

# 6 Efficacy Study of Vemurafenib in Children With Recurrent or Progressive BRAF<sup>V600E</sup>- or BRAF<sup>InsT</sup>-Mutant Brain Tumors: PNOC002

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## ABSTRACT

**PURPOSE** Pediatric gliomas constitute the most prevalent central nervous system tumors in children, and aberrations in BRAF signaling contribute to their pathogenesis by disrupting the MAPK pathway. Targeted inhibition of this pathway using agents such as vemurafenib may hold therapeutic promise.

**PATIENTS AND METHODS** PNOC002 was a multicenter trial conducted through the Pediatric Neuro-Oncology Consortium in patients younger than 25 years with recurrent or progressive BRAF<sup>V600E</sup>-mutant brain tumors. This combined phase 0/1 study aimed to establish the recommended phase II dose (RP2D) and assess preliminary efficacy, including tumor growth trajectories and rebound (defined as  $\geq 25\%$  increase in lesion size within 6 months, usually within 3 months, of stopping therapy).

**RESULTS** Thirty-patients (range, 3–23 years) were treated at the RP2D of 550 mg/m<sup>2</sup> twice a day: 22 low-grade glioma (LGG) and 8 high-grade glioma (HGG). PFS at 6 months (PFS6) for the entire cohort was 80% (95% CI, 67 to 96). In patients with LGG, PFS6 was higher at 86% (95% CI, 73 to 100), compared with 63% (95% CI, 37 to 100) in patients with HGG. The best responses were stable disease (13 patients) and partial responses (13 patients). Four patients experienced PD, with three patients in the HGG cohort. Responsiveness varied by lesion type, with cystic lesions showing a larger and longer-lasting decrease in tumor size than solid lesions. Of 13 patients with LGG who discontinued treatment and had follow-up imaging, 3 (23%) experienced rebound within 78–97 days. The most common grade 3 adverse event was maculopapular rash (57%).

**CONCLUSION** Vemurafenib showed efficacy in children with recurrent or progressive BRAF<sup>V600E</sup>-mutant brain tumors with acceptable toxicity. However, the rebound rate of 23% warrants further investigation.

## ACCOMPANYING CONTENT

-  Graphical Abstract
-  [Data Sharing Statement](#)
-  [Data Supplement](#)
-  [Protocol](#)

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## INTRODUCTION

Astrocytomas are the most common group of pediatric brain tumors.<sup>1</sup> Patients who undergo surgical removal of low-grade astrocytomas typically experience favorable outcomes, whereas patients with malignant astrocytomas or unresectable, recurrent low-grade astrocytomas have a worse prognosis. Molecular profiling has expanded treatment options for pediatric gliomas by identifying actionable alterations in the mitogen-activated protein kinase pathway.<sup>2–5</sup>

BRAF (v-raf murine viral oncogene homolog B1) has been implicated as an oncogene in numerous cancers, including brain tumors.<sup>6,7</sup> BRAF<sup>V600E</sup> is the second most commonly

observed mutation in pediatric low-grade glioma (LGG), and it is also present in a subgroup of both primary and secondary high-grade glioma (HGG).<sup>4,8</sup> The mutation constitutively activates MAPK signaling and can be targeted with selective BRAF inhibitors, including vemurafenib, dabrafenib, and encorafenib.<sup>9–11</sup>

An additional BRAF oncogenic mutation, BRAF<sup>InsT</sup>, has been found in a small fraction of pediatric gliomas.<sup>12</sup> BRAF<sup>InsT</sup> results in the insertion of an additional threonine residue in close proximity to the mutational hotspot valine at position 600. This mutant displays an in vitro kinase activity and cellular MEK/ERK activation potential comparable with those of BRAF<sup>V600E</sup>, and it is transforming in fibroblasts.<sup>12,13</sup>

## CONTEXT

### Key Objective

To evaluate the efficacy of vemurafenib in children and young adults with recurrent or progressive BRAF-mutant glioma, characterize changes in solid and cystic tumor components over time, and determine the frequency of early tumor rebound after treatment discontinuation.

### Knowledge Generated

At 550 mg/m<sup>2</sup> twice daily, 6-month progression-free survival was 80% overall, 86% in low-grade glioma (LGG), and 63% in high-grade glioma, with partial response or stable disease in 26 of 30 patients. Cystic components showed greater and more sustained reduction than solid components, and rebound occurred in three of 13 evaluable patients with LGG (23%) 78–97 days after treatment discontinuation.

### Relevance

Vemurafenib provides clinically meaningful disease control in BRAF-mutant pediatric and young adult glioma. Component-specific imaging may improve response assessment, while the observed early rebound supports close surveillance and careful planning when stopping therapy.

Recent studies have investigated the use of BRAF inhibitors, with or without MEK inhibitors, as new treatment approaches for pediatric gliomas harboring BRAF<sup>V600E</sup> mutations.<sup>14–16</sup> In recurrent LGG, BRAF inhibitors have produced frequent and durable responses during treatment, although regrowth may occur after discontinuation and activity appears lower in high-grade disease.<sup>17</sup> A randomized phase II trial showed superior response, progression-free survival, and tolerability with dabrafenib plus trametinib compared with standard chemotherapy in children with recurrent BRAF<sup>V600E</sup>-mutant LGG.<sup>14</sup> We previously reported that vemurafenib monotherapy had promising antitumor activity and manageable toxicity in children with recurrent or progressive BRAF<sup>V600E</sup>-mutant brain tumors.<sup>18</sup>

In this report, we extend our prior work on the BRAF inhibitor vemurafenib in children with recurrent BRAF<sup>V600E</sup> gliomas and report on efficacy and safety, including patients treated with the BRAF<sup>InsT</sup> variant.

## PATIENTS AND METHODS

### Study Design

PNO002 was a prospective, multicenter phase 0/1 trial with an efficacy expansion cohort evaluating vemurafenib in patients with BRAF<sup>V600E</sup>- or BRAF<sup>InsT</sup>-mutant primary CNS tumors at 12 US centers from April 2014 through November 2018. Final study follow-up was completed in July 2024. Prior reports described dose escalation, safety, and pharmacokinetics. The present analysis focuses on antitumor activity among patients treated at the recommended phase II dose (RP2D).<sup>18,19</sup> Eligible patients were younger than 25 years, had a histologically confirmed primary CNS tumor harboring BRAF<sup>V600E</sup> or BRAF<sup>InsT</sup>, and had MRI-confirmed progressive

disease. Full eligibility criteria, protocol procedures, and consent requirements are provided in the Protocol and Supplement M1.

### Ethics

The study was reviewed and approved by the institutional review board of each participating institution. A written, signed, informed consent form and a Health Insurance Portability and Accountability Act authorization was obtained before any study-specific assessments were initiated.

### Treatment

Patients received oral vemurafenib 550 mg/m<sup>2</sup> twice daily, with a maximum dose of 960 mg twice daily, in 28-day cycles. Treatment continued until progression, unacceptable toxicity, or elective discontinuation after at least 24 cycles. Continued treatment beyond 24 months was permitted when clinically beneficial and tolerable. Patients who progressed within 6 months after discontinuation could restart vemurafenib according to the protocol.

### Response Assessment

Brain and/or spine MRI was obtained within 14 days before enrollment and every two treatment cycles. Response was reviewed centrally and retrospectively. Patients were evaluable if they had measurable disease at baseline, received at least one cycle, and underwent at least one follow-up assessment. Bidimensional tumor measurements were compared with the reference scan. Complete response required disappearance of disease for at least 8 weeks. Partial response required at least a 50% reduction for at least 8 weeks; progressive disease required at least a 25% increase in summed lesion size or a new lesion. All other outcomes

were classified as stable disease. Full imaging criteria are provided in the Protocol.

## Statistical Analysis

The efficacy expansion used a Simon min-max two-stage design testing a response rate of 5% versus 20%, with 90% power and a 10% type I error, and allowed enrollment of up to 32 evaluable patients. Descriptive statistics summarized baseline characteristics and adverse events. Progression-free survival (PFS) was measured from treatment initiation to progression or death and overall survival (OS) from treatment initiation to death. Distributions were estimated using Kaplan-Meier methods. PFS6 was the proportion alive and progression-free at 182 days. Longitudinal percentage change in solid and cystic lesions was evaluated using a linear mixed-effects model with time, lesion type, and their interaction as fixed effects and a patient-level random intercept. Rebound in patients with LGG was defined as at least a 25% increase in lesion size within 6 months after treatment cessation, using the last MRI before cessation as baseline.<sup>20</sup>

Safety analyses included all patients who received at least one RP2D dose. Additional statistical and protocol details are provided in the Data Supplement.

## RESULTS

### Patient Characteristics

Forty patients enrolled in PNOC002, of whom 30 received the RP2D and comprise this analysis cohort (Table 1). Median age was 10.5 years (range, 3–23), and 12 patients (40%) were female. Twenty-two patients had LGG and eight had HGG. Detailed tumor location, histology, and lesion characteristics are presented in Table 1. Twenty-nine patients had a BRAF<sup>V600E</sup> mutation, and one patient was found to have a BRAF<sup>InsT</sup> (PNOC-009). BRAF<sup>InsT</sup>-expressing cells demonstrated sensitivity to BRAF inhibition comparable with BRAF<sup>V600E</sup>-expressing cells in a supporting preclinical experiment (Data Supplement, Fig S1).

### Clinical Outcomes

#### Survival

PFS6 for the entire cohort was 80% (95% CI, 67 to 96; Fig 1A). In patients with LGG, PFS6 was higher at 86% (95% CI, 73 to 100) than in patients with HGG at 63% (95% CI, 37 to 100; Figs 1B and 1C). With a median follow-up of 25.7 months (95% CI, 19.2 to 36.2) for the complete cohort, median PFS and OS estimates for LGGs were not reached. For patients with HGG, median PFS was 16.5 months (95% CI, 2.3 to NA) and median OS was 33.6 months (95% CI, 33.6 to NA). Centrally reviewed best radiographic responses comprised 10 cases of stable disease (SD), 11 partial responses (PR), and 1 progressive disease (PD) in patients with LGG, and 3 SD, 2

PR, and 3 PD in patients with HGG. Figure 2 displays the corresponding waterfall plot for patients with LGG and patients with HGG. The patient harboring a BRAF<sup>InsT</sup> alteration (PNOC-009) was diagnosed with a HGG (glioblastoma, not otherwise specified [NOS]) and had PFS and OS outcomes comparable with those of the other patients with HGG. Two patients with LGG had received MEK inhibitor therapy before enrollment. Their PFS and OS outcomes were comparable with those of the other patients with LGG.

At 1, 2, and 3 years, PFS for the entire cohort was 79.7% (95% CI, 66.5 to 95.6, n = 22), 63.0% (95% CI, 46.9 to 84.6, n = 12), and 56.0% (95% CI, 38.5 to 81.5, n = 6), respectively. For patients with HGG, the corresponding PFS rates were 62.5% (95% CI, 36.5 to 100.0, n = 4), 46.9% (95% CI, 21.5 to 100.0, n = 3), and 46.9% (95% CI, 21.5 to 100.0, n = 1). For patients with LGG, the rates were 86.1% (95% CI, 72.7 to 100.0, n = 18), 68.7% (95% CI, 50.5 to 93.5, n = 9), and 60.1% (95% CI, 40.1 to 90.1, n = 5), respectively. OS for the entire cohort was 100.0% (95% CI, 100.0 to 100.0%, n = 26), 100.0% (95% CI, 100.0 to 100.0, n = 16), and 90.9% (95% CI, 75.4 to 100.0, n = 8), respectively. In the HGG subgroup, OS was 100.0% (95% CI, 100.0 to 100.0, n = 6), 100.0% (95% CI, 100.0 to 100.0, n = 4), and 50.0% (95% CI, 12.5 to 100.0, n = 1), respectively. In the LGG subgroup, OS remained 100.0% at all three time points, with 20, 12, and 7 patients at risk, respectively.

### Tumor Growth Patterns

Individual tumor trajectories are shown in Figures 3A and 3B. Most LGG patients with an initial decrease remained below baseline, whereas patients with HGG showed either sustained reduction or continued progression.

We further evaluated growth trajectories across all measured lesions in patients with LGG, categorizing lesions as solid when they were entirely solid, and as cystic when they exhibited either wholly cystic or mixed solid-cystic characteristics. At baseline, cystic lesions on average had an estimated percent change (PC) that was 8.8 percentage points lower than noncystic lesions, but this difference was not statistically significant, indicating that baseline PC values were comparable between cystic and noncystic lesions ( $\beta = -8.76$ , SE = 5.57,  $t = -1.57$ ,  $P = .12$ ). A linear mixed-effects model with random intercepts for participant indicated a significant interaction between time (in days) and lesion type ( $P < .001$ ). In the noncystic lesion group (reference category), PC demonstrated a modest but statistically significant increase over time ( $\beta = .012$ , SE = 0.004,  $t = 3.24$ ,  $P = .0013$ ). By contrast, cystic lesions exhibited a significantly steeper decline in PC over time, as reflected by a negative interaction term ( $\beta = -0.038$ , SE = 0.006,  $t = -6.37$ ,  $P < .001$ , Fig 3C). In conclusion, lesion type significantly influenced longitudinal percentage-change trajectories, with noncystic lesions showing a small increase of approximately 0.01 percentage points per day while cystic lesions showed an overall decrease of approximately 0.03 percentage points per day. For HGG lesions, evaluating

**TABLE 1.** Baseline Characteristics of the Study Population

| Characteristic                           | No. | Overall, N = 30 <sup>a</sup> (%) | HGG<br>n = 8 <sup>a</sup> (%) | LGG<br>n = 22 <sup>a</sup> (%) | P <sup>b</sup> |
|------------------------------------------|-----|----------------------------------|-------------------------------|--------------------------------|----------------|
| Age                                      | 30  | 10.5 (3.0, 23.0)                 | 11.5 (5.0, 23.0)              | 8.5 (3.0, 19.0)                | .323           |
| Sex                                      | 30  |                                  |                               |                                | 1.000          |
| Female                                   |     | 12 (40)                          | 3 (38)                        | 9 (41)                         |                |
| Male                                     |     | 18 (60)                          | 5 (63)                        | 13 (59)                        |                |
| Tumor type                               | 30  |                                  |                               |                                | .000           |
| Anaplastic astrocytoma                   |     | 1 (3.3)                          | 1 (13)                        | 0 (0)                          |                |
| Astrocytoma, NOS                         |     | 2 (6.7)                          | 0 (0)                         | 2 (9.1)                        |                |
| Fibrillary astrocytoma                   |     | 1 (3.3)                          | 0 (0)                         | 1 (4.5)                        |                |
| Ganglioglioma                            |     | 5 (17)                           | 0 (0)                         | 5 (23)                         |                |
| Glioblastoma, NOS                        |     | 3 (10)                           | 3 (38)                        | 0 (0)                          |                |
| Glioma, malignant                        |     | 3 (10)                           | 3 (38)                        | 0 (0)                          |                |
| Low-grade astrocytoma NOS                |     | 1 (3.3)                          | 0 (0)                         | 1 (4.5)                        |                |
| Malignant neoplasm of brain, unspecified |     | 1 (3.3)                          | 1 (13)                        | 0 (0)                          |                |
| Pilocytic astrocytoma                    |     | 12 (40)                          | 0 (0)                         | 12 (55)                        |                |
| Pleomorphic xanthoastrocytoma            |     | 1 (3.3)                          | 0 (0)                         | 1 (4.5)                        |                |
| Tumor location                           | 30  |                                  |                               |                                | .350           |
| Posterior fossa                          |     | 6 (20)                           | 3 (38)                        | 3 (14)                         |                |
| Suprasellar/optic pathway                |     | 8 (27)                           | 1 (13)                        | 7 (32)                         |                |
| Supratentorial                           |     | 16 (53)                          | 4 (50)                        | 12 (55)                        |                |
| Number of lesions                        | 30  |                                  |                               |                                | .184           |
| 1                                        |     | 25 (83)                          | 7 (88)                        | 18 (82)                        |                |
| 2                                        |     | 4 (13)                           | 0 (0)                         | 4 (18)                         |                |
| 3                                        |     | 1 (3.3)                          | 1 (13)                        | 0 (0)                          |                |
| Cohort                                   | 30  |                                  |                               |                                | .014           |
| Expansion-crushed                        |     | 6 (20)                           | 4 (50)                        | 2 (9.1)                        |                |
| Expansion-efficacy                       |     | 15 (50)                          | 4 (50)                        | 11 (50)                        |                |
| Phase I                                  |     | 9 (30)                           | 0 (0)                         | 9 (41)                         |                |

Abbreviations: HGG, high-grade glioma; LGG, low-grade glioma; NOS, not otherwise specified.

<sup>a</sup>Median (range); No. (%).

<sup>b</sup>Wilcoxon rank sum test; Fisher's exact test.

growth trajectories with a mixed-effects model was not feasible due to sample size limitations.

## Rebound Rate

We further assessed the rate of tumor rebound after discontinuation of vemurafenib. Of 30 evaluable patients, 18 underwent post-treatment MRI, including 13 in the LGG cohort and 5 in the HGG cohort. In the LGG group, 3 of 13 patients (23%) met criteria for rebound, defined as a  $\geq 25\%$  increase in total lesion size within 6 months of treatment cessation (Fig 4A). These cases included two solid/cystic lesions and one solid lesion. Of the three patients who met rebound criteria, participant 001 (rebound at 97 days; low-grade astrocytoma, NOS) resumed vemurafenib 111 days after discontinuing study treatment and subsequently demonstrated a decrease in tumor size. Participant 003 (rebound at 78 days; pilocytic astrocytoma) received no anticancer therapy, and for participant 004 (rebound at 84 days; pilocytic astrocytoma), therapy information was

unavailable. Among the 10 LGG patients without rebound, three had solid lesions and seven had mixed solid/cystic lesions. In the HGG cohort, two of five patients (40%) crossed the 25% threshold, comprising one solid/cystic and one solid lesion (Fig 4B). However, this should be interpreted as evidence of progression rather than rebound, considering the generally aggressive course of HGGs. Notably, one patient (participant 030) returned below baseline within 6 months but received treatment with dabrafenib and trametinib when progression was noted during the first evaluation scan after stopping study treatment. Participant 029 did not receive any anticancer therapy. Of the three remaining HGG patients without progression, two had solid lesions and one had a mixed solid/cystic lesion.

## Adverse Events

Study drug-related grade 3 or higher AEs affecting the most patients included maculopapular rash affecting 17 patients (57%, 22 events). With adequate supportive care, the

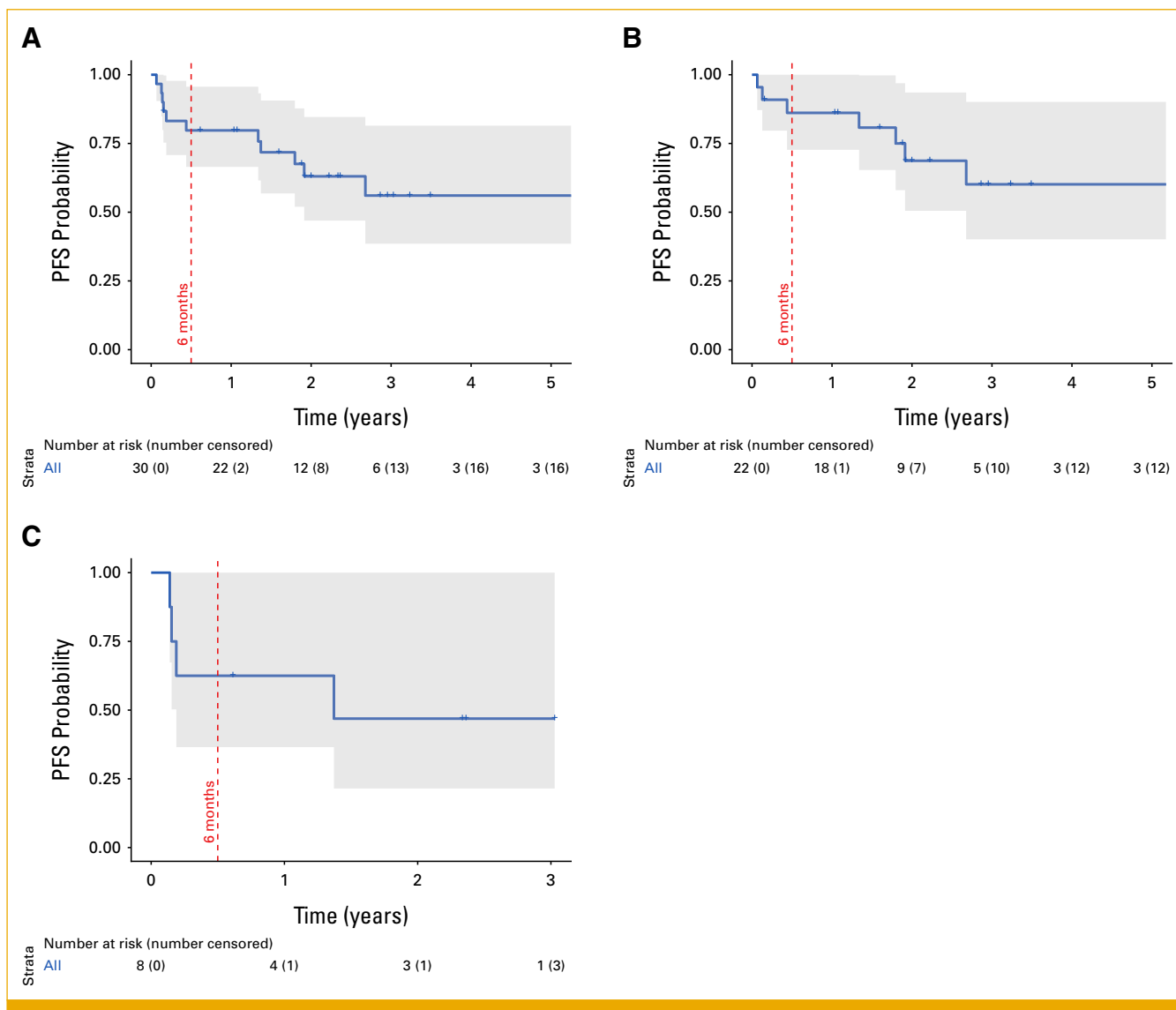


**FIG 1.** PFS Kaplan-Meier curves showing (A) the overall cohort, (B) the LGG cohort, and (C) the HGG cohort, with corresponding 6-month PFS (PFS6) rates. HGG, high-grade glioma; LGG, low-grade glioma; PFS, progression-free survival.

maculopapular rash resolved in 18 events across 14 patients. Fever affected three patients (10%, three events). Increased blood bilirubin and pruritus each affected two patients (6.7%), with five and three occurrences, respectively (Table 2). Of particular note was the absence of secondary squamous cell carcinoma (keratoacanthoma) in our expansion cohort, as well as the absence of any grade 4 toxicities. Of note, in our prior phase 1 study, squamous cell carcinoma was reported in one patient. The Data Supplement (Table S1) shows adverse events stratified by tumor group.

Other kinase inhibitors, including those targeting the EGFR family, have demonstrated correlations between the severity of drug-related toxicities, particularly cutaneous reactions, and clinical outcomes. In our study, we evaluated the relationship between the most frequently observed adverse events and patient outcomes in patients with LGG. No

statistically significant associations were observed for overall grade 3 toxicities or for grade 3 and grade 2 maculopapular rash. Among patients with HGG, the sample size was insufficient to permit robust statistical inference.

#### ctDNA

BRAF<sup>V600E</sup> was not detected in plasma ctDNA by droplet digital PCR.

#### DISCUSSION

We evaluated vemurafenib at the recommended phase 2 dose in pediatric patients with BRAF<sup>V600E</sup>- or BRAF<sup>InsT</sup>-mutant LGG and HGG. To our knowledge, this is the first prospective trial of vemurafenib in pediatric glioma. Previous evidence has been limited mainly to case reports and a prospective study with restricted accrual.<sup>21,22</sup>

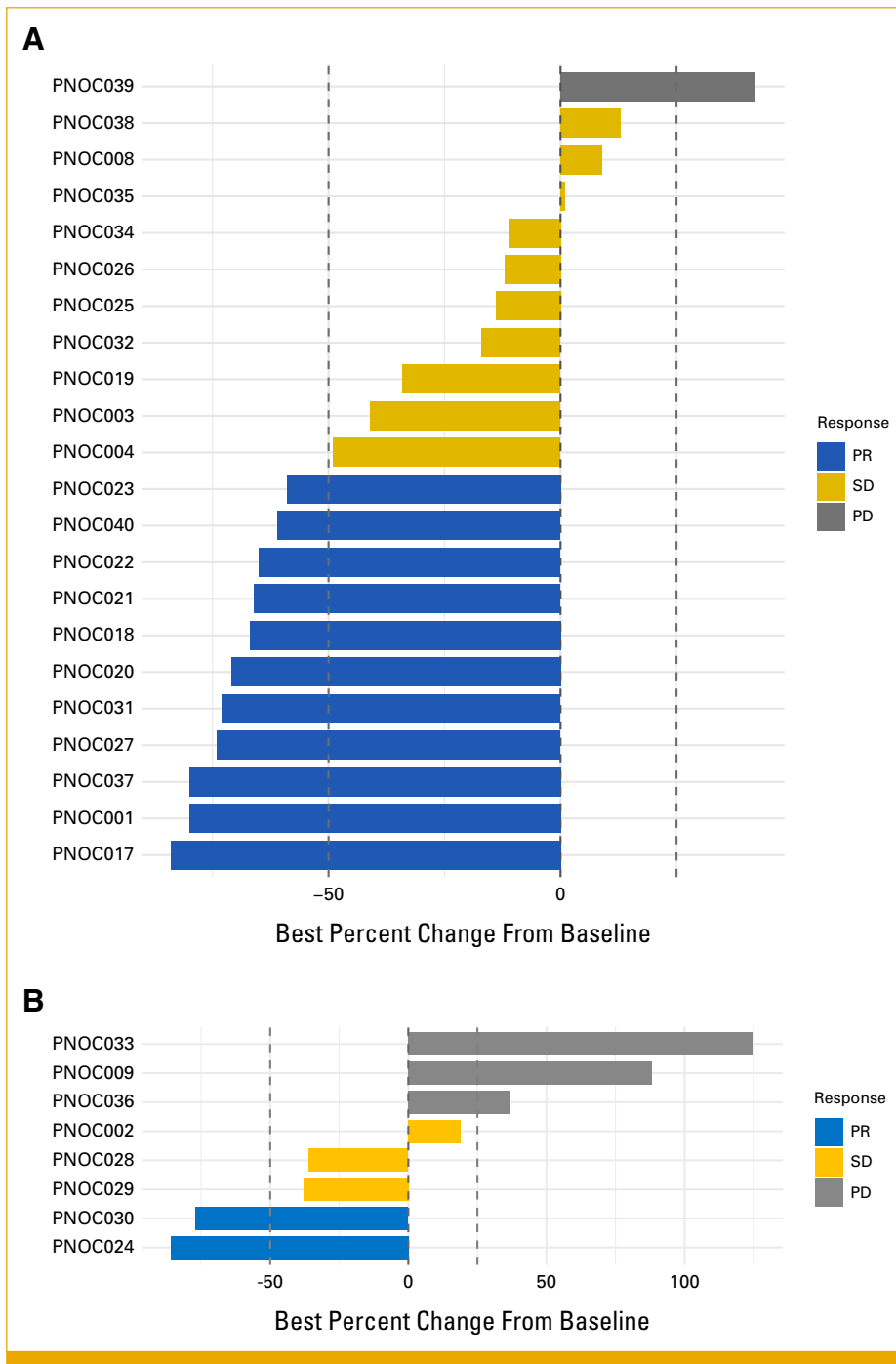


**FIG 2.** Waterfall plots showing the best PC in tumor size from baseline and corresponding responses in (A) LGG and (B) HGG cohorts. HGG, high-grade glioma; LGG, low-grade glioma; PC, percent change; PD, progressive disease; PR, partial responses; SD, stable disease.

Across the LGG cohort, vemurafenib achieved clinically meaningful disease control with a manageable safety profile, with most patients attaining stable disease or partial response, consistent with suppression of oncogenic MAPK signaling in BRAF-driven pediatric gliomas.<sup>11,14,23</sup> Outcomes were broadly similar to those reported with dabrafenib monotherapy in pediatric LGG, including comparable proportions of partial response and stable disease and a similar

1-year PFS rate.<sup>16</sup> In HGG, interpretation is limited by the small sample size and differences in study populations. Although response distributions and PFS estimates differed modestly from published dabrafenib data, cross-study comparisons are vulnerable to differences in histology, molecular context, prior therapy, disease burden, early censoring, and response assessment.<sup>15</sup> Overall, our results are consistent with prior pediatric CNS tumor experience

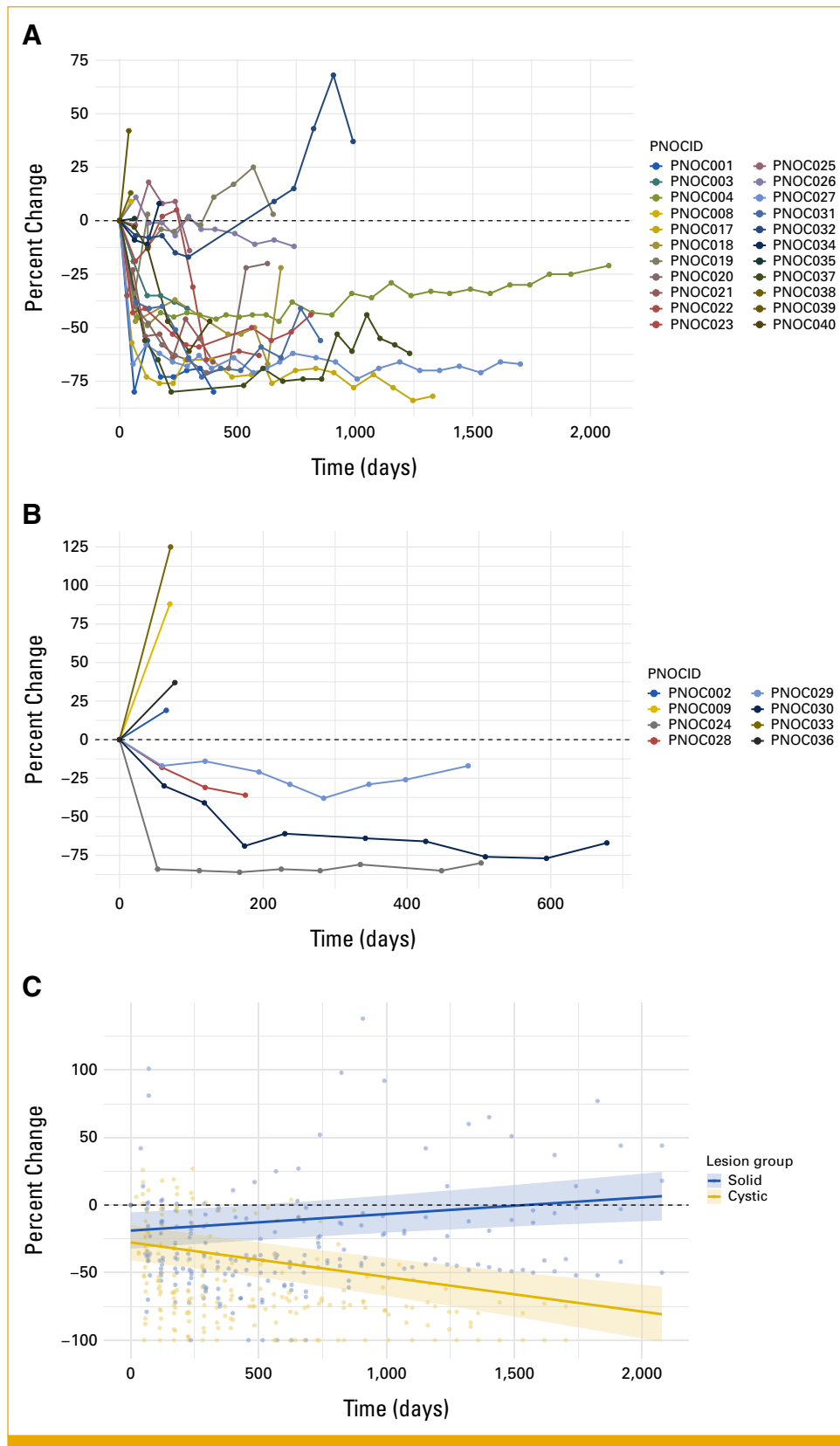


**FIG 3.** Longitudinal PC in tumor lesion size for (A) LGG, (B) HGG, and (C) visualization of the mixed-effects model depicting PC over time in solid and cystic lesions in patients with LGG. HGG, high-grade glioma; LGG, low-grade glioma; PC, percent change.

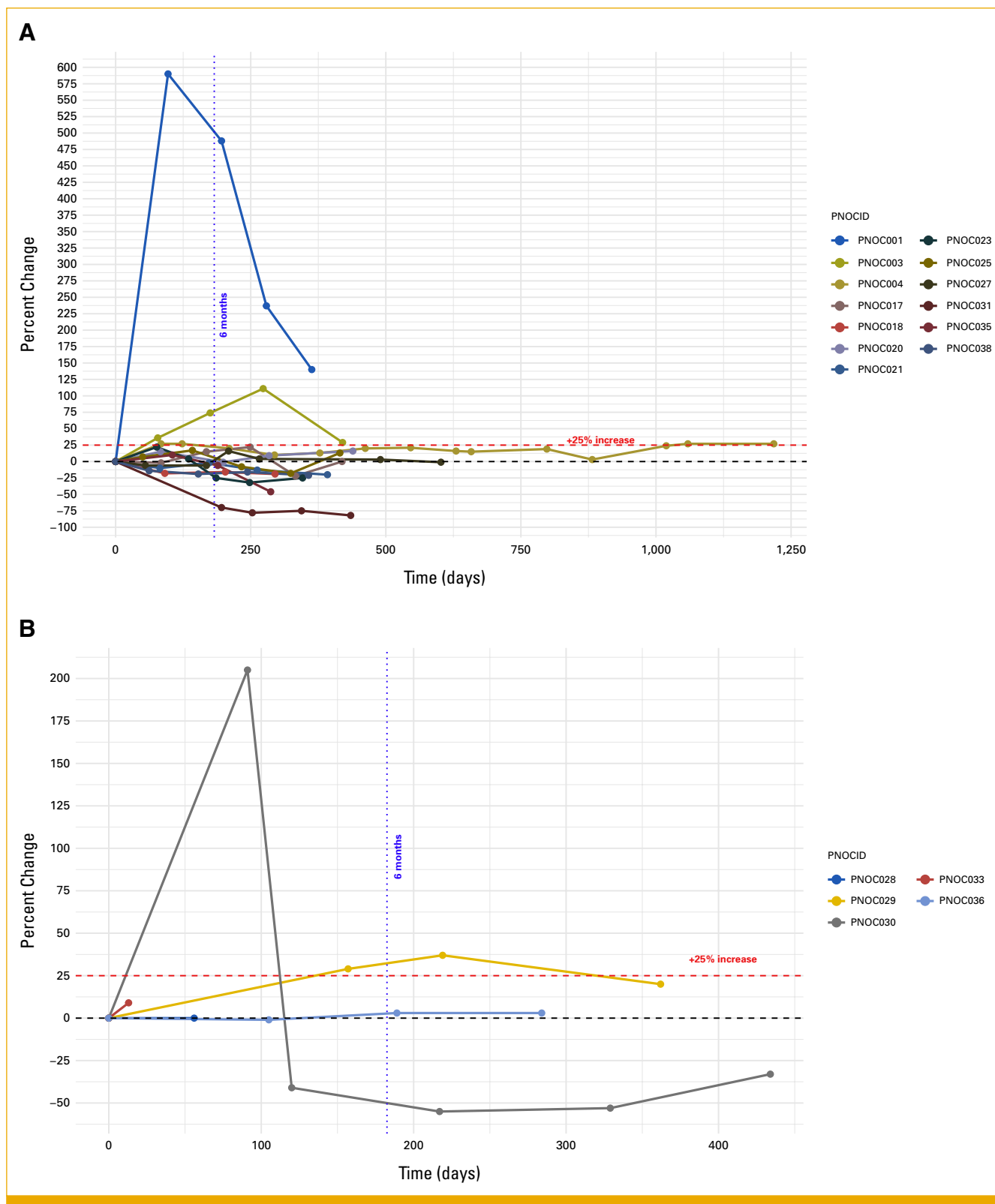


**FIG 4.** Longitudinal PC in tumor lesion size after treatment discontinuation, illustrating patients with rebound—defined as a  $\geq 25\%$  increase within 6 months of treatment stoppage—in (A) LGG and (B) HGG. HGG, high-grade glioma; LGG, low-grade glioma; PC, percent change.

showing that selective BRAF inhibition can produce objective responses and durable disease stabilization in recurrent or progressive BRAF<sup>V600E</sup>-mutant gliomas at tolerable doses.

Adequately powered randomized trials are required to determine comparative benefit. Within our study, the differing response patterns between LGG and HGG are biologically

**TABLE 2.** Adverse Events Grade  $\geq 3$  Related to Study Drug

| Toxicity Category                                    | Adverse Event Term                                                            | Worst Grade (CTCAE v4.0) | No. of Patients (%) | Events (No.) | Outcome Summary (%)                   |
|------------------------------------------------------|-------------------------------------------------------------------------------|--------------------------|---------------------|--------------|---------------------------------------|
| Blood and lymphatic system disorders                 | Anemia                                                                        | 3                        | 1 (3.3)             | 1            | Unresolved (100)                      |
| Eye disorders                                        | Eye disorders—Other<br>Corneal keratitis (n = 1)<br>Posterior uveitis (n = 1) | 3                        | 1 (3.3)             | 2            | Resolved (100)                        |
| General disorders and administration site conditions | Fever                                                                         | 3                        | 3 (10)              | 3            | Resolved (100)                        |
| Immune system disorders                              | Serum sickness                                                                | 3                        | 1 (3.3)             | 1            | Resolved (100)                        |
| Infections and infestations                          | Skin infection                                                                | 3                        | 1 (3.3)             | 1            | Unknown (100)                         |
| Investigations                                       | Alanine aminotransferase increased                                            | 3                        | 1 (3.3)             | 1            | Resolved (100)                        |
| Investigations                                       | Alkaline phosphatase increased                                                | 3                        | 1 (3.3)             | 1            | Resolved (100)                        |
| Investigations                                       | Blood bilirubin increased                                                     | 3                        | 2 (6.7)             | 5            | Resolved (100)                        |
| Investigations                                       | Lymphocyte count decreased                                                    | 3                        | 1 (3.3)             | 1            | Resolved (100)                        |
| Investigations                                       | White blood cell decreased                                                    | 3                        | 1 (3.3)             | 1            | Resolved (100)                        |
| Musculoskeletal and connective tissue disorders      | Arthralgia                                                                    | 3                        | 1 (3.3)             | 1            | Resolved (100)                        |
| Respiratory, thoracic, and mediastinal disorders     | Pneumonitis                                                                   | 3                        | 1 (3.3)             | 1            | Resolved (100)                        |
| Skin and subcutaneous tissue disorders               | Pruritus                                                                      | 3                        | 2 (6.7)             | 3            | Unresolved (100)                      |
| Skin and subcutaneous tissue disorders               | Rash acneiform                                                                | 3                        | 1 (3.3)             | 1            | Resolved (100)                        |
| Skin and subcutaneous tissue disorders               | Rash maculopapular                                                            | 3                        | 17 (56.7)           | 22           | Resolved (81.8);<br>unresolved (18.2) |
| Skin and subcutaneous tissue disorders               | Skin and subcutaneous tissue disorders—other<br>Keratosis pilaris             | 3                        | 1 (3.3)             | 1            | Unresolved (100)                      |

NOTE. Includes only grade  $\geq 3$  AEs considered related to study drug.

plausible and likely reflect a combination of intrinsic growth kinetics and tumor–microenvironment interactions as well as a higher likelihood of molecular heterogeneity and MAPK pathway reactivation in HGG, which can limit the depth and durability of benefit from single-agent BRAF blockade.<sup>24–26</sup>

Our longitudinal imaging analyses add nuance to response interpretation by showing that responses are associated with lesion type, with cystic lesions exhibiting larger and more sustained volumetric reductions than solid lesions over time. This pattern aligns with the possibility that changes in cystic disease are due to both antiproliferative effects and therapy-related changes in cyst fluid dynamics, such as production, resorption, and permeability. Meanwhile, solid components may be limited by residual viable cells and microenvironmental factors that lead to earlier response plateauing or incomplete response regression.<sup>27</sup> Nonetheless, these findings may also be confounded by histomolecular subtype and anatomic location. In addition, a predominantly solid imaging phenotype may function as a surrogate for less circumscribed, more infiltrative growth and/or deeper regions, and consequently a lower probability of achieving gross total resection. Clinically, these data support lesion-aware response assessment, and motivate incorporation of compartment-specific volumetrics into outcome evaluation and clinical trial correlatives.<sup>28</sup> Comparative analyses of cohorts treated with alternative BRAF inhibitors and other treatment modalities are additionally needed to establish the generalizability and potential clinical relevance of this observation.

To our knowledge, evidence of tumor rebound has been largely confined to case reports and preclinical studies.<sup>29,30</sup> To our knowledge, this prospective clinical trial is the first to systematically quantify rebound in pediatric LGG after treatment discontinuation, applying predefined standardized response/progression criteria and protocol-specified assessment intervals.<sup>20</sup> Previous studies have shown that MAPK inhibition and subsequent treatment discontinuation are associated with increased cytokine signaling and microglial recruitment, which may influence both therapeutic response during treatment and rebound growth after withdrawal.<sup>29</sup> In our pediatric LGG cohort, the rebound rate was 23%, underscoring the need for standardized, risk-adapted post-discontinuation surveillance and evidence-based strategies to anticipate, detect, and manage regrowth early. By applying uniform definitions rather than heterogeneous retrospective criteria, this work strengthens inference regarding rebound incidence and timing and facilitates clearer comparisons across molecular subgroups and treatment durations. In addition, framing rebound as a clinically meaningful trial end point is actionable because it can inform optimal treatment duration, guide surveillance intensity after cessation, and support rational sequencing of subsequent therapy (including escalation to combination or next-line MAPK-directed strategies) for patients at higher risk of regrowth. As this study was not designed to evaluate treatment discontinuation strategies, no conclusions can be drawn regarding the optimal timing or method of vemurafenib cessation, including whether gradual tapering is preferable to abrupt discontinuation. Future

prospective studies should systematically compare discontinuation approaches and assess their effects on rebound growth, progression, and long-term disease control.

The safety profile of vemurafenib at the RP2D was consistent with our phase 1 report and adult experience.<sup>18</sup> Common grade 3 adverse events included maculopapular rash, fever, increased blood bilirubin, and pruritus. Most were manageable with dose adjustments or supportive care. No grade 4 toxicities, secondary squamous cell carcinomas, or new safety signals occurred in the expansion cohort. Although BRAF<sup>V600E</sup> was not detected in blood-derived ctDNA, more sensitive contemporary approaches may improve the utility of liquid biomarkers in future glioma studies.<sup>31</sup>

For this study, several limitations warrant consideration. The overall sample size was modest, with particularly small numbers in the HGG subgroup, which may limit precision and generalizability. The open-label, single-arm design without a comparator introduces potential sources of bias. In addition, the duration of follow-up may be insufficient to fully characterize long-term outcomes and delayed or late-onset adverse events. Finally, the diagnosis of HGG was based on institutional pathologic assessment. In the absence of systematic documentation of molecular features such as *CDKN2A* homozygous deletion or *TP53* mutation, some tumors classified as HGG may have represented biologically lower-grade entities, including pleomorphic

xanthoastrocytoma. This diagnostic uncertainty should be considered when interpreting the subgroup findings.

The therapeutic landscape for BRAF V600–altered gliomas has increasingly shifted toward combined BRAF and MEK inhibition and newer RAF inhibitors designed to address dimer-dependent signaling and broaden activity beyond V600 monomer-driven disease.<sup>14,32</sup> Nevertheless, our results establish that single-agent vemurafenib can provide clinically meaningful activity with manageable toxicity in BRAF V600–dependent pediatric glioma. Vemurafenib may therefore remain relevant when combination therapy is not feasible or when a single-agent strategy is preferred to limit cumulative treatment burden. These findings also provide prospective evidence that BRAF<sup>V600E</sup> inhibition alone can produce durable radiographic stabilization in selected patients. Because this study did not directly compare vemurafenib with combined BRAF and MEK inhibition, the additional benefit of MEK inhibition cannot be determined. Prospective comparative studies are required to address this question.

In conclusion, vemurafenib demonstrated clinically meaningful disease control and manageable toxicity in pediatric BRAF-altered gliomas. Lesion-specific response patterns and the observed risk of rebound after treatment discontinuation support prospective evaluation of treatment duration, post-treatment surveillance, and sequencing of RAF-/MAPK-directed therapies.

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