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Original research

Efficacy of encorafenib plus binimetinib in patients with BRAF-mutated melanoma brain metastases: Results from the Dutch Melanoma Treatment Registry

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ABSTRACT

Aim: Data on the effectiveness of encorafenib/binimetinib in melanoma patients with brain metastases (BMs) are limited.

Methods: All patients with *BRAF V600*-mutated melanoma and BMs treated with encorafenib/binimetinib between 2019 and 2022 in the Netherlands were included from the nationwide Dutch Melanoma Treatment Registry. Patients previously treated with other BRAF/MEK inhibitors were excluded. We analyzed objective response rates (ORR), progression-free survival (PFS), and overall survival (OS). Multivariable Cox regression identified factors associated with survival. Subgroup analyses included asymptomatic versus symptomatic BMs and line of treatment (first-line versus later-line).

Results: In total, 190 patients were included. Symptomatic BMs were present in 63 % of patients. Encorafenib/binimetinib was the first-line treatment in 64 % of all patients, while 36 % had prior immunotherapy. Overall, the ORR was 69.4 %, median PFS was 5.5 months (95 %CI 4.9–6.2), and median OS 11.9 months (95 %CI 10.0–15.7). Age $\geq$ 70, ECOG PS $\geq$ 2, symptomatic BMs, and elevated LDH were significantly associated with worse survival. Patients with prior immunotherapy had a median PFS of 6.9 months (95 %CI 4.3–9.6) and OS of 17.9 months (95 %CI 13.7–31.2), while this was 4.9 months (95 %CI 4.3–5.5) and 10.1 months (95 %CI

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8.1–13.0) in treatment-naïve patients. Median PFS and OS in patients with asymptomatic versus symptomatic BMs were 6.1 months (95 %CI 4.9–9.8) and 20.5 (95 %CI 14.0-NA) versus 5.3 months (95 %CI 4.9–6.3) and 10.7 (95 %CI 8.9–13.7), respectively.
Conclusions: Encorafenib/binimetinib has clinical activity in real-world melanoma patients with BMs. Their prognosis is determined by the presence of symptomatic BMs, age, ECOG PS, and LDH levels.

1. Introduction

The prognosis of advanced melanoma patients significantly improved after the introduction of targeted therapy and immunotherapy [1]. However, the management of melanoma brain metastases remains a challenge, which is a concerning issue given that approximately 50 % of advanced melanoma patients develop brain metastases during their disease course [2–7]. Patients with active brain metastases were excluded from registration trials in metastatic melanoma. Previous research from the Dutch Melanoma Treatment Registry (DMTR) showed worse treatment outcomes for trial-ineligible patients [4]. Brain metastases were the main reason for exclusion. The fact that patients with active brain metastases were excluded from most phase III trials specifically complicates translating the results of these trials to this specific patient group [8,9].

Combination immunotherapy with ipilimumab/nivolumab has emerged as the preferred first-line systemic therapy for patients with asymptomatic brain metastases, regardless of their *BRAF* mutation status [8,10,11]. However, in distinct melanoma patients with a *BRAF V600* mutation, targeted therapy with BRAF/MEK inhibitors is preferred over immunotherapy. This applies to those with asymptomatic brain metastases and concurrent autoimmune disease or poor condition and patients dependent on corticosteroids at the initiation of systemic therapy (>10 mg prednisolone or its equivalent) [12]. Depending on the extent of brain metastases and symptoms, surgery, radiotherapy, (induction) therapy with BRAF/MEK inhibitors followed by immunotherapy are treatment options that can be considered for patients with symptomatic brain metastases [8,13,14]. While post-approval trials have been conducted for other BRAF/MEK inhibitor combination therapies in melanoma patients with brain metastases, limited evidence is available for encorafenib plus binimetinib in these patients [13,14]. Recently published studies, all including a relatively low number of patients, have reported promising clinical benefits of encorafenib plus binimetinib in melanoma patients with brain metastases [15,16]. The largest study, including 48 patients, primarily focused on the use of encorafenib plus binimetinib with subsequent radiotherapy in patients with *BRAF V600*-mutant melanoma and brain metastases, showed a high intra-cranial response rate (70.8 %) after two months of systemic treatment [17].

In the nationwide Dutch Melanoma Treatment Registry (DMTR), patient-, tumor-, and treatment characteristics, clinical outcomes, and patient-reported measures are registered for all (neo)adjuvant-treated melanoma patients and all advanced melanoma patients in the Netherlands, regardless of whether they received therapy [18]. Originally created for quality assurance and hospital benchmarking, this mandatory patient registry also provides valuable data for research among specific patient subgroups [4,19]. This study used data from the DMTR to investigate response rates, progression-free survival (PFS), and OS of patients with melanoma brain metastases treated with encorafenib plus binimetinib. Moreover, we described toxicity and tried to identify characteristics of those achieving long-term survival.

2. Materials and methods

This study was conducted using data from the DMTR, a nationwide patient registry including all (neo)adjuvant-treated and advanced melanoma patients from all 14 melanoma centers in the Netherlands. Data are prospectively collected and registered by trained data managers based on information extracted from electronic health records. Entries are checked annually a medical oncologist in each melanoma center. The medical ethics committee (METC Leiden) deemed research using DMTR data exempt from the Dutch Medical Research Involving Human Subjects Act in compliance with Dutch regulations [18,20].

2.1. Patient selection

All *BRAF V600*-mutated melanoma patients with brain metastases who started encorafenib binimetinib combination therapy between 2019 and 2022 were included. The data cut-off was December 31, 2023. Patients with mucosal or uveal melanoma were excluded. No prior (adjuvant) treatment with other BRAF/MEK inhibitors was allowed. Other types of prior treatment, including (adjuvant) immunotherapy, were allowed.

2.2. Statistical analysis

Patient- and tumor characteristics at the start of encorafenib plus binimetinib treatment were described using descriptive statistics. Depending on their distribution, continuous variables were compared with the students' *t*-test or the Mann-Whitney U-test, and categorical variables were compared with the Pearsons' chi-square test. Median treatment duration was described, with treatment duration defined as the period from therapy start date until therapy stop date. Patients with missing stop dates due to ongoing treatment at the time of data cut-off or missing follow-up data were excluded from the treatment duration analysis. The reversed Kaplan-Meier method was used to calculate the median follow-up duration [21]. Response evaluation was based on the RECIST 1.1 criteria and clinical judgment of the treating medical team [22]. Notably, separate intracranial responses are not included in the DMTR; therefore, reported responses reflect overall response. Best Overall Response (BOR) and overall Objective Response Rate (ORR) were described. The BOR was categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). PD included both disease progression and melanoma-related death. The overall ORR was defined as the percentage of evaluable patients who achieved either a complete response (CR) or partial response (PR). Patients were assessed as not evaluable for overall ORR if they died from a non-melanoma-related cause before the first response evaluation or if the response evaluation was not registered. The Kaplan-Meier method was used to calculate progression-free survival (PFS) and overall survival (OS). PFS was calculated from the start date of encorafenib plus binimetinib treatment to progression or death. A sensitivity analysis was performed after exclusion of patients who received encorafenib plus binimetinib as an induction therapy, followed by ipilimumab and nivolumab. Patients undergoing induction therapy were identified by meeting all of the following criteria: a treatment duration of 120 days or less, treatment discontinuation without progression, and subsequent treatment with ipilimumab and nivolumab combination therapy. Toxicity rates and reasons for treatment discontinuation were described. A multivariable Cox proportional hazard model was performed to identify prognostic factors associated with survival. Additionally, subgroup analyses of response, PFS, and OS were performed on patients with asymptomatic versus patients with symptomatic brain metastases and for first-line treatment versus second- or later-line treatment. We assessed symptomatology based on clinical judgement of the treating physician, as documented in the Electronic Health Record. Since the

specification of corticosteroid doses and specific neurological symptoms are not recorded in the DMTR, and given the ongoing debate on the definition of symptomatic brain metastases, this approach allowed us to categorize patients in a way that reflects clinical practice [23,24]. Baseline patient- and tumor characteristics were described for patients surviving < 1 year, > 1 year, and > 2 years. The statistical analyses were performed using Rstudio version 4.2.3, packages dplyr, tidyverse, tableone, ggplot2, survival, survminer, forestmodel.

3. Results

3.1. Patient-, tumor-, and treatment characteristics

In total, 190 patients with melanoma and brain metastases treated with encorafenib plus binimetinib between 2019 and 2022 were included. The median follow-up duration was 26.9 months (95 % confidence interval (95 % CI) 23.4–29.7 months). Patient- and tumor characteristics can be found in Table 1. Encorafenib plus binimetinib was the first-line systemic treatment in 122 patients (64 %). At the start of encorafenib plus binimetinib treatment, the median age was 64, and 81 patients (43 %) were female. Most patients had symptomatic brain metastases (120 patients; 63 %). Of all patients, 70 (37 %) had liver metastases, and in 130 (68 %), metastases were located in three or more organs. Fifteen patients (7 % of all patients) received brain radiotherapy before the start of encorafenib plus binimetinib therapy. For treatment duration analysis, 40 patients with missing stop therapy stop dates were excluded. The median treatment duration was 92 days (IQR: 67–170); however, this was 130 days (IQR: 61–208) after excluding patients who received encorafenib plus binimetinib as induction therapy.

3.2. Response, progression-free survival, and overall survival

In all patients together, the complete response (CR) rate was 2.2 %, the partial response (PR) rate was 67.2 %, and the overall ORR was 69.4 % (Table 2). The median PFS was 5.5 months (95 % CI 4.9–6.2) (Fig. 1A), and the median OS was 11.9 months (95 % CI 10.0–15.7) (Fig. 1B). Median PFS and OS for patient groups based on specific characteristics (Eastern Cooperative Oncology Group Performance Status (ECOG PS), lactate dehydrogenase (LDH) levels, age) are detailed in Supplementary Table 1. After excluding 43 patients who received encorafenib plus binimetinib as an induction therapy, the median PFS was 5.8 months (95 % CI 4.9–6.5), and the median OS was 9.7 months (95 % CI 8.4–13.9) (Supplementary Figure 1).

3.3. Toxicity and treatment discontinuation

In total, 9 % (n = 17) of all patients experienced grade ≥ 3 toxicity. Two (1.1 %) experienced skin toxicity, 10 (5.3 %) liver toxicity, 2 (1.1 %) nephrotoxicity, 3 (1.6 %) diarrhea/colitis, and 1 (0.5 %) had recurrent anemia. The reason for treatment discontinuation of encorafenib plus binimetinib was registered for 153 patients. Any grade toxicity was the reason for treatment discontinuation in 12 patients (6 %), disease progression or death in 44 patients (23 %), and 97 patients (51 %) discontinued encorafenib plus binimetinib treatment for other reasons (e.g., poor patient condition, patient wish or switch to other treatment in the absence of progression/toxicity).

3.4. Previous systemic therapies

Of all patients, 122 patients (64 %) had no previous systemic treatment, 51 patients (27 %) had one systemic treatment line, 11 patients (6 %) had two systemic treatment lines, and six patients (3 %) had three systemic treatment lines before BRAF/MEK inhibitor combination therapy with encorafenib plus binimetinib. Previous therapies included ipilimumab monotherapy (n = 3), anti-PD-1 monotherapy (n = 38), and ipilimumab/nivolumab combination therapy (n = 46), with four patients receiving other therapies (Supplementary Table 2). Among the patients who had received anti-PD-1, 22 received it as adjuvant treatment.

Table 1
Patient-, tumor- and treatment characteristics for patients with melanoma and brain metastases treated with encorafenib plus binimetinib.

	***n* = 190**
Age at treatment start (median [IQR])	64 [53,72]
Sex (%)	
Male	109 (57.4)
Female	81 (42.6)
ECOG PS (%)	
0	34 (17.9)
1	79 (41.6)
≥ 2	62 (32.6)
Unknown	15 (7.9)
Primary tumor location (%)	
Primary unknown	37 (19.5)
Head/neck	23 (12.1)
Trunk	102 (53.7)
Extremities	27 (14.2)
Acral	1 (0.5)
LDH level[a] (%)	
Normal	92 (48.4)
250–500	58 (30.5)
> 500	35 (18.4)
Unknown	5 (2.7)
Liver metastasis (%)	
No	115 (60.5)
Yes	70 (36.8)
Unknown	5 (2.6)
Brain metastasis (%)	
Asymptomatic	57 (30.0)
Symptomatic	120 (63.2)
Unknown	13 (6.8)
Corticosteriod use	96 (50.5)
Number of organ sites metastasized (%)	
< 3	60 (31.6)
≥ 3	130 (68.4)
Type of *BRAF*-mutation (%)	
V600E	128 (67.4)
V600K	27 (14.2)
Other[b]	15 (7.9)
Unknown	20 (10.5)
Brain surgery[c] (%)	
No	181 (95.3)
Yes	9 (4.7)
Brain radiotherapy[c] (%)	
No	161 (84.7)
Yes	29 (15.3)
Line of treatment (%)	
1	122 (64.2)
2	51 (26.8)
3	11 (5.8)
4	6 (3.2)

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group Performance Status; IQR = interquartile range, LDH = lactate dehydrogenase.
a) LDH concentration measured in U/L.
b) Other BRAF-mutations include V600R (n = 6); V600* (n = 2); V660E (n = 1); V600D (n = 1); G469R (n = 1); L597S (n = 1); E469A (n = 1); V600_S602delins (n = 1); undifferentiated (n = 1).
c) Before encorafenib/binimetinib initiation.

3.5. Subsequent systemic therapies

Most patients (51 %; n = 97) did not receive subsequent systemic therapies after encorafenib plus binimetinib combination therapy. A total of 93 patients (49 %) received one or more subsequent lines of systemic therapy: 41 patients (22 % of all patients) received one line of subsequent systemic therapy, 45 patients (24 %) received two, six patients (3 %) received three, and one patient (0.5 %) received four. Among patients receiving one or more subsequent lines, sixty-three (68 %) received subsequent targeted therapy, 87 of these patients

Table 2
Best Overall Response (BOR) and overall Objective Response Rate (ORR) in patients with melanoma and brain metastases treated with encorafenib plus binimetinib. Patients with missing response data were excluded (n = 10). Patients who died from melanoma-related causes before treatment evaluation were assessed as having progressive disease (PD).

	n = 180
BOR (%)	
CR	4 (2.2)
PR	121 (67.2)
SD	18 (10.0)
PD	37 (20.6)
ORR	69.4 %

Abbreviations: BOR = Best Overall Response; CR = complete response; ORR = Objective Response Rate; PD = progressive disease; PR = partial response; SD = stable disease.

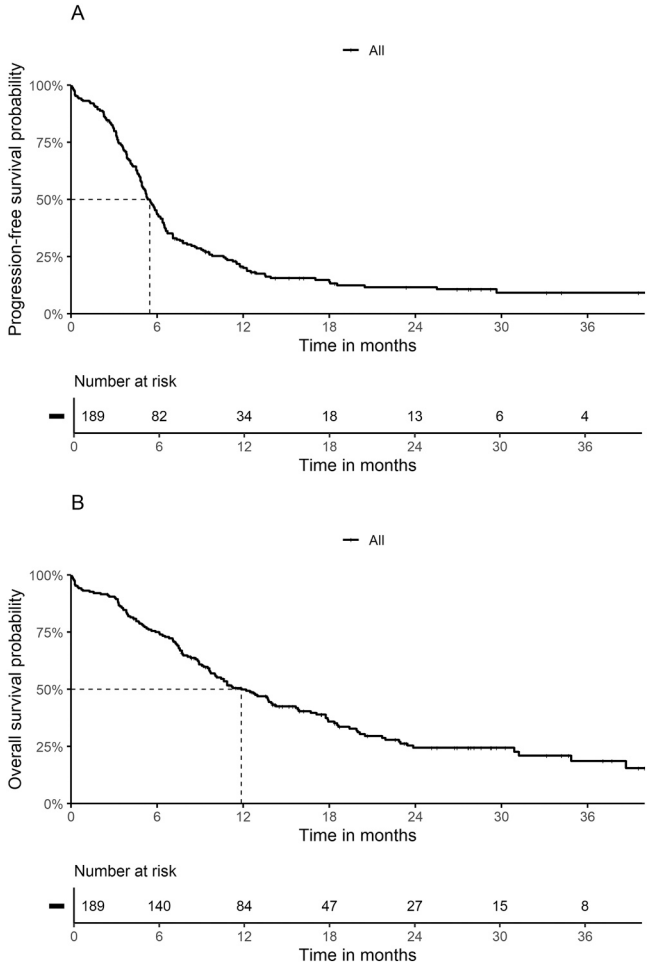

Fig. 1. (A) Progression-free survival (PFS) and (B) overall survival (OS) in all encorafenib plus binimetinib-treated patients with melanoma and brain metastases. One patient was excluded due to missing data.

(94 %) received subsequent immunotherapy, and two patients (2 %) received other subsequent systemic therapies. The subsequent systemic therapy lines are specified in Supplementary Table 3.

3.6. Brain-targeted radiotherapy and brain surgery

Among the 67 patients who received brain-targeted radiotherapy at any point during their disease course, most patients (n = 53) underwent one course of radiotherapy. Most patients received this treatment before encorafenib plus binimetinib initiation (n = 24); 13 received radiotherapy during, and another 17 after encorafnib plus binimetinib discontinuation. Additionally, two patients received brain-targeted radiotherapy before and during, two patients before and after, one patient during and after, and one patient before, during, and after their encorafenib and binimetinib therapy (Supplementary Table 4). Stereotactic radiotherapy was the most commonly administered type (33.7 %). Palliative radiotherapy was administered in 11.1 % of cases, adjuvant radiotherapy in 2.1 % and unspecified types in 0.5 %. Some patients had multiple courses of radiotherapy; therefore, the total number of courses exceeds 67. More details are described in Supplementary Table 4. Of the ten patients who underwent brain surgery during their disease course, nine patients underwent surgery before, and one underwent surgery during encorafenib binimetinib combination therapy.

3.7. Prior immunotherapy and no previous treatment

Patients with prior immunotherapy and without previous systemic therapy were analyzed separately. Both groups' patient- and tumor characteristics can be found in Supplementary Table 5. Prior immunotherapies are specified in Supplementary Table 2. The overall ORR was 68.7 % in treatment-naïve patients (n = 115) and 70.8 % in patients who had previously received immunotherapy (n = 65) (Supplementary Table 6). In treatment-naïve patients, median PFS and OS were 4.9 months (95 % CI 4.3–5.5) and 10.1 months (95 % CI 8.1–13.0), while in patients who had received prior immunotherapy, these were 6.9 months (95 % CI 4.3–9.6) and 17.9 months (95 % CI 13.7–31.2), respectively.

3.8. Symptomatic versus asymptomatic brain metastases

Patient- and tumor characteristics for patients with symptomatic versus asymptomatic brain metastases can be found in Supplementary Table 7. For this subgroup analysis, ten patients for whom symptomatology was unknown were excluded. Within the group of patients with specified symptomatology, 57 were identified as asymptomatic and 120 as symptomatic. Corticosteroids, for which indication was not recorded, were administered to 19 % of asymptomatic patients (n = 11) and 71 % of symptomatic patients (n = 85). Among the patients with asymptomatic brain metastases receiving corticosteroids, eight patients had a history of immunotherapy-related toxicity for which corticosteroids were administered. The overall ORR for asymptomatic and symptomatic brain metastases was 72.7 % and 69.3 %, respectively. The median PFS was 6.1 months (95 % CI 4.9–9.8) in patients with asymptomatic brain metastases and 5.3 months (95 % CI 4.9–6.3) in symptomatic brain metastases (p = 0.267) (Fig. 2A). Additionally, the OS for patients with asymptomatic and those with symptomatic brain metastases was 20.5 (95 % CI 14.0-NA) and 10.7 (95 % CI 8.9–13.7) months (p = 0.006), respectively (Fig. 2B).

3.9. Factors associated with survival and long-term survival

Factors independently associated with worse survival in all melanoma patients with brain metastases were age ≥ 70 (HR_{adj} 1.83; 95 % CI 1.21–2.76; p = 0.004), ECOG PS ≥ 2 (HR_{adj} 2.63; 95 % CI 1.76–3.92; p < 0.001), symptomatic brain metastases (HR_{adj} 1.68; 95 % CI 1.10–2.56; p = 0.016), elevated LDH levels between 250 and 500 U/L (HR_{adj} 1.88; 95 % CI 1.22–2.91; p = 0.004), and elevated LDH levels ≥ 500 U/L (HR_{adj} 2.95; 95 % CI 1.74–4.99; p < 0.001). Sex and number of less or more than 3 organ sites involved were not significantly associated with survival (Figure 3).

The baseline characteristics of long-term survivors (survival ≥2

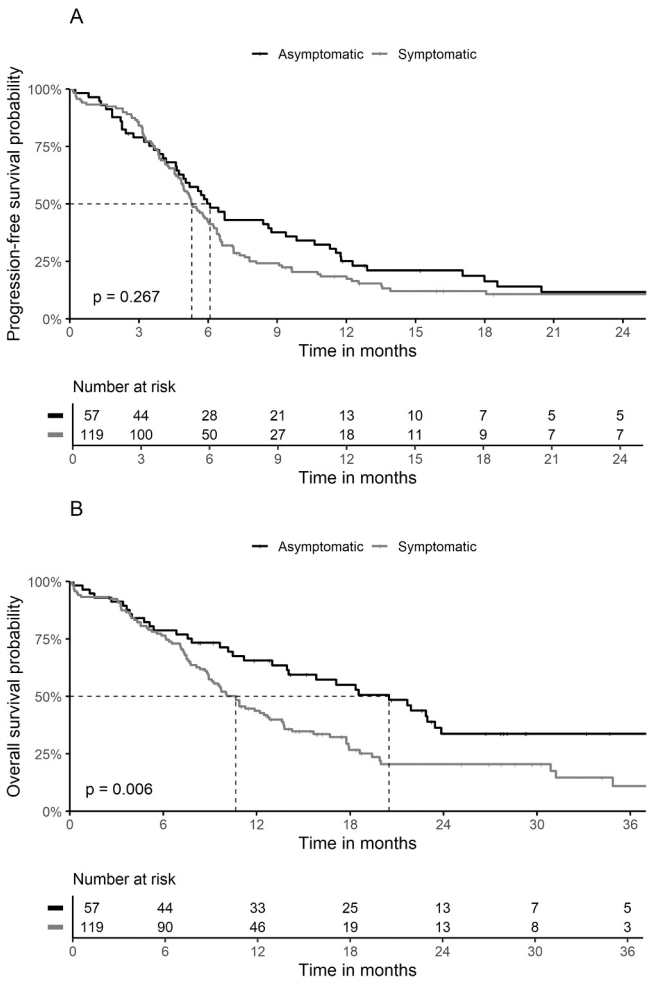

Fig. 2. (A) Progression-free survival (PFS) and (B) overall survival (OS) in patients with asymptomatic and symptomatic brain metastases. One patient was excluded due to missing data.

years) were favorable compared to patients not achieving 1-year survival (Table 3). Patients reaching 2-year survival more frequently had an ECOG PS $\leq$ 1 (93 % vs. 48 %), less often had unknown primary tumors (7 % vs. 22 %) and liver metastases (26 % vs. 42 %), and more often had normal LDH levels (63 % vs. 32 %) and asymptomatic brain metastases (48 % vs. 23 %).

4. Discussion

To our knowledge, we present the largest population-based study investigating encorafenib plus binimetinib in patients with *BRAF V600*-mutated melanoma with brain metastases. The results of our study indicate a clinical benefit of encorafenib plus binimetinib combination therapy for patients with *BRAF V600*-mutated melanoma and brain metastases. The median PFS in this study was 5.5 months, and the median OS was 11.9 months in unselected patients. In subgroup analyses, the median PFS was similar for patients with asymptomatic brain metastases and patients with symptomatic brain metastases (6.1 versus 5.3 months), while a significantly longer OS was observed for patients with asymptomatic brain metastases (20.5 versus 10.7 months). Also, patients receiving encorafenib plus binimetinib in the first line had a shorter median PFS and OS of 4.9 and 10.1 months, respectively, than patients treated with encorafenib plus binimetinib in second or later lines, for whom the median PFS and OS were 6.9 months and 17.9 months, respectively.

In the Cox regression analysis of OS, characteristics associated with worse survival—elevated LDH levels, symptomatic brain metastases, higher ECOG PS, and older age—were consistent with the patient and tumor characteristics observed in individuals who did not survive beyond two years.

In the COLUMBUS trial, encorafenib plus binimetinib was investigated in patients with *BRAF V600E/K*-mutated advanced melanoma, showing prolonged median PFS (14.9 months) and OS (33.6 months) compared to vemurafenib monotherapy or encorafenib monotherapy. Only nine patients with previous locally treated and stable brain metastases were included in the encorafenib plus binimetinib arm (n = 192), which likely contributed to the more favorable survival outcomes observed in this group compared to our cohort [25]. In addition to the presence of brain metastases, other baseline patient and tumor characteristics in our cohort were less favorable; the median age

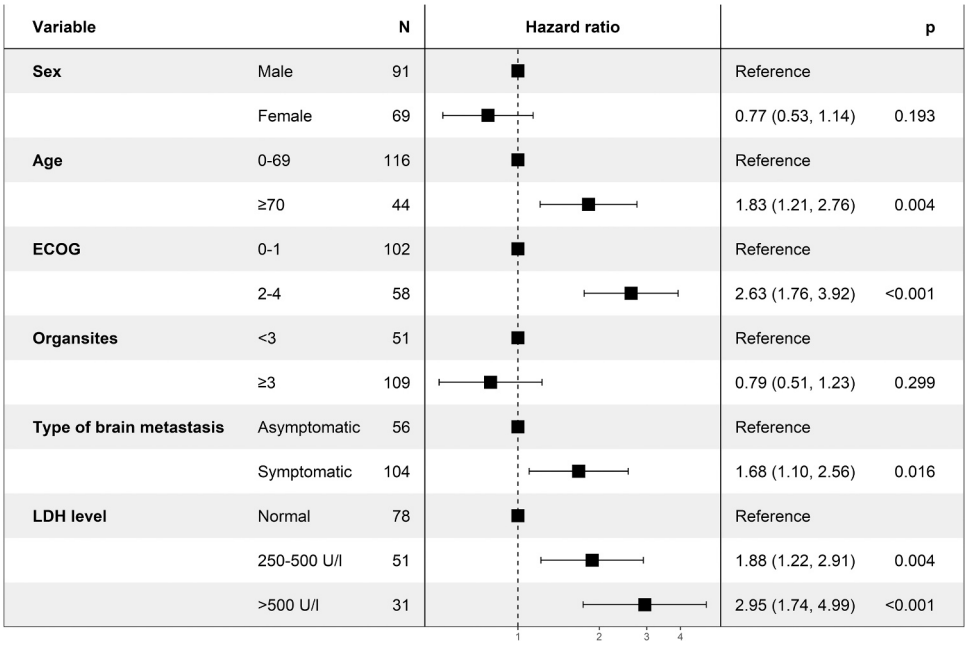

Fig. 3. Multivariable Cox proportional hazard model for death within patients with melanoma and brain metastases treated with encorafenib plus binimetinib.

Table 3
Patient characteristics for patients with melanoma and brain metastases treated with encorafenib plus binimetinib not reaching long-term survival versus 1- and 2-year survivors. One patient was excluded due to missing data.

	Patients surviving< 1 year *n = 105*	Patients surviving≥ 1 year *n = 83*	Patients surviving≥ 2 years *n = 27*
Age at start of treatment (median [IQR])	67 [55,74]	62 [50,69]	62 [51,67]
Sex (%)			
Male	63 (60.0)	44 (53.0)	15 (55.6)
Female	42 (40.0)	39 (47.0)	12 (44.4)
ECOG PS (%)			
0	10 (9.5)	24 (28.9)	9 (33.3)
1	40 (38.1)	37 (44.6)	16 (59.3)
≥ 2	49 (46.7)	13 (15.7)	1 (3.7)
Unknown	6 (5.7)	9 (10.8)	1 (3.7)
Primary tumor location (%)			
Primary unknown	23 (21.9)	13 (15.7)	2 (7.4)
Head/neck	12 (11.4)	11 (13.3)	4 (14.8)
Trunk	55 (52.4)	46 (55.4)	16 (59.3)
Extremities	15 (14.3)	12 (14.5)	4 (14.8)
Acral	1 (0.5)	1 (1.2)	1 (3.7)
LDH level[a] (%)			
Normal	34 (32.4)	56 (67.5)	17 (63.0)
250–500	37 (35.2)	21 (25.3)	7 (25.9)
> 500	29 (27.6)	6 (7.2)	3 (11.1)
Unknown	5 (4.8)	0 (0.0)	0 (0.0)
Liver metastasis (%)			
No	57 (54.3)	58 (69.9)	19 (70.4)
Yes	44 (41.9)	24 (28.9)	7 (25.9)
Unknown	4 (3.8)	1 (1.2)	1 (3.7)
Brain metastasis (%)			
Asymptomatic	24 (22.9)	33 (39.8)	13 (48.1)
Symptomatic	73 (69.5)	46 (55.4)	13 (48.1)
Unknown	8 (7.6)	4 (4.8)	1 (3.7)
Number of organ sites metastasized (%)			
< 3	28 (26.7)	32 (38.6)	9 (33.3)
≥ 3	77 (73.3)	51 (61.4)	18 (66.7)
Type of *BRAF*-mutation (%)			
V600E	64 (61.0)	62 (74.7)	19 (70.4)
V600K	18 (17.1)	9 (10.8)	4 (14.8)
Other	8 (7.6)	7 (8.4)	4 (14.8)
Unknown	15 (14.3)	5 (6.0)	0 (0.0)
Brain surgery[b] (%)	0 (0.0)	6 (7.2)	3 (11.1)
Brain radiotherapy[b](%)	11 (10.5)	18 (21.7)	8 (29.6)

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group Performance Status; IQR = interquartile range, LDH = lactate dehydrogenase.
a) LDH measured in U/L.
b) Before encorafenib/binimetinib initiation.

was higher, patients more frequently had LDH levels above the upper limit of normal, more often metastases in three or more organ sites, and higher ECOG PS. Patients with an ECOG PS > 1 were excluded from the COLUMBUS trial, while 32.6 % of our cohort had an ECOG PS > 1.

Post-approval trials involving dabrafenib plus trametinib and vemurafenib plus cobimetinib have been conducted in melanoma patients with brain metastases [26]. These studies demonstrated a wide range of median OS varying from 8.9 to 24.3 months in different subgroups of patients [14,27,28]. No post-approval clinical trial data was available for encorafenib plus binimetinib in patients with *BRAF*-mutant melanoma and brain metastases until recently [29]. Evidence from the recent phase II EBRAIN (GEM1802) investigating encorafenib plus binimetinib with or without radiotherapy supports the use of this treatment strategy. A median intracranial PFS, extracranial PFS, and OS of 8.5 months (95 % CI 6.4–11.8), 7.7 months (95 % CI 6.1–11.8), and 15.9 months (95 % CI 10.7–21.4) were observed, respectively. The PFS and OS were longer than observed in our cohort, which could be due to the radiotherapy added in absence of progression but might also be explained by the more favorable patient characteristics in the EBRAIN study. Patients were younger (median age 54 vs. 64), had better ECOG PS (ECOG PS 0 in 54 % vs. 18 %), and more often had asymptomatic brain metastases (52 % vs. 30 %) compared to our cohort. One other, retrospective, study of encorafenib plus binimetinib in advanced melanoma patients included 25 patients with brain metastases and showed response rates and PFS similar to our results; an ORR of 70.8 % and PFS of 6.3 months (95 % CI 6.1–10.3) [16].

The phase II COMBI-MB trial investigated dabrafenib plus trametinib combination therapy in 125 patients with *BRAF V600*-mutated melanoma and brain metastases and a good ECOG PS of 0 or 1. The overall response rates varied from 44 % to 65 %, the median PFS from 4.2 to 7.2 months, and the median OS from 10.1 to 24.3 months [14]. The relatively advantageous median OS of 24.3 months was found in a highly selected cohort of 16 patients: *BRAF V600E*-positive, asymptomatic brain metastases, ECOG PS 0–1, and previous brain-directed radiotherapy. The median OS was < 12 months in the other selected cohorts. While an indirect comparison should be interpreted cautiously due to differences in the study populations, this aligns with our findings.

Vemurafenib and cobimetinib combination therapy in patients with melanoma brain metastases has not been explicitly investigated in a clinical trial. However, vemurafenib monotherapy and a triplet regimen of atezolizumab, vemurafenib, and cobimetinib have been studied. The TRICOTEL study examined the latter regimen in 65 patients with *BRAF V600*-mutated melanoma and brain metastases. They showed an ORR of 54 %, median PFS of 5.5 months, and OS of 13.7 months [24]. Despite a higher overall ORR in our cohort (69 %), the median PFS and OS are comparable, considering that patients in the TRICOTEL study were younger, less frequently had symptomatic brain metastases, and had lower ECOG PS. McArthur et al. investigated vemurafenib monotherapy in 289 patients with *BRAF V600*-mutated melanoma and brain metastases. They found a median PFS of 3.7–4.0 months and a median OS of 8.9–9.6 [13]. Even with more favorable patient- and tumor characteristics, PFS and OS are lower than our study shows. The availability of other treatment options may contribute to differences in OS; by the end of the study inclusion period in 2015, anti-PD-1-based therapies had not yet been widely introduced, and MEK inhibitors were not incorporated into this monotherapy strategy.

In 2023, Kähler et al. published a non-interventional study investigating the combination of vemurafenib and cobimetinib in patients with V600-mutated melanoma, including 41 patients with brain metastases. While no notable differences in patient characteristics were present, they described a similar median PFS (5.2 versus 5.5 months) and shorter median OS (7.4 versus 11.9 months) [30].

Although we present the largest cohort of patients with *BRAF V600*-mutated melanoma and brain metastases treated with encorafenib plus binimetinib, this study also faces insurmountable limitations. Selection bias is unavoidable in this population-based study. Unfortunately, intracranial response rate is not recorded in the DMTR. Consequently, OS serves as the primary and most reliable outcome measure in this research. A similar limitation regarding data availability within the DMTR concerns the number and size of brain metastases, corticosteroid doses, and type of neurological symptoms. The debate over the definition of symptomatic brain metastases further complicates the clinical implications of the subgroup analyses based on symptomatology [23,24]. We also know that under-registration of adverse events within the DMTR occurs specifically for targeted therapies. Therefore, this research limits comparisons and conclusions regarding the safety rates and profile of encorafenib plus binimetinib. Due to a limited sample size within certain subgroups, the subgroup analyses should be interpreted with caution. Additionally, this study lacks power to perform other subgroup analyses (e.g. patients with elevated LDH).

The implications of this research for clinical practice are mainly to inform patients and their caregivers of differences in treatment

effectiveness in subgroups of patients. In the presence of brain metastases, the prognosis of these patients is determined by the symptomatology and additional risk factors, including age, ECOG PS, and LDH levels. Alternative treatment strategies should be investigated for subgroups of patients who do not benefit similarly from currently available treatment options. Future research should prioritize patients with brain metastases, as the prognosis of this group did not improve equally.

5. Conclusions

In conclusion, this study shows the effectiveness of encorafenib plus binimetinib in patients with *BRAF V600*-mutated melanoma and brain metastases. Survival outcomes vary significantly among different subgroups, highlighting the need for future research to focus on treatment strategies within subgroups with the poorest prognosis.

CRediT authorship contribution statement

M. Bloem: Conceptualization, Methodology, Software, Data curation, Formal analysis, Writing – original draft. **K.P.M. Suijkerbuijk:** Conceptualization, Methodology, Project administration, Writing – review & editing, Supervision. **M.J.B. Aarts:** Project administration, Writing – review & editing. **F.W.P.J. van den Berkmortel:** Project administration, Writing – review & editing. **C.U. Blank:** Project administration, Writing – review & editing. **W.A.M. Blokx:** Project administration, Writing – review & editing. **M.J. Boers-Sonderen:** Project.administration, Writing – review & editing. **C.D.M. Boreel:** Software, Data curation, Writing – review & editing. J.**W.D. de Groot:** Project administration, Writing – review & editing. **J.B.A.G. Haanen:** Project administration, Writing – review & editing. **G.A.P Hospers:** Project administration, Writing – review & editing. **E. Kapiteijn:** Project administration, Writing – review & editing. **O.J. van Not:** Software, Data curation, Writing – review & editing. **D. Piersma:** Project administration, Writing – review & editing. **B. Rikhof:** Project administration, Writing – review & editing. **A.M. Stevense- den Boer:** Project administration, Writing – review & editing. **A.A.M van der Veldt:** Project administration, Writing – review & editing. **G. Vreugdenhil:** Project administration, Writing – review & editing. **M.W.J.M. Wouters:** Conceptualization, Methodology, Project administration, Writing – review & editing, Supervision. **A.J.M. van den Eertwegh:** Conceptualization, Methodology, Project administration, Writing – review & editing, Supervision.

Ethics statement

Not applicable.

Funding

Pierre Fabre (project sponsorship).

Declaration of Competing Interest

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

AE participates in the Advisory Boards of Bristol-Myers Squibb, MSD Oncology, Ipsen, Pierre Fabre, Janssen Cilag BV. All fees were paid to the institution.

GH has received grants from Seerave and Bristol-Myers Squibb, paid to the institution. GH participates in the Advisory Boards of Bristol-Myers Squibb, Roche, MSD, Novartis, Sanofi, Pierre Fabre, and Amgen. All fees were paid to the institution.

KS has received grants from Abbvie, Novartis, Genmab, Philips and Pierre Fabre, and participates in the Advisory Boards of Abbvie and Sairopa. All fees were paid to the institution.

MA has received personal payment for the GUCS review; a national, online presentation "Highlight medical oncologie GU" in the Netherlands. MA received personal support from ASCO (2022) to attend the meeting. MA participated in the Advisory Boards of Amgen, Bristol Myers Squibb, Novartis, MSD-Merck, Merck-Pfizer, Pierre Fabre, Sanofi, Astellas, Bayer, and received a research grant from Merck-Pfizer. All fees were paid personally.

AV participates in the Advisory Boards of Bristol-Myers Squibb, MSD, Ipsen, Eisai, Roche, Novartus, Sanofi, and Pfizer. All fees were paid to the institution.

DP has received payment from Novartis for education about melanoma for new employees, and from BMS for case writing for educational purpose. DP participates in the Advisory Boards of Peirre Fabre.

All remaining authors have declared no conflicts of interest.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2025.115514.

Data Availability

Data will be made available upon reasonable request.

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