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Original Research

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Abstract ***Background:*** The treatment landscape has completely changed for advanced melanoma. We report survival outcomes and the differential impact of prognostic factors over time in daily clinical practice.
Methods: From a Dutch nationwide population-based registry, patients with advanced melanoma diagnosed from 2013 to 2017 were analysed (n = 3616). Because the proportional hazards assumption was violated, a multivariable Cox model restricted to the first 6 months and a multivariable landmark Cox model from 6 to 48 months were used to assess overall survival (OS) of cases without missing values. The 2017 cohort was excluded from this analysis because of the short follow-up time.
Results: Median OS of the 2013 and 2016 cohort was 11.7 months (95% confidence interval [CI]: 10.4–13.5) and 17.7 months (95% CI: 14.9–19.8), respectively. Compared with the 2013 cohort, the 2016 cohort had superior survival in the Cox model from 0 to 6 months (hazard ratio [HR] = 0.55 [95% CI: 0.43–0.72]) and in the Cox model from 6 to 48 months (HR = 0.68 [95% CI: 0.57–0.83]). Elevated lactate dehydrogenase levels, distant metastases in ≥3 organ sites, brain and liver metastasis and Eastern Cooperative Oncology Group performance score of ≥1 had stronger association with inferior survival from 0 to 6 months than from 6 to 48 months. BRAF-mutated melanoma had superior survival in the first 6 months (HR = 0.50 [95% CI: 0.42–0.59]).
Conclusion(s): Prognosis for advanced melanoma in the Netherlands has improved from 2013 to 2016. Prognostic importance of most evaluated factors was higher in the first 6 months after diagnosis. BRAF-mutated melanoma was only associated with superior survival in the first 6 months.

1. Introduction

Before 2011 dacarbazine was the only approved systemic treatment option for advanced melanoma with a median overall survival of approximately 6–8 months [1,2].

Since 2011 results from pivotal phase III trials investigating immune checkpoint inhibitors and MAP kinase pathway–targeted therapies have completely changed the treatment landscape for metastatic melanoma. Immune checkpoint inhibitors, monoclonal antibodies blocking immune checkpoints CTLA-4 (ipilimumab) or PD-1 (nivolumab or pembrolizumab) expressed by immune cells, reverse the negative regulation of CTLA-4 and PD-1 on the immune response against melanoma. These immune checkpoint inhibitors can be given as single agents (ipilimumab, nivolumab and pembrolizumab) or in combination (ipilimumab plus nivolumab). Targeted therapies inhibit signalling through mutated BRAF V600 and/or its downstream target MEK in the mitogen-activated protein kinase pathway, thereby inhibiting cell proliferation. BRAF inhibitors (dabrafenib or vemurafenib) are mostly administered in combination with MEK inhibitors (trametinib or cobimetinib, respectively, and recently the combination of encorafenib plus binimetinib was approved), but can also be administered as monotherapy. Long-term outcomes from these phase III trials showed a median survival ranging from 17 to 36 months, clearly indicating the enormous progression in the treatment of advanced melanoma patients [3–8].

However, phase III trials handle strict inclusion criteria to estimate treatment effect in a homogeneous population and reported results do not always apply to the real-world patient population. Donia *et al.* [9] (2017) estimated that in Denmark more than 50% of the real-world patient population with advanced melanoma would normally have been excluded from trial participation. Population-based research can provide additional information on the effectiveness of these new systemic therapies in the general patient population.

Since 2013 every patient diagnosed with unresectable stage IIIc or stage IV (advanced) melanoma in the Netherlands is registered in the Dutch Melanoma Treatment Registry (DMTR) [10]. Using this nationwide population-based registry, we studied the overall survival (OS) and treatment patterns in a longitudinal manner and the differential impact of prognostic factors over time.

2. Methods

2.1. Study design and patient population

A cohort study design was used to compare OS by the year of diagnosis of advanced melanoma. Data from the nationwide population-based DMTR, in which all patients who were referred to a melanoma center were followed from diagnosis of advanced melanoma until death, were used. From 1st July 2013, all patients with advanced melanoma could (and can) only receive new systemic treatments in one of 14 designated melanoma treatment centres [10]. We selected patients of ≥18 years diagnosed with advanced melanoma between 1st July 2013 and December 31, 2017 (The data-set cutoff date was 1st June 2019). Patients with mucosal or uveal melanoma were excluded. An initial data analysis was performed in accordance with the conceptual framework described by Huebner *et al.* [11] (see supplement).

2.2. Statistical analysis

Baseline patient and tumour characteristics were analysed by the year of diagnosis with descriptive statistics. The Kaplan–Meier method was used to estimate OS with the corresponding two-sided 95% confidence intervals (CIs). OS was defined as time from diagnosis of unresectable stage IIIc or stage IV melanoma to death from any cause. In subgroup analyses for patients treated with systemic therapy, OS was defined as time from start of systemic therapy to death from any cause. Median follow-up time was estimated with the reverse Kaplan–Meier method [12].

Cox proportional hazards models were fitted to estimate the association between year of diagnosis and OS in a multivariable analysis adjusting for age, sex, baseline Eastern Cooperative Oncology Group performance score (ECOG PS), baseline lactate dehydrogenase (LDH), stage, distant metastases (<3 organ sites or ≥3 organ sites involved), brain metastasis, liver metastasis and BRAF mutational status. The proportional hazards assumption was investigated by means of scaled Schoenfeld residuals. Because the proportional hazards assumption was violated for year of diagnosis and other variables, separate models were fitted. One Cox model was restricted to the first 6 months, and the second Cox model was a landmark model from 6 to 48 months. The time point of 6 months was based on visual inspection of

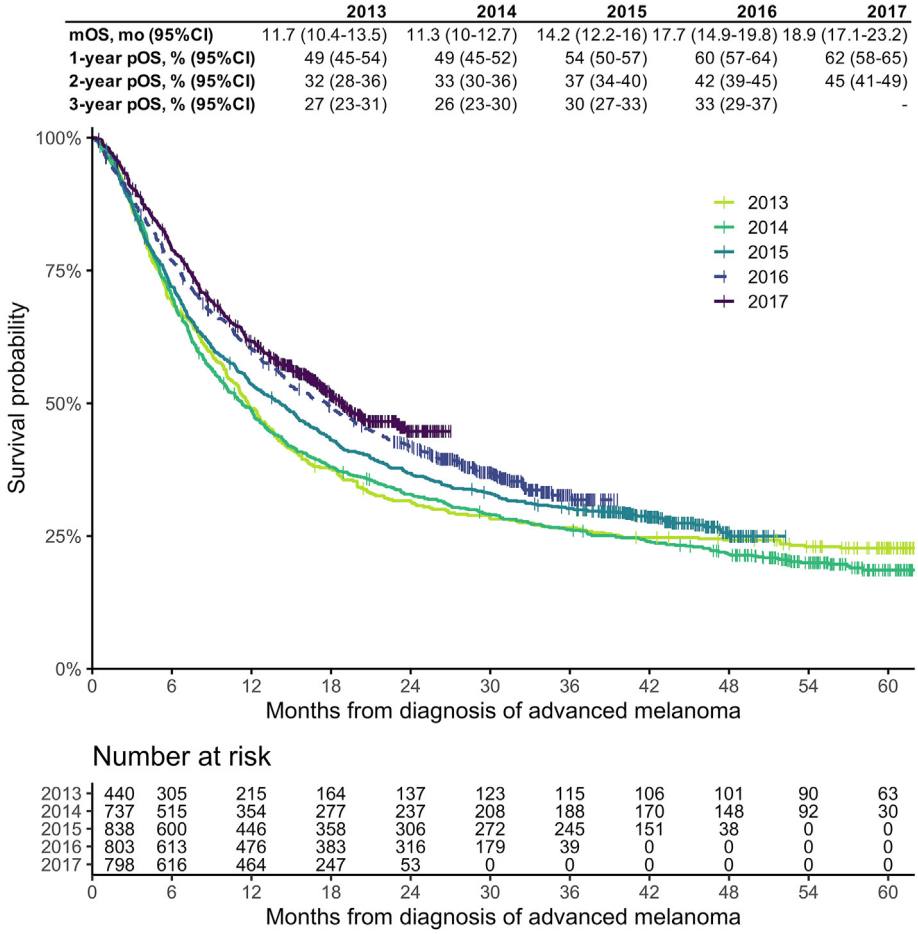

Fig. 1. Kaplan–Meier curves of overall survival of all patients diagnosed with unresectable stage IIIC or stage IV melanoma between 2013 and 2017. Overall survival was estimated from diagnosis of unresectable stage IIIC or stage IV melanoma. OS, overall survival; mOS, median overall survival; pOS, overall survival probability; mo, months; CI, confidence interval; NE, not estimable.

Table 1
Patient characteristics of patients with unresectable stage IIIc or stage IV melanoma. Distribution of categories was based on non-missing data and missing data <2.5% are not shown in this table. The chi-square test was used for categorical variables and one-way ANOVA for numerical variables. Values are *n* (%) unless otherwise indicated.

Year of diagnosis	2013	2014	2015	2016	2017	Total	*P*-value[a]
Patients; *n*	440	737	838	803	798	3616	
Median age, year (range)	61 [50, 70]	65 [55, 73]	64 [53, 72]	65 [55, 73]	66 [55, 73]	64 [54, 73]	<0.001
Age categories							
<50 yr	107 (24.3)	108 (14.7)	144 (17.2)	125 (15.6)	130 (16.3)	614 (17.0)	0.002
50–59 yr	90 (20.5)	157 (21.3)	184 (22.0)	162 (20.2)	159 (19.9)	1257 (34.8)	
60–69 yr	125 (28.4)	216 (29.3)	226 (27.0)	218 (27.1)	208 (26.1)	752 (20.8)	
>70 yr	118 (26.8)	256 (34.7)	284 (33.9)	298 (37.1)	301 (37.7)	993 (27.5)	
Female	202 (46.0)	296 (40.2)	324 (38.7)	325 (40.5)	341 (42.7)	1488 (41.2)	0.103
ECOG PS							
0	223 (56.9)	352 (53.7)	440 (56.8)	362 (49.3)	366 (49.9)	1743 (53.0)	0.083
1	121 (30.9)	210 (32.0)	228 (29.5)	257 (35.0)	252 (34.4)	1068 (32.5)	
2	38 (9.7)	64 (9.8)	70 (9.0)	77 (10.5)	86 (11.7)	335 (10.2)	
≥3	10 (2.6)	30 (4.6)	36 (4.7)	39 (5.3)	29 (4.0)	144 (4.4)	
Unknown	48	81	64	68	65	326	
LDH value							
Normal	284 (70.6)	461 (66.8)	493 (61.8)	456 (59.7)	471 (60.8)	2165 (63.1)	<0.001
1× ULN	62 (15.4)	136 (19.7)	185 (23.2)	226 (29.6)	212 (27.4)	821 (23.9)	
>2× ULN	56 (13.9)	93 (13.5)	120 (15.0)	82 (10.7)	92 (11.9)	443 (12.9)	
Unknown	38	47	40	39	29	193	
Stage							
IIIc	36 (8.2)	40 (5.5)	50 (6.0)	65 (8.1)	64 (8.0)	255 (7.1)	0.177
IV-M1a	35 (8.0)	63 (8.6)	67 (8.0)	67 (8.4)	41 (5.1)	273 (7.6)	
IV-M1b	45 (10.3)	77 (10.5)	92 (11.0)	81 (10.1)	86 (10.8)	381 (10.6)	
IV-M1c	322 (73.5)	551 (75.4)	626 (75.0)	586 (73.3)	606 (76.0)	2691 (74.8)	
Metastases in ≥ 3 organ sites	201 (45.9)	349 (47.6)	359 (42.9)	358 (44.7)	364 (45.7)	1631 (45.2)	0.451
Brain metastasis							
Absent	323 (74.9)	520 (72.4)	596 (72.2)	582 (73.4)	539 (69.6)	2560 (72.3)	0.402
Asymptomatic	38 (8.8)	54 (7.5)	75 (9.1)	62 (7.8)	80 (10.3)	309 (8.7)	
Symptomatic	70 (16.2)	144 (20.1)	154 (18.7)	149 (18.8)	155 (20.0)	672 (19.0)	
Unknown	9	19	13	10	24	75	
Liver metastasis	144 (33.0)	201 (27.7)	245 (29.7)	211 (26.6)	223 (28.3)	1024 (28.7)	0.168
BRAF mutant	250 (56.8)	372 (50.5)	464 (55.4)	420 (52.3)	436 (54.6)	1942 (53.7)	0.155

[a] *P*-value of statistical tests comparing characteristics of patients diagnosed 2013, 2014, 2015, 2016 and 2017 was based on non-missing values.
ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; ULN, upper limit of normal; yr, year.

(change of) hazards ratios over time. The cohort 2017 was excluded from this analysis, because of the short follow-up time and risk of informative censoring for the landmark Cox model from 6 to 48 months.

The complete case analysis were presented, as results were almost identical to the pooled results after the multiple imputation by chained equations (Table S1) [13]. The multivariable Cox models with 'unknown' categories for ECOG PS, LDH and BRAF mutational status are shown in the supplement (Table S2). Statistical software used was R (version 3.5.2: packages car, tidyverse, survival and mice).

3. Results

Between 1st July 2013 and 31st December 2017, 3616 patients with unresectable stage IIIc or stage IV melanoma were included in the DMTR. Baseline characteristics were balanced across cohort years except for age and LDH value (Table 1). Median age of the whole cohort was 64 years, and 41% were female patients; 1264 (35%) patients had elevated baseline LDH value of 1× upper limit of normal (ULN) and in 443 (13%) LDH value was >2× ULN; 2811 (78%) had ECOG PS of 0 or 1; 2691 (75%) had stage IV-M1c disease; 981 (27%) had brain metastasis of which 672 (19%) were symptomatic; 1942 (54%) patients had BRAF-mutated melanoma.

During this cohort period new systemic therapies were approved in the Netherlands (Fig. S2), although some patients were treated in compassionate use or named patient programs. The percentage of patients treated with systemic therapy increased from 76% (333/440) in 2013 to 89% (709/798) in 2017. After an initial increase during 2013 and 2014 only ≤1.0% of patients received first-line ipilimumab and monotherapy with BRAF inhibitors in 2017 (Fig. 3). Of the patients diagnosed in 2017, 47% received an anti–PD-1 antibody and 30% BRAF plus MEK inhibitors as first-line treatment. Ipilimumab plus nivolumab combination therapy in the first line was administered in 15% of patients. Overall

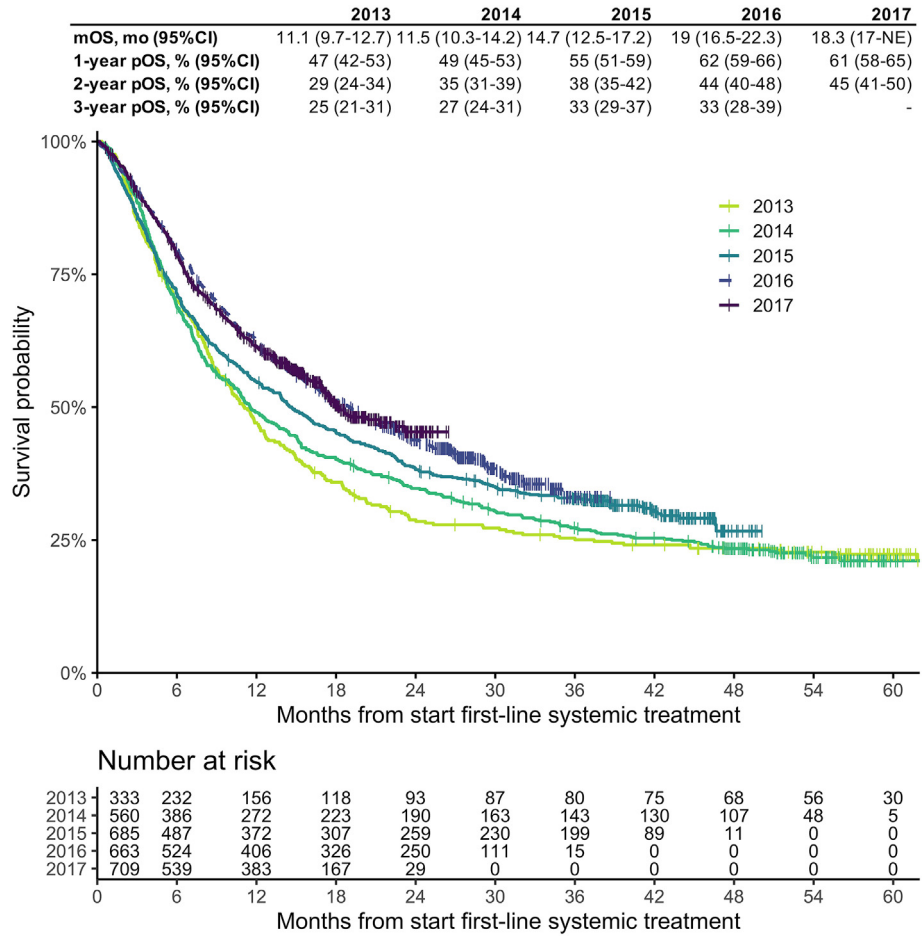

Fig. 2. Kaplan–Meier curves of overall survival of patients diagnosed with unresectable stage IIIC or stage IV melanoma between 2013 and 2017 who received systemic treatment. Overall survival was estimated from start of first-line systemic therapy. Patients characteristics can be found in the supplement. OS, overall survival; mOS, median overall survival; pOS, overall survival probability; mo, months; CI, confidence interval; NE, not estimable.

grade III or IV toxicity occurred in 29% of patients treated with ipilimumab, in 22% with BRAF inhibitors, in 23% with BRAF plus MEK inhibitors and in 15% patients treated with an anti–PD-1 antibody (Table 2). Fifty-four patients who received combination therapy ipilimumab plus nivolumab had grade III–IV toxicity. Between 0.1 and 0.5% deaths related to systemic therapy were reported for ipilimumab, monotherapy with BRAF inhibitors, anti–PD-1 antibody and BRAF plus MEK inhibitors. For ipilimumab plus nivolumab no deaths related to treatment were reported.

Median OS for all patients diagnosed in 2013 increased from 11.7 months (95% CI: 10.4–13.5) to 18.9 months (95% CI: 17.1–23.2) in 2017 (Fig. 1). The one- and three-year OS probabilities were 49% (95% CI: 45–54) and 27% (95% CI: 23–31) for 2013 and 60% (95% CI: 57–64) and 33% (95% CI: 29–37) for 2016, respectively. The one- and two-year OS probability for 2017 were 62% (95% CI: 58–65) and 45% (95% CI: 41–49; Fig. 1), respectively.

Median OS from start of first-line systemic therapy for systemically treated patients diagnosed in 2013 of 11.1 months (95% CI: 9.7–12.7) increased to 18.3 months (95% CI: 17-not estimable) for systemically treated patients diagnosed in 2017. Corresponding one- and three-year OS probabilities were 47% (95% CI: 42–53) and 25% (95% CI: 21–31) for 2013 and 62% (95% CI: 59–66) and 33% (95% CI: 28–39) for 2016. The one- and two-year OS probability for 2017 were and 61% (95% CI: 58–65) and 45% (95% CI: 41–50; Fig. 2). Median follow-up for 2013, 2014, 2015, 2016 and 2017 were 61 months, 55 months, 43 months, 31 months and 19 months, respectively.

The first multivariable Cox model, in which we analysed the first 6 months separately because of non-proportional hazards, showed there was no significant difference in survival between patients diagnosed in 2013, 2014 and 2015 (Table 3). Only patients diagnosed in 2016 had superior survival in the first 6 months compared with patients diagnosed in 2013 (HR = 0.55

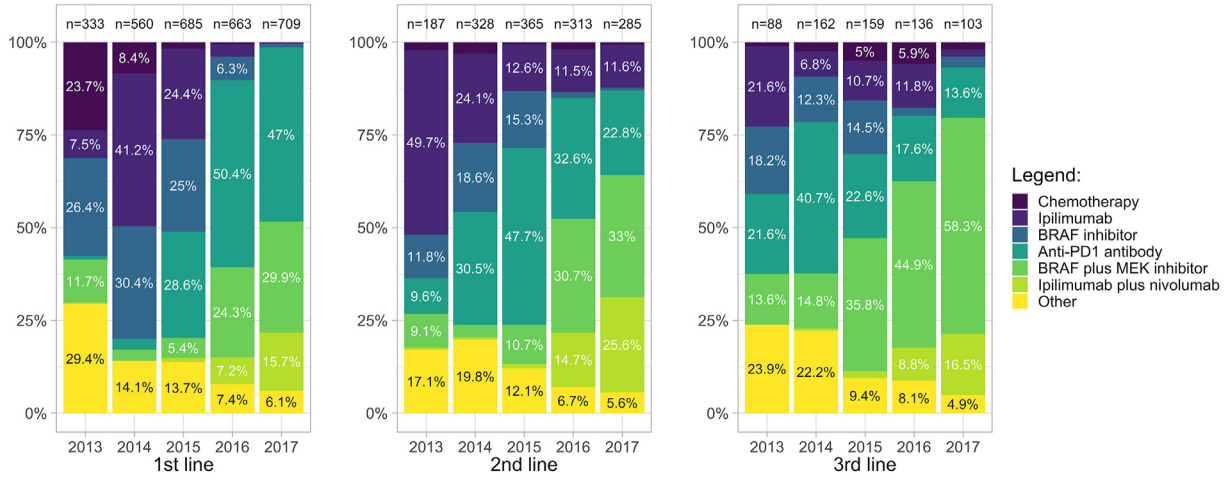

Fig. 3. Treatments by the line of systemic therapy and by the year of diagnosis. Some patients received treatments before their approval in the Netherlands via named patient or compassionate use programs.

[95% CI: 0.43–0.72, p < 0.001]). Survival during the first 6 months was also superior for female patients (HR = 0.78 [95% CI: 0.66–0.93, p = 0.005]) and for patients with a BRAF-mutated melanoma (HR = 0.50 [95% CI: 0.42–0.59, p < 0.001]). The ECOG PS of ≥1, elevated LDH value, brain metastasis, liver metastasis and distant metastases in ≥3 organs sites were all statistically significantly associated with poorer survival (Table 3).

The second Cox model, in which we performed a landmark analysis from 6 to 48 months, showed that patients diagnosed in 2015 and 2016 had superior survival compared with those of 2013 (resp. HR = 0.79 [95% CI: 0.65–0.94, p = 0.01] and HR = 0.68 [95% CI: 0.57–0.83, p < 0.001]). The ECOG PS of ≥1, elevated LDH, distant metastases in ≥3 organ sites, and liver and brain metastasis had an ongoing statistically significant negative effect on survival. The HRs of ECOG PS of ≥1 were remarkably lower than in the first 6 months. Age of ≥60 years had was negatively associated with survival. Superior survival in the first 6 months of female sex and BRAF-mutated melanoma disappeared in the landmark analysis from 6 months (Table 3).

4. Discussion

This is a nationwide population-based study of a real-world population with unresectable stage IIIc or stage IV melanoma in the era of new systemic treatments. A significant improvement in OS was achieved from 2013 to 2016. Median OS of 18.9 months for all patients diagnosed in 2017. In 2017, 89% of all patients with advanced melanoma in the Netherlands received first-line systemic treatment which consisted largely of anti–PD-1 antibodies (47%), BRAF plus MEK inhibitors (30%) or ipilimumab plus nivolumab (16%). No new safety signals were found, and, within experienced hands, these treatments can be administered safely in real-world setting.

Survival outcomes of patients with advanced melanoma who received systemic therapy from 2013 to 2017 is in line with results of phase III trials. Median survival

Table 2
Treatments and grade III–IV toxicity of patients with unresectable stage IIIc or stage IV melanoma. Values are *n* (%) unless otherwise indicated.

Year of diagnosis	2013	2014	2015	2016	2017	Total
Patients; *n*	440	737	838	803	798	3616
Treatment[a]						
No treatment received	46 (10.5)	67 (9.1)	76 (9.1)	70 (8.7)	45 (5.6)	304 (8.4)
Local therapy	61 (13.9)	110 (14.9)	77 (9.2)	70 (8.7)	44 (5.5)	362 (10.0)
Systemic (and local) therapy	333 (75.7)	560 (76.0)	685 (81.7)	663 (82.6)	709 (88.8)	2950 (81.6)
Grade III–IV toxicity; *n*/total[b] **(%)**						
Chemotherapy	0/84 (0.0)	2/60 (3.3)	2/22 (9.1)	0/18 (0.0)	0/5 (0.0)	4/189 (2.1)
Ipilimumab	30/136 (22.1)	91/318 (28.6)	69/229 (30.1)	26/76 (34.2)	12/37 (32.4)	228/796 (28.6)
BRAF inhibitor	34/126 (27.9)	55/247 (22.4)	51/250 (20.4)	11/50 (22.0)	2/12 (16.7)	153/685 (22.3)
Anti–PD-1 antibody	9/44 (22.5)	28/182 (15.4)	56/406 (13.8)	69/460 (15.0)	56/412 (13.6)	218/1500 (14.5)
BRAF plus MEK inhibitor	17/68 (25.0)	14/52 (26.9)	29/133 (21.8)	81/318 (25.5)	71/366 (19.4)	212/937 (22.6)
Ipilimumab plus nivolumab	0/2 (0.0)	2/3 (66.7)	6/15 (40.0)	57/106 (53.8)	109/201 (54.2)	174/327 (53.2)

[a] Based on what patients received until time of data-set cutoff date.
[b] Number of patients with grade III–IV toxicity of a total of patients treated in the first, second or third line.

Table 3a
Two multivariable Cox regression models for overall survival. One Cox model was restricted to the first 6 months, and one Cox model was a landmark model from 6 months and restricted to 48 months.

Variable	Restricted to <6 months				Landmark model from 6 to 48 months			
	n	HR	95% CI	*P*-value	*n*	HR	95% CI	*P*-value
Year of diagnosis								
2013	368	1			263	1		
2014	626	0.82	(0.64–1.05)	0.115	464	0.95	(0.79–1.14)	0.559
2015	751	0.82	(0.64–1.05)	0.111	558	0.79	(0.65–0.94)	0.01
2016	703	0.55	(0.43–0.72)	<0.001	565	0.68	(0.57–0.83)	<0.001
Age								
<50 yr	441	1			348	1		
50–59 yr	544	1.12	(0.85–1.47)	0.436	425	1.10	(0.91–1.33)	0.33
60–69 yr	689	1.23	(0.95–1.58)	0.116	511	1.28	(1.07–1.54)	0.007
70–79 yr	583	1.20	(0.92–1.56)	0.186	438	1.40	(1.16–1.69)	<0.001
≥80 yr	191	1.48	(1.06–2.06)	0.022	128	1.90	(1.48–2.45)	<0.001
Sex								
Male	1459	1			1062	1		
Female	989	0.78	(0.66–0.93)	0.005	788	0.96	(0.85–1.08)	0.475
ECOG PS								
0	1338	1			1181	1		
1	782	2.23	(1.81–2.74)	<0.001	543	1.39	(1.22–1.59)	<0.001
2	227	4.72	(3.70–6.04)	<0.001	99	1.79	(1.41–2.26)	<0.001
≥3	101	7.28	(5.37–9.86)	<0.001	27	2.67	(1.78–4.02)	<0.001
LDH								
Normal	1572	1			1328	1		
1× ULN	565	1.37	(1.12–1.69)	0.003	394	1.24	(1.07–1.44)	0.004
>2× ULN	311	2.49	(2.00–3.10)	<0.001	128	1.68	(1.35–2.10)	<0.001
Stage								
IIIc	150	1			142	1		
IV-M1a	189	1.10	(0.43–2.80)	0.836	179	0.95	(0.68–1.32)	0.756
IV-M1b	262	1.25	(0.55–2.87)	0.595	243	1.25	(0.93–1.68)	0.142
IV-M1c	1847	3.19	(1.56–6.51)	0.001	1286	1.49	(1.14–1.94)	0.003
Distant metastases								
<3 organ sites	1305	1			1117	1		
≥3 organ sites	1143	1.55	(1.28–1.87)	<0.001	733	1.29	(1.13–1.47)	<0.001
BRAF status								
Wild-type	1056	1			746	1		
Mutant	1392	0.50	(0.42–0.59)	<0.001	1104	1.06	(0.93–1.19)	0.386

ECOG PS, Eastern Cooperative Oncology Group performance score; LDH, lactate dehydrogenase; ULN, upper limit of normal; HR, hazard ratio; CI, confidence interval; yr, year.

and possible plateau at 48 months that we observed compares to early ipilimumab monotherapy trials which showed a median survival of 11.4 months and a plateau after 4 years at 22% [14]. Survival outcomes of patients diagnosed in 2016 or 2017 compare with outcomes of later phase III trials. Three-year OS results from the KEYNOTE-001 study showed median survival of 23.8 months [15]. In the coBRIM-trial median OS was 22.3 months, and in the Combi-D and Combi-V trials median OS of 26.2 months was reached [4,16]. These phase III trials are indicative of survival outcomes of sequential treatment with immunotherapy and targeted therapy as a large proportion of patients received second-line immunotherapy. Survival in real-world could further improve with optimised (sequential) treatment of anti–PD-1 antibodies, BRAF plus MEK inhibitors and ipilimumab plus nivolumab [17,18]. It still remains uncertain whether survival of 2016 and 2017 will stabilise with longer follow-up and, if so, what the plateau in the survival curves will be. There are indications that the mortality due to (all stage) melanoma in the Netherlands is stabilising while the incidence of (all stage) melanoma is increasing [19].

We found that the proportional hazards assumption was violated. This can be explained by our unselected real-world population that partly consisted of patients not able to receive (systemic) treatment because of poor prognosis. It seems two periods, where different mechanisms are dominant, can be distinguished. In the first 6 months, risk factors dominate that determine short-term mortality and the ability to receive and respond to systemic treatment. Early results of the DMTR showed a median OS of 4.5 months in untreated patients [10]. In the period beyond 6 months, risk factors prevail that impact whether a durable response is reached and sustained. In addition, immune checkpoint inhibitors are known for non-proportional hazards, because of the delayed treatment effect and a later constant effect due to durable treatment effect [20].

Table 3b
Two multivariable Cox regression models for the association of brain and liver metastasis with overall survival adjusted for year of diagnosis, age, sex, Eastern Cooperative Oncology Group performance score, lactate dehydrogenase, distant metastasis and BRAF mutational status (Stage was excluded because of its correlation with the factors of interest). One Cox model was restricted to the first 6 months, and one Cox model was a landmark model from 6 months and restricted to 48 months.

Variable	Restricted to <6 months				Landmark model from 6 to 48 months			
	n	HR	95% CI	*P*-value	*n*	HR	95% CI	*P*-value
Liver metastasis								
No	1685	1			1402	1		
Yes	709	1.53	(1.26–1.87)	<0.001	422	1.28	(1.1–1.48)	0.001
Brain metastasis								
Absent	1783	1			1447	1		
Asymptomatic	196	1.51	(1.13–2.01)	0.006	139	1.48	(1.2–1.82)	<0.001
Symptomatic	415	2.40	(1.98–2.92)	<0.001	238	1.64	(1.39–1.95)	<0.001

HR, hazard ratio; CI, confidence interval.

We observed sex and BRAF mutational status are not of prognostic importance for long-term survival. For sex, Joosse *et al.* [21,22] (2014) hypothesised that unfavourable melanoma outcome in men may be due to sex-related biological features. Our results emphasise that more research is required to unravel the underlying mechanisms and effect of sex differences on survival. Superior survival of patients with BRAF-mutated melanoma in the first 6 months could have been due to high response rates and shorter time to (dramatic) response of targeted therapy [3,23,24]. For BRAF wild-type melanoma treatment options are limited to immunotherapy. Prolonged time to response and lower response rates of immunotherapy could explain early death of non-responders and/or patients with a poor prognosis [25,26]. The possibility to achieve a durable tumour response with immunotherapy may underlie that patients with BRAF wild-type melanoma who survived the first 6 months have a similar prognosis as patients with BRAF-mutated melanoma.

Our study confirms baseline elevated LDH levels, stage IV-M1c disease, distant metastases in ≥3 organ sites and liver metastasis as important prognostic factors for survival [16,27,28]. Brain metastasis and, especially, ECOG PS of ≥2, both important exclusion criteria for phase III trials, were negatively associated with survival. For most prognostic factors the negative effect on prognosis decreased after 6 months. For age, however, the negative association with OS of ≥60 years of age slightly increased after 6 months.

This study has limitations as 15% of patients had one or more missing value in variables necessary for analysis (non-complete cases). Although hazard ratios after multiple imputation and complete cases were similar, OS of non-complete cases was inferior to complete cases (supplement Fig. S1). The unknown categories of ECOG PS and LDH are negatively associated with survival (supplement Table S2). Therefore, when interpreting hazard ratios, it should be taken into account that the underlying hazard for death in the total study population is higher than that for complete cases.

We also must address an imbalance in patient characteristics between cohort years. Patients diagnosed in 2013 had lower LDH values and were younger than the patient population in the other cohort years. Only patients who were seen in a melanoma center were registered in the DMTR. Referral of patients by hospitals to one of the 14 designated melanoma centres could have been more conservative in 2013. This indicates that of cohort year 2013 has selection bias, but in latter cohort years this selection bias disappeared.

In the study period lead time bias could have had an effect on OS as it paid off to search more intensively for metastasis with new systemic treatment options available. This could have led to stage migration in which metastasis are caught sooner and disease stage is determined earlier, achieving an artificial survival benefit [29]. This phenomenon could not be investigated as we had no information on lymph node staging and some patients had advanced melanoma at diagnosis. No guideline changes for staging occurred in the Netherlands in our study period, and we assume that lead time bias and stage migration only had a small effect.

Outcomes of our study reflect daily practice as we studied an unselected population-based patient population with advanced melanoma, including patients normally excluded from trial participation. The impact of these exclusion criteria on survival in real-world highlights that results of phase III trials are not automatically generalisable to real-world. Our study provides additional information to the phase III trials. This can help support informed decision-making, help selection of suitable patients for treatment, set realistic treatment goals and intensify follow-up of a patient if necessary. The DMTR will remain of interest for the international melanoma community, and collaboration with melanoma registries around the world could be of interest for research on rare melanomas. This makes population-based registries such as the DMTR an important instrument to improve value of new systemic therapies after registration [30].

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Conflict of interest statement

AvdE reports advisory relationships with Amgen, Bristol-Myers Squibb, Roche, Novartis, MSD, and Pierre-Fabre. AvA reports consultancy/advisory relationships with Amgen, Bristol-Myers Squibb, Novartis, MSD-Merck, Merck-Pfizer, and 4SC and research grants not related to this paper from Amgen, BMS, and Novartis. JdG reports personal fees outside the submitted work from Bristol-Myers Squibb, Roche, Pierre-Fabre, Servier, and MSD, Novartis. GH reports consultancy/advisory relationships with Amgen, Bristol-Myers Squibb, Roche, MSD, Pfizer, and Novartis and research grants not related to this paper from Bristol-Myers Squibb, and Seerave. EK has consultancy/advisory relationships with Amgen, Bristol-Myers Squibb, Novartis, Roche, Merck, Pierre-Fabre, EISAI, Bayer, and Genzyme-Sanofi and research grants not related to this paper from Novartis and Bristol-Myers Squibb. KS advisory relationships with Bristol-Myers Squibb, Roche, Novartis, MSD, and Pierre-Fabre. AvdV reports consultancy relationships with Bristol-Myers Squibb, MSD, Roche, Novartis, Pierre-Fabre, Pfizer, Sanofi, Ipsen, and Eisai. JH reports advisory relationships with Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, Celsius Therapeutics, GSK, Immunocore, Ipsen, MSD, Merck Serono, Novartis, Neon Therapeutics, Pfizer, Roche/Genentech, Sanofi, and Seattle Genetics and research grants not related to this paper from Novartis, Bristol-Myers Squibb, MSD, and Neon Therapeutics. All grants were paid to the institutions. The funders had no role in the writing of this article or decision to submit it for publication.

Appendix A. Supplementary data

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