Phase II Trial of Dabrafenib Plus Trametinib in Relapsed/Refractory *BRAF* V600–Mutant Pediatric High-Grade Glioma

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DOI https://doi.org/10.1200/JCO.23.00558

ABSTRACT

PURPOSE *BRAF* V600 mutation is detected in 5%-10% of pediatric high-grade gliomas (pHGGs), and effective treatments are limited. In previous trials, dabrafenib as monotherapy or in combination with trametinib demonstrated activity in children and adults with relapsed/refractory *BRAF* V600–mutant HGG.

METHODS This phase II study evaluated dabrafenib plus trametinib in patients with relapsed/refractory *BRAF* V600–mutant pHGG. The primary objective was overall response rate (ORR) by independent review by Response Assessment in Neuro-Oncology criteria. Secondary objectives included ORR by investigator determination, duration of response (DOR), progression-free survival, overall survival (OS), and safety.

RESULTS A total of 41 pediatric patients with previously treated *BRAF* V600–mutant HGG were enrolled. At primary analysis, median follow-up was 25.1 months, and 51% of patients remained on treatment. Sixteen of 20 discontinuations were due to progressive disease in this relapsed/refractory pHGG population. Independently assessed ORR was 56% (95% CI, 40 to 72). Median DOR was 22.2 months (95% CI, 7.6 months to not reached [NR]). Fourteen deaths were reported. Median OS was 32.8 months (95% CI, 19.2 months to NR). The most common all-cause adverse events (AEs) were pyrexia (51%), headache (34%), and dry skin (32%). Two patients (5%) had AEs (both rash) leading to discontinuation.

CONCLUSION In relapsed/refractory *BRAF* V600–mutant pHGG, dabrafenib plus trametinib improved ORR versus previous trials of chemotherapy in molecularly unselected patients with pHGG and was associated with durable responses and encouraging survival. These findings suggest that dabrafenib plus trametinib is a promising targeted therapy option for children and adolescents with relapsed/refractory *BRAF* V600–mutant HGG.

ACCOMPANYING CONTENT

Appendix

Protocol

Accepted June 28, 2023
Published August 29, 2023

J Clin Oncol 00:1-10

View Online Article

INTRODUCTION

Gliomas are the most common primary brain and CNS tumors, accounting for almost half of these tumors in children and adolescents.[1,2] Pediatric high-grade gliomas (pHGGs) account for approximately 10% of childhood CNS tumors and are a leading cause of childhood cancer-related death.[2] Maximal surgical resection followed by focal radiotherapy (patients age 3 years and older) and chemotherapy is the current standard for newly diagnosed pHGG.[3,4] Despite efforts to expand and improve treatment options, overall response rates (ORRs) are <20%,[5-9] and 2-year survival rates remain ≤35%.[2] Most patients develop recurrent disease, and limited data available in the relapsed/refractory setting show typical response rates of ≤12%.[5,6,10] There is no accepted standard of care for recurrent pHGG, and the multiagent chemotherapy regimens currently used are associated with burdensome toxicity and limited benefit.[11]

Recent advances in the molecular characterization of pHGG have led to refinements in diagnosis and classification and identified potential molecular targets for new therapeutic options.[12,13] The *BRAF* V600E mutation has been identified as a critical oncogenic driver in many cancer types, including colorectal cancer, melanoma, non–small-cell lung cancer (NSCLC), papillary thyroid carcinoma, and gliomas in adult and pediatric populations.[14-16] An estimated 5%-10% of pHGGs harbor the *BRAF* V600E mutation. The prognostic role of this mutation is unproven, but the mutation is

CONTEXT

Key Objective

What is the efficacy and safety of dabrafenib plus trametinib in pediatric patients with relapsed/refractory *BRAF* V600–mutant high-grade glioma?

Knowledge Generated

In a phase II study of 41 pediatric patients with relapsed/refractory *BRAF* V600–mutant high-grade glioma, dabrafenib plus trametinib was associated with an independently assessed overall response rate of 56%, with median duration of response of 22.2 months; although historical data in the *BRAF* V600–mutant population are limited, these results compare favorably with current approaches to relapsed/refractory pediatric high-grade glioma. Safety was consistent with the established profile of dabrafenib plus trametinib in adult patients.

Relevance *(S. Bhatia)*

Molecularly targeted therapy with dabrafenib plus trametinib appears promising for children and adolescents with relapsed/refractory *BRAF* V600–mutant high-grade glioma. However, long-term effects remain unknown.*

*Relevance section written by *JCO* Associate Editor Smita Bhatia, MD, MPH, FASCO.

seen predominantly in favorable histologic subtypes of pHGG.[17,18]

Dabrafenib is a BRAF inhibitor approved for treatment of adults with *BRAF* V600E–mutant melanoma,[19] and has demonstrated clinically meaningful activity as monotherapy in a phase I/II trial in relapsed/refractory *BRAF* V600–mutant pHGG.[20] Combination of dabrafenib with trametinib (a mitogen-activated protein kinase kinase [MEK] inhibitor) is well established in the treatment of *BRAF* V600–mutant melanoma, NSCLC, and anaplastic thyroid cancer in adults; more recently, dabrafenib plus trametinib was also approved for the tumor-agnostic treatment of patients age 6 years and older with *BRAF* V600E–mutant solid tumors that progressed after previous treatment, and patients age 1 year and older with *BRAF* V600E–mutant low-grade glioma (LGG) who require systemic therapy.[19,21]

This phase II trial combined two pediatric cohorts (HGG: single-arm in the relapsed/refractory setting; LGG: randomized comparison in the first-line setting) in a single study to evaluate the efficacy and safety of dabrafenib plus trametinib in pediatric patients with *BRAF* V600E–mutant gliomas. Here, we report the results from the pHGG cohort.

METHODS

Study Design and Patients

The pHGG cohort of this phase II trial (ClinicalTrials.gov identifier: NCT02684058) enrolled patients who are from age 1 year to younger than 18 years with Karnofsky/Lansky performance status ≥50%. All had disease relapse or progression or lack of response to first-line therapy (presumed to include optimal surgical approach, with radiation and/or chemotherapy); locally determined *BRAF* V600–mutant HGG (2016 WHO classification system)[22]; and centrally confirmed measurable disease per Response Assessment in Neuro-Oncology (RANO) criteria. *BRAF* V600 mutation was assessed locally by validated tissue-based test (molecular-based strongly preferred where available), or at a sponsor-selected central reference laboratory if local testing was unavailable; samples were provided for central confirmation. Key exclusion criteria included pHGG without a *BRAF* V600 mutation; previous treatment with dabrafenib or another RAF inhibitor, trametinib or another MEK inhibitor, or extracellular signal-regulated kinase inhibitors; neurofibromatosis type 1 diagnosis; or known *RAS* mutation.

The study Protocol (online only) and all amendments were approved by the appropriate ethics committee at each participating site. This trial was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guideline and the principles of the Declaration of Helsinki. Written informed consent was obtained from each patient or their parent or legal guardian.

Treatment

Patients received dabrafenib orally divided into two equal doses per day (5.25 mg/kg/d for patients younger than 12 years; 4.5 mg/kg/d for patients age 12 years and older), plus trametinib orally once daily (0.032 mg/kg/d for patients younger than 6 years; 0.025 mg/kg/d for patients age 6 years and older). These pediatric dosages were based on the established exposure-response relationship in adult patients and on tolerability and exposure information obtained in two previous phase I/II studies in pediatric patients.[23,24] Dabrafenib was

available as capsules and as dispersible tablets for oral suspension, and trametinib was available as tablets and a powder for oral solution.

Patients were permitted to continue study treatment until loss of clinical benefit as determined by investigator, unacceptable toxicity, start of new anticancer therapy, discontinuation at investigator or patient/guardian discretion, loss to follow-up, or death. Patients with disease progression by RANO criteria were allowed to continue study treatment if the investigator determined that the patient was likely to have a favorable benefit-risk balance from continued treatment.

Assessments

Tumor assessments by magnetic resonance imaging were performed following a specific imaging protocol to include T1-weighted postgadolinium and T2 fluid-attenuated inversion recovery acquisition sequences. Scans were conducted at screening (≤28 days before initiation of study treatment), every 8 weeks for the first 56 weeks, every 16 weeks thereafter while on treatment and during post-treatment follow-up, and at any time there was suspicion of disease progression. Patients who discontinued treatment without documented disease progression (or death) per RANO criteria continued tumor assessment as part of post-treatment follow-up. All scans were submitted to a central imaging center. Partial and complete responses (CRs) were confirmed by repeat assessments ≥4 weeks after the criteria for response were first met. Unless otherwise specified, all responses presented were confirmed over time, as assessed by independent review using RANO criteria.[25] Clinical data necessary for RANO response determination (ie, steroid usage, clinical/neurologic status) were provided to the central imaging center after the initial response had been determined exclusively by radiologic criteria and were then incorporated into the RANO response determination.

Adverse events (AEs) were assessed and graded according to the Common Terminology Criteria for Adverse Events, version 4.03.

End Points

The primary end point was ORR (defined as the proportion of patients with a best overall response [BOR] of confirmed CR or partial response [PR]) by independent assessment per RANO criteria. Secondary end points included ORR by investigator assessment, duration of response (DOR), progression-free survival (PFS), time to response, clinical benefit rate (CBR; defined as the proportion of patients with a BOR of CR or PR or an overall lesion response of stable disease lasting for ≥24 weeks), overall survival (OS), and safety.

Statistical Analysis

Efficacy and safety were assessed in the as-treated population (all patients who received at least one dose of therapy). An interim analysis was planned for when the initial 16 patients all had ≥20 weeks of follow-up or withdrew early. An ORR of ≤25% by independent assessment would prompt consideration to terminate the study. The study continued after the interim analysis, and the primary analysis was planned for 32 weeks after the last patient was enrolled, a time at which all patients had an opportunity to undergo four tumor response assessments. On the basis of a hypothesized response rate of 35%, the lower bound of the 95% CI would exclude 20% (which is greater than the response rate previously reported with current standard-of-care agents in molecularly unselected patients) with a sample size of 40 patients.[5-9] The exact 95% CI for the ORR was determined by Clopper and Pearson methodology. Descriptive statistics were used to summarize ORR and CBR. The Kaplan-Meier method was used to estimate DOR, PFS, time to response, and OS.

RESULTS

Patients and Treatment

From December 28, 2017, through August 17, 2020, a total of 41 patients with *BRAF*-mutated pHGG were enrolled from 28 sites in 13 countries (Appendix Table A1, online only). Baseline characteristics are summarized in Table 1. Median age was 13 years (range, 2.0-17.0 years), median time since diagnosis was 17.4 months, all patients had previous therapy, and 48.8% had grade 4 disease by WHO 2016 criteria[22] at initial diagnosis per investigator assessment. Central histological determinations were reported by investigators following WHO 2016 criteria, which were the criteria available at the time of diagnosis; most common histologies were glioblastoma multiforme (n = 13), anaplastic pleomorphic xanthoastrocytoma (n = 6), HGG not otherwise specified (n = 4), pleomorphic xanthoastrocytoma (n = 4), and anaplastic astrocytoma (n = 3). Of the 35 patients with available molecular data, 23 (65.7%) had homozygous deletion of *CDKN2A/B*, 3 (8.6%) had histone H3K27M mutations, and 6 (17.1%) had *TP53* alterations.

At data cutoff (August 23, 2021), median follow-up was 25.1 months. Treatment was discontinued in 20 patients (48.8%); the primary reason was reported as progressive disease in 16 patients (39.0%, including one patient with an AE of rash that also contributed to discontinuation), AE in one (2.4%), physician decision in one (2.4%), and death in two (4.9%, both due to serious AEs that were not treatment related per investigators; Appendix Table A2, online only). Of the 21 patients (51.2%) who remained on treatment, 19 (46.3%) did not have investigator-assessed progressive disease per RANO criteria, and two (4.9%) were treated beyond progression. Median treatment duration was 16.7 months (range, 0.3-39.6 months; Appendix Table A2). Dose interruptions/reductions occurred with dabrafenib in 29 patients (70.7%) and trametinib in 30 (73.2%; Appendix Table A3, online only).

TABLE 1. Baseline Characteristics

Category	N = 41, No. (%)
Age, years, median (range)	13.0 (2.0-17.0)
12 months to <6 years	5 (12.2)
6 to <12 years	10 (24.4)
12 to <18 years	26 (63.4)
Female	23 (56.1)
Race	
White	25 (61.0)
Asian	11 (26.8)
Black or African American	1 (2.4)
Not reported	1 (2.4)
Unknown	3 (7.3)
Ethnicity	
Not Hispanic or Latino	26 (63.4)
Hispanic or Latino	5 (12.2)
Not reported	7 (17.1)
Unknown	3 (7.3)
Weight, kg, median (range)	44.9 (11.3-155.6)
Height, cm, median (range)	156.15 (81.0-181.5)
BMI, kg/m^2, median (range)	18.34 (10.4-48.8)
Karnofsky/Lansky performance status[a]	
100	15 (36.6)
90	13 (31.7)
80	7 (17.1)
70	1 (2.4)
<70	5 (12.2)
Previous therapy	41 (100)
Surgery[b]	40 (97.6)
Radiotherapy	37 (90.2)
Antineoplastic therapy	33 (80.5)
Time since last radiotherapy, months	
1 to <3	1 (2.4)
3 to <6	9 (22.0)
6 to <12	9 (22.0)
≥12	18 (43.9)
Time since diagnosis, months, median (range)	17.4 (2.7-174.3)
Histologic grade at initial diagnosis[c,d]	
I	3 (7.3)
II	4 (9.8)
III	13 (31.7)
IV	20 (48.8)
Missing	1 (2.4)
Histology at initial diagnosis[c,d]	
Anaplastic astrocytoma	3 (7.3)
Anaplastic ganglioglioma	2 (4.9)
Anaplastic pilocytic astrocytoma	1 (2.4)
Anaplastic pleomorphic xanthoastrocytoma	6 (14.6)
Diffuse midline glioma (H3K27M-mutated)	2 (4.9)
Diffuse midline glioma, NOS	1 (2.4)
Epithelioid glioblastoma multiforme	1 (2.4)
Ganglioglioma	1 (2.4)
Glioblastoma multiforme	13 (31.7)
HGG, NOS	4 (9.8)
LGG, NOS	1 (2.4)
Oligodendroglioma	1 (2.4)
Pleomorphic xanthoastrocytoma	4 (9.8)
Unknown	1 (2.4)
Central molecular profile, genetic aberration/evaluable patients, No. (%)[e,f]	
CDKN2A/B homozygous deletion	23/35 (65.7)
Histone H3 mutation	3/35 (8.6)
TP53 mutation/deletion	6/35 (17.1)
BRAF V600E mutation[g]	41 (100)

(continued in next column)

Abbreviations: HGG, high-grade glioma; LGG, low-grade glioma; NOS, not otherwise specified.
[a]Karnofsky performance status was used for patients age 16 years and older, and Lansky performance status was used for patients age younger than 16 years.
[b]Data on previous surgery were missing for one patient.
[c]Histologic data were investigator determined at initial diagnosis and may not necessarily reflect histology at study entry.
[d]Per WHO 2016 classification.[22]
[e]Samples from six patients had insufficient tumor content for molecular profiling.
[f]Patients may appear in more than one molecular profile category.
[g]Local *BRAF* status is presented when available; five patients were enrolled on the basis of central *BRAF* status.

Efficacy

The primary objective was met with an ORR (CR + PR) by independent review per RANO criteria of 56.1% (95% CI, 39.7 to 71.5; Fig 1A). There were 12 confirmed CRs (29.3%) and 11 PRs (26.8%). Efficacy was further evidenced by reduction of target lesion measurements irrespective of BOR; approximately 90% of patients had 50% reduction, and approximately half the patients had 100% reduction in target lesions from baseline to on-therapy evaluations. Results per investigator assessment were consistent with the independent review. Most responses occurred within 4 months by independent assessment (Fig 2A). After 1 year or at last assessment, most patients continued to have a reduction in tumor size compared with baseline per independent review (Fig 1B).

Independently reviewed responses using RANO criteria were observed across most histologic subtypes and molecular profiles, including in patients with H3K27M (1 of 3) and CDKN2A/B (13 of 23) mutations (Appendix Table A4, online only). The CBR (CR + PR + stable disease ≥24 weeks) by independent review was 65.9% (95% CI, 49.4 to 79.9). In the 23 responders who had CRs or PRs by independent review, median DOR was 22.2 months (95% CI, 7.6 months to not reached [NR]; Fig 2B). Kaplan-Meier estimates of DOR at 6 and 12 months were 84.7%

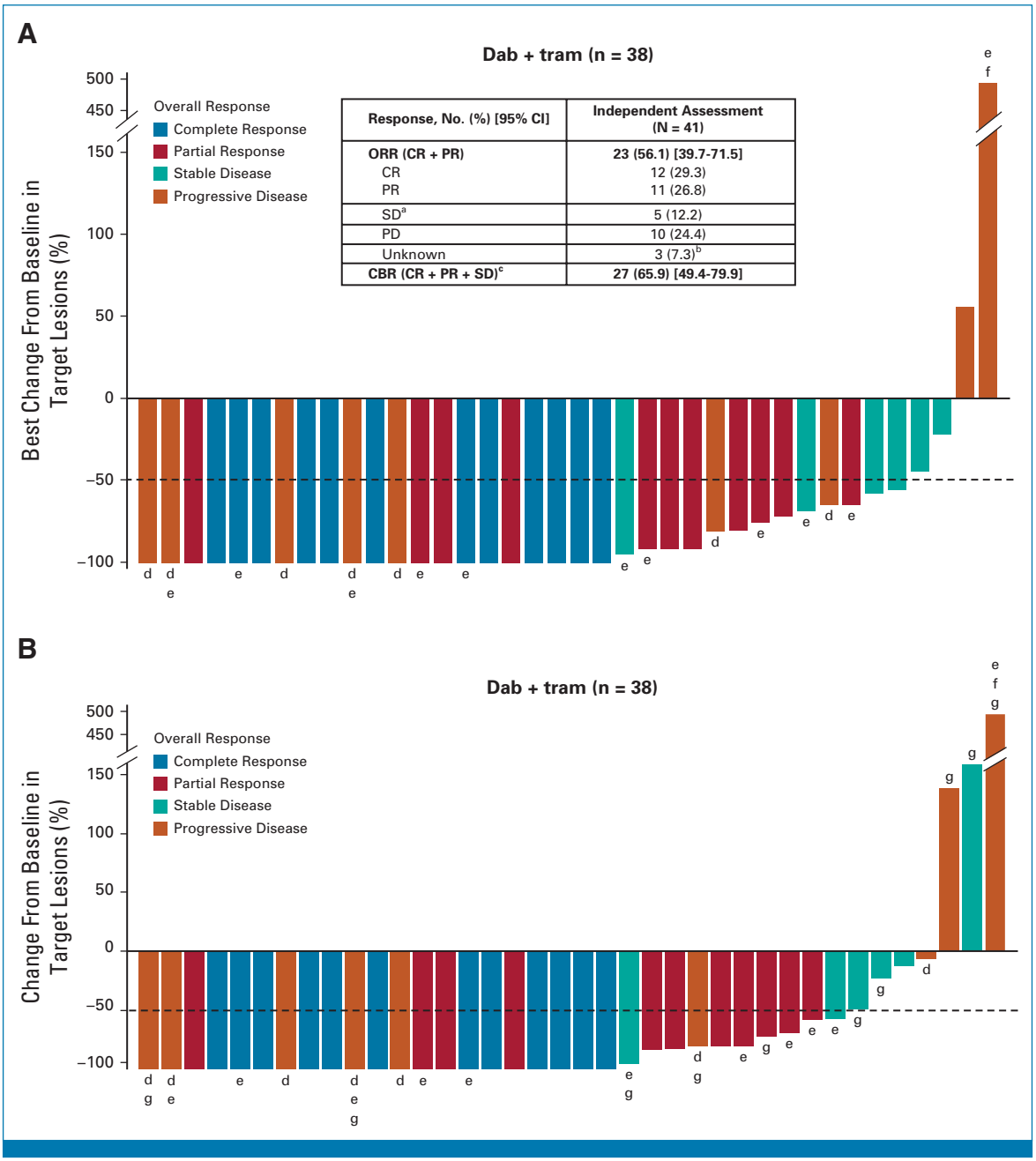

FIG 1. (A) Best change from baseline in tumor measurement (independent review per RANO criteria). (B) Percent changes from baseline in tumor measurements at 1 year/last assessment (independent review per RANO criteria; full analysis set). Patients for whom the percent change of target lesions was not available or for whom the BOR was unknown were excluded from the analysis. If the change in tumor size at 1 year/last visit before day 322 was not confirmed by a repeat scan, the BOR may not be consistent with the percent change from baseline. Only patients with measurable disease at baseline were included. Waterfall plots are based on radiographic response per RANO criteria, without consideration of clinical status or corticosteroid use. One patient with a BOR of PD had a radiographic response of SD. [a]SD for ≥16 weeks is recorded at ≥15 weeks (ie, ≥105 days) from treatment start date. [b]One patient did not have a valid postbaseline assessment and two had SD and/or unconfirmed CR/PR only occurring before week 16. [c]SD for ≥24 weeks is recorded at ≥23 weeks (ie, ≥161 days) from treatment start date. [d]Percent change in target lesion contradicted by overall lesion response of PD. [e]Patients not in the evaluable set. The evaluable set, used for sensitivity analyses, comprised all patients in the as-treated population with centrally confirmed HGG through histology, centrally confirmed positive *BRAF* V600 mutation status, adequate tumor assessment at baseline, and a follow-up tumor assessment ≥8 weeks after starting treatment (unless disease progression was observed before that time) or had discontinued for any reason. [f]Percent change is 491.43. [g]Patient did not have an assessment at 1 year (defined as day 322-399), and their last visit before day 322 is presented in the figure. BOR, best overall response; CBR, clinical benefit rate; CR, complete response; dab, dabrafenib; HGG, high-grade glioma; ORR, overall response rate; PD, progressive disease; PR, partial response; RANO, Response Assessment in Neuro-Oncology; SD, stable disease; tram, trametinib.

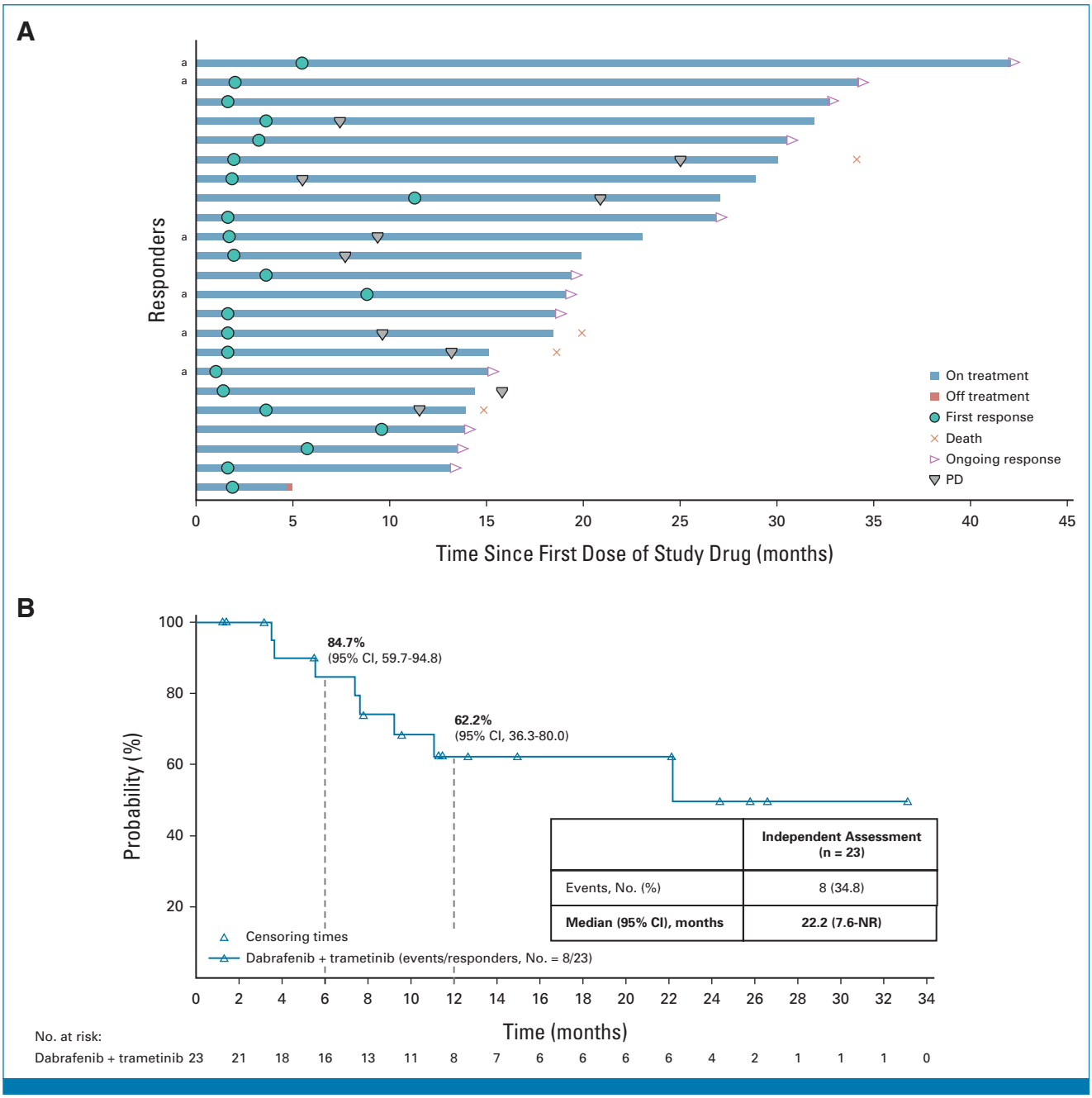

FIG 2. (A) Time to onset of response by independent assessment. Only the first occurrence of each response (CR, PR) and/or PD are displayed. (B) Duration of response by independent assessment. Off treatment indicates one patient who discontinued treatment due to an adverse event but remained in follow-up for tumor assessment until data cutoff. All other patients either discontinued treatment due to progressive disease or death, or remained on treatment until data cutoff. [a]Patients not in the evaluable set. The evaluable set, used for sensitivity analyses, comprised all patients in the as-treated population with centrally confirmed HGG through histology, centrally confirmed positive *BRAF* V600 mutation status, adequate tumor assessment at baseline, and a follow-up tumor assessment ≥8 weeks after starting treatment (unless disease progression was observed before that time) or had discontinued for any reason. CR, complete response; HGG, high-grade glioma; NR, not reached; PD, progressive disease; PR, partial response.

and 62.2%, respectively. Response results were similar when assessed by investigators (Appendix Table A5, online only).

At the time of data cutoff, 24 patients (58.5%) had a PFS event by independent review, including 21 (51.2%) with disease progression and three (7.3%) who died before documented disease progression (one due to HGG and two due to serious AEs that were not treatment-related per investigators; Fig 3). Median PFS was 9.0 months (95% CI, 5.3 to 24.0 months); 6- and 12-month Kaplan-Meier PFS rate estimates were 66.8% and 44.1%, respectively. By investigator assessment, 20 patients

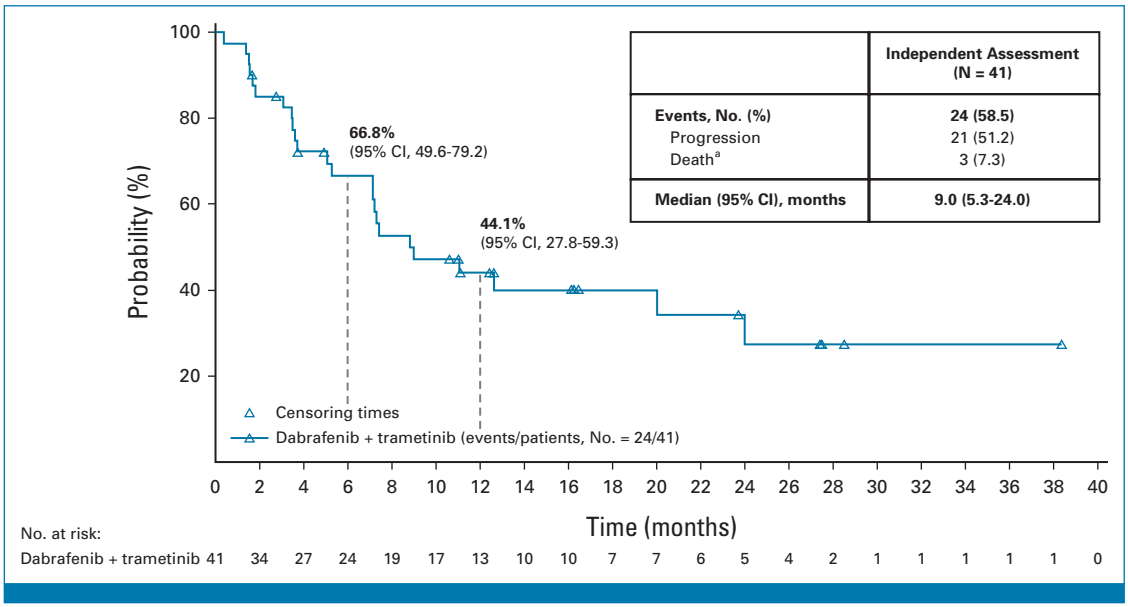

FIG 3. Progression-free survival by independent assessment. [a]Only includes patients who died without known disease progression.

(48.8%) had a PFS event, and median PFS was 17.1 months (95% CI, 12.5 months to NR; Appendix Table A6, online only).

There were 14 deaths (34.1%); 12 were due to HGG and two were due to serious AEs that were not treatment-related per investigators (encephalomyelitis and intracranial pressure increased [1 patient each]; Table 2). OS data were immature at the time of the analysis; median OS was 32.8 months (95% CI, 19.2 months to NR), and estimated 12- and 24-month Kaplan-Meier OS rates were 76.3% (95% CI, 59.3 to 86.9) and 58.6% (95% CI, 37.6 to 74.7), respectively.

Safety

All 41 patients experienced at least one AE, and 28 patients (68.3%) experienced an AE of grade ≥3 (Table 3). The most common AEs of any grade and cause were pyrexia (n = 21; 51.2%), headache (n = 14; 34.1%), dry skin (n = 13; 31.7%), vomiting (n = 12; 29.3%), and diarrhea (n = 10; 24.4%). AEs leading to dose reduction or interruption occurred in 26 (63.4%) patients, of which 14 (34.1%) were grade ≥3; two patients discontinued treatment due to AEs (both rash), and immediate rebound progression occurred in one of these patients. A serious AE of any grade and grade ≥3 occurred in 25 (61.0%) and 22 (53.7%) patients, respectively (Appendix Table A7, online only). The most common serious AEs were headache (n = 3; 7.3%) and pyrexia (n = 3; 7.3%). Notably, the incidences of serious AEs affecting the heart, eyes, and bone were infrequent.

Treatment-related AEs of any grade and grade ≥3 were reported in 34 (82.9%) and 11 (26.8%) patients, respectively; seven patients (17.1%) experienced serious treatment-related AEs (Table 3). Three fatal serious AEs occurred: apnea, encephalomyelitis, and intracranial pressure increased (n = 1 each), none of which were treatment-related. For the patient with apnea, the primary reason for death was reported by the investigator as HGG.

DISCUSSION

In this phase II trial in patients with relapsed/refractory *BRAF* V600–mutant pHGG (which represents ≈5%-10% of pHGGs),[17,18] dabrafenib plus trametinib demonstrated tolerable safety and frequent and durable responses that were superior to those in molecularly unselected historical cohorts treated with traditional chemotherapy. Specifically, the primary end point, ORR (CR + PR) by independent assessment per RANO criteria, was substantially higher in this study than in previous studies (56.1% *v* <20%),[5-9] and many responses were prolonged (median, 22.2 months). To our knowledge, there are no reports on recurrent pHGG

TABLE 2. Overall Survival

Overall Survival	N = 41
Months, median (95% CI)	32.8 (19.2 to NR)
12-month rate (95% CI), %	76.3 (59.3 to 86.9)
24-month rate (95% CI), %	58.6 (37.6 to 74.7)
Deaths, No. (%)	14 (34.1)
Study indication	12 (29.3)
Other	2 (4.9)

Abbreviation: NR, not reached.

TABLE 3. AEs (safety analysis set)

Category	N = 41, No. (%)		
	Any Grade	Grade ≥3	Death
Any AE	41 (100)	28 (68.3)	3 (7.3)
Treatment-related	34 (82.9)	11 (26.8)	0
AEs leading to discontinuation	2 (4.9)[a]	0	0
Treatment-related	1 (2.4)	0	0
AEs leading to dose reduction/interruption	26 (63.4)	14 (34.1)	2 (4.9)
AEs requiring additional therapy	39 (95.1)	23 (56.1)	1 (2.4)
Serious AEs	25 (61.0)	22 (53.7)	3 (7.3)
Treatment-related	7 (17.1)	6 (14.6)	0
Fatal	3 (7.3)	3 (7.3)	3 (7.3)
Treatment-related	0	0	0
Occurred in ≥12% of patients			
Any	41 (100)	28 (68.3)	0
Pyrexia	21 (51.2)	1 (2.4)	0
Headache	14 (34.1)	4 (9.8)	0
Dry skin	13 (31.7)	0	0
Vomiting	12 (29.3)	2 (4.9)	0
Diarrhea	10 (24.4)	1 (2.4)	0
Rash	9 (22.0)	1 (2.4)	0
Nausea	8 (19.5)	0	0
Cough	7 (17.1)	0	0
Upper respiratory tract infection	7 (17.1)	0	0
Epistaxis	6 (14.6)	0	0
Fatigue	6 (14.6)	0	0
Neutropenia	6 (14.6)	1 (2.4)	0
Rash maculopapular	6 (14.6)	0	0
Abdominal pain	5 (12.2)	0	0
Constipation	5 (12.2)	0	0
Erythema	5 (12.2)	0	0
Oropharyngeal pain	5 (12.2)	0	0
Weight increased	5 (12.2)	0	0
WBC count decreased	5 (12.2)	1 (2.4)	0

Abbreviation: AE, adverse event.
[a]Both patients discontinued treatment due to rash.

specifically in patients with *BRAF* V600 mutations. However, this current study showed encouraging PFS and OS results compared with results from a meta-analysis including studies in recurrent molecularly unselected pHGG treated with chemotherapy, targeted therapy, immunotherapy, or radiotherapy; median PFS was 9.0 months in this current study versus 3.5 months in the meta-analysis, and median OS was 32.8 versus 5.6 months, respectively.[26]

In a phase I/II study (ClinicalTrials.gov identifier: NCT01677741), dabrafenib monotherapy demonstrated meaningful clinical efficacy in refractory, recurrent, or progressive *BRAF* V600–mutant pHGG.[20] Although dabrafenib improved outcomes as monotherapy, this current study indirectly shows that dabrafenib plus trametinib yields a numerically higher independently determined overall response (56% *v* 45%), including CRs (29% *v* 10%), than dabrafenib alone.[20] However, these cross-trial comparisons should be interpreted with caution in the absence of randomized trial data. In other disease states in which BRAF plus MEK inhibitors are well established, such as melanoma, combination therapy is used almost exclusively versus monotherapy due in part to delayed emergence of acquired resistance mutations in other MAPK pathway components.[27-30] We report that even with combination BRAF plus MEK inhibition, pHGG can progress after initial responses; although presumably this is a consequence of acquired resistance similar to that observed in other *BRAF* V600–mutant cancers, biomarker samples from the time of progression were insufficient to confirm this mechanism. Notably, RANO criteria for progressive disease are sensitive to increases over previous nadir measurements, which may not reflect a sustained progression of disease, and in our study, some patients continued treatment beyond the time of independently determined progressive disease/before investigator determined progression and continued to derive clinical benefit.

Homozygous *CDKN2A/B* deletion has been identified as a favorable prognostic factor in pHGG[31]; in the few patients with molecular data available in this current study, those with and without this deletion responded. Additionally, patients with H3-mutant pHGG generally have worse prognosis than those with wild-type disease[32]; one of the three patients with known H3-mutant pHGG enrolled in this study had a confirmed BOR of PR by independent review. By contrast, tumors harboring the *BRAF* V600E mutation typically have characteristics similar to those of pleomorphic xanthoastrocytoma and LGG, and are associated with better prognosis at the time of initial diagnosis than *BRAF* V600 wild-type pHGG.[31] It is unclear if the improved prognosis in this molecular subtype of pHGG would also be observed in the relapsed/refractory setting. The prolonged median DOR of 22.2 months and improved ORR and survival observed in this study appear favorable versus historical results in the relapsed/refractory setting; however, comparisons should be taken cautiously as data specifically in the *BRAF* V600E–mutant relapsed/refractory population are lacking.

Overall, the safety profile was manageable, with two patients discontinuing therapy due to an AE. The most frequently observed toxicities were pyrexia and headache, similar to those identified from the larger studies in adults with melanoma and NSCLC,[33,34] as well as those seen with dabrafenib monotherapy in pediatric patients.[20] Although the safety profiles of historical comparator cytotoxic regimens in pHGG vary, toxicity is generally considered a barrier to the high-dose chemotherapies typically used for relapsed/refractory disease.[35] Thus, targeted therapy may offer improved tolerability, at least in the short term, although potential long-term effects are not addressed by this study. Dabrafenib, trametinib, and the combination are being studied in an ongoing follow-up and rollover study (ClinicalTrials.gov identifier: NCT03975829) in pediatric patients, which will provide further insights.[36]

Recent advances in understanding pHGG molecular drivers, development of agents specifically targeting these oncogenic drivers, and expanded use of tumor molecular profiling allow for more selective and optimal therapies for molecularly selected subpopulations. Results from the ongoing Children's Oncology Group nonrandomized phase II trial (ACNS1723; ClinicalTrials.gov identifier: NCT03919071) evaluating the efficacy of dabrafenib plus trametinib after radiotherapy for treatment of pediatric patients with newly diagnosed *BRAF* V600–mutant pHGG are awaited.[37] A retrospective review of outcomes in pediatric patients with newly diagnosed *BRAF* V600–mutant pHGG who were treated with BRAF inhibitors with or without MEK inhibitors suggests improved outcomes over those seen with chemotherapy.[38]

Limitations of this study include the single-arm design with comparison to historical data from molecularly unselected pHGG cohorts, study inclusion on the basis of the 2016 WHO classification system versus the latest 2021 version, and limited specimens suitable for additional central molecular profiling. Nevertheless, the data presented here suggest that treatment with dabrafenib plus trametinib in relapsed or refractory *BRAF* V600–mutant pHGG resulted in improved efficacy, with a higher ORR and prolonged survival, and a manageable safety profile relative to historical expectations on the basis of molecularly unselected cohorts. The acceptability of this therapy to the patient, family, and treating medical team is evidenced by the long median treatment duration (16.7 months) and only two patients discontinuing therapy due to an AE. Furthermore, these results are particularly striking, given the diversity of histologic and molecular features represented in the studied population. These results support a critical role for targeted therapy in the management of pediatric gliomas and highlight the importance of performing molecular profiling in these patients at diagnosis. Considering the historically poor outcomes for pediatric patients with *BRAF* V600–mutant HGG, dabrafenib plus trametinib may be a promising therapeutic option in these patients for whom effective therapies are limited.

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DISCLAIMER

The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR, or the Department of Health.

PRIOR PRESENTATION

Presented in part at the 2022 ASCO Annual Meeting, Chicago, IL, June 3-7, 2022.

SUPPORT

Supported by Novartis Pharmaceuticals Corporation. Additionally, D.R.H. is supported by funding from the NIHR Great Ormond Street Hospital Biomedical Research Centre.

CLINICAL TRIAL INFORMATION

NCT02684058

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.23.00558.

DATA SHARING STATEMENT

Novartis is committed to sharing with qualified external researchers, access to patient-level data, and supporting clinical documents from eligible studies. Requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided are anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. This trial data availability is according to the criteria and process described on ClinicalStudyDataRequest.com.

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ACKNOWLEDGMENT

The authors thank the patients and their families, as well as all investigators and site personnel, for making this trial possible. Medical writing and editorial assistance were provided by Christina Kim, PharmD, and Amy Ghiretti, PhD, of Articulate Science, LLC, a part of Nucleus Global, an Inizio Company.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Phase II Trial of Dabrafenib Plus Trametinib in Relapsed/Refractory *BRAF* V600–Mutant Pediatric High-Grade Glioma

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

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No other potential conflicts of interest were reported.

APPENDIX 1

TABLE A1. List of Study Sites and Investigators (enrolled ≥1 patient in the high-grade glioma cohort)

Site	Investigator
Fundacion FLENI, Buenos Aires, Argentina	Blanca Diez
Universidade Federal de São Paulo, Sao Paulo, Brazil	Andrea Cappellano
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Universitaetsklinikum Essen, Essen, Germany	Gudrun Fleischhack
Universitaetsklinikum Hamburg Eppendorf, Hamburg, Germany	Uwe Kordes
Universitaetsmedizin Charite, Berlin, Germany	Pablo Hernaiz-Driever
Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy	Maura Massimino
IRCCS Istituto Giannina Gaslini, Genova, Italy	Maria Luisa Garre
IRCCS Ospedale Pediatrico Bambino Gesu, Roma, Italy	Franco Locatelli
National Center for Child Health and Development, Tokyo, Japan	Keita Terashima
Osaka City General Hospital, Osaka, Japan	Keiko Okada
Kyushu University Hospital, Fukuoka, Japan	Yuki Koga
Prinses Maxima Centrum, Utrecht, the Netherlands	Jasper Van der Lugt
National Medical Research Center for Pediatric Hematology, Moscow, Russia	Alexey Maschan
Hospital Nino Jesus, Madrid, Spain	Alvaro Lassaletta
Karolinska Universitetssjukhuset Solna, Stockholm, Sweden	Stefan Holm
Great Ormond Street Hospital for Children, London, United Kingdom	Darren Hargrave
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Washington University School of Medicine, St Louis, MO	Karen Gauvain
Johns Hopkins University, Baltimore, MD	Kenneth Cohen
Texas Children's Hospital, Houston, TX	Patricia Baxter

TABLE A2. Disposition and Duration of Exposure

Category	(N = 41), No. (%)
Treated	41 (100)
Treatment ongoing[a]	21 (51.2)
Without progressive disease[b]	19 (46.3)
Treatment beyond progressive disease	2 (4.9)
Discontinued	20 (48.8)
Progressive disease	16 (39.0)
Death	2 (4.9)
Adverse event	1 (2.4)
Physician decision	1 (2.4)
Post-treatment follow-up for patients who discontinued	
Did not enter	15 (36.6)
Entered	5 (12.2)
Ongoing	2 (4.9)
Died	3 (7.3)
Survival follow-up	
Did not enter	7 (17.1)
Entered	8 (19.5)
Ongoing	2 (4.9)
Died	6 (14.6)

Category	Dabrafenib + trametinib
Duration of exposure, months, median (range)[a]	16.7 (0.3-39.6)
Duration of exposure categories, weeks, No. (%)[c]	
<8	2 (4.9)
8 to <24	7 (17.1)
24 to <56	9 (22.0)
56 to <112	15 (36.6)
≥112	8 (19.5)

Abbreviation: RANO, Response Assessment in Neuro-Oncology.
[a]Ongoing at the time of the data cutoff date, August 23, 2021.
[b]Investigator-assessed progressive disease per RANO criteria.
[c]Duration of exposure is the number of days from the first date when a nonzero dose of any component of study treatment was administered to the last date when a nonzero dose of any component of study treatment was administered, up to and including the data cutoff. Individual durations of exposure to dabrafenib and trametinib were the same as the combination.

TABLE A3. Dose Adjustments and Discontinuations

	N = 41, No. (%)	
Category	Dabrafenib	Trametinib
Patients with dose reduction/ interruption		
No dose reduction/interruption	12 (29.3)	11 (26.8)
≥1 dose reduction/interruption	29 (70.7)	30 (73.2)
1	5 (12.2)	9 (22.0)
2	6 (14.6)	7 (17.1)
>2	18 (43.9)	14 (34.1)
Patients with dose reduction	19 (46.3)	10 (24.4)
1	4 (9.8)	7 (17.1)
2	4 (9.8)	1 (2.4)
>2	11 (26.8)	2 (4.9)
Reasons for dose reduction[a]		
AEs	13 (31.7)	7 (17.1)
Per protocol	11 (26.8)	2 (4.9)
Physician decision	3 (7.3)	2 (4.9)
Patient/guardian decision	3 (7.3)	0
Patients with dose interruption	26 (63.4)	28 (68.3)
1	6 (14.6)	9 (22.0)
2	6 (14.6)	5 (12.2)
>2	14 (34.1)	14 (34.1)
Reasons for dose interruption[a]		
AEs	23 (56.1)	24 (58.6)
Per protocol	4 (9.8)	2 (4.9)
Dispensing error	1 (2.4)	1 (2.4)
Dosing error	3 (7.3)	2 (4.9)
Physician decision	4 (9.8)	5 (12.2)
Patient/guardian decision	4 (9.8)	6 (14.6)
Patients with ≥1 dose re-escalation	12 (29.3)	5 (12.2)
Patients with permanent discontinuation	20 (48.8)	20 (48.8)
Reasons for treatment discontinuation		
AEs	1 (2.4)	1 (2.4)
Death	2 (4.9)	2 (4.9)
Physician decision	2 (4.9)	2 (4.9)
Progressive disease	15 (36.6)	15 (36.6)

Abbreviation: AE, adverse event.
[a]Patients may be counted under multiple reasons for dose reduction/ interruption.

TABLE A4. ORR by Investigator-Determined Histology

Subgroup[a]	ORR[b] (N = 41), Responses/Patients, No. (%)	95% CI[c]
Histology at initial diagnosis[d,e]		
Anaplastic astrocytoma	2/3 (66.7)	9.4 to 99.2
Anaplastic ganglioglioma	2/2 (100)	15.8 to 100
Anaplastic pilocytic astrocytoma	0/1	0 to 97.5
Anaplastic pleomorphic xanthoastrocytoma	4/6 (66.7)	22.3 to 95.7
Diffuse midline glioma (H3K27M-mutated)	0/2	0 to 84.2
Diffuse midline glioma, NOS	0/1	0 to 97.5
Epithelioid glioblastoma multiforme	1/1 (100)	2.5 to 100
Ganglioglioma	1/1 (100)	2.5 to 100
Glioblastoma multiforme	7/13 (53.8)	25.1 to 80.8
HGG, NOS	1/4 (25.0)	0.6 to 80.6
LGG, NOS	1/1 (100)	2.5 to 100
Oligodendroglioma	1/1 (100)	2.5 to 100
Pleomorphic xanthoastrocytoma	3/4 (75.0)	19.4 to 99.4
Unknown	0/1	0 to 97.5
Central molecular profile[f,g]		
CDKN2A/B homozygous deletion	13/23 (56.5)	34.5 to 76.8
No *CDKN2A/B* homozygous deletion	10/18 (55.5)	NA
Histone H3	1/3 (33.3)	0.8 to 90.6
Non–histone H3	22/38 (57.9)	NA
TP53 mutation/deletion	3/6 (50.0)	11.8 to 88.2
No *TP53* mutation/deletion	20/35 (57.1)	NA

Abbreviations: CR, complete response; HGG, high-grade glioma; LGG, low-grade glioma; NA, not available; NOS, not otherwise specified; ORR, overall response rate; PR, partial response; RANO, Response Assessment in Neuro-Oncology.

[a]Percentages are taken out of the n in each subgroup.

[b]ORR includes patients with a best overall confirmed response of CR or PR per independent review using RANO criteria.

[c]The exact binomial 95% CI (Clopper-Pearson) is presented.

[d]Histologic data were investigator determined at initial diagnosis and may not necessarily reflect histology at study entry.

[e]Per WHO 2016 classification.

[f]Six patients had insufficient tumor content for molecular profiling and are represented in the categories of patients without a given mutation.

[g]Patients may appear in more than one molecular profile category.

TABLE A5. ORR and DOR by Investigator and Independent Assessment

Response	Investigator Assessment (N = 41)	Independent Assessment[a] (N = 41)
ORR (CR + PR), No. (%) (95% CI)	24 (58.5) (42.1 to 73.7)	23 (56.1) (39.7 to 71.5)
CR, No. (%)	10 (24.4)	12 (29.3)
PR, No. (%)	14 (34.1)	11 (26.8)
SD,[b] No. (%)	7 (17.1)	5 (12.2)
PD, No. (%)	9 (22.0)	10 (24.4)
Unknown,[c] No. (%)	1 (2.4)[c]	3 (7.3)[c]
CBR (CR + PR + SD),[d] No. (%) (95% CI)	30 (73.2) (57.1 to 85.8)	27 (65.9) (49.4 to 79.9)

Response	Investigator Assessment (n = 24)	Independent Assessment (n = 23)
DOR		
Events, No. (%)	8 (33.3)	8 (34.8)
Months, median (95% CI)	26.6 (14.9 to NR)	22.2 (7.6 to NR)
6-month rate (95% CI), %	95.7 (72.9 to 99.4)	84.7 (59.7 to 94.8)
12-month rate (95% CI), %	81.7 (58.2 to 92.7)	62.2 (36.3 to 80.0)

Abbreviations: CBR, clinical benefit rate; CR, complete response; DOR, duration of response; NR, not reached; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.
[a]Results by independent assessment from Figure 1 are included for comparison.
[b]SD for ≥16 weeks is recorded at ≥15 weeks (ie, ≥105 days) from treatment start date.
[c]No valid postbaseline assessment.
[d]SD for ≥24 weeks is recorded at ≥23 weeks (ie, ≥161 days) from treatment start date.

TABLE A6. Progression-Free Survival by Investigator Assessment

Progression-Free Survival	Investigator Assessment (N = 41)
Events, No. (%)	20 (48.8)
Progression	19 (46.3)
Death[a]	1 (2.4)
Months, median (95% CI)	17.1 (12.5 to NR)
6-month rate (95% CI), %	72.7 (56.1 to 83.9)
12-month rate (95% CI), %	67.4 (50.5 to 79.7)

Abbreviation: NR, not reached.
[a]Only includes patients who died without known disease progression.

TABLE A7. Most Common Serious Adverse Events Occurring in ≥4% of Patients

	N = 41, No. (%)	
Preferred Term	Any Grade	Grade ≥3
Any	25 (61.0)	22 (53.7)
Headache	3 (7.3)	2 (4.9)
Pyrexia	3 (7.3)	1 (2.4)
General physical health deterioration	2 (4.9)	2 (4.9)
Intracranial pressure increased	2 (4.9)	2 (4.9)