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Original Research

Population mortality in advanced melanoma patients with and without response and progression; data from the Dutch Melanoma Treatment Registry

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Abstract ***Introduction:*** When analysing patient survival, one is often interested in cause of death. Little is known about the presence of population mortality in advanced melanoma patients. The aim of this study was to assess population mortality after different response states in advanced melanoma patients in the Netherlands, and analyse the contribution of disease and population mortality for different age groups.
Methods: We selected patients diagnosed between 2013 and 2019 with unresectable IIIC or stage IV melanoma, registered in the Dutch Melanoma Treatment Registry. A multi-state model with response states integrating population mortality was fitted. One-year landmark analyses were performed to assess outcomes after each response state.
Results: Overall, 5119 patients were selected. Five-year probabilities of melanoma-related mortality in patients alive in complete response at one year after diagnosis increased with age, and was 17.2% (95% confidence interval: 13.0–21.4) for patients aged <65 years and 28.7% (95% confidence interval: 24.3–33.1) in patients aged ≥80 years. Population mortality only played a large role for older patients (75 years and above) alive at 1 year after diagnosis with a partial or complete response.
Conclusion: Even though survival outcomes of advanced melanoma patients have improved over the last decade, the vast majority of patients still die due to melanoma-related mortality.

1. Introduction

Overall survival (OS) of patients with advanced melanoma has increased over the last decade due to the introduction of immunotherapy (anti-PD-1 ligands and CTLA-4 inhibitors) [1–3] and targeted therapy (BRAF & MEK-inhibitors) [4–7]. Median age at diagnosis ranges from 50 to 65 years in clinical phase III trials [1,7], and is higher in real-world populations [8]. For older patients, population mortality (the risk of death that they would have faced in the absence of their disease and treatment) is not negligible.

The probabilities of population mortality and excess (disease-related) mortality can be estimated by statistical methods, even if cause of death is not available in the data. Studies reporting on the reliability of cause of death are conflicting [9–11]. In many cases, information on cause of death is incomplete, unreliable and ambiguous. In this approach, the study cohort is matched to an artificial cohort from the general population with the same distribution of demographic covariates, e.g. age, sex, year of diagnosis and country. Population mortality tables are easily available for most western countries. By subtracting the population mortality risk based on these tables from the total mortality risk, the excess mortality, which can be interpreted as death directly or indirectly attributable to the disease and its treatment, can be calculated.

Two important drivers of the contribution of population mortality to all mortality are age and response status (e.g. complete response, partial response, stable disease (SD) and progression). Patients with a complete response (CR) have the same risk for population mortality as patients who have progressed. However, this risk translates into different probabilities: because the probability of dying due to advanced melanoma is smaller, the probability of dying due to other causes (population mortality) is higher than for patients after progression. An analysis of these series of events (diagnosis-response-progression-death) with the integration of population mortality has been enabled by a recent extension of statistical methods by Manevski *et al.* [12],

who have incorporated relative survival in a multi-state model. These models have been published for patients after allogeneic haematopoietic cell transplantation (Weller *et al. submitted*) and for breast cancer [13], but not yet for advanced melanoma, where they are also relevant, due to the recent prolonged survival and the number of older patients.

In this study, we have developed such a model for data from the Dutch Melanoma Treatment Registry (DMTR) to estimate melanoma-related mortality and population mortality in four age groups of advanced melanoma patients. The detailed data from this registry offer a unique opportunity to study the roles of excess and population mortality in relation to response status and progression.

2. Materials and methods

2.1. Study design and population

This study used data from the DMTR, a population-based registry including all patients diagnosed with unresectable stage IIIc and IV melanoma in the Netherlands. Patients are followed during the course of their disease until death or a ten- year follow-up. A follow-up is performed every three months by trained data managers. The involved medical oncologists check the entered data. A detailed description of the DMTR has been published by Jochems *et al.* [14].

For the purpose of this study, we selected patients of 18 years and older, diagnosed with unresectable stage IIIc and IV melanoma between 1-1-2013 and 31-12-2019. This interval was chosen based on the availability of data as the DMTR started in 2013, and allowing a sufficiently long follow-up to study long-term outcomes.

2.2. Statistical analysis

Baseline patient and tumour characteristics were analysed using descriptive statistics. Characteristics described were sex, age at diagnosis (<65, 65–74, 75–79 and ≥80 years), baseline Eastern Cooperative Oncology Group (ECOG) performance status (ECOG PS; 0–1, ≥2), stage (according to AJCC 8th edition) (unresectable IIIc, IV-M1a, IV-M1b and IV-M1c, IV-M1d), baseline lactate dehydrogenase levels (LDH; normal, 250–500 U/L, >500U/L), brain metastasis (none, asymptomatic and symptomatic), liver metastasis (yes, no), number of organ sites with metastases (<3 organ sites, ≥3 organ sites involved) and $BRAF^{V600}$ mutation status (mutant and wild-type). Response status was based on a combination of Response Evaluation Criteria in Solid Tumours v1.1 and on (clinical) judgement by the medical team.

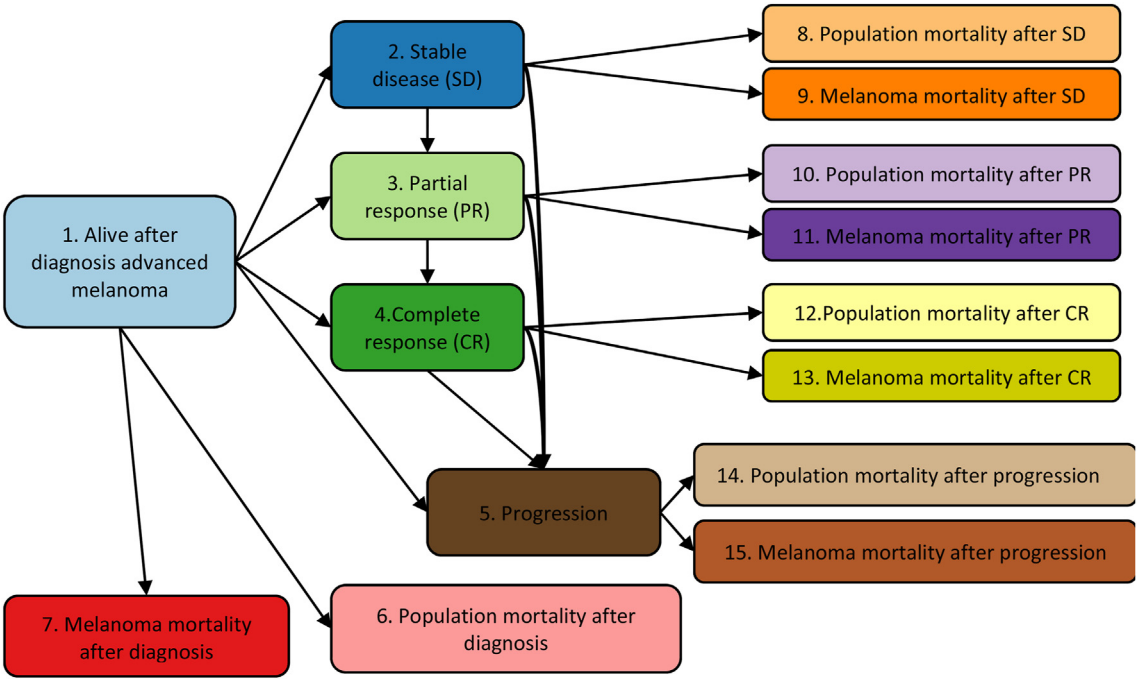

Fig. 1. A multistate relative survival model. All patients start in the state alive after diagnosis with advanced melanoma (state 1). They can progress to stable disease (state 2), partial response (state 3), complete response (state 4), progression (state 5) and death (state 6–15). After stable disease, partial response and complete response (state 2–4), patients can make a transition to progression (state 5). Each arrow indicates a transition to a next state. All death states are absorbing, which means that patients cannot leave them once they have entered them. This model attempts to separate death due to advanced melanoma and population mortality based on the observed transitions to death by means of techniques from relative survival.

Outcomes were melanoma-related mortality and population mortality after diagnosis,SD, partial response (PR), CR and progression after first-line treatment by age group. Responses after second or later treatment lines were not considered in the model. Melanoma-related mortality was defined as death due to advanced melanoma or due to its treatment. Age groups were chosen based on their OS from diagnosis in a Kaplan–Meier estimate, where we observed a gradual decrease in OS with increasing age (Supplement 1). Survival was defined as the time from diagnosis with unresectable stage IIIc or IV disease to death from any cause. Patients alive or lost to follow-up were right-censored at the time of last registered contact. Patients with a follow-up longer than 5 years were artificially censored at 5 years. A median follow-up time was calculated using reverse Kaplan–Meier method [15]. Also, probabilities of being alive after different intermediate events (events taking place between diagnosis and death) were calculated.

Melanoma mortality and population mortality were derived from thetotal mortality using relative survival techniques. These techniques compare the total mortality in a study population to mortality in the general population matched by age, sex and year of diagnosis using country-specific life tables from the Human Mortality Database (http://www.mortality.org). A more detailed description of these techniques is described in Supplement 2. To assess the impact of melanoma-related mortality and population mortality, taking into account the occurrence and timing of response and progression, we used a novel multi-state model where we combined observed transitions (to response states and death) and unobserved transitions (to population/excess mortality) [12]. The multi-state model used is shown in Fig. 1; it is a Markov time-inhomogeneous model. Cumulative hazards of transitions were assessed over a time period of 5 years. Transition probabilities between states were also calculated until 5 years after diagnosis. We performed a landmark analysis at 12 months, analysing outcomes of patients alive and in different intermediate states (SD, PR, CR and progression) at 12 months, to assess the impact of response on outcomes and to focus on groups with a better prognosis for whom population mortality is more relevant. We also assessed cumulative incidence of starting a first-line systemic therapy before death for all age groups.

All analyses were performed in R Studio version 4.0.2 using the following packages: tidyverse [16], survival [17], relsurv [18] and mstate [19–21].

3. Results

Between 2013 and 2019, 5119 patients were diagnosed with unresectable stage IIIc and IV melanoma. Patients and tumour characteristics are shown in Table 1. The dataset was closed on 7th April 2021. Overall, median age was 66, with 2419 patients (47.3%) aged <65 years, 1512 patients (29.5%) were aged 65–74 years, 591 patients (11.5%) were aged 75–79 years and 597 patients (11.7%) were aged ≥80 years. Patient and tumour characteristics stratified by the age category are shown in Supplement 3. Overall, with increasing age, patients had a poorer ECOG PS, less stage IV-M1d disease, less brain metastases, less organs with metastases and more often $BRAF^{V600}$ wild-type melanoma.

Table 1
Patient and tumour characteristics at diagnosis of advanced melanoma of the patients included in this study.

	Total	N = 5119 N (%)
Age (median (range))		66 (19–97)
Sex (%)	Male	3013 (58.9)
	Female	2106 (41.1)
ECOG PS (%)	0–1	3813 (84.5)
	≥2	697 (15.5)
	Missing	609
Stage (%)	IIIc unresectable	301 (5.9)
	IV-M1a	447 (8.8)
	IV-M1b	607 (11.9)
	IV-M1c	2346 (46.0)
	IV-M1d	1397 (27.4)
	Missing	21
LDH (%)	Normal	2918 (61.3)
	1–2x ULN	1148 (24.1)
	>2x ULN	692 (14.5)
	Missing	361
Brain metastases (%)	No	3590 (72.0)
	Yes, asymptomatic	498 (10.0)
	Yes, symptomatic	899 (18.0)
	Missing	132
Liver metastases (%)	No	3453 (68.3)
	Yes	1604 (31.7)
	Missing	62
Organ sites with metastases (%)	<3	2860 (55.9)
	≥3	2259 (44.1)
$BRAF^{V600}$ mutation (%)	Wild-type	2128 (46.1)
	Mutant	2491 (53.9)
	Missing	500

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Score, LDH, lactate dehydrogenase.

3.1. Outcomes

Kaplan–Meier estimates of OS for the four age categories are shown in Supplement 1. A median follow-up of the cohort was 39.8 months (95% confidence interval (CI): 38.0–41.6). Outcomes stratified by age are shown in Fig. 2. Observed transitions for the four age groups are shown in Supplement 4-7. Cumulative hazards of transitions are shown in Supplement 8-11. We observed that most transitions from diagnosis to SD, PR and CR occur in the first months after starting first-line treatment. We also observe transitions between intermediate states such as from SD to PR or PR to CR. Progression from each state occurs continuously, independently of

Table 2
Probabilities of melanoma mortality and population mortality (in %) at 2 and 5 years after time of diagnosis with advanced melanoma according to the state from where the patients died (diagnosis, stable disease, partial response, complete response and progression), stratified by age group. 'Overall' indicates the sum of mortality from the diagnosis, stable disease, partial response, complete response and progression states (all mortality). Since total and population hazard must always be positive, their difference (excess hazard) can, under rare circumstances, be negative, leading to negative probabilities. Although contra-intuitive, these negative quantities can be interpreted as meaning that for certain patient groups survival is better than that of the general population since they represent a relatively fit group. For states, see Fig. 1, and for probabilities, over time see Fig. 2. Abbreviations: CI, confidence interval.

State	Diagnosis		Stable disease		Partial response		Complete response		Progression		Overall	
	Population mortality % (95% CI)	Melanoma mortality % (95% CI)	Population mortality % (95% CI)	Melanoma mortality % (95% CI)	Population mortality % (95% CI)	Melanoma mortality % (95% CI)	Population mortality % (95% CI)	Melanoma mortality % (95% CI)	Population mortality % (95% CI)	Melanoma mortality % (95% CI)	Population mortality % (95% CI)	Melanoma mortality % (95% CI)
At 2 years												
<65 years	0.2 (0.2–0.2)	8.0 (7.4–8.5)	0.1 (0.1–0.1)	1.6 (1.1–2.1)	0.3 (0.3–0.3)	1.2 (0.8–1.5)	0.1 (0.1–0.1)	0.1 (0.0–0.3)	0.4 (0.3–0.4)	42.3 (41.2–43.5)	1.1 (1.1–1.2)	53.2 (51.6–54.7)
65–74 years	0.9 (0.9–0.9)	12.9 (11.6–14.3)	0.6 (0.5–0.6)	2.1 (1.9–2.2)	1.0 (0.9–1.1)	1.0 (0.5–1.6)	0.5 (0.5–0.5)	−0.3 (0.0–0.1)	1.4 (1.4–1.5)	42.0 (41.9–42.1)	4.4 (4.3–4.6)	57.7 (57.5–58.0)
75–79 years	1.9 (1.8–1.9)	16.6 (15.2–18.0)	1.2 (0.9–1.5)	2.0 (1.1–2.9)	2.0 (2.0–2.1)	0.7 (0.5–0.9)	0.9 (0.7–1.0)	−0.2 (0.0–1.1)	2.0 (1.5–2.5)	39.1 (31.6–46.7)	8.0 (7.5–8.5)	58.3 (56.3–60.2)
≥80 years	4.2 (3.8–4.7)	23.1 (22.8–23.5)	1.9 (1.7–2.1)	3.6 (2.3–4.8)	3.5 (3.2–3.7)	−0.7 (0.0–0.8)	1.3 (1.1–1.5)	0.1 (0.0–0.4)	2.6 (2.5–2.7)	35.0 (30.7–39.2)	13.5 (12.4–14.6)	61.1 (55.7–66.5)
At 5 years												
<65 years	0.2 (0.2–0.2)	8.0 (7.4–8.7)	0.2 (0.2–0.2)	1.7 (1.2–2.1)	0.5 (0.5–0.5)	1.5 (0.9–2.1)	0.4 (0.4–0.4)	0.2 (0.0–1.0)	0.9 (0.8–1.0)	55.1 (53.8–56.4)	2.2 (2.1–2.3)	66.4 (65.0–67.8)
65–74 years	0.9 (0.9–0.9)	12.9 (11.6–14.3)	0.8 (0.7–1.0)	2.0 (1.5–2.5)	1.7 (1.4–2.0)	0.7 (0.6–0.7)	1.7 (1.5–1.9)	−1.1 (0–0.5)	3.1 (3.0–3.3)	53.4 (51.0–55.7)	8.3 (7.8–8.8)	67.9 (66.6–69.2)
75–79 years	1.9 (1.9–1.9)	17.0 (15.0–18.9)	1.7 (0.4–3.0)	2.5 (1.8–3.2)	4.0 (3.3–4.7)	0.4 (0.0–1.5)	3.0 (2.6–3.5)	−1.8 (0–1.8)	4.6 (2.9–6.4)	47.5 (40.6–54.3)	15.3 (14.2–16.4)	65.5 (65.2–65.8)
≥80 years	4.7 (4.3–5.1)	22.9 (22.9–22.9)	2.5 (1.4–3.6)	4.4 (1.9–7.0)	5.6 (4.7–6.5)	−0.5 (0.0–2.1)	3.7 (3.2–4.3)	1.3 (0–3.2.0)	5.4 (4.9–5.8)	39.4 (37.7–41.2)	21.9 (20.0–23.9)	67.6 (62.1–73.0)

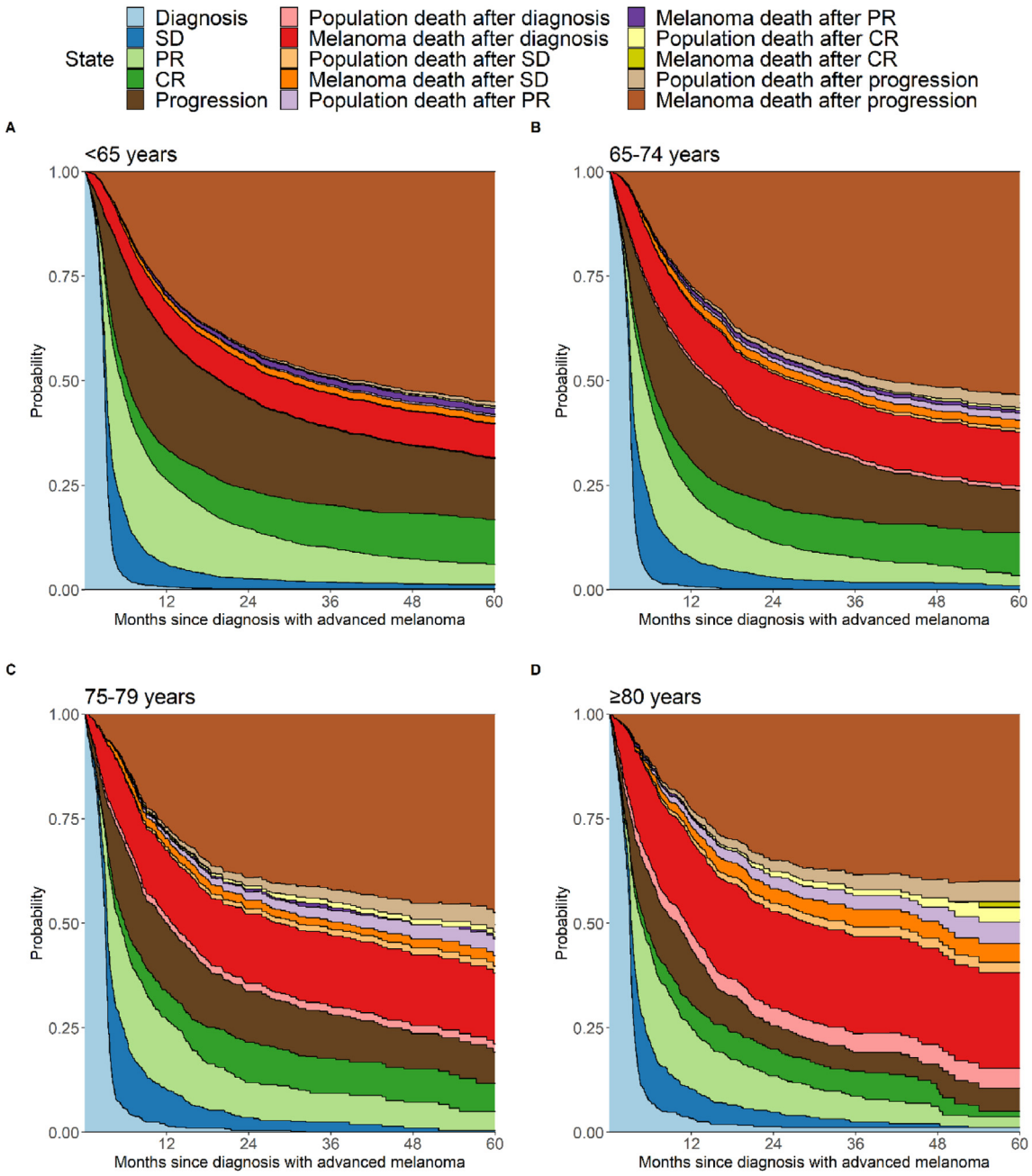

Fig. 2. Outcome probabilities since diagnosis with advanced melanoma based on a multistate model (see Fig. 1). Curves are stacked, meaning that the probabilities of different outcomes are indicated by the distances between the lines. Probabilities are displayed for four age groups: **A.** <65 years. **B.** 65–74 years, **C.75–79, D.** ≥80 years. Abbreviations: SD = stable disease, PR = partial response, CR = complete response.

the intermediate state or time. Supplement 12-13 show that older patients are less likely to receive a systemic therapy before death.

Two-year population mortality increased from 1.1% (95% CI: 1.1–1.1) in patients aged <65 years to 13.5% (95% CI: 12.9–14.1) in patients aged ≥80 years (Table 2). Five-year population mortality increased from 2.2% (95% CI: 2.1–2.3) in patients aged <65 years to 21.9% (95% CI: 20.0–23.9) in patients aged ≥80 years. The contribution of population mortality varied strongly between the different intermediate states and age categories (Table 2). Five-year probabilities of melanoma mortality after diagnosis (direct transition, without intermediate events; see Fig. 1, State 7) increased with age, and was 8.0% (95% CI: 7.4–8.5) in patients aged <65 years and 23.1% (95% CI: 22.8–23.5) in patients aged ≥80 years. A small proportion of patients with a SD died directly from this state due to melanoma mortality and 5-year probabilities which increased with age, 1.7% (95% CI: 1.2–2.1) in patients aged <65 years and 4.4% (95% CI: 1.9–7.0) in patients aged ≥80 years (State 9 in Fig. 1). Five-year probabilities of melanoma mortality after progression decreased with age; they were 55.1%

Table 3
Probabilities (in %) to be alive in one of the intermediate states (diagnosis, stable disease, partial response and complete response) from the time of diagnosis with advanced melanoma stratified by age group. For states, see Fig. 1, and for probabilities over time, see Fig. 2. Abbreviations: CI = confidence interval, SD = stable disease, PR = partial response, CR = complete response.

State	Diagnosis (%, 95% CI)	SD (%, 95% CI)	PR (%, 95% CI)	CR (%, 95% CI)
At 2 years				
<65 years	0.3 (0.1–0.4)	2.4 (1.4–3.4)	11.9 (10.5–13.3)	9.3 (9.0–9.6)
65–74 years	0.2 (0.0–0.5)	2.7 (1.3–4.2)	8.3 (7.5–9.1)	8.7 (6.2–11.3)
75–79 years	0.4 (0.0–0.9)	3.1 (1.5–4.6)	8.4 (6.6–10.1)	9.6 (7.6–11.7)
≥80 years	1.4 (0.1–2.7)	3.4 (1.8–4.9)	8.7 (6.6–10.8)	6.4 (6.1–6.7)
At 5 years				
<65 years	0.2 (0.1–0.3)	1.1 (0.8–1.3)	4.8 (4.5–5.0)	10.7 (9.6–11.8)
65–74 years	0.0 (0–0.3.0)	1.0 (0.0–2.6)	2.4 (1.8–3.0)	10.2 (5.3–15.2)
75–79 years	0.0 (0.0–0.0)	0.5 (0.0–0.9)	4.4 (0.9–7.9)	6.8 (4.3–9.3)
≥80 years	1.1 (0–2.4.0)	0.0 (0.0–0.0)	2.5 (0.9–4.1)	1.4 (0.0–6.3)

(95% CI: 53.8–56.4) in patients aged <65 years and 39.4% (95% CI: 37.7–41.2) in patients aged ≥80 years (State 15).

Two-year probabilities of being alive in CR ranged from 9.3% (9.0.6–9.6) in patients aged <65 years and 6.4% (6.1–6.7) in patients aged ≥80 years (Table 3). These percentages decreased at 5-year, with probabilities being 10.7% (95% CI: 9.6–11.8) in patients aged <65 years and 1.4% (95% CI: 0.0–6.3) in patients aged ≥80 years. The probabilities to be alive with SD or in PR at 2 and 5 years after diagnosis were low for all age groups.

3.2. Landmark analyses

After a SD in the first year after diagnosis for patients still alive at the 1-year landmark without subsequent events, the probability of melanoma-related mortality was 35.1% (95% CI: 29.5–40.6) at 5 years after diagnosis for patients aged <65 years and 51.3% (95% CI: 49.9–52.6) in patients aged ≥80 years (Table 4). Outcomes stratified by age are shown in Supplement 14-17.

In the landmark analysis, the probabilities to reach or stay in states with a relatively good prognosis were also estimated (Table 5). Five-year probabilities of being in CR in patients with a SD after diagnosis, who were still alive at the 1-year landmark, ranged from 12.3% (95% CI: 12.1–12.4) for patients aged <65 years and 1.6% (95% CI: 0.0–3.8) in patients aged ≥80 years. Five-year probabilities to be in CR were larger in patients with a PR after diagnosis, who were still alive at the 1-year landmark: 26.2% (95% CI: 22.0–30.4) for patients aged <65 years and 4.1% (95% CI: 2.0–2.6) for patients aged ≥80 years. Five-year probabilities to be in CR in patients who were still alive at the 1-year landmark and remained in the CR state ranged from 62.7% (95% CI: 59.0–66.5) for patients aged <65 years and 11.6% (95% CI: 10.8–12.5) in patients aged ≥80 years.

4. Discussion

Our data show that in patients with advanced melanoma, even though outcomes have improved considerably over the last decade, the largest proportion of mortality is caused by excess mortality, e.g. advanced melanoma-related mortality. The poorer outcomes for older patients are mainly caused by increased population mortality and, to a lesser extent, by more melanoma mortality. At 5 years after diagnosis, for older patients the contribution of population mortality to all mortality is much higher than at 2 years after diagnosis. Population-related mortality only plays a substantial role in patients ≥75 years with a PR or CR, which are two relatively small subgroups. As expected, the most frequent outcome is melanoma-related mortality after progression.

This is the first study in advanced melanoma to split population and melanoma mortality, and to split all mortality in melanoma-related and population mortality after different intermediate states. This information can help clinicians provide their patients with information regarding their additional risk of death within each intermediate disease state compared to thegeneral population. This study complements the current knowledge about the prognosis of advanced melanoma patients after diagnosis with information about the prognosis after the development of a response or progression of the disease after a first-line therapy. In addition, this study can help to increase awareness that older patients have a substantial risk of population mortality, especially those who respond well to the treatment of advanced melanoma.

The landmark analysis shows that population mortality in advanced melanoma patients ≥80 years with a CR is larger than excess mortality. This is in line with our expectations that the relative importance of population mortality increases after patients survived the first period after diagnosis, and if they have a response. In patients aged 65–74 years with a CR, excess mortality is even negative. Although this seems difficult to interpret, it does have a meaning: mortality for this subgroup is smaller than that of the matched general population (excess mortality is defined as all mortality minus population mortality). This is remarkable, and may be caused by a selection of very fit patients in the 70–74

Table 4
Probabilities of melanoma mortality and population mortality (in %) at 5 years after the time of diagnosis with advanced melanoma alive at the 1-year landmark in different states, according to the state from where the patients died (diagnosis, stable disease, partial response, complete response and progression), stratified by age group. 'Overall' indicates the sum of mortality from the diagnosis, stable disease, partial response, complete response and progression states (all mortality). Since total and population hazard must always be positive, their difference (excess hazard) can under rare circumstances be negative, leading to negative probabilities. For states we refer to Fig. 1. Abbreviations: CI = confidence interval, SD = stable disease, PR = partial response, CR = complete response.

State To →	Stable disease		Partial response		Complete response		Progression		Overall	
	Population mortality % (95% CI)	Melanoma mortality % (95% CI)	Population mortality % (95% CI)	Melanoma mortality % (95% CI)	Population mortality % (95% CI)	Melanoma mortality % (95% CI)	Population mortality % (95% CI)	Melanoma mortality % (95% CI)	Population mortality % (95% CI)	Melanoma mortality % (95% CI)
From↓										
SD (N = 318)										
<65 years (N = 127)	1.7 (1.4–2)	5.2 (4.7–5.8)	0.2 (0.1–0.4)	0.4 (0.4–0.5)	0.3 (0.2–0.5)	0.1 (0.0–0.2)	1.0 (1.0–1.0)	29.3 (23.6–35.0)	3.3 (3.2–3.4)	35.1 (29.5–40.6)
65–74 years (N = 101)	6.1 (3.8–8.5)	−0.8 (0.0–0.1)	0.6 (0.0–1.8)	−0.2 (0.0–0.7)	1.1 (0.6–1.6)	−0.8 (0.0–0.2)	4.4 (4.0–4.7)	39.5 (37.4–41.6)	12.2 (12.1–12.3)	37.6 (28.1–47.2)
75–79 years (N = 50)	10.5 (6.7–14.3)	5.0 (0.0–13.2)	1.6 (0.0–3.3)	−0.1 (0.0–0.3)	3.0 (0.0–6.8)	−2.4 (0.0–1.5)	8.4 (3.7–13.1)	37.5 (23.5–51.4)	23.5 (21.7–25.4)	39.9 (25.4–54.5)
≥80 years (N = 40)	17.2 (12.7–21.6)	30.5 (25.6–35.4)	1.4 (0.0–3.1)	−0.1 (0.0–2.4)	2.8 (1.4–4.2)	2.0 (1.7–2.3)	7.7 (4.1–11.3)	18.9 (12.3–25.5)	29.1 (25.1–33.1)	51.3 (49.9–52.6)
PR (N = 881)										
<65 years (N = 475)	–	–	1.6 (1.4–1.8)	3.4 (2.8–4.0)	0.7 (0.6–0.9)	0.3 (0.1–0.5)	0.8 (0.7–0.8)	22.0 (19.5–24.4)	3.1 (2.9–3.4)	25.7 (24.7–26.6)
65–74 years (N = 231)	–	–	6.9 (4.8–8.9)	−1.2 (0.0–3.0)	3.0 (1.9–4.2)	−2.0 (0.0–0.3)	3.3 (3.3–3.3)	27.1 (25.3–28.9)	13.2 (12.3–14.1)	23.9 (23.2–24.5)
75–79 years (N = 93)	–	–	16.3 (10.4–22.1)	1.8 (0.0–4.9)	5.0 (2.3–7.6)	−4.0 (0.0–0.4)	5.0 (4.3–5.8)	22.2 (16.0–28.5)	26.3 (21.7–30.8)	20.0 (0.0–61.7)
≥80 years (N = 82)	–	–	23.6 (21.9–25.3)	−6.5 (0.0–23.4)	8.0 (2–13.9)	4.9 (0–22.1)	9.0 (3.2–14.9)	23.0 (14.8–31.3)	40.6 (39.2–42.1)	21.4 (4.6–38.2)
CR (N = 346)										
<65 years (N = 172)	–	–	–	–	2.8 (2.1–3.5)	1.3 (0.0–3.1)	0.6 (0.4–0.7)	15.9 (9.2–22.7)	3.3 (3.2–3.5)	17.2 (13.0–21.4)
65–74 years (N = 107)	–	–	–	–	12.9 (12.3–13.5)	−9.3 (0.0–3.3)	2.2 (1.8–2.7)	17.5 (13.3–21.6)	15.1 (14.9–15.3)	8.2 (7.5–8.8)
75–79 years (N = 37)	–	–	–	–	24.4 (20.3–28.5)	−17.3 (0.0–2.1)	3.9 (2.7–5.2)	17.6 (16.9–18.4)	28.4 (26.1–30.6)	0.4 (0.0–5.7)
≥80 years (N = 30)	–	–	–	–	33.9 (31.7–36.1)	12.5 (2.8–22.3)	8.0 (1.2–14.8)	16.2 (0.2–32.2)	41.9 (26.3–57.5)	28.7 (24.3–33.1)
Progression (N = 1122)										
<65 years (N = 622)	–	–	–	–	–	–	1.8 (1.7–1.9)	70.9 (65.6–76.3)	1.8 (1.5–2.0)	70.9 (66.3–75.6)
65–74 years (N = 341)	–	–	–	–	–	–	6.4 (5.2–7.6)	75.2 (70.4–79.9)	6.4 (6.2–6.6)	75.2 (68.0–82.3)
75–79 years (N = 88)	–	–	–	–	–	–	11.3 (6.5–16.1)	75.7 (53.3–98.1)	11.3 (10.7–11.9)	75.7 (66.4–84.9)
≥80 years (N = 71)	–	–	–	–	–	–	11.4 (7.0–15.9)	83.4 (68.3–98.5)	11.4 (8.8–14.1)	83.4 (75.4–91.5)

Table 5
Probabilities (in %) to be alive in one of the intermediate states (diagnosis, stable disease, partial response and complete response) after the time of diagnosis with advanced melanoma alive at the 1-year landmark in different states, stratified by age group. For states, we refer to Fig. 1. Abbreviations: CI = confidence interval, SD = stable disease, PR = partial response, CR = complete response.

State	To →	Diagnosis % (95% CI)	SD % (95% CI)	PR % (95% CI)	CR % (95% CI)	Death after diagnosis % (95% CI)
From↓						
Diagnosis (N=)						
<65 years (N = 127)		28.1 (2.6–53.7)	0.0 (0.0–0.0)	3.1 (0.0–8.9)	7.5 (0.0–15.7)	1.1 (0.0–2.3)
65–74 years (N = 101)		0.0 (0.0–0.0)	4.7 (4.6–4.8)	0.5 (0.0–1.8)	9.7 (7.4–12.1)	2.0 (0.8–3.1)
75–79 years (N = 50)		0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	5.7 (0.0–32.6)	4.5 (2.1–7.0)
≥80 years (N = 40)		34.3 (8.0–60.6)	0.0 (0.0–0.0)	1.1 (0.0–2.7)	0.3 (0.0–1.8)	26.7 (7.7–45.6)
SD (N = 318)						
<65 years (N = 127)		–	19.1 (18.2–20.1)	4.1 (3.6–4.6)	12.3 (12.1–12.4)	–
65–74 years (N = 101)		–	13.9 (8.2–19.6)	2.0 (0.0–4.5)	13.2 (0.0–27.2)	–
75–79 years (N = 50)		–	5.6 (0.0–24.4)	3.2 (0.6–5.9)	8.0 (3.4–12.6)	–
≥80 years (N = 40)		–	0.0 (0.0–0.0)	1.5 (1.2–1.7)	1.6 (0.0–3.8)	–
PR (N = 881)						
<65 years (N = 475)		–	–	22.3 (18.6–25.9)	26.2 (22.0–30.4)	–
65–74 years (N = 231)		–	–	14.3 (7.7–21.0)	28.8 (28.7–28.8)	–
75–79 years (N = 93)		–	–	24.5 (14.4–34.6)	13.8 (10.2–17.4)	–
≥80 years (N = 82)		–	–	16.2 (0.0–41.1)	4.1 (2.2–6.0)	–
CR (N = 346)						
<65 years (N = 172)		–	–	–	62.7 (59.0–66.5)	–
65–74 years (N = 107)		–	–	–	62.1 (53.6–70.6)	–
75–79 years (N = 37)		–	–	–	55.7 (43.0–68.4)	–
≥80 years (N = 30)		–	–	–	11.6 (10.8–12.5)	–

years CR group compared to the general population, or that those patients reaching a CR are fitter compared to those who progress. Other explanations might be that patients have lived healthier after diagnosis with advanced melanoma, with better outcomes than the general population as a result.

Previous studies of Jochems *et al.* [22] and de Glas *et al.* [23] studied outcomes of systemic therapy in older patients with metastatic melanoma. The study of Jochems *et al.* used a registered variable for cause of death, and found borderline significance in 3-year melanoma-specific mortality between patients aged ≤60 years and ≥75 years. Our study confirms their results in a comparable DMTR cohort, using a different method. Two-year melanoma-specific mortality was higher for patients aged ≥80 years compared to patients aged <65 years (61.1% versus 53.2%) but this difference disappeared at 5-year (67.6% versus 66.4%) (Table 2). An advantage of the current study is that it does not depend on a registered variable, which in the literature has shown to cause some problems as the exact cause of death is often hard to assess [24]. A downside of the relative survival method is that we can only estimate melanoma mortality and population mortality on a cohort basis, without being able to assess whether an individual has died due to melanoma mortality or population mortality.

Our aim was to interpret melanoma non-progression mortality as treatment-related mortality, as has been previously done in a study in myelodysplastic syndromes/secondary acute myeloid leukaemia patients after allogeneic haematopoietic stem cell transplantation [25]. However, as a progression was not always registered correctly and mortality due to melanoma also took place without a registered progression, we could not assess treatment-related mortality as a separate outcome. In the current study, melanoma mortality is defined as disease- and treatment-related mortality in advanced melanoma. Since a systemic treatment of advanced melanoma consists mostly of immunotherapy and targeted therapy, and mortality due to toxicity of a systemic treatment is very rare in advanced melanoma (<1%) [26,27], almost all of this must be disease related. Compared to other studies in cancer using relative survival, excess mortality is relatively large. This may be caused by the inclusion of advanced melanoma patients only. Other studies on cancer included patients of lower stages of the disease as well.

There are limitations to our study. This study used observational data from patients diagnosed between 2013 and 2019 and registered in the DMTR. This is a relatively short follow-up period to estimate relative survival. The relative contribution of population mortality increases when we look at a time-period of 10 years as the risk for population mortality becomes increasingly more relevant for an older population. Firstly, similar analyses should be repeated when 10-year follow-up data are available to focus on excess mortality over a longer follow-up period. Secondly, in order to use population mortality tables, it has to be assumed that population mortality risk in our study population is equal to mortality risk in the general population. This assumption cannot be fully checked. The risk

of melanoma is partly determined by genetic factors and overexposure to UVradiation from the sun, which might be associated with socio-economic status and, thus, health status. However, risk-factors predisposing for poor health such as body mass indexand smoking behaviour do not play a role in this context. A very small minority of advanced melanoma patients has not been registered in the DMTR due to their poor disease status. Altogether, the nationwide coverage of the registry and the fact that it is disease-based and not treatment-based make the assumption of equal mortality risk plausible. Thirdly, patients aged 65–74 and 75–79 years with a CR had better life expectancy than the general population. In these subgroups, population mortality was larger than the observed mortality causing the probability for melanoma mortality to be negative. In these instances, the relative survival assumption was violated. It seems that the groups having reached a CR were more fit than the general population. Fourthly, risk factors associated with survival differ between different age groups, but were not analysed in our models. We argue that the effect of age is strong, even after correcting for risk factors. This has been shown in a previous study by Jochems *et al.* [22], where the difference in unadjusted and adjusted hazard ratio of age for death was small. Possibly, this is caused by the mix of risk factors: in our study, older patients have significantly worse ECOG PS but significantly less brain metastases and lower disease stage and less organ sites with metastases (Supplement 4). Future studies could extend the model to include response to second-line treatment or study the subgroups of patients reaching a CR through SD or PR. Our current study did not include enough patients to answer these questions. In our study, we found a relatively large number of patients (especially among older patients) who died directly from the diagnosis state, i.e. without a registered response or progression. Several reasons contribute to reaching this state, which have not been disentangled here in order to not complicate the analysis further: patients had not started systemic therapy; they died before a response assessment was performed, or switched to second-line treatment without a response assessment after first-line treatment.

5. Conclusions

In conclusion, this study shows that the majority of the 5-year mortality is caused by melanoma-related mortality. We observe an increase in the 5-year probability of mortality with increasing age, but this is primarily caused by the increase in population mortality. Population mortality only plays a substantial role in patients older than 74 years, who achieved a PR or CR in the first year after diagnosis and who were still alive at the 1-year landmark. Even though survival outcomes of advanced melanoma patients have improved over the last decade, their mortality is still much increased compared to the general population due to the melanoma.

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

AvdE has advisory relationships with Amgen, Bristol Myers Squibb, Roche, Novartis, MSD, Pierre Fabre, Sanofi, Pfizer, Ipsen and Merck; and has received research study grants not related to this paper from Sanofi, Roche, Bristol Myers Squibb, Idera and TEVA; and has received travel expenses from MSD Oncology, Roche, Pfizer and Sanofi; and has received speaker honoraria from BMS and Novartis.

MBS has consultancy/advisory relationships with Pierre Fabre, MSD and Novartis.

JdG has consultancy/advisory relationships with Bristol Myers Squibb, Pierre Fabre, Servier, MSD and Novartis.

GH has consultancy/advisory relationships with Amgen, Bristol Myers Squibb, Roche, MSD, Pfizer, Novartis and Pierre Fabre; and has received research grants not related to this paper from Bristol Myers Squibb and Seerave, and were paid to the institution.

EK has consultancy/advisory relationships with Bristol Myers Squibb, Novartis, Merck and and Pierre Fabre; and received research grants not related to this paper from Bristol Myers Squibb.

KS has advisory relationships with Bristol Myers Squibb, Novartis, MSD, Pierre Fabre and Abbvie; and received honoraria from Novartis, MSD and Roche.

AvdV has consultancy relationships with Bristol Myers Squibb, MSD, Roche, Novartis, Pierre Fabre, Pfizer, Sanofi, Ipsen, Eisai and Merck.

CUB has received commercial research grants from Novartis, BristolMyers Squibb and NanoString; is a paid advisory board member for Bristol Myers Squibb, MSD, Roche, Novartis, GlaxoSmithKline, AstraZeneca, Pfizer, Lilly, GenMab and Pierre Fabre; and holds ownership interest in Uniti Cars, Neon Therapeutics and Forty Seven.

JH has advisory relationships with, Achilles Therapeutics, Bristol Myers Squibb BioNTech, Immunocore, Ipsen, Instil Bio, Iovance Bio, MSD, Merck Serono, Molecular Partners, Novartis, Neogene Therapeutics, Pfizer, Roche/Genentech, Sanofi and T-Knife; and has received research grants not related to this paper from Asher Bio, Amgen, Bristol Myers Squibb, MSD, BioNTech, Neogene Therapeutics and Novartis.

MA has advisory board/consultancy honoraria from Amgen, Bristol Myers Squibb, Novartis, MSD-Merck, Merck-Pfizer, Pierre Fabre, Sanofi, Astellas and Bayer. Research grants from Merck-Pfizer, not related to current work and paid to institute.

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Author contributions

Conceptualisation: JvB, LdW, MW, AvdE, JH, DH, CB, MA, FvdB, JdG, GH, EK, DP, RvR, KS, AS, AvdV, MBS, GV and DM; Formal analysis: JvB, LdW, MW, AvdE and JH; Methodology: JvB, LdW, MW, AvdE, DH and DM; Resources: MW, AvdE, JH, MA, FvdB, JdG, GH, EK, DP, RvR, KS, AtT, AvdV, MBS and GV; Investigation: JvB, LdW, MW, AvdE, JH, DH, MA, FvdB, JdG, GH, EK, DP, RvR, KS, AtT, AvdV, MBS, GV and DM; Writing—original draft: JvB, LdW, MW, AvdE, JH and DH; Writing—review and editing: JvB, LdW, MW, AvdE, JH, DH, MA, FvdB, JdG, GH, EK, DP, RvR, KS, AtT, AvdV, MBS, GV and DM.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ejca.2023.01.006.

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