A Phase I 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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Abstract

Purpose: The 2-part, phase I/IIa, 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.

Patients and Methods: This phase I dose-finding part treated patients ages 1 to <18 years with BRAF V600 mutation–positive tumors with oral dabrafenib 3 to 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 was 75.6 weeks (range, 5.6–148.7 weeks), with 63% treated for >52 weeks and 52% undergoing treatment at data cutoff date. 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(0–12) and achievement of adult exposure levels at the recommended phase II 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 II 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...
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 II dose of dabrafenib was determined in this phase I dose-finding part of a phase I/IIa 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 AUC, 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.

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 (pLGG), BRAF V600E mutation occurs across a spectrum of pLGGs, including pilocytic (6.2%), pilomyxoid (5.0%), and diffuse fibrillary astrocytomas (8.1%); gangliogioma (20.7%); and pleomorphic xanthoastrocytoma (50.8%; refs. 6–8). The BRAF V600E mutation has also been detected in high-grade gliomas (HGG), 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; 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.

Study design and treatment

The global phase I/IIa study BRF116013 (NCT01677741) was open at multiple institutions to determine the safety, tolerability, and pharmacokinetics of oral dabrafenib in children and adolescents with advanced BRAF V6000–mutated, positive solid tumors (Supplementary Fig. S1). The institutions where the phase I part was conducted can be found in Supplementary Table S1. Phase I assessments included adverse event (AE) and safety monitoring and the dabrafenib pharmacokinetic endpoints of maximum concentration (Cmax), time to reach maximum concentration (tmax), and area under the plasma concentration–time curve from time 0 to 12 hours (AUC0–12) on treatment day 15.

This phase I, dose-escalation study was conducted to identify the recommended phase II (RP2D) dose(s) of dabrafenib for use in the phase II, 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). Because of low enrollment in the youngest age category, the RP2D was instead determined per protocol in 2 age categories: 1 to 12 years and >12 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 whereas data from the first 3 patients in each cohort were collected (up to 6 patients per cohort; Supplementary Table S2; ref. 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 and 75 mg), investigational capsules (10 and 25 mg), or

Patients and Methods

Patients

The study population consisted of patients ages 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 ≥1,000/µL; hemoglobin ≥8.0 g/dL, platelets ≥75,000/µL; estimated or radioisotopic determination of glomerular filtration rate ≥60 ml/min/1.73 m² 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.

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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 ($t_{\text{max}}$ 1 hour) and a higher $C_{\text{max}}$ 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$_{0-C}=$ of 6,536 ng·h/mL and $C_{\text{max}}$ of 1,662 ng/mL. A single 150-mg dabrafenib capsule had a geometric mean AUC$_{0-C}=$ of 12,100 ng·h/mL and $C_{\text{max}}$ of 2,160 ng/mL in a phase III 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 (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$_{0-C}=$ was between approximately 4,000 ng·h/mL and approximately 5,500 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 III adult study, in which, patients received 150 mg twice daily. An MTD was not identified in adults during the phase 1 evaluation despite dose escalation up to 300 mg twice daily (18). Dose-escalation decisions were current trial-based on all available safety and on-time pharmacokinetics data and could occur after 3 patients had been fully evaluated for 28 days with no observed DLTs. The DLT-eligible 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 for at least 1 cycle, 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 $\geq$ 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; 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 1,000 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 $\leq 11.0\%$, respectively, and accuracy was adequate, with a percentage bias within 15.0% in validation samples.

The pharmacokinetic population was defined as those patients fulfilling the all-treated population criteria who contributed samples for pharmacokinetic 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$_{0-C}=$) that was within the 95% CI of the geometric mean exposure measured in adults at steady state in the phase 3 study (3,749–5,485 ng·h/mL). Pharmacokinetic endpoints included $C_{\text{max}}$, $t_{\text{max}}$, and AUC$_{0-C}=$. Patients who underwent intrapatient dose escalation may have contributed pharmacokinetic data at more than 1 dose level.

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

Statistical analysis

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 United States (Table 1). There were 12 male and 15 female patients. Fifteen patients had been diagnosed with pLGG (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 (Supplementary 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.

Table 1. Patient demographics and baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>3.0 mg/kg (n = 3)</th>
<th>3.75 mg/kg (n = 10)</th>
<th>4.5 mg/kg (n = 8)</th>
<th>5.25 mg/kg (n = 6)</th>
<th>All patients (N = 27)</th>
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<td>Age, median (range), years</td>
<td>8.0 (4–14)</td>
<td>14 (3–17)</td>
<td>6 (0–17)</td>
<td>7.5 (3–12)</td>
<td>9.0 (0–17)</td>
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<td>Sex</td>
<td>Male, n (%)</td>
<td>1 (33)</td>
<td>5 (50)</td>
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<td></td>
<td>Female, n (%)</td>
<td>2 (67)</td>
<td>5 (50)</td>
<td>5 (62.5)</td>
<td>3 (50)</td>
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<td>Race</td>
<td>Asian, n (%)</td>
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<td>2 (20)</td>
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<td>Black, n (%)</td>
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<td>White, n (%)</td>
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<td>8 (80)</td>
<td>7 (87.5)</td>
<td>6 (100)</td>
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<td>1 (17)</td>
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<td>1 (10)</td>
<td>4 (75)</td>
<td>1 (17)</td>
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<tr>
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<td>0</td>
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<td>1 (17)</td>
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<td>High-grade glioma</td>
<td>2 (67)</td>
<td>1 (10)</td>
<td>0</td>
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<tr>
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<td>Anaplastic astrocytoma</td>
<td>1 (33)</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
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<td>Anaplastic glioma</td>
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<td>1 (10)</td>
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<td>Glioblastoma multiforme</td>
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<td>2 (20)</td>
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<td>Langerhans cell histiocytosis</td>
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<td>1 (12.5)</td>
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<td>Neuroblastoma</td>
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<td>Papillary thyroid cancer</td>
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<td>Metastatic disease at screening</td>
<td>Yes</td>
<td>1 (33)</td>
<td>3 (30)</td>
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<tr>
<td></td>
<td>No</td>
<td>2 (67)</td>
<td>7 (70)</td>
<td>6 (75)</td>
<td>5 (83)</td>
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<tr>
<td>Karnofsky or Lansky performance status, n (%)</td>
<td>100%</td>
<td>1 (33)</td>
<td>5 (50)</td>
<td>3 (37.5)</td>
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<tr>
<td></td>
<td>90%</td>
<td>1 (33)</td>
<td>3 (30)</td>
<td>1 (12.5)</td>
<td>1 (17)</td>
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<td></td>
<td>80%</td>
<td>1 (33)</td>
<td>1 (10)</td>
<td>1 (12.5)</td>
<td>1 (17)</td>
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<tr>
<td></td>
<td>70% or less</td>
<td>1 (33)</td>
<td>1 (10)</td>
<td>3 (37.5)</td>
<td>1 (17)</td>
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Table 2. Patient disposition and exposure to dabrafenib

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>3.0 mg/kg (n = 3)</th>
<th>3.75 mg/kg (n = 10)</th>
<th>4.5 mg/kg (n = 8)</th>
<th>5.25 mg/kg (n = 6)</th>
<th>All patients (N = 27)</th>
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</thead>
<tbody>
<tr>
<td>Treatment ongoing, n (%)</td>
<td>1 (33)</td>
<td>5 (50)</td>
<td>4 (50)</td>
<td>4 (67)</td>
<td>14 (52)</td>
</tr>
<tr>
<td>Discontinued due to progression</td>
<td>1 (33)</td>
<td>4 (40)</td>
<td>3 (37.5)</td>
<td>1 (17)</td>
<td>9 (33)</td>
</tr>
<tr>
<td>Electively discontinued</td>
<td>1 (33)</td>
<td>1 (10)</td>
<td>1 (12.5)</td>
<td>–</td>
<td>3 (11)</td>
</tr>
<tr>
<td>Died</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (17)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Duration of treatment, median (range), weeks</td>
<td>40.3 (9.7–148.7)</td>
<td>71.7 (57.7–130.4)</td>
<td>78.4 (56.5–109.3)</td>
<td>75.7 (25.1–77.1)</td>
<td>75.6 (5.6–148.7)</td>
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<tr>
<td>Weeks of exposure, n (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>&lt;3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3 to 6</td>
<td>0</td>
<td>1 (10)</td>
<td>1 (25)</td>
<td>2 (7)</td>
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<tr>
<td>&gt;6 to 12</td>
<td>1 (33)</td>
<td>0</td>
<td>1 (25)</td>
<td>0</td>
<td>2 (7)</td>
</tr>
<tr>
<td>&gt;12</td>
<td>2 (67)</td>
<td>9 (90)</td>
<td>6 (75)</td>
<td>6 (100)</td>
<td>23 (85)</td>
</tr>
</tbody>
</table>

Ongoing at the time of data cutoff, April 1, 2016.
Includes any death reported that occurred within 28 days of last dose.
Patient had progression of disease prior to death.
The upper end of the treatment range represents patients with ongoing treatment at the time of data cutoff, April 1, 2016.

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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 I 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, whereas 22.2% of patients experienced a grade 3 or 4 study drug–related event. AEs 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). AEs 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

### Table 3. Adverse events

<table>
<thead>
<tr>
<th>Category</th>
<th>3.0 mg/kg (n = 3)</th>
<th>3.75 mg/kg (n = 10)</th>
<th>4.5 mg/kg (n = 8)</th>
<th>5.25 mg/kg (n = 6)</th>
<th>All patients (N = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Grade 3 or 4</td>
<td>All</td>
<td>Grade 3 or 4</td>
<td>All</td>
</tr>
<tr>
<td>On-treatment deaths, n (%)a</td>
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<td>0</td>
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<td>Adverse events, n (%)</td>
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<td>1 (33)</td>
<td>6 (60)</td>
<td>8 (100)</td>
<td>6 (100)</td>
</tr>
<tr>
<td>Suspected to be related to study drug</td>
<td>3 (100)</td>
<td>10 (100)</td>
<td>1 (10)</td>
<td>8 (100)</td>
<td>5 (83)</td>
</tr>
<tr>
<td>Serious adverse events, n (%)</td>
<td>0</td>
<td>4 (40)</td>
<td>4 (40)</td>
<td>5 (62.5)</td>
<td>3 (50)</td>
</tr>
<tr>
<td>Suspected to be related to study drug</td>
<td>0</td>
<td>1 (10)</td>
<td>2 (25)</td>
<td>2 (25)</td>
<td>1 (17)</td>
</tr>
<tr>
<td>AEs leading to discontinuation, n (%)</td>
<td>0</td>
<td>1 (10)</td>
<td>1 (12.5)</td>
<td>1 (12.5)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>AEs requiring dose reductions, n (%)</td>
<td>0</td>
<td>1 (10)</td>
<td>3 (38)</td>
<td>2 (25)</td>
<td>4 (15)</td>
</tr>
</tbody>
</table>

*aDeaths occurring >28 days after last study dose are not included. No deaths were suspected to be related to the study drug.
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 neurologic 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 AUC0–20/C20 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 and the 4.5 mg/kg cohorts (data for the 4.5 mg/kg dose was collected after 15 days at the new dose level). The dabrafenib dose at which older pediatric patients (ages >12 years) reached the target median plasma AUC at steady state was 4.5 mg/kg/day, whereas younger patients (ages ≤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 AUC0–12 target concentration was reached in both the age groups. Although patients ages <2 years were included as an a priori age category, only 1 patient ages <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 pharmacokinetic analyses for capsule and suspension formulations were not

Table 4. Summary of selected dabrafenib pharmacokinetic parameters by dose cohort

<table>
<thead>
<tr>
<th>Parameter</th>
<th>3.0 mg/kg (n = 3)</th>
<th>3.75 mg/kg (n = 10)</th>
<th>4.5 mg/kg (n = 8)</th>
<th>5.25 mg/kg (n = 10)</th>
<th>All patients (N = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (range) (ng/mL)</td>
<td>3 (1.558, 993-2,044)</td>
<td>10 (1.197, 661-3,168)</td>
<td>10 (1.478, 984-4,004)</td>
<td>6 (1.484, 822-3,631)</td>
<td></td>
</tr>
<tr>
<td>Tmax (range) (hours)</td>
<td>3 (1.08, 1.00-2.02)</td>
<td>10 (2.04, 0.48-3.92)</td>
<td>10 (2.00, 1.00-3.00)</td>
<td>6 (2.11, 1.02-3.03)</td>
<td></td>
</tr>
<tr>
<td>AUC0–12 (range) (ng h/mL)</td>
<td>3 (2.971, 1.591-6,604)</td>
<td>10 (3.340, 2,164-8,293)</td>
<td>10 (3.886, 2,172-13,448)</td>
<td>6 (4.090, 3,125-5,656)</td>
<td></td>
</tr>
<tr>
<td>≤12 years</td>
<td>2 (2.281, 1.591-2.971)</td>
<td>4 (2.925, 2,164-8,293)</td>
<td>7 (3.846, 2,172-5,371)</td>
<td>6 (4.090, 3,125-5,656)</td>
<td></td>
</tr>
<tr>
<td>&gt;12 years</td>
<td>1 (6,624) (NA-NA)</td>
<td>6 (3,825, 2,164-8,293)</td>
<td>3 (5,486, 1,426-13,448)</td>
<td>0 (NA)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable.

aCmax, Tmax, and AUC0–12 values from study part 1 on day 15 are reported as the median (min-max).

bTwo patients who were originally assigned to the 3.75 mg/kg cohort had dose escalations to 4.5 mg/kg daily, and pharmacokinetic data were also collected after 15 days of dosing at the new dose level. Thus, these 2 patients contributed pharmacokinetic data to both the 3.75 and 4.5 mg/kg cohorts.
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 pharmacokinetics. 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 II 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 I 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 (i.e., “histology-agnostic”) approach expanded the opportunity to identify if the pediatric patient population(s) are likely to benefit from BRAF inhibition (i.e., 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 I trial, dabrafenib was well tolerated at doses that generated pharmacokinetics 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 III dose of dabrafenib 150 mg twice daily. The pediatric RP2Ds for dabrafenib were established at 5.25 mg/kg/day in patients ages <12 years and 4.5 mg/kg/day in patients ages ≥12 years divided into 2 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 (i.e., acetaminophen or corticosteroids; refs. 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 erythrodysesthesis, 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 (e.g., phospho-ERK inhibition), treatment response rate, progression-free survival, and pyrexia, supporting the recommended dabrafenib adult dose of 150 mg twice daily (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 I studies. The current trial used an initial starting dose level of 80% of the adult approval 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 ages ≥12 years (not to exceed the adult daily dose of 300 mg).

This pharmacokinetic-based dose-escalation approach is based on the likelihood that therapeutic benefit in children will be achieved by targeting the adult dabrafenib exposure, principally the steady-state AUC0–12 following dabrafenib 150 mg twice daily administration. The geometric mean dabrafenib AUC0–12 after the administration of 150 mg bid in the adult phase III study BRF113683 [NCT01227889; patients with BRAF-mutant metastatic melanoma (n = 17)] was 4,341 ng·h/mL (95% CI, 3,599–5,235 ng·h/mL; refs. 39, 40). These phase III data were consistent with the results obtained from the monotherapy arm of study BRF113220 part D [NCT01726378; patients with BRAF-mutant metastatic melanoma (n = 11)], where geometric mean dabrafenib AUC0–12 after administration of 150 mg twice daily was 4,663 ng·h/mL (range, 3,511–6,194 ng·h/mL; ref. 38). Therefore, in part 1, the dabrafenib dose was increased until the MTD was reached (based on toxicity) or in the absence of patients reaching the MTD, the dose at which the median AUC0–12 was between approximately 4,000 ng·h/mL and approximately 5,500 ng·h/mL.

On the basis of the safety and pharmacokinetic data from study part 1, dabrafenib at the RP2Ds was further evaluated in study part 2. Additional analyses of the pharmacokinetic data for both parts 1 and 2 were planned to further explore the relationship of pharmacokinetic to body size and age. These analyses were also used to confirm the dabrafenib dose and adjust as appropriate to ensure that the majority of pediatric patients received a dose that resulted in exposures within the range associated with response in adults.
Novel therapeutics are needed for the treatment of pediatric malignancies to address the higher number of deaths due to pediatric cancer and the substantial proportion of patients experiencing long-term consequences from current therapies (38). Collectively, a growing understanding of the molecular drivers of pediatric cancers, the 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 I 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 \( \text{BRAF} \) V600 mutations, and established RP2Ds that achieve dabrafenib exposure levels suitable for the activity evaluation in these settings, which is reported separately.

Disclosure of Potential Conflicts of Interest

M.W. Kieran is an employee/paid consultant for Bristol-Myers Squibb. I.J. Dunkel is an employee/paid consultant for Aprexigen, Bayer, Bristol-Myers Squibb, Celgene, Eisai, and Pfizer, and reports receiving commercial research grants from Bristol-Myers Squibb, Genentech, and Novartis. D.R. Hargrave is an unpaid consultant/advisory board member for Dabrafenib and Trametinib. K.J. Cohen is an unpaid consultant/advisory board member for Novartis. C.A. Pratilas is an employee/paid consultant for Genentech and Trametinib. K.J. Cohen, T.R. Hummel, V. Shen, C.A. Pratilas, A.D.J. Pearson, L. Tseng, N. Nebot, S. Green, M.W. Russo, J.A. Whitlock


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References


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