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Original Research

An open-label, multicentre safety study of vemurafenib in patients with *BRAF*^{V600}-mutant metastatic melanoma: final analysis and a validated prognostic scoring system

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Abstract ***Background:*** The oncogenic BRAF inhibitor vemurafenib improves outcomes for patients with advanced $BRAF^{V600}$ mutation-positive melanoma compared with cytotoxic chemotherapy. Vemurafenib is now approved for use in this patient population.
Patients and methods: In this open-label, multicentre study, patients with previously treated or untreated melanoma and the $BRAF^{V600}$ mutation received vemurafenib 960 mg twice daily. The primary endpoint was safety. In a post hoc analysis, overall survival (OS) was analysed according to a prognostic scoring system developed using Eastern Cooperative Oncology Group performance status, existence of brain metastases and baseline serum lactate dehydrogenase level. The index was validated using data from patients treated with vemurafenib or dacarbazine in three clinical trials and data from patients treated with vemurafenib plus cobimetinib in two studies. The study is registered with ClinicalTrials.gov (NCT01307397).
Results: Between March 2011 and January 2013, 3224 patients were enrolled, and 3219 patients received ≥1 dose of vemurafenib (safety population); median follow-up time was 33.4 months. Vemurafenib's long-term benefits were confirmed, and no new safety signals identified. The prognostic index showed between-group differences in OS, with tight, non-overlapping confidence intervals. Validation in a pooled group of 666 vemurafenib-treated clinical trial patients revealed a similar pattern; the pattern was similar in 280 patients treated with vemurafenib plus cobimetinib.
Conclusions: Final results from the vemurafenib safety study confirm vemurafenib's tolerability in $BRAF^{V600}$ mutation-positive patients and resemble those seen in real-world clinical practice. This index may be useful in patients on combination therapy and as a basis for further work.

1. Introduction

Drugs targeting aberrant signalling in $BRAF^{V600}$-mutated melanoma, such as the oncogenic BRAF inhibitors vemurafenib and dabrafenib, have revolutionised the treatment of this disease [1,2]. Furthermore, recently reported results of four randomised trials have shown superior efficacy for the combination of BRAF and MEK inhibition versus single-agent BRAF inhibition [3–6]. Based on these studies, two combination regimens – vemurafenib plus cobimetinib and dabrafenib plus trametinib – are now approved for the treatment of patients with unresectable or metastatic melanoma harbouring the $BRAF^{V600}$ mutation.

The open-label vemurafenib safety study was designed to establish the efficacy and tolerability of vemurafenib in patients more characteristic of those encountered in clinical practice than in typical randomised trials. The study was performed in patients with metastatic melanoma and documented $BRAF^{V600}$ mutation with no other satisfactory treatment options. In order to include a broad spectrum of patients representative of those seen in real-world clinical practice, the study had fewer inclusion and exclusion criteria than normally used in randomised clinical studies. Interim results have been published previously [7]. The study design allowed inclusion of patients with poor performance status (PS), brain metastases and other baseline characteristics associated with poor outcomes, as well as those more conventionally included in clinical trials. In our interim analysis, we reported that worse Eastern Cooperative Oncology Group (ECOG) PS, increased serum lactate dehydrogenase (LDH) level and brain metastases had an adverse impact on overall survival (OS) [7]. Baseline LDH level was also identified as an influential factor on OS and progression-free survival (PFS) in pooled analyses of dabrafenib plus

trametinib studies [8] and vemurafenib plus cobimetinib [9] in advanced melanoma.

We now report the final safety and efficacy data from the study and describe a new prognostic scoring system for patients undergoing treatment with vemurafenib for $BRAF^{V600}$ mutation-positive metastatic melanoma. This prognostic scoring system was further validated in independent datasets.

2. Methods

2.1. Study design and patients

This open-label, multicentre study, conducted in 44 countries in Europe, North America and Latin America and including Australia, South Africa, India and South Korea, has been described in detail elsewhere [7]. In brief, patients had measurable or non-measurable histologically confirmed, unresectable stage IIIC or IV melanoma, with documented $BRAF^{V600}$ mutation (determined by the cobas 4800 BRAF V600 Mutation Test; Roche Molecular Systems, Branchburg, NJ, USA) and could have had prior systemic treatment for metastatic melanoma.

The protocol was approved by institutional review boards/independent ethics committees at each participating study centre; the study was conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent.

2.2. Procedures

Patients received vemurafenib 960 mg twice daily until disease progression, unacceptable toxicity, withdrawal of consent or death. Adverse events (AEs) were assessed at every visit during treatment and at the end of treatment. Follow-up for serious AEs, secondary primary malignancy and survival status continued every 12 weeks after treatment discontinuation for ≥24 months after the last patient was enrolled or until death, withdrawal of consent or loss to follow-up.

2.3. Outcomes

The primary endpoint was the safety of vemurafenib. Safety was assessed during treatment at clinic visits every 28 days. AEs were assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). The main secondary efficacy variable was the proportion of patients with investigator-assessed confirmed tumour response (Response Evaluation Criteria in Solid Tumors version 1.1), summarised in evaluable patients with measurable disease at baseline (Supplemental Methods). This was a more conservative approach than used in previous interim analyses of this study, in which response was assessed in patients with measurable disease at baseline and ≥1 post-treatment tumour assessment. PFS and OS, as defined previously [7], were also secondary endpoints (Supplemental Methods).

2.4. Statistical analysis

All analyses were performed on the safety population, which included all patients who received ≥1 dose of study medication. Statistical analyses were performed using SAS (version 9.2; SAS Institute Inc., Cary, NC, USA). The planned sample size of approximately 3300 patients allowed detection of non-frequent AEs (irrespective of grade); for example, an AE incidence of 1% could be estimated with a precision of 0.3–0.4% (95% CI, 0.7–1.4%).

PFS and OS were estimated using Kaplan–Meier methods. Patients who were withdrawn or lost to follow-up were censored at the date of last evaluable tumour assessment for PFS or the last date the patient was known to be alive for OS. Predefined patient subgroups were analysed: with versus without brain metastases; normal versus elevated serum LDH concentrations (within versus above the upper limit of normal [ULN] range of the individual institution); metastatic disease (M1a, M1b and M1c); patients with PS of 0 or 1 versus ≥2; and age <75 years versus ≥75 years.

OS for patients who received ≥1 dose of study medication was analysed according to baseline ECOG PS, presence or absence of brain metastases and serum LDH level using descriptive statistics. A prognostic scoring system based on these characteristics was derived post hoc and validated using three further independent datasets: patients treated with vemurafenib monotherapy in BRIM2 [10], BRIM3 [11] and coBRIM [3], those treated with dacarbazine in BRIM3 and patients treated with vemurafenib plus cobimetinib in the BRIM7 [12] and coBRIM studies [3].

This report relates to the final analysis (data cut-off 24 February 2016) after the last visit of the last patient had occurred.

This trial is registered with ClinicalTrials.gov, number NCT01307397.

3. Results

The intent-to-treat population included 3224 patients; the safety population consisted of 3219 patients (Supplemental Fig. A.1). At data cut-off for the final analysis, when all patients had discontinued treatment, the median follow-up duration (first treatment to last date known to be alive) was 33.4 months (95% CI, 32.9–34.1 months; interquartile range [IQR] 13.2–37.7 months). Post-study access to vemurafenib was provided for patients according to the study protocol. Patient

baseline characteristics are shown in Supplemental Table A.1 and Supplemental Table A.2.

AEs are summarised in Table 1; these were largely consistent with previously published data [7]. AEs occurred in 3121 patients (97%) and were considered related to treatment in 2907 patients (90%). Serious AEs were reported in 1114 patients (35%) and were deemed related to treatment in 749 patients (23%).

Death was recorded for 2054 patients (64%). The primary causes of death were disease progression (n = 1932; 94%) and AEs (n = 85; 4%); 25 deaths (1%) were due to other reasons, and the cause of death was unknown in 12 patients (0.6%). Twenty-seven deaths were considered potentially related to vemurafenib (Table 2); 2026 were considered unrelated to vemurafenib; and the relationship between one death and vemurafenib was not known.

Table 1
Adverse events occurring in ≥5% of patients overall in the safety study, irrespective of causality, by preferred term.

Adverse event, n (%)[a]	All (n = 3219)		
	Grade 1/2	Grade 3/4	Overall
Any adverse event	3073 (95)	1701 (53)	3121 (97)
Arthralgia	1328 (41)	116 (4)	1363 (42)
Alopecia	870 (27)	4 (<1)	873 (27)
Fatigue	803 (25)	68 (2)	837 (26)
Hyperkeratosis	822 (26)	11 (<1)	830 (26)
Nausea	705 (22)	36 (1)	722 (22)
Photosensitivity	659 (20)	41 (1)	681 (21)
Skin papilloma	617 (19)	6 (<1)	623 (19)
Diarrhoea	575 (18)	35 (1)	592 (18)
Rash	537 (17)	44 (1)	557 (17)
Dry skin	538 (17)	0	538 (17)
ECG QT prolongation	489 (15)	54 (2)	523 (16)
Decreased appetite	469 (15)	26 (1)	482 (15)
Headache	443 (14)	27 (1)	460 (14)
Vomiting	436 (14)	38 (1)	459 (14)
Weight decrease	404 (13)	19 (1)	414 (13)
Pyrexia	370 (11)	22 (1)	388 (12)
Asthenia	360 (11)	48 (1)	384 (12)
Pruritus	316 (10)	5 (<1)	320 (10)
Erythema	319 (10)	10 (<1)	327 (10)
Sunburn	309 (10)	22 (1)	319 (10)
Myalgia	302 (9)	17 (1)	310 (10)
Pain in extremity	267 (8)	11 (<1)	276 (9)
Keratoacanthoma	21 (1)	260 (8)	272 (8)
Hypertension	152 (5)	141 (4)	265 (8)
Squamous cell carcinoma of the skin	0	261 (8)	261 (8)
Seborrhoeic keratosis	264 (8)	1 (<1)	267 (8)
Actinic keratosis	241 (7)	14 (<1)	253 (8)
Peripheral oedema	233 (7)	6 (<1)	239 (7)
Melanocytic nevus	224 (7)	6 (<1)	229 (7)
Anaemia	175 (5)	85 (3)	228 (7)
Musculoskeletal pain	216 (7)	7 (<1)	222 (7)
Constipation	195 (6)	7 (<1)	201 (6)
Rash erythematous	192 (6)	9 (<1)	196 (6)
Back pain	185 (6)	12 (<1)	195 (6)
PPE syndrome	184 (6)	16 (<1)	193 (6)
Dysgeusia	189 (6)	1 (<1)	191 (6)
Cough	190 (6)	2 (<1)	191 (6)
Rash maculopapular	172 (5)	27 (1)	181 (6)
Abdominal pain	150 (5)	26 (1)	173 (5)
Nasopharyngitis	171 (5)	0	171 (5)
Conjunctivitis	169 (5)	1 (<1)	170 (5)
Insomnia	161 (5)	1 (<1)	163 (5)

ECG, electrocardiogram; PPE, palmar-plantar erythrodysesthesia.
[a] Number of patients with at least one adverse event.

Table 2
Grade 5 adverse events and deaths due to disease progression reported by the investigator as related to vemurafenib.

Patient No.	Death
Adverse events	
1	Disseminated intravascular coagulation; cerebral haemorrhage
2	Worsening of general condition
3	Toxic epidermal necrolysis
4	Bleeding brain metastasis
5	Suspected intra-abdominal bleeding (of splenetic metastasis)
6	Bleeding brain metastasis
7	Multiorgan failure
8	Haemorrhagic stroke
9	Suspected torsade du pointes
10	Worsening of general health
11	Cardiogenic shock
12	Acute myocardial infarction
13	Brain haemorrhage
14	Lung toxicity
15	Multiorgan insufficiency
16	Sepsis
17	Dyspnoea
18	Cerebral bleed
19	Multiorgan dysfunction
20	Chronic fatigue syndrome
21	Intracerebral haematoma
22	Death of unknown cause
23	Pneumonia
Progression of disease	
24	Disease progression
25	Disease progression
26	Disease progression
27	Disease progression

New primary melanomas occurred in 54 patients (2%); cutaneous squamous cell cancers occurred in 471 patients (15%) and non-cutaneous squamous cell cancers occurred in three patients. Other primary malignancies were reported in 102 patients (3%); the most common primary malignancy was basal cell carcinoma, which occurred in 74 patients (2%) – a rate similar to earlier reports from this study [13].

Responses were seen in 996 of 2982 patients with measurable disease at baseline, for a best overall response rate of 33.4% (95% CI, 31.7–35.1%). The median PFS was 5.6 months (95% CI, 5.5–5.8 months; IQR 3.5–10.9 months); median OS was 12.1 months (95% CI, 11.5–12.7 months; IQR 6.0–28.7 months) and 2-year OS was 29% (95% CI, 27.1–30.7 months). Efficacy outcomes are summarised in Table 3; Kaplan–Meier survival curves for the overall population are shown in Supplemental Fig. A.2.

A total of 572 patients (18%) continued vemurafenib after disease progression; the median duration of

Table 3
Efficacy outcomes in vemurafenib-treated patients (n = 3219).

Outcome	Overall	Brain metastases		LDH concentration		ECOG PS		Age (y)	
		Absent	Present	Normal	Elevated[a]	0/1	2	<75	≥75
No. of patients	3219	2405	753	1508	1625	2880	309	2962	257
Measurable disease[b]	2982 (93)	2194 (91)	728 (97)	1347 (89)	1558 (96)	2654 (92)	299 (97)	2746 (93)	236 (92)
Patients with response[c]									
Complete response	126 (4)	118 (5)	6 (1)	98 (7)	21 (1)	121 (5)	4 (1)	121 (4)	5 (2)
Partial response	870 (29)	704 (32)	154 (21)	494 (37)	352 (23)	813 (31)	50 (17)	808 (29)	62 (26)
Stable disease	1393 (47)	1019 (46)	358 (49)	571 (42)	799 (51)	1230 (46)	149 (50)	1278 (47)	115 (49)
Disease progression	339 (11)	206 (9)	128 (18)	102 (8)	229 (15)	286 (11)	49 (16)	318 (12)	21 (9)
Not evaluable[d]	254 (9)	147 (7)	82 (11)	82 (6)	157 (10)	204 (8)	47 (16)	221 (8)	33 (14)
Survival time, mo									
Progression-free									
Events	2810 (87)	2034 (85)	720 (96)	1225 (81)	1514 (93)	2494 (87)	289 (94)	2596 (88)	214 (83)
	5.6	6.3	3.7	7.7	3.7	6.0	3.5	5.6	5.6
	(5.5−5.8; *3.5 to 10.9*)	(6.0−6.5; *3.6 to 12.2*)	(3.7−3.9; *2.4 to 6.5*)	(7.4−8.4; *4.6 to 15.4*)	(3.7−3.9; *2.8 to 6.7*)	(5.7−6.3; *3.6 to 11.2*)	(3.3−3.6; *2.1 to 5.4*)	(5.5−5.8; *3.5 to 10.9*)	(4.9−6.2; *3.5 to 10.6*)
Overall									
Events	2054 (64)	1437 (60)	569 (76)	822 (55)	1177 (72)	1778 (62)	256 (83)	1882 (64)	172 (67)
	12.1	15.0	7.4	19.7	7.4	13.4	4.7	12.3	9.5
	(11.5−12.7; *6.0 to 28.7*)	(14.1−16.0; *7.1 to 37.5*)	(6.8−7.9; *4.4 to 12.9*)	(18.5−21.2; *10.2 to NE*)	(6.9−7.9; *4.4 to 14.4*)	(12.7−14.2; *6.8 to 31.9*)	(4.2−5.4; *3.1 to 7.8*)	(11.7−13.0; *6.0 to 29.7*)	(8.3−11.2; *5.3 to 23.9*)

ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; NE, not estimable; PS, performance status.
Data are median (95% CI; *IQR*) or number of patients (%).

[a] Defined as levels above the upper limit of normal range of the individual institution.

[b] Number of patients with measurable disease at baseline.

[c] Percentages based on the number of patients with measurable disease at baseline.

[d] Single assessment with: response not evaluable, complete response or partial response <6 weeks from treatment start not confirmed by a second assessment; stable disease with a single assessment <6 weeks from treatment start; no post-baseline tumour assessments; or where all assessments were not evaluable.

Table 4
Overall survival by LDH concentration and ECOG PS for patients in the vemurafenib safety study (n = 3048).

ECOG performance status			
Overall survival, months (95% CI; *IQR*)	0	1	2+
All patients (n = 3048)			
LDH normal	21.6 (20.0–24.3; *12.0 to NE*)	16.8 (14.6–19.4; *8.5 to 38.4*)	7.7 (5.8–9.4; *4.5 to 13.2*)
Events	511/988 (52)	241/422 (57)	48/62 (77)
LDH > ULN to 2 × ULN	11.8 (10.7–13.4; *6.7 to 24.8*)	8.6 (7.8–9.7; *5.4 to 16.0*)	5.3 (4.8–6.0; *3.7 to 8.3*)
Events	301/482 (62)	238/338 (70)	80/98 (82)
LDH >2 × ULN	6.9 (5.9–8.6; *4.5 to 12.3*)	5.0 (4.5–5.5; *3.1 to 8.7*)	3.6 (3.3–4.0; *2.6 to 5.8*)
Events	156/220 (71)	245/301 (81)	117/137 (85)
Patients with brain metastases (n = 731)			
LDH normal	13.5 (11.1–15.2; *7.5 to 25.5*)	10.5 (8.0–12.8; *6.7 to 18.7*)	4.6 (2.2–5.9; *2.9 to 6.7*)
Events	109/169 (64)	54/81 (67)	15/15 (100)
LDH > ULN to 2 × ULN	7.6 (6.4–9.0; *4.8 to 11.1*)	7.0 (5.6–7.8; *4.5 to 11.0*)	5.2 (3.3–6.5; *3.0 to 7.4*)
Events	86/117 (74)	85/105 (81)	30/31 (97)
LDH >2 × ULN	5.9 (4.9–7.1; *4.5 to 8.4*)	4.4 (3.6–5.6; *2.9 to 8.0*)	3.1 (2.4–4.6; *2.0 to 5.7*)
Events	43/57 (75)	93/105 (89)	40/51 (78)
Patients without brain metastases (n = 2317)			
LDH normal	24.6 (21.8–28.2; *13.2 to NE*)	19.4 (16.4–22.3; *9.6 to NE*)	9.2 (7.4–12.2; *5.8 to 32.8*)
Events	402/819 (49)	187/341 (55)	33/47 (70)
LDH > ULN to 2 × ULN	14.9 (12.6–16.4; *7.7 to 29.4*)	9.7 (8.2–12.2; *6.1 to 18.1*)	5.4 (4.9–6.2; *3.9 to 8.3*)
Events	215/365 (59)	153/233 (66)	50/67 (75)
LDH >2 × ULN	8.4 (6.4–9.6; *4.5 to 14.1*)	5.3 (4.7–5.9; *3.6 to 9.2*)	3.8 (3.4–4.2; *3.1 to 6.0*)
Events	113/163 (69)	152/196 (78)	77/86 (90)

Data are median (95% CI; *IQR*) or number of events/number of patients (%).
ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; NE, not estimable; ULN, upper limit of normal.

treatment after progression was 3.9 months (IQR 2.1–7.1 months). A further 822 patients (26%) began treatment with a new systemic therapy after discontinuation of vemurafenib; the most common of treatments were ipilimumab (n = 296; 9%), dacarbazine (n = 110; 3%) and temozolomide (n = 77; 2%).

Among the 3219 patients enrolled in the study, 3048 could be categorised according to baseline ECOG PS (0, 1 or ≥2), serum LDH level (normal, >ULN to 2 × ULN or >2 × ULN) and presence or absence of brain metastases. Their OS was calculated according to these categories to explore the use of a prognostic scoring system. Serum LDH level differentiated distinct prognostic groups within each category of ECOG PS (Table 4). Conversely, ECOG PS differentiated prognostic groups within different LDH strata. In general, outcomes for patients with brain metastases were worse than for those without; notably, the median OS for patients with an ECOG PS of 0 and a normal LDH level was 13.5 months for those with brain metastases versus 24.6 months for patients with no brain metastases.

A scoring system was constructed in which 2, 1 and 0 points were allocated for ECOG PS ≥ 2, 1 and 0, respectively. Similarly, 2, 1 and 0 points were allocated for serum LDH level >2 × ULN, >ULN to 2 × ULN and normal LDH level, respectively. Patients were categorised into groups based on this scoring system. In the safety study, median OS was best for patients with no brain metastases and ECOG PS of 0 (819 of 3048 patients; 27% of the overall group) and worst in patients with brain metastases and a score of 3 (187 patients; 6% of the overall group) at 24.6 and 4.1 months, respectively (Fig. 1). Kaplan–Meier survival curves according to prognostic score for patients with and without brain metastases are shown in Fig. 2. Survival curves for all patients combined are shown in Supplemental Fig. A.3.

Baseline data from 717 patients who received vemurafenib monotherapy in other studies (BRIM2, n = 132; BRIM3, n = 337; coBRIM, n = 248) were pooled as a validation cohort for the prognostic score analysis [3,10,11]. Baseline characteristics of this patient group are shown in Supplemental Table 1. A total of 666 patients without brain metastases and ECOG PS 0 or 1 had data available for calculation of prognostic scores. Differences in median OS were seen between the prognostic score groups, OS declined with increasing prognostic score (Fig. 1A). Application of the prognostic scoring system to this group of patients revealed a pattern similar to that seen in the safety study, with shorter OS in patients with higher prognostic scores. Application of prognostic scoring to 336 dacarbazine-treated patients in BRIM3 and to 280 patients who received vemurafenib plus cobimetinib in the BRIM7 and coBRIM studies revealed a similar pattern (Fig. 1A). Together, these data suggest that vemurafenib may have least beneficial effect in patients with brain metastases and indicate that pretreatment screening for brain metastases could enable consideration of alternative, more intensive treatment strategies, such as combinations of radiotherapy, targeted therapy and immunotherapy.

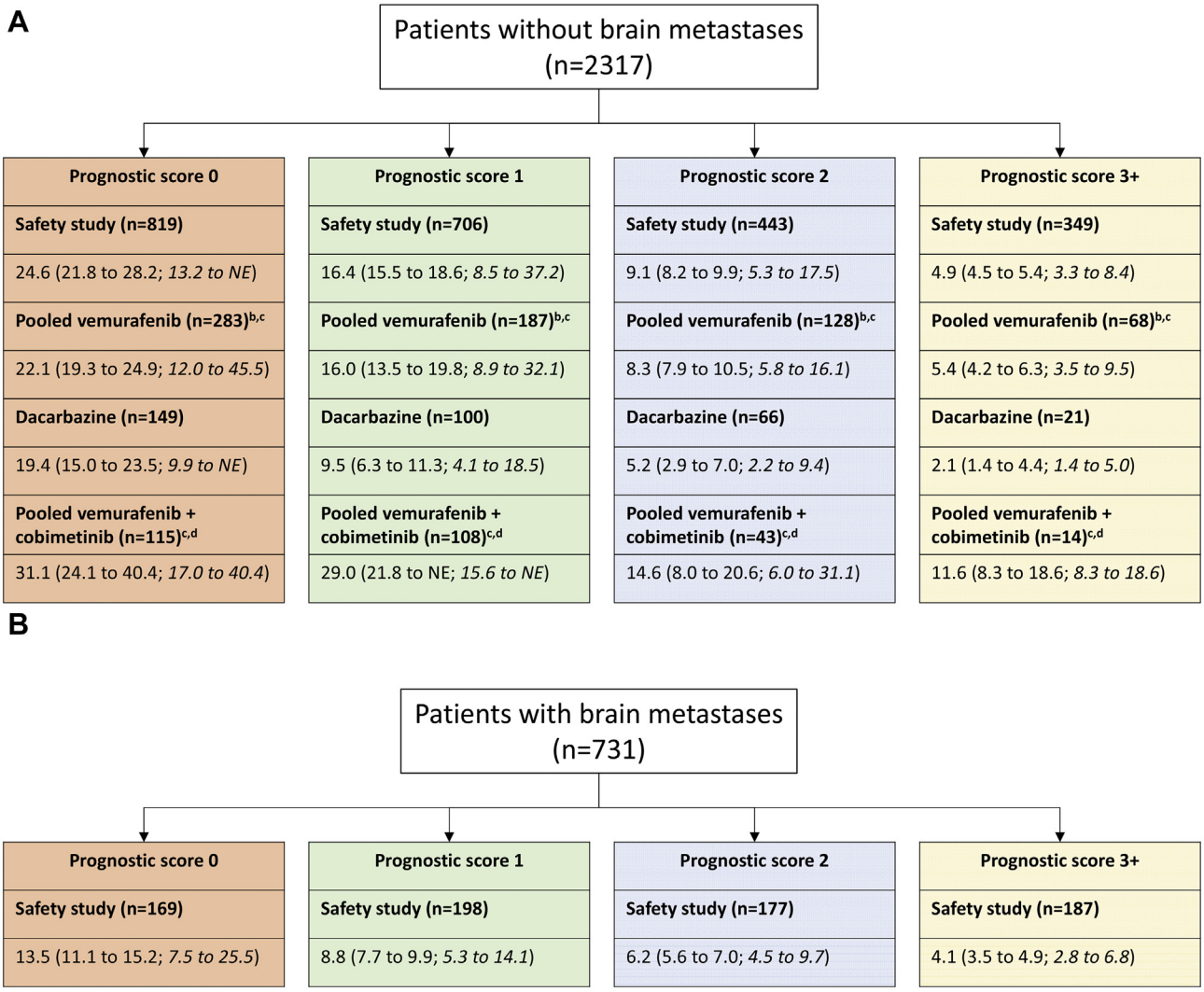
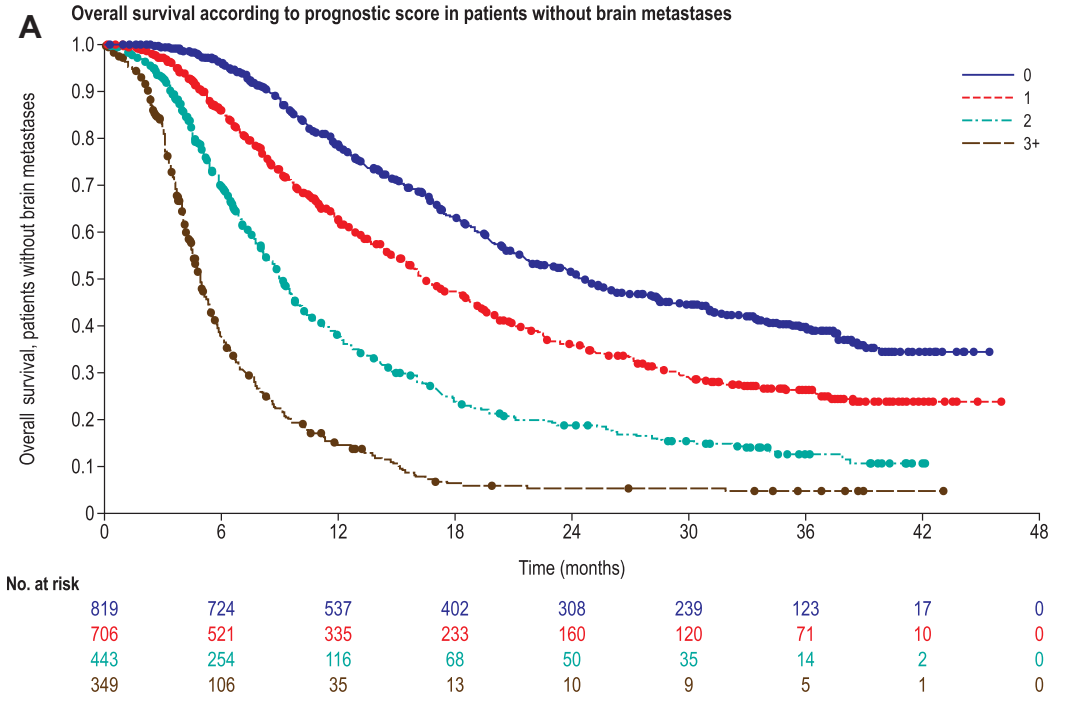


Fig. 1. Overall survival according to prognostic score[a] for vemurafenib-treated patients (A) without brain metastases and (B) with brain metastases. Data are median (95% CI; *IQR*) or number of events/number of patients (%). [a]Scoring system: 0 points allocated for ECOG PS 0, 1 point for ECOG PS 1 and 2 points for ECOG PS $\geq$ 2; 0 points allocated for normal LDH level, 1 point for LDH level > ULN to 2 × ULN and 2 points for serum LDH level >2 × ULN. [b]Vemurafenib-treated patients in BRIM2, BRIM3 and coBRIM [3,10,11]. [c]The independent datasets did not include patients with brain metastases or ECOG PS $\geq$ 2. [d]Patients treated with vemurafenib plus cobimetinib in BRIM7 [12] and coBRIM [3]. ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; NE, not estimable; PS, performance status; ULN, upper limit of normal.

4. Discussion

This final analysis of the vemurafenib safety study, which was performed after a median follow-up of 33.4 months, confirmed the safety and efficacy findings published previously [7]. Efficacy was similar to that reported previously; however, in a more conservative approach to response assessment in this final analysis, all patients with measurable disease, including those without a post-baseline tumour assessment, were included in the analysis. As a result, the proportion of patients with stable disease was lower than previously reported, and the proportion considered not evaluable was higher.

The development of a prognostic scoring system allows estimation of survival outcomes for patients with $BRAF^{V600}$-mutated melanoma treated with vemurafenib. Perhaps, the most striking feature of these data is the heterogeneity of outcomes, and the finding that 25% of patients in the safety study dataset had a median OS of approximately 2 years. It is tempting to speculate that these patients might have intrinsically less aggressive melanoma and might respond well to other systemic therapies, for example, immune checkpoint inhibitors. Studies have shown that BRAF inhibition can produce a favourable tumour microenvironment, leading to increased CD4+ and CD8+ T-cell infiltration and a reduction in immunosuppressive cytokines [14–16], suggesting that long-term benefit from vemurafenib treatment may be due to vemurafenib-induced immune response. Given the similarity in mechanism of action



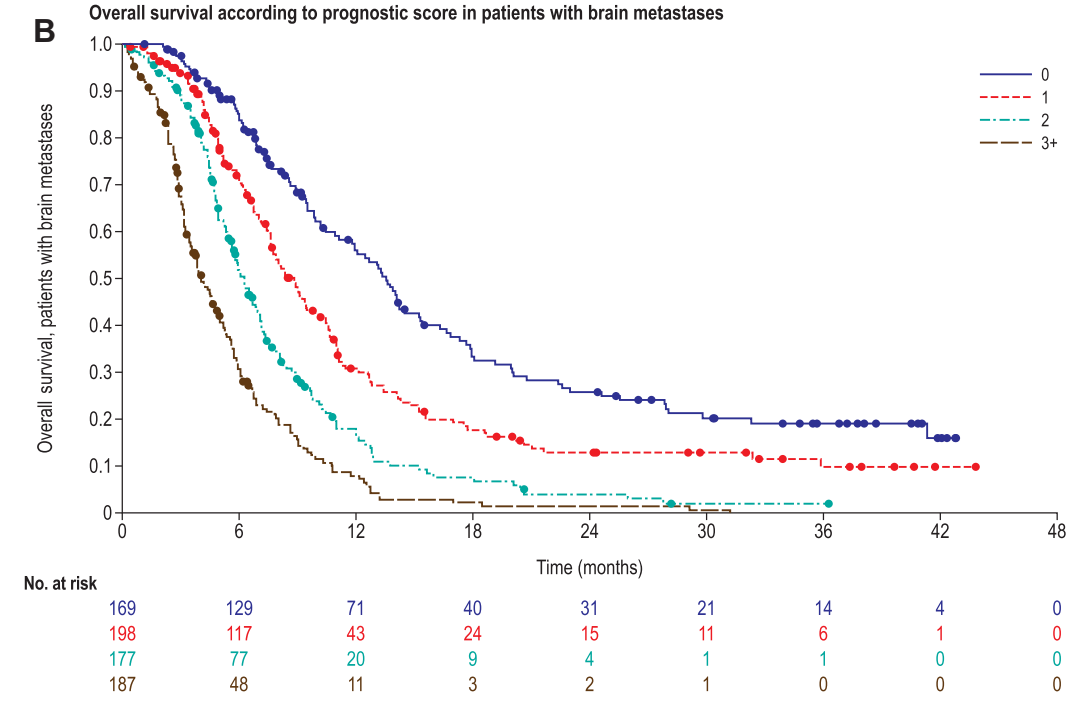


Fig. 2. Kaplan–Meier estimates of overall survival in the safety study according to prognostic score: (A) in all patients; (B) in patients with brain metastases; and (C) in patients without brain metastases. Overall survival was the time from the first vemurafenib dose to the date of any-cause death; patients alive at the time of analysis were censored.

between vemurafenib and dabrafenib, it might be expected that our prognostic index will also hold true for dabrafenib; however, validation is necessary. Further validation is also necessary to determine if the index can be used for combined BRAF and MEK inhibitor treatment; the presented results from 280 patients who received combined vemurafenib and cobimetinib suggest that this might be the case. Notably, in this dataset, the OS for patients with ECOG PS 0 and 1 appeared to be similar: 31.1 (95% CI, 24.1–40.4) and 29.0 (95% CI, 21.8

to not estimable) months, respectively. Recent pooled analyses identified baseline LDH concentration as a significant factor for OS and PFS in patients treated with combined BRAF and MEK inhibition [8,9]; however, baseline ECOG PS was a significant factor in the dabrafenib plus trametinib analysis [8] but not in the vemurafenib plus cobimetinib analysis, and the role of brain metastases was not reported in either analysis. Another pooled analysis of data from BRIM2, BRIM3, BRIM7 and coBRIM confirmed the importance of LDH, PS and presence of liver metastases as prognostic factors for PFS [17] and OS [18] in patients treated with vemurafenib plus cobimetinib. It should also be noted that the validation datasets described in the present study were limited by exclusion of patients with brain metastases and those with ECOG PS 2.

The prognostic scoring system we propose is simple to use in routine practice and has the potential for more widespread investigation, for example, in patients undergoing treatment with checkpoint inhibitors or combined BRAF and MEK inhibition. Although imaging of the central nervous system may not be necessary, establishing the presence of brain metastases may anticipate local interventions and provides additional important prognostic information. When tabulated by prognostic group, event numbers were proportionately greater in the worst prognosis groups, permitting greatest confidence in these survival estimates. The short duration of OS is notable in groups containing patients with very high LDH levels and significant disease-related symptoms. Although these patients might derive clinical benefit from BRAF-targeted therapy, treatment duration is usually limited. This finding suggests that in patients with $BRAF^{V600}$-mutated metastatic melanoma, combination immunotherapy [19] may be warranted ab initio or after induction with MAPK inhibitor therapy. Moreover, we observed a clear distinction in outcomes between patients with serum LDH levels between normal and 2 × ULN and those with LDH levels >2 × ULN. Clinical trials often report stratification by normal versus elevated LDH level; our data suggest, however, that the stratification presented herein might be more useful. To further improve survival outcomes, the greatest research efforts should be directed towards patients with elevated LDH levels and those with brain metastases, which significantly worsen a patient's prognosis even if they have favourable ECOG PS and serum LDH levels.

In conclusion, the final results of the vemurafenib safety study are generally consistent with interim reports and vemurafenib clinical trials, suggesting that vemurafenib is effective and tolerable in patients with $BRAF^{V600}$-mutated melanoma, including those with poor prognostic indicators. The prognostic scoring system presented herein may need further investigation in larger data sets, particularly for the combination of BRAF and MEK inhibition.

Conflict of interest statement

J.L. has received grants from BMS, MSD, Pfizer and Novartis, personal fees from Eisai, BMS, MSD, GSK, Kymab, Pfizer, Novartis, Roche/Genentech, Secama, Pierre Fabre and EUSA Pharma outside the submitted work. M.P.B. has received grants, personal fees and non-financial support from F. Hoffmann-La Roche Ltd during the conduct of the study and has received other fees (honoraria) from Merck Sharp and Dohme, GlaxoSmithKline, Novartis, Bristol-Myers Squibb and Amgen outside the submitted work. A.M.A. has received other fees (financial support for the conduct of the study) from Roche during the conduct of the study and has received personal fees from BMS, MSD, Novartis and Roche outside the submitted work. A.H. has received other fees (clinical trial support, speaker's honoraria or consultancy fees) from Amgen, BMS, Merck Serono, MSD, Novartis. Oncosec, Philogen, Pierre Fabre, Provectus, Regeneron and Roche during the conduct of the study. P.Q. has received personal fees (for advisory boards) from BMS, MSD, Novartis and Roche outside the submitted work. MDV has received other fees (consultancy, advisory board and honoraria) from Roche, Novartis, Merck and Bristol-Myers Squibb outside the submitted work. P.A.A. has received grants from Bristol-Myers Squibb, Roche/Genentech and Array and has received personal fees from Bristol-Myers Squibb, Roche/Genentech, Array, Merck Sharp and Dohme, Novartis, Amgen, Merck Serono and Pierre Fabre outside the submitted work. I.K. has received other fees (advisory board) from BMS, MSD and Novartis outside the submitted work. C.G. has received grants and personal fees from Roche during the conduct of the study and has received grants from Novartis and personal fees from Amgen, MSD, Novartis, LEO, BMS and Philogen outside the submitted work. V.C.S has received personal fees (advisory board) from MSD, Roche, Novartis, BMS and Merck Serono outside the submitted work. M.Man. has received grants from Roche and personal fees from Roche, BMS, MSD and Novartis outside the submitted work. H.G. has received grants from BMS, Roche, MSD and Novartis and personal fees from BMS, Roche, MSD, Novartis and Amgen outside the submitted work. E.E. has received personal fees (advisory board) from Roche outside the submitted work. G.H. has received other fees (advisory board) from Roche during the conduct of the study. P.L. has received grants from BMS, Merck and Novartis and personal fees from Agenus, Amgen, BMS, Chugai, GSK, Lytix Biopharma, Merck, Nektar, Novartis and Roche and other fees from Agenus, Amgen, BMS, GSK, Lytix Biopharma, Merck, Nektar, Novartis and Roche outside the submitted work. A.G. has received personal fees from MSD, Merck, BMS, Roche and Eisai and other fees (travel

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Authors' contributions

J.L. was chair of the study steering committee and was involved in study oversight, data gathering and analysis and manuscript writing. M.P.B. was involved in data gathering, analysis, interpretation and writing. A.M.A. was involved in recruitment of patients, data analysis, gathering and interpretation, revision of the manuscript and approval for submission. A.H. was involved in study design, data gathering and analysis and manuscript writing and revisions. P.Q. contributed to the study design, data gathering, analysis and interpretation. M.D.V. was involved in study design, literature search, data gathering and interpretation and writing. P.A.A. was involved in the literature search, reviewing and proofing figures, study design, data collection, analysis and interpretation and writing. I.K. was involved in data gathering and provided comments for the manuscript. J.S. was involved in data gathering, analysis, interpretation and writing. B.N. was involved in data gathering and reviewing of the manuscript and figures. C.G. was involved in data gathering, analysis, interpretation and writing. V.C.S. was involved in data gathering, analysis, interpretation, writing and approval. M.Man. was involved in data gathering, analysis, interpretation and writing. H.G. was involved in data gathering and interpretation and approved and commented on the first circulated draft of the manuscript. E.E. was involved in literature searches, reviewing and proofing figures, data gathering, analysis, interpretation and writing. G.H. was involved in data gathering, analysis, interpretation and writing. P.L. was involved in data gathering, analysis, interpretation and writing. M.N. was involved in data gathering, analysis, interpretation and writing. A.G. was involved in data gathering, analysis, interpretation and writing. G.L. was involved in data gathering, analysis, interpretation and writing. P.R. was involved in data gathering, analysis, interpretation and writing. W.M. was involved in data gathering, analysis and interpretation and review and approval of the final manuscript. M.D. was the biostatistician involved in the study and contributed to study design and conduct, data analysis and interpretation and manuscript writing. M.Mak. was the senior international medical leader from F. Hoffmann-La Roche and was involved in study design, statistical analysis plan, study oversight, data analysis and interpretation, manuscript writing and approval to submit. C.B. contributed to the design of the manuscript, literature research, data gathering and interpretation and writing.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2018.11.018.

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