Clinical Cancer Research

Efficacy and Safety of Dabrafenib in Pediatric Patients with *BRAF* V600 Mutation–Positive Relapsed or Refractory Low-Grade Glioma: Results from a Phase I/IIa Study

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Abstract

Purpose: Pediatric low-grade glioma (pLGG) is the most prevalent childhood brain tumor. Patients with *BRAF* V600 mutation–positive pLGG may benefit from treatment with dabrafenib. Part 2 of a phase I/IIa study, open-label study (NCT01677741) explores the activity and safety of dabrafenib treatment in these patients.

Patients and Methods: Patients ages 1 to <18 years who had *BRAF* V600–mutant solid tumors (≥1 evaluable lesion) with recurrent, refractory, or progressive disease after ≥1 standard therapy were treated with oral dabrafenib 3.0 to 5.25 mg/kg/day (part 1) or at the recommended phase II dose (RP2D; part 2). Primary objectives were to determine the RP2D (part 1, results presented in a companion paper) and assess clinical activity (part 2). Here, we report the clinical activity, including objective response rates (ORRs) using Response Assessment in Neuro-Oncology criteria and safety across parts 1 and 2.

Results: Overall, 32 patients with pLGG were enrolled (part 1, $n = 15$; part 2, $n = 17$). Minimum follow-up was 26.2 months. Among all patients, the ORR was 44% [95% confidence interval (CI), 26–62] by independent review. The 1-year progression-free survival rate was 85% (95% CI, 64–94). Treatment-related adverse events (AE) were reported in 29 patients (91%); the most common was fatigue (34%). Grade 3/4 treatment-related AEs were reported in 9 patients (28%).

Conclusions: Dabrafenib demonstrated meaningful clinical activity and acceptable tolerability in patients with *BRAF* V600–mutant pLGG.

Introduction

Glioma accounts for nearly two-thirds of all pediatric malignant central nervous system tumors and comprises a diverse spectrum of low-grade [e.g., pilocytic astrocytoma, diffuse (fibrillary) astrocytoma, and ganglioglioma] and high-grade (e.g., anaplastic astrocytoma and glioblastoma) malignancies (1–3). Patients with pediatric low-grade glioma (pLGG) can be cured with complete surgical resection; however, most patients with incompletely resected tumor will require additional treatment (4). Current options for patients whose tumors are not amenable to definitive surgery or whose tumors have recurred or progressed include radiotherapy and chemotherapy, which may provide 3-year progression-free survival rates up to approximately 70% but are associated with significant morbidities (e.g., cognitive/neurologic dysfunction, secondary malignancies, and infertility; refs. 4–7).

A greater understanding of the molecular mechanisms underlying pLGG has led to the identification of potential targets that can be evaluated for clinical intervention (8). Genetic alterations that result in constitutive activation of the BRAF kinase, including a nucleotide transversion resulting in the substitution of valine (V; most commonly with glutamic acid (E) at position 600 (i.e., V600E point mutation) or a tandem duplication resulting in the fusion of *KIAA1549* and *BRAF* (i.e., *BRAF:KIAA1549*)], have been implicated in the development of pLGG (9–11). In one large

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Translational Relevance

Low-grade gliomas (LGG) are the most frequently occurring brain tumors in pediatric patients. This study represents the largest clinical trial demonstrating the activity and safety of a BRAF inhibitor (dabrafenib) in pediatric patients with tumors harboring a *BRAF* V600 driver mutation. Meaningful clinical benefit with dabrafenib was demonstrated in pediatric patients with relapsed or refractory *BRAF* V600–mutant LGG, with an objective response rate of 44% and a 1-year estimated progression-free survival rate of 85% by independent review. The safety profile was favorable and consistent with adverse events observed in adult patients. These safety and preliminary efficacy data demonstrate the potential of dabrafenib as a novel therapy in a pediatric patient population who have few effective treatment options, providing support for further investigation in patients with *BRAF* V600 mutation–positive tumors, including LGG.

series, *BRAF* V600E mutations were detected in 19% of pLGGs across a broad range of histologies (12). Pleomorphic xanthoastrocytomas and gangliogliomas have been reported to have the highest incidence of *BRAF* V600E mutations among pLGGs, whereas pilocytic astrocytoma has the highest incidence of *BRAF:KIAA1549* gene fusions (13, 14). *BRAF* V600 mutation–positive LGG in pediatric patients has been associated with poor responses to chemotherapy and radiation as well as shorter duration of response and worse long-term outcomes versus non-*BRAF* V600 LGG (12); thus, these patients represent an important subpopulation in need of improved treatment options.

Dabrafenib, a potent and selective *BRAF* V600 inhibitor, has demonstrated clinical benefit in adult patients across a spectrum of *BRAF* V600–positive solid tumors and is currently approved as a single agent and in combination with the MEK inhibitor trametinib in patients with unresectable or metastatic *BRAF* V600E/K–mutant melanoma. Dabrafenib as monotherapy or in combination with trametinib has shown activity against melanoma brain metastases in these patients (15). In addition, dabrafenib plus trametinib is approved in patients with *BRAF* V600 mutation–positive non–small cell lung cancer (NSCLC) or anaplastic thyroid cancer and as an adjuvant therapy in patients with *BRAF* V600 mutation–positive resectable melanoma. The efficacy of dabrafenib in these adult populations suggests the potential for clinical benefit in pediatric patients with other tumor types driven by the *BRAF* V600 mutation, including pLGG.

On the basis of the mechanistic rationale, the ability to screen for the relevant driver mutations, and the availability of an age-appropriate formulation, we conducted a two-part, phase I/IIa, single-arm, open-label trial evaluating the safety, tolerability, and clinical activity of dabrafenib in pediatric patients (>12 months) with advanced *BRAF* V600 mutation–positive solid tumors (16). Part 1 was a dose escalation study to determine the recommended phase II dose (RP2D) of dabrafenib in pediatric patients with advanced *BRAF* V600 mutation–positive solid tumors (including LGG) for subsequent evaluation in part 2 of the study and is reported in the companion paper to this article (16). Age-dependent dose escalation of dabrafenib in part 1 established the RP2D at 5.25 mg/kg/day in patients <12 years of age and 4.5 mg/kg/day in patients ≥12 years of age, with no dose-limiting toxicities (DLT) observed (16). Part 2 included four tumor-specific expansion cohorts of patients with *BRAF* V600 mutation–positive tumors (LGG, high-grade glioma [HGG], Langerhans cell histiocytosis, and other tumors such as melanoma and papillary thyroid carcinoma). Here, we report the activity and safety of dabrafenib treatment in pediatric patients with *BRAF* V600–mutant relapsed or refractory LGG.

Patients and Methods

Study design and participants

We performed a phase I/IIa multicenter, open-label study in pediatric patients with advanced *BRAF* V600 mutation–positive solid tumors (NCT01677741). The completed part 1 is detailed in a separate report (16). The dose escalation decisions were made on the basis of the DLTs observed during the first 28 days, overall toxicity profile, and pharmacokinetics data. Part 2 was an expansion study conducted in four *BRAF* V600 mutation–positive tumor-specific cohorts at 18 sites in eight countries (Australia, Canada, Denmark, France, Germany, Spain, United Kingdom, and United States). Patients enrolled in part 2 were treated with the established RP2D from part 1. Patients participated only in part 1 or part 2 of the study. The study will be completed after the last patient has been treated for ≥6 months in the last accruing stratum.

Eligible patients with LGG were aged 1 to <18 years and had at least one evaluable *BRAF* V600 mutation–positive tumor according to Response Assessment in Neuro-Oncology (RANO) criteria, determined locally by a Clinical Laboratory Improvement Amendments–approved laboratory (or equivalent), adequate organ function, and a Karnofsky (for ≥16 years of age) or Lansky (for <16 years of age) performance score of ≥50. Baseline evaluable (but not measurable) disease was required. Patients were required to have recurrent, refractory, or progressive disease following receipt of ≥1 prior standard therapy. Patients could not have received chemotherapy or radiotherapy within 3 weeks (or 6 weeks for nitrosoureas or mitomycin C) or an investigational agent within 28 days (or five half-lives or twice the duration of the biological effect) prior to the first dose of dabrafenib. Only in part 2, patients were excluded if they had received previous treatment with a RAF inhibitor (including dabrafenib) or a MEK inhibitor; previous treatment with sorafenib was permitted. Treatment with dabrafenib was continued until disease progression, lack of clinical benefit from continued treatment, unacceptable toxicity, initiation of a new therapy, or consent withdrawal.

The study was conducted in accordance with the provisions of the Declaration of Helsinki, Good Clinical Practice guidelines and all applicable regulatory requirements. The protocol was approved by the institutional review board or human research ethics committee at each study center. Written informed consent (or assent, for age-appropriate patients according to institutional guidelines) was obtained from each patient, patient's parent, or legal guardian prior to the performance of any study-specific procedures.

Procedures

For part 1 (see companion paper; ref. 16), the initial cohort received a starting dose of 3.0 mg/kg/day, as two divided daily doses. Dabrafenib dose levels evaluated in part 1 were 3.0, 3.75 (corresponds to the approved adult dose of 150 mg twice daily), 4.5, and 5.25 mg/kg. The total daily dose was split evenly into

morning and evening doses to follow the twice-daily regimen as administered in adults. Standard dabrafenib capsule strengths (50 mg and 75 mg) were administered to children who were able to swallow capsules. Lower strength capsules (10 mg and 25 mg) and an oral suspension formulation were used for patients who could not swallow the larger capsules. Follow-up dermatologic skin assessments were performed every 2 to 3 months for 6 months following discontinuation of dabrafenib or until initiation of another anticancer therapy.

The primary endpoint was objective response rate (ORR) as determined using RANO criteria. Responses were determined both by the investigator and by an independent pediatric neuroradiologist. Imaging was performed using MRI. Radiographic tumor assessment occurred at baseline and every 8 weeks thereafter through 56 weeks; subsequent scans were obtained every 12 weeks or as per the standard of care. Clinical activity was assessed on the basis of the RANO criteria (17). Adverse events (AE) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 criteria.

Outcomes

The RP2D of 5.25 mg/kg/day in patients <12 years of age and 4.5 mg/kg/day in patients ≥12 years of age was determined in part 1 of the study and is described in the companion paper (16). Further evaluation of the safety, tolerability, pharmacokinetics, and clinical activity of dabrafenib in tumor-specific pediatric populations was performed in part 2 of the study.

Statistical analysis

Data were summarized using descriptive statistical methods. For the part 1 dose escalation phase (16), a minimum of 3 patients per dose level were evaluated to determine the RP2D. For the part 2 expansion, ≥10 patients per disease cohort were enrolled. Planned analysis populations for statistical considerations included the all-treated population of patients who received ≥1 dose of study treatment. The all-treated population was used for the safety and efficacy analyses and for summarizing the baseline and disease characteristics.

Safety data were based on the initial dose of dabrafenib assigned and were summarized for AEs and laboratory abnormalities based on the maximum toxicity grade. The extent of exposure was summarized for all patients. For the results described here, data were grouped for all pediatric patients with LGG enrolled across parts 1 and 2.

Efficacy analyses were conducted in the all-treated population. In addition, sensitivity analysis was performed on the response-evaluable population, which was defined as the proportion of all-treated patients with a predose and ≥1 postdose efficacy assessment. For efficacy analyses, assessments of response were based on the RANO criteria for all pediatric patients with LGG (17, 18). Per RANO criteria, a patient must have measurable disease at baseline in order to qualify for a complete response (CR) or partial response (PR) determination. The ORR was defined as the proportion of all treated patients with the best overall response of CR or PR [95% confidence intervals (CI) were calculated]. Both CR and PR were confirmed by repeat assessments not less than 4 weeks after the criteria for response were first met (17). The duration of response was defined as the time from the initial response (CR or PR) to the first documented disease progression or death.

Results

From December 2013 through July 2015, 32 pediatric patients with investigator-determined *BRAF* V600 mutation–positive, refractory or recurrent LGG were enrolled across 15 centers in Australia, Canada, France, Spain, and the United States across three dose levels and were included in the efficacy and safety analyses (Supplementary Fig. S1). Fifteen patients were enrolled in part 1 (dose finding) and 17 were enrolled in part 2 (at the RP2D). In part 1, the RP2D was determined (16). Patients enrolled in part 2 were treated at the RP2D, determined as dabrafenib 5.25 mg/kg/day for patients <12 years of age (n = 9) and 4.5 mg/kg/day for patients ≥12 years of age (n = 8). There was no correlation between dose and response in this relatively small study. Overall, 24 patients were treated at the age-defined RP2D (7 in part 1 and 17 in part 2). Demographics and baseline disease characteristics of pediatric patients with LGG are summarized in Table 1. The median age was 8.5 years (range: 2–17), and 22 of 32 patients (69%) were <12 years of age. Pilocytic astrocytoma (n = 13; 41%), ganglioglioma (n = 7; 22%), and pleomorphic xanthoastrocytoma (n = 3; 9%) were the most common LGG diagnoses; other tumors are reported in Table 1. All 32 patients had a documented progression. The median time since initial LGG diagnosis (in 26 patients with available data) was 32 months (range: 6–190). Ten of 32 patients did not have progressive disease within the previous 4 months and were eligible for enrolment with indolent disease as per the phase I part of the study. Twenty-two patients (69%) were initially diagnosed with grade 1 disease, 9 patients (28%) with grade 2 disease, and 1 patient had undetermined grade 1 or grade 2 disease. Most patients had a good Karnofsky/Lansky performance status; only 13% of the patients had a performance status below 80 at baseline. Prior treatments were predominantly chemotherapy (n = 28; 88%) and radiotherapy (n = 6; 19%). Five patients had a best overall response of PR to the most recent therapy received before starting dabrafenib treatment; no prior CRs were reported.

As of the data cutoff date (September 12, 2017) with a minimum follow-up of 26.2 months, 15 patients (47%) were continuing treatment with dabrafenib (Table 1).

The study set no minimum treatment duration and the most common reason for treatment discontinuation was physician and/or parent decision. Four patients (13%) discontinued because of disease progression, including 1 patient who discontinued at week 8 of the treatment and underwent subsequent therapy but later died because of disease progression. This patient was enrolled into this study 11 years after the initial diagnosis of LGG (pilocytic astrocytoma). At autopsy, this patient's tumor was found to have transformed into a *BRAF* V600–mutated, *PDGFRA*-amplified glioblastoma (World Health Organization grade 4). Two patients (6%) discontinued dabrafenib because of AEs. The median duration of dabrafenib exposure was 108 weeks (range: <1–185; Table 1; Fig. 1A), and 17 patients (53%) were on treatment for >2 years. Ten patients (31%) had dose reductions and/or interruptions.

The confirmed ORR with dabrafenib by independent radiological review was 44% (14/32, 95% CI, 26–62) and included 1 patient with CR and 13 with PR (Table 2). Five of these 32 patients were not evaluable for CR or PR per RANO criteria due to nonmeasurable but evaluable disease at study entry; these 5 patients were evaluable for and met the definition of stable disease (SD). An example of PR (ongoing at data cutoff) achieved

Table 1. Patient demographics, baseline characteristics, prior treatments, disposition, and dabrafenib exposure[a]

Characteristic	Part 1			Part 2	All patients treated with dabrafenib at RP2D ($n = 24$)	All patients with LGG ($N = 32$)
	Dabrafenib 3.75 mg/kg ($n = 3$)	Dabrafenib 4.5 mg/kg ($n = 6$)	Dabrafenib 5.25 mg/kg ($n = 6$)	Dabrafenib RP2D ($n = 17$)		
Median age (range), years	8 (4–13)	8.5 (2–16)	7.5 (3–11)	11 (2–17)	9.5 (2–17)	8.5 (2–17)
<2 years, *n*	0	0	0	0	0	0
2–<6 years, *n*	1	2	2	5	7	10
6–<12 years, *n*	1	3	4	4	8	12
12–≤18 years, *n*	1	1	0	8	9	10
Sex, *n* (%)						
Male	2 (67)	5 (83)	3 (50)	9 (53)	13 (54)	19 (59)
Female	1 (33)	1 (17)	3 (50)	8 (47)	11 (46)	13 (41)
Race, *n* (%)						
White	3 (100)	5 (83)	6 (100)	13 (76)	19 (79)	27 (84)
Black	0	1 (17)	0	2 (12)	3 (13)	3 (9)
Asian	0	0	0	2 (12)	2 (8)	2 (6)
Performance status, *n* (%)[b]						
100	2 (67)	3 (50)	3 (50)	9 (53)	12 (50)	17 (53)
80–90	1 (33)	1 (17)	2 (33)	7 (41)	10 (42)	11 (34)
<80	0	2 (33)	1 (17)	1 (6)	2 (8)	4 (13)
Histology at initial diagnosis, *n* (%)						
Pilocytic astrocytoma	1 (33)	3 (50)	1 (17)	8 (47)	10 (42)	13 (41)
Ganglioglioma	0	1 (17)	1 (17)	5 (29)	6 (25)	7 (22)
Pleomorphic xanthoastrocytoma	0	0	1 (17)	2 (12)	3 (13)	3 (9)
Pilomyxoid astrocytoma	1 (33)	0	0	1 (6)	1 (4)	2 (6)
Other[c]	1 (33)	2 (33)	3 (50)	1 (6)	4 (17)	7 (22)
Histologic grade at initial diagnosis, *n* (%)[d]						
Grade I	2 (67)	4 (67)	4 (67)	12 (71)	16 (67)	22 (69)
Grade II	1 (33)	2 (33)	2 (33)	4 (24)	7 (29)	9 (28)
Median time since initial diagnosis (range), months	36 (32–39)	15 (11–90)	39 (18–83)	26 (6–190)	31 (6–190)	32 (6–190)
Prior treatments, *n* (%)[e]						
Chemotherapy	3 (100)	5 (83)	6 (100)	14 (82)	20 (83)	28 (88)
Radiotherapy	1 (33)	1 (17)	1 (17)	3 (18)	5 (21)	6 (19)
Small-molecule therapy	0	0	1 (17)	1 (6)	2 (8)	2 (6)
Immunotherapy	0	0	0	1 (6)	1 (4)	1 (3)
Other	0	0	0	3 (18)	3 (13)	3 (9)
Median time from last recurrence to dabrafenib start (range), months[f]	NA	NA	0.8 (0.2–1.3)	1.1 (0.1–81.5)	1.1 (0.1–81.5)	1.1 (0.1–81.5)
Median time from last progression to dabrafenib start (range), months[g]	7.6 (0.5–14.7)	0.8 (0.5–1.1)	1.8 (0.2–26.2)	1.6 (0.1–10.3)	1.5 (0.1–26.2)	1.1 (0.1–26.2)
Continuing treatment, *n* (%)	2 (67)	3 (50)	2 (33)	8 (47)	10 (42)	15 (47)
Discontinued treatment, *n* (%)	1 (33)	3 (50)	4 (67)	9 (53)	14 (58)	17 (53)
Reasons for discontinuation						
Investigator discretion	1 (33)	1 (17)	4 (67)	5 (29)	10 (42)	11 (34)
Disease progression	0	2 (33)	0	2 (12)	2 (8)	4 (13)
Adverse event	0	0	0	2 (12)	2 (8)	2 (6)
Median duration of exposure to dabrafenib (range), weeks	157 (62–159)	120 (8–185)	96 (25–152)	105 (<1–149)	104 (<1–152)	108 (<1–185)
Patients with dose reductions and/or interruptions, *n* (%)	1 (33)	3 (50)	1 (17)	5 (29)	6 (25)	10 (31)

Abbreviation: NA, not applicable.

[a]As of data cutoff (September 12, 2017).

[b]Using Karnofsky (≥16 years of age; $n = 28$) or Lansky (<16 years of age; $n = 4$) performance status, as appropriate.

[c]Desmoplastic neuroepithelial neoplasm, cervicomedullary tumor, glioneuronal brain stem tumor, posterior fossa brain tumor, optic pathway glioma, gliomatosis cerebri, and other low-grade glioma.

[d]One patient had missing data for disease grade at initial diagnosis but was confirmed to have LGG.

[e]Patients may have had multiple therapies and prior therapy type was undetermined in 2 patients; best response to last therapy received included 5 patients with a partial response, 13 patients with stable disease, and 9 patients with progressive disease (response to last therapy was undetermined in 5 patients).

[f]In 11 patients with recurrence.

[g]In 25 patients with disease progression.

after 8 weeks of dabrafenib therapy in an 11-year-old male patient with *BRAF* V600–mutant ganglioglioma is shown by MR image (Fig. 2). Eight of 32 patients (25%) had a first response within 4 months of dabrafenib initiation. The median time to first response was 3.8 months (range: 1.7–24.0; Fig. 1A). The median duration of response was 26 months (95% CI, 9—not estimable). Eight of 14 patients had an ongoing response at the time of data cutoff, and 6 of 14 patients who relapsed had a duration of response of more than 2 years to dabrafenib. The disease control rate (CR + PR + SD) by independent review was 78% (95% CI, 60–91). Among the 27 patients with measurable disease as determined by independent radiologic review, 19 (73%) had at least one occurrence of a maximum reduction in lesion size of at least 50% from baseline (Fig. 1B).

The disease control rate (CR + PR + SD) by investigator assessment was 88% (95% CI, 71–97). Among the 31 patients

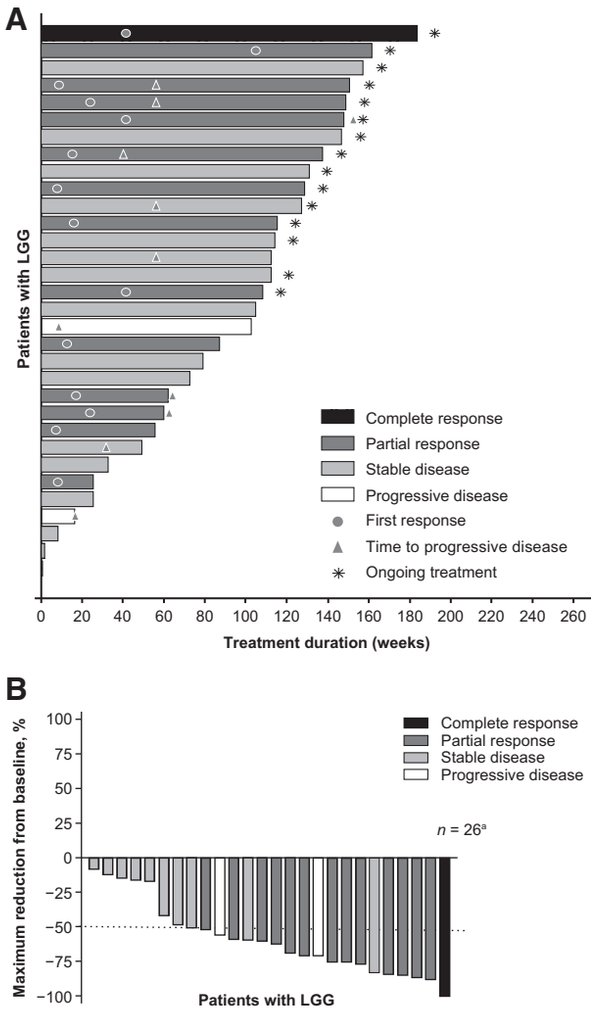

Figure 1.

Dabrafenib treatment duration and best response. **A,** Duration of exposure to dabrafenib analyzed by best overall response assessed by independent review using the RANO criteria. **B,** Best reduction in tumor size analyzed by best overall response, assessed by independent review using the RANO criteria, for the subset of patients with measurable disease. Dashed line represents a 50% reduction from baseline, which corresponds to the threshold for partial response per the RANO criteria. [a]Includes only patients with measurable disease and ≥1 postbaseline evaluation. Five of these patients had the best overall response as stable disease, with no confirmation from the scan results; 1 patient was not evaluable.

with measurable lesions as per investigator assessment, 22 (71%) achieved a maximum reduction in lesion size of at least 50% from baseline (Supplementary Fig. S2). Eleven of the patients with a best overall response of SD by independent review had significant tumor reductions that were categorized by investigators as PRs, accounting for most of the observed discordance between the independent and investigator assessment of response.

A total of 11 disease progression events were determined by independent review, three of which occurred after ending dabrafenib treatment. Five of the 8 patients determined as disease progression on treatment with independent review were continuing treatment at the data cutoff; these patients did not have progression per investigator assessment. The median progression-free survival (independent review) was 35.0 months (interquartile range: 12.9—not estimable), and the Kaplan–Meier estimate of the proportion of patients with progression-free survival at 1 year of dabrafenib treatment was 85% (95% CI, 64–94; Fig. 3). One survival event occurred after treatment discontinuation.

Treatment-related AEs of any grade occurred in 29 patients (91%); the most common were fatigue (34%), rash (31%), dry skin (28%), pyrexia (28%), and maculopapular rash (28%; Table 3). Grade 3/4 treatment-related AEs were reported in 9 patients (28%) and included maculopapular rash ($n = 3$), arthralgia, lymphocytopenia, increased weight, thrombocytopenia, back pain, increased blood alkaline phosphatase, hypotension, neutropenia, and migraine ($n = 1$ each). In this pediatric population, there were no cases of squamous cell carcinoma of the skin or keratoacanthoma, as have been reported commonly in adult patients treated with dabrafenib. Note that new or increased size of melanocytic nevi was reported in 8 of 32 patients (25%), all grade 1 or 2. AEs were well managed by supportive care, dose interruption, and dose reduction. Ten patients had AEs that led to dose interruptions and/or reductions. AEs of allergic reaction/hypersensitivity ($n = 1$) and hip pain/arthralgia with erythema nodosum ($n = 1$) led to treatment discontinuation in 2 patients (6%). Treatment-related serious AEs of any grade occurred in 5 patients (16%) and were reported as grade 3/4 in 3 patients (9%), which included arthralgia, disseminated intravascular coagulation with hypotension, and maculopapular rash ($n = 1$ each). No treatment-related deaths occurred in the study; 1 patient died due to disease progression 2 weeks after discontinuing the therapy.

Discussion

This study represents the largest report of successful outcomes from a clinical trial of a *BRAF* V600–targeted therapy in a pediatric population selected on the basis of a specific driver mutation. Previous reports have been limited to case study observations (19–22) and the report of an adult glioma subset from the vemurafenib basket trial that included 9 adult patients with *BRAF* V600–mutant LGG (23). In this study, we demonstrated clinical activity of dabrafenib in pediatric patients with *BRAF* V600–mutant relapsed or refractory LGG in a clinical trial setting; a high proportion of these patients had a radiographic response. Dabrafenib was tolerable and demonstrated a manageable safety profile with a minimum follow-up of >2 years. These results in pediatric patients add to those previously reported for adult patients with other *BRAF* V600 mutation–positive tumors, including melanoma, NSCLC, anaplastic thyroid cancer, and gliomas (24–27). Taken together, these data clearly demonstrate the clinical benefit of targeting the V600 mutation with dabrafenib in pediatric patients with relapsed refractory *BRAF* V600 mutation–positive LGG.

Current treatment options for pediatric patients with progressive or recurrent LGG are limited to radiotherapy and chemotherapy. These are associated with various clinically significant long-term adverse effects, including risk of secondary malignancies, cognitive impairment, hormonal deficiencies, vasculopathies, and infertility (5), which are of particular concern in a pediatric patient population. Standard chemotherapy treatments

Table 2. Dabrafenib efficacy

Characteristic	Part 1			Part 2	All patients treated with dabrafenib at RP2D ($n = 24$)	All patients with LGG ($N = 32$)
	Dabrafenib 3.75 mg/kg ($n = 3$)	Dabrafenib 4.5 mg/kg ($n = 6$)	Dabrafenib 5.25 mg/kg ($n = 6$)	Dabrafenib RP2D ($n = 17$)		
Independent review[a]						
Best overall response, *n* (%)						
Complete response	0	1 (17)	0	0	0	1 (3)
Partial response	2 (67)	2 (33)	2 (33)	7 (41)	9 (38)	13 (41)
Stable disease[b]	1 (33)	3 (50)	4 (67)	8 (47)	13 (54)	16 (50)
Progressive disease	0	0	0	2 (12)	2 (8)	2 (6)
Objective response, *n* (%) [95% CI]	2 (67) [9–99]	3 (50) [12–88]	2 (33) [4–78]	7 (41) [18–67]	9 (38) [19–59]	14 (44) [26–62]
Median duration of response (range), months	—	—	—	—	11.0 (3.7–14.5)	11.0 (7.4–14.5)
Disease control, *n* (%) [95% CI]	3 (100) [29–100]	5 (83) [36–100]	5 (83) [36–100]	12 (71) [44–90]	18 (75) [53–90]	25 (78) [60–91]
Median progression-free survival (95% CI), months[c]	35 (15–NE)	(NE–NE)	13 (13–NE)	(NE–NE)	14 (13–NE)	35 (13–NE)
1-year progression-free survival rate (95% CI), %[c]	100 (100–100)	80 (20–97)	100 (100–100)	78 (46–92)	79 (53–92)	85 (64–94)

Abbreviation: NE, not estimable.
[a]Using RANO criteria.
[b]Includes 5 patients with independent review of stable disease but lacking any confirmation scan results.
[c]Kaplan–Meier estimate.

seem to have worse efficacy in patients with *BRAF* V600–mutant LGG than in those with non-*BRAF* V600 LGG (13), including a 10-year progression-free survival of 27% versus 60%. The apparent ORR (CR + PR at the 6-month milestone) observed in historical cohorts of this population treated with chemotherapy is approximately 10% (13). In this study, an ORR of 44% and a 1-year progression-free survival rate of 85% were reported by independent review using the RANO criteria. Approximately half of responders by independent review had an ongoing response at the time of data cutoff. Notably, among patients assessed by independent review, only two had a best response of progressive disease.

The most common reason for discontinuation of treatment in this study was physician and/or parent decision with the majority having at least 1 year of treatment. It is likely that the typical duration of standard chemotherapy for pLGG of 12 to 24 months had an impact on the decision to stop therapy in patients with SD or better. Further data generation is needed to determine the optimal duration of treatment and if patients can be retreated successfully. Anecdotal reports from investigators of this clinical trial showed that retreatment with dabrafenib can result in tumor control.

Observations from experienced neuro-oncologists and neuroradiologists involved in the study suggest that *BRAF* V600–mutant LGG tumors may have some unique characteristics on MRI, which can prove challenging in recording tumor response consistently and accurately as illustrated by the disconcordance seen between the local and central independent review in this study. Generally, LGG tumors are monitored for response by T2/FLAIR MRI sequences, and these T2/FLAIR images are recommended for the observation of tumor size changes in LGG assessment (28). However, some of the LGG tumors on this study appeared more like typical HGG tumors and displayed enhancement in postgadolinium T1-weighted images ("T1 enhancement"). Furthermore, this enhancement can decrease quickly upon initiation of treatment with dabrafenib and occurs before changes in tumor size are observed on T2/FLAIR sequences. There are a few reports of rapid increase in T1 enhancement upon elective cessation of treatment, with subsequent decrease upon rechallenge with dabrafenib. The

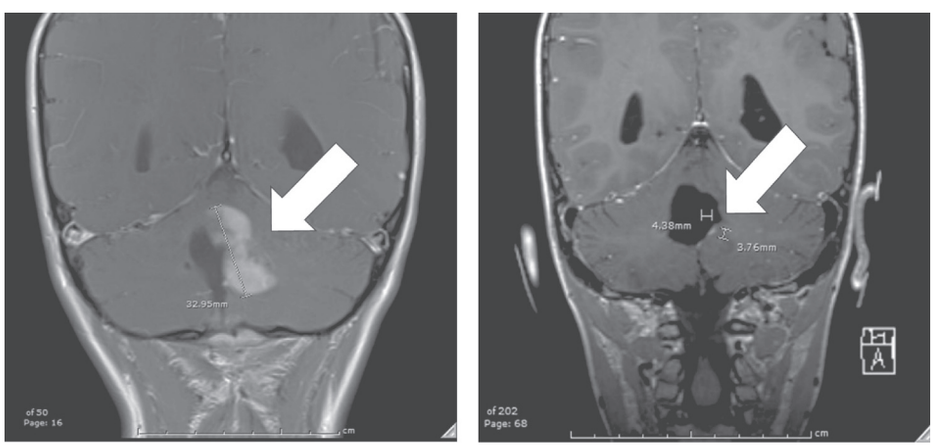

Figure 2.
MR images of a partial response (ongoing) achieved after 8 weeks of dabrafenib therapy in an 11-year-old male patient with *BRAF* V600–mutant ganglioglioma determined using coronal T1 postgadolinium contrast sequence. The arrows indicate the location of the tumor.

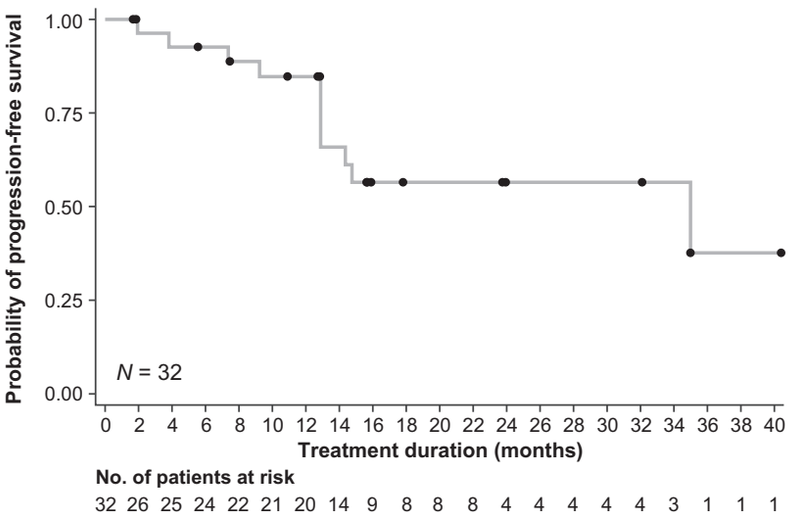

Figure 3.
Kaplan–Meier progression-free survival. Kaplan–Meier estimates of progression-free survival. Eleven disease progression events occurred; eight were on-treatment and three were off-treatment. Tumor assessments were by independent review using the RANO criteria.

mechanism of this rapid change in T1 enhancement is not well understood, nor is its biologic significance. Until more experience is gained, caution should be exercised, as these rapid changes in the size of apparent T1-enhancing *BRAF* V600–mutant LGG tumors on starting or stopping dabrafenib treatment may not accurately represent true changes in tumor size.

The safety profile of dabrafenib in pediatric patients with LGG was manageable and was consistent with that observed in adult patients across other indications, except for the absence of observations of squamous cell carcinoma (as of April 2019). Similar to the observations in patients with melanoma and NSCLC (24, 25), fatigue and pyrexia were among the most common treatment-related AEs observed in pediatric patients with LGG treated with dabrafenib; these AEs and others were manageable and did not lead to discontinuation.

Table 3. Safety summary and treatment-related AEs

	All patients with LGG ($N = 32$)	
	All grade	**Grade 3/4**
Patients with a treatment-related AE, *n* (%)	29 (91)	9 (28)
Treatment-related AEs (in >20% of patients), *n* (%)		
Fatigue	11 (34)	0
Rash	10 (31)	0
Dry skin	9 (28)	0
Pyrexia	9 (28)	0
Rash maculopapular	9 (28)	3 (9)
Arthralgia	8 (25)	1 (3)
Headache	7 (22)	0
Vomiting	7 (22)	0
AEs leading to discontinuation, *n* (%)	2 (6)	2 (6)
Treatment-related deaths, *n* (%)	0	0
Patients with a treatment-related serious AE, *n* (%)	5 (16)	3 (9)
Treatment-related serious AEs, *n* (%)		
Arthralgia	1 (3)	1 (3)
Disseminated intravascular coagulation	1 (3)	1 (3)
Ejection fraction decreased	1 (3)	0
Febrile neutropenia	1 (3)	0
Hypotension	1 (3)	1 (3)
Pyrexia	1 (3)	0
Rash maculopapular	1 (3)	1 (3)

Recent research from several different groups led to the identification of multiple molecular aberrations in pLGG tumors (20, 21, 29), including a *BRAF* V600–mutation rate of 15% to 20% across LGG histologies (12, 13). A recent study of gene expression profiling of 151 LGG biopsies from pediatric patients demonstrated that *BRAF* gene abnormalities were observed across a variety of histologic subtypes, with *BRAF*:*KIAA1549* fusions occurring most frequently in pilocytic astrocytomas and *BRAF* V600 point mutations occurring most frequently in pleomorphic xanthoastrocytomas and gangliogliomas (29). Taken together with the results of the current report, these data suggest that only specific patient subgroups may be more likely to derive benefit from dabrafenib therapy. It is important to note that patients with the *BRAF* gene fusion or duplications should not receive BRAF inhibitor therapy, as preclinical data demonstrate that BRAF inhibition activates the MAPK signaling pathway in cells with wild-type *BRAF* at V600 (30). Furthermore, a phase II study of the multikinase inhibitor sorafenib, which targets BRAF, VEGFR, PDGFR, and c-kit, in pediatric patients with recurrent low-grade astrocytomas—some of whom harbored *BRAF* duplications—indicated that sorafenib treatment was associated with accelerated tumor growth (31). The authors concluded that sorafenib may have led to paradoxical ERK activation that caused rapid tumor progression. These data underscore the importance of detailed molecular profiling prior to treatment with BRAF inhibitors in patients with pLGG.

The results presented here provide additional rationale for increased efforts worldwide to molecularly characterize newly diagnosed tumors in children, with the intent to identify targetable aberrations for each patient. Indeed, efforts ongoing at centers around the world, including INFORM (German Cancer Research Center), MAPPYACTS (NCT02613962; Gustave Roussy, France), PEDS-MIONCOSEQ (University of Michigan, Ann Arbor, MI), BASIC3 (Baylor College of Medicine, Houston, TX), iCat (NCT01853345; Dana-Farber Cancer Institute, Houston, TX), SMPaeds—Stratified Medicine Pediatrics (ISRCTN21731605; United Kingdom), and the Pediatric MATCH program (US NCI) among others, are showing good promise in the ability to provide targeted therapies for pediatric

patients with cancer who may otherwise have limited treatment options (32–35). Although the tumors of patients enrolled in this study were already determined to harbor the *BRAF* V600 mutation, it is apparent that broad molecular profiling of LGG tumors (as well as other pediatric tumor types) at diagnosis may lead to enhanced treatment options for an increasing number of patients with pediatric cancer (36).

Overall, these results demonstrate a distinct clinical benefit and favorable tolerability for dabrafenib in pediatric patients with *BRAF* V600 mutation–positive relapsed or refractory LGG and provide support for further evaluation in this population. Determination of optimal duration of treatment and biological correlates of response to dabrafenib remains an important area of study. As has been demonstrated in several *BRAF* V600–mutant adult tumor types, the addition of trametinib to dabrafenib therapy may provide improved outcomes in pediatric patients with *BRAF* V600–mutant LGG. A phase II study of dabrafenib in combination with the MEK inhibitor trametinib in pediatric patients with *BRAF* V600 mutation–positive newly diagnosed LGG or recurrent HGG (NCT02684058) is ongoing.

Disclosure of Potential Conflicts of Interest

D.R. Hargrave is an employee/paid consultant for selumetinib and cobimetinib, reports receiving commercial research grants from selumetinib, and is an advisory board member/unpaid consultant for dabrafenib and trametinib. E. Bouffet is an advisory board member/unpaid consultant for Novartis. I.J. Dunkel is an employee/paid consultant for Apexigen, Bayer, Bristol-Myers Squibb, Celgene, and Pfizer, and reports receiving commercial research grants from Bristol-Myers Squibb, Novartis, and Genentech. M.W. Russo is an employee/paid consultant for and holds ownership interest (including patents) in Novartis. L. Tseng is an employee/paid consultant for and holds ownership interest (including patents) in Novartis Pharmaceuticals. K. Dasgupta is an employee/paid consultant for Novartis. E. Gasal is an employee/paid consultant for and holds ownership interest (including patents) in Novartis. M.W. Kieran is an employee/paid consultant for Novartis. No potential conflicts of interest were disclosed by the other authors.

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