient level records; 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; *= hazard ratio with age is for every year increase; **=patient switched from index SACT to a subsequent SACT; ***ordered p-value; NA = not applicable

Discussion

Summary of key findings

To our knowledge, this is one of the first studies to use routinely collected administrative healthcare data to describe outcomes of both targeted and immunotherapy treatment used in routine clinical practice for MM. The results have shown how SACT use for MM has varied in the West of Scotland, as HTA decisions were available. Immunotherapy choice changed from ipilimumab monotherapy to either ipilimumab in combination with nivolumab or pembrolizumab monotherapy whilst dabrafenib in combination with trametinib became the preferred targeted treatment choice instead of vemurafenib monotherapy. Our cohort included patients typically excluded from clinical trials, i.e. those with non-cutaneous melanomas, ECOG PS ≥2, and brain metastases, thereby providing additional 'real world' information to supplement the evidence from clinical trials. The inclusion of these patients may help explain why the median OS reported in our cohort (9.4 months (95% CI 8.0-11.6)) was less than demonstrated in clinical trials.

The longest observed OS in this study was 18.5 months (95% CI 14.4-not estimable) for patients receiving ipilimumab with nivolumab, whilst dabrafenib monotherapy had the shortest at 5.6 months (95% CI 4.5-7.3) – however, there were a number of differences in the baseline characteristics of patients receiving different SACT regimens. The results of the multivariable analysis, adjusted for these differences, showed that both 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)) improved OS compared to ipilimumab alone. This was expected as ipilimumab monotherapy was the first SACT available for prescription in this cohort but is no longer used as standard of care for

patients with MM due to longer OS with other SACT; ipilimumab is now used only as a second or third line treatment for patients who progress on other SACT.

A number of negative prognostic factors have been identified in the literature for MM patients such as non-cutaneous primary site (mucosal and ocular melanomas), LDH levels above the upper limit of normal, and poorer ECOG PS [22,23], and the results of our study support this. Our findings also suggest that baseline NLR score may be a useful additional prognostic tool to inform MM treatment discussions, with scores of 1 suggesting a poorer outcome, mirroring reports of NLR as a prognostic marker in other tumour types, [24-26]. Patients who switch to a subsequent SACT appear to have improved OS, but this may simply be due to immortal time bias [27]; it is not possible to discern whether patients are living longer because they receive more than one SACT, or if patients receive multiple SACT because they live longer. With the exception of ipilimumab monotherapy, which was initially accepted for use as a second line SACT in Scotland, the vast majority of the patients received SACT as a first line treatment. Further subgroup analysis for OS by line of treatment was not possible due to small patient numbers within each subset.

Our study showed differences in duration of SACT and median OS between immunotherapy and targeted treatments. Immunotherapies had a treatment duration between 2 and 3 months with median OS ranging from 6.3 -18.5 months whilst duration of treatment was found to be longer for targeted SACT. Interestingly, dabrafenib and trametinib treatment had a longer duration of treatment but a shorter median OS than vemurafenib (8.9 vs 6.2 months; 11.5 vs 13.0 months respectively). However, almost 60% of patients who received vemurafenib went on to receive subsequent SACT which suggests that the OS observed in the vemurafenib cohort may be influenced by subsequent SACT. Unfortunately, data to determine whether patients stopped, or

switched, SACT due to adverse effects, limited tolerability or progressive disease were not available, which restricted our ability to fully interpret our findings.

This study also provides evidence to support the use of ERL as a robust, efficient method to report outcomes of SACT, because the results from ERL and IPLR were similar, despite some differences in data availability. Median OS was consistent between ERL and IPLR and the small numerical differences in hazard ratios in both multivariable models had a minor impact on the interpretation of the results.

Comparison with other studies

There have been a number of publications reporting real world outcomes with SACT for advanced melanoma in routine care around the world, using data collected either directly from patient records or extracted from patient records then collated in disease specific registries, both of which are different to the ERL method used in this study. Areheden *et al* gathered data from patient medical records at a single institution in Sweden for 116 patients who only received immunotherapy (pembrolizumab or nivolumab); their study reported a median OS of 27.9 months (95% CI, 19.8–36.0) [28]. The longer OS in the Swedish study may in part be attributable to patients having less severe disease than our cohort; 50% M0-M1b and over 60% with LDH values within normal limits compared to only 30% and 50%, respectively, in our cohort.

Both immunotherapy and targeted treatments were included in a study by Donia *et al* using information from the Danish Metastatic Melanoma Database (DAMMED) [29] to show how OS has changed for patients in Denmark with MM, excluding ocular melanomas. Their results showed median OS of 16.5 months in "trial-like" patients in 2012 to 'not yet reached' in 2016. In "trial-excluded" patients, who accounted for 61% of the study population and were older, with a poorer ECOG PS and more severe disease than the "trial included" patients, median OS improved from 4.2 months in 2012

to 6.9 months in 2016 [30], which is comparable to the OS for our cohort. IPLR methodology has also been used in a number of other studies from Europe [31-33], Australia [34], Japan [35], the United States of America and Canada [36-39], with the European and Australian studies producing OS more closely aligned with the results from our study: ranging between four to eight months with ipilimumab [31,32,35]; 9.8 months (95%CI 8.9-11.0) with vemurafenib [32]; or 12.4 months (95%CI 8.6-14.4) with BRAF/MEK inhibitors [33] and 13.8 months (95%CI 8.0-not reached) with combination ipilimumab and nivolumab [34]. In contrast, OS in the studies carried out in the United States and Canada was generally longer than our cohort, ranging from 11.7 to 33.6 months [36-39]. North American studies included patients with stage III melanoma which could explain the improvement in mOS.

A study using ERL in place of IPLR, to describe the outcomes of SACT in patients with MM between 2014 and 2018, was carried out by Corrie *et al,* using routine Public Health England data sources [40]. This work was restricted to cutaneous melanomas, due to ease of identification with ICD10 codes, and included only immunotherapy SACT. Three-year OS was reported for ipilimumab (n=724), pembrolizumab (n=1174), and ipilimumab in combination with nivolumab (n=372) (32% (95% CI 28-35); 40% (95% CI 37-43); 56% (95% CI 49-62), respectively) [40]. Limiting the study to only cutaneous MM may contribute to the improved OS but further comparisons to our cohort are not possible due to the limited patient characteristics reported.

Strengths, limitations and future work

A key strength of this study is the inclusivity of both treatment type (immunotherapy and targeted treatments) and primary melanoma site (cutaneous, ocular and mucosal

melanomas). Utilising two methods of data collection has enabled the results from ERL to be robustly scrutinised and provides a level of quality assurance for ERL, supporting the ongoing use of this method for other studies.

The non-randomised nature of observational studies means that the patient numbers in each group are not standardised which limited our ability to compare smaller subsets and means our results should be interpreted cautiously. There were also some gaps in the data available for this study: recording of ECOG PS was only mandatory in WoSCAN from July 2015; BRAF status was missing for 142 (39.2%) patients in ERL due to results being reported from laboratories outside WoSCAN and therefore not accessible for this study; reasons for stopping or switching treatment were unavailable; and information from radiology reports, which could be used to determine response to treatment and baseline disease severity, are not currently accessible via ERL. Our study also showed that AJCC cancer staging along with information on brain metastases, only available in IPLR, are useful for prognostic purposes, suggesting that capturing this information routinely, via ERL, would be of benefit. SMR01 (hospital admissions) and PIS (primary care prescriptions) have been used to obtain information on the incidence of adverse effects of SACT, but small patient numbers prevented disclosure of results.

This study has generated a number of interesting findings and avenues for future work. There is scope to expand this study to include patients from across Scotland and update the results by including those who started SACT after 2018. The increase in patient numbers might allow the numbers of patients receiving each SACT to be more balanced; allow further time for follow up; expand work to investigate incidence of adverse effects; and enable additional clinical questions, such as the optimal sequencing

of targeted treatment and immunotherapy in patients who are BRAF mutant to be answered.

Conclusion

This study contributes to the growing body of literature reporting outcomes with SACT for MM use in routine clinical practice. Describing our patient population and reporting outcomes at a local level provides additional information for patients and clinicians when making treatment decisions. Gaining understanding of real world patients enables findings from clinical trials, and other real world studies, to be contextualised to inform and enrich shared decision making between patients and clinicians. The potential to continue to use routinely collected administrative healthcare data via ERL to update this study over a longer time period and explore outcomes of SACT in other tumour types is encouraging.

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Data Availability

The data that support the findings of this study are available on request from the corresponding author, [JC]. The data are not publicly available due to restrictions that could compromise the privacy of research participants.

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Appendix 1. Univariable analysis for patients receiving systemic anticancer therapy for advanced melanoma in the West of Scotland between 2010 and 2017

Co-variate	level	N	no. of events	Median OS in months (95% CI)	Univariable 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-NR)	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	
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	
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	**less than 1 year**	86	58	10.3 (6-16)	0.87 (0.62-1.23)	0.4329	0.8177
	1-3 years	110	76	8 (5.6-11.1)	1		
	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	
	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	
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	
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; NR=not reached;

*=numbers<5

Appendix 2 –Univariable analysis of baseline characteristics captured from individual patient level records of patients receiving systemic anti-cancer treatments for advanced melanoma in the West of Scotland

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
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
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	**N or unknown**	299	196	11.5 (9.2-14.9)	1 (-)	
date	**Y**	63	52	4.9 (3.9-7.3)	1.95 (1.43-2.66)	0
M stage at index	**M0-M1b**	111	56	20.9 (14.8-36.8)	1 (-)	
date	**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 3 - 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	8.0	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	
Variable		**% patients**						

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	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	
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	
	Wildtype	85.0	97.8	65.9	0.0	0.0	0.0	0.0000

BRAF Status	**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