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BRIM-P: A phase I, open-label, multicenter, dose-escalation study of vemurafenib in pediatric patients with surgically incurable, *BRAF* mutation-positive melanoma

Julia C. Chisholm[1], **Jozef Suvada**[2], **Ira J. Dunkel**[3], **Michela Casanova**[4], **Weijiang Zhang**[5], **Natasha Ritchie**[6], **YounJeong Choi**[7], **Jane Park**[7], **Meghna Das Thakur**[7], **Stephen Simko**[7], **Nga Wan Rachel Tam**[7], and **Andrea Ferrari**[4]

[1]Children and Young People's Unit, The Royal Marsden NHS Foundation Trust, Sutton, UK

[2]Department of Pediatric Hematology and Oncology, Children´s Teaching Hospital and St. Elizabeth University, Bratislava, Slovakia

[3]Memorial Sloan Kettering Cancer Center, New York, New York

[4]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

[5]Roche Innovation Center, New York, New York

[6]Roche Products Limited, Welwyn Garden City, UK

[7]Genentech, South San Francisco, California

Abstract

Background—Vemurafenib, a selective inhibitor of BRAF kinase, is approved for the treatment of adult stage IIIc/IV *BRAF V600* mutation-positive melanoma. We conducted a phase I, open-label, dose-escalation study in pediatric patients aged 12–17 years with this tumor type (NCT01519323).

Procedure—Patients received vemurafenib orally until disease progression. Dose escalation was conducted using a 3+3 design. Patients were monitored for dose-limiting toxicities (DLTs) during the first 28 days of treatment to determine the maximum tolerated dose (MTD). Safety/tolerability, tumor response, and pharmacokinetics were evaluated.

Results—Six patients were enrolled (720 mg twice daily [BID]; n=3]; 960 mg BID [n=3]). The study was terminated prematurely due to low enrollment. No DLTs were observed; thus, the MTD could not be determined. All patients experienced at least one adverse event (AE); the most common were diarrhea, headache, photosensitivity, rash, nausea, and fatigue. Three patients experienced serious AEs, one patient developed secondary cutaneous malignancies, and five

Correspondence: Julia C. Chisholm, Children and Young People's Unit, Royal Marsden Hospital, Downs Road, Sutton, Surrey, SM2 5PT, UK. julia.chisholm@rmh.nhs.uk, Phone: +44 208 661 3549; Fax: +44 208 661 3617.

CONFLICT OF INTEREST

JCC reports consulting/advisory roles for F. Hoffmann-La Roche Ltd and Merck, and travel, accommodation, or expenses from F. Hoffmann-La Roche Ltd. IJD reports consulting roles for Bayer HealthCare Pharmaceuticals, Bristol-Myers Squibb, Eisai, and Pfizer. MC reports consulting/advisory roles for F. Hoffmann-La Roche Ltd. WZ and NR report current employment and stocks/shares at F. Hoffmann-La Roche Ltd. YJC, JP, MDT, SS, and NWRT report current employment at Genentech and stocks/shares in F. Hoffmann-La Roche Ltd. All other authors have no conflicts of interest to report.

patients died following disease progression. Mean steady-state plasma concentrations of vemurafenib following 720 mg and 960 mg BID dosing were similar or higher, respectively, than in adults. There were no objective responses. Median progression-free survival and overall survival were 4.4 months (95% confidence interval [CI]=2.7–5.2) and 8.1 months (95% CI=5.1–12.0), respectively.

Conclusions—A recommended and effective dose of vemurafenib for patients aged 12–17 years with metastatic or unresectable melanoma was not identified. Extremely low enrollment in this trial highlights the importance of considering the inclusion of adolescents with adult cancers in adult trials.

Keywords

vemurafenib; *BRAF* mutation; pediatric; melanoma; clinical trial; oncology

INTRODUCTION

The incidence of melanoma in individuals aged <20 years in the United States is 4.2 cases per 1 million and increasing.[1] Although rare in young children, 73% of melanoma cases before the age of 20 years occur in adolescents aged 15–19 years, with melanoma accounting for 7% of all malignancies in this age group.[2,3] Approximately 85–90% of pediatric melanoma patients in this age range present with localized disease that is amenable to surgical resection.[4] A further 10% of pediatric patients have resectable disease with regional spread (stage IIIa/IIIb), and there are reports of treatment with high-dose interferon alfa 2b adjuvant therapy.[5–7] Unresectable (stage IIIc) or metastatic (stage IV) melanoma is exceptionally rare in pediatric patients, and outcome is particularly poor with an estimated 5-year overall survival (OS) of 12–20%.[8,9]

Elucidation of oncogenic mutations in melanoma has led to the development of novel targeted therapies, which have improved survival in adults with advanced melanoma. Approximately 50% of adult melanomas carry a somatic *BRAF* mutation in codon V600, most commonly V600E, leading to constitutive BRAF activation.[10–13] BRAF activation results in downstream mitogen-activated protein kinase kinase (MEK) and extracellular signal-regulated kinase phosphorylation, and ultimately to the activation of transcription factors responsible for regulating cell cycle and protein synthesis. While not independently sufficient to promote oncogenesis, *BRAF V600* mutations are a major regulator of melanoma cell proliferation.

Vemurafenib, a selective inhibitor of BRAF kinase, is indicated for use in adults with *BRAF V600* mutation-positive stage IIIc/IV melanoma.[14] The phase III BRAF Inhibitor in Melanoma 3 (BRIM-3) trial compared vemurafenib with dacarbazine in treatment-naïve adult patients with *BRAF V600*-mutant stage IIIc/IV melanoma.[15] Compared with dacarbazine, vemurafenib significantly improved progression-free survival (PFS) and OS, and was associated with 63% and 74% relative reductions in the risk of death and in the risk of death or disease progression, respectively ($P < 0.001$ for both comparisons).[15] Response rates were 48% for vemurafenib and 5% for dacarbazine.[15] The most common adverse events (AEs) associated with vemurafenib during clinical development were arthralgia, rash,

fatigue, alopecia, keratoacanthoma or squamous cell carcinoma (SCC), photosensitivity, nausea, and diarrhea.[15–17]

There is a lack of prospectively evaluated therapies in adolescents with metastatic melanoma. Given the poor outcomes observed in this population[8] and the improved outcomes reported with vemurafenib in adult patients with metastatic melanoma,[15,17] we conducted a clinical trial of vemurafenib in adolescent patients with *BRAF V600* mutation-positive stage IIIc/IV melanoma.

METHODS

Study design

BRAF Inhibitor in Melanoma – Pediatric (BRIM-P; NCT01519323; NO25390) was a phase I, open-label, multicenter, single-arm, dose-escalation study of oral vemurafenib in patients aged 12–17 years. The study was sponsored by F. Hoffmann-La Roche Ltd and conducted at 26 sites in 10 countries between December 2011 and December 2015.

The protocol was approved by participating institutions' review boards, and the trial was conducted in accordance with the principles of the Declaration of Helsinki and International Conference on Harmonization guidelines for Good Clinical Practice. All patients and/or parent or legal guardians provided written, informed consent, and patient safety was reviewed by an independent Data Safety Monitoring Board.

The study included a dose-escalation phase, using a 3 + 3 design[18] (see supplementary materials), and a planned extension phase where additional patients would be recruited to further evaluate safety and efficacy. The starting dose was 720 mg twice daily (BID) for patients who weighed ≥45 kg; for patients who weighed <45 kg, the starting dose was 480 mg BID regardless of the dose-escalation cohort open at the time of enrollment. All patients were to receive oral vemurafenib at their assigned dose until the maximum tolerated dose (MTD) for the extension phase was determined.

Study participants

Pediatric patients (aged 12–17 years) with histologically confirmed, surgically-incurable and unresectable stage IIIc or IV melanoma that tested positive for the *BRAF V600* mutation (Cobas® 4800 *BRAF V600* Mutation Test, Roche Molecular Systems, Inc., Branchburg, NJ) were enrolled. Other key inclusion criteria included a Karnofsky Performance Score of >50 (patients aged ≥16 years) or a Lansky score of ≥60 (patients aged <16 years), a life expectancy >3 months and adequate hematologic, hepatic, and renal function. Patients with asymptomatic, previously treated, radiographically stable central nervous system (CNS) lesions were eligible if the patient had not required CNS-directed therapy for at least 3 months prior to starting treatment, and had not required glucocorticoids or anticonvulsants for at least 21 days prior to starting treatment. Patients were excluded if they had any of the following: active or untreated CNS lesions; a history of spinal cord compression or carcinomatous meningitis; prior treatment with selective/specific BRAF or MEK inhibitors or vemurafenib; were pregnant or lactating; a QTc ≥450 msec or a history of congenital long

QT syndrome. Concomitant treatment with any other anticancer therapy was not permitted (see supplementary materials).

Objectives

The primary objective of the study was to estimate the MTD and identify the recommended dose of oral vemurafenib for pediatric patients aged 12–17 years with unresectable stage IIIc/IV *BRAF* mutation-positive melanoma. Secondary objectives were evaluations of the safety and tolerability, efficacy, and pharmacokinetic profile of vemurafenib in this population. Exploratory objectives included investigation into potential biomarkers.

Safety assessments

Patients were evaluated for dose-limiting toxicities (DLTs; see supplementary materials) during the first 28 days of study treatment. Safety and tolerability were assessed by monitoring the frequency and intensity of AEs throughout the study and until 28 days after the last dose of vemurafenib. Additionally, patients were monitored during study treatment and the subsequent 6-month follow-up period for the occurrence of new primary melanoma and SCC (cutaneous and non-cutaneous). AEs were graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, version 4.0). Additional safety assessments were performed throughout the study until 28 days after the last dose of vemurafenib and included laboratory parameters (hematology, urinalysis, and clinical chemistry), performance status (Karnofsky or Lansky), vital signs, physical examinations, and electrocardiograms (until treatment completion only). Evaluations (dermatologic, physical, and radiologic) to identify cutaneous and non-cutaneous SCC and new primary melanoma were performed regularly during the study; suspicious lesions were biopsied on an as-needed basis, and evaluations were continued following the last dose of vemurafenib until loss to follow-up, death, withdrawal of consent, or study closure. Patients who developed an SCC or suspicious skin lesion could opt to continue or discontinue the trial based on consultation with the investigator.

Efficacy assessments

Tumor response was assessed by computed tomography (CT) scan or magnetic resonance imaging at baseline (reference measure), after 4 weeks (cycle 2), and then every 8 weeks (cycles 4–12) or 12 weeks (thereafter) until the completion of treatment. Findings were judged according to the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1).

Pharmacokinetic assessments

Venous blood samples (2 ml) were collected pre-dose (morning), and at 2, 4, 8, 12, and 24 hr post-dose on days 1 and 22, and pre-dose and 2 hr post-dose every 4 weeks (cycles 2–4), 8 weeks (cycles 6–12), and 12 weeks (thereafter) until the end of treatment. All samples were collected following an 8-hr overnight fast, and patients continued to fast for 4 hr after the morning drug administration on days 1 and 22. Plasma concentrations of vemurafenib were determined using validated liquid chromatography-tandem mass spectrometry. The lower

limit of quantitation for vemurafenib in human plasma was 0.025 μg/ml, with linearity demonstrable to 50 μg/ml (upper limit of quantitation), using a sample volume of 0.05 ml.

Statistical analyses

Target enrollment for the planned extension phase was 20 patients. The primary analysis variable was the MTD, defined as one dose level below the dose that induced a DLT in at least one of three patients following expansion of that dose level (i.e., two of six patients, or fewer if unacceptable toxicity prohibited further enrollment into a dose level). All safety findings were summarized using descriptive statistics. Secondary efficacy variables included PFS, OS, best overall response rate (BORR), and clinical benefit rate. PFS and OS were estimated using Kaplan-Meier methodology. Pharmacokinetic parameters were obtained by non-compartmental methods using WinNonlin software (version 6.4; Pharsight Corporation, Mountain View, CA). Data from samples collected on days 1 and 22 were used to obtain the maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve between time zero and 12 hr ($AUC_{0–12}$); the accumulation ratio was calculated using $AUC_{0–12}$ values (day 22:day 1). Vemurafenib concentrations and pharmacokinetic parameters are presented using descriptive statistics.

Exploratory biomarker assessments

Whole blood samples for biomarker assessments were collected at the start of treatment. Tumor tissue samples from *BRAF* mutation screening were retained for exploratory molecular analyses; SCC or suspicious lesion tissue samples were also collected. Mutations (single nucleotide variations [SNVs], small insertion/deletions [indels], structural variations, including inter- and intra-chromosomal rearrangements, and copy number variations (CNV)) and mutation load were assessed in tumor tissue using targeted genomic profiling methods (see supplementary materials).[19–21]

RESULTS

Patients

A total of six patients, all weighing ≥45 kg, were enrolled into two dose cohorts. Three patients received vemurafenib at a dose of 720 mg BID, and three patients subsequently received vemurafenib at a dose of 960 mg BID. Baseline characteristics and prior therapies are presented in Table 1. Patients in the 720 mg BID dose cohort received 76, 83, and 138 days of treatment, respectively; patients in the 960 mg BID dose cohort received 130, 144, and 291 days of treatment, respectively. All patients were enrolled between January 2013 and August 2014; study enrollment was discontinued in December 2015 due to the inability to recruit eligible patients.

Safety and tolerability

All six patients received at least one dose of vemurafenib and were included in the safety population. An MTD could not be determined, because no DLTs were observed in the small number of patients enrolled.

All patients experienced at least one AE. The most common AEs (reported in ≥3 patients) were diarrhea and headache (each occurring in four [66.7%] patients), and photosensitivity, rash, nausea, and fatigue (each occurring in three [50%] patients). The majority of AEs were grade 1 or 2 in severity, and four patients experienced grade ≥3 AEs (Table 2). There were no AEs leading to discontinuation or dose reduction of vemurafenib. Two patients had an AE (nephrolithiasis, n = 1; skin infection, n = 1) that required vemurafenib to be temporarily withheld.

Serious AEs were reported in three patients during the study (Table 3). Patient 6, a 16-year-old white male, developed a cutaneous SCC that was considered related to vemurafenib, and the patient concomitantly experienced a cutaneous basal cell carcinoma (BCC; two lesions reported). The patient underwent excision of the SCC and BCC, and no further therapy for these lesions was administered. No patients had a prolongation of QTc >500 msec.

All six patients discontinued study treatment following disease progression. Five of the six patients died subsequent to disease progression, and four patient deaths were attributed to progressive disease (PD). One death occurred due to an AE of intracranial tumor hemorrhage in a patient with pre-existing intracranial disease (Patient 4). The AE occurred 10 days after the patient had discontinued the study drug due to PD (confirmed by brain CT). In the opinion of the investigator, the event of intracranial tumor hemorrhage was not related to the study drug.

Efficacy

All patients were assessed for tumor response during the dose-escalation phase and were included in the efficacy population. The BORR was 0% (95% CI = 0–45.93) as no patient had a confirmed response. One patient had an unconfirmed partial response (observed at only one time point; Supplementary Fig. S1). Four patients had a BORR status of stable disease for >6 weeks; therefore, the clinical benefit rate was 66.7% (Table 4). Median PFS was 4.4 months (95% CI = 2.7–5.2), and all six patients subsequently experienced disease progression. Median OS was 8.1 months (95% CI = 5.1–12.0), and one patient was alive at the time of study closure 16.9 months after study drug initiation. No patients were enrolled in the efficacy extension phase.

Pharmacokinetics

All patients had at least one post-dose blood sample and were included in the pharmacokinetic population. Individual steady-state plasma concentration-time profiles (day 22) are presented by vemurafenib dose in Figure 1. Steady-state concentration was relatively constant over the dosing interval in both dose cohorts following oral administration of 720 mg BID or 960 mg BID vemurafenib. Mean C_{max} (% coefficient of variation [CV]) following single doses of vemurafenib 720 mg and 960 mg BID (day 1) were 2.593 μg/ml (72%) and 7.897 μg/ml (52%), respectively; corresponding values at steady state (day 22) were 50.367 μg/ml (26%) and 93.367 μg/ml (18%), respectively. Mean $AUC_{0–12}$ (CV) following single doses of vemurafenib 720 mg and 960 mg BID (day 1) were 19.510 μg·hr/ml (76%) and 67.967 μg·hr/ml (58%), respectively; corresponding values at steady state (day 22) were 498.333 μg·hr/ml (28%) and 982.333 μg·hr/ml (23%), respectively. Inter-

patient variability in vemurafenib exposure was greater on day 1 (CV: 52–76%) compared with day 22 (i.e., steady state; CV: 18–28%). Substantial accumulation (day 22:day 1) was observed following multiple oral doses of vemurafenib (720 mg and 960 mg BID); individual accumulation ratios (AUC, day 22:day 1) ranged from approximately 11 to 67.

Tumor whole exome sequencing

Whole exome sequencing (WES) was performed in melanoma samples and paired normal blood samples from all six patients. The most prevalent SNVs (Supplementary Fig. S2), and SNVs detected in mitogen-activated protein kinase (MAPK) signaling pathway genes (Fig. 2) and known to be relevant to melanoma,[22–25] are described here. Eighty-five percent of SNVs were cytidine to thymidine (C > T) or guanine to adenine (G > A) transitions. Supplementary Table S1 shows all coding and non-coding variants (SNVs and indels) as detected by WES in each sample. Figure 2 shows genes affected by copy number gains and losses in each sample. No CNV changes were seen in melanoma-associated genes (Supplementary Table S2). In five of six patients, WES confirmed the presence of a *BRAF V600E* mutation, as originally detected using the Cobas® 4800 *BRAF V600* mutation test. No *BRAF V600E* mutation could be detected in one patient, likely due to low quality of formalin-fixed, paraffin-embedded DNA and poor next-generation sequencing coverage (Supplementary Table S3).

The median observed mutation load in the coding regions was approximately 10.27 mutations/Mb (range, 4.83–31.26; Fig. 2). Mutation load, calculated from the WES data, did not show a correlation with time to progression.

DISCUSSION

The tolerability of vemurafenib in the small number of adolescent patients treated during this study was consistent with that observed in adults. The MTD of vemurafenib in pediatric and adolescent patients could not be determined as no DLTs were observed in the six treated patients (720 mg BID, n = 3; 960 mg BID, n = 3). The absence of DLTs should be interpreted cautiously given the small sample size. Secondary cutaneous malignancies (SCC and BCC) were observed in one patient, consistent with previous findings in adults.[15–17]

The pharmacokinetic characteristics of vemurafenib in adolescent patients were generally consistent with those observed in adults.[26] As in adults, substantial accumulation of vemurafenib was observed following multiple BID doses in both dose cohorts. Inter-individual variability in vemurafenib exposure was greater following a single dose than at steady state, and steady-state exposure was relatively constant over the dosing interval. Steady-state vemurafenib plasma exposures in adolescent patients were found to be similar or higher than those observed in adults.[26] For example, the mean steady-state C_{max} following vemurafenib 720 mg BID was similar in adolescents (~50 μg/ml) to that observed in adults (~53 μg/ml); in contrast, the mean steady-state plasma concentration following vemurafenib 960 mg BID appeared greater in adolescents (~93 μg/mL) than in adults (~61 μg/mL).[26]

Based on the limited data available in this study, a dose recommendation cannot be made for patients with metastatic or unresectable melanoma <18 years of age. Given the established adult MTD of 960 mg BID, and the similar or higher exposure to vemurafenib in adolescents versus adults, further prospective evaluation of vemurafenib doses above 960 mg BID in patients aged <18 years and weighing ≥45 kg is not warranted. This study provides no information about dosing in patients aged <18 years who weigh <45 kg.

Unlike adult patients with *BRAF V600*-mutated metastatic melanoma, in whom objective responses to vemurafenib have been observed in 48–53% of cases in phase II and III trials,[15,17] no objective responses were observed in adolescents with this tumor type. This cannot be attributed to drug resistance induced by prior chemotherapeutic intervention, as only two patients received systemic therapy prior to study enrollment. Moreover, the patient with the longest time to disease progression was the only one to receive cytotoxic chemotherapy prior to enrollment. Furthermore, drug exposure was equal to or higher than that observed in adults, and compliance with study drug administration was high. Finally, prolonged periods of study drug withholding due to toxicity or noncompliance did not occur. Thus, a clinical rationale to explain the apparent inferior outcomes in adolescents relative to adults has not been identified. Given the small sample size, the possibility that the difference may have occurred due to chance cannot be excluded.

Exploratory biomarker analysis detected no previously characterized genetic aberrations associated with resistance to vemurafenib therapy that would explain the lack of drug response (including loss of phosphatase and tensin homolog [PTEN][27] or neurofibromatosis-1,[28] *BRAF* copy number amplification,[29] CDK4 mutations and cyclin D1 amplifications,[30] and NRAS or MEK mutations[31]).

Consistent with previous findings, our results suggest that the pediatric melanoma samples examined in the present study are heterogeneous, with mutations relevant to melanoma oncogenesis occurring in a mutually exclusive manner.[32] The high proportion of C > T and G > A transitions are consistent with damage by ultraviolet radiation.[33–37] The median mutation load in this pediatric cohort was also consistent with that observed previously in pediatric and adult samples.[32,38]

The primary limitations of this study were its low enrollment and consequent termination, for which there are several potential reasons. Foremost, metastatic melanoma requiring systemic therapy is exceedingly rare in adolescents.[2] While the annual incidence of melanoma is approximately 4/1,000,000 pediatric patients,[1] metastatic cancer at presentation comprises less than 3% of disease.[8] Additionally, high cure rates of patients with regional disease treated with surgery and high-dose interferon alfa 2b limit the number of patients who recur with metastatic disease later on.[5–7] Treatment of this adult cancer in adolescents occurs in both pediatric and adult oncology facilities, potentially limiting adequate patient concentration in, and referral to, tertiary study sites.[3,39–41] Additionally, the majority of patients with melanoma who were considered for enrollment were *BRAF V600* mutation negative, were not within the eligible age range, or had a disease stage that was too low. Finally, the standard-of-care treatment for metastatic melanoma has evolved considerably since the study began. Approval of six new medications (in addition to vemurafenib) for

adult patients with unresectable or metastatic melanoma (cobimetinib, pembrolizumab, nivolumab, trametinib, dabrafenib, and ipilimumab) in the United States and European Union since the time of study initiation resulted in the potential availability of alternate therapeutic approaches for pediatric patients eligible for enrollment in this trial. Therefore, other clinical trials or off-label usage by treating physicians may have reduced enrollment.

Our experience highlights the need to identify appropriate solutions for conducting early phase trials in patients <18 years of age with cancers that are more typically seen in adults. Given that similar tolerability, pharmacokinetics, and recommended doses are typically observed in adolescents (relative to adults) in the evaluation of most drugs,[37] the inclusion of adolescents with adult cancers is warranted in early phase trials to facilitate therapeutic development in younger patients. This holds particularly true considering that even a large adolescent multinational study may not recruit sufficient patients and may ultimately provide therapy considered obsolete relative to a rapidly evolving adult therapeutic landscape. Novel collaborative strategies among adult and pediatric centers and study sponsors are needed to facilitate referral of rare adolescent patients to tertiary centers recruiting on such trials. When dedicated phase I pediatric studies are warranted, mechanism-of-action based enrollment (as opposed to disease-specific enrollment) should be seriously considered so as not to risk successful completion of pharmacokinetic and tolerability objectives or render development of new drugs unfeasible in other potential pediatric indications. The experience of this trial, to which few patients were accrued despite extensive recruitment efforts, highlights the necessity of a multi-stakeholder approach among academics, regulators, industry sponsors, and advocacy groups to ensure broad pediatric development strategies, proper molecular prioritization, and minimized risk of low-enrolling or non-feasible trials.[42]

In conclusion, a recommended dose of vemurafenib in patients with *BRAF V600*-mutated metastatic or unresectable melanoma aged <18 years and weighing ≥45 kg was not identified in this study. No new safety signals were observed. No objective tumor responses were observed in this limited pediatric population. Based on limited data from six adolescent patients in two dose groups, the pharmacokinetic characteristics of vemurafenib appeared similar to those in adult patients. Inclusion of adolescents in adult trials and mechanism-of-action approaches in pediatric trials are critical potential mitigation strategies to ensure the timely evaluation of adolescents with rare diseases and successful completion of pharmacology and tolerability objectives in early phase trials in pediatric-aged patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviation Definition

AE	Adverse event
$AUC_{0–12}$	Area under the concentration time curve during one dose interval (12 hours)
BCC	Basal cell carcinoma
BID	Twice daily
BORR	Best overall response rate
BRIM-3	BRAF Inhibitor in Melanoma 3
BRIM-P	BRAF Inhibitor in Melanoma - Pediatric
CI	Confidence interval
C_{max}	Maximum plasma concentration
CNS	Central nervous system
CNV	Copy number variation
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of variation
DLT	Dose-limiting toxicity
MAPK	Mitogen-activated protein kinase
MedDRA	Medical Dictionary for Regulatory Activities
MEK	Mitogen-activated protein kinase kinase
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NGS	Next-generation sequencing
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PTEN	Phosphatase and tensin homolog
qPCR	Quantitative polymerase chain reaction
RECIST	Response Evaluation Criteria in Solid Tumors
SCC	Squamous cell carcinoma

SNV	Single nucleotide variation
WES	Whole exome sequencing

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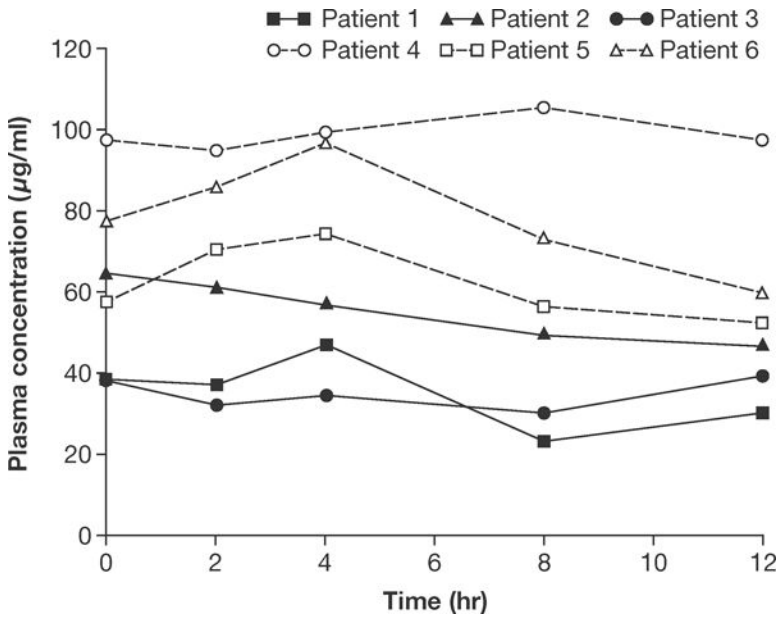

FIGURE 1.

Individual steady-state (day 22) plasma concentration-time profiles following treatment with vemurafenib 720 mg BID (patients 1–3) or 960 mg BID (patients 4–6). BID, twice daily.

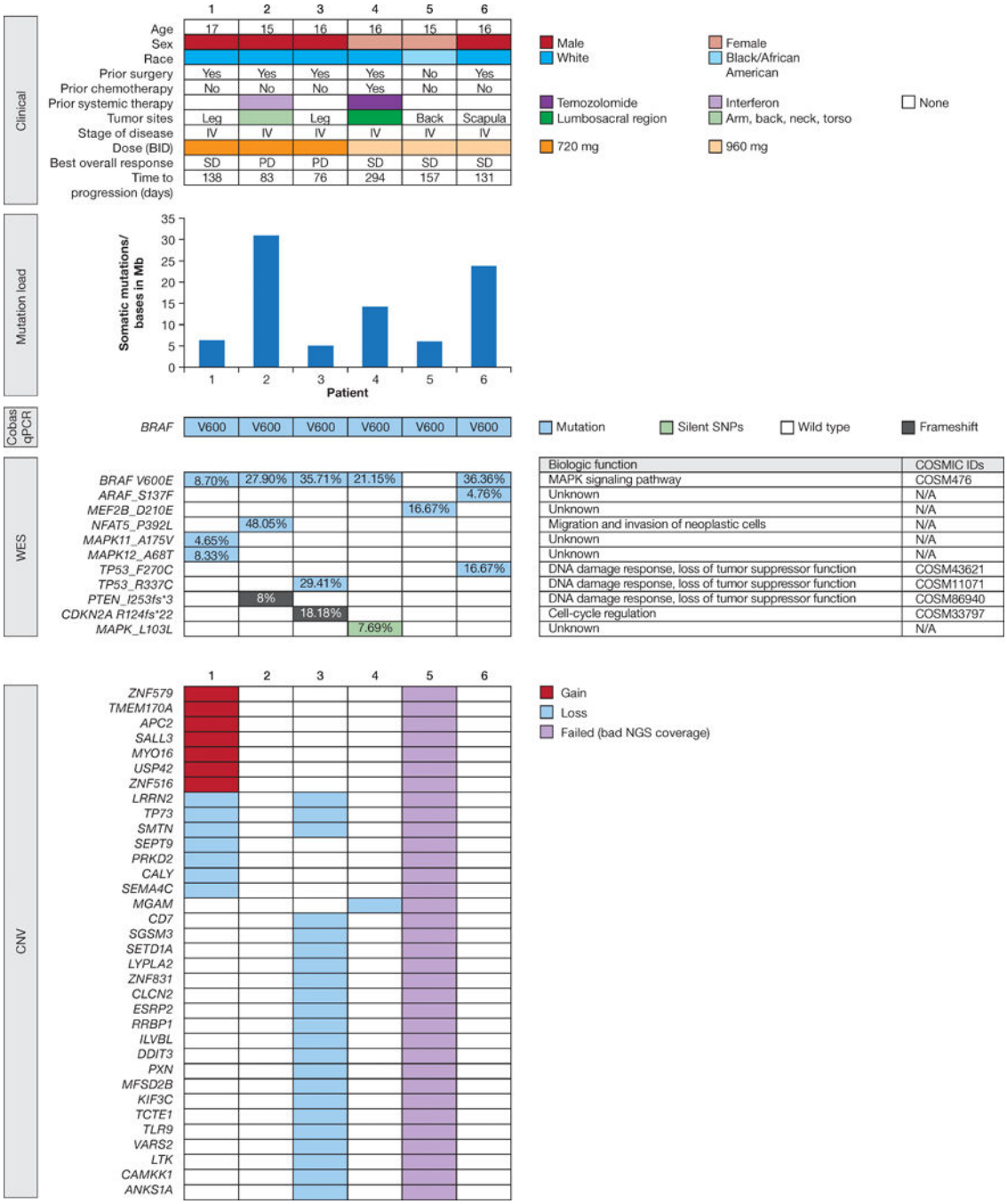

FIGURE 2.

The genomic data for six pediatric melanomas analyzed by cobas® 4800 *BRAF V600* Mutation Test and WES. The mutation load plot displays the number of somatic mutations per Mb. The SNVs shown here are related to the MAPK pathway. The CNV plot lists genes that either have a loss (blue) or a gain (red), or failed samples (grey).

CNV, copy number variation; MAPK, mitogen-activated protein kinase; SNV, single nucleotide variation; WES, whole exome sequencing.

TABLE 1

Baseline characteristics, prior therapy and disease burden

Patient	Sex	Age, years	Weight, kg	BMI, kg/m^2	Race	Histologic subtype	Surgical excision[a]	Systemic therapy[a]	Target lesion sites[b]	Non-target lesion sites[b]	Vemurafenib dose, mg BID
1	Male	17	52.4	17.3	White	Nodular	Yes	None	Liver, lymph node	Lung, skin	720
2	Male	15	138.5	40.0	White	Nodular	Yes	IFN	Lung	Lung, sacrum	720
3	Male	16	64.7	19.7	White	Superficial spreading	Yes	None	Lymph node	Lymph node	720
4	Female	16	59.5	21.9	White	NA	Yes	TMZ	Brain	Brain	960
5	Female	15	86.4	34.1	Black or AA	NA	No	None	Skin, lymph node, soft tissue	Soft tissue	960
6	Male	16	49.2	18.3	White	Superficial spreading	Yes	None	Liver	Bone, lung, liver	960

AA, African-American; BID, twice daily; IFN, interferon; NA, not available; TMZ, temozolomide.

[a] Prior to study entry.

[b] At study entry.

TABLE 2

AEs of grade ≥3 intensity occurring in any patient

AE (MedDRA preferred term)	Vemurafenib 720 mg BID (n = 3)	Vemurafenib 960 mg BID (n = 3)	All patients (n = 6)	Vemurafenib treatment-related[b]
Any AE	2 (66.7)	2 (66.7)	4 (66.7)	
Neck pain	0	1 (33.3)	1 (16.7)	No
Spinal pain	1 (33.3)	0	1 (16.7)	No
BCC	0	1 (33.3)[a]	1 (16.7)	Yes
Intracranial tumor hemorrhage	0	1 (33.3)	1 (16.7)	No
SCC	0	1 (33.3)	1 (16.7)	Yes
Photosensitivity	1 (33.3)	0	1 (16.7)	Yes
Maculopapular rash	0	1 (33.3)	1 (16.7)	No
Diarrhea	0	1 (33.3)	1 (16.7)	No
Scrotal abscess	0	1 (33.3)	1 (16.7)	Yes
Lymphocyte count decreased	0	1 (33.3)	1 (16.7)	No
Hypokalemia	0	1 (33.3)	1 (16.7)	No
Headache	0	1 (33.3)	1 (16.7)	No

AE, adverse event; BCC, basal cell carcinoma; BID, twice daily; MedDRA, Medical Dictionary for Regulatory Activities; SCC, squamous cell carcinoma.

[a] One case report with two lesions.

[b] As determined by the investigator.

Data are expressed as number of patients (%).

TABLE 3

Serious AEs

Patient	AE (MedDRA preferred term)	Vemurafenib dose, mg BID	Onset, study day	Duration, days	Grade[a]	Vemurafenib treatment-related[b]
1	Spinal pain	720	160	19	3	No
4	Nephrolithiasis	960	32	5	2	No
	Adrenal insufficiency		171	7	2	No
	Intracranial tumor hemorrhage[c]		304	5	5	No
6	Maculopapular rash	960	9	105	3	No
	BCC		85	12	3	Yes
	SCC		85	12	3	Yes

AE, adverse event; BCC, basal cell carcinoma; BID, twice daily; MedDRA, Medical Dictionary for Regulatory Activities; SCC, squamous cell carcinoma.

[a]Maximum observed CTCAE grade.

[b]As determined by the investigator.

[c]Occurred 10 days after the patient had discontinued study drug due to PD (confirmed by brain CT).

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TABLE 4

Best overall response, time to progression, and overall survival in pediatric patients receiving vemurafenib 720 mg or 960 mg BID

Vemurafenib dose, mg BID	Best overall response	Time to progression, months	Patient status	Overall survival, months
720	SD	4.5	Died	6.1
720	PD	2.7	Died	12.0
720	PD	2.5	Died	3.1
960	SD	9.7	Died	10.1
960	SD	5.2	Alive	16.9[a]
960	SD[b]	4.3	Died	5.1

BID, twice daily; PD, progressive disease; SD, stable disease.

[a]Censored observation.

[b]Patient had an unconfirmed partial response (observed at only one time point).