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Nationwide Outcomes of Advanced Melanoma According to BRAF^{V600} Status

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Objective: The aim of this study was to evaluate treatment patterns and overall survival (OS) of patients with BRAF^{V600} wild-type and BRAF^{V600}-mutant advanced melanoma in the Netherlands.

Methods: We selected patients of 18 years and over, diagnosed between 2016 and 2017 with unresectable stage IIIC or IV melanoma, registered in the Dutch Melanoma Treatment Registry. To assess the association of BRAF^{V600}-mutation status with OS we used the Cox proportional-hazards model.

Results: A total of 642 BRAF^{V600} wild-type and 853 mutant patients were included in the analysis. Median OS did not differ significantly between both groups, 15.2 months (95% confidence interval [CI]: 13.2-19.2) versus 20.6 months (95% CI: 18.3-25.0). Survival rates at 6 and 12 months were significantly lower for BRAF^{V600} wild-type patients compared with BRAF^{V600}-mutant patients, 72.0% (95% CI: 68.6-75.6) and 56.0% (95% CI: 52.2-60.0) versus 83.4% (95% CI: 80.9-85.9) and 65.7% (95% CI: 62.6-69.0). Two-year survival was not significantly different between both groups, 41.1% (95% CI: 37.2-45.3) versus 47.0% (95% CI: 43.6-60.6). Between 0 and 10 months, BRAF^{V600}

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In compliance with Dutch regulations, the DMTR was approved by a medical ethics committee (METC Leiden University Medical Center, 2013) and is not considered subject to the Medical Research Involving Human Subjects Act.

J.v.B.: was involved in data curation, formal analysis, investigation, software, writing—original draft. M.W.J.M.W.: was involved in project administration, conceptualization, methodology, supervision, writing—review and editing. L.C.d.W.: was involved in conceptualization, methodology, writing—review and editing. D.H.H.: was involved in the conceptualization, methodology, supervision, writing—review and editing. J.B.H., C.U.B., M.J.B.A., F.W.P.J.v.d.B., J.-W.B.d.G., G.A.P.H., E.K., D.P., R.S.v.R., K.P.M.S., W.A.M.B., A.J.t.T., A.A.M.v.d.V., G.V., and M.J.B.: carried out project administration, data curation, writing—review and editing. A.J.M.v.d.E.: was involved in project administration, data curation, conceptualization, supervision, writing—review and editing.

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wild-type patients had a decreased survival with a hazard ratio for OS of 2.00 (95% CI: 1.62-2.46) but this effect disappeared after 10 months. At 12 months, BRAF^{V600}-mutant patients had started with second-line systemic treatment more often compared with BRAF^{V600} wild-type patients (50% vs. 19%).

Conclusion: These results suggest that advanced BRAF^{V600} wild-type melanoma patients have worse survival than BRAF^{V600}-mutated patients during the first 10 months after diagnosis because of less available treatment options.

Key Words: advanced melanoma, BRAF mutation, National Registry, BRAF/MEK inhibitors, anti-PD-1-ligands, checkpoint inhibitors, CTLA-4 inhibitor

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The incidence of melanoma has been rising in many European countries in the past decades.[1,2] Before 2011, systemic treatment with dacarbazine was the only registered treatment option for patients with unresectable stage IIIC or IV melanoma. Since then, new treatment options have entered the field of advanced melanoma. Pivotal phase III trials have shown superiority of immune checkpoint inhibitors (anti-programmed cell death protein 1 [PD-1] and anti-cytotoxic T-lymphocyte–associated protein 4 [CTLA-4]) and targeted therapies (BRAF and MEK inhibitors) over treatment with dacarbazine.[3–6] As a result, overall survival (OS) of metastatic melanoma patients increased since their introduction.[7]

BRAF-targeted and MEK-targeted therapies inhibit signaling through the mitogen-activated protein kinase pathway, causing an inhibition of cell proliferation. BRAF inhibitors (dabrafenib, encorafenib, and vemurafenib) are mostly administered in combination with MEK inhibitors (trametinib, binimetinib, and cobimetinib). Combination of both treatments resulted in improved OS compared with monotherapy.[8] Advantages of targeted therapy are its high response rate and generally rapid regression of disease in symptomatic patients.[9] Previous studies have shown that ~50% of melanoma patients have a BRAF^{V600E} or BRAF^{V600K} mutation.[10,11]

In phase III clinical trials with anti-PD-1 monotherapy, clinical outcomes for BRAF^{V600} wild-type and BRAF^{V600}-mutant patients were comparable.[3,12] However, in the real-world setting, treatment options for BRAF^{V600} wild-type patients with a poor prognosis due to brain metastases or a poor performance status are limited. Treatment options for BRAF^{V600} wild-type patients consist of PD-1 inhibitors (nivolumab and pembrolizumab), CTLA-4 inhibitors (ipilimumab), a combination of ipilimumab plus nivolumab, talimogene laherparepvec (T-VEC) for patients with injectable (sub)cutaneous and lymph node metastases, and dacarbazine. The disadvantage of PD-1 inhibitors and CTLA-4 inhibitors is that their antitumor effect may take several months to occur.[13] This may be less of a problem for the combination of ipilimumab plus nivolumab, with rapid responses being more frequently observed.[14] However, patients with poor prognostic factors, who require a rapid response, have a diminished overall response rate to checkpoint inhibition. Therefore, we hypothesized that due to the limited number of systemic treatment options and the delayed time to response, BRAF^{V600} wild-type patients have a worse prognosis when compared with BRAF^{V600}-mutant patients.

This study uses data from the Dutch Melanoma Treatment Registry (DMTR) to describe the treatment and OS of BRAF^{V600} wild-type patients in the Dutch population. The aim of this study is (1) to provide insights into the treatment of BRAF^{V600} wild-type patients in Dutch daily practice; (2) assess the OS of BRAF^{V600} wild-type patients compared with BRAF^{V600}-mutant patients; and (3) develop a risk classification for BRAF^{V600} wild-type patients.

METHODS

Study Design and Population

This longitudinal observational study used data from the DMTR. The DMTR is a population-based registry, started on July 1, 2013, capturing all patients with unresectable stage IIIC or IV melanoma in the Netherlands. A detailed description of the DMTR setup has been published by Jochems et al.[15]

For the purpose of this study, we selected patients of 18 years and over, diagnosed with unresectable stage IIIC and IV melanoma between January 1, 2016 and December 31, 2017 (dataset cutoff date was August 1, 2019). We chose this period as both BRAF/MEK inhibitors and anti-PD-1 monotherapy were equally available in every melanoma center. Uveal and mucosal melanoma were excluded from the analysis.

Statistical Analysis

Baseline patient and disease characteristics of BRAF^{V600} wild-type patients were analyzed using descriptive statistics. Patients were considered wild-type in case they did not have a

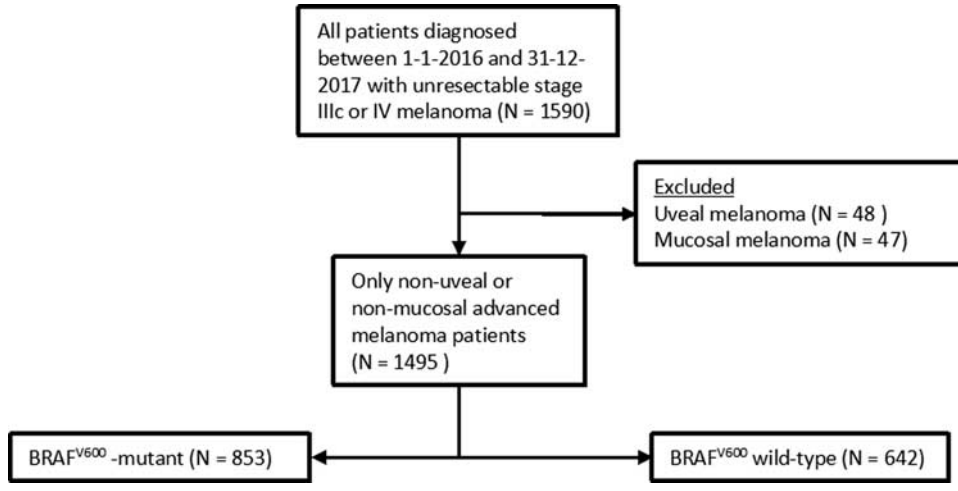

FIGURE 1. Flowchart of the included patients in this study.

proven BRAF^{V600} mutation. Categorical variables were compared using the χ^2 test. OS was defined as the time from diagnosis with unresectable IIIc or stage IV disease until death from any cause and was estimated using the Kaplan-Meier method with corresponding 2-sided 95% confidence intervals (CIs). OS between subgroups was compared using log-rank tests for categorical variables. Patients alive or lost to follow-up were right censored at the time of the last registered contact. Time to next treatment was defined as time from start of systemic treatment to start of a new treatment or death from any cause. Second-line treatment and death before second-line treatment were considered as competing risks; their probabilities were calculated by cumulative incidence curves. A second pair of cumulative incidence curves was calculated from start of second-line treatment to third-line treatment and death before third-line treatment.

Univariable and multivariable Cox proportional-hazards models were used to assess the association of prognostic factors with OS. OS was artificially censored at 24 months. The proportional-hazards assumption was tested with the scaled Schoenfeld residuals. Prognostic factors assessed were age at diagnosis, baseline Eastern Cooperative Oncology Group (ECOG) performance status, baseline lactate dehydrogenase (LDH) levels, distant metastasis, brain metastasis, and liver metastasis. We made age binary as we observed a nonlinear effect of age, starting at age ±75 years. As the proportional-hazards assumption was violated for brain metastases, LDH, and BRAF^{V600}-mutation status, we fitted different effects of these variables in the model in the periods between 0 and 10 months and between 10 and 24 months to investigate the association between BRAF mutation status and OS, adjusting for other risk factors.

Multivariable cause-specific Cox proportional-hazards models with the same predictors were used to estimate the association of prognostic factors with second-line treatment and death without next treatment. Statistical software used was R (version 3.5.2; packages car, tidyverse, survival, survminer).

RESULTS

Between January 1, 2016 and December 31, 2017, a total of 1495 patients with unresectable stage IIIC or IV melanoma were registered in the DMTR. In total, 642 patients had no BRAF^{V600} mutation (Fig. 1). When compared with the BRAF^{V600}-mutant patients, BRAF^{V600} wild-type patients were older, had fewer organ sites with metastases, less brain metastases, and had a lower disease substage (Table 1).

Systemic treatment of BRAF^{V600} wild-type patients differed from BRAF^{V600}-mutant patients. Of BRAF^{V600} wild-type patients 75.1% received anti-PD-1, 16.0% received ipilimumab plus nivolumab, 2.1% received ipilimumab, and 0.4% received chemotherapy as the first-line systemic treatment. Of all BRAF^{V600}-mutant patients, 46.5% received BRAF/MEK inhibitors, 31.6% received anti-PD-1, 8.7% received ipilimumab plus nivolumab, 1.8% received ipilimumab, and 5.4% received BRAF inhibitors as first-line systemic treatment. Of the BRAF^{V600} wild-type patients, 80.8% did not receive a second-line systemic treatment versus 47.1% in the BRAF^{V600}-mutant group. Of BRAF^{V600} wild-type patients 3.7% received third-line systemic treatment versus 25.4% in the BRAF^{V600}-mutant group (Supplement 1, Supplemental Digital Content 1, http://links.lww.com/AJCO/A360, Figs. 2A, B). Patient and tumor characteristics during the first-line treatment are shown in Supplement 2 (Supplemental Digital Content 1, http://links.lww.com/AJCO/A360). Patient characteristics of BRAF^{V600} wild-type patients who received no systemic treatment or local therapy only are shown in Supplement 3 (Supplemental Digital Content 1, http://links.lww.com/AJCO/A360).

TABLE 1. Baseline Characteristics of BRAF^{V600} Wild-type Versus BRAF^{V600}-mutant Patients

	n (%)		
	BRAF^{V600} Wild-type	**BRAF^{V60} Mutant**	***P***
N	642	853	
Age, median (range) (y)	69 (21-92)	62 (19-96)	<0.001
Age categories (y)			
<75	462 (72.0)	730 (85.6)	<0.001
≥75	180 (28.0)	123 (14.4)	
Sex			
Male	400 (62.3)	486 (57.0)	0.043
Female	242 (37.7)	367 (43.0)	
ECOG performance status			
0-1	473 (73.7)	603 (70.7)	0.336
≥2	85 (13.2)	127 (14.9)	
Missing	84 (13.1)	123 (14.4)	
Stage			
Unresectable IIIc	57 (8.9)	54 (6.3)	0.004
IV-M1a	59 (9.2)	67 (7.9)	
IV-M1b	103 (16.1)	94 (11.0)	
IV-M1c	267 (41.7)	363 (42.7)	
IV-M1d	155 (24.1)	273 (32.1)	
LDH (U/L)			
Normal	373 (58.3)	478 (56.4)	0.272
250-500	169 (26.4)	236 (27.9)	
>500	61 (9.5)	103 (12.2)	
Missing	37 (5.8)	30 (3.5)	
Brain metastases			
No	474 (75.4)	568 (67.5)	0.004
Yes, asymptomatic	44 (7.0)	89 (10.6)	
Yes, symptomatic	111 (17.6)	184 (21.9)	
Liver metastases			
No	472 (74.2)	601 (71.3)	0.235
Yes	164 (25.8)	242 (28.7)	
No. organ sites			
0-2	357 (55.7)	400 (47.0)	0.001
≥3	284 (44.3)	451 (53.0)	
NRAS-mutation status			
Wild-type	231 (36.0)	646 (75.7)	<0.001
Mutant	345 (53.7)	15 (1.8)	
Unknown	66 (10.3)	192 (22.5)	

Missing data of <2.5% are not shown.
ECOG indicates Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase.

Median OS was not significantly different between BRAF^{V600} wild-type and BRAF^{V600}-mutant patients, 15.2 months (95% CI: 13.2-19.2) versus 20.6 months (95% CI: 18.3-25.0). However, survival rates at 6 and 12 months were significantly lower for BRAF^{V600} wild-type patients compared with BRAF^{V600}-mutant patients, 72.0% (95% CI: 68.6-75.6) versus 83.4% (95% CI: 80.9-85.9) and 56.0% (95% CI: 52.2-60.0) versus 65.7% (95% CI: 62.6-69.0), respectively (Fig. 3A). Twenty-four-month survival was not significantly different between both groups, 41.1% (95% CI: 37.2-45.3) versus 47.0% (95% CI: 43.6-60.6), respectively. When analyzing patients with stage IV-M1c/d disease separately, 6- and 12-month survival rates of BRAF^{V600} wild-type patients were also significantly lower as compared with BRAF^{V600}-mutant patients (62.6%, 95% CI: 58.2-67.5 vs. 79.8%, 95% CI: 76.8-83.0 and 46.3%, 95% CI: 41.8-51.4 vs. 58.3%, 95% CI: 54.6-62.3, respectively). Similar to the survival rates of all patients at 24 months, survival of BRAF^{V600} wild-type patients with stage IV-M1c/d

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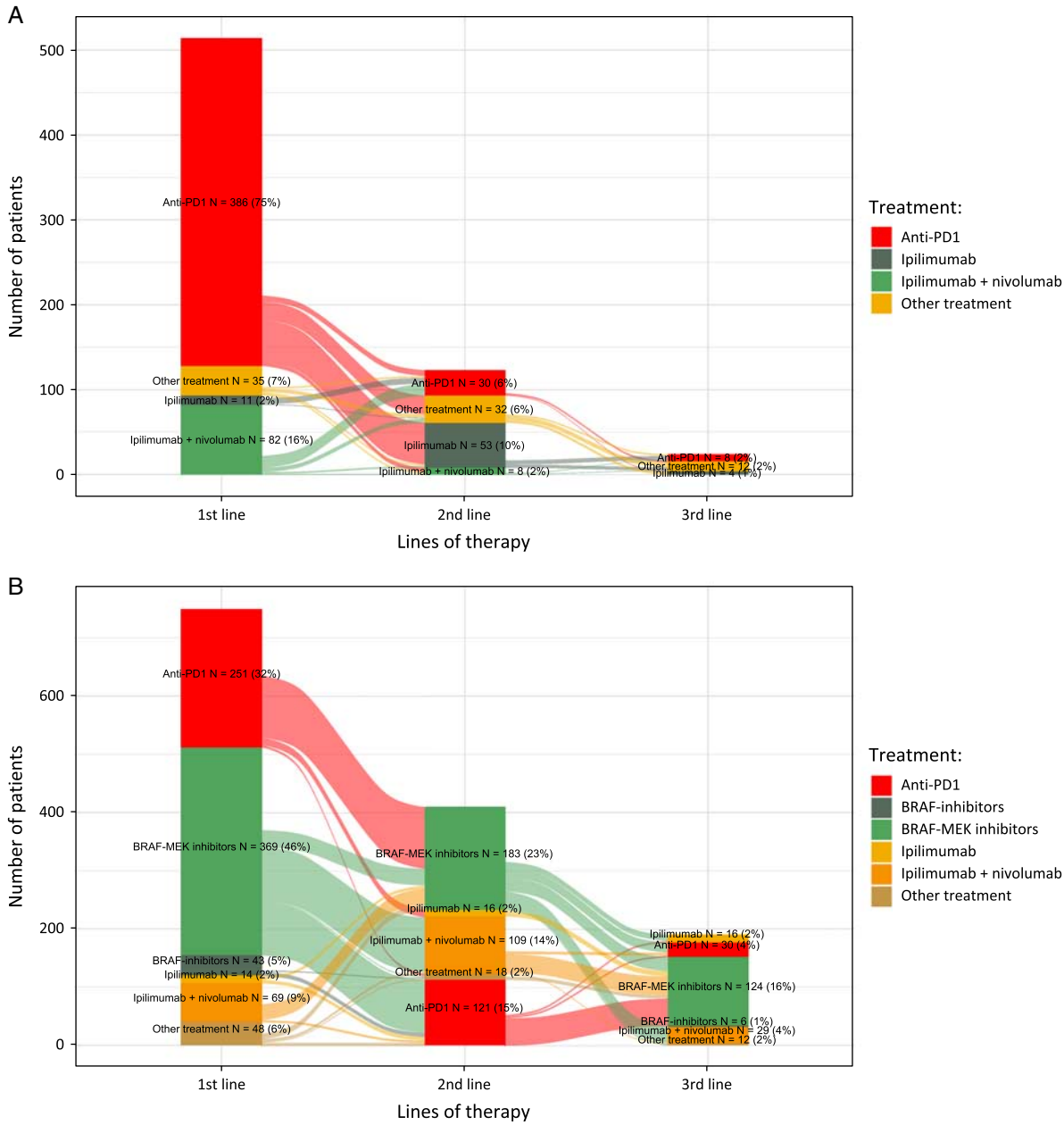

FIGURE 2. Sankey diagrams of BRAF^{V600} wild-type patients (A) and BRAF^{V600}-mutant patients (B) diagnosed in 2016-2017. Other treatment consists of trial medication and chemotherapy. Percentages displayed are calculated based on the number of patients starting first-line systemic therapy. Patients start in the first line of systemic treatment (outer left) and move one column to the right once they receive a new systemic treatment. Each flow represents a number of patients transferring to the next systemic treatment line. PD-1 indicates programmed cell death protein 1. full color online

disease was not significantly different when compared with BRAF^{V600}-mutant patients, 32.6% (95% CI: 28.2-37.7) versus 38.7% (95% CI: 34.9-42.8) (Fig. 3B). Kaplan-Meier curves of stages IV-M1a/b, IV-M1c, and M1d are shown in Supplement 4 (Supplemental Digital Content 1, http://links.lww.com/AJCO/A360), Supplements 5 and 6 (Supplemental Digital Content 1, http://links.lww.com/AJCO/A360). Kaplan-Meier curves of propensity score–matched cohorts are shown in Supplement 7 (Supplemental Digital Content 1, http://links.lww.com/AJCO/A360).

In the multivariable Cox regression of all patients, an age of 75 years and above, an ECOG performance status of ≥ 2, liver metastases, and a number of organ sites ≥ 3 were negatively associated with OS (Table 2). In the first 10 months, BRAF^{V600} wild-type patients had twice the hazard compared with BRAF^{V600}–mutant-type patients (hazard ratio [HR] = 2.00, 95% CI: 1.62-2.46). After 10 months, there was no significant difference between mutant and wild-type patients (HR = 1.05, 95% CI: 0.81-1.35). HRs of elevated LDH (LDH 1×upper limit of normal: HR = 1.76, 95% CI: 1.39-2.23 and >2×upper limit of normal: HR = 3.79, 95% CI: 2.83-5.05) and brain metastases (asymptomatic brain metastases: HR = 1.44, 95% CI: 1.03-1.99, symptomatic brain metastases: HR 3.05, 95% CI: 2.44-3.86) were

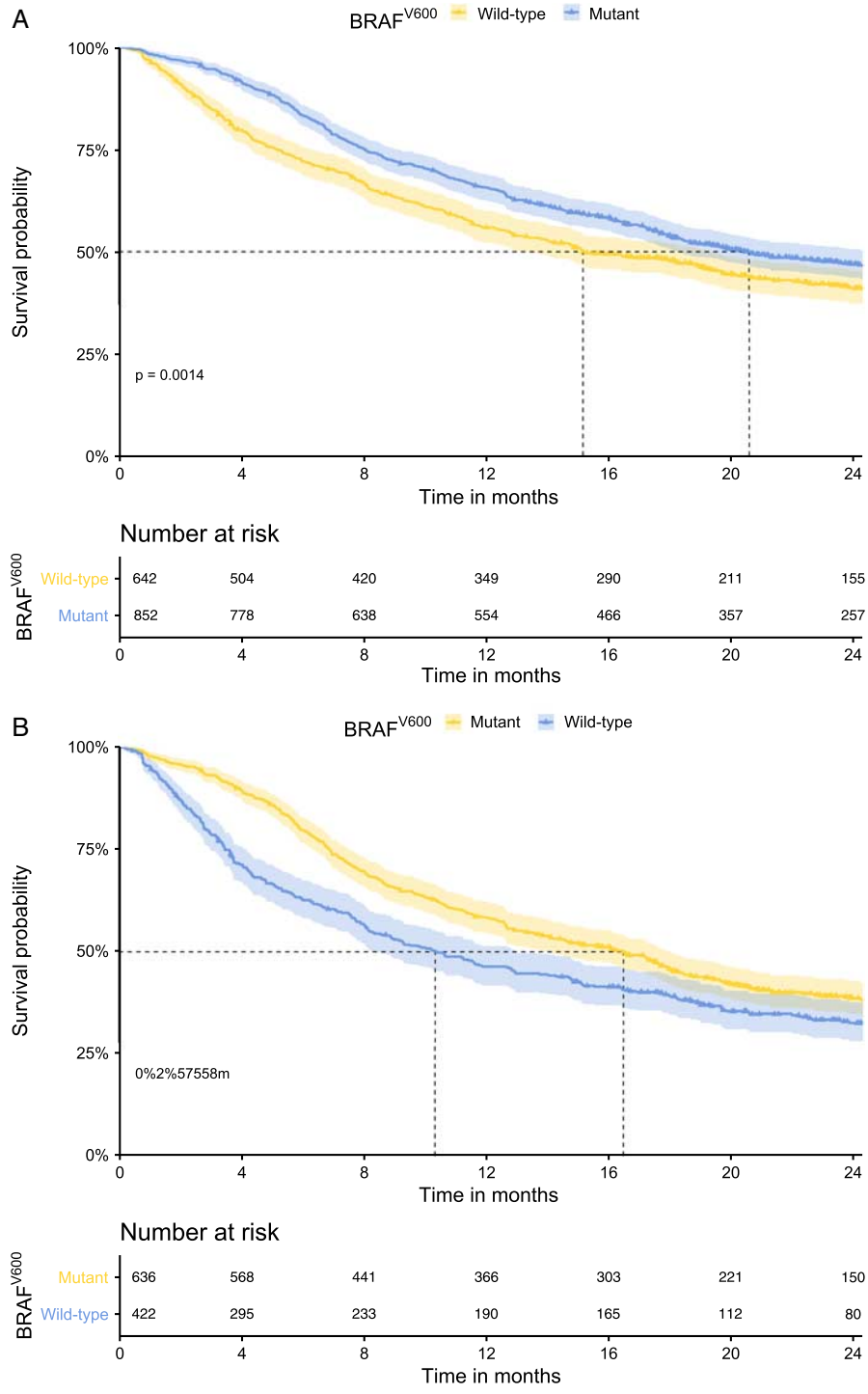

FIGURE 3. Kaplan-Meier estimates of OS of all melanoma (A) and stage IV-M1c/d (B) patients diagnosed between 2016 and 2017, stratified according to BRAF^{V600} mutation status. Confidence interval is displayed by the shadow of both curves. full color online

significantly different from normal LDH levels and no brain metastases during the first 10 months.

To assess the probability of switching to second-line treatment and the risk of death before switching we assessed the cumulative incidences (Fig. 4A). Cumulative incidence of second-line treatment at 12 months was significantly lower for BRAF^{V600} wild-type patients when compared with BRAF^{V600}-mutant patients, 19.1% (95% CI: 15.9-22.8) versus 50.4% (95% CI: 47.0-54.0), respectively. Cumulative incidence of death without next treatment at 12 months was higher for wild-type patients, 31.8% (95% CI: 28.0-36.1) versus 18.2% (95% CI: 15.9-21.1) (Fig. 4A). At 6 and 24 months, we observed the same differences in cumulative incidence.

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TABLE 2. Multivariable Cox Regression Analysis of Overall Survival Including All Patients (BRAF^{V600} Mutant and BRAF^{V600} Wild-type)

		Multivariable (0-10 mo)			Multivariable (10-24 mo)		
	N	HR	95% CI	*P*	HR	95% CI	*P*
Age (y)							
<75	964	1			1		
≥75	238	1.66	1.38-2.01	<0.001	1.66	1.38-2.01	<0.001
Sex							
Female	486	1			1		
Male	716	1.01	0.87-1.19	0.859	1.01	0.87-1.19	0.859
ECOG performance status							
0-1	1008	1			1		
≥2	194	2.60	2.14-3.16	<0.001	2.60	2.14-3.16	<0.001
LDH (U/L)							
Normal	722	1			1		
250-500	347	1.76	1.39-2.23	<0.001	0.83	0.63-1.11	0.195
>500	133	3.79	2.83-5.05	<0.001	1.33	0.79-2.23	0.291
Brain metastases							
No	863	1			1		
Yes, asymptomatic	112	1.44	1.03-1.99	<0.05	1.16	0.76-1.79	0.499
Yes, symptomatic	227	3.05	2.44-3.86	<0.001	1.37	0.97-1.93	0.071
Liver metastases							
No	864	1			1		
Yes	338	1.35	1.12-1.63	<0.01	1.35	1.12-1.63	<0.01
No. organ sites							
0-2	625	1			1		
≥3	577	1.46	1.21-1.75	<0.001	1.46	1.21-1.75	<0.001
BRAF^{V600} mutation							
Mutant	688	1			1		
Wild-type	514	2.00	1.62-2.46	<0.001	1.05	0.81-1.35	0.728

HRs of age, sex, ECOG performance status, liver metastases, and number of organ sites are equal in both intervals as they did not violate the proportional-hazards assumption.

CI indicates confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; LDH, lactate dehydrogenase.

The cause-specific hazards multivariable Cox-regression analysis for BRAF^{V600} wild-type patients showed that patients with LDH levels of 250 to 500 U/L and patients with liver metastases had lower hazards of receiving second-line treatment (Supplement 8, Supplemental Digital Content 1, http://links.lww.com/AJCO/A360). The cause-specific hazards multivariable Cox-regression analysis for BRAF^{V600}-mutant patients showed that age 75 years and above had a lower hazard of receiving second-line treatment (Supplement 9, Supplemental Digital Content 1, http://links.lww.com/AJCO/A360). An age of 75 years and above, ECOG performance status ≥2, elevated LDH, symptomatic brain metastases, and the number of organ sites ≥3 all had higher hazards for death without next treatment in both BRAF^{V600} wild-type and BRAF^{V600}-mutant patients. The results of the cumulative incidence of third-line treatment show similar results (Fig. 4B).

DISCUSSION

Our data suggest that patients without a BRAF^{V600} mutation have twice the hazard of death within the first 10 months when compared with BRAF^{V600}-mutant patients. This is the first study to describe such an effect. Special emphasis is given to stage IV-M1c/d patients, as a proportion of this stage with poor prognostic characteristics is not included in clinical trials. In our cohort, stage IV-M1c/d wild-type patients have significantly lower survival during the first 12 months since diagnosis when compared with IV-M1c/d BRAF^{V600}-mutant patients. However, the survival advantage of BRAF^{V600}-mutant patients versus BRAF^{V600} wild-type patients diminishes and is no longer significant at 24 months.

This report describes the treatment and outcomes of BRAF^{V600} wild-type patients with advanced melanoma in a population-based setting. In contrast to registries where patients with poor prognostic factors such as brain metastases and poor performance status are included, these patients have mostly been excluded from clinical trials. The use of national registrations provides complementary insight into the clinical outcomes of these patients.

Patients in this study were older and had stage IV-M1c/d more often when compared with the randomized clinical trials of Ascierto et al[16] and Robert et al.[3] This finding emphasizes that the population treated in randomized controlled trials (RCTs) does not match the 'real-world' population and as a result, clinical outcomes are different as well. When we compare our results from the real world to the RCT of Ascierto and colleagues we find a difference in 1-year survival rate of 15% (71% vs. 56%). This RCT of Ascierto and colleagues randomized treatment-naive BRAF^{V600} wild-type patients to either nivolumab or dacarbazine. The large difference in survival between both studies is most likely caused by the fact that in the present study patients with ECOG ≥2 and brain metastases were included as well.

Overall, fewer treatment options are available for BRAF^{V600} wild-type patients, which is illustrated by the fact that 46.7% of patients did not receive any second-line treatment before death. BRAF^{V600} wild-type patients have a lower probability of receiving a second-line treatment (19% vs. 50%) and inversely have a higher probability of dying during first-line treatment or before second-line treatment (32% vs. 18%). We used competing risks analysis to investigate whether the difference in OS between BRAF^{V600} wild-type and BRAF^{V600}-mutant patients was caused by availability of fewer systemic treatment options.

BRAF^{V600} wild-type stage IV-M1c/d patients have significantly lower median OS than BRAF^{V600}-mutant patients, possibly because their only systemic treatment option with proven

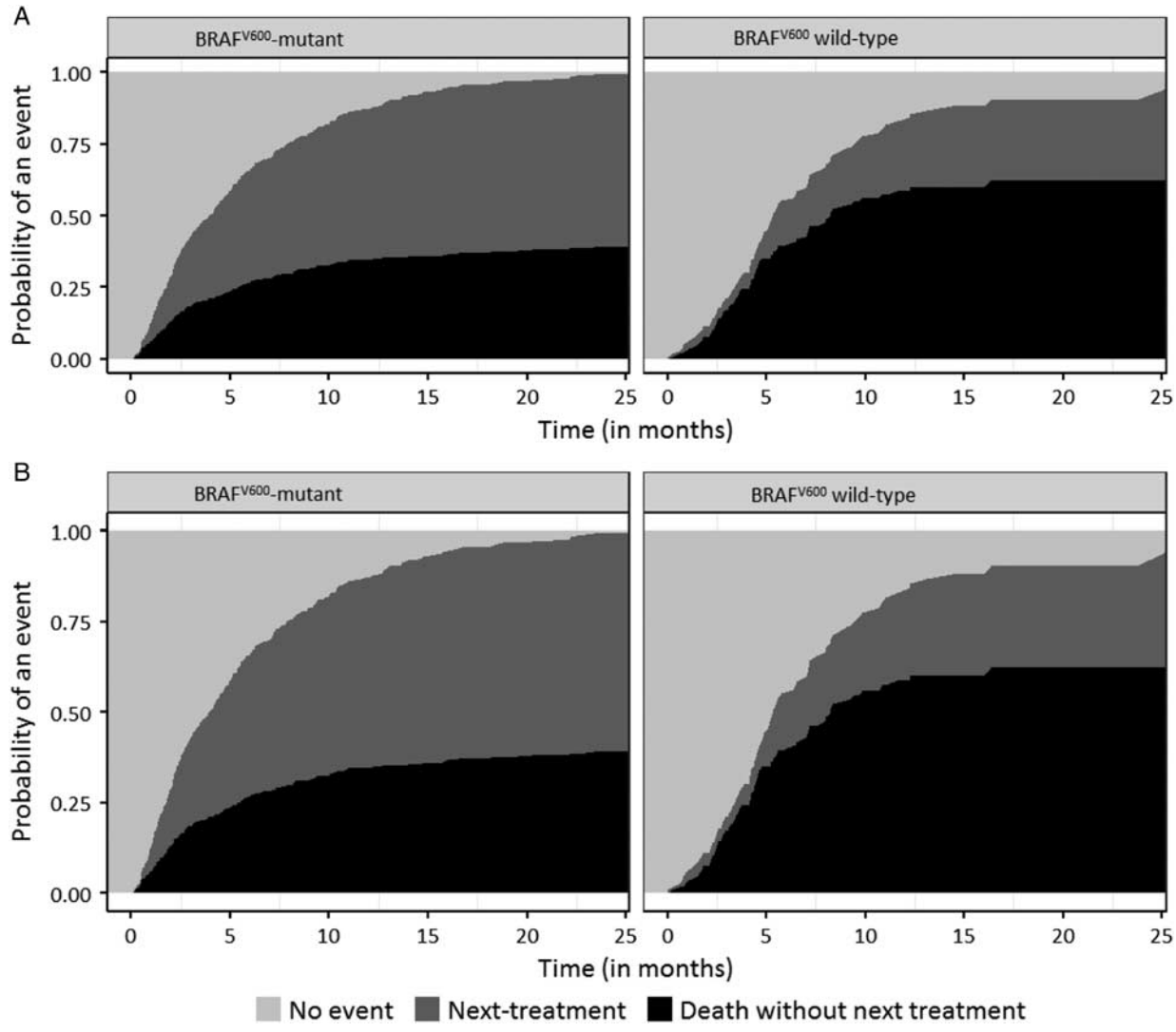

FIGURE 4. Competing risk analysis of first-line (A) and second-line (B) BRAF^{V600} wild-type versus BRAF^{V600}-mutant patients.

survival benefit is immunotherapy. Previous clinical phase II studies have shown that pembrolizumab and ipilimumab have response rates of 20% to 25% in patients with stable brain metastases.[17,18] In contrast, BRAF/MEK combination therapy of dabrafenib+trametinib has a relatively high response rate of ± 60% in patients with brain metastases, but responses are generally short lived.[19] This probably explains why in patients with brain metastases, we see a survival advantage for BRAF^{V600}-mutant patients during the first 10 months. A study using a combination of ipilimumab and nivolumab shows promising results for patients with brain metastases with relatively long-lasting responses of ~50%.[20] The current study included only 82 BRAF^{V600} wild-type patients, treated with first-line ipilimumab plus nivolumab and 8 wild-type patients treated with second-line ipilimumab plus nivolumab. Additional patients are needed to assess clinical outcomes of BRAF^{V600} wild-type versus BRAF^{V600}-mutant patients with brain metastases treated with ipilimumab plus nivolumab in real-world practice.

The results of the multivariable Cox-regression analysis for OS confirm previous data on prognostic factors associated with OS.[21,22] In the cause-specific Cox regression for BRAF^{V600}-mutant patients, we found that patients age 75 years and above were less likely to receive second-line treatment (HR: 0.58, $P = 0.004$) than patients below 75 years. This is in line with expectations of not exposing the elderly with advanced melanoma to many lines of systemic treatment.

We observed a low percentage of patients treated with ipilimumab plus nivolumab in BRAF^{V600} wild-type (16%) and BRAF^{V600}-mutant (8%) patients in the analyzed period. Possibly this is caused by the introduction of this combination in the end of 2016. Regional differences in the Netherlands might have existed as combination therapy was not equally implemented throughout the country around this period. In current practice, the proportion of patients treated with ipilimumab plus nivolumab in the Netherlands is larger. Because the efficacy of ipilimumab plus nivolumab is relatively low in patients with poor performance, high LDH, and symptomatic brain metastases, we think that the observed survival difference between BRAF^{V600}-mutated and wild-type patients will persist.

There are limitations to our study. This study uses observational data from the DMTR. Since the start of this registry in 2013, data managers have been trained and an online

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registration platform warns the data managers for inconsistent or missing values. As a second step, the registered data is checked and approved by medical oncologists. We therefore argue that data are of high quality. This study did not allow us to compare clinical outcomes of first-line anti-PD-1 in BRAF^{V600} wild-type patients versus BRAF^{V600}-mutant patients due to the observational nature of this study. In the Netherlands fit BRAF^{V600}-mutant patients were treated with checkpoint inhibitors, whereas BRAF^{V600}-mutant patients in poor condition received first-line BRAF/MEK inhibitors, we would introduce confounding by indication.

This is the first report that uses real-world and population-based data describing the treatment of BRAF^{V600} wild-type advanced melanoma patients. Although OS of metastatic melanoma has greatly improved due to the introduction of targeted therapy and immunotherapy over the last decade, there is still progress to be made. Especially for BRAF^{V600} wild-type patients, treatment options are limited. The presented results suggest that due to the limited treatment options available, advanced BRAF^{V600} wild-type melanoma patients are less likely to survive the first 10 months after diagnosis compared with BRAF^{V600}-mutant patients.

REFERENCES

1. Fitzmaurice C, Allen C, Barber RM, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the Global Burden of Disease Study Global Burden. *JAMA Oncol*. 2017;3:524–548.
2. Holterhues C, Hollestein LM, Nijsten T, et al. Burden of disease due to cutaneous melanoma has increased in the Netherlands since 1991. *Br J Dermatol*. 2013;169:389–397.
3. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus ipilimumab in advanced melanoma. *N Engl J Med*. 2015;372:2521–2532.
4. Ascierto PA, McArthur GA, Dréno B, et al. Cobimetinib combined with vemurafenib in advanced BRAFV600-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. *Lancet Oncol*. 2016;17:1248–1260.
5. Chapman PB, Robert C, Larkin J, et al. Vemurafenib in patients with BRAFV600 mutation-positive metastatic melanoma: final overall survival results of the randomized BRIM-3 study. *Ann Oncol*. 2017;28:2581–2587.
6. Hauschild A, Grob JJ, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. *Lancet*. 2012;380:358–365.
7. Donia M, Ellebaek E, Øllegaard TH, et al. The real-world impact of modern treatments on the survival of patients with metastatic melanoma. *Eur J Cancer*. 2019;108:25–32.
8. Robert C, Karaszewska B, Schachter J, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. *N Engl J Med*. 2015;372:30–39.
9. Yushak M, Chapman P, Robert C, et al. Systemic therapy options for patients with unresectable melanoma. *Am Soc Clin Oncol Educ Book*. 2017;37:661–672.
10. Colombino M, Capone M, Lissia A, et al. BRAF/NRAS mutation frequencies among primary tumors and metastases in patients with melanoma. *J Clin Oncol*. 2012;30:2522–2529.
11. Heppt MV, Siepmann T, Engel J, et al. Prognostic significance of BRAF and NRAS mutations in melanoma: a German study from routine care. *BMC Cancer*. 2017;17:536.
12. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med [Internet]*. 2019. Available at: http://www.ncbi.nlm.nih.gov/pubmed/31562797.
13. Hodi FS, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med*. 2010;363:711–723.
14. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med*. 2012;366:2443–2454.
15. Jochems A, Schouwenburg MG, Leeneman B, et al. Dutch Melanoma Treatment Registry: quality assurance in the care of patients with metastatic melanoma in the Netherlands. *Eur J Cancer*. 2017;72:156–165.
16. Ascierto PA, Long GV, Robert C, et al. Survival outcomes in patients with previously untreated BRAF wild-type advanced melanoma treated with nivolumab therapy: three-year follow-up of a randomized phase 3 trial. *JAMA Oncol*. 2019;5:187–194.
17. Margolin K, Ernstoff MS, Hamid O, et al. Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. *Lancet Oncol*. 2012;13:459–465.
18. Goldberg SB, Gettinger SN, Mahajan A, et al. Pembrolizumab for patients with melanoma or non-small-cell lung cancer and untreated brain metastases: early analysis of a non-randomised, open-label, phase 2 trial. *Lancet Oncol*. 2016;17:976–983.
19. Davies MA, Saiag P, Robert C, et al. Dabrafenib plus trametinib in patients with BRAFV600-mutant melanoma brain metastases (COMBI-MB): a multicentre, multicohort, open-label, phase 2 trial. *Lancet Oncol*. 2017;18:863–873.
20. Tawbi HA, Forsyth PA, Algazi A, et al. Combined nivolumab and ipilimumab in melanoma metastatic to the brain. *N Engl J Med*. 2018;379:722–730.
21. Nosrati A, Tsai KK, Goldinger SM, et al. Evaluation of clinicopathological factors in PD-1 response: derivation and validation of a prediction scale for response to PD-1 monotherapy. *Br J Cancer*. 2017;116:1141–1147.
22. Schadendorf D, Long GV, Stroiakovski D, et al. Three-year pooled analysis of factors associated with clinical outcomes across dabrafenib and trametinib combination therapy phase 3 randomised trials. *Eur J Cancer*. 2017;82:45–55.