An integrated view on assuring quality for multimodal therapy in oncologic care

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4 Vemurafenib in BRAF-mutant metastatic melanoma patients in real-world clinical practice: prognostic factors associated with clinical outcomes

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ABSTRACT

The aim of this population-based study was to identify the factors associated with clinical outcomes in vemurafenib-treated patients and to evaluate outcomes across subgroups of patients with different risk profiles. Data were retrieved from the Dutch Melanoma Treatment Registry. Time to next treatment (TTNT) and overall survival (OS) of all metastatic melanoma patients who received vemurafenib between 2012 and 2015 were assessed using Kaplan–Meier estimates. A risk score was developed on the basis of all prognostic factors associated with TTNT and OS derived from multivariable Cox regression analyses. Patients were stratified according to the presence of prognostic risk factors by counting the number of factors, ranging from 0 to 6. A total of 626 patients received vemurafenib with a median follow-up of 35.8 months. The median TTNT and OS were 4.7 months [95% confidence intervals (CI): 4.4–5.1] and 7.3 months (95%CI: 6.6–8.0). The strongest prognostic factors were serum lactate dehydrogenase (LDH) level, Eastern Cooperative Oncology Group performance score, number of organ sites involved and brain metastases. Patients with a favourable risk profile (no risk factors) had a median TTNT and OS of 7.1 (95%CI: 5.8–8.5) and 15.4 months (95%CI: 10.0–20.9). The median OS more than halved for patients with greater than or equal to 2 risk factors compared with patients with no risk factors. The clinical outcomes of vemurafenib in metastatic melanoma patients with a favourable risk profile are comparable with the results of the trials. Combining prognostic factors into a risk score could be valuable to stratify patients into favourable and poor-prognosis groups.

INTRODUCTION

With the introduction of targeted therapies and immune checkpoint inhibitors, the treatment of metastatic melanoma has been revolutionized [1–6]. The BRIM-3 study showed an improved progression-free and overall survival (OS) of the BRAF inhibitor vemurafenib compared with standard chemotherapy in BRAF-mutant metastatic melanoma [1]. Vemurafenib was the first targeted therapy for metastatic melanoma to be approved by the European Medicines Agency in 2012 [7]. Since then, vemurafenib has increasingly been used in patients with poor prognostic factors as it can induce rapid antitumour response and symptom relief [8].

Patients with poor prognostic factors, such as an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of greater than or equal to 2 and/or symptomatic brain metastases, represent a significant group in real-world clinical practice [9,10], but were excluded from the pivotal trial [1]. Several open-label studies of vemurafenib in metastatic melanoma showed that an ECOG PS greater than or equal to 2, presence of brain metastases and an elevated lactate dehydrogenase (LDH) serum level are among the strongest predictors of impaired outcomes [11,12]. However, there is little evidence on the association of these factors on clinical outcomes in real-world daily practice. Most open-label studies excluded patients with symptomatic brain metastases [11,12] representing over 10% of systemically treated metastatic melanoma patients [13]. Second, the prognostic relevance of combining risk factors has not yet been studied. It is therefore very important to know to what extent the results achieved in the pivotal trials and open-label studies can be extrapolated to real-world melanoma patients treated with vemurafenib.

Furthermore, reliable real-world outcome data of vemurafenib could function as a valuable benchmark for future population-based outcome studies of metastatic melanoma patients treated with the more recently registered drugs, such as concurrent treatment with a MEK and BRAF inhibitor [5], monotherapy or combination therapy with immune checkpoint inhibitors targeting anti-PD1 and/or anti-CTLA-4 [3,6,14]. Therefore, the aim of this population-based study is to identify the prognostic factors associated with clinical out-comes in BRAF-mutant metastatic melanoma patients in real-world clinical practice in The Netherlands. Second, we assessed differences in clinical outcomes across subgroups of patients with multiple prognostic baseline factors.

METHODS

Data: the Dutch melanoma treatment registry

Data were retrieved from the Dutch Melanoma Treatment Registry (DMTR), a population-based registry that was set up to monitor the safety and effectiveness of the new drugs in real-world clinical practice and to assess the quality of melanoma care in The Netherlands. The DMTR registers information on baseline patient and tumour characteristics, treatments, treatment-related adverse events (grade 3 or 4 according to the common terminology criteria for adverse events, version 4) and clinical outcomes of all Dutch patients with unresectable stage IIIc or IV melanoma. A detailed description of the set-up of the DMTR has been published previously [13]. In compliance with Dutch regulations, the DMTR was approved by the medical ethical committee and was not subject to the Medical Research Involving Human Subjects Act.

Patients

All patients with BRAF-mutant unresectable or meta-static (stage IIIc or stage IV) cutaneous melanoma or with a BRAF-mutant melanoma of unknown primary in The Netherlands who received vemurafenib (monotherapy) between 1 July 2012 and 30 June 2015 were included (follow-up data cut-off was 20 November 2016).

Statistical analysis

Descriptive statistics were used to describe the baseline characteristics at the start of vemurafenib treatment. The median time to next treatment (TTNT) and OS with the corresponding two-sided 95% confidence intervals (CI) were analyzed using the Kaplan–Meier method. TTNT is a commonly used measure to assess treatment effectiveness in real-world studies [15] and was determined from the start of vemurafenib to the start of subsequent systemic therapy or death from any cause. The median OS was defined as the time from the start of vemurafenib to the date of death from any cause. Follow-up time was calculated using the inverse Kaplan–Meier method [16]. TTNT and OS were compared between subgroups using log-rank tests for categorical variables and a univariate Cox proportional hazard regression for continuous variables. Subgroups of patients were stratified according to sex, baseline ECOG PS (0, 1, and ≥ 2), baseline LDH level [< 1 × above the upper limit of normal

(ULN) range of 250 U/l, 1–2 × ULN, ≥ 2 × ULN], metastatic stage at baseline (M1a, M1b, and M1c), type of BRAF mutation (V600E, V600K or other), number of organ sites involved at baseline counted as any organ with at least one metastasis (< 3 vs. ≥ 3) and brain metastases at baseline (absent, asymptomatic, or symptomatic). Age was analyzed as a continuous variable.

A backward stepwise multivariable Cox regression analysis was used to identify the baseline prognostic factors associated significantly with OS and TTNT. All factors of the above-mentioned subgroups were entered in the model. Variables with a P value greater than 0.05 were removed from the stepwise model.

A clinical risk score was developed by counting the four prognostic factors of the Cox regression analysis: ECOG PS 0, LDH less than 1 × ULN, no brain metastases and less than 3 organ sites involved counted as 0; ECOG PS 1, LDH 1–2 × ULN and brain metastases counted as 1; and ECOG PS 2 and LDH greater than or equal to 2 × ULN counted as 2. Patients were stratified according to the presence of prognostic risk factors, ranging from 0 to 6.

Missing data were imputed for the Cox regression analyses using multiple imputations by chained equations. To stabilize the results, 10 imputed data sets were produced [17].

All statistical analyses were carried out in PASW Statistics version 20 (SPSS Inc., Chicago, Illinois, USA).

RESULTS

Patient and treatment characteristics

A total of 626 patients with unresectable stage IIIc or IV BRAF-mutant melanoma received vemurafenib from 1 July 2012 until 30 June 2015. The median follow-up was 35.8 months (95%CI: 32–39.5). Most patients had M1c disease (83%), almost one-fifth of patients had an ECOG PS of greater than or equal to 2 (19%) and 19% had symptomatic brain metastases (Table 1). In total, 42% of patients had an elevated serum LDH level. The imputed baseline characteristics were comparable with the observed baseline characteristics (Supplementary Table S1).

Most patients (n = 506; 81%) were treatment naïve. Almost one-fifth received previous systemic therapy (19%), including ipilimumab (6%), chemotherapy (3%),

Table 1. Baseline characteristics of all consecutive patients diagnosed with irresectable melanoma in The Netherlands between July 2012- and July 2015 (n=626) at start of treatment with vemurafenib.

	N (%)
Median age (range), years	59 (23-90)
Age group	
< 50	159 (25)
50-59	157 (25)
60-69	177 (28)
≥70	133 (21)
Gender	
Male	349 (56)
Female	277 (44)
ECOG PS	
0	223 (36)
1	218 (35)
≥2	118 (19)
Unknown	67 (11)
LDH category[a]	
<ULN	343 (55)
≥1 to <2 x ULN	125 (20)
≥2 x ULN	138 (22)
Unknown	20 (3)
Disease stage	
Stage IIIc	12 (2)
M1a	34 (5)
M1b	36 (6)
M1c	522 (83)
Unknown M stage	22 (3)
BRAF mutation	
V600E	505 (81)
V600K	59 (9)
Other	46 (7)
Unknown	16 (3)
Number of organ sites[b]	
<3	215 (35)
≥3	341 (56)
Unknown	58 (9)

Table 1. Baseline characteristics of all consecutive patients diagnosed with irresectable melanoma in The Netherlands between July 2012- and July 2015 (n=626) at start of treatment with vemurafenib. (*continued*)

	N (%)
Brain metastases	
No	394 (63)
Asymptomatic	58 (9)
Symptomatic	119 (19)
Unknown	55 (9)
Previous systemic therapy	
Treatment naive	506 (81)
Previously treated	120 (19)
Median time from advanced melanoma diagnosis to start of vemurafenib (IQR), months	1.4 (0.8-2.8)
Treatment naive	1.2 (0.7-2.1)
Previously treated[c]	6.8 (3.1-12.4)

ECOG PS = Eastern Cooperative Oncology Group performance status; IQR = interquartile range; LDH= lactate dehydrogenase, ULN=upper limit of normal.
[a] ULN is defined at 250 U/L
[b] Patients with stage IV disease (N=613)

dabrafenib (2%), vemurafenib (1%), therapy within a trial (1%) or multiple regimens (7%) (Table 1). At the time of analysis, 95% patients discontinued treatment with vemurafenib, mostly because of disease progression (n = 362; 58%). Other reasons were adverse events (17%), death (8%), preference of the patient (4%), planned in advance (4%) and unknown (10%). Of those who discontinued treatment, 254 (41%) patients received subsequent therapy, including ipilimumab (20%), dabrafenib (9%), anti-PD1 (7%), combination therapy of BRAF and MEK inhibitor (2%), chemotherapy (2%) and retreatment with vemurafenib (1%).

Survival outcomes

The median TTNT and OS were 4.7 months (95%CI: 4.4–5.1) and 7.3 months (95%CI: 6.6–8.0), respectively. Survival rates at 1 and 2 years were 32% (95%CI: 28–35) and 15% (95%CI: 12–18), respectively (Figure 1a and b, Table 2). Table 2 shows the median TTNT, OS and 1-year and 2-year survival rates of the subgroup analyses. Patients with an ECOG PS of greater than or equal to 2 had the lowest

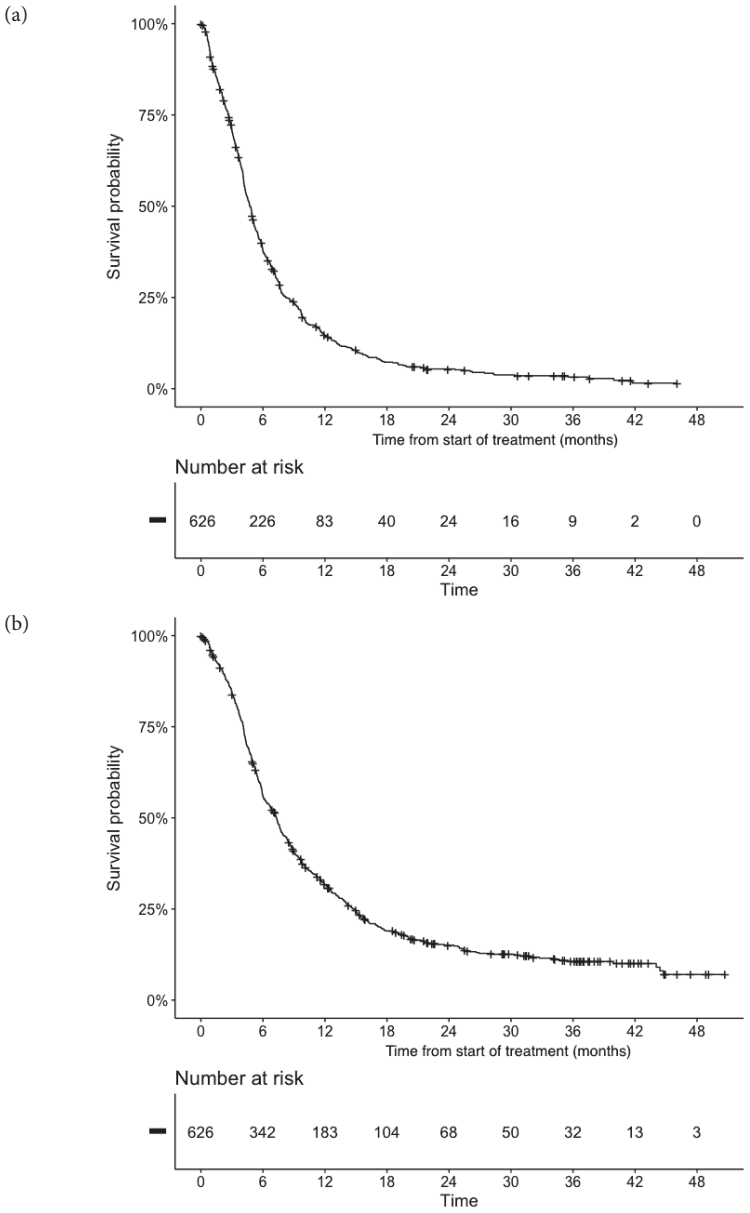

Figure 1. Kaplan–Meier curves of time to next treatment (a) and overall survival (b) of the overall study population.

Table 2. Kaplan-Meier estimates of time to next treatment, median overall survival and 1-year and 2-year survival rates according to prognostic baseline risk factors

Subgroup	*N*	Median TTNT (95%CI), mo	*P*	Median OS (95% CI), mo	1-Year OS (95% CI), %	2-Year OS (95% CI), %	*P*
Age	626	4.7 (4.4-5.1)	0.653	7.3 (6.6-8)	32 (28-35)	15 (12-18)	0.597
Sex							
Male	349	4.8 (4.4-5.3)	0.51	7.2 (6.2-8.2)	31 (26-36)	14 (10-18)	0.932
Female	277	4.7 (4.2-5.2)		7.6 (6.6-8.5)	32 (26-38)	15 (10-19)	
ECOG PS							
0	223	5.5 (4.9-6.1)	<0.001	10.1 (7.9-12.3)	45 (39-52)	21 (15-27)	<0.001
1	218	5.0 (4.5-5.5)		6.7 (5.7-7.7)	25 (19-31)	12 (7-16)	
≥2	118	3.5 (2.9-4.1)		4.1 (3.5-4.6)	13 (7-19)	6 (1-11)	
LDH category							
<ULN	343	5.9 (5.3-6.5)	<0.001	10.0 (8.6-11.5)	42 (37-48)	22 (17-26)	<0.001
≥1 to <2 x ULN	125	4.1 (3.4-4.8)		6.0 (4.8-7.1)	24 (17-32)	6 (1-10)	
≥2 x ULN	138	3.7 (3.3-4.1)		4.4 (3.9-4.9)	8 (3-12)	4 (0-7)	
Disease stage							
IIIc	12	5.5 (0.0-13.9)	<0.001	25.0 (NR-NR)	58 (30-86)	49 (20-78)	<0.001
M1a	34	6.8 (4.8-8.7)		13.8 (11.8-15.9)	63 (47-80)	31 (14-47)	
M1b	36	7.2 (5.0-9.5)		19.9 (12.8-27.0)	67 (51-82)	34 (18-50)	
M1c	522	4.5 (4.2-4.9)		6.4 (5.7-7.0)	26 (22-29)	11 (8-13)	

Table 2. Kaplan-Meier estimates of time to next treatment, median overall survival and 1-year and 2-year survival rates according to prognostic baseline risk factors (*continued*)

Subgroup	*N*	Median TTNT (95%CI), mo	*P*	Median OS (95% CI), mo	1-Year OS (95% CI), %	2-Year OS (95% CI), %	*P*
BRAF mutation							
V600E	501	4.9 (4.5-5.3)		7.4 (6.7-8.2)	34 (29-38)	16 (12-19)	
V600K	59	(4.0 (2.6-5.5)	0.09	5.6 (3.4-7.8)	27 (16-38)	12 (2-22)	0.13
Other	49	4.8 (3.4-6.2)		5.5 (4.4-6.6)	24 (12-37)	11 (1-20)	
No. of organ sites							
< 3	215	5.8 (5.1-6.5)	<0.001	9.7 (7.6-11.8)	42 (36-48)	24 (18-29)	<0.001
≥ 3	341	4.3 (3.9-4.7)		6.1 (5.3-6.8)	24 (20-29)	9 (6-12)	
Brain metastases							
No	394	5.0 (4.4-5.4)		8.4 (7.5-9.2)	36 (31-41)	18 (14-22)	
Asymptomatic	58	4.9 (3.3-6.5)	0.02	7.6 (4.8-10.4)	30 (17-42)	4 (0-10)	<0.001
Symptomatic	119	4.3 (3.7-4.9)		5.4 (4.4-6.3)	17 (10-24)	5 (0-11)	

CI = confidence interval, ECOG PS = Eastern Cooperative Oncology Group performance score, LDH= lactate dehydrogenase, mo= months, NA= not applicable, NR= not reached, OS= overall survival , TTNT = time to next treatment, ULN = upper limit of normal.

median TTNT and OS (3.5 and 4.1 months, respectively) as well as patients with LDH level greater than or equal to 2 × ULN (3.7 and 4.4 months, respectively). The 1-year survival rates were also the lowest in these subgroups of patients. The 1-year survival rate of patients with asymptomatic brain metastases was comparable with that of patients without brain metastases, but decreased considerably to a 2-year survival rate of 5% compared with a 2-year survival rate of 18% for patients without brain metastases. The median OS of patients with previous systemic therapy was not significantly different compared with treatment-naive patients (6.6 months 95%CI: 4.8–8.4 vs. 7.4 months 95%CI: 6.6–8.2, respectively).

Multivariable Cox regression shows that ECOG PS, LDH level and the number of organ sites involved were associated significantly with TTNT and survival (Table 3). The presence of brain metastases was only significantly associated with survival.

Table 3. Multivariable Cox regression analysis of baseline factors associated with overall survival and time to next treatment in patients treated with of vemurafenib

	OS		TTNT	
Covariate	HR (95% CI)[a]	*P*	HR (95% CI)[a]	*P*
ECOG PS				
0	reference		reference	
1	1.5 (1.2-1.8)	<0.001	1.1 (0.9-1.3)	0.304
≥2	2.0 (1.5-2.6)	<0.001	1.7 (1.3-2.1)	<0.001
LDH category				
<ULN	reference		reference	
≥1 to <2 x ULN	1.6 (1.3-2.0)	<0.001	1.7 (1.3-2.1)	<0.001
≥2 x ULN	2.2 (1.8-2.8)	<0.001	1.8 (1.4-2.2)	<0.001
Brain metastases				
No	reference		-	
Asymptomatic	1.2 (0.9-1.6)	0.27	-	-
Symptomatic	1.5 (1.2-1.8)	<0.001	-	-
Number of organ sites				
< 3	reference		reference	
≥3	1.5 (1.2-1.8)	<0.001	1.4 (1.2-1.6)	<0.001

ECOG PS = Eastern Cooperative Oncology Group performance status; HR = hazard ratio; LDH = lactate dehydrogenase; OS = overall survival; TTNT= time to next treatment

[a] Analysis is carried out with an imputed dataset

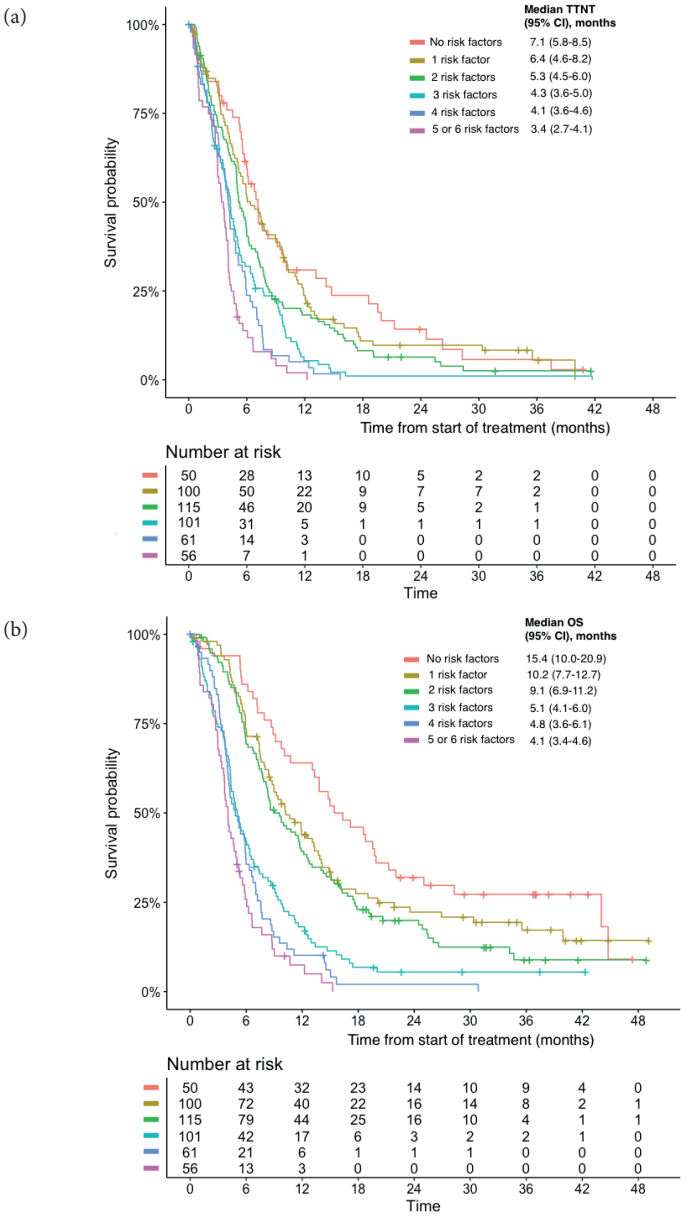

Figure 2. Kaplan-Meier curves of time to next treatment (a) and overall survival (b) according to the number of risk factors at baseline. CI = confidence interval; TTNT = time to next treatment .

A risk score was created with all factors from the multi-variable cox regression, ranging from 0 to 6 factors. Patients with five or six risk factors were merged as only seven patients had six risk factors. Patients with a favourable risk profile (no risk factors; n = 50) had a median TTNT and OS of 7.1 and 15.4 months, respectively (Figure 2a and b). The median TTNT almost halved for patients with four risk factors compared with patients with no risk factors. The median OS decreased considerably for patients with three risk factors compared with patients without any risk factors (5.1 vs. 17.0 months). Patients with five or six risk factors (n = 56) had the lowest median TTNT and OS of 3.4 and 4.1 months, respectively.

DISCUSSION

This study shows that ECOG PS, LDH level and number of organ sites involved were the prognostic factors associated most strongly with TTNT and OS in BRAF-mutant metastatic melanoma patients treated with vemurafenib in real-world clinical practice. We also showed that combining prognostic factors into a clinical risk score could be useful to stratify patients into favourable or poor-prognosis groups.

The median OS in Dutch clinical practice was lower than that reported in the phase III BRIM-3 trial of vemurafenib (7.3 vs. 13.6 months, respectively) [1]. This is most likely because of the relatively large number of patients with less favourable prognostic factors in our population-based study. Over one-third of our study population would have been ineligible for phase III trial enrolment because of symptomatic brain metastases and/or an ECOG PS greater than or equal to 2. Even in the safety study of vemurafenib [11], a lower rate of ECOG PS of greater than or equal to 2 was reported (10 vs. 19% in our study) and patients with symptomatic brain metastases were excluded. The multivariable Cox regression analysis confirmed that both factors impaired survival significantly.

On the basis of the results of our subgroup analyses, the median OS for patients with an ECOG PS greater than or equal to 2 appears to be comparable with survival data reported in the safety study (4.1 vs. 4.9 months, respectively [18]). Similar results were observed for patients with symptomatic brain metastases (5.4 months in our

study vs. 5.1 months in the open-label pilot study of patients with symptomatic brain metastases treated with vemurafenib [19]). Compared with the historic series with an estimated median OS of 2.1 months for patients with brain metastases [20], our study may indicate a benefit of targeted therapy in this subgroup.

Consistent with previous results [11,12], a baseline LDH level of greater than or equal to 2 ULN was an important independent predictor of inferior survival (hazard ratio: 2.2). Although long-term outcomes remain poor, it is known that targeted therapies are capable of inducing rapid antitumour responses and might be more effective in this subgroup compared with immunotherapy [21]. Previous studies on immunotherapies in metastatic melanoma confirmed that benefit was unlikely, reporting a median OS of 2.3 after ipilimumab therapy for patients with an LDH level of greater than or equal to 2 ULN [21] and 2.9 months after anti-PD1 therapy for patients with an LDH level of greater than or equal to 2.5 ULN [22]. Although a direct comparison of outcomes is not possible between studies, our results may indicate more activity of targeted therapy in this patient group. Findings from a pooled analysis of trials of concurrent treatment with a MEK and BRAF inhibitor showed even more promising results for this subgroup of patients with a median OS of 8.8 months [23].

Combining the risk factors instead of assessing them separately could be useful to stratify patients into favourable or poor-prognosis groups and may support clinical-decision making. The median TTNT and OS of 7.1 and 15.4 months in patients with a favourable risk profile (no risk factors) could indicate that durable benefit is possible with vemurafenib in well-defined patient subgroups. However, the majority of patients had one or more risk factors, with almost 70% of patients having multiple risk factors (≥2). The poor outcomes in patients with an unfavourable risk profile (≥3 risk factors; median OS of <5 months) underline the unmet medical need for patients with multiple risk factors treated with vemurafenib monotherapy. In recent years, concurrent treatment with a MEK and BRAF inhibitor has become the standard of care for BRAF-mutant metastatic melanoma patients, including for patients with poor prognostic factors. It will be important to assess whether the superior efficacy achieved in the trials of combined targeted therapies [5,24] may also be achieved in these high-risk groups in daily practice.

This population-based study has some limitations. Registries are generally more prone to missing data compared with clinical trials. The clinical risk score could not be calculated for 23% of patients because data were missing on one or more of the selected risk factors. However, reliable survival data could still be analyzed because of the large sample size and long follow-up. Furthermore, data managers were trained extensively and medical oncologists supervise the registration process to ensure high-quality data [13]. This study only focused on the clinical outcomes TTNT and OS. As vemurafenib is commonly used for symptom relief in unfit patients with a high disease load, the emphasis is predominantly on improving the quality of life. The DMTR is currently collecting quality of life data and we are planning to assess the overall benefit of vemurafenib treatment, especially in patients with poor prognostic factors.

Conclusion

In conclusion, our results show that the clinical outcomes of vemurafenib in BRAF-mutant metastatic melanoma patients with a favourable risk profile are comparable with the pivotal trials. However, our results also emphasize that trial results are not generalizable to a more heterogeneous patient population in daily practice as the majority of patients have a less favourable risk profile. Real-world data from clinical practice complement the knowledge on clinical outcomes in high-risk metastatic melanoma patients, in particular, on patients with multiple risk factors.

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APPENDICES

Supplementary Table 1. Imputed baseline characteristics of patients treated with vemurafenib

	Real-world data *N*= 626 *N* (%)	Imputed data *N*= 626 *N* (%)
Median age (range), years	59 (23-90)	59 (23-90)
Age group		
< 50	159 (25)	159 (25)
50-59	157 (25)	157 (25)
60-69	177 (28)	177 (28)
≥70	133 (21)	133 (21)
Sex		
Male	349 (56)	349 (56)
Female	277 (44)	277 (44)
ECOG PS		
0	223 (40)	248 (40)
1	218 (39)	244 (39)
≥2	118 (21)	134 (21)
Unknown	67 (11)	
LDH category[a]		
<ULN	343 (57)	347 (55)
≥ULN	263 (43)	279 (45)
≥1 to <2 x ULN	125 (21)	130 (21)
≥2 x ULN	138 (23)	149 (24)
Unknown	20 (3)	
Disease stage		
Stage IIIc	12 (2)	12 (2)
M1a	34 (6)	35 (6)
M1b	36 (6)	37 (6)
M1c	522 (86)	542 (87)
Unknown M stage	22 (3)	
Number of organ sites[b]		
<3	215 (39)	238 (37)
≥3	341 (61)	387 (63)
Unknown	58 (9)	

Supplementary Table 1. Imputed baseline characteristics of patients treated with vemurafenib (*continued*)

	Real-world data *N*= 626 *N* (%)	Imputed data *N*= 626 *N* (%)
Brain metastases		
No	406 (70)	437 (70)
Asymptomatic	58 (10)	62 (10)
Symptomatic	119 (20)	127 (20)
Unknown	43 (7)	
Previous systemic therapy		
Treatment naive	506 (81)	506 (81)
Previously treated	120 (19)	120 (19)

yrs=years; PS = performance score; LDH= lactate dehydrogenase, ULN=upper limit of normal.
[a] ULN is defined at 250 U/L
[b] Patients with stage IV disease (N=614)