Observational Study Protocol

INVESTIGATING SECULAR TRENDS IN THE SURVIVAL OF MELANOMA PATIENTS IN ENGLAND

Study Investigators

Bristol-Myers Squibb
Robert Carroll

Bristol-Myers Squibb Research and Development
Sanderson Rd
Denham
Uxbridge UB8 1DH
United Kingdom

Evidera
Beth Nordstrom
Anna Schultze
Surbhi Shah

Evidera
Metro Building, 6th Floor
1 Butterwick
London W6 8DL
United Kingdom

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Original Protocol	26-Nov-18	Not Applicable

SYNOPSIS

Observational Study Protocol

Protocol Title: Investigating Secular Trends in the Survival of Melanoma Patients in England

Department: Centre for Observational Research and Data Science (CORDS)

Objective(s): The primary objectives of this study are to:

(1) Describe the demographic and clinical characteristics of patients diagnosed with malignant melanoma

(2) Describe trends in one-year overall and net survival over time among the overall population of malignant melanoma patients and among subgroups of interest (disease stage and socioeconomic status [SES])

(3) Model changes in survival over time among these patients

Study Design: Observational cohort study

Study Population: Patients aged 18 years and above who were diagnosed with malignant melanoma at any stage from 1 January 1985 to 31 December 2015 will be identified from English Cancer Registry data held by Public Health England (PHE). The study period will span from 1 January 1985 until the latest available data (currently projected to be 31 December 2016). The study index date will be set as the date of initial diagnosis with malignant melanoma. The follow-up period will start on the day following the index date and will continue until death or end of the study observation period (December 31, 2016 or the date of most recent available data, whichever is latest). Patients with unknown gender or whose malignant melanoma diagnosis occurred at autopsy will be excluded. Patients will be further stratified into subgroups according to stage at diagnosis (as available) and SES.

Data Collection Methods: We will utilise existing cancer registration data from PHE. The cancer registration dataset includes data on demographics, characteristics of the tumour, patients' vital status and basic information regarding the treatment received. This information is submitted by National Health Services (NHS) providers to National Cancer Registration and Analysis Service (NCRAS) on a monthly basis in line with the requirements of the national standard for reporting cancer data, the Cancer Outcomes and Services Dataset (COSD).

Data Analyses: Descriptive statistics will be used to summarise the demographic and clinical characteristics of the overall population as well as for the subgroups of interest. Variables anticipated to be key predictors of survival (age and stage at diagnosis) will also be presented stratified by calendar year. The number and percentage of deaths will be presented stratified by calendar year. The non-parametric Kaplan-Meier (KM) method will be used to estimate overall one-year survival, and one-year net survival will be estimated as the relative survival, i.e., the ratio of observed to expected survival. Observed survival will be estimated using life-table methods and an actuarial estimator. The expected survival will be derived from published life-tables. Estimates of the RS will be age-standardised to the international standard cancer patient population. Trends in the relative survival will be modelled in the framework of generalized linear models (GLMs) using a Poisson assumption for the observed number of deaths, with models stratified by subgroups of interest. Trends in overall survival will be modelled using Cox proportional hazards models. To model a potential non-linear relationship between the survival and calendar year of diagnosis, smoothing functions such as restricted cubic splines (fractional polynomials) will be used.

Sample Size/Power: All eligible patients will be included. As the dataset has nationwide coverage, all statistics will be calculated directly using the entire population of interest, rather than a sample. Because of this there is no sampling variation, and sample size calculations are therefore not applicable.

Limitations/Strengths: Analyses of changes in cancer survival over time can be susceptible to lead-time bias and bias due to stage migration as a result of improved diagnostics; findings will need to be interpreted bearing such limitations in mind. In addition, the dataset contains limited information regarding the medical history of patients. It is also important to note that changes in survival over time can have multiple explanations, and these analyses will not attempt to identify causal effects.

However, the study also has several key strengths. The cancer registration data from PHE covers the entire English population, and results will therefore be generalisable to the population of England. There will also be limited losses-to-follow-up. The dataset further contains variables not commonly available in United Kingdom (UK) primary or secondary care data sources, such as cancer stage. This will allow for a more granular description of mortality trends within subgroups known to have very different survival experiences. The long duration of available data will also allow trends in melanoma mortality to be described over an extensive time-period.

TABLE OF CONTENTS

1 INTRODUCTION

1.1 Study Rationale

Melanoma, also known as malignant or cutaneous melanoma, is a type of skin cancer that arises from the uncontrolled proliferation of pigmented skin cells, melanocytes. It is the fifth-most common cancer in the UK, accounting for nearly 4% of all new cancer cases.[1] Over the last decade, the incidence of melanoma has increased by more than 50% in the UK, with rates in males and females increasing with 64% and 39%, respectively[2]. These incidence rates are further projected to rise by 7% between 2014 and 2035.[3] Survival rates for melanoma vary depending of the stage of the disease. According to the UK Office of National Statistics (ONS), one-year net survival for melanoma is indistinguishable from that in the general population among patients diagnosed at stage I, but considerably lower among those diagnosed at stage IV.[4] Studies suggests that patients with stage IV melanoma have a median survival of just 6 to 10 months.[5]

While surgery and radiation therapy are effective for patients with localised and regional melanoma, metastatic or late-stage melanoma patients do not respond well to these treatment options.[6] The development of gene targeted and immuno-oncology (IO) treatments, such as BRAF inhibitors (e.g., vemurafenib, dabrafenib, and encorafenib), MEK inhibitors (e.g., trametinib, cobimetinib and binimetinib), cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) blockers (e.g., ipilimumab) and programmed-death-1 (PD-1) inhibitors (e.g., nivolumab and pembrolizumab) have transformed the treatment options available to melanoma patients.[7] These agents have raised survival expectations and shifted the treatment paradigm for metastatic melanoma.[8]

Despite both IO and gene targeted melanoma treatments showing good efficacy in the clinical trial setting[9], there are few studies evaluating the public health impact of these treatments by considering outcomes on a population level. One retrospective study utilised the National Cancer Database in the United States (US) from 2004-2015 to evaluate the impact of targeted therapies and IO agents, first approved by the Food and Drug Administration (FDA) in 2011, on survival among stage IV melanoma patients. The findings of the study demonstrated a 31% relative increase in 4-year overall survival among patients diagnosed after 2011 compared to patients diagnosed prior to 2011.[10]

Our study aims to provide a detailed evaluation of melanoma survival over time in England. As previous studies have shown that melanoma survival varies significantly according to patient demographic characteristics, and particularly socioeconomic status (SES)[11,12], we will also evaluate whether any observed changes over time vary within different subgroups, specifically disease stage and SES.

Research Question

The research question is:

1. What are the trends in survival over time among patients with malignant melanoma, and do these trends vary according to disease stage or the socioeconomic status of patients?

2 OBJECTIVES

2.1 Primary Objectives

The specific objectives of this study are to:

1. Describe the demographic and clinical characteristics of patients diagnosed with malignant melanoma
2. Describe trends in one-year overall and net survival over time among the overall population of malignant melanoma patients and among subgroups of interest (disease stage and SES)
3. Model changes in survival over time among these patients

2.2 Secondary Objectives

Not Applicable.

2.3 Exploratory Objectives

Not Applicable.

3 STUDY DESIGN

3.1 Overview of Study Design

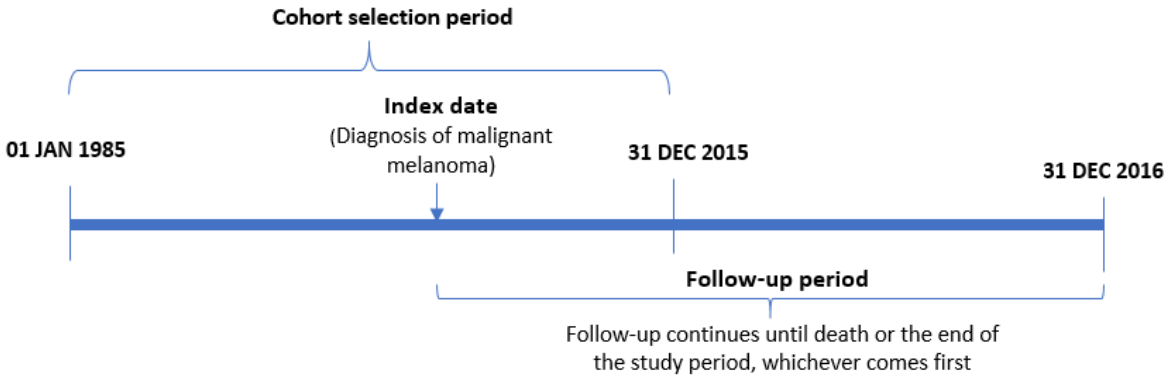
This is an observational cohort study of patients diagnosed with malignant melanoma using cancer registration data from Pubic Health England (PHE).

3.2 Study Population

The study population will include patients diagnosed with malignant melanoma at any stage from 1 January 1985 to one year prior to the end of available data (currently assumed to be 31 December 2015) using ICD-10 codes (Table 1).

The study period will span from 1 January 1985 until the latest available data (currently assumed to be 31 December 2016). The study index date will be set as the date of initial diagnosis with malignant melanoma. The follow-up period will start on the day following the index date and will continue until death or the end of the study observation period (31 December 2016 or the date of most recent available data, whichever is latest). Figure 1 below further illustrates the study periods.

Figure 1. Study Design



3.2.1 Inclusion Criteria

Patients will be included in the study if they meet all of the following criteria:

1. Patients with an ICD-10 code for malignant melanoma
2. Patients aged 18 years or above at their index date

Codes which will be used to identify the population are shown in Table 1.

Table 1. Codes used to identify patients with melanoma

ICD-10 code	Description
C43	**Malignant melanoma of skin**
C43.0	Malignant melanoma of lip
C43.1	Malignant melanoma of eyelid, including canthus
C43.2	Malignant melanoma of ear and external auricular canal
C43.3	Malignant melanoma of other and unspecified parts of face
C43.4	Malignant melanoma of scalp and neck
C43.5	Malignant melanoma of trunk
C43.6	Malignant melanoma of upper limb, including shoulder
C43.7	Malignant melanoma of lower limb, including hip
C43.8	Overlapping malignant melanoma of skin
C43.9	Malignant melanoma of skin, unspecified

3.2.2 Exclusion Criteria

Patients will be excluded if they meet any of the following criteria:

1. Unknown gender

2. Patients whose melanoma diagnosis occurred at autopsy

3.2.3 Subgroups of Interest

The two subgroups of interest are stage at diagnosis and SES.

- **Disease Stage:** Disease stage at index:
    - Stage 0
    - Stage I
    - Stage II
    - Stage III
    - Stage IV

  Disease stage has only been recorded consistently in NCRAS data since 2012. Analyses in early calendar years may therefore be limited to descriptive assessments within the subset of patients who have this data available.

- **SES**: Estimates of SES will be based on the index of multiple deprivation (IMD). This index has seven domains of deprivation—income, employment, health and disability, education, crime, barriers to housing and services, and living-environment.[13] Data on IMD is provided as quintiles of IMD, from least to most deprived. Depending on the number of people available within each IMD strata, it may be necessary to group the IMD strata together to allow for analyses.

3.3 Data Source

This study will utilise cancer registration data from PHE. PHE's National Cancer Registration and Analysis Service (NCRAS) is responsible for maintaining a population-based registry of all cases of cancer diagnosed and/or treated in England. NCRAS routinely collects both patient and tumour-level data from more than 500 local and regional datasets. The cancer registration data tables include data on the patient, their diagnosis, tumour characteristics and details of the care and treatment received. This information is submitted by NHS providers to NCRAS on a monthly basis in line with the requirements of the national standard for reporting cancer data, the Cancer Outcomes and Services Dataset (COSD).[14]

Specific information provided in the cancer registration data includes the following:

1. Patient tables: Variables include sex, ethnicity, vital status, and cause of death
2. Tumour tables: Variables include age at diagnosis and tumour-related information, such as tumour site and grade, morphology, and histology

Data is available from the 1 January 1985, and there is an approximate one-year lag time between dataset updates.

3.4 Definitions of Study Variables

3.4.1 Outcomes/Endpoint Variables

The primary outcomes of interest in this study are overall and relative survival[15]. Definitions of both the OS and RS are provided in Table 2.

Table 2. Outcome Definitions

Outcome/Endpoint	Definition	Timing
Overall Survival (OS)	Time since the index date (initial diagnosis) +1 until date of death due to any cause. Individuals still alive at the end of follow-up will be censored at the last day of available data.	From the day after index until the last day of available data (during follow-up)
Relative Survival (RS)	RS is defined as the ratio of observed to expected survival, expressed as a percentage. Observed survival at one-year post index will be estimated using the life table method with an actuarial estimator. The expected survival will be estimated using life tables published by the ONS[16]. The RS will consequently be age-standardised to the international standard cancer patient population.[17]	From the day after index until the last day of available data (during follow-up)

3.4.2 Exposure/Independent Variables of Interest

The exposure of interest is time, e.g., the calendar year of diagnosis, defined in Table 3.

Table 3. Exposure Definition

Exposure	Categories	Definition	Timing
Year of Diagnosis	Each year between 1985 – 2015	Derived using the "diagnosisyear" variable	At index date

3.4.3 Other Covariates/Control Variables

Several demographic and clinical characteristics will be examined in the study cohort. They are summarised in Table 4.

Table 4. Covariate Definitions

Covariate	Categories	Definition	Timing
Ethnicity	White, Non-White or Unknown	Derived using the "Ethnic Group" variable, as follows: White = A (White British), B (White Irish), C (Any Other White Background); Unknown = Z (Not stated), X (Not known) Non-white = All other categories	At index date
Sex	Male, Female or Unknown	Derived using the variable "Sex", as follows: 1=Male 2=Female	At index date
Vital Status	Alive, Dead or Exit posting	Derived using the "vitalstatus" variable, as follows: A =Alive, D =Dead, X =Exit posting	During follow-up
Age at Diagnosis	0–4 yrs., 5–9 yrs., 10–14 yrs., 15–19 yrs., 20–24 yrs., 25–29 yrs., 30–34 yrs., 35–39 yrs., 40–44 yrs., 45–49 yrs., 50–54 yrs., 55–59 yrs., 60–64 yrs., 65–69 yrs., 70–74 yrs., 75–79 yrs., 80–84 yrs.	Derived using the "fiveyearageband" variable	At index date
SES	1 (least deprived) to 5 (most deprived)	Derived using the IMD quintile variable	At index date

Covariate	Categories	Definition	Timing
Basis of Tumour Diagnosis	Categorisation to be determined in collaboration with NCRAS	Derived using the "basisofdiagnosis" variable to exclude cases diagnosed via autopsy or death certificate	At index date
Site of Tumour	Categorisation to be determined in collaboration with NCRAS	Derived using the "site_ICD10_O2" variable to capture location of malignant melanoma	At index date
Morphology of the Cancer	Categorisation to be determined in collaboration with NCRAS	Derived using the "morph_ICD10_O2" variable to enable description of malignant melanoma	At index date
Behaviour of the Cancer	Categorisation to be determined in collaboration with NCRAS	Derived using the "behavior_ICD10_O2" variable to enable description of malignant melanoma	At index date
T stage	Categorisation to be determined in collaboration with NCRAS	T stage flagged by the registry as the 'best' T stage, derived using the variable T_BEST	At index date
N stage	Categorisation to be determined in collaboration with NCRAS	N stage flagged by the registry as the 'best' N stage	At index date
M stage	Categorisation to be determined in collaboration with NCRAS	M stage flagged by the registry as the 'best' M stage	At index date
Tumour Grade	Well differentiated, moderately differentiated,	Derived using the "grade" variable, as follows:	At index date

Covariate	Categories	Definition	Timing
	poorly differentiated, undifferentiated, or unknown	GX = Grade of differentiation is not appropriate or cannot be assessed G1 = Well differentiated G2 = Moderately differentiated G3 = Poorly differentiated G4 = Undifferentiated / anaplastic	
Clark's Stage	1, 2, 3, 4, 5 or unknown	Derived using the "clarks" variable, as follows: 1, 2, 3, 4, 5, blank	At index date
Breslow Thickness of Tumour	(< or = 0.75 mm, 0.76-1.50 mm, 1.51-4.00 mm, and >4.00 mm[18])	Derived using the "breslow" variable to enable description of tumour	At index date
Tumour Stage at Diagnosis	Stage 0, I, II, III, IV, or unknown	Derived using the "stage_best" variable to enable description of tumour, as follows: 0, 0A, 0IS = Stage 0 1, 1A, 1A1, 1A2, 1B, 1B1, 1B2, 1C, 1E = Stage 1 2, 2A, 2A1, 2A2, 2B, 2C, 2E, 2S = Stage 2 3, 3A, 3B, 3C, 3E, 3S = Stage 3 4, 4A, 4B, 4C, 4S = Stage 4 6 = missing or unknown	At index date

4 STATISTICAL ANALYSIS

4.1 Statistical Analysis Methods

4.1.1 Analysis Plan for Primary Objectives

Objective: *Describe the demographic and clinical characteristics of patients diagnosed with malignant melanoma*

Outcome: *N/A*

Populations: *Overall, within each disease stage and within each SES stratum*

The demographic and clinical characteristics of the overall malignant melanoma cohort will be summarised using descriptive statistics. Means, standard deviations (SD), medians, and interquartile ranges (IQR) will be reported for continuous variables; while counts and percentages will be reported for categorical variables. Descriptions will be stratified by disease stage and SES. Variables anticipated to be key predictors of survival (age and stage at diagnosis) will also be presented stratified by calendar year.

Objective: *Describe one-year overall and relative survival over time among the overall population of malignant melanoma patients and among subgroups of interest (disease stage and SES)*

Outcome: *Number of deaths, OS and RS*

Populations: *Overall, within each disease stage and within each SES stratum*

The overall deaths occurring in the population, as well as within each subgroup, will be presented stratified by calendar year as numbers and percentages.

The non-parametric KM method will be used to estimate one-year OS for the overall study cohort and within each subgroup of interest, stratified by calendar year of diagnosis. The cumulative proportions will be presented together with 95% confidence intervals (CI).

Relative survival will be calculated as the ratio of overall survival for malignant melanoma patients during the one-year period following index date to the overall survival among a comparable cancer free population over the same one-year period. Observed survival will be estimated using life table methods and an actuarial estimator. This estimates a survival probability utilising the total number of events occurring during a specific time interval, in this case one year, as the numerator. The denominator is the effective sample size of the time interval of interest, calculated as the number of people under follow-up at the beginning of that interval minus half of number of people censored during that interval.

Expected survival for the comparable population will be obtained using life tables of the published annual probabilities of survival[16]. Estimates of the RS will be age-standardised to the international standard cancer patient population[18], and the final methodology will be detailed within the statistical analysis plan (SAP).

Objective: *Model changes in survival over time*

Outcome: *OS and RS*

Populations: *Overall*

Trends in OS will be modelled using multivariable Cox proportional hazards (PH) models. Cox PH models are a class of survival models that relate the duration of time until an event occurs to covariates that may influence the timing of the event. Covariates in the models will include baseline demographic and clinical characteristics. The key exposure of interest will be calendar year of diagnosis. Trends in RS will be modelled in the framework of generalized linear models (GLMs) using a Poisson assumption for the observed number of death. To model a potential non-linear relationship between the survival (both OS and RS) and the year of diagnosis, smoothing functions such as restricted cubic splines (fractional polynomials) will be used, which implies that the trends will be linear before the first and after the last knot and polynomial and smooth between adjacent knots.

All analyses will be repeated within the subgroups of interest, provided there are enough individuals and consequent deaths to estimate survival within each stratum. Strata where survival cannot be estimated will be presented as blank ("-'') within tables. If numbers allow, differences will be evaluated formally within the Cox/GLM models as relevant using interaction terms.

All analyses will be performed using Stata 12.0 (StataCorp, College Station, Texas) and SAS 9.4 (SAS Institue, Inc., Cary, North Carolina).

4.1.2 Analysis Plan for Secondary Objectives

Not applicable

4.1.3 Analysis Plan for Exploratory Objectives

Not applicable

4.2 Power/Sample Size

All eligible patients will be included. As the dataset has nationwide coverage, all statistics will be calculated directly using the entire population of interest, rather than a sample. Because of this there is no sampling variation, and sample size calculations are therefore not applicable.

5 STUDY LIMITATIONS/STRENGTHS

Analyses of changes in cancer survival over time can be susceptible to lead-time bias and bias due to stage migration as a result of improved diagnostics.[19] Lead-time bias refers to the bias introduced into studies of survival due to the progressively earlier diagnosis of a condition, e.g., due to the introduction of screening. Stage migration refers to the tendency for cancers to be diagnosed as late-stage or metastatic more readily in later calendar years, due to the use of more sensitive diagnostics or updated staging systems. Findings will have to be interpreted bearing such limitations in mind, as well as taking into account the concurrent trends in melanoma incidence and mortality.

Additional limitations include the fact that information on comorbidities and other potentially relevant clinical variables will not be available, meaning that we are limited in the extent to which we can describe patients' characteristics. There is also a relatively high degree of missingness in some variables, notably disease stage, with this variable only being reliably collected by the NCRAS from 2012 onwards.

It is also important to note that secular trends in survival over time can have multiple explanations, and we will not be able to determine the causes of any changes in the survival trends.

However, the study also has several key strengths. The cancer registration data from PHE covers the entire English population, and the results will therefore be generalisable to the population of England. There will also be limited losses-to-follow-up. The dataset further contains variables not commonly available in UK primary- or secondary-care data sources, such as cancer stage. This will allow for a more granular description of mortality trends within subgroups known to have very different survival experiences. The long duration of available data will also allow trends in melanoma mortality to be described over an extensive time-period.

6 STUDY CONDUCT

This study will be conducted in accordance with International Society for Pharmacoepidemiology (ISPE) Guidelines for Good Pharmacoepidemiology Practices (GPP) and applicable regulatory requirements.

6.1 Ethics Committee Review and Informed Consent

6.1.1 Ethics Committee Review

This study will undergo proportionate review by an NHS ethics committee if the data fails to meet k-3 anonymisation as per the ISB1523 anonymisation standards for publishing health and social care data.[20] The assessment of the anonymisation standards will be taken by an NCRAS analyst. In the first instance, the study team will seek to modify the study variable definitions to meet k-3 anonymisation standards.

6.1.2 Informed Consent

This study does not require informed consent to be obtained from the patients.

6.2 Quality Control

NCRAS receives data from a range of healthcare service providers, which may be of varying quality. The data is therefore subject to quality and accuracy checks before being used in analyses.[21] This process includes checking for internal consistency and identifying and removing duplicates, following guidelines published by the International Agency for Research on Cancer and the UK and Ireland Association of Cancer Registrations series of performance indicators. Records which fail these checks are not reported. In addition to checks performed by NCRAS, NHS Digital routinely updates cancer records with information on a patient's vital status. At the

time of data extraction, it is estimated that fewer than 0.3% of patients diagnosed cannot be traced during each relevant time-period.[21]

The analyses described in this protocol will follow Evidera's standard approach to quality control, governed by standard operating procedures. These procedures include internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, quality-control procedures for programming, standards for writing analysis plans, and requirements for senior scientific review.

All work will be subject to quality-control and documentation procedures to make certain that the final report is accurate and thorough and the analyses can be reproduced. All key study documents, such as the analysis plan, abstraction forms, and study reports, will undergo quality-control review, senior scientific review, and editorial review.

6.3 Database Retention and Archiving of Study Documents

As per Evidera Standard Operating Procedures (SOPs), data received will be stored on-site during the conduct of the research project in accordance with all contractual, legal and regulatory requirements. In general, records will not be retained on-site in excess of six months, unless a current need exists. Study/Project records may be retained on-site for longer than six months if project needs require. At a minimum of annually, each Evidera office conducts a record review to ensure that any datasets or related programs eligible for off-site storage or destruction are either moved or destroyed, as applicable. Records of the annual review will be kept. Data stored off-site will be kept for, in sequential order, per contract requirements; applicable local law or regulation requirements; or two years following study/project closure. Data will be destroyed in accordance with the Evidera Records Retention Procedure SOPs, which involves first removing the security groups that grant access to the data and consequently deleting the data from the storage location.

7 ADVERSE EVENT REPORTING

This study is not designed to capture safety events on a BMS product, and therefore, adverse event (AE) collection and reporting is not required. However, investigators/HCPs should follow local requirements for product safety reporting.

8 GLOSSARY OF TERMS AND LIST OF ABBREVIATIONS

8.1 Glossary of Terms

Term	Definition
Overall Survival	Overall survival is defined as the length of time between a defined time-point, such as the date of diagnosis of a condition, and the date of death. This is commonly presented as the proportion of patients still alive by a given time-point, estimated using non-parametric methods such as the Kaplan-Meier estimator.
Net survival	Net survival is a hypothetical measurement, defined as patient survival corrected for the effect of other causes of death. In registry studies, net survival is commonly estimated through the calculation of relative survival, both due to the absence of reliable cause of death information as well as the inherent challenges of determining a single cause of death for many patients.
Relative Survival	Relative survival is the ratio of the observed survival rate in a population to the expected survival rate of a similar cohort of people in the general population; matched on age, sex and year of observation. It is commonly expressed as a percentage. It is often used to estimate net or "excess" mortality due to a specific condition, such as cancer, when cause of death information is not known or poorly recorded.
Lead-time bias	Lead-time bias refers to the bias introduced into studies of survival due to the progressively earlier diagnosis of a condition, e.g., due to the introduction of screening.
Stage migration	Stage migration refers to the tendency for cancers to be diagnosed as late-stage or metastatic more readily in later calendar years, due to the use of more sensitive diagnostics or updated staging systems.

8.2 List of Abbreviations

Term	Definition
CORDS	Centre for Observational Research and Data Science
COSD	Cancer Outcomes and Services Dataset
CTLA-4	cytotoxic T-lymphocyte-associated antigen-4
FDA	Food and Drug Administration
GLM	Generalised Linear Models
IMD	indices of multiple deprivation
IO	immuno-oncology
IQR	interquartile ranges

KM	Kaplan-Meier
NCRAS	National Cancer Registration and Analysis Service
NHS	National Health Services
ONS	Office of National Statistics
OS	overall survival
PD-1	programmed-death-1
PHE	Public Health England
RS	relative survival
SD	standard deviations
SOP	standard operating procedure
SES	socioeconomic status
UK	United Kingdom
US	United States

9 REFERENCES

1. Research C. Melanoma skin cancer incidence. Melanoma skin cancer statistics. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/melanoma-skin-cancer#heading-Zero. Accessed 18 October, 2018.
2. Research C. Melanoma skin cancer incidence statistics. Melanoma skin cancer incidence by sex and UK country. . https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/melanoma-skin-cancer/incidence#heading-Zero. Accessed 18 October 2018.
3. Smittenaar CR, Petersen KA, Stewart K, Moitt N. Cancer incidence and mortality projections in the UK until 2035. *Br J Cancer.* 2016;115(9):1147-1155.
4. ONS. Cancer survival by stage at diagnosis for England (experimental statistics): Adults diagnosed 2012, 2013 and 2014 and followed up to 2015. 2016; https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancersurvivalbystageatdiagnosisforenglandexperimentalstatistics/adultsdiagnosed20122013and2014andfollowedupto2015. Accessed 19 October, 2018.
5. Sosman JA, Kim KB, Schuchter L, et al. Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib. *N Engl J Med.* 2012;366(8):707-714.
6. Rughani MG, Gupta A, Middleton MR. New treatment approaches in melanoma: current research and clinical prospects. *Ther Adv Med Oncol.* 2013;5(1):73-80.
7. Ugurel S, Rohmel J, Ascierto PA, et al. Survival of patients with advanced metastatic melanoma: The impact of novel therapies. *Eur J Cancer.* 2016;53:125-134.
8. Pasquali S, Chiarion-Sileni V, Rossi CR, Mocellin S. Immune checkpoint inhibitors and targeted therapies for metastatic melanoma: A network meta-analysis. *Cancer Treat Rev.* 2017;54:34-42.
9. Franken M, Leeneman B, Gheorghe M, et al. Comparative Effectiveness Of Novel Treatments For Advanced Melanoma: A Systematic Literature Review And Network Meta-Analysis Of Effectiveness And Safety Outcomes. *Value in Health.* 2017;20(9):A412-A413.
10. Dobry AS, Zogg CK, Hodi FS, Smith TR, Ott PA, Iorgulescu JB. Management of metastatic melanoma: improved survival in a national cohort following the approvals of checkpoint blockade immunotherapies and targeted therapies. *Cancer Immunol Immunother.* 2018.
11. Rutherford MJ, Ironmonger L, Ormiston-Smith N, et al. Estimating the potential survival gains by eliminating socioeconomic and sex inequalities in stage at diagnosis of melanoma. *Br J Cancer.* 2015;112 Suppl 1:S116-123.
12. Exarchakou A, Rachet B, Belot A, Maringe C, Coleman MP. Impact of national cancer policies on cancer survival trends and socioeconomic inequalities in England, 1996-2013: population based study. *BMJ.* 2018;360:k764.
13. Pereira Gray D, Henley W, Chenore T, Sidaway-Lee K, Evans P. What is the relationship between age and deprivation in influencing emergency hospital admissions? A model using data from a defined, comprehensive, all-age cohort in East Devon, UK. *BMJ Open.* 2017;7(2):e014045.
14. PHE. PHE cancer data sets, linkage and availability (v1.1). https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_

data/file/638073/cancer_data_sets_linkage_and_availability.pdf Accessed 18 October, 2018.
15. Lambert PC, Dickman PW, Nelson CP, Royston P. Estimating the crude probability of death due to cancer and other causes using relative survival models. *Stat Med.* 2010;29(7-8):885-895.
16. Statistics OfN. National life tables: UK. 2018; https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables. Accessed 18 October 2018.
17. Corazziari I, Quinn M, Capocaccia R. Standard cancer patient population for age standardising survival ratios. *Eur J Cancer.* 2004;40(15):2307-2316.
18. Marghoob AA, Koenig K, Bittencourt FV, Kopf AW, Bart RS. Breslow thickness and clark level in melanoma: support for including level in pathology reports and in American Joint Committee on Cancer Staging. *Cancer.* 2000;88(3):589-595.
19. Dickman PW, Adami HO. Interpreting trends in cancer patient survival. *J Intern Med.* 2006;260(2):103-117.
20. National Health Service (NHS). ISB1523: Anonymisation Standard for Publishing Health and Social Care Data. February 2013; https://digital.nhs.uk/data-and-information/information-standards/information-standards-and-data-collections-including-extractions/publications-and-notifications/standards-and-collections/isb1523-anonymisation-standard-for-publishing-health-and-social-care-data.
21. Office for National Statistics. Cancer survival statistical bulletins QMI. February 2018; https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/methodologies/cancersurvivalstatisticalbulletinsqmi. Accessed November 2018.