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Long-term outcome in *BRAF*^{V600E} melanoma patients treated with vemurafenib: Patterns of disease progression and clinical management of limited progression

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Abstract

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Conflict of Interest Disclosures

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Introduction—Vemurafenib induces tumour regression in most patients with *BRAF*^{V600E}-mutant melanoma; eventually, most experience progressive disease (PD). Long-term follow-up of patients with *BRAF*^{V600E} melanoma treated in the phase 1 vemurafenib trial is reported.

Methods—Patients received vemurafenib 240–1120 mg (dose escalation cohort) or 960 mg (extension cohort) orally twice daily. Clinical response was evaluated every 8 weeks by RECIST. Patients with PD amenable to local therapy (surgery or radiotherapy) were allowed to continue vemurafenib after progression. Overall survival (OS) from time of treatment initiation and from PD was estimated. Sites of PD were recorded.

Results—Forty-eight patients (escalation cohort, $n = 16$; extension cohort, $n = 32$) received therapeutic doses of vemurafenib (≥240 mg twice daily). Forty-three patients had PD by the time of this analysis, and 5 remained progression free (follow-up time, 1.2–56.1 months). Median OS was 14 months (range, 1.2–56.1); 3- and 4-year melanoma-specific survival rate in the extension cohort was 26% and 19%, respectively. Median OS was 26.0 months (range, 7.7–56.1) among 20 patients who continued vemurafenib after local therapy. Median treatment duration beyond initial PD was 3.8 months (range, 1.1–26.6). In the extension cohort, 6 and 5 patients were alive after 3 and 4 years, respectively, on vemurafenib monotherapy.

Conclusions—Some patients with melanoma achieved long-term survival with vemurafenib monotherapy. Continuation of vemurafenib after PD might be beneficial in some patients because remaining disease might continue to respond to BRAF inhibition.

Keywords

vemurafenib; BRAF inhibitor; metastatic melanoma

1. Introduction

Oncogenic BRAF signalling is implicated in ~50% of melanomas, making BRAF a key therapeutic target [1–3]. BRAF inhibition blocks cell growth in most *BRAF*-mutant melanoma cell lines [4–9]. The most common oncogenic *BRAF* mutation involves substitution of glutamic acid for valine at codon 600 (V600E) in exon 15 [5,7]. Vemurafenib is a potent inhibitor of *BRAF*^{V600E} [7,10].

The phase 1 trial of vemurafenib in patients with advanced solid tumours (ClinicalTrials.gov ID, NCT00405587) identified a biologically active serum concentration with twice-daily dosing of ≥240 mg [11]. A maximum tolerated dose (MTD) of 960 mg twice daily was identified, and unconfirmed, investigator-assessed partial response (PR) occurred in 24 of 32 patients in an extension cohort at this dose; complete response (CR) occurred in 2 patients [11]. Estimated median progression-free survival (PFS) in the extension cohort was >7 months; overall survival (OS) had not been reached at the time of the initial report [11]. A phase 2 study of vemurafenib in patients with metastatic melanoma harbouring *BRAF*^{V600} mutations showed a confirmed, independently reviewed overall response rate of 53%, median PFS of 6.8 months, and median OS of 15.9 months [12]. Results of the randomised phase 3 study (BRIM3) showed that vemurafenib improved OS compared with dacarbazine (hazard ratio for death, 0.70; 95% confidence interval [CI], 0.57–0.87; $P = 0.0008$) in

patients with *BRAF*^{V600E} [12–14]. Vemurafenib has been approved in more than 80 countries for the treatment of *BRAF*^{V600E}-mutant metastatic melanoma.

Herein we report long-term survival of patients with *BRAF*-mutant melanoma treated with vemurafenib in the phase 1 study and evaluate long-term efficacy among patients who did and did not continue vemurafenib after confirmation of progressive disease (PD).

2. METHODS

Methodology of the phase 1 study of vemurafenib was reported previously [11].

2.1 Study design

There were 2 stages: dose escalation and extension. The dose escalation cohort identified a recommended phase 2 dose, defined as the highest dose at which ≤1 of 6 patients had dose-limiting toxicities (MTDs) [11]. An extension cohort evaluated response rate at the recommended phase 2 dose (960 mg twice daily) in patients with prospectively confirmed *BRAF*^{V600E}-mutant melanoma [11]. Patients continued treatment until occurrence of unacceptable adverse events (AEs) or PD. Safety evaluations were conducted every 4 weeks and AEs were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 [11].

2.2 Treatment after progressive disease

PD was defined per Response Evaluation Criteria In Solid Tumors (RECIST), version 1.0 [15]. Patients with PD limited to sites suitable for local therapy (surgery or radiotherapy) could continue receiving vemurafenib after local therapy [11].

2.3 Study population

Patients ≥18 years of age with any histologically confirmed solid tumour refractory to standard therapy, or for which standard or curative therapy did not exist, were eligible [11]. Patients had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–1; life expectancy ≥3 months [16]; adequate hematologic, hepatic, and renal function; and no progressive or unstable brain metastases.

Current analyses are restricted to patients with *BRAF*^{V600E}-mutant melanoma, identified by certified *BRAF* sequencing analysis at each study centre in the dose escalation cohort (n = 16) or polymerase chain reaction–based assay (cobas 4800 *BRAF* V600 Mutation Test; Roche Molecular Systems, Pleasanton, CA, USA) in the extension cohort (n = 32). These patients received vemurafenib ≥240 mg twice daily.

2.4 Study assessments

This analysis describes long-term follow-up and clinical characteristics of patients who experienced durable clinical response and long-term survival. PD patterns in patients receiving vemurafenib and outcomes after local therapy for PD in patients continuing vemurafenib were assessed. Computed tomography (CT) was performed every 8 weeks during therapy. Tumour response was assessed according to RECIST v1.0 [15]. End points

were objective response (CR or PR) confirmed ≥4 weeks after initial documentation, duration of objective response (defined as time from initial CR or PR to PD or death), and PFS.

PFS (defined as time from first treatment to first documentation of PD or death, whichever occurred first) and OS (defined as time from enrolment to death as a result of any cause) were estimated using the Kaplan-Meier method. Sub-group analyses were conducted based on PD pattern and subsequent therapy. Survival outcomes were analysed for patients in the extension cohort who survived >3 years and for 20 patients who received vemurafenib for >30 days after disease progression. The >30 days' duration was chosen to distinguish between i) patients who continued with vemurafenib after progression but only until the results of the confirmatory biopsy for tissue analysis, and ii) patients who continued with vemurafenib after progression and local therapy. Median survival beyond initial PD (defined as time from PD to death as a result of any cause) and melanoma-specific survival were assessed.

2.4 Statistical analysis

Descriptive statistics (mean, standard deviation [SD], range) are presented. Kaplan-Meier survival curves were generated by SAS version 8.1 (SAS Institute, Cary, NC, USA). Data cutoff was March 6, 2014.

3. RESULTS

Between August 2008 and August 2009, 48 patients with $BRAF^{V600E}$-metastatic melanoma were enrolled in the phase 1 trial; they received vemurafenib ≥240 mg twice daily (16 in the dose escalation cohort and 32 in the extension cohort) [11]. Patient demographics and key baseline characteristics are shown in Table 1. At the time of analysis, median follow-up duration was 13.8 months (range, 1.2–56.1) for all patients and 12.3 months (range, 1.2–56.1) for the extension cohort.

3.1 Clinical outcome and OS

Median PFS for all patients was 7.2 months (range, 0.9–56.0). Median PFS was similar in patients who received vemurafenib for <30 or >30 days after PD (6.4 months versus 6.7 months) (Table 2).

Characteristics of patients who experienced long-term benefit from vemurafenib were determined in an exploratory analysis of survival, baseline characteristics, and post-progression treatment in subsets of patients with short (<6 months, $n = 19$) and prolonged (>12 months, $n = 15$) PFS. Assessed baseline characteristics were serum lactate dehydrogenase level, stage, mean sum of target lesions on CT, and ECOG PS. The only characteristics associated with PFS >12 months were mean sum of target lesions and ECOG PS (Table 3). Mean (±SD) sums of target lesions were 168 mm (±113 mm) and 65 mm (±37 mm) for patients with short and long PFS, respectively ($P = 0.002$).

Median OS from study initiation for all 48 patients was 14.0 months (range, 1.2–56.1) (Table 2). Median OS in patients who discontinued at first PD was 11.0 months (range, 1.2–

35.4), whereas median OS in patients who continued vemurafenib for >30 days after PD was 26.0 months (range, 7.7–56.1). Figure 1 shows time to response and progression and patient status.

3.2 Long-term OS (years from treatment initiation)

Eight patients treated with vemurafenib 960 mg twice daily were alive >3 years after treatment initiation; 6 patients survived ≥4 years. Three- and 4-year melanoma-specific survival (censoring patients who did not die of melanoma) duration for the 32 patients in the extension cohort was 26% (95% CI, 10.4–41.3) and 19% (95% CI, 5.5–33.3), respectively (Fig. 2). One additional patient experienced PR (per RECIST v1.0) but died 27.8 months after initiation (2 months after vemurafenib discontinuation) with no evidence of PD; therefore, death was considered unrelated to melanoma or vemurafenib. Clinical characteristics of these patients are in Table 4; 3 had CR and 6 had PR as investigator-assessed best overall response in target lesions after vemurafenib; 4 of these patients had stage M1c.

As of March 2014, 3 of 9 patients were alive without PD (>49.3, >54.3 and >54.5 months after initiation, respectively). Median duration from vemurafenib initiation to initial PD in the 5 patients with PD was 14.7 months (range, 3.6–16.8). Median duration from initial PD to last follow-up was 33.2 months (range, 27.6–40.4). Among these 5 patients, 1 died of lymphoma, 2 underwent surgical resection of progressing lesions, 1 discontinued vemurafenib and subsequently received nivolumab then ipilimumab plus vemurafenib and 1 discontinued vemurafenib and subsequently received trametinib then ipilimumab before death because of PD. Six of 8 patients who survived >3 years received only vemurafenib therapy; among these patients, 5 survived >4 years and continued to receive only vemurafenib therapy.

3.3 Site and frequency of PD

Forty-four patients had PD at the time of analysis. PD sites included skin/soft tissue (38%), brain/central nervous system (CNS) (27%), lungs (21%), nodes (15%), liver (13%), gastrointestinal tract (10%), and bone (4%) (Table 2). Among those 44 patients, 20 (45%) experienced PD at ≥1 metastatic site, including an original lesion site, and 19 (43%) experienced it at new sites without progression at existing sites. Five patients had symptomatic progression reported as PD. Brain metastases developed in 12 of 28 patients (43%) with new metastases (with or without PD at target or non-target lesions) and in 9 of 19 patients (47%) with PD at only new sites.

Twenty patients (45.5%) received vemurafenib for >30 days after PD because of the overall clinical benefit they experienced from the treatment; most of these initial instances of PD were considered isolated by the Investigator, and the remainder were controlled (limited PD). Lesions were treated with local therapy (surgery or radiation). Median treatment duration beyond initial PD was 3.8 months (range, 1.1–26.6).

Median OS beyond initial progression was 6.1 months (range, 0–41.0) in all 44 patients with PD, 3.4 months (range, 0–26.9) in those who discontinued <30 days after progression (n =

24), and 10.0 months (range, 3.6–41.0) in those who received vemurafenib for >30 days after progression ($n = 20$) (Table 2).

Of the 48 patients in the total population, 23 (48%) received at least one subsequent treatment, including systemic therapy (n = 18), radiotherapy (n = 8), surgery (n = 2). Systemic therapies most commonly consisted of MEK inhibitors, combined BRAF inhibitor + MEK inhibitor, temozolomide, ipilimumab, carboplatin + paclitaxel, nab-paclitaxel, and other investigational agents.

3.4 Adverse events in patients monitored long term

The most common AEs reported by ≥20% of the total population ($N = 48$) included arthralgia (64.6%), fatigue (62.5%), rash (58.3%), alopecia (52.1%), photosensitivity (45.8%), nausea (45.8%), diarrhoea (37.5%), vomiting (33.3%), squamous cell carcinoma of the skin (33.3%), palmar–plantar erythrodysesthesia syndrome (31.3%), pyrexia (31.3%), myalgia (31.3%), anorexia (31.3%), hyperglycaemia (29.2%), headache (29.2%), cough (27.1%), extremity pain (27.1%), dry skin (27.1%), pruritus (27.1%), peripheral edema (27.1%), constipation (25.0%), hypokalaemia (25.0%), sunburn (22.9%), hypercholesterolemia (22.9%), hyperkeratosis (22.9%), weight decrease (22.9%), skin papilloma (20.8%), hypertriglyceridemia (20.8%) and hyponatremia (20.8%). AEs according to grade in the total population (supplementary Table S1) and AEs in patients who received vemurafenib for >30 days after progression, and in patients who discontinued vemurafenib after PD confirmation (supplementary Table S2), appear in the Supporting Information. Treatment-emergent adverse events leading to dose reductions occurred in 22 (45.8%) patients, and treatment with vemurafenib was discontinued because of adverse events in 3 (6.3%) patients.

4. DISCUSSION

Our data suggest that OS >3 years without PD may be possible for some patients with $BRAF^{V600E}$-mutated metastatic melanoma receiving single-agent BRAF inhibitor treatment. For a subset of patients with PD at sites accessible to local therapy (20 of 44 patients), continuation of vemurafenib might be clinically beneficial after local therapy. In the total population, patients who had PFS >12 months had lower baseline tumour load and ECOG PS of 0. Characteristics common among patients with OS >3 years included non-CNS metastases and baseline ECOG PS of 0.

A recent single-centre retrospective analysis of patients in single-agent dabrafenib or vemurafenib clinical trials also showed benefit of treatment with BRAF inhibitors beyond progression. Median OS from initiation of BRAF inhibitor therapy was longer in patients who continued BRAF inhibitors after RECIST-defined PD than in those who did not (17.8 months versus 7.0 months; $P < 0.001$); OS from the date of PD was also longer (11.6 months versus 2.0 months; $P < 0.001$) [17].

Interestingly, our 3-year OS rate (26%) is similar to that reported for ipilimumab [18]. With combination targeted therapies (i.e. BRAF inhibitor and MEK inhibitor)—which are superior to single-agent BRAF inhibitor therapies—now available, it is possible to

conjecture that subsets of patients with *BRAF*^{V600}-mutant melanoma could achieve long-term survival approximating that possible with ipilimumab or other checkpoint inhibitors, such as anti-PD1 antibodies. It remains to be seen which patient and melanoma characteristics are predictive of long-term disease control with BRAF inhibitor-based therapy.

The observed heterogeneity in progression patterns suggests that the differential responses to continued BRAF inhibition beyond progression are attributed to differences in tumor biology and reflect limitations in the method of measuring tumor response by RECIST criteria [19]. Among described patterns of resistance, some may be associated with more widespread or rapid onset of resistance, and others with focal progression or more prolonged response [20–22]. Recent analyses of progressing tumours during BRAF inhibitor therapy provide evidence of divergent clonal evolution at different metastatic sites [20]. This could underlie the phenomenon of ongoing disease control and isolated progression at sites amenable to local therapy, as observed in this cohort.

Drugs targeting other escape pathways might potentially overcome resistance to BRAF inhibition. Recent phase 2 studies showed that patients previously exposed to BRAF inhibitors did not respond to single-agent trametinib [23], a selective MEK inhibitor, but 5 of 26 patients responded to sequential treatment with dabrafenib, another selective BRAF inhibitor, and trametinib. Recently, the combination of BRAF inhibitor and MEK inhibitor (dabrafenib and trametinib) was shown to provide superior response rates and PFS to dabrafenib alone [24,25] or vemurafenib alone [26], and is now approved for patients with *BRAF*-mutant advanced melanoma in the United States. Similarly, the combination of vemurafenib and the MEK inhibitor cobimetinib, currently under investigation in a phase 3 study (coBRIM), met its primary end point, significantly improving PFS compared with vemurafenib alone in patients with previously untreated *BRAF*^{V600}-mutant advanced melanoma [27].

Analyses similar to those reported here, comparing PD patterns, therapy after progression, and long-term survival between BRAF/MEK combinations and BRAF-inhibitor monotherapy, are the next steps to identify possible differences in long-term outcomes. Recently, Hauschild et al presented long-term follow-up (median 16.9 months) of patients enrolled in the phase 3 BREAK-3 trial, which compared dabrafenib to dacarbazine in 250 patients with *BRAF*^{V600E} metastatic melanoma [28]. Twenty-four patients originally randomized to dabrafenib and three patients originally randomized to dacarbazine and crossed over to dabrafenib remained on dabrafenib and 19/27 (70%) of these patients were without PD on dabrafenib. Median time on dabrafenib for the 19 patients was 31.0 months (range 26.8–33.6) [28]. However, identifying characteristics associated with long-term PFS on dabrafenib was complicated by the crossover design of BREAK-3 [28]. Difficulties were also encountered in BRIM3: the crossover design from dacarbazine to vemurafenib complicated sensitivity analyses exploring survival benefits of vemurafenib compared to dacarbazine [14]. Careful planning of future trials to incorporate the possibility of long-term administration and the potential for BRAF inhibitor administration after PD is warranted.

Limitations of the current study include the following: the study was not initially designed to explore long-term OS, the number of patients was small, the groups were not prospectively defined, selection bias might have skewed survival data, and a control population was lacking.

Novel treatment options now exist with the introduction and approval of anti-PD1 agents for patients with recurrent or progressive metastatic melanoma with $BRAF^{V600}$ mutation after BRAF inhibitor and ipilimumab progression [29]. However, the observed response rates of 20–30% and the uncertain durability call for careful individualization of all the available therapies in order to maximize patient survival. Our analyses suggest that continued vemurafenib to control BRAF-sensitive clones is one option to manage limited PD after vemurafenib therapy. Additionally, we demonstrated that it is possible to achieve long-term OS in metastatic melanoma patients receiving vemurafenib.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- We report long-term follow-up of the phase 1 vemurafenib trial.
- Analyses were restricted to *BRAF*^{V600E} melanoma patients.
- Some patients achieved long-term survival with vemurafenib monotherapy.
- Continuation of vemurafenib after progression might be beneficial in some patients.

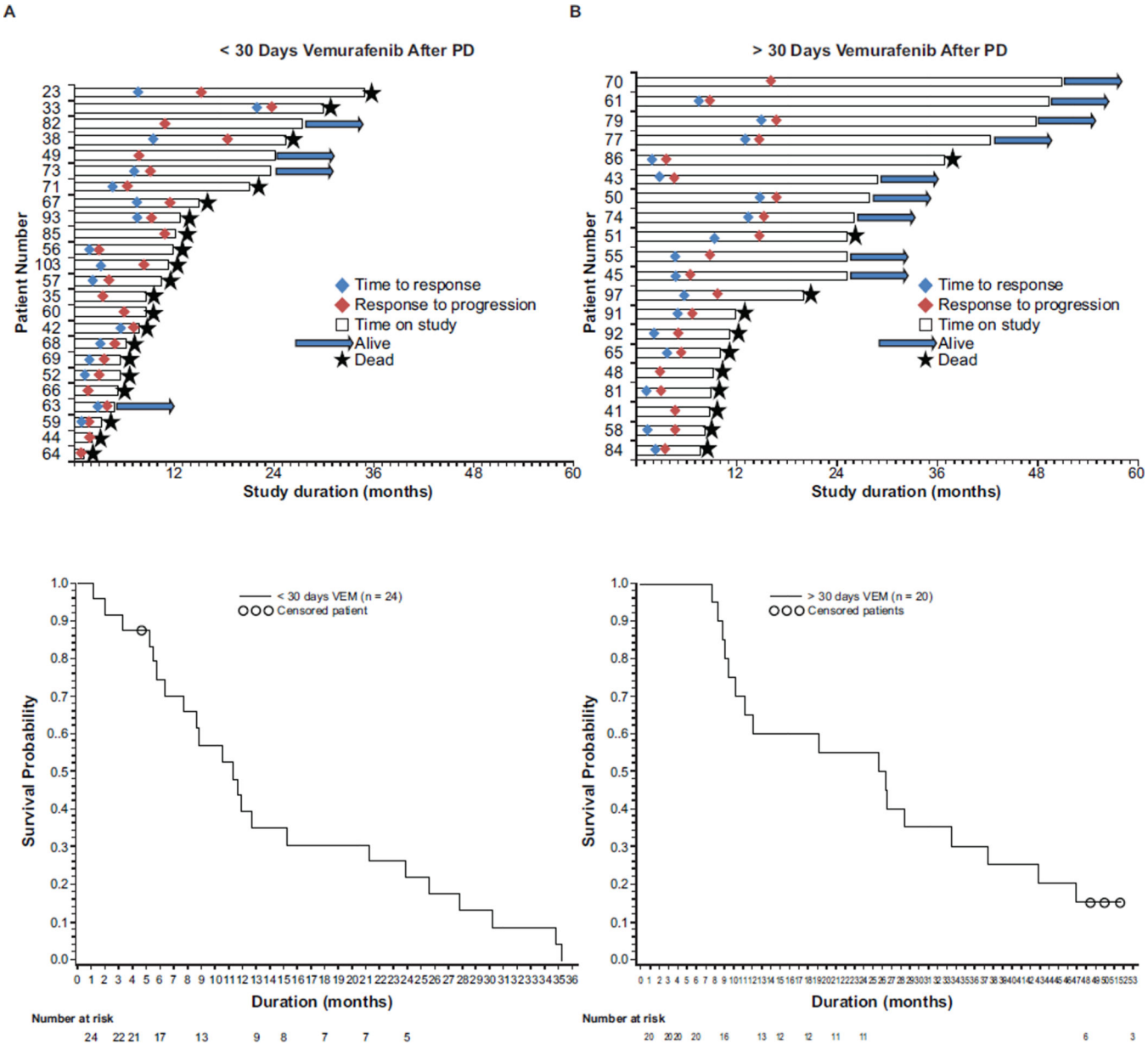

Fig 1.

Time to response, progression, OS, and individual status (deceased/living) for patients with PD during treatment with vemurafenib doses ≥240 mg twice daily. Kaplan-Meier plots show the number of patients alive over time. (A) Patients with disseminated PD received vemurafenib therapy for <30 days after progression. (B) Patients with localised PD continued vemurafenib therapy for >30 days after progression. OS, overall survival; PD, progressive disease; VEM, vemurafenib.

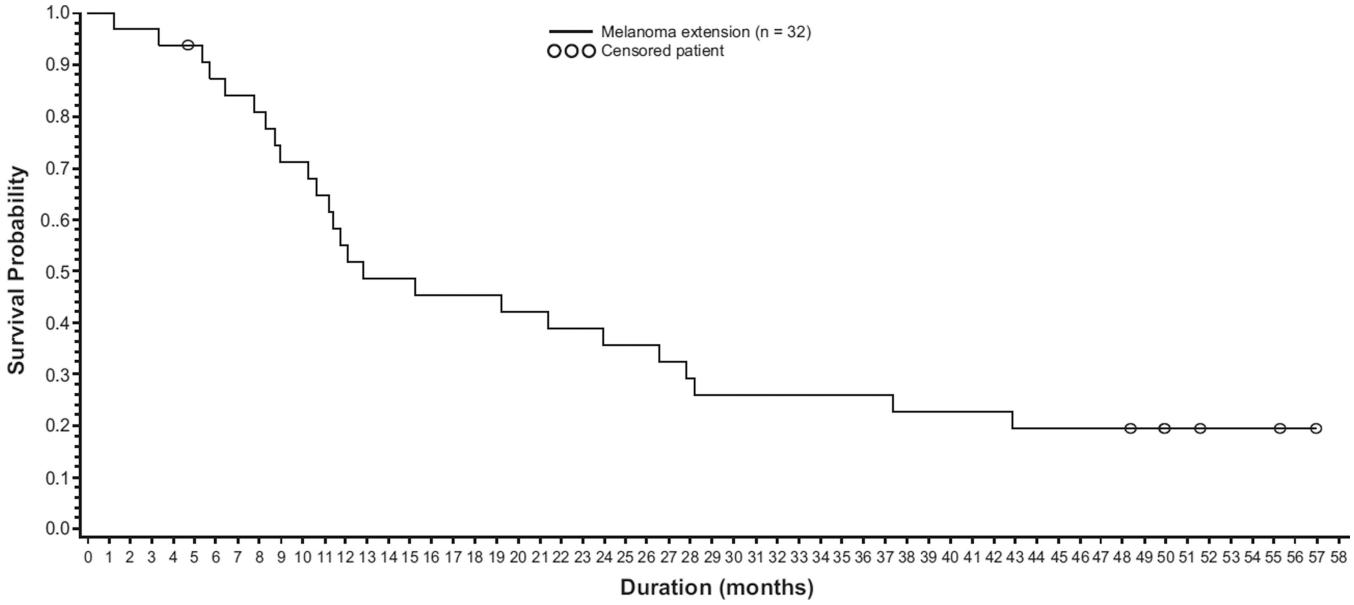

Fig. 2.
Kaplan-Meier estimate of melanoma-specific overall survival (n = 32).

Table 1

Patient demographics and baseline characteristics

Characteristic	Patients *n* = 48 (dose escalation [*n* = 16] dose extension [*n* = 32])	Vemurafenib treatment after PD *N* = 44	
		>30 days (*n* = 20)[a]	Discontinued (*n* = 24)[b]
Age, years, median (range)	53 (22–88)	52 (22–65)	53 (23–88)
Male, *n* (%)	27 (56)	15 (75)	11 (46)
Confirmed stage M1c disease, *n* (%)	35 (73)	12 (60)	22 (92)
ECOG PS of 1, *n* (%)	27 (56)	12 (60)	15 (63)
Received ≥2 previous systemic therapies, *n* (%)	26 (54)	10 (50)	16 (67)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; PD, progressive disease.

[a] All 20 patients experienced limited disease progression and continued vemurafenib after local therapy.

[b] All 24 patients received <30 days of vemurafenib after disease progression only for the purpose of tumour biopsy at the time of disease progression.

Table 2

Sites of disease progression, subsequent therapy, and outcomes (PFS and OS)

	All patients[a] *n* = 48	Vemurafenib treatment after PD *n* = 43	
		>30 days (*n* = 20)[b]	Discontinued (*n* = 24)[c]
Median PFS, months (range)	7.2 (0.9–56.0)	6.7 (2.9–17.1)	6.4 (0.9–24.2)
Median treatment duration beyond initial PD, months (range)	—	3.8 (1.1–26.6)	—
Median OS beyond initial PD, months (range)	6.1 (0–41.0)[d]	10.0 (3.6–41.0)	3.4 (0–26.9)
Median OS from initiation of vemurafenib, months (range)	14.0 (1.2–56.1)	26.0 (7.7–56.1)	11.0 (1.2–35.4)
Site of progression, *n* (%)[e]			
Skin/soft tissue	18 (38)	10 (53)	8 (33)
Brain/CNS/spine	13 (27)	6 (32)	7 (29)
Lungs/chest wall	10 (21)	5 (26)	5 (21)
Liver	6 (13)	1 (5)	5 (21)
Lymph nodes	7 (15)	5 (26)	2 (8)
Gastrointestinal tract	5 (10)	1 (5)	4 (17)
Spleen	4 (8)	—	4 (17)
Symptomatic PD only	3 (6)	—	3 (13)
Bone	2 (4)	1 (5)	1 (4)
Adrenal glands	1 (2)	1 (5)	—

Abbreviations: CNS, central nervous system; OS, overall survival; PD, progressive disease; PFS, progression-free survival.

[a] No progressive disease was recorded for 5 patients.

[b] All 20 patients experienced limited disease progression and continued vemurafenib after local therapy for an overall clinical benefit. One patient (included in this group) did not meet strict RECIST criteria for progression; however, determination of progression was made based on positron emission/computed tomography.

[c] All 24 patients received <30 days of vemurafenib after PD, only for the purpose of tumour biopsy at the time of disease progression.

[d] This occurred among the 44 patients who experienced PD while receiving vemurafenib.

[e] Only sites affected by the earliest recorded progression of disease are represented. Percentage exceeds 100% because some patients experienced multiple sites of disease progression. Data are unknown for 6 patients in the group receiving vemurafenib treatment after PD >30 days (*n* = 19).

Table 3

Baseline characteristics of patients with short and long duration of PFS

Characteristics	PFS <6 months 19 of 48 patients (40%)	PFS >12 months 15 of 48 patients (31%)	*P*
LDH >ULN, %	42	40	0.11[a]
Stage M1c, % (95% CI)	74 (49–91)	52 (27–79)	0.28[a]
Sum of baseline target lesions, mm, mean (±SD)	168 (±113)	65 (±37)	0.002
ECOG PS of 1, % (95% CI)	74 (49–91)	27 (7–55)	0.01[a]

Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; PFS, progression-free survival; LDH, lactate dehydrogenase; SD, standard deviation; ULN, upper limit of normal.

[a] *P* value determined by Fisher exact test.

Table 4

Characteristics of patients who experienced long-term survival[a]

Patient	Age, years	Sex	Stage	Previous therapies	Baseline ECOG PS	Baseline serum LDH level[b]	Extent of disease	Sites of disease progression	Initial vemurafenib dose, mg/day	Duration of vemurafenib treatment, months	INV-assessed BOR	Greatest decrease in target lesion size, %	Pre-PD PFS duration. months	OS duration, months	Post-PD to last follow-up duration, months	Subsequent systemic therapies after vemurafenib
61	41	M	M1c	0	1	Normal	Lymph node, liver	Lymph node	1920	29.0	PR[g]	97.7	8.8	49.2	40.4	None
70[c]	62	M	M1c	0	0	Normal	Lymph node, skin	Subcutaneous skin	1920	42.4	PR[g]	28.1	16.2	50.9	34.7	None
75	37	M	M1c	1	0	High	Lymph node, retroperitoneal, intra-abdominal mass, and abdomen	None	1,920	54.3	PR	43.8	N/A	54.3	N/A	None
76	58	F	M1a	1	0	ND	Lymph node	None	1920	53.9	CR	100	N/A	54.5	N/A	None
77[d]	51	M	M1a	7	1	Normal	Soft tissue	Soft tissue	1920	34.1	CR	100	14.7	42.3	27.6	None
79	56	M	M1c	0	0	High	Lymph node, adrenal	Brain	1920	18.7	PR	75.6	16.8	47.7	30.9	PH1-0882; nivolumab, ipilimumab
86	56	M	M1b	4	0	Normal	Soft tissue	Soft tissue	1920	7.8	PR	100[h]	3.6	36.8	33.2	AMG 208 (c-MET i), E7080 + TMZ, E7080 monotherapy, vemurafenib + ipilimumab + sirolimus
105[e]	59	F	M1a	1	0	Normal	Lymph node	None	1920	43.5	CR	100	N/A	49.3	N/A	None
62[f]	68	F	M1a	0	0	High	Pelvis, lymph node, skin	None	1920	25.0	PR	62.3	N/A	27.8	N/A	None

Abbreviations: BOR, best overall response; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; FDG-PET, fluorodeoxyglucose positron emission tomography; INV, investigator; LDH, lactate dehydrogenase; Met, metformin; N/A, not applicable; ND, not determined; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; TMZ, temozolomide.

[a]Long-term survival was defined as >3 years.

[b]Graded as high, normal, or low, based on institutional standards.

[c]Patient had lymph nodes that converted from FDG-PET avid to FGD-PET non-responsive in September 2010 and was included in the PD group based on clinician experience. Patient's target lesion growth did not meet RECIST criteria for PD.

[d] Patient died of lymphoma, not melanoma.

[e] Dose decreased from 960 mg twice daily to 720 mg twice daily.

[f] Patient included because of death at 27.8 months not related to melanoma; patient experienced continued PR for duration and no evidence of melanoma relapse.

[g] CR after surgery.

[h] Patient classified as partial responder because of development of new non-target lesions.