End-of-life use of systemic therapy in patients with advanced melanoma: a nationwide cohort study

Breeschoten, J. van; Ismail, R.K.; Wouters, M.W.J.M.; Hilarius, D.L.; Wreede, L.C. de; Haanen, J.B.; ... ; Eertwegh, A.J.M. van den

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original contributions

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Jesper van Breeschoten, PharmD[1,2]; Rawa K. Ismail, PharmD[1,3]; Michel W.J.M. Wouters, MD, PhD[1,4,5]; Doranne L. Hilarius, PharmD, PhD[6]; Liesbeth C. de Wreede, PhD[5]; John B. Haanen, MD, PhD[7,8,9]; Christian U. Blank, MD, PhD[7,8]; Maureen J.B. Aarts, MD, PhD[10]; Franchette W.P.J. van den Berkmortel, MD, PhD[11]; Jan Willem B. de Groot, MD, PhD[12]; Geke A.P. Hospers, MD, PhD[13]; Ellen Kapiteijn, MD, PhD[9]; Djura Piersma, MD, PhD[14]; Rozemarijn S. van Rijn, MD, PhD[15]; Marion A. Stevense-den Boer, MD, PhD[16]; Astrid A.M. van der Veldt, MD, PhD[17]; Gerard Vreugdenhil, MD, PhD[18]; Marye J. Boers-Sonderen, MD, PhD[19]; Karijn P.M. Suijkerbuijk, MD, PhD[20]; and Alfons J.M. van den Eertwegh, MD, PhD[2]

QUESTION ASKED: What percentage of Dutch patients with advanced melanoma start a new systemic therapy within 45 and 90 days of death and does this percentage differ between melanoma centers?

SUMMARY ANSWER: A total of 503 (13.2%) patients with advanced melanoma, who died between 2013 and 2019, received a new systemic therapy ≤ 45 days before death and 29% of all patients started a new systemic therapy within the last 90 days before death (N = 1,120). The percentage of patients receiving a new systemic therapy within 45 and 90 days before death was significantly different between Dutch melanoma centers.

WHAT WE DID: We selected all patients diagnosed with unresectable stage IIIc or IV melanoma that were registered in the Dutch Melanoma Treatment Registry who died between 2013 and 2019. Retrospectively, we investigated what percentage of patients received a new systemic therapy in the last 45 and 90 days before death. Practice variation between centers was assessed using funnel plots using with 95% and 99% confidence limits. We also investigated the type of systemic therapies started, adverse events (AEs) in the last phase of life, and costs associated with these systemic therapies.

WHAT WE FOUND: In the Netherlands, a minority of Dutch patients with advanced melanoma started a new systemic therapy in the last phase of life. However, the percentages varied between Dutch melanoma centers.

BIAS AND CONFOUNDING FACTORS: The current treatment landscape is different from 2013 to 2014 when anti–programmed cell death protein-1 and BRAF/MEK inhibitors were not available. Secondary, this study does not provide insights on which patients are unlikely to benefit from starting a new systemic therapy as we retrospectively selected patients who died.

REAL-LIFE IMPLICATIONS: The results of this study are important for both clinicians and patients. Clinicians might be unaware of the percentage of patients they are treating in the last phase of life with a new systemic therapy and how this percentage compares with other centers. To better understand the rationale of starting a new systemic therapies, comparisons between individual centers should take place. For patients, it is important to know that severe AEs in the last phase of life seem rare. If the patient understands that treatment may have a positive effect on the course of disease, and agrees with the risk of potentially severe AEs, there is no reason to not start a new systemic therapy.

CORRESPONDING AUTHOR
Jesper van Breeschoten, PharmD, Rijnsburgerweg 10, 2333AA Leiden, the Netherlands; e-mail: j.vanbreeschoten@dica.nl.

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abstract

PURPOSE The introduction of immune checkpoint inhibitors and targeted therapies improved the overall survival of patients with advanced melanoma. It is not known how often these costly treatments with potential serious side effects are ineffectively applied in the last phase of life. This study aimed to investigate the start of a new systemic therapy within 45 and 90 days of death in Dutch patients with advanced melanoma.

METHODS We selected patients who were diagnosed with unresectable IIIC or stage IV melanoma, registered in the Dutch Melanoma Treatment Registry, and died between 2013 and 2019. Primary outcome was the probability of starting a new systemic therapy 45 and 90 days before death. Secondary outcomes were type of systemic therapy started, grade 3/4 adverse events (AEs), and the total costs of systemic therapies.

RESULTS Between 2013 and 2019, 3,797 patients with unresectable IIIC or stage IV melanoma were entered in the registry and died. The percentage of patients receiving a new systemic therapy within 45 and 90 days before death was significantly different between Dutch melanoma centers (varying from 6% to 23% and 20% to 46%, respectively). Thirteen percent of patients (n = 146) developed grade 3/4 AEs in the last period before death. The majority of patients with an AE required hospital admission (n = 102, 69.6%). Mean total costs of systemic therapy per cohort year of the patients who received a new systemic therapy within 90 days before death were 2.3%-2.8% of the total costs spent on melanoma therapies.

CONCLUSION The minority of Dutch patients with metastatic melanoma started a new systemic therapy in the last phase of life. However, the percentages varied between Dutch melanoma centers. Financial impact of these therapies in the last phase of life is relatively small.

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INTRODUCTION

Clinical outcomes of patients with advanced melanoma have improved in recent years because of the introduction of new systemic therapies such as anti–programmed cell death protein-1 (PD-1) antibodies,[1,2] BRAF/MEK inhibitors,[3,4] anti–cytotoxic T-cell lymphocyte-4 inhibitors (ipilimumab),[5] and combination therapy of ipilimumab plus nivolumab.[6] However, a large proportion of these patients still do not achieve long-term remission and disease control. In addition, severe adverse events (AEs) caused by these systemic therapies are common.

Grade 3/4 AEs occur in ±10% of patients receiving monotherapy anti–PD-1 antibodies,[1,2] ±30% of patients receiving ipilimumab,[2,5] ±60% in patients receiving combination therapy of ipilimumab plus nivolumab,[6] and 48%-50% of patients receiving BRAF/MEK inhibitors.[3,4] Not only are these AEs common, but they can also influence the quality of life of patients.[7] Quality of life is especially important at the end of life where newly initiated therapies should ideally not cause any harm. The randomized clinical trials investigating these new therapies for advanced melanoma have measured quality of life as part of the marketing authorization process. However, these trials included relatively healthy patients,[8] leading to a gap in knowledge in using these systemic therapies at the end of life. Another downside of these systemic therapies is the financial burden for the health care system. The costs of the systemic therapies are high, and the initiation of a new treatment at the end of life with uncertainty about the effect should be well considered.

Clinicians treating patients with advanced melanoma deal with a complex disease with uncertainty about the

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prognosis, progression, side effects, and possible outcomes.[9,10] Treatment with BRAF/MEK inhibitors can provide patients with symptom relief in the last phase beyond progression as palliative therapy. A recent study shows that the use of systemic therapies in the last 30 days of life declined compared with the period before introduction of immune checkpoint inhibitors.[11] Little is known on the use of systemic therapies at the end of life in patients with advanced melanoma in specific patient subgroups. Retrospective evaluation of its effect might minimize unnecessary exposure to possible AEs and overtreatment at the end of life; this is important, also with high costs of therapy in mind. This study aimed to describe (1) the use of systemic therapies at the end of life of Dutch patients with advanced melanoma, (2) grade 3/4 AEs in the last phase of life, and (3) assess the costs of patients treated in the last phase of life.

METHODS

Patients

The study population consisted of patients with unresectable stage IIIc or stage IV melanoma (≥ 18 years) treated with systemic therapy who died between 2013 and 2019 (data set cutoff date was December 5, 2020). Only patients with a known date of death were included. Patients participating in clinical trials were also included.

Data Sources

This study used data from the Dutch Melanoma Treatment Registry (DMTR). Since July 1, 2013, all patients with unresectable stage IIIC or stage IV melanoma seen in one of the 14 melanoma centers have been registered in the DMTR. Trained data managers follow patients every 3 months during the first year and register changes in disease status, patients' characteristics, or treatment characteristics. In the following years, if a patient is clinically stable, follow-up is performed every 6 months. In case of progression, follow-up is performed every 4 months. A detailed description of the DMTR setup has been published by Jochems et al. [12] In compliance with Dutch regulations, the DMTR was approved by a medical ethical committee (METC Leiden University Medical Center, 2013) and is not considered subject to the Medical Research Involving Human Subjects Act.

Primary and Secondary Outcomes

The primary outcome was the probability of starting a new systemic therapy within 45 and 90 days before the date of death. If patients started multiple systemic therapies, we selected the most recent systemic therapy and corresponding patient and tumor characteristics. Systemic therapies included anti–PD-1, BRAF/MEK inhibitors, ipilimumab, combination therapy of ipilimumab plus nivolumab, or chemotherapy as monotherapy. Secondary outcomes were ≥grade 3 AEs according to Common Terminology Criteria for Adverse Events in the last 45 and 90 days before death, the number of treatment lines before last therapy, the number of individual doses given before death, and how frequently reintroduction of a previously used systemic therapy occurred. The number of doses is only registered for ipilimumab, anti–PD-1 antibodies, and combination therapy of ipilimumab plus nivolumab. We estimated the total number of days under treatment with BRAF/MEK inhibitors using the registered start and stop date. Unit costs were used to calculate total costs and total costs per patient. To estimate costs of dabrafenib plus trametinib, a schedule of dabrafenib twice daily plus trametinib once daily was used. For vemurafenib plus cobimetinib, a schedule of vemurafenib twice daily plus cobimetinib once daily was used with a break of seven days for cobimetinib after 21 days. For encorafenib plus binimetinib, a schedule of encorafenib once daily plus binimetinib twice daily was used. Costs of patients with dose reductions of BRAF/MEK inhibitors were adjusted on the basis of the date of the reduction and the dosage given after reduction. The costs represented in this study may not reflect actual costs as confidential financial agreements are made between the melanoma center and the pharmaceutical company and agreements between the pharmaceutical companies and the Ministry of Health.

Statistical Analysis

Baseline patient and disease characteristics of patients during the initiation of their last systemic treatment were analyzed using descriptive statistics. These characteristics included age, sex, lactate dehydrogenase (normal, 250-500 U/L and > 500 U/L), stage (unresectable IIIc, IV-M1a, M1b, and IV-M1c), Eastern Cooperative Oncology Group Performance Score (ECOG PS; 0-1 and ≥ 2), distant metastases (< 3 organ sites and ≥ 3 organ sites involved), liver metastases (yes/no), brain metastases (none, asymptomatic, and symptomatic) and *BRAF* ^{V600} mutation status (wild-type or mutant). Baseline patient and disease characteristics of the centers with the lowest and highest percentages of new systemic therapies were compared.

The percentage of patients started with a new systemic therapy within ≤ 45 and ≤ 90 days before death is presented in funnel plots using 95% and 99% confidence limits that vary with the volume of patients per hospital.[13,14]

Data handling and statistical analyses were performed using the R software system for statistical computing (version 4.0.2.; packages tidyverse,[15] survival,[16] and survminer[17]).

RESULTS

Use of Systemic Therapies at the End of Life

A total of 503 (13.2%) patients with advanced melanoma, who died between 2013 and 2019, received a new systemic therapy ≤ 45 days before death (Fig 1). Twenty-nine percent of all patients started a new systemic therapy within the last 90 days before death (N = 1,120). In total, 78

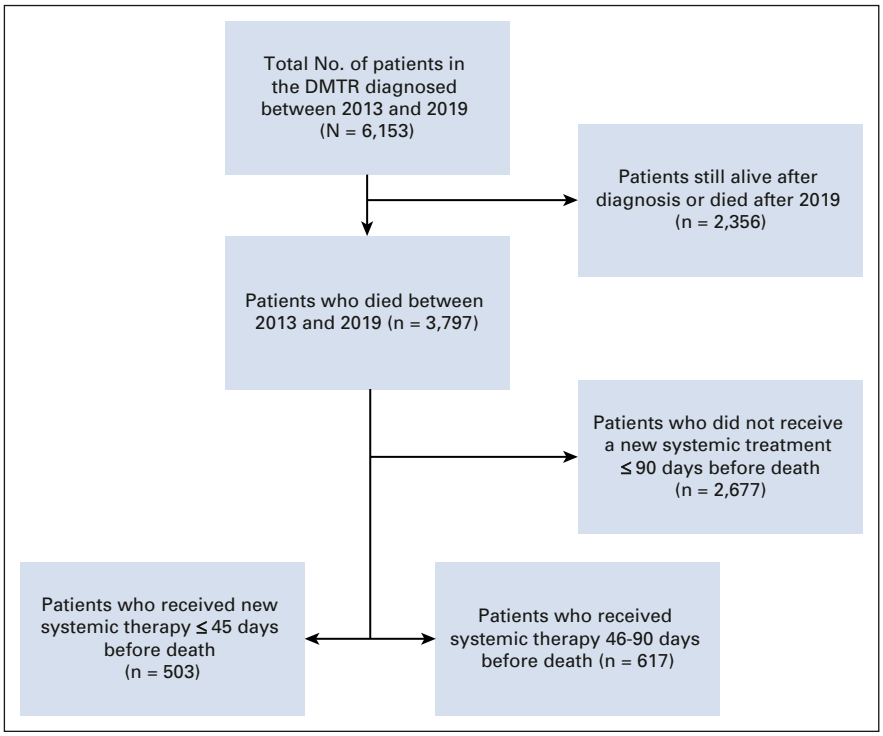

FIG 1. Study flowchart depicting the patients who died between 2013 and 2019 (N = 3,797) included for the analyses. Most analyses were on the basis of patients who received new systemic therapy ≤ 45 days (n = 503) or 46-90 days (n = 617) before death. DMTR, Dutch Melanoma Treatment Registry.

patients started two systemic therapies within 90 days of death. Three patients started three new systemic therapies within 90 days of death. Overall, the percentage of patients treated with a new systemic therapy ≤ 45 and ≤ 90 days before death did not change over the years (Fig 2). Patient and tumor characteristics at the initiation of the last systemic treatment are described in Table 1. Overall, at the start of a new systemic therapy, 30.0% of patients had an ECOG PS ≥ 2, 95.2% had stage IV-M1c disease, and 72.0% had metastases in ≥ 3 organ sites. The main cause of death was melanoma-related in the majority of the patients (73%-82%), independent of whether they started a systemic therapy within 45 or 90 days before death (Table 1).

Variation Between Melanoma Centers

Between the 14 melanoma centers, the percentage of patients for whom new systemic therapies were initiated ≤ 45 and ≤ 90 days before death varied between 6%-23% and 20%-46%, respectively (Fig 3). The funnel plot shows that one center had a significantly higher percentage and two centers had a significantly lower percentage of patients who started with a new systemic therapy within 45 days of death using the 95% CI compared with the mean. Patient and tumor characteristics of patients treated in the three melanoma centers with the highest and lowest percentage of systemic therapy initiation at the end of life are shown in the Data Supplement (online only). Overall, no significant differences in patient and tumor characteristics were observed between the centers with the lowest versus the highest percentage of newly initiated systemic therapies. Centers with the lowest percentage had less patients with symptomatic brain metastases, although this difference was not significant.

Type of Systemic Therapy

The type of systemic therapy initiated ≤ 45 and ≤ 90 days before death is shown in Table 2. In 216 of the 503 (42.9%) patients who died within 45 days, systemic therapy was initiated in the first line. First-line systemic treatment consisted mainly of anti–PD-1 antibodies (20.4%), combination therapy of ipilimumab plus nivolumab (17.1%), BRAF-inhibitor monotherapy (24.5%), and combination therapy of BRAF/MEK inhibitors (13.4%). Second- and third-line systemic therapy was initiated in, respectively, 35.1% and 13.7% of the patients. In 41 patients (8.2%), fourth-line or higher was initiated within 45 days of death. BRAF monotherapy and combination therapy of BRAF/MEK inhibitors were predominantly started in patients with brain metastases (54.1%). In total, 24.1% (n = 121) and 26.8% (n = 300) of patients received radiotherapy within the same episode as their last systemic therapy. Of these 300 patients, 259 (86%) received palliative radiotherapy, 29 patients (10%) received

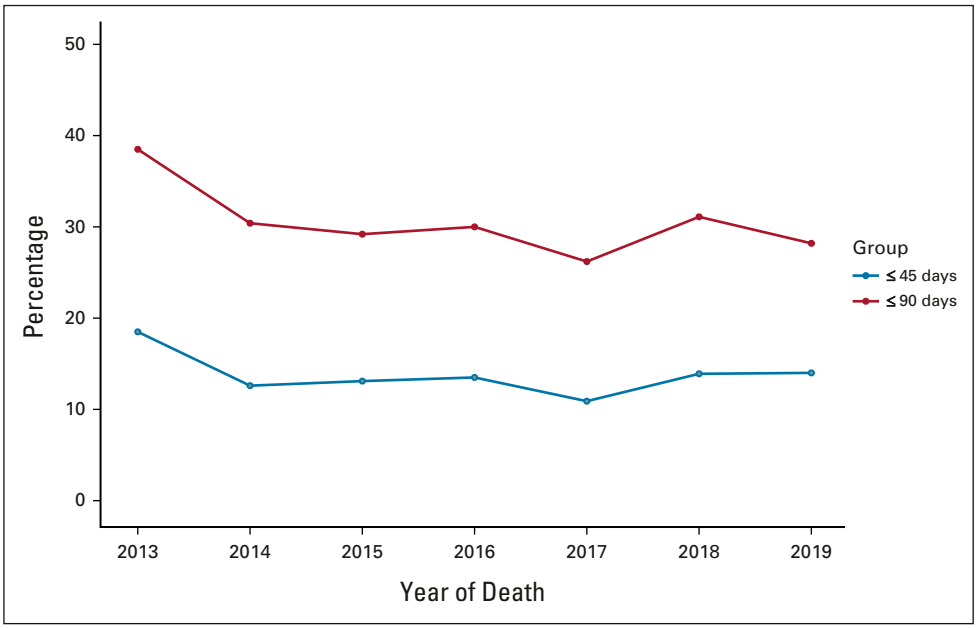

FIG 2. Percentage of patients who started a new systemic therapy ≤ 45 and ≤ 90 days before death from the total number of patients who died over all years of death.

stereotactic radiation, and the remaining 11 (4%) patients received unspecified forms of radiotherapy.

Adverse Events and Reintroduction

Of all patients dying within 90 days after starting a new systemic therapy, 146 (13.0%) patients developed a total of 185 grade 3/4 AEs in this last period before their death. The most common grade 3/4 AEs were skin toxicities, colitis, hepatitis, and endocrine AEs affecting 18 (12.3%), 32 (21.9%), 18 (12.4%), and 20 (13.7%) patients, respectively (Data Supplement). Nineteen patients developed grade 3-5 AEs while receiving anti–PD-1 inhibitors (1.7%), 46 during BRAF inhibitors (4.1%), 29 during ipilimumab (2.6%), and 35 (3.1%) during ipilimumab plus nivolumab. Reintroduction of a systemic therapy used earlier occurred in 37 patients (12.1%). The reason for discontinuing the reintroduced systemic therapy in the earlier treatment line was progression in 20 patients (32.3%), toxicity in 15 patients (24.2%), planned in 13 patients (21.0%), and for other reasons in 24 patients (38.7%). For patients with an AE, hospital admission was necessary for 102 (69.9%) patients, one patient was admitted to the intensive care unit (0.7%), and one death occurred as a result of grade 5 toxicity (0.7%). In total, 9.1% of patients who died within 90 days of starting a new systemic therapy were admitted to the hospital.

Number of Doses and Costs

In total, 614 ipilimumab doses and 732 anti–PD-1 antibody courses were registered in the DMTR in patients who received a new systemic therapy within 90 days of death. Of the patients who started a new systemic therapy within 45 days of death, 207 ipilimumab courses and 222 anti–PD-1 antibody courses were registered. On the basis of list prices, the total costs of the courses in the last 45 and 90 days before death are €3.537.934 and €10.688.871, respectively. On the basis of list prices, the total costs of BRAF/MEK inhibitors are €849.623 and €3.699.462 for the courses administered to patients who received a new systemic therapy within 45 and 90 days of death, respectively. Total costs of immune-checkpoint inhibitors and BRAF/MEK inhibitors combined were €4.387.557 and €14.388.333 for patients who received a new systemic therapy within 45 and 90 days of death, respectively. Mean costs per year were €626.793 and €2.055.476 for all patients starting a new systemic therapy within 45 and 90 days of death, respectively. Mean costs per patient were €8.722 and €12.846, respectively.

DISCUSSION

To our knowledge, this is the first study that evaluates the use of systemic therapies in the end of life of patients with advanced melanoma. Our study of a nationwide cohort of patients with advanced melanoma who died between 2013 and 2019 shows that 503 (13.2%) patients with advanced melanoma started a new systemic treatment within 45 days before death, and 1,120 patients (29.5%) had started a new systemic therapy within 90 days of death. Thirteen percent of patients experienced treatment-related severe AEs during these 90 days. However, a large proportion of patients with a grade 3/4 AE required hospital admission (69.9%). Mean total costs per year of the last treatment lines within 45 and 90 days before death were €626.793 and €2.055.476, respectively. We observed a significant difference in the percentage of new systemic therapies

TABLE 1. Characteristics at the Last Episode of the Patients Who Died Within 45 and 46-90 Days of Death and Patients Who Died But Did Not Start a Systemic Therapy Within 90 Days of Death

Baseline Variable	Started ≤ 45 Days (n = 503)	Started 46-90 Days (n = 617)	Died But Not Started ≤ 90 Days (n = 2,677)
Age, years, median (range)	63 (19-93)	63 (21-90)	67 (20-97)
Sex, No. (%)			
Male	330 (65.6)	360 (58.3)	1,553 (58.0)
Female	173 (34.4)	257 (41.7)	1,123 (42.0)
ECOG performance status, No. (%)			
0-1	254 (50.5)	396 (64.2)	1,674 (62.5)
≥ 2	151 (30.0)	138 (22.4)	524 (19.6)
Unknown	98 (19.5)	83 (13.5)	479 (17.9)
Stage (seventh edition AJCC), No. (%)			
Unresectable IIIc	5 (1.0)	9 (1.5)	88 (3.3)
IV-M1a	6 (1.2)	9 (1.5)	74 (2.8)
IV-M1b	8 (1.6)	17 (2.8)	151 (5.6)
IV-M1c	479 (95.2)	578 (93.7)	2,321 (86.7)
Unknown	5 (1.0)	4 (0.6)	43 (1.6)
LDH, No. (%)			
Normal	162 (32.2)	227 (37.8)	1,287 (52.4)
250-500 U/L	152 (30.2)	201 (33.5)	682 (27.8)
> 500 U/L	177 (35.2)	172 (28.7)	485 (19.8)
Unknown/not determined	12 (2.4)	17 (2.8)	223 (8.3)
Brain metastases, No. (%)			
No	227 (45.1)	328 (53.2)	1,604 (59.9)
Yes, asymptomatic	83 (16.5)	105 (17.0)	318 (11.9)
Yes, symptomatic	170 (33.8)	149 (24.1)	655 (24.5)
Unknown	23 (4.6)	35 (5.7)	100 (3.7)
Liver metastases, No. (%)			
No	234 (46.5)	305 (50.7)	1,567 (59.8)
Yes	257 (51.1)	296 (49.3)	1,054 (40.2)
Unknown	12 (2.4)	16 (2.6)	56 (2.1)
Organ sites, No. (%)			
0-2	141 (28.0)	195 (31.6)	1,225 (45.8)
≥ 3	362 (72.0)	422 (68.4)	1,452 (54.2)
BRAF^{V600}-mutation, No. (%)			
Wild-type	198 (39.4)	263 (42.6)	1,444 (53.9)
Mutant	305 (60.6)	354 (57.4)	1,233 (46.1)

(continued on following page)

started between some of the 14 melanoma centers in the Netherlands.

We observed that the type of systemic therapy initiated ≤ 45 days before death varied between melanoma centers. All types of systemic therapies were started (BRAF monotherapy, BRAF/MEK inhibitors, ipilimumab, anti–PD-1, and combination therapy of ipilimumab plus nivolumab). The majority of systemic therapies were started as first-line treatment (42.9%). Overall, of all patients who died within 90 days of death of starting a systemic therapy, 30% started with BRAF monotherapy or combination therapy of BRAF/MEK inhibitors, which is a relative over-representation as only 60.6% of patients harbor a *BRAF*-mutation and are eligible for BRAF/MEK inhibitors. These therapies can provide patients with major symptom relief or palliation in the last phase of life.

Only a small proportion of the study population that died within 90 days of starting a new systemic therapy developed grade 3/4 AEs (13.0%). This percentage is lower than the randomized clinical trials, where the percentage of patients experiencing grade 3/4 AEs ranged from 20% to 59%.[1-6] The real-world patients included in this study were older, with a higher ECOG PS, and with more brain metastases compared with these randomized clinical trials. However, in the Checkmate-67, the median time until onset of these AEs ranged from 3.7 to 12.2 months.[6] The selected patients in this study received a maximum of 1.5 months of systemic therapy. A possible explanation for the low percentage of AEs is that the included patients could not develop toxicity in the short time they received systemic therapy. Previous research has shown that the percentage of real-world patients experiencing grade 3/4 AEs in the DMTR is similar to randomized clinical trials,[18] and more advanced disease is associated with a lower risk of grade 3/4 AEs.[19]

Although starting systemic therapy in the last phase of life can be meaningful, it is important to have insight into its financial impact. It is estimated that the mean total costs of Dutch patients with advanced melanoma measured from diagnosis are €89.240.[20] The current study estimates that mean total costs per cohort year in 2013-2019 for patients who died within 90 days of starting a new systemic therapy were €2.055.476. A previous study has shown that the total budget impact per cohort year of patients with advanced melanoma ranged between 73 and 90 million Euros.[21] This budget impact may increase with emerging treatments for melanoma such as LAG-3,[22] tumor-infiltrating lymphocytes, [23] and tebentafusp.[24] The costs of new systemic therapies in the last 45/90 days before death are a relatively small proportion (2.3%-2.8%). Patients starting a new systemic therapy only receive a small amount of courses, which could explain the small proportion of total costs. Starting a new systemic therapy should still be considered with caution in patients with poor condition who have doubts about starting a new systemic therapy. However, costs could be limited when patients die early after the onset of treatment. Unfortunately, no model

TABLE 1. Characteristics at the Last Episode of the Patients Who Died Within 45 and 46-90 Days of Death and Patients Who Died But Did Not Start a Systemic Therapy Within 90 Days of Death (continued)

Baseline Variable	Started ≤ 45 Days (n = 503)	Started 46-90 Days (n = 617)	Died But Not Started ≤ 90 Days (n = 2,677)
Cause of death, No. (%)			
Melanoma-related	414 (82.3)	498 (80.7)	1,952 (72.)
Toxicity because of treatment	7 (1.4)	8 (1.3)	6 (0.2)
Comorbidity	9 (1.8)	4 (0.6)	31 (1.2)
Other	17 (3.4)	19 (3.1)	65 (2.4)
Unknown	56 (11.1)	88 (14.2)	575 (21.5)

NOTE. In the Dutch Melanoma Treatment Registry, an episode is created when patients start a new systemic therapy.

Abbreviations: AJCC, American Joint Committee on Cancer; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase.

exists to predict individual response to immunotherapy or targeted therapies.

During the total study period, differences exist between melanoma centers in the percentage of patients receiving a new systemic therapy in the Netherlands. This information is important for both clinicians and patients. Clinicians might be unaware of the percentage of patients they are treating in the last phase of life with a new systemic therapy and how this percentage compares to other centers. By providing this information on differences between centers, the variation in the percentage of patients who are treated with systemic therapy in the last phase of life might become smaller. The results of this study have been discussed with the Dutch melanoma centers. To better understand the rationale of starting a new systemic therapies, comparisons between individual centers should take place. The current study did not measure quality of life in patients who received new systemic therapies ≤ 45 days before death. It would be interesting to investigate the quality of life in these patients, especially those who receive systemic therapy for symptom relief. In the current population, severe AEs in the last phase of life seem rare. If the patient understands that treatment may have a positive effect on the course of disease, and agrees with the risk of potentially severe AEs, there is no reason to not start a new systemic therapy.

This study has several limitations. First, we had to estimate the costs of BRAF/MEK inhibitors on the basis of the start and stop data. We argue that the estimated total and mean costs are a near-approximation of the true costs of the studied population. Second, this study only investigated Dutch patients with advanced melanoma. Although

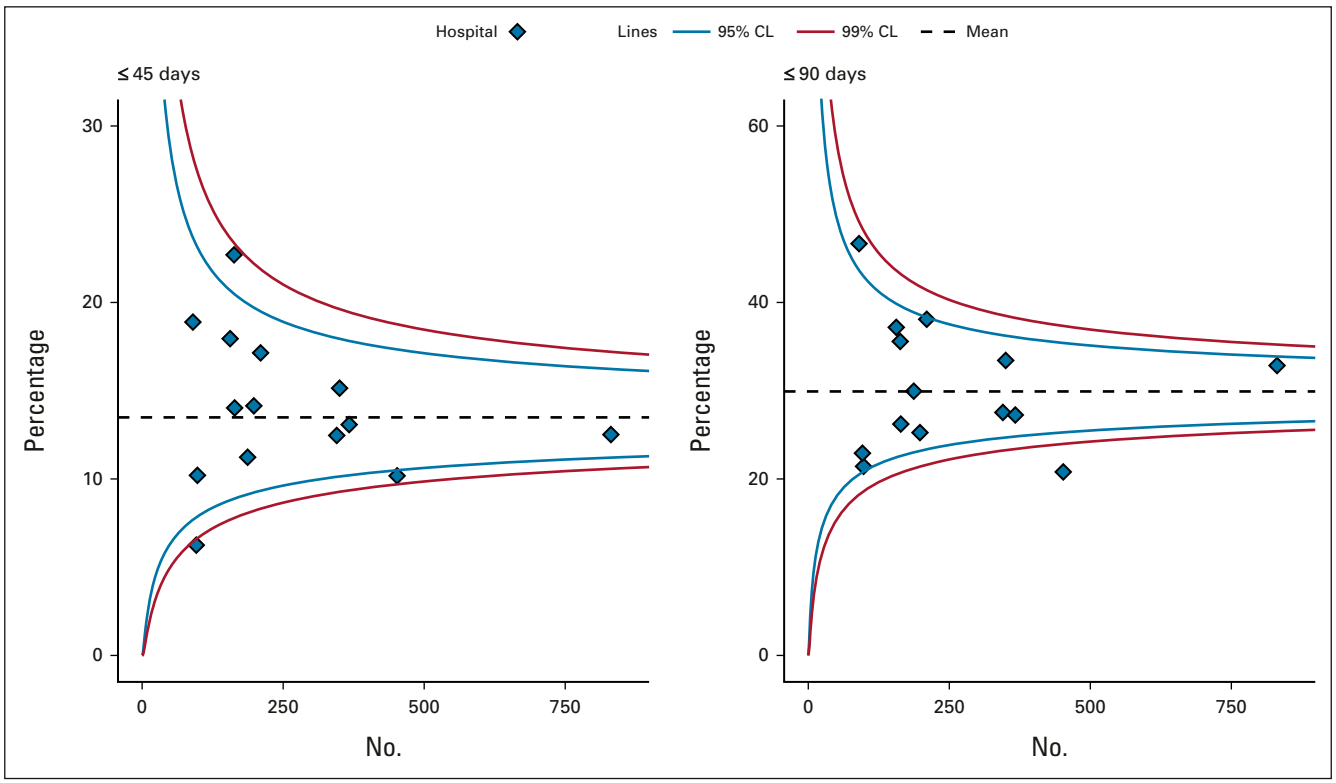

FIG 3. Variation between melanoma centers in the percentage of patients who started a new systemic therapy ≤ 45 (left) and ≤ 90 (right) days before death among all deceased patients. The dotted line represents the average percentage of patients receiving a new systemic therapy ≤ 45 and ≤ 90 days before death. Hospitals falling outside the control limits deviate significantly from the national average. CL, control limit.

TABLE 2. Type of Systemic Therapy Started ≤ 45 (top) and ≤ 90 Days (bottom) Before Date of Death, Stratified for Line of Treatment

Line of Systemic Therapy	First-Line	Second-Line	Third-Line	≥ Fourth-Line	Total
≤ 45 days					
Total No. of patients, %	216 (42.9)	177 (35.2)	69 (13.7)	41 (8.2)	503 (100.0)
Anti–PD-1 antibodies	44 (20.4)	31 (17.5)	6 (8.7)	6 (14.6)	87 (17.3)
BRAF monotherapy	53 (24.5)	15 (8.5)	13 (18.8)	5 (12.2)	86 (17.1)
BRAF/MEK inhibitors	29 (13.4)	17 (9.6)	19 (27.5)	14 (34.1)	80 (15.7)
Chemotherapy	23 (10.6)	8 (4.5)	4 (5.8)	2 (4.9)	37 (7.4)
Ipilimumab	22 (10.2)	43 (24.3)	10 (14.5)	1 (2.4)	76 (15.1)
Ipilimumab plus nivolumab	37 (17.1)	43 (24.3)	7 (10.1)	4 (9.8)	94 (18.1)
Other systemic therapy	7 (3.2)	19 (10.7)	10 (14.5)	9 (22.0)	45 (8.9)
Unknown	1 (0.5)	1 (0.6)	0 (0.0)	0 (0.0)	2 (0.4)
≤ 90 days					
Total No. of patients, %	514 (45.9)	350 (31.3)	166 (14.8)	90 (8.0)	1,120 (100.0)
Anti–PD-1 antibodies	117 (22.8)	71 (20.3)	24 (14.5)	16 (17.8)	228 (20.4)
BRAF monotherapy	122 (23.7)	31 (8.9)	23 (13.9)	10 (11.1)	186 (16.6)
BRAF/MEK inhibitors	60 (11.7)	29 (8.3)	47 (28.3)	31 (34.4)	167 (14.9)
Chemotherapy	51 (9.9)	19 (5.4)	12 (7.2)	5 (5.6)	87 (7.8)
Ipilimumab	67 (13.0)	93 (26.6)	20 (12.0)	3 (3.3)	183 (16.3)
Ipilimumab plus nivolumab	71 (13.8)	72 (20.6)	14 (8.4)	7 (7.8)	164 (14.6)
Other systemic therapy	23 (4.5)	33 (9.4)	26 (15.7)	17 (18.9)	99 (8.8)
Unknown	1 (0.2)	1 (0.3)	0 (0.0)	0 (0.0)	2 (0.2)

NOTE. Only the most recent therapies are shown in this table. Patients who started with BRAF monotherapy who received BRAF/MEK combination therapy in the previous line of treatment were not seen as a start of new therapy.

Abbreviation: PD-1, programmed cell death protein-1.

treatment options for advanced melanoma are comparable across Western countries, it is unknown how our results compare with other countries. Third, we included patients who died between 2013 and 2019. Many of these patients who died between 2013 and 2014 received BRAF monotherapy or ipilimumab monotherapy as a last systemic therapy. This does not represent the current treatment landscape. Fourth, we could not show the characteristics of patients who stopped or did not start systemic therapy > 45 days before death. Only characteristics at the start of systemic therapy are registered in the DMTR. Fifth, only costs of the systemic therapies itself are included in this study. Costs of infusion and other care are not included. Finally, this study does not provide insights on which patients are unlikely to benefit. A previous study of patients with advanced melanoma has shown that patients with elevated lactate dehydrogenase, brain metastases, and a poor ECOG PS had lower OS.[8] Future studies could focus on developing a prediction model for treatment outcomes when starting a systemic therapy in different phases of the disease.

In conclusion, this nationwide study shows the percentage of newly initiated systemic therapies within 45 and 90 days before death. Only a small percentage of these patients experience grade 3/4 AEs, but a large proportion of patients with a grade 3/4 AE had to be admitted to the hospital. The costs of new systemic therapies in the last 45/90 days before death are a relatively small proportion of the total costs of patients with advanced melanoma (2.3%-2.8%). Future studies should be aimed at identifying prognostic factors that predict a short-term poor outcome.

AFFILIATIONS

[1]Dutch Institute for Clinical Auditing, Leiden, the Netherlands
[2]Department of Medical Oncology, Amsterdam UMC, VU University Medical Center, Cancer Center Amsterdam, Amsterdam, the Netherlands
[3]Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht, the Netherlands
[4]Department of Surgical Oncology, Netherlands Cancer Institute, Amsterdam, the Netherlands
[5]Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, the Netherlands
[6]Department of Pharmacy, Rode Kruis Ziekenhuis, Beverwijk, the Netherlands
[7]Department of Medical Oncology and Immunology, Netherlands Cancer Institute, Amsterdam, the Netherlands
[8]Division of Molecular Oncology and Immunology, Netherlands Cancer Institute, Amsterdam, the Netherlands

[9]Department of Medical Oncology, Leiden University Medical Center, Leiden, the Netherlands
[10]Department of Medical Oncology, GROW School for Oncology and Developmental Biology. Maastricht University Medical Center, Maastricht, the Netherlands
[11]Department of Medical Oncology, Zuyderland Medical Center Sittard, Sittard-Geleen, the Netherlands
[12]Isala Oncology Center, Isala, Zwolle, the Netherlands
[13]Department of Medical Oncology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands
[14]Department of Internal Medicine, Medisch Spectrum Twente, Enschede, the Netherlands
[15]Department of Internal Medicine, Medical Center Leeuwarden, Leeuwarden, the Netherlands
[16]Department of Internal Medicine, Amphia Hospital, Breda, the Netherlands
[17]Department of Medical Oncology, Erasmus Medical Center, Rotterdam, the Netherlands
[18]Department of Internal Medicine, Maxima Medical Center, Eindhoven, the Netherlands
[19]Department of Medical Oncology, Radboud University Medical Center, Nijmegen, the Netherlands
[20]Department of Medical Oncology, University Medical Center Utrecht, Utrecht, the Netherlands

CORRESPONDING AUTHOR

Jesper van Breeschoten, PharmD, Rijnsburgerweg 10, 2333AA Leiden, the Netherlands; e-mail: j.vanbreeschoten@dica.nl.

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AUTHOR CONTRIBUTIONS

Conception and design: Jesper van Breeschoten, Rawa K. Ismail, Michel W.J.M. Wouters, Doranne L. Hilarius, Karijn P.M. Suijkerbuijk, Alfons J.M. van den Eertwegh
Administrative support: Doranne L. Hilarius, Rawa K. Ismail, Michel W.J.M. Wouters, Doranne L. Hilarius, Alfons J.M. van den Eertwegh
Provision of study materials or patients: Michel W.J.M. Wouters, John B. Haanen, Christian U. Blank, Franchette W.P.J. van den Berkmortel, Jan Willem B. de Groot, Geke A.P. Hospers, Ellen Kapiteijn, Djura Piersma, Rozemarijn S. van Rijn, Marion A. Stevense-den Boer, Astrid A.M. van der Veldt, Gerard Vreugdenhil, Marye J. Boers-Sonderen, Karijn P.M. Suijkerbuijk, Alfons J.M. van den Eertwegh
Collection and assembly of data: Jesper van Breeschoten, Michel W.J.M. Wouters, John B. Haanen, Christian U. Blank, Franchette W.P.J. van den Berkmortel, Jan Willem B. de Groot, Geke A.P. Hospers, Ellen Kapiteijn, Djura Piersma, Rozemarijn S. van Rijn, Marion A. Stevense-den Boer, Astrid A.M. van der Veldt, Gerard Vreugdenhil, Marye J. Boers-Sonderen, Karijn P.M. Suijkerbuijk, Alfons J.M. van den Eertwegh
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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End-of-Life Use of Systemic Therapy in Patients With Advanced Melanoma: A Nationwide Cohort Study

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Rawa K. Ismail
Employment: MSD

John B. Haanen
Stock and Other Ownership Interests: Neogene Therapeutics
Consulting or Advisory Role: MSD Oncology (Inst), Pfizer (Inst), Bristol Myers Squibb (Inst), Novartis (Inst), Roche/Genentech (Inst), Ipsen (Inst), Achilles Therapeutics (Inst), Immunocore (Inst), Sanofi (Inst), Third Rock Ventures (Inst), Neogene Therapeutics, Molecular Partners (Inst), bioNTech (Inst), T-Knife (Inst), PokeAcell (Inst), Instil Bio (Inst), Iovance Biotherapeutics (Inst)
Research Funding: MSD (Inst), Bristol Myers Squibb (Inst), Novartis (Inst), Neon Therapeutics (Inst), Amgen (Inst), BioNTech (Inst), Asher Biotherapeutics (Inst)

Christian U. Blank
Stock and Other Ownership Interests: Immagene
Consulting or Advisory Role: Roche/Genentech (Inst), MSD Oncology (Inst), Bristol Myers Squibb (Inst), Novartis (Inst), GlaxoSmithKline (Inst), Pfizer (Inst), AstraZeneca (Inst), Lilly (Inst), Pierre Fabre (Inst), GenMab (Inst), Third Rock Ventures
Research Funding: Bristol Myers Squibb (Inst), Novartis (Inst), NanoString Technologies (Inst), 4SC (Inst)
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Travel, Accommodations, Expenses: Bristol Myers Squibb

Maureen J.B. Aarts
Research Funding: Pfizer (Inst)

Jan Willem B. de Groot
Consulting or Advisory Role: Bristol Myers Squibb, Pierre Fabre, Servier

Geke A.P. Hospers
Consulting or Advisory Role: Roche (Inst), MSD (Inst), Amgen (Inst), Bristol Myers Squibb (Inst), Novartis (Inst), Pierre Fabre (Inst), Sanofi (Inst)
Research Funding: Bristol Myers Squibb (Inst), Seerave Foundation (Inst)

Ellen Kapiteijn
Consulting or Advisory Role: Pierre Fabre (Inst), Bristol Myers Squibb (Inst), Novartis (Inst), Lilly (Inst), Ipsen (Inst), Delcath Systems (Inst)
Research Funding: BMS (Inst), Pierre Fabre (Inst)

Djura Piersma
Consulting or Advisory Role: Pierre Fabre (Inst), Novartis (Inst)

Astrid A.M. van der Veldt
Consulting or Advisory Role: Ipsen (Inst), Roche (Inst), Bristol Myers Squibb (Inst), Pfizer (Inst), MSD Oncology (Inst), Sanofi (Inst), Pierre Fabre (Inst), Novartis (Inst), Eisai (Inst), Merck (Inst)
Research Funding: Bayer (Inst)
Travel, Accommodations, Expenses: Roche, MSD Oncology, Novartis, Bayer

Karijn P.M. Suijkerbuijk
Consulting or Advisory Role: Bristol Myers Squibb (Inst), Novartis (Inst), MSD (Inst), Pierre Fabre (Inst), AbbVie (Inst)
Speakers' Bureau: Roche (Inst), Novartis (Inst)
Research Funding: Bristol Myers Squibb Foundation (Inst), TigaTx (Inst), Philips Research (Inst)

Alfonsus J.M. van den Eertwegh
Honoraria: Bristol Myers Squibb
Consulting or Advisory Role: Bristol Myers Squibb, MSD Oncology, Amgen, Roche, Novartis, Sanofi, Pfizer, Ipsen, Merck, Pierre Fabre
Research Funding: Roche, Sanofi, BMS

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