Clinical Cancer Research

# Phase I Dose-Escalation and -Expansion Study of the BRAF Inhibitor Encorafenib (LGX818) in Metastatic *BRAF*-Mutant Melanoma

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## Abstract

**Purpose:** Encorafenib, a selective BRAF inhibitor (BRAFi), has a pharmacologic profile that is distinct from that of other clinically active BRAFis. We evaluated encorafenib in a phase I study in patients with BRAFi treatment-naïve and pretreated *BRAF*-mutant melanoma.

**Experimental Design:** The pharmacologic activity of encorafenib was first characterized preclinically. Encorafenib monotherapy was then tested across a range of once-daily (50–700 mg) or twice-daily (75–150 mg) regimens in a phase I, open-label, dose-escalation and -expansion study in adult patients with histologically confirmed advanced/metastatic *BRAF*-mutant melanoma. Study objectives were to determine the maximum tolerated dose (MTD) and/or recommended phase II dose (RP2D), characterize the safety and tolerability and pharmacokinetic profile, and assess the preliminary antitumor activity of encorafenib.

**Results:** Preclinical data demonstrated that encorafenib inhibited BRAF V600E kinase activity with a prolonged off-rate and suppressed proliferation and tumor growth of *BRAF* V600E–mutant melanoma models. In the dose-escalation phase, 54 patients (29 BRAFi-pretreated and 25 BRAFi-naïve) were enrolled. Seven patients in the dose-determining set experienced dose-limiting toxicities. Encorafenib at a dose of 300 mg once daily was declared the RP2D. In the expansion phase, the most common all-cause adverse events were nausea (66%), myalgia (63%), and palmar–plantar erythrodysesthesia (54%). In BRAFi-naïve patients, the overall response rate (ORR) and median progression-free survival (mPFS) were 60% and 12.4 months [95% confidence interval (CI), 7.4–not reached (NR)]. In BRAFi-pretreated patients, the ORR and mPFS were 22% and 1.9 months (95% CI, 0.9–3.7).

**Conclusions:** Once-daily dosing of single-agent encorafenib had a distinct tolerability profile and showed varying antitumor activity across BRAFi-pretreated and BRAFi-naïve patients with advanced/metastatic melanoma. *Clin Cancer Res; 23(18); 5339–48.* *©2017 AACR.*



## Introduction

Melanoma is responsible for the majority of skin cancer–related deaths worldwide (1), and approximately 232,000 new cases of melanoma were diagnosed in 2012 (2). Most melanomas harbor alterations in components of the RAF/MEK/mitogen-activated protein kinase (MAPK) signaling transduction pathway, which drives cell proliferation, differentiation, and survival and can therefore lead to malignant cell proliferation (3).

Mutations in the *BRAF* gene occur in approximately 50% of melanoma cases (4). Over 90% of *BRAF* mutations are valine 600 substitutions (V600; ref. 4). Vemurafenib and dabrafenib are currently the only approved BRAF inhibitors (BRAFis) for the treatment of *BRAF* V600–mutant melanoma (5–8). Unfortunately, most patients treated with BRAFis develop resistance and exhibit disease progression within 6 to 8 months of starting therapy, despite substantial initial tumor regression (9). Dual inhibition of the MAPK pathway with combined BRAF and MEK inhibitors have become the new standard of care in melanoma therapy following the approval of dabrafenib plus trametinib, and vemurafenib plus cobimetinib combination therapies,

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**Note:** Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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## Translational Relevance

*BRAF* mutations occur in approximately 50% of melanoma cases. Treatment with currently approved BRAF inhibitors (BRAFi) in patients with *BRAF*-mutant melanoma results in disease progression within 6 to 8 months of starting treatment. Combined therapies of BRAF and MEK inhibitors (dabrafenib + trametinib; vemurafenib + cobimetinib) have been approved after demonstrating superior efficacy compared with BRAFi monotherapy. Encorafenib (LGX818), a selective BRAFi, was evaluated preclinically and in a single-agent phase I clinical study. Encorafenib showed more potent and prolonged pharmacodynamic activity compared with vemurafenib and dabrafenib. Clinical activity was observed in both BRAFi-pretreated and BRAFi-naïve patients at the recommended phase II dose (300 mg once daily). The safety profile was distinct compared with other approved BRAFis, with lower rates of cutaneous squamous cell carcinoma and photosensitivity, but higher rates of palmar–plantar erythrodysthesia and facial paresis. These findings highlight the potential of encorafenib in the treatment of *BRAF*-mutant melanoma in future combination studies.

which demonstrated superior response to single-agent BRAFis in advanced melanoma (10–13).

BRAFis are associated with a number of proliferative and malignant cutaneous side effects, including cutaneous squamous cell carcinomas (SCC) and keratoacanthomas. Paradoxical activation of wild-type BRAF/CRAF is proposed to be the underlying mechanism of these adverse effects (AE; ref. 14). Highly selective BRAFis that are effective at low doses and with fewer side effects are ideal candidates for both single-agent and combination treatments. Encorafenib is a potent, selective RAF kinase inhibitor with promising activity in preclinical models, including increased potency compared with vemurafenib (15). Presented here are results from preclinical studies demonstrating the pharmacologic properties of encorafenib as well as a phase I dose-escalation and dose-expansion study of single-agent encorafenib in patients with metastatic *BRAF*-mutant melanoma.

## Materials and Methods

### Pharmacologic characterization of encorafenib in preclinical models

The potency of encorafenib, vemurafenib, and dabrafenib were measured in biochemical assays using methods previously described (16). Inhibition of BRAF V600E was evaluated in cell lines and xenograft tumors by measuring phosphorylated ERK (pERK) and total ERK using an immunoassay (Meso Scale Discovery). Cell proliferation assays were performed following 3 days of drug exposure with viability measured using CellTiter Glo 2.0. Mouse xenograft studies were performed in 6- to 8-week-old female nude mice following subcutaneous implantation of A375 cells ($5 \times 10^6$) in 50% Matrigel or 3-mm × 3-mm pieces of the HMEX1906 primary human melanoma xenograft model. All laboratory animal work was conducted following appropriate laws and guidelines of the US Department of Agriculture, Office of Laboratory Animal Welfare, Association for Assessment and Accreditation of Laboratory Animal Care, and the Guide for the Care and Use of Laboratory Animals.

### Phase I clinical trial

***Patient eligibility.*** Key inclusion criteria were: age ≥18 years old; evaluable, histologically confirmed, locally advanced/metastatic *BRAF* V600-mutant melanoma (unresectable stage IIIB-IV); and World Health Organization performance status ≤2. Key exclusion criteria were: prior MEK inhibitor therapy; prior systemic anticancer treatment ≤4 weeks, or major surgery ≤2 weeks prior to starting the study; symptomatic/untreated leptomeningeal disease or brain metastases; acute/chronic pancreatitis; clinically significant cardiac disease; or impairment of gastrointestinal function. All patients were required to provide written informed consent obtained before any screening procedure. This study was conducted according to the ethical principles of the Declaration of Helsinki.

***Study design and treatments.*** This phase I open-label, multicenter study included a dose-escalation and -expansion phase (NCT01436656). Patients were treated until disease progression, unacceptable toxicity, or withdrawal of informed consent. The primary objective was to determine the maximum tolerated dose (MTD) and/or recommended phase II dose (RP2D). Secondary objectives were to characterize the safety and tolerability and assess preliminary clinical antitumor activity and the pharmacokinetic profile of oral encorafenib. Exploratory objectives included assessing potential correlations of molecular status of RAF/MEK/MAPK and PI3K/AKT signaling molecules with clinical outcomes.

In the dose-escalation phase, patients were treated with either once-daily or twice-daily encorafenib in either microemulsion (50 or 100 mg once daily) or capsule (50–700 mg once daily, or 75–150 mg twice daily) formulation, administered in 28-day cycles. As the microemulsion and capsule formulations did not differ significantly in pharmacokinetic exposures or safety profiles at 50 and 100 mg once daily, patients treated with the microemulsion were later transitioned to capsules at the same dose, for convenience. A Bayesian logistic regression model employing the escalation with overdose control (EWOC) principle was used to guide dose escalation and to estimate the MTD. The study started treating cohorts of 1–3 patients at the prespecified dose levels. Cohorts were expanded between 3 and 6 patients when dose-limiting toxicities (DLT) were identified, or additional cohorts of 1–6 evaluable patients were added when a dose level showed signs of activity and satisfied EWOC criteria. The dose-escalation phase was continued until the MTD and/or RP2D of oral encorafenib was determined. The MTD was defined as the highest drug-dose expected, based on the Bayesian logistic regression model, to not cause a DLT in more than 33% of the treated patients in the first cycle of encorafenib treatment.

The dose-expansion phase evaluated the safety and preliminary antitumor activity at the estimated MTD/RP2D in patients with locally advanced/metastatic melanoma (BRAFi-naïve or BRAFi-pretreated). Most patients enrolled received either 300 or 450 mg once-daily encorafenib. In addition, a small cohort of patients was treated with stepwise dosing of encorafenib from 300 mg (up to day [D] 15) to 450 mg (from D15 onward if patients experienced no clinically significant grade 3/4 AEs at the lower dose level). A third group of patients with metastatic

colorectal cancer were enrolled in this trial (17), but their data will be published in a separate article.

***Study procedures.*** *Safety assessments.* Data regarding all adverse events (AE) and serious AEs (SAE) were collected, along with the severity and relationship to the study drug; AEs and SAEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0 (18).

*Efficacy assessments.* All potential sites of tumor lesions were locally assessed by radiologic techniques every 8 weeks per Response Evaluation Criteria In Solid Tumors (RECIST) v1.0 (19) for the dose-escalation phase and per RECIST v1.1 (20) for the dose-expansion phase. All complete and partial responses were confirmed by a second assessment at least 4 weeks later.

*Pharmacokinetic assessments.* Blood samples for full pharmacokinetic profiles were collected on cycle 1 day 1 (C1D1), C1D8, and C1D15. Patients treated with stepwise dosing had samples collected on C1D1, C1D15, and C2D1 for dose expansion. Plasma encorafenib concentrations were measured using a validated liquid chromatography–tandem mass spectrometry assay.

*Somatic mutation and biomarker assessments.* Representative tumor tissue was used to determine the mutation status of other genes relevant to RAF/MEK/ERK signaling to identify potential predictive markers of efficacy. Next-generation sequencing was conducted at Foundation Medicine using a T5a panel.

## Statistical Analysis

The analysis was based on all patients' data from the dose escalation and expansion phases up to the time when all patients had completed at least 8 cycles of treatment or discontinued the study. Data are summarized with respect to demographic and baseline characteristics and efficacy and safety observations. Continuous variables are summarized as median and ranges. Categorical variables are expressed as frequencies and percentages. Progression-free survival (PFS) and overall survival (OS) were estimated using the Kaplan–Meier method and medians were reported with corresponding 95% confidence intervals (CI).

## Results

### Preclinical characterization

***Pharmacologic characterization of encorafenib in preclinical models.*** Encorafenib inhibited BRAF V600E kinase activity in a biochemical assay at similar concentrations as dabrafenib and vemurafenib (Supplementary Table S1); however, the dissociation half-life was considerably increased (>30 hours) compared with dabrafenib (2 hours) and vemurafenib (0.5 hours; Supplementary Table S1; Fig. 1A). Washout experiments in A375 cells confirmed the long dissociation half-life of encorafenib, as the phosphorylated ERK half maximal effective concentration (pERK $EC_{50}$) only shifted 2-fold following washout compared with 14-fold and 23-fold for dabrafenib and vemurafenib, respectively (Supplementary Table S1). In a broader survey of *BRAF* V600–mutant cell lines, encorafenib was more potent at inhibiting proliferation, with most cell lines having $IC_{50}$ <40 nmol/L, whereas slightly higher concentrations of dabrafenib (<100 nmol/L) and significantly higher concentrations of vemurafenib (<1 μmol/L) were required to inhibit proliferation of most cell lines (Supplementary Fig. S1).

Single-dose pharmacokinetic/pharmacodynamic studies in human melanoma xenograft models (*BRAF* V600E) showed that oral doses of encorafenib as low as 6 mg/kg resulted in strong (75%) and sustained (>24 hours) decreases in pERK (Fig. 1B), consistent with a prolonged dissociation half-life. Encorafenib induced tumor regression in multiple *BRAF*-mutant human tumor xenograft models grown in immunocompromised mice (Fig. 1C and D). Although maximum encorafenib antitumor activity appeared to be achieved at 5 mg/kg twice daily (Fig. 1E), higher doses were required to prevent the emergence of resistance and improve conditional survival (Fig. 1F).

Encorafenib was well tolerated, and exposure was dose proportional at all doses tested in mice (Supplementary Fig. S2A–S2B). To determine the effect of encorafenib on cell proliferation that may potentially lead to SSC growth, epithelial hyperplasia and hyperkeratosis in the forestomach of mice were investigated over a dose range. Epithelial hyperplasia and hyperkeratosis were observed at very high encorafenib doses, in contrast to both vemurafenib (4/5 mice) and dabrafenib (5/5 mice), with which gastric hyperplasia and hyperkeratosis were observed at clinically relevant doses (Supplementary Fig. S2C).

### Phase I clinical trial

***Patient disposition and characteristics.*** Fifty-four patients with *BRAF*-mutant melanoma (25 BRAFi-naïve and 29 BRAFi-pretreated patients) were enrolled and treated in the dose-escalation phase. At the time of data analysis cutoff (August 18, 2014), 49 patients had discontinued treatment (22 BRAFi-naïve and 27 BRAFi-pretreated patients); the most common reason for treatment discontinuation was disease progression [$n$ = 41; 16 (64.0%) BRAFi-naïve and 25 (86.2%) BRAFi-pretreated patients, respectively], followed by AEs ($n$ = 5; 9.3%). Thirty-five additional patients (17 BRAFi-naïve and 18 pretreated patients) were treated in the dose-expansion phase; 27 of these patients discontinued treatment by the time of data cutoff (11 BRAFi-naïve and 16 BRAFi-pretreated patients). The most common reason for discontinuation was disease progression [$n$ = 17; 3 (17.6%) BRAFi-naïve and 14 (77.8%) BRAFi-pretreated patients, respectively], followed by AEs ($n$ = 8; 22.9%). In BRAFi-pretreated patients, the median time from prior BRAFi treatment to the start of encorafenib was 38.5 days (range, 11–331). Patient characteristics are summarized in Table 1.

***Determination of MTD/RP2D.*** The dose-determining set consisted of 49 patients treated across 11 dose levels. Seven patients (14.3%), of whom 3 were treated above 450 mg once daily, experienced at least 1 DLT during cycle 1. The most frequent DLT was neuralgia (2 patients, 4.1%). All other DLTs occurred in 1 patient each [asthenia, confusional state, diarrhea, facial paresis, fatigue, headache, insomnia, musculoskeletal pain, neck pain, palmar–plantar erythrodysesthesia (PPED) syndrome and rash; 2% each; Supplementary Table S2]. On the basis of the Bayesian model, 450 mg once daily was declared the MTD.

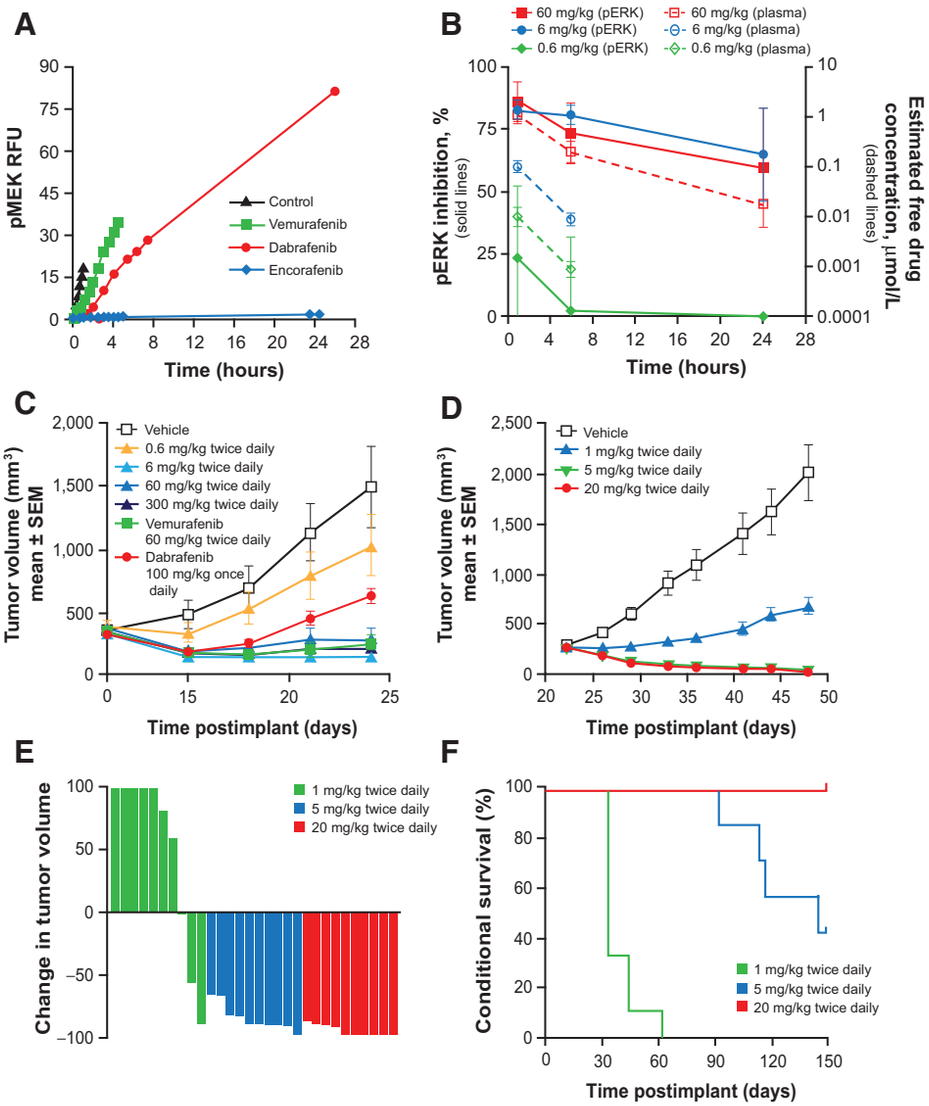


**Figure 1.**

Pharmacologic characterization of encorafenib. **A,** Impact of BRAF inhibitors on phosphorylated MEK (pMEK) in *BRAF* V600E–mutant cells. **B,** Tumor pERK inhibition and plasma encorafenib concentration across varying doses (0.6–60 mg/kg) of encorafenib. Female nude mice bearing A375 (*BRAF* V600E) human melanoma tumor xenografts were given a single oral dose of vehicle or encorafenib, and plasma and tumor samples were collected at predetermined time points. Phosphorylated ERK levels were measured in tumor lysates using a Meso Scale Discovery assay (normalized to total ERK) and the percent of inhibition was plotted relative to vehicle controls. **C,** Efficacy of encorafenib, dabrafenib, and vemurafenib in the A375 human melanoma tumor xenograft model grown in nude mice ($n = 5$ per group). Encorafenib and vemurafenib were dosed twice daily on an 8- to 16-hour interval and dabrafenib was dosed once daily by oral gavage for 14 days. Tumor volume and body weight were measured twice per week. No signs of toxicity or mortality were observed (see Supplementary Fig. S2A). **D,** Efficacy of encorafenib in the HMEX1906 primary human melanoma xenograft model grown in nude mice ($n = 8$/group); **E,** Waterfall plot of change in volume for each tumor in each treatment group from the experiment depicted in 1D. Each bar represents the maximum treatment effect observed for each mouse. **F,** Mice from the experiment depicted in 1D were dosed continually, and the endpoint of conditional survival was marked on the day at which each tumor regrew to its predose baseline. RFU, relative fluorescence units.

In the dose-expansion phase, 9 patients (33.3%), of whom 6 were treated at the 450 mg once-daily MTD, experienced at least 1 DLT during cycle 1. At the MTD, DLTs included myalgia (33.3%), arthralgia (26.7%), fatigue (20.0%), asthenia (13.3%), seventh nerve paralysis (6.7%), and insomnia (6.7%; Supplementary Table S2). All DLTs were grade 3. Of these 9 patients, 7 required a dose reduction to 300 mg once-daily. At this time, the 450 mg once-daily MTD no longer met the EWOC criteria with a risk of excessive toxicity of 37.9%. Thus, the 300 mg once-daily dose level was better tolerated and declared the RP2D. The risk of excessive toxicity at 300 mg once daily was 0.6%.

Review of the twice-daily dosing cohort revealed that the tolerability of this dosing schedule did not justify twice-daily

**Table 1.** Baseline patient and disease characteristics

| | Dose escalation | | Dose expansion | | |
|---|---|---|---|---|---|
| **Characteristic** | **BRAFi-naïve (*n* = 25)** | **BRAFi-pretreated (*n* = 29)** | **BRAFi-naïve (*n* = 15)** | **BRAFi-pretreated (*n* = 18)** | **All melanoma[a] (*n* = 35)** |
| Median age (range), years | 51.0 (33–70) | 50.0 (22–78) | 61.0 (43–79) | 54.0 (26–74) | 59.0 (26–79) |
| Sex, *n* (%) | | | | | |
| Female | 8 (32) | 10 (35) | 5 (33) | 14 (78) | 20 (57) |
| Male | 17 (68) | 19 (65) | 10 (67) | 4 (22) | 15 (43) |
| WHO performance status, *n* (%) | | | | | |
| 0 | 19 (76) | 16 (55) | 12 (80) | 8 (44) | 20 (57) |
| 1 | 5 (20) | 12 (41) | 3 (20) | 10 (56) | 15 (43) |
| 2 | 1 (4) | 1 (3) | 0 (0) | 0 (0) | 0 (0) |
| *BRAF* V600 mutation status, *n* (%) | | | | | |
| V600E | 23 (92) | 26 (90) | 13 (87) | 17 (94) | 31 (89) |
| Other | 2 (8) | 3 (10) | 2 (13) | 1 (6) | 4 (11) |
| LDH at baseline, *n* (%) | | | | | |
| ≤ULN | 16 (64) | 16 (55) | 10 (67) | 4 (22) | 14 (40) |
| >ULN | 9 (36) | 13 (45) | 5 (33) | 14 (78) | 21 (60) |
| Stage at current diagnosis, *n* (%) | | | | | |
| Stage IIIb | 1 (4) | 0 (0) | 1 (7) | 0 (0) | 1 (3) |
| Stage IIIc | 0 (0) | 0 (0) | 1 (7) | 0 (0) | 1 (3) |
| Stage Iva | 2 (8) | 1 (3) | 2 (13) | 0 (0) | 2 (6) |
| Stage IVb | 0 (0) | 4 (14) | 4 (27) | 1 (6) | 5 (14) |
| Stage IVc | 22 (88) | 24 (83) | 7 (47) | 17 (94) | 26 (74) |
| Previous BRAFi | | 29 (100) | | 18 (100) | |
| Treatment, *n* (%) | | | | | |
| Vemurafenib | | 28 (97) | | 16 (89) | |
| Dabrafenib | | 0 (0) | | 2 (11) | |
| Investigational | | 1 (3) | | 0 (0) | |
| BRAFi | | | | | |
| Median time between discontinuation of BRAFi and study start, days (range) | | 26 (12–319) | | 38.5 (11–331) | |

Abbreviations: BRAFi, BRAF inhibitor; LDH, lactate dehydrogenase; ULN, upper limit of the normal range; WHO, World Health Organization.
[a]Includes 2 patients in the stepwise group; 300 mg (first 15 days of treatment) to 450 mg (from day 15 onward if patients experienced no clinically significant grade 3 or 4 adverse events at the lower dose level).

dosing in view of potentially reduced compliance compared with the once-daily dosing schedule. In conjunction with the known long dissociation half-life of encorafenib, a once-daily dosing regimen was selected for future dosing.

***Safety and tolerability.*** *Dose-escalation phase.* The median duration of exposure was 15.1 weeks (range, 0.7–142), and 5 patients had ongoing treatment at the time of data cutoff. All 54 patients experienced at least 1 AE (Table 2). Grade 3/4 AEs were reported in 38 patients (70.4%); 6 patients (11.1%) had grade 4 AEs. The most common AEs (>40%) were PPED syndrome (51.9%), hyperkeratosis (50.0%), arthralgia (44.4%), nausea (44.4%), and pruritus (40.7%). Fifty-two patients had at least 1 AE suspected to be study drug related; of these, 18 patients (33.3%) had grade 3 AEs. Grade 3/4 study drug–related AEs reported (≥5% of patients) were fatigue (9.3%) and PPED syndrome (7.4%). Notably, the incidence of secondary neoplasms was low; SCC and keratoacanthoma were reported in 2 patients (3.7%) each. Three patients (5.6%) experienced facial paresis (including facial paresis and seventh nerve paralysis) at 100 mg once-daily, 100 mg twice-daily, and 450 mg once-daily dose levels. Pyrexia was reported in 2 patients (3.7%) and photosensitivity reactions were reported in 7 patients (13%).

Five patients (9.3%) experienced AEs leading to treatment discontinuation; these were PPED syndrome (3.7%, 100 and 450 mg once daily), headache (1.9%, 700 mg once daily), hyperkeratosis (1.9%, 550 mg once daily), and neuralgia (1.9%, 300 mg once daily). Eleven on-treatment deaths (defined as occurring during treatment or within 30 days of the last dose of study medication) were reported. One death, which was due to general health deterioration, was considered to be related to the study treatment by the study investigator; however, the role of disease progression, which was documented 19 days prior to death, may also be a plausible explanation for the outcome. The patient had ongoing events at the time of death, including dysphagia, confusional state, and a new melanoma. The remaining 10 on-treatment deaths (1 during treatment and 9 within 30 days of the last encorafenib dose) were due to progressive disease and unrelated to the study treatment.

*Dose expansion phase.* The median duration of exposure for all patients was 12.1 weeks (range, 0.1–90.7), and 8 patients had treatment ongoing at the time of data cutoff. In patients who had been pretreated with a BRAFi, exposure duration was 8.9 weeks (range, 0.4–90.7) in the MTD group and 5.6 weeks (range, 0.4–10.9) in the RP2D group. For BRAFi-naïve patients this was 6.3 weeks (range, 0.1–71.7) in the MTD group and 38.6 weeks (range, 0.4–53.9) in the RP2D group.

AEs experienced in the dose-expansion phase were similar to those experienced in the dose-escalation phase (Table 2). Thirty-four (97.1%) patients had at least 1 AE suspected to be study drug-related. The most frequent study drug-related AEs (>40%) were myalgia (62.9%), nausea (57.1%), PPED syndrome (54.3%), arthralgia (48.6%), vomiting (45.7%), alopecia (42.9%), dry skin (42.9%), and insomnia (40.0%). One patient (2.9%) experienced SCC of the head and neck,

**Table 2.** Adverse events occurring in ≥30% of patients in the dose-expansion phase

| | BRAFi-naïve ($n = 15$), *n* (%) | | BRAFi-pretreated ($n = 18$), *n* (%) | | All melanoma[a] ($n = 35$), *n* (%) | |
|---|---|---|---|---|---|---|
| **Adverse event** | **All grades** | **Grade 3/4** | **All grades** | **Grade 3/4** | **All grades** | **Grade 3/4** |
| **Irrespective of study drug relationship** | | | | | | |
| Nausea | 9 (60.0) | 1 (6.7) | 13 (72.2) | 3 (16.7) | 23 (65.7) | 4 (11.4) |
| Myalgia | 8 (53.3) | 2 (13.3) | 13 (72.2) | 3 (16.7) | 22 (62.9) | 5 (14.3) |
| PPED syndrome | 6 (40.0) | 0 (0.0) | 11 (61.1) | 3 (16.7) | 19 (54.3) | 4 (11.4) |
| Arthralgia | 6 (40.0) | 3 (20.0) | 9 (50.0) | 3 (16.7) | 17 (48.6) | 7 (20.0) |
| Vomiting | 5 (33.3) | 1 (6.7) | 10 (55.6) | 2 (11.1) | 17 (48.6) | 3 (8.6) |
| Insomnia | 4 (26.7) | 1 (6.7) | 10 (55.6) | 1 (5.6) | 16 (45.7) | 2 (5.7) |
| Alopecia | 7 (46.7) | 0 (0) | 8 (44.4) | 0 (0) | 15 (42.9) | 0 (0) |
| Dry skin | 6 (40.0) | 0 (0.0) | 9 (50.0) | 1 (5.6) | 15 (42.9) | 1 (2.9) |
| Hyperkeratosis | 6 (40.0) | 1 (6.7) | 6 (33.3) | 0 (0) | 14 (40.0) | 1 (2.9) |
| Headache | 4 (26.7) | 0 (0) | 9 (50.0) | 2 (11.1) | 13 (37.1) | 2 (5.7) |
| Keratosis pilaris | 3 (20.0) | 0 (0) | 9 (50.0) | 2 (11.1) | 13 (37.1) | 2 (5.7) |
| Pruritus | 5 (33.3) | 0 (0) | 6 (33.3) | 1 (5.6) | 13 (37.1) | 1 (2.9) |
| Asthenia | 1 (6.7) | 0 (0) | 9 (50.0) | 3 (16.7) | 11 (31.4) | 3 (8.6) |
| Constipation | 5 (33.3) | 0 (0) | 5 (27.8) | 0 (0) | 11 (31.4) | 0 (0) |
| **Suspected study drug-related** | | | | | | |
| Myalgia | 8 (53.3) | 2 (13.3) | 13 (72.2) | 3 (16.7) | 22 (62.9) | 5 (14.3) |
| Nausea | 8 (53.3) | 1 (6.7) | 11 (61.1) | 1 (5.6) | 20 (57.1) | 2 (5.7) |
| PPED syndrome | 6 (40.0) | 0 (0) | 11 (61.1) | 3 (16.7) | 19 (54.3) | 4 (11.4) |
| Arthralgia | 6 (40.0) | 3 (20.0) | 9 (50.0) | 3 (16.7) | 17 (48.6) | 7 (20.0) |
| Vomiting | 5 (33.3) | 1 (6.7) | 9 (50.0) | 2 (11.1) | 16 (45.7) | 3 (8.6) |
| Alopecia | 7 (46.7) | 0 (0) | 8 (44.4) | 0 (0) | 15 (42.9) | 0 (0) |
| Dry skin | 6 (40.0) | 0 (0) | 9 (50.0) | 1 (5.6) | 15 (42.9) | 1 (2.9) |
| Insomnia | 4 (26.7) | 1 (6.7) | 10 (55.6) | 1 (5.6) | 14 (40.0) | 2 (5.7) |
| Hyperkeratosis | 6 (40.0) | 1 (6.7) | 5 (27.8) | 0 (0) | 13 (37.1) | 1 (2.9) |
| Keratosis pilaris | 3 (20.0) | 0 (0) | 9 (50.0) | 2 (11.1) | 13 (37.1) | 2 (5.7) |
| Pruritus | 5 (33.3) | 0 (0) | 5 (27.8) | 1 (5.6) | 12 (34.3) | 1 (2.9) |
| Asthenia | 1 (6.7) | 0 (0) | 9 (50.0) | 3 (16.7) | 11 (31.4) | 3 (8.6) |

Abbreviation: PPED, palmar-plantar erythrodysesthesia.

[a]Includes 2 patients in the stepwise group; 300 mg (first 15 days of treatment) to 450 mg (from day 15 onward if patients experienced no clinically significant grade 3 or 4 adverse events at the lower dose level).

and keratoacanthoma was not observed. Four patients (11.4%) experienced facial paresis (seventh nerve paralysis) at 300 mg once daily ($n = 1$), at 450 mg once daily ($n = 2$), and in the stepwise group ($n = 1$). Pyrexia was reported in 2 patients (5.7%), and photosensitivity reactions were reported in 1 patient (2.9%).

Eight patients (22.9%) had AEs leading to discontinuation of study drug; the most common AEs were arthralgia and myalgia (5.7% each). Two on-treatment deaths (both within 30 days of the last dose of encorafenib) were reported and were not considered to be related to study treatment.

***Pharmacokinetics.*** Encorafenib was rapidly absorbed and detectable in plasma at 0.5 hours postdose and across all dose levels peaked ($T_{max}$) at approximately 2 hours (Fig. 2). Terminal half-life ($T_{1/2}$) was short (2.9–4.4 hours), remained constant across doses, and was similar between C1D1 and C1D15 (Supplementary Table S3). Plasma concentrations of encorafenib

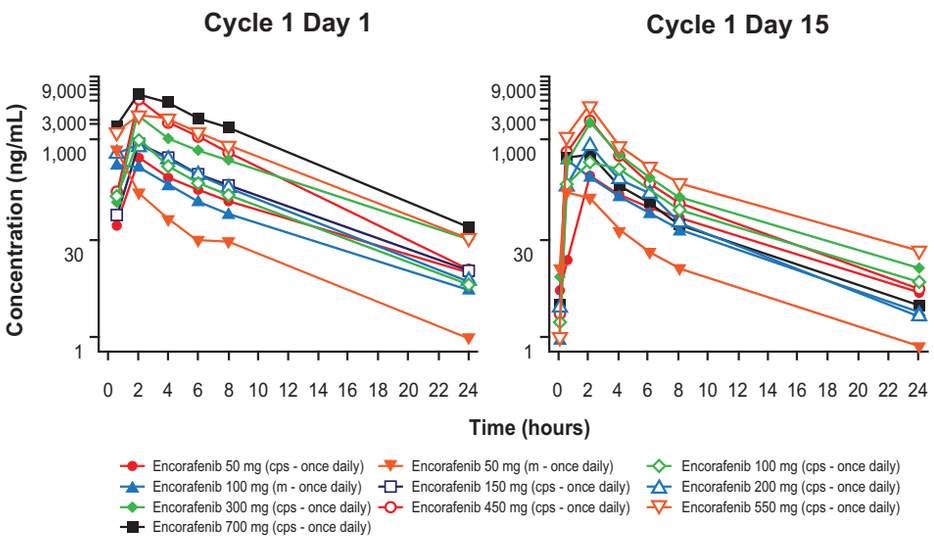


**Figure 2.**
Median semilogarithmic concentration–time profiles for plasma concentration of encorafenib by time and treatment group in the dose-escalation phase. cps, capsule; m, microemulsion.

**Table 3.** Summary of best overall response for patients in the dose-escalation and dose-expansion phases

| | Dose escalation | | Dose expansion | | |
|---|---|---|---|---|---|
| **Best overall response** | **BRAFi-naïve ($n = 25$), *n* (%)** | **BRAFi-pretreated ($n = 29$), *n* (%)** | **BRAFi-naïve ($n = 15$), *n* (%)** | **BRAFi-pretreated ($n = 18$), *n* (%)** | **All melanoma[a] ($n = 35$), *n* (%)** |
| CR | 2 (8.0) | 1 (3.4) | 1 (6.7) | 0 | 1 (2.9) |
| PR | 13 (52.0) | 2 (6.9) | 8 (53.3) | 4 (22.2) | 13 (37.1) |
| Unconfirmed CR[b] | 0 | 0 | 1 (6.7) | 0 | 1 (2.9) |
| Stable disease | 5 (20.0) | 10 (34.5) | 1 (6.7) | 2 (11.1) | 4 (11.4) |
| Unconfirmed CR/PR[c] | 1 (4.0) | 0 | 0 | 1 (5.6) | 1 (2.9) |
| Progressive disease | 0 | 14 (48.3) | 1 (6.7) | 10 (55.6) | 11 (31.4) |
| Unconfirmed CR/PR | 0 | 0 | 0 | 0 | 0 |
| Unknown | 5 (20.0) | 2 (6.9) | 4 (26.7) | 2 (11.1) | 6 (17.1) |
| Unconfirmed CR/PR[d] | 1 (4.0) | 0 | 1 (6.7) | 0 | 1 (2.9) |
| ORR | 15 (60.0) | 3 (10.3) | 9 (60.0) | 4 (22.2) | 14 (40.0) |
| 95% CI | 38.7–78.9 | 2.2–27.4 | 32.3–83.7 | 6.4–47.6 | 23.9–57.9 |
| Disease control rate | 20 (80.0) | 13 (44.8) | 10 (66.7) | 6 (33.3) | 18 (51.4) |
| 95% CI | 59.3–93.2 | 26.4–64.3 | 38.4–88.2 | 13.3–59.0 | 34.0–68.6 |

Abbreviations: CR, complete response; ORR, overall response rate; PR, partial response.

[a]Includes 2 patients in the stepwise group; 300 mg (first 15 days of treatment) to 450 mg (from day 15 onward if patients experienced no clinically significant grade 3 or 4 adverse events at the lower dose level).

[b]Unconfirmed CR due to no confirmatory scan before data cutoff.

[c]Unconfirmed CR/PR due to PR followed by progressive disease at the confirmatory scan.

[d]Unconfirmed CR/PR due to PR followed by patient discontinuation due to AE.

were lower on C1D15 than C1D1 across all dose levels, suggesting time-dependent pharmacokinetics. Plasma clearance was increased 2-fold between C1D1 and C1D15, whereas the area under the plasma concentration–time curve for a dosing interval (AUCτ) and maximum plasma concentration ($C_{max}$) showed that systemic exposure was also lower at C1D15 (Supplementary Table S3), possibly due to autoinduction via the CYP34A pathway. Trough plasma concentrations did not show an appreciable difference by C2D1, suggesting that steady-state conditions had been reached by C1D15. Mixed-effect modeling on once-daily capsule data of C1D1 and C1D15 confirmed that AUC and $C_{max}$ were approximately dose proportional over the complete dose range (Supplementary Table S3).

***Efficacy.*** In the dose-escalation phase, the overall response rates (ORR) for BRAFi-naïve and BRAFi-pretreated patients were 60.0% and 10.3%, respectively (Table 3; Fig. 3A). In the dose-expansion phase, the ORRs were 60.0% and 22.2% for BRAFi-naïve and BRAFi-pretreated patients, respectively (Table 3; Fig. 3B). PFS and OS were assessed for patients in the dose-expansion phase only. Median PFS for BRAFi-naïve patients was 12.4 months [95% CI, 7.4–not reached (NR)], and the PFS rate at 6 months was 91.7% (95% CI, 76.0–100). Median PFS for BRAFi-pretreated patients was 1.9 months (95% CI, 0.9–3.7), with a PFS rate at 6 months of 11.8% (95% CI, 0.0–27.1; Fig. 3C). Median OS was not reached for BRAFi-naïve patients and was 9.07 months (95% CI, 3.68–10.84) for BRAFi-pretreated patients (Fig. 3D).

***Biomarker analysis.*** The mutation status of archival or fresh tumor samples collected at baseline was analyzed centrally by next-generation sequencing. No correlation was observed between the best percentage change from baseline and mutation status (Supplementary Fig. S3A and S3B).

## Discussion

Preclinical studies demonstrate that encorafenib is more potent and has prolonged pharmacodynamic activity compared with approved BRAF inhibitors vemurafenib and dabrafenib. Antitumor activity of encorafenib was demonstrated in human *BRAF* V600E–mutant melanoma xenografts at doses as low as 5 mg/kg; however, higher doses were required to prevent the emergence of resistance in this model. Positive preclinical findings led to further investigation of encorafenib in clinical trials. Data from a more comprehensive investigation of the preclinical comparative pharmarmacology of encorafenib and other BRAF inhibitors are in preparation for publication.

The primary objective of this phase I study was to determine the MTD and/or RP2D of encorafenib. The MTD was established at 450 mg once daily based on data from the dose escalation phase; however, after reviewing the safety and tolerability data in the dose-expansion phase, the MTD was not considered to be a viable RP2D because 7 of 9 patients who exhibited a DLT during the first cycle required a dose reduction to 300 mg once daily. Therefore, the 300-mg once-daily dose level was declared the RP2D. Review of the overall safety profile of the 450-mg and 300-mg once-daily doses continued to show meaningfully higher rates of DLTs and grade 3 AEs at the MTD, supporting 300-mg once daily as the RP2D for encorafenib as a single agent.

Encorafenib showed signs of promising activity in this study, with ORRs in the dose-expansion phase of 60% in patients with melanoma who were BRAFi-naïve. Minimal efficacy was seen in patients who received prior BRAFi treatment. BRAFi-pretreated patients received encorafenib between 1.5 and 47 weeks following their BRAFi treatment. Objective responses to BRAFi retreatment have been reported in patients progressing on BRAFi therapy following a treatment break (21, 22). Therefore, treatment interruption may account for some of the responses observed in pretreated patients in this study due to removal of the selective pressure of MAPK inhibition. Correlative analyses between the length of the BRAFi treatment-break interval and response to subsequent BRAFi will help further understand tumor response dynamics. Encorafenib showed durable response in BRAFi-naïve patients, with a median PFS of

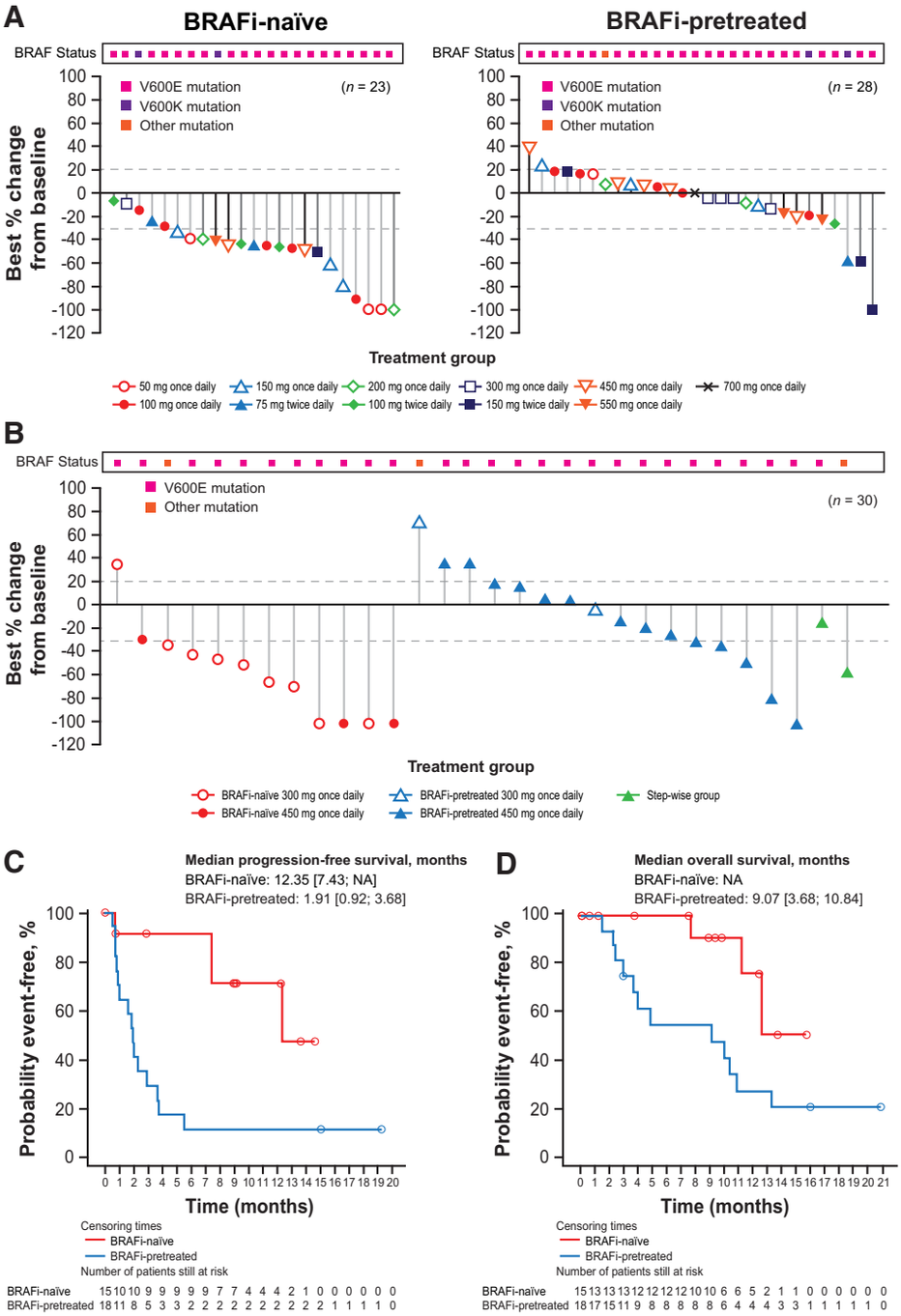


**Figure 3.**
Efficacy of encorafenib by treatment group. Best percentage of change in sum of longest diameters in target lesion from baseline by treatment group in the dose-escalation (**A**) and dose-expansion phases (**B**), Kaplan–Meier plot of progression-free survival (**C**), and overall survival (**D**), by patient group in the dose-escalation phase. NA, not applicable.

12.4 months—longer than that reported in vemurafenib (5.3 months; ref. 23) and dabrafenib (4.5–6.2 months) in the same setting (24). Data from the randomized COLUMBUS trial confirm this observation (25).

Encorafenib was well tolerated, with most AEs being grade 2 or lower in severity. Single-agent BRAFis have been associated with characteristic AEs, which are proposed to be the result of aberrant wild-type BRAF/CRAF activation. Dermatologic events were among the most common AEs observed in the dose escalation and expansion phases. PPED and hyperkeratosis were reported in over 40% of patients, higher than the rates reported with the approved BRAF inhibitors. Although hyperkeratosis is a characteristic and diagnostic feature of PPED according to the NCI CTCAE v4.0 reporting criteria (18), hyperkeratosis was often experienced in locations other than the hands and feet. Cutaneous SCC has been reported in 12%–21% of patients with melanoma following treatment with vemurafenib monotherapy (23, 26, 27) and in 9%–

19% of patients following dabrafenib monotherapy (11, 24, 28), in contrast with the low rates (3%–4%) observed in this study. These observations are intriguing given the lower rate of hyperplasia observed in the gastric epithelium of mice treated with encorafenib. A recent study profiling the paradoxical activation of ERK across the BRAF inhibitors vemurafenib, dabrafenib, and encorafenib suggests that differences in the potency of pERK induction in $HRAS^{mut}$, $BRAF^{wt}$ keratinocytes relative to the potency of pERK inhibition in *BRAF* V600E melanoma cells may account for the varying rates of cutaneous SCC between the compounds (29).

Facial paresis has been reported in cases of patients treated with vemurafenib (30, 31). Symptoms typically resolve when treatment is stopped and may be resolved with steroid treatment, suggesting a possible autoimmune mechanistic trigger. Facial paresis (regardless of causality) was observed in 7 patients (7.9%) treated with encorafenib. The low rates of pyrexia, photosensitivity, and cutaneous SCC suggest a tolerability profile that is different from either vemurafenib or dabrafenib (5, 7). Further studies are needed to better understand the mechanisms that underlie these differences, which may include on-target and off-target effects (32).

It is important to note that the standard of care with BRAF-targeted therapy has changed dramatically since the commencement of this study. Specifically, there are now 3 randomized trials demonstrating superior response rates, PFS, and OS in patients receiving combinations of BRAF and MEK inhibitors (dabrafenib plus trametinib, and vemurafenib plus cobimetinib) compared with single-agent BRAFi therapy (11–13, 28), which led to the approval of these combinations for the treatment of patients with unresectable or metastatic melanoma with a *BRAF* V600E or V600K mutation. Preliminary results from combination studies have suggested that pairing encorafenib with the MEK inhibitor binimetinib mitigates some dermatologic AEs that were associated with single-agent encorafenib, a finding that has also been reported with the combination of dabrafenib and trametinib (33), and appears to be associated with efficacy comparable with other BRAF/MEK inhibitor combinations (28, 34, 35). The efficacy and safety of encorafenib is currently being further investigated in combination with binimetinib, and compared with that of encorafenib or vemurafenib alone, in an ongoing phase III study (COLUMBUS, NCT01909453; ref. 25).

## Disclosure of Potential Conflicts of Interest

J.-P. Delord is a consultant/advisory board member for Astra Zeneca and Roche. C. Robert is a consultant/advisory board member for Amgen, Array, Bristol-Myers Squibb, MSD, Novartis, and Roche. R. Kudchakar reports receiving commercial research grants from Merck, and is a consultant/advisory board member for Bristol-Myers Squibb. R. Sullivan, R.F. Kefford, M. Hidalgo, and R. Dummer are consultant/advisory board members for Novartis. M.S. Carlino is a consultant/advisory board member for Bristol-Myers Squibb, MSD, and Novartis. D. Stuart holds ownership interest (including patents) in Novartis. No potential conflicts of interest were disclosed by the other authors.

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