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Title:

A Phase 1 and Pharmacokinetic Study of Oral Dabrafenib in Children and Adolescent Patients With Recurrent or Refractory *BRAF* V600 Mutation–Positive Solid Tumors

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Statement of Translational Relevance:

Currently, there are approved agents for patients with *BRAF* V600–mutant melanoma, NSCLC, and other indications; however, the safety and efficacy of these agents have not been established in pediatric patients. *BRAF* V600 mutations occur in several pediatric tumor types, and when present, are often driver mutations. No BRAF inhibitors are currently approved for these pediatric indications. The recommended phase 2 dose of dabrafenib was determined in this phase 1 dose-finding part of a phase 1/2a study evaluating the BRAF inhibitor dabrafenib in pediatric patients with *BRAF* V600–mutated solid tumors. Furthermore, the safety profile was consistent with that observed in adult patients. Pharmacokinetic analyses demonstrated a dose-dependent increase in area under the curve, when dosed on a weight basis, and target exposure levels established in adults were reached. Together, these findings have provided the foundation for development of dabrafenib in pediatric patients with *BRAF* V600–mutated cancers.

Abstract

Purpose: The 2-part, phase 1/2a, open-label study (NCT01677741) sought to determine the safety, tolerability, pharmacokinetics, and preliminary activity of dabrafenib in pediatric patients with advanced *BRAF* V600–mutated cancers.

Experimental Design: This phase 1 dose-finding part treated patients aged 1 to <18 years with *BRAF* V600 mutation–positive tumors with oral dabrafenib 3–5.25 mg/kg/day to determine the RP2D based on safety and drug exposure target.

Results: Between May 2013 and November 2014, 27 patients (12 male; median age, 9 years [range, 1-17 years]) with *BRAF* V600–mutant solid tumors recurrent/refractory to treatment (low- or high-grade glioma, Langerhans cell histiocytosis, neuroblastoma, or thyroid cancer) were enrolled. The median treatment duration at data cutoff was 75.6 weeks (range, 5.6-148.7 weeks), with 63% treated for > 52 weeks and 52% undergoing treatment. The most common grade 3/4 adverse events suspected to be related to study drug were maculopapular rash and arthralgia (2 patients each). No dose-limiting toxicities were observed. Pharmacokinetic analyses showed a dose-dependent increase in $AUC_{0\text{-}12}$ and achievement of adult exposure levels at the recommended phase 2 doses of 5.25 mg/kg/day (age <12 years) and 4.5 mg/kg/day (age ≥12 years) divided into 2 equal doses daily, not exceeding 300 mg daily.

Conclusions: In this first clinical trial in pediatric patients with pretreated *BRAF* V600–mutant tumors, dabrafenib was well tolerated while achieving target exposure levels; the average treatment duration was >1 year with many patients still on treatment. The phase 2 component is also closed and will be reported separately.

Introduction

Advances in our understanding of the functional consequences of genetic changes in pediatric cancers and the advent of targeted therapeutics in oncology have created newer opportunities to treat and potentially cure a subset of childhood malignancies characterized by actionable mutations. The genetic changes that modulate intracellular signaling pathways are recognized as having a central role in deregulated cancer cell growth, independent of tumor type. One example is the mutation of BRAF kinase, which results, in most cases, in constitutive enzymatic activity, promotion of RAF/MEK/ERK pathway signaling, and unregulated cancer cell growth (1).

BRAF V600 mutations are being identified in an increasing number of pediatric cancers (2). *BRAF* V600E, the most frequent mutation, has been identified in 50% of pediatric patients with malignant melanoma (3), which is similar to the frequency in adult patients. In patients with Langerhans cell histiocytosis (LCH), *BRAF* V600E is also observed in 57% of patients and has been shown to be more common in younger patients (4, 5). Although the *KIAA1549:BRAF* fusion is the most common *BRAF* alteration in pediatric low-grade gliomas (pLGGs), *BRAF* V600E mutation occurs across a spectrum of pLGGs, including pilocytic (6.2%), pilomyxoid (5.0%), and diffuse fibrillary astrocytomas (8.1%); ganglioglioma (20.7%); and pleomorphic xanthoastrocytoma (50.8%) (6-8). The *BRAF* V600E mutation has also been detected in high-grade gliomas (HGGs), including glioblastoma multiforme (9%). These data suggest that *BRAF* V600E may be a targetable driver mutation in a number of pediatric cancers.

BRAF V600E mutation and *BRAF* fusion events occur in pediatric brain tumors, and both alterations increase BRAF kinase activity and downstream pathway activation (2, 9); however, only *BRAF* V600 mutations are sensitive to the first-generation RAF inhibitors vemurafenib and dabrafenib. Dabrafenib is a potent and selective RAF kinase inhibitor that targets the *BRAF* V600 mutation. Multiple adult tumor types involving a *BRAF* V600 mutation have been shown to respond to treatment with dabrafenib, including melanoma (10-12), non–small cell lung cancer (13), and anaplastic thyroid cancer (14, 15). These data provide a strong rationale for exploring the activity of dabrafenib using a "histology-agnostic" approach to patient inclusion rather than an approach based on current adult indications for dabrafenib in pediatric patients with *BRAF* V600–mutant tumors. We report dose-finding, safety, and pharmacokinetics (PK) results from phase 1 of a 2-part, phase 1/2a, multicenter, open-label drug development study of dabrafenib in pediatric patients with advanced *BRAF* V600–mutated solid tumors.

Materials and Methods

Patients

The study population consisted of patients aged 1 to 18 years with recurrent, refractory, or progressive *BRAF* V600–mutant solid tumors who had received at least 1 prior therapy. *BRAF* V600 mutations were determined locally by a Clinical Laboratory Improvement Amendments–approved laboratory (or equivalent local certification). Patients with advanced melanoma could be enrolled and receive dabrafenib as first-line treatment. Additional eligibility requirements included adequate organ function (absolute

neutrophil count ≥ 1000/μL; hemoglobin ≥ 8.0 g/dL; platelets ≥ 75000/μL; estimated or radioisotopic determination of glomerular filtration rate ≥ 60 mL/min/1.73 m^2 or serum creatinine within normal ranges for age/sex; adequate liver function defined by bilirubin ≤ 1.5 times the upper limit of normal [ULN] and both aspartate aminotransferase and alanine aminotransferase ≤ 2.5 times ULN; and adequate cardiac function defined by a left ventricular ejection fraction of ≥ 50% and a corrected QT interval of < 450 milliseconds) and a Karnofsky or Lansky performance status of ≥ 50%. Patients were not eligible if they had received chemotherapy or radiotherapy within 3 weeks (or 6 weeks for nitrosoureas or mitomycin C) or an investigational agent within 28 days (or 5 half-lives or twice the duration of the biological effect) prior to the first dose of dabrafenib; a history of leukemia or another malignancy; a history of myocardial infarction, unstable angina, peripheral vascular disease, familial QTc prolongation, abnormal cardiac valve morphology, or other cardiac issues; or other uncontrolled medical conditions. This study was conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol was approved by the institutional review board at each institution and relevant authorities in each country. The parent/guardian of all patients provided written informed consent and assent was obtained from patients when appropriate.

Study design and treatment

The global phase 1/2a study BRF116013 (NCT01677741) was open at multiple institutions to determine the safety, tolerability, and PK of oral dabrafenib in children and adolescents with advanced *BRAF* V600 mutation–positive solid tumors (Supplementary Fig. S1). The institutions where the phase 1 part was conducted can be found in

Supplementary Table S1. Phase 1 assessments included adverse event (AE) and safety monitoring and the dabrafenib PK end points of maximum concentration (C_{max}), time to reach maximum concentration (t_{max}), and area under the plasma concentration-time curve from time 0 to 12 hours (AUC_{0-12}) on treatment day 15.

This phase 1, dose-escalation study was conducted to identify the recommended phase 2 (RP2D) dose(s) of dabrafenib for use in the phase 2, tumor-specific cohort expansion study (Supplementary Fig. S1). The RP2D was originally to be determined in 3 age groups (≤ 2 years, > 2 years and ≤ 12 years, > 12 years). Due to low recruitment in the youngest age category, the RP2D was instead determined per protocol in 2 age categories: 1 to 12 years and > 12 to 18 years. At least 3 patients per dose level were required to allow determination of an RP2D, with 6 patients required at the final dose level. The dose-escalation protocol used a modified Rolling 6 Design based on the classic 3 + 3 dose-escalation study design but allowed for continued recruitment of patients while data from the first 3 patients in each cohort were collected (up to 6 patients per cohort) (Supplementary Table S2) (16). This design allowed for up to 6 patients to be enrolled concurrently at 1 dose level until the dose level was cleared. Dose-level enrollment depended on the number of patients enrolled at the current dose level, the number of patients who experienced a dose-limiting toxicity (DLT) at the current dose level, and the number of patients enrolled but with data pending at the current dose level.

Dabrafenib was given as commercially available capsules (50 mg and 75 mg), investigational capsules (10 mg and 25 mg), or investigational suspension formulations for patients unable to swallow capsules. A preliminary study showed that administration

of dabrafenib as a suspension formulation resulted in faster absorption (t_{max}, 1 hour) and a higher C_{max} but similar overall exposure relative to administration of dabrafenib capsules (17). Dabrafenib administered as an oral suspension formulation using a 95-mg single dose had a geometric mean $AUC_{0-\infty}$ of 6536 ng•h/mL and C_{max} of 1662 ng/mL. A single 150-mg dabrafenib capsule had a geometric mean $AUC_{0-\infty}$ of 12100 ng•h/mL and C_{max} of 2160 ng/mL in a phase 3 study (BREAK-3/BRF113468). Based on cross-study comparisons, the bioavailability of dabrafenib as a suspension formulation has been shown to be approximately 85% relative to that of dabrafenib capsules. The initial patient cohort received a starting dose of 3.0 mg/kg/day given as 2 equal doses twice daily (bid; 80% of the recommended adult dose). The daily dose was increased or decreased by increments of 0.75 mg/kg and was not to exceed 300 mg (the adult recommended dose).

The dabrafenib dose was to be escalated until the maximum tolerated dose (MTD) was reached (based on toxicity), or if the MTD was not reached, until the median AUC_{0-12} was between approximately 4000 ng•h/mL and approximately 5500 ng•h/mL. This target range was the 95% confidence interval (CI) of the geometric mean steady-state plasma exposure observed in the pivotal phase 3 adult study, in which, patients received 150 mg bid. An MTD was not identified in adults during the phase 1 evaluation despite dose escalation up to 300 mg bid (18). Dose-escalation decisions in the current trial were based on all available safety and on-time PK data and could occur after 3 patients had been fully evaluated for 28 days with no observed DLTs. The DLT-evaluable population included all patients who received adequate treatment during the first 28 days (> 75% of planned study drug doses) and patients who were withdrawn or

who required a dose reduction during the first 28 days. Intrapatient dose escalation was allowed if the current dose level was tolerated by the patient, and the next higher dose level had already demonstrated tolerability. Patients could withdraw from study treatment at any time at their own request, at the request of their parents, or at the discretion of the investigator for safety, behavioral or administrative reasons. Treatment with dabrafenib was continued until disease progression, lack of clinical benefit, unacceptable toxicity, initiation of a new therapy, or consent withdrawal.

Safety

The safety population consisted of all patients who received at least 1 dose of dabrafenib. Safety was assessed continuously during the treatment through physical examination, skin assessment, measurement of vital signs, electrocardiography, echocardiograms, and recorded AEs graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 (19). An AE was considered a DLT if it occurred within the first 28 days of treatment with dabrafenib, if it was considered by the investigator to be related to treatment with dabrafenib, and if it met at least 1 of several additional protocol-specified criteria: grade 4 hematologic AE; grade 3 or 4 nonhematologic AE; treatment delay > 7 days due to an unresolved AE; left ventricular ejection fraction less than the lower limit of normal, with an absolute decrease of > 10% from baseline; a grade 2 nonhematologic AE that was determined to be dose limiting; or an AE requiring a dose reduction.

Pharmacokinetic assay and analysis

Plasma samples were analyzed for dabrafenib and its metabolites (hydroxy-dabrafenib, desmethyl-dabrafenib, and carboxy-dabrafenib) using a validated analytical method (20), with an analytical range of 1 to 1000 ng/mL. Quality control samples prepared at 3 different concentrations were analyzed with each batch of samples. The precision (coefficient of variation) within and between runs was ≤ 9.7% and ≤ 11.0%, respectively, and accuracy was adequate, with a percentage bias within 15.0% in validation samples.

The PK population was defined as those patients fulfilling the all-treated population criteria who contributed samples for PK analysis. Blood samples were collected for determination of plasma concentrations of dabrafenib and its metabolites (data not reported) at multiple time points on study day 1 (data not reported) and day 15, with the goal of identifying, where possible, a dose in each age group that resulted in a median dabrafenib area under the concentration-time curve over the dosing interval ($AUC_{0-\tau}$) that was within the 95% CI of the geometric mean exposure measured in adults at steady state in the phase 3 study (3749-5485 ng•h/mL). Pharmacokinetic end points included C_{max}, t_{max}, and AUC_{0-12}. Patients who underwent intrapatient dose escalation may have contributed PK data at more than 1 dose level.

Pharmacokinetic parameters were calculated by standard noncompartmental methods using Phoenix WinNonlin 6.4 (Certara USA). All calculations of noncompartmental parameters were based on actual sampling times.

Statistics

All data were summarized or listed based on the relevant analysis population. Patient data were summarized based on the dosing cohort, to which, the patient was

originally assigned. Adverse events were summarized by frequency and proportion of total patients and maximum toxicity grade for each initial dose level of dabrafenib. Additional selected analyses and summaries were provided by age group as appropriate.

Results

Between May 2013 and November 6, 2014, 27 patients with *BRAF* V600–mutant solid tumors that were recurrent or refractory to treatment (median age, 9.0 years [range, 1-17 years]) were enrolled across 12 centers in Canada, France, United Kingdom, and USA (Table 1). There were 12 male and 15 female patients. Fifteen patients had been diagnosed with pLGG and the rest of them had HGG (n = 8), LCH (n = 2), neuroblastoma (n = 1), or papillary thyroid cancer (n = 1). All patients had previously undergone surgery and 10 (37%) received prior radiotherapy (Table S3). Twenty-six of 27 (96%) had received 1 or more prior chemotherapy regimens (n = 26 [96%]), radioactive therapy (n = 1 [4%]), and/or small-molecule targeted therapy (n = 2 [7%]). One patient with pilocytic astrocytoma (pLGG) had 3 previous surgical resections as well as radiotherapy (54 Gy), but cytotoxic chemotherapy was not considered appropriate for this patient's disease. Thus, this patient had no prior cytotoxic chemotherapy at the time of study entry. The median time elapsed from initial cancer diagnosis to study entry was 20.1 months (range, 1-151 months).

At the time of this analysis (April 1, 2016; data cutoff), the median duration of treatment was 75.6 weeks (range, 5.6-148.7 weeks), with 23 patients (85%) treated longer than 12 weeks (Table 2, Fig. 1). Fourteen of 27 patients were still on treatment,

10 had stopped treatment due to disease progression or lack of efficacy (including 1 patient who died within the 28-day follow-up period), and 3 with pLGG (2 with pilocytic astrocytoma, 1 with ganglioglioma) had electively stopped treatment after prolonged therapy and disease stability. Five patients (2 with HGG, 1 pLGG, 1 LCH, and 1 solid tumor/other) underwent intrapatient dose escalation, all from starting doses of 3.75 mg/kg.

Progression was identified in 26 of 27 patients during the course of their disease prior to study entry. Six patients did not have progressive disease within the previous 4 months and were presumed to have indolent disease at study entry; if these 6 patients are excluded from the assessment of duration of exposure, the median duration of exposure was 57 weeks and remains suggestive of clinical benefit.

No patient experienced a DLT during this phase 1 trial. All patients experienced at least 1 AE. Sixteen patients (59.3%) had a grade 3 or 4 AE regardless of relationship to study drug (Table 3). The most frequently reported grade 3 or 4 AEs were pyrexia, maculopapular rash, arthralgia, hypokalemia, neutropenia, pneumonia, and weight increase (n = 2 each; 7.4%). Since none of these AEs occurred during the initial 28-day period, they were not DLTs. A summary of AEs regardless of study drug relationship is provided in Supplementary Table S4. Twelve of 27 patients (44.4%) experienced a serious AE (none at 3.0 mg/kg, 4 of 10 patients at 3.75 mg/kg, 5 of 8 patients at 4.5 mg/kg, and 3 of 6 patients at 5.25 mg/kg). The most frequent serious AEs were pyrexia (14.8%), pneumonia (11.1%), and seizure (7.4%).

Twenty-six of 27 patients (96.3%) experienced an AE thought to be related to study drug, while 22.2% of patients experienced a grade 3 or 4 study drug–related event. Adverse events suspected to be related to study drug were reported across a range of body systems, including skin disorders (85%), general disorders and administration site conditions (52%), gastrointestinal disorders (44%), and metabolism and nutritional disorders (41%) (Supplementary Table S5). Adverse events suspected to be related to study drug included fatigue (33%), vomiting (30%), headache (26%), and hypophosphatemia (26%), none of which were above grade 2 (Table 4). The most common grade 3 or 4 AEs suspected to be related to study drug were arthralgia and maculopapular rash (each n = 2, 7%). No patients discontinued treatment for study drug–related AEs, and there were no reports of patients with secondary development of cutaneous squamous cell carcinoma. As of the data cutoff of April 2016, there were no reports of secondary malignancy. Following data cutoff and during the preparation of this manuscript, there was a report of a secondary malignancy, Epstein-Barr virus–associated diffuse large B-cell lymphoma. The patient enrolled at 14 months of age with refractory V600–mutant multisystem LCH and was treated at 4.5 mg/kg/day dose level. After 30 months of treatment, the patient was diagnosed with Epstein-Barr virus positive diffuse large B-cell lymphoma and was withdrawn from the study. This patient had a history of multiple episodes of viral pneumonia and was found to have low immune function. Based on patient history and lack of previously reported cases of lymphoma related to dabrafenib, the development of diffuse large B-cell lymphoma in this patient was not thought to be related to dabrafenib.

There was 1 death reported within 28 days of discontinuing dabrafenib therapy. A patient with pLGG treated at the 5.25-mg dose who discontinued treatment after 5 months due to progressive disease and subsequently experienced progressive neurological status deterioration and died 14 days after discontinuing treatment. The death was deemed unrelated to study drug (Table 2).

Pharmacokinetic analyses showed a clear dose-dependent increase in AUC_{0-12} in all patients (Table 5). Two patients assigned to the 3.75-mg/kg cohort had dose escalations to 4.5 mg/kg daily and contributed pharmacokinetic data to both the 3.75-mg/kg and the 4.5-mg/kg cohorts (data for the 4.5-mg/kg dose were collected after 15 days at the new dose level). The dabrafenib dose at which older pediatric patients (aged > 12 years) reached the target median plasma AUC at steady state was 4.5 mg/kg/day, while younger patients (aged ≤ 12 years) achieved the target median plasma concentration at the 5.25-mg/kg/day dose. RP2D was defined at these doses where the previously established median adult plasma AUC_{0-12} target concentration was reached in both the age groups. Although patients aged < 2 years were included as an a priori age category, only 1 patient aged < 2 years was enrolled, preventing the determination of a distinct dose recommendation for this age group. An age-appropriate suspension formulation was available for the younger patients or those who could not swallow capsules, but separate PK analyses for capsule and suspension formulations were not conducted due to the low sample size for the suspension formulation and the possibility that age or body size could confound any observed trends in PK. However, the exposure observed in patients taking the suspension formulation was consistent

with the exposure in the trial as a whole. No MTD for dabrafenib in pediatric patients was identified.

Antitumor activity of dabrafenib monotherapy was a secondary objective in this dose-finding study. The 27 patients reported here had different tumor types, treatment dose levels, and prognoses. The phase 2 disease-specific expansion cohort portion of this trial will be the subject of forthcoming disease-oriented efficacy reports that will include efficacy data of patients in this phase 1 portion of the study.

Discussion

This is the first reported clinical trial using dabrafenib for the treatment of pediatric patients with tumors harboring *BRAF* V600 mutations. The study enrolled patients with a variety of tumor histologies that were molecularly determined to have a mutation at *BRAF* V600. This molecularly driven (ie, “histology-agnostic”) approach expanded the opportunity to identify if the pediatric patient population(s) are likely to benefit from BRAF inhibition (ie, those with *BRAF* V600 mutations), while avoiding the constraints of enrollment based on rare pediatric histologies selected to match adult indications. In this pediatric phase 1 trial, dabrafenib was well tolerated at doses that generated PK similar to that reported in adult clinical trials of dabrafenib (18). The observed toxicities were similar to those identified from the more extensive adult experience (10, 11, 21), with a notable exception that there were no reports of cutaneous squamous cell carcinoma in this pediatric population. There were no DLTs during the 28-day observation period and no MTD was reached. The RP2D was defined after the pediatric exposures achieved target steady state levels that were observed in

adults who were receiving the efficacious phase 3 dose of dabrafenib 150 mg twice daily. The pediatric RP2Ds for dabrafenib were established at 5.25 mg/kg/day in patients aged < 12 years and 4.5 mg/kg/day in patients aged ≥ 12 years divided into two equal doses per day.

Long-term toxicity of treatments used for pediatric cancer are of concern. The current radiation and cytotoxic therapies can have significant long-term effects on the health and development of children, and the long-term detrimental health effects from pediatric cancer treatment are evident in greater than 40% of survivors (22). Overall, the AEs observed in this study were consistent with the current safety profile of the BRAF inhibitors, dabrafenib and vemurafenib in adults (23-25) and included skin toxicities, pyrexia, fatigue, headache, arthralgia, and gastrointestinal events. Pyrexia events are usually episodic, mainly occurring during the first month of treatment, and they usually resolve with dose reduction and/or interruption and supportive treatment (ie, acetaminophen or corticosteroid) (26, 27). The most common skin toxicities associated with BRAF inhibitors in adults, for which, prophylaxis and management guidelines have been published (27-29), include rash, alopecia, dry skin, hyperkeratosis, papillomas, palmar-plantar erythrodysesthesia, cutaneous squamous cell carcinoma, pruritus, and photosensitivity. Although there were no cases of cutaneous squamous cell carcinoma or other secondary malignancies reported in this pediatric population at the time of this analysis, benign nevi can emerge in patients on BRAF inhibitor treatment for prolonged durations (21, 30, 31). The long-term follow-up will be required to better understand any late effects associated with dabrafenib treatment in pediatric patients.

The rationale for dabrafenib dose selection in this study included the aim of achieving the adult exposure associated with efficacy. In adults, dabrafenib exposure-response relationships have been characterized based on a variety of clinical data, including tumor biomarkers (eg, phospho-ERK inhibition), treatment response rate, progression-free survival, and pyrexia, supporting the recommended dabrafenib adult dose of 150 mg bid (23, 25). In addition, a low incidence of DLTs was observed during the clinical evaluation of dabrafenib in adults (18, 23-25, 32); therefore, a true adult MTD for dabrafenib has not been established, and the observance of a true MTD in pediatric patients was not anticipated.

Establishing an appropriate rationale for methods used to determine pediatric patient dosing regimens is an ongoing challenge in drug development (33). The favorable benefit-risk profile of dabrafenib in adults supported the use of adult dose-exposure data as a basis for dabrafenib target exposure levels in pediatric patients. Similar approaches have been used previously to develop new drugs for use in treating pediatric cancers (33-35). One potential approach is to start pediatric dosing at an adult RP2D, with close monitoring and an established protocol for dose modifications (36-38); this approach could improve efficiency and substantially shorten pediatric phase 1 studies. The current trial used an initial starting dose level of 80% of the adult approved dose (3.0 mg/kg/day vs 3.75 mg/kg/day approved for an 80-kg adult) but identified higher RP2Ds of 5.25 mg/kg/day for patients aged < 12 years and 4.5 mg/kg/day for patients aged ≥ 12 years (not to exceed the adult daily dose of 300 mg).

This PK-based dose-escalation approach is based on the likelihood that therapeutic benefit in children will be achieved by targeting the adult dabrafenib

412 exposure, principally the steady-state AUC_{0-12} following dabrafenib 150 mg bid
413 administration. The geometric mean dabrafenib AUC_{0-12} after the administration of
414 150 mg bid in the adult phase 3 study BRF113683 (NCT01227889; patients with *BRAF*-
415 mutant metastatic melanoma [n = 17]) was 4341 ng•h/mL (95% CI, 3599-5235 ng•h/mL)
416 (39, 40). These phase 3 data were consistent with the results obtained from the
417 monotherapy arm of study BRF113220 part D (NCT01726738; patients with *BRAF*-
418 mutant metastatic melanoma [n = 11]), where geometric mean dabrafenib AUC_{0-12} after
419 administration of 150 mg bid was 4663 ng•h/mL (range, 3511-6194 ng•h/mL) (38).
420 Therefore, in part 1, the dabrafenib dose was increased until the MTD was reached
421 (based on toxicity) or in the absence of patients reaching the MTD, the dose at which
422 the median AUC_{0-12} was between approximately 4000 ng•h/mL and approximately
423 5500 ng•h/mL.

424 On the basis of the safety and PK data from study part 1, dabrafenib at the
425 RP2Ds was further evaluated in study part 2. Additional analyses of the PK data for
426 both parts 1 and 2 were planned to further explore the relationship of PK to body size
427 and age. These analyses were also used to confirm the dabrafenib dose and adjust as
428 appropriate to ensure that the majority of pediatric patients received a dose that resulted
429 in exposures within the range associated with response in adults.

430 Novel therapeutics are needed for the treatment of pediatric malignancies to
431 address the higher number of deaths due to pediatric cancer and the substantial
432 proportion of patients experiencing long-term consequences from current therapies (38).
433 Collectively, a growing understanding of the molecular drivers of pediatric cancers, the
434 availability of therapeutics that block the activity of specific driver mutations, and the

increasing use of tumor molecular profiling have created an opportunity to select optimized treatments for these patients. A molecularly targeted approach to patient risk assessment and therapy selection has the potential to improve the benefit-risk profile of a treatment relative to that of the previous, more traditional approaches. This report describes the phase 1 results indicating the successful testing of a therapeutic agent in patients with pediatric cancer selected for treatment based on the molecular profile of their tumors rather than based on tumor histologic classification. This molecular selection also allowed for the enrollment of a greater number of eligible patients with one of several tumor types expressing the targeted mutation, whereas the traditional histologic approach would have restricted the enrollment to the exceedingly rare patients with pediatric melanoma. This study demonstrated the safety and tolerability of dabrafenib in pediatric patients with solid tumors harboring *BRAF* V600 mutations, and established RP2Ds that achieve dabrafenib exposure levels suitable for the activity evaluation in these settings, which is reported separately.

Authors' Contributions

Conception and design: M.W. Kieran, B. Geoerger, D. Hargrave

Development of methodology: B. Geoerger, D. Hargrave, M.W. Russo

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References

1. Burotto M, Chiou VL, Lee JM, Kohn EC. The MAPK pathway across different malignancies: A new perspective. *Cancer* **2014**;120(22):3446–56.

2. Kieran MW. Targeting BRAF in pediatric brain tumors. Am Soc Clin Oncol Educ Book **2014**:e436-40.

3. Daniotti M, Ferrari A, Frigerio S, Casieri P, Miselli F, Zucca E, *et al*. Cutaneous melanoma in childhood and adolescence shows frequent loss of INK4A and gain of KIT. *J Invest Dermatol* **2009**;129(7):1759–68.

4. Badalian-Very G, Vergiliok JA, Degar BA, MacConaill LE, Brandner B, Calicchio ML, *et al.* Recurrent BRAF mutations in Langerhans cell histiocytosis. *Blood* **2010**;1116(11):1919–23.

5. Brown NA, Furtado LV, Betz BL, Kiel MJ, Weigelin HC, Lim MS, *et al*. High prevalence of somatic MAP2K1 mutations in BRAF V600E-negative Langerhans cell histiocytosis. *Blood* **2014**;124(10):1655–58.

6. Dougherty MJ, Santi M, Brose MS, Ma C, Resnick AC, Sievert AJ, *et al*. Activating mutations in BRAF characterize a spectrum of pediatric low-grade gliomas. *Neuro Oncol* **2010**;12(7):621–30.

7. MacConaill LE, Campbell CD, Kehoe SM, Bass AJ, Hatton C, Niu L, *et al*. Profiling critical cancer gene mutations in clinical tumor samples. *PLoS One* **2009**;4(11):e7887.

8. Penman CL, Faulkner C, Lowis SP, Kurian KM. Current understanding of BRAF alterations in diagnosis, prognosis, and therapeutic targeting in pediatric low-grade gliomas. *Front Oncol* **2015**;5(54):1–10.

9. Pfister S, Janzarik WG, Remke M, Ernst A, Werft W, Becker N, *et al*. BRAF gene duplication constitutes a mechanism of MAPK pathway activation in low-grade astrocytomas. *J Clin Invest* **2008**;118(5):1739–49.

10. Hauschild A, Grob JJ, Demidov LV, Jouary T, Gutzmer R, Millward M, *et al*. Dabrafenib in BRAF-mutated metastatic melanoma: A multicentre, open-label, phase 3 randomised controlled trial. *Lancet* **2012**;380(9839):358–65.

11. Flaherty KT, Infante JR, Daud A, Gonzalez R, Kefford RF, Sosman J, *et al*. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. *N Engl J Med* **2012**;367(18):1694–1703.

12. Davies MA, Robert C, Long GV, Grob JJ, Flaherty KT, Arance A, *et al*. COMBI-MB: A phase II study of combination dabrafenib (D) and trametinib (T) in patients (pts) with BRAF V600–mutant (mut) melanoma brain metastases (MBM). *J Clin Oncol* **2017**;35(suppl):abstr 9506.

13. Planchard D, Kim TM, Mazieres J, Quoix E, Riely G, Barlesi F, *et al*. Dabrafenib in patients with BRAF(V600E)-positive advanced non-small-cell lung cancer: A single-arm, multicentre, open-label, phase 2 trial. *Lancet Oncol* **2016**;17(5):642–50.

14. Falchook GS, Millward M, Hong D, Naing A, Piha-Paul S, Waguespack SG, *et al*. BRAF inhibitor dabrafenib in patients with metastatic BRAF-mutant thyroid cancer. *Thyroid* **2015**;25(1):71–77.

15. Shah MH, Wei L, Wirth LJ, Daniels GA, De Souza JA, Timmers CD, *et al*. Results of randomized phase II trial of dabrafenib versus dabrafenib plus trametinib in BRAF-mutated papillary thyroid carcinoma. *J Clin Oncol* **2017**;35(suppl):abstr 6022.

16. Skolnik JM, Barrett JS, Jayaraman B, Patel D, Adamson PC. Shortening the timeline of pediatric phase I trials: The rolling six design. *J Clin Oncol* **2008**;26(2):190–95.

17. Bershas DA, Ouellet D, Mamaril-Fishman DB, Nebot N, Carson SW, Blackman SC. Metabolism and disposition of oral dabrafenib in cancer patients: Proposed participation of aryl nitrogen in carbon-carbon bond cleavage via decarboxylation following enzymatic oxidation. *Drug Metab Dispos* **2013**;41(12):2215–24.

18. Falchook GS, Long GV, Kurzrock R, Kim KB, Arkenau TH, Brown MP, *et al*. Dabrafenib in patients with melanoma, untreated brain metastases, and other solid tumours: A phase 1 dose-escalation trial. *Lancet* **2012**;379(9829):1893–1901.

19. US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Bethesda, MD: National Institutes of Health. Available from: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.

20. Ouellet D, Gibiansky E, Leonowens C, O'Hagan A, Haney P, Switzky J, *et al*. Population pharmacokinetics of dabrafenib, a BRAF inhibitor: Effect of dose, time, covariates, and relationship with its metabolites. *J Clin Pharmacol* **2014**;54(6):696–706.

21. Chu EY, Wanat KA, Miller CJ, Amaravadi RK, Fecher LA, Brose MS, *et al*. Diverse cutaneous side effects associated with BRAF inhibitor therapy: A clinicopathologic study. *J Am Acad Dermatol* **2012**;67(6):1265–72.

22. Hudson MM, Tyc VL, Srivastava DK, Gattuso J, Quargnenti A, Crom DB, *et al*. Multi-component behavioral intervention to promote health protective behaviors in childhood cancer survivors: The protect study. *Med Pediatr Oncol* **2002**;39(1):2,1; discussion 2.

543 23. Novartis Pharmaceuticals Corporation. Tafinlar (dabrafenib). Full prescribing information.
544 East Hanover, NJ: 2015.

545 24. Carlos G, Anforth R, Clements A, Menzies AM, Carlino MS, Chou S, *et al*. Cutaneous toxic
546 effects of BRAF inhibitors alone and in combination with MEK inhibitors for metastatic
547 melanoma. *JAMA Dermatol* **2015**;151(10):1103–09.

548 25. Novartis Europharm Limited. Tafinlar (dabrafenib). Summary of product characteristics.
549 West Sussex, UK: 2017.

550 26. Menzies AM, Ashworth MT, Swann S, Kefford RF, Flaherty K, Weber J, *et al*.
551 Characteristics of pyrexia in BRAFV600E/K metastatic melanoma patients treated with
552 combined dabrafenib and trametinib in a phase I/II clinical trial. *Ann Oncol* **2015**;26(2):415–21.

553 27. Daud A, Tsai K. Management of treatment-related adverse events with agents targeting the
554 MAPK pathway in patients with metastatic melanoma. *Oncologist* **2017**;22(7):823–33.

555 28. Welsh SJ, Corrie PG. Management of BRAF and MEK inhibitor toxicities in patients with
556 metastatic melanoma. *Ther Adv Med Oncol* **2015**;7(2):122–36.

557 29. Sinha R, Edmonds K, Newton-Bishop JA, Gore ME, Larkin J, Fearfield L. Cutaneous
558 adverse events associated with vemurafenib in patients with metastatic melanoma: Practical
559 advice on diagnosis, prevention and management of the main treatment-related skin toxicities.
560 *Br J Dermatol* **2012**;167(5):987–94.

561 30. Giurcaneanu C, Nitipir C, Popa LG, Forsea AM, Popescu I, Bumbacea RS. Evolution of
562 melanocytic nevi under vemurafenib, followed by combination therapy with dabrafenib and
563 trametinib for metastatic melanoma. *Acta Dermatovenerol Croat* **2015**;23(2):114–21.

564 31. Nowara E, Huszno J, Slomian G, Nieckula J. Skin toxicity in BRAF(V600) mutated
565 metastatic cutaneous melanoma patients treated with vemurafenib. *Postepy Dermatol Alergol*
566 **2016**;33(1):52–56.

567 32. Algazi AP, Moon J, Chmielowski B, Lo R, Kendra KL, Lao CD, *et al*. SWOG S1221: A phase
568 1 dose escalation study co-targeting MAPK-dependent and MAPK-independent BRAF inhibitor
569 resistance in BRAF mutant advanced solid tumors with dabrafenib, trametinib, and
570 GSK2141795 (ClinicalTrials.gov NCT01902173). *J Clin Oncol* **2017**;35(suppl):abstr 2578.

571 33. Cella M, Gorter de Vries F, Burger D, Danhof M, Della Pasqua O. A model-based approach
572 to dose selection in early pediatric development. *Clin Pharmacol Ther* **2010**;87(3):294–302.

573 34. Balis FM, Fox E. Challenges of developing new drugs for childhood cancers. *Clin Invest*
574 **2012**;2(3):291–300.

575 35. Paoletti X, Geoerger B, Doz F, Baruchel A, Lokiec F, Le Tourneau C. A comparative
576 analysis of paediatric dose-finding trials of molecularly targeted agent with adults' trials. *Eur J*
577 *Cancer* **2013**;49(10):2392–2402.

578 36. Long GV, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, Larkin J, *et al*. Combined
579 BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. *N Engl J Med*
580 **2014**;371(20):1877–88.

581 37. Abernethy DR, Burckart GJ. Pediatric dose selection. *Clin Pharmacol Ther* **2010**;87(3):270–
582 71.

583 38. Moreno L, Pearson ADJ, Paoletti X, Jimenez I, Geoerger B, Kearns PR, *et al*. Early phase
584 clinical trials of anticancer agents in children and adolescents - an ITCC perspective. *Nat Rev*
585 *Clin Oncol* **2017**;14(8):497–507.

586 39. GlaxoSmithKline. A phase III randomized, open-label study comparing GSK2118436 to
587 DTIC in previously untreated subjects with BRAF mutation positive advanced (stage III) or
588 metastatic (stage IV) melanoma. Clinical Study Report 2012; BRF113683. https://www.gsk-
589 clinicalstudyregister.com/files2/brf113683-clinical-study-report-redact-v02.pdf. Accessed March
590 19, 2018.

591 40. GlaxoSmithKline. An open-label, dose-escalation, phase I/II study to investigate the safety,
592 pharmacokinetics, pharmacodynamics and clinical activity of the BRAF inhibitor GSK2118436 in
593 combination with the MEK inhibitor GSK1120212 in subjects with BRAF mutant metastatic
594 melanoma. Clinical Study Report 2012; BRF113220. https://www.gsk-
595 clinicalstudyregister.com/files2/gsk-113220-clinical-study-report-redact.pdf. Accessed March 19,
596 2018.

Tables

Table 1. Patient demographics and baseline characteristics

Characteristic	Dose				All Patients (N = 27)
	3.0 mg/kg (n = 3)	3.75 mg/kg (n = 10)	4.5 mg/kg (n = 8)	5.25 mg/kg (n = 6)	
Age, median (range), years	8.0 (4-14)	14 (3-17)	6 (0-17)	7.5 (3-12)	9.0 (0-17)
< 1	0	0	1 (12.5)	0	1 (4)
1 to ≤ 2	0	0	0	0	0
2 to ≤ 6	1 (33)	2 (20)	3 (37.5)	2 (33)	8 (30)
6 to ≤ 12	1 (33)	2 (20)	3 (37.5)	3 (50)	9 (33)
12 to ≤ 18	1 (33)	6 (60)	1 (12.5)	1 (17)	9 (33)
Sex					
Male, n (%)	1 (33)	5 (50)	3 (37.5)	3 (50)	12 (44)
Female, n (%)	2 (67)	5 (50)	5 (62.5)	3 (50)	15 (56)
Race					
Asian, n (%)	0	2 (20)	0	0	2 (7)
Black, n (%)	0	0	1 (12.5)	0	1 (4)
White, n (%)	3 (100)	8 (80)	7 (87.5)	6 (100)	24 (88.9)
Diagnosis					
Low-grade glioma					
Low-grade glioma NOS	0	0	0	3 (50)	3 (11)
Ganglioglioma	0	1 (10)	2 (25)	1 (17)	4 (15)

Pilocytic astrocytoma	0	1 (10)	4 (75)	1 (17)	6 (22)
Pilomyxoid astrocytoma	0	1 (10)	0	0	1 (4)
Pleomorphic xanthoastrocytoma	0	0	0	1 (17)	1 (4)
High-grade glioma					
Anaplastic astrocytoma	2 (67)	1 (10)	0	0	3 (11)
Anaplastic glioma	1 (33)	0	0	0	1 (4)
Anaplastic ganglioglioma	0	1 (10)	0	0	1 (4)
Anaplastic pleomorphic xanthoastrocytoma	0	1 (10)	0	0	1 (4)
Glioblastoma multiforme	0	2 (20)	0	0	2 (7)
Langerhans cell histiocytosis	0	1 (10)	1 (12.5)	0	2 (7)
Neuroblastoma	0	0	1 (12.5)	0	1 (4)
Papillary thyroid cancer	0	1 (10)	0	0	1 (4)
Metastatic disease at screening					
Yes	1 (33)	3 (30)	2 (25)	1 (17)	7 (26)
No	2 (67)	7 (70)	6 (75)	5 (83)	20 (74)
Karnofsky or Lansky performance status, n (%)[a]					
100%	1 (33)	5 (50)	3 (37.5)	3 (50)	12 (44)
90%	1 (33)	3 (30)	1 (12.5)	1 (17)	6 (22)
80%	0	1 (10)	1 (12.5)	1 (17)	3 (11)
≤ 70%	1(33)	1 (10)	3 (37.5)	1 (17)	6 (22)

[a] Baseline performance status was assessed using Karnofsky (age ≥ 16 years) or Lansky (age < 16 years) criteria as appropriate.

Table 2. Patient disposition and exposure to dabrafenib

Characteristic	Dose				All Patients (N = 27)
	3.0 mg/kg (n = 3)	3.75 mg/kg (n = 10)	4.5 mg/kg (n = 8)	5.25 mg/kg (n = 6)	
Treatment ongoing, n (%)[a]	1 (33)	5 (50)	4 (50)	4 (67)	14 (52)
Discontinued due to progression	1 (33)	4 (40)	3 (37.5)	1 (17)	9 (33)
Electively discontinued	1 (33)	1 (10)	1 (12.5)	—	3 (11)
Died[b]	0	0	0	1 (17)[c]	1 (4)[c]
Duration of treatment, median (range[d]), weeks	40.3 (9.7-148.7)	71.7 (5.7-130.4)	78.4 (5.6-109.3)	75.7 (25.1-77.1)	75.6 (5.6-148.7)
Weeks of exposure, n (%)					
< 3	0	0	0	0	0
3 to 6	0	1 (10)	1 (12.5)	0	2 (7)
> 6 to 12	1 (33)	0	1 (12.5)	0	2 (7)
> 12	2 (67)	9 (90)	6 (75)	6 (100)	23 (85)

[a] Ongoing at the time of data cutoff, April 1, 2016.

[b] Includes any death reported that occurred within 28 days of last dose.

[c] Patient had progression of disease prior to death

[d] The upper end of the treatment range represents patients with ongoing treatment at the time of data cutoff, April 1, 2016.

607 **Table 3.** Adverse events

	Dose								All Patients (N = 27)	
	3.0 mg/kg (n = 3)		3.75 mg/kg (n = 10)		4.5 mg/kg (n = 8)		5.25 mg/kg (n = 6)			
Category	**All**	**Grade 3 or 4**	**All**	**Grade 3 or 4**	**All**	**Grade 3 or 4**	**All**	**Grade 3 or 4**	**All**	**Grade 3 or 4**
On-treatment deaths, n (%)[a]	0	0	0	0	0	0	1 (17)	0	1 (4)	0
Adverse events, n (%)	3 (100)	1 (33)	10 (100)	6 (60)	8 (100)	4 (50)	6 (100)	5 (83)	27 (100)	16 (59)
Suspected to be related to study drug	3 (100)	0	10 (100)	1 (10)	8 (100)	2 (25)	5 (83)	3 (50)	26 (96)	6 (22)
Serious adverse events, n (%)	0	0	4 (40)	4 (40)	5 (62.5)	3 (37.5)	3 (50)	3 (50)	12 (44)	10 (37)
Suspected to be related to study drug	0	0	1 (10)	1 (10)	2 (25)	1 (12.5)	1 (17)	1 (17)	4 (15)	3 (11)
AEs leading to discontinuation, n (%)	0	0	1 (10)	0	1 (12.5)	1 (12.5)	0	0	2 (7)	1 (4)
AEs requiring dose reductions, n (%)	0	0	1 (10)	0	3 (38)	2 (25)	0	0	4 (15)	2 (7)

608 [a] Deaths occurring > 28 days after last study dose are not included. No deaths were suspected to be related to the study drug.

609 **Table 4.** Adverse events, suspected to be study drug related, by preferred term (> 10% overall)

Preferred Term	Dose				All Patients (N = 27)
	3.0 mg/kg (n = 3)	3.75 mg/kg (n = 10)	4.5 mg/kg (n = 8)	5.25 mg/kg (n = 6)	
Total, n (%)	3 (100)	10 (100)	8 (100)	5 (83)	26 (96)
Fatigue	1 (33)	3 (30)	2 (25)	3 (50)	9 (33)
Vomiting	1 (33)	2 (20)	3 (37.5)	2 (33)	8 (30)
Headache	0	3 (30)	2 (25)	2 (33)	7 (26)
Hypophosphatemia	2 (67)	1 (10)	2 (25)	2 (33)	7 (26)
Alanine aminotransferase increased	1 (33)	3 (30)	1 (12.5)	1 (17)	6 (22)
Anemia	1 (33)	2 (20)	0	3 (50)	6 (22)
Aspartate aminotransferase increased	1 (33)	2 (20)	1 (12.5)	2 (33)	6 (22)
Keratosis pilaris	1 (33)	1 (10)	2 (25)	2 (33)	6 (22)
Nausea	0	3 (30)	2 (25)	1 (17)	6 (22)
Pyrexia	1 (33)	3 (30)	1 (12.5)	1 (17)	6 (22)
Rash	0	3 (30)	2 (25)	1 (17)	6 (22)
Dry skin	0	3 (30)	1 (12.5)	1 (17)	5 (18.5)

Melanocytic nevus	1 (33)	2 (20)	2 (25)	0	5 (18.5)
Rash maculopapular	0	1 (10)	2 (25)	2 (33)	5 (18.5)
Abdominal pain	0	1 (10)	1 (12.5)	2 (33)	4 (15)
Alopecia	1 (33)	3 (30)	0	0	4 (15)
Arthralgia	1 (33)	1 (10)	2 (25)	0	4 (15)
Eczema	0	1 (10)	1 (12.5)	2 (33)	4 (15)
Hypokalemia	1 (33)	1 (10)	0	2 (33)	4 (15)
Lymphocytopenia	0	2 (20)	0	2 (33)	4 (15)
Pruritus	0	2 (20)	0	2 (33)	4 (15)
Abdominal pain upper	0	1 (10)	1 (12.5)	1 (17)	3 (11)
Decreased appetite	0	0	0	3 (50)	3 (11)
Diarrhea	0	0	2 (25)	1 (17)	3 (11)
Hypercalcemia	0	2 (20)	1 (12.5)	0	3 (11)
Hypernatremia	0	2 (20)	1 (12.5)	0	3 (11)
Hypoalbuminemia	0	1 (10)	0	2 (33)	3 (11)
Hypomagnesemia	0	2 (20)	0	1 (17)	3 (11)
Pain in extremity	0	1 (10)	2 (25)	0	3 (11)
Thrombocytopenia	0	2 (20)	0	1 (17)	3 (11)

Rash papular	0	0	3 (37.5)	0	3 (11)
Skin lesion	0	2 (20)	0	1 (17)	3 (11)
Leukopenia	1 (33)	1 (10)	0	1 (17)	3 (11)
Xerosis	1 (33)	1 (10)	1 (12.5)	0	3 (11)

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613 **Table 5.** Summary of selected dabrafenib pharmacokinetic parameters by dose cohort[a]

Parameter	n	3.0 mg/kg	n	3.75 mg/kg	n	4.5 mg/kg[b]	n	5.25 mg/kg
C_{max} (range), ng/mL	3	1558 (993-2044)	10	1197 (661-3168)	10	1478 (984-4004)	6	1484 (822-3631)
T_{max} (range), h	3	1.08 (1.00-2.02)	10	2.04 (0.48-3.92)	10	2.00 (1.00-3.00)	6	2.11 (1.02-3.03)
AUC_{0-12} (range), ng•h/mL	3	2971 (1591-6604)	10	3340 (2164-8293)	10	3886 (2172-13448)	6	4090 (3125-5656)
≤ 12 years	2	2281 (1591-2971)	4	2925 (2604-3639)	7	3846 (2172-5331)	6	4090 (3125-5656)
> 12 years	1	6604 (NA-NA)	6	3825 (2164-8293)	3	5486 (3426-13448)	0	NA

614

615 NA, not applicable.

616 [a] C_{max}, t_{max}, and AUC_{0-12} values from study part 1 on day 15 are reported as the median (min-max).

617 [b] Two patients who were originally assigned to the 3.75-mg/kg cohort had dose escalations to 4.5 mg/kg daily, and pharmacokinetic
618 data were also collected after 15 days of dosing at the new dose level. Thus, these 2 patients contributed pharmacokinetic data to
619 both the 3.75-mg/kg and 4.5-mg/kg cohorts.

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Figures

Figure 1. Duration of exposure to dabrafenib (safety population). * Treatment ongoing as of April 2016. LGG, low-grade glioma; HGG, high-grade glioma; LCH, Langerhans cell histiocytosis; NB, neuroblastoma; PTC, papillary thyroid cancer.