ORIGINAL ARTICLE

Dabrafenib plus Trametinib in Pediatric Glioma with *BRAF* V600 Mutations

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ABSTRACT

BACKGROUND

Detection of the *BRAF* V600E mutation in pediatric low-grade glioma has been associated with a lower response to standard chemotherapy. In previous trials, dabrafenib (both as monotherapy and in combination with trametinib) has shown efficacy in recurrent pediatric low-grade glioma with *BRAF* V600 mutations, findings that warrant further evaluation of this combination as first-line therapy.

METHODS

In this phase 2 trial, patients with pediatric low-grade glioma with *BRAF* V600 mutations who were scheduled to receive first-line therapy were randomly assigned in a 2:1 ratio to receive dabrafenib plus trametinib or standard chemotherapy (carboplatin plus vincristine). The primary outcome was the independently assessed overall response (complete or partial response) according to the Response Assessment in Neuro-Oncology criteria. Also assessed were the clinical benefit (complete or partial response or stable disease for ≥24 weeks) and progression-free survival.

RESULTS

A total of 110 patients underwent randomization (73 to receive dabrafenib plus trametinib and 37 to receive standard chemotherapy). At a median follow-up of 18.9 months, an overall response occurred in 47% of the patients treated with dabrafenib plus trametinib and in 11% of those treated with chemotherapy (risk ratio, 4.31; 95% confidence interval [CI], 1.7 to 11.2; P<0.001). Clinical benefit was observed in 86% of the patients receiving dabrafenib plus trametinib and in 46% receiving chemotherapy (risk ratio, 1.88; 95% CI, 1.3 to 2.7). The median progression-free survival was significantly longer with dabrafenib plus trametinib than with chemotherapy (20.1 months vs. 7.4 months; hazard ratio, 0.31; 95% CI, 0.17 to 0.55; P<0.001). Grade 3 or higher adverse events occurred in 47% of the patients receiving dabrafenib plus trametinib and in 94% of those receiving chemotherapy.

CONCLUSIONS

Among pediatric patients with low-grade glioma with *BRAF* V600 mutations, dabrafenib plus trametinib resulted in significantly more responses, longer progression-free survival, and a better safety profile than standard chemotherapy as first-line therapy. (Funded by Novartis; ClinicalTrials.gov number, NCT02684058.)

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N Engl J Med 2023;389:1108-20.
DOI: 10.1056/NEJMoa2303815

Gliomas, a heterogeneous group of histologically distinct tumors, account for approximately 45% of all pediatric tumors of the central nervous system.[1] In 2016, the World Health Organization (WHO) classified gliomas according to histologic grade as low-grade (grades I and II, including pilocytic astrocytoma and ganglioglioma) and high-grade (III and IV, including anaplastic astrocytoma and glioblastoma).[1-3] The 2021 version of the classification incorporates both histologic and molecular features.[4]

The mainstay of therapy for pediatric low-grade glioma is maximal safe resection.[5,6] However, additional therapies are often required when tumors are not amenable to complete resection or have progressed or recurred.[7] Although current therapies provide 5-year overall survival of approximately 95%,[8] patients who receive chemotherapy often have multiple relapses or progressions and worsening of functional decline, including visual impairment and hypothalamic dysfunction.[9] In addition, radiation is associated with the risk of long-term neurologic and cognitive impairments and is therefore generally reserved for older patients after less toxic treatments have been exhausted.[5,10]

Recently, there have been significant advances in understanding of the molecular features of pediatric gliomas.[11-14] The *BRAF* V600E mutation has been detected in 15 to 20% of pediatric low-grade gliomas,[13] most frequently in pleomorphic xanthoastrocytoma, pilocytic astrocytoma, and ganglioglioma subtypes.[15] Such mutations result in constitutive activation of the mitogen-activated protein kinase (MAPK) signaling pathway.[13,16,17] Several retrospective analyses have shown that patients who have tumors with the *BRAF* V600E mutation may have a poorer response to chemotherapy, resulting in shorter progression-free and overall survival, findings that confirm the need for improved treatment options in this molecularly selected population.[11,13]

Dabrafenib is a selective inhibitor targeting *BRAF* V600 mutations, and trametinib is a MEK1–2 inhibitor. Combination of the two drugs has resulted in enhanced clinical benefit and a reduction in the incidence of cutaneous adverse events in adults with solid tumors.[18-23] More recently, dabrafenib monotherapy showed promising activity in a phase 1–2 trial involving previously treated children with low-grade glioma with *BRAF* V600 mutations,[24] results that supported pediatric evaluation of dabrafenib plus trametinib. A phase 1–2 trial (ClinicalTrials.gov number, NCT02124772) evaluated the side-effect profile and preliminary clinical activity of dabrafenib plus trametinib in pretreated pediatric patients with low-grade glioma with *BRAF* V600 mutations. Here, we report the subsequent results of a phase 2, randomized, open-label trial that evaluated the efficacy and safety of dabrafenib plus trametinib as compared with standard care (carboplatin plus vincristine) as first-line therapy in this molecularly selected population.[25]

A Quick Take is available at NEJM.org

Methods

Patients

Patients were 1 to 17 years years of age and had received a diagnosis of pediatric low-grade glioma with *BRAF* V600 mutations, as assessed locally according to the 2016 WHO criteria[4] or at a central reference laboratory if local assessment was unavailable. All the patients had centrally confirmed measurable disease according to Response Assessment in Neuro-Oncology (RANO) criteria,[26,27] were scheduled to receive first-line systemic therapy, and had a performance status of at least 50 on either the Karnofsky scale (for patients ≥16 years of age) or the Lansky scale (for those <16 years of age). Both scales range from 0 to 100, with higher scores indicating better functioning.

Trial Design and Treatments

Patients were randomly assigned in a 2:1 ratio to receive a combination of oral dabrafenib divided into two equal doses per day (<12 years of age, 5.25 mg per kilogram of body weight per day; ≥12 years of age, 4.5 mg per kilogram per day) plus trametinib once daily (<6 years of age, 0.032 mg per kilogram; ≥6 years, 0.025 mg per kilogram) or standard chemotherapy (carboplatin plus vincristine) according to the doses and schedule used in the Children's Oncology Group A9952 trial.[28] Liquid formulations of dabrafenib and trametinib were available.

Treatment was continued until loss of clinical benefit (as determined by the investigator), development of unacceptable toxic effects, initiation of a new anticancer therapy, completion of the protocol-defined number of cycles (in the chemotherapy group), loss to follow-up, or death.

Continuation of dabrafenib plus trametinib after investigator-determined disease progression was allowed if there was an expectation of continued clinical benefit. Patients in the chemotherapy group were permitted to cross over to receive dabrafenib plus trametinib as part of trial therapy after centrally confirmed disease progression (according to RANO criteria).[26,27]

TRIAL OVERSIGHT

The trial was sponsored by Novartis. A steering committee guided and modified components of the trial design and protocol (available with the full text of this article at NEJM.org); an independent monitoring committee reviewed safety data (see the Methods section in the Supplementary Appendix, also available at NEJM.org). The protocol and all amendments were approved by the appropriate ethics committee at each participating site.

The trial was conducted in accordance with the Good Clinical Practice guidelines of the International Council for Harmonisation and the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients or from their parents or legal guardians.

Data collection and reporting were managed by each site; the sponsor had final responsibility for the design of the trial and its protocol, maintenance of the database, and conduct of the trial. Data were analyzed by the sponsor and interpreted in collaboration with the authors. All the authors had access to the data, were involved in the decision to submit the manuscript for publication, and participated in the writing, reviewing, and editing of the manuscript, with medical writing support funded by the sponsor.

OUTCOMES AND ASSESSMENTS

The primary outcome in the intention-to-treat population was the overall response, which was defined as the percentage of patients with a best overall confirmed complete or partial response by independent central assessment, according to RANO criteria.[26,27] Tumor assessments by magnetic resonance imaging were performed according to a specific imaging protocol (2017 RANO criteria) including T2-weighted fluid attenuated inversion recovery (FLAIR) and T1-weighted acquisition sequences.[26,27,29]

Secondary outcomes related to clinical efficacy were the investigator-assessed response, duration of response, progression-free survival, time to response, and clinical benefit by both investigator and independent assessments, overall survival, and patient-reported outcomes on the Patient-Reported Outcomes Measurement Information System (PROMIS) Global Health 7+2–Parent Proxy Questionnaire.[30] Baseline biomarker assessment was a prespecified exploratory outcome; specific analyses were defined post hoc. Visual acuity was assessed according to the protocol and was analyzed post hoc. Adverse events were graded according to the Common Terminology Criteria for Adverse Events, version 4.03. Additional details are provided in the Supplementary Methods.

STATISTICAL ANALYSIS

We estimated that the enrollment of 102 patients would provide at least 80% power to detect a relative increase of 30% in the overall response (which was estimated at 50% with dabrafenib plus trametinib and 20% with chemotherapy) in the primary analyses by independent assessment. In making this estimation, we used a Mantel–Haenszel chi-square test at a one-sided level of statistical significance of 2.5%. We summarized the overall response using descriptive statistics and the Clopper–Pearson method to calculate two-sided exact binomial 95% confidence intervals. We used odds ratios, as calculated by means of logistic regression, and risk ratios with associated two-sided 95% confidence intervals to estimate the treatment effect. The primary analysis was planned for 32 weeks after the last patient had been enrolled, at which time all the patients had an opportunity to undergo four tumor-response assessments.

Efficacy was assessed in all the patients who had undergone randomization, and safety was assessed in all the patients who had received at least one dose of a trial therapy. Hierarchical testing was extended to independently assessed progression-free and overall survival to control for the overall type I error. The Kaplan–Meier method was used to estimate response duration, progression-free and overall survival, and time to response. Hazard ratios and two-sided 95% confidence intervals for progression-free and overall survival were estimated with the use of a Cox model, with significance assessed by means

of the log-rank test at a one-sided 2.5% level of significance.

RESULTS

PATIENTS AND TREATMENT

From September 2018 through December 2020, a total of 110 patients underwent randomization (73 to receive dabrafenib plus trametinib and 37 to receive chemotherapy) at 58 sites in 20 countries (Fig. S1 in the Supplementary Appendix). The patients' characteristics were well balanced between the two treatment groups at baseline (Table 1 and Tables S1 and S2). The most frequent investigator-determined histologic types of glioma were pilocytic astrocytoma (in 34 patients), ganglioglioma (in 30), low-grade glioma not otherwise specified (in 20), and pleomorphic xanthoastrocytoma (in 11). Four patients in the chemotherapy group withdrew before receiving treatment on the basis of a decision by the parent or guardian (in 3 patients) or by the investigator (in 1 patient).

At the data-cutoff date on August 23, 2021, the median follow-up was 18.9 months (range, 7.9 to 35.4 months). At that time, the assigned treatment was still being administered to 61 patients (84%) who were receiving dabrafenib plus trametinib and to 8 patients (22%) who were receiving chemotherapy (Table S3). Twelve patients who were assigned to receive dabrafenib plus trametinib discontinued treatment, most commonly because of progressive disease (in 5 of 73 [7%]); in the chemotherapy group, 9 completed treatment and 16 discontinued, also most commonly because of progressive disease (in 9 of 37 [24%]). In the chemotherapy group, 9 patients had centrally confirmed progression and crossed over to receive dabrafenib plus trametinib.

The median duration of exposure was 17.4 months with dabrafenib and 7.8 months with carboplatin; exposures to trametinib and vincristine were similar to those with dabrafenib and carboplatin, respectively (Table S3). Dose interruptions occurred in 56 of 73 patients (77%) receiving dabrafenib, 53 of 73 patients (73%) receiving trametinib, 23 of 33 patients (70%) receiving carboplatin, and 22 of 33 patients (67%) receiving vincristine; dose reductions occurred in 45 (62%) receiving dabrafenib, 14 (19%) receiving trametinib, 21 (64%) receiving carboplatin, and 11 (33%) receiving vincristine (Table S4).

TUMOR RESPONSE

After a median follow-up of 18.9 months, the independently determined overall response (the primary outcome) occurred in 47% of the patients (34 of 73) treated with dabrafenib plus trametinib and in 11% (4 of 37) of those treated with chemotherapy (risk ratio, 4.31; 95% confidence interval [CI], 1.7 to 11.2; P<0.001) (Fig. 1A, Table 2, and Fig. S2). Independently determined clinical benefit (complete or partial response or stable disease for ≥24 weeks) was observed in 86% of the patients treated with dabrafenib plus trametinib and in 46% of those treated with chemotherapy (risk ratio, 1.88; 95% CI, 1.3 to 2.7). Results according to investigator assessment were similar to those according to independent assessment (Table S5). Of the 9 patients who were assigned to the chemotherapy group and who subsequently had centrally confirmed progressive disease and crossed over to receive dabrafenib plus trametinib, 3 had an initial response according to independent assessment (6 according to investigator assessment), and 8 continued to receive therapy at the data cutoff (Fig. S3).

Among the patients who received dabrafenib plus trametinib, most responses occurred within 4 months after randomization according to both independent assessment (Fig. 1B) and investigator assessment (Fig. S4). Of the 21 patients who had an early response, 9 were subsequently found to have progressive disease according to independent review but not according to investigator review; these patients continued to receive dabrafenib plus trametinib for several more months. Representative scans are provided in Figure S5. The superiority of dabrafenib plus trametinib over chemotherapy in response persisted in preplanned sensitivity analyses, which included an analysis that considered the 4 patients who had been randomly assigned to the chemotherapy group but did not receive chemotherapy as having had a response.

Patients who received dabrafenib plus trametinib had an independently assessed overall response that was the same as or higher than that in the chemotherapy group in all histologic

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Dabrafenib plus Trametinib (N=73)	Chemotherapy (N=37)
Age		
Median (range) — yr	10 (1–17)	8 (1–17)
Distribution — no. (%)		
1 to <6 yr	20 (27)	14 (38)
6 to <12 yr	25 (34)	11 (30)
12 to 17 yr	28 (38)	12 (32)
Male sex — no. (%)	29 (40)	15 (41)
Karnofsky–Lansky performance status — no. (%)†		
100	40 (55)	18 (49)
90	20 (27)	9 (24)
80	5 (7)	2 (5)
70	3 (4)	3 (8)
<70	2 (3)	0
Missing data	3 (4)	5 (14)
Reason to treat — no. (%)‡		
Blindness in 1 eye and low vision in other	2 (3)	2 (5)
Clinical progression	21 (29)	7 (19)
Deterioration of visual acuity	19 (26)	11 (30)
Diencephalic syndrome of infancy	1 (1)	0
Neurologic symptoms	31 (42)	19 (51)
Nystagmus	9 (12)	5 (14)
Pressure effect of tumor mass	17 (23)	10 (27)
Radiologic progression	44 (60)	15 (41)
Vision abnormalities	22 (30)	19 (51)
Median time since diagnosis (range) — mo	4.9 (0.9–199.9)	2.4 (0.7–62.2)
Histologic grade at initial diagnosis — no. (%)§		
1	60 (82)	28 (76)
2	12 (16)	8 (22)
3	0	0
4	0	0
Missing data	1 (1)	1 (3)
Histologic type — no. (%)§		
Astrocytoma	1 (1)	1 (3)
Desmoplastic astrocytoma not otherwise specified	0	1 (3)
Desmoplastic infantile astrocytoma	2 (3)	1 (3)
Diffuse astrocytoma	1 (1)	1 (3)
Diffuse glioma not otherwise specified	2 (3)	0
Ganglioglioma	21 (29)	9 (24)
Glioneuronal not otherwise specified	2 (3)	1 (3)
Infantile desmoplastic ganglioglioma	1 (1)	0
Low-grade glioma not otherwise specified	14 (19)	6 (16)

Table 1. (Continued.)

Characteristic	Dabrafenib plus Trametinib (N=73)	Chemotherapy (N=37)
Pilocytic astrocytoma	22 (30)	12 (32)
Pleomorphic xanthoastrocytoma	6 (8)	5 (14)
Missing data	1 (1)	0
BRAF mutational status — no. (%)¶		
V600E	70 (96)	35 (95)
Nonmutant	0	1 (3)
Other	3 (4)	0
Missing data	0	1 (3)

* Percentages may not total 100 in each category because of rounding. Additional details regarding the patients' characteristics at baseline are provided in Table S1 in the Supplementary Appendix.
† Karnofsky performance status applies to patients who are 16 years of age or older and Lansky performance status to those under the age of 16 years. Both scales range from 0 to 100, with higher scores indicating better functioning.
‡ Patients may have had more than one reason for treatment.
§ Histologic data were determined by the investigator at the time of the initial diagnosis and may not necessarily reflect the histologic type at trial entry.
¶ Local *BRAF* status is listed when available; 4 patients were enrolled on the basis of centrally determined *BRAF* status. Among the patients who received dabrafenib plus trametinib, 3 patients had local *BRAF* status recorded as "other" after it had been centrally determined as V600E. Among the patients who received chemotherapy, 1 patient discontinued participation in the trial after confirmation of a non–*BRAF* V600 mutation, and 1 withdrew consent before treatment with no local result entered and before central analysis.

subtypes (Table S6). In addition, among the patients for whom molecular data were available, responses were observed regardless of the presence or absence of *CDKN2A* homozygous deletion. According to Kaplan–Meier analysis, the median response duration by independent review was 20.3 months (95% CI, 12.0 to not evaluable) with dabrafenib plus trametinib and was not evaluable in the 4 patients who had a response with chemotherapy (Table 2).

PROGRESSION-FREE SURVIVAL

As determined by independent assessment, progression-free survival was significantly longer with dabrafenib plus trametinib (median, 20.1 months; 95% CI, 12.8 to not evaluable) than with chemotherapy (median, 7.4 months; 95% CI, 3.6 to 11.8; P<0.001), for a hazard ratio of 0.31 (95% CI, 0.17 to 0.55) (Fig. 2). At 6 months, the estimated progression-free survival was 87% (95% CI, 77 to 93) with dabrafenib plus trametinib and 58% (95% CI, 39 to 73) with chemotherapy; the percentages at 12 months were 67% (95% CI, 53 to 77) and 26% (95% CI, 10 to 46), respectively. As determined by investigator assessment during the trial period, 9 patients in each group had disease progression, and the median progression-free survival was not evaluable in either group; at 12 months, progression-free survival was 91% with dabrafenib plus trametinib and 74% with chemotherapy (hazard ratio, 0.37; 95% CI, 0.14 to 0.93) (Fig. S6).

OVERALL SURVIVAL

No deaths were reported among the patients who received dabrafenib plus trametinib; 1 death was reported (from low-grade glioma) in the chemotherapy group. This death occurred more than 30 days after the last dose of randomized treatment. This patient had crossed over to receive dabrafenib plus trametinib for 22 weeks and died 23 days after the last crossover dose.

PATIENT-REPORTED OUTCOMES

The difference in the overall least-squares means of scores between the trial groups for global health and fatigue favored dabrafenib plus trametinib over chemotherapy at all scheduled time points (Fig. S7). Outcomes on the pain subscale were similar in the two groups.

VISUAL ACUITY

The change from baseline in visual acuity was assessed in patients with tumors located near the optic chiasm (25 with dabrafenib plus trametinib and 11 with chemotherapy) (Table S7).

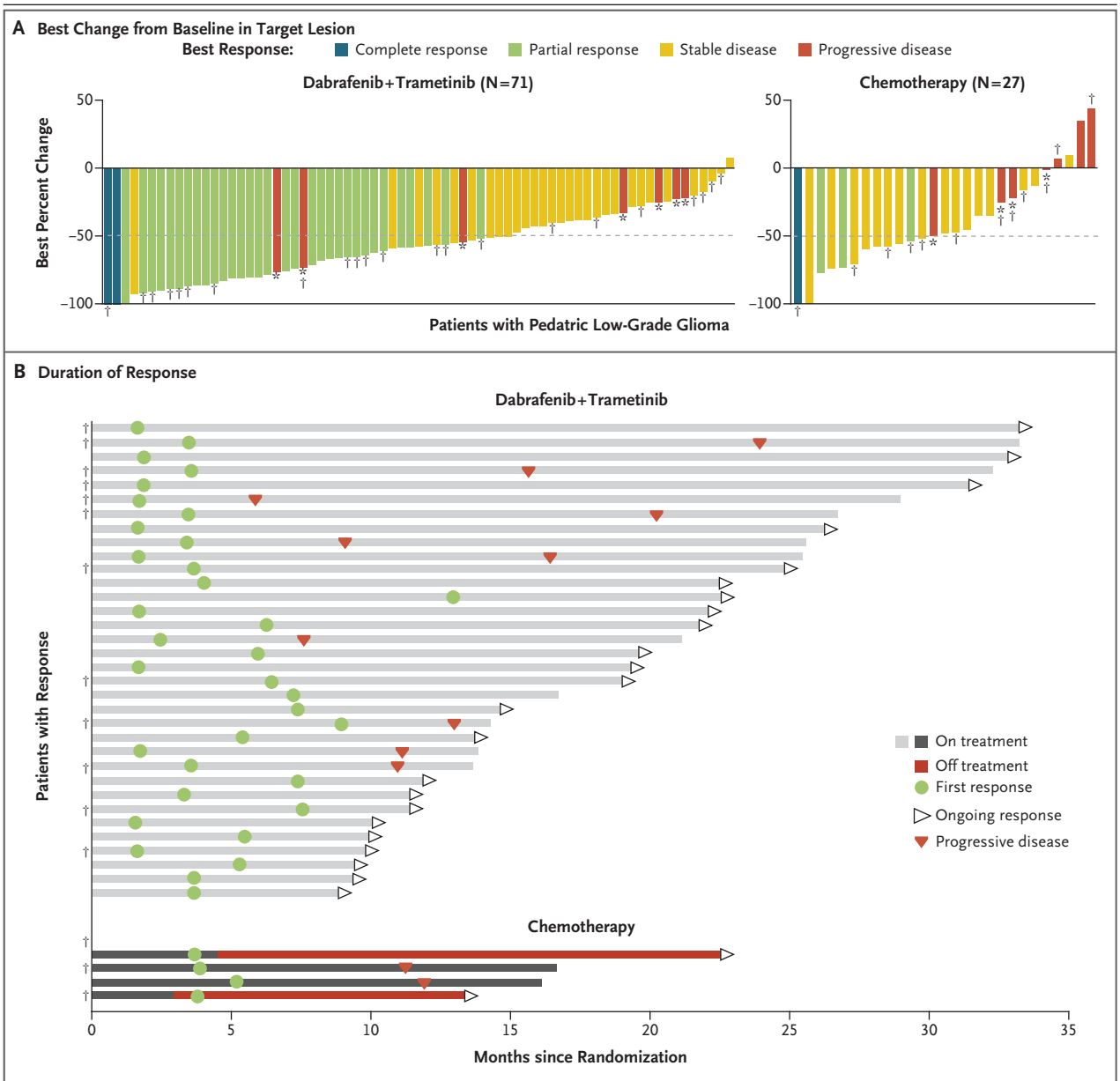

Figure 1. Best Change from Baseline in Tumor Measurement and Duration of Response.

Panel A shows the best change from baseline, according to independent review with the Response Assessment in Neuro-Oncology (RANO) criteria, among the patients who received dabrafenib plus trametinib and those who received chemotherapy (carboplatin plus vincristine). Patients for whom the percent change in the target lesion was contradicted by a finding of progressive disease are indicated by an asterisk. Patients who were not included in the evaluable set are indicated by a dagger. (The evaluable set, used for sensitivity analyses, consisted of all the patients in the as-treated population with centrally confirmed measurable disease, centrally confirmed positive *BRAF* V600 mutational status, adequate tumor assessment at baseline, and a follow-up tumor assessment at least 8 weeks after the initiation of treatment.) Excluded from the analysis were patients for whom the best percent change in target lesions was not available or the response had been categorized as unknown. The single best scan result was used to calculate the best change from baseline. If this change in tumor size was not confirmed by a repeat scan, the best response may not be consistent with the best change from baseline. Panel B shows the duration of response with display of only the first occurrence of each response or progression.

Table 2. Tumor Response.*

Variable	Dabrafenib plus Trametinib (N=73)	Chemotherapy (N=37)	Odds Ratio (95% CI)†	Risk Ratio (95% CI)†	P Value‡
Overall response: complete or partial					
No. of patients (%)	34 (47)	4 (11)	7.19 (2.30–22.40)	4.31 (1.70–11.20)	<0.001
95% CI — %	35–59	3–25			
Type of response — no. (%)					
Complete	2 (3)	1 (3)	—	—	
Partial	32 (44)	3 (8)	—	—	
Stable disease§	30 (41)	15 (41)	—	—	
Progressive disease (%)	8 (11)	12 (32)	—	—	
Unknown	1 (1)¶	6 (16)‖	—	—	
Clinical benefit: complete or partial response or stable disease for ≥24 wk**					
No. of patients — no. (%)	63 (86)	17 (46)	7.41 (2.90–18.80)	1.88 (1.30–2.70)	<0.001
95% CI — %	76–93	30–63			
Duration of overall response					
Disease progression or death in patients with response — no. (%)	10 (29)	2 (50)	—	—	
Median duration of response (95% CI) — mo	20.3 (12.0–NE)	NE (6.6–NE)	—	—	
Patients with continuing response — % (95% CI)			—	—	
At 6 mo	86 (66–94)	100 (100–100)			
At 12 mo	70 (46–85)	50 (6–85)			

* The listed tumor response was assessed by independent review according to the Response Assessment in Neuro-Oncology (RANO) criteria. NE denotes not evaluable.
† Odds ratios (dabrafenib plus trametinib as compared with chemotherapy) and two-sided 95% confidence intervals were calculated with the use of logistic regression with the trial treatment as the only covariate. For both odds ratios and risk ratios, values of more than 1 favor dabrafenib plus trametinib.
‡ P values were computed by means of the chi-square test (Mantel–Haenszel method) at a one-sided significance level of 2.5%.
§ In this category, stable disease was recorded 15 weeks or later after the initiation of treatment.
¶ One patient had stable disease or unconfirmed complete or partial response that occurred before the week 16 visit.
‖ Four patients did not have a valid postbaseline assessment. Two patients had stable disease or unconfirmed complete or partial response that occurred before the week 16 visit.
** In this category, stable disease was recorded at 23 weeks or later after the initiation of treatment.

Although visual acuity remained stable in most patients in the two groups, visual acuity per eye was improved in more patients who received dabrafenib plus trametinib than in those who received chemotherapy (14 of 41 eyes examined [34%] vs. 2 of 18 eyes examined [11%]).

SAFETY

Overall, 106 patients were included in the safety analysis (73 for dabrafenib plus trametinib and 33 for chemotherapy). All the patients had at least one adverse event, with a lower proportion of grade 3 or higher events in patients receiving dabrafenib plus trametinib than in those receiving chemotherapy (47% vs. 94%) (Table 3). The most common adverse events of any grade with dabrafenib plus trametinib as compared with chemotherapy were pyrexia (in 68% vs. 18%), headache (in 47% vs. 27%), and vomiting (in 34% vs. 48%). Adverse events of grade 3 or

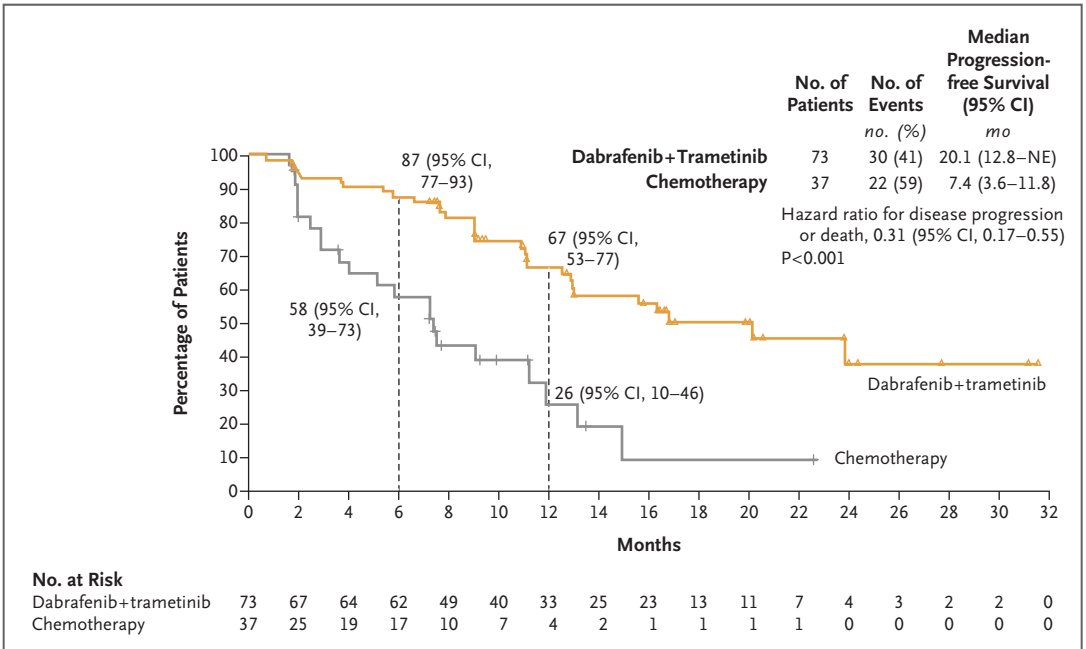

Figure 2. Progression-free Survival.

Progressive-free survival was measured in the two trial groups by independent review according to RANO criteria. The vertical dashed lines indicate the values at 6 months and 12 months. NE denotes not evaluable.

higher that occurred in at least 15% of the patients who received dabrafenib plus trametinib and chemotherapy, respectively, were a decreased white-cell count (in 0 and 15%), anemia (in 0 and 24%), and decreased neutrophil count (in 5% and 48%). Carboplatin allergy was reported in 7 patients (21%) in the chemotherapy group. Among the patients who received dabrafenib plus trametinib, 32 (44%) had weight gain reported as an adverse event or as an increase of at least 2 percentile-for-age categories in body-mass index (BMI). Tumors were found to be located in the optic pathway or hypothalamic region in 25 patients (34%); of these patients, 12 (48%) met the criteria for weight gain, as did 20 of 48 patients (42%) with tumors located elsewhere. Additional treatment-related adverse events are listed in Table S8.

The frequency of adverse events leading to a dose adjustment or interruption was similar in the two groups: 79% with dabrafenib plus trametinib and 79% with chemotherapy. Among the patients who received dabrafenib plus trametinib, dose adjustments or interruptions were more frequent because of pyrexia (in 53% vs. 0 with chemotherapy) and were less frequent because of a decreased neutrophil count (in 3% vs. 27% with chemotherapy). Although skin toxic effects (including dry skin and rash) occurred more frequently with dabrafenib plus trametinib, only 8% of patients had resultant dose interruption or adjustment. Permanent discontinuation because of adverse events was less common with dabrafenib plus trametinib than with chemotherapy (4% vs. 18%) (Table S9).

DISCUSSION

In this randomized cohort of 110 children who had low-grade glioma with *BRAF* V600 mutations, we found that responses to dabrafenib plus trametinib were more frequent than responses to standard chemotherapy (carboplatin plus vincristine) (47% vs. 11%, P<0.001). In addition, responses were observed across the diverse histologic types of glioma in this trial, findings that support broad use of dabrafenib plus trametinib as first-line therapy in this population. The use of dabrafenib plus trametinib also had a clear and sustained benefit with respect to

progression-free survival as compared with chemotherapy, with 1-year progression-free survival of 67% and 26%, respectively.

In a report from the Children's Oncology Group,[28] a complete or partial response according to RANO criteria was observed in 35% of unselected patients with low-grade glioma who received standard chemotherapy. However, among patients with the *BRAF* V600E mutation, this response fell to 10%,[31] a result that is consistent with our finding of 11% response in the chemotherapy group. In addition, 10-year progression-free and overall survival in patients with *BRAF* V600 wild-type low-grade glioma are 60% and 92%, respectively, but are lower in patients with the *BRAF* V600E mutation (27% and 84%, respectively).[13] In our trial, the investigator-determined 1-year progression-free survival in the chemotherapy group (74%) was similar to the investigator-determined 2-year progression-free survival in a historical cohort of patients with unselected pediatric low-grade glioma treated with chemotherapy.[32] Thus, the results of our randomized, prospective trial clearly show the superiority of dabrafenib plus trametinib in these patients, with findings from the control group that were consistent with inferior outcomes observed in retrospective analyses involving patients with *BRAF* V600 mutations treated with chemotherapy.[13,31] The clinical benefit of dabrafenib plus trametinib as compared with chemotherapy is further supported by greater improvements in visual acuity and global health.

A discrepancy in progression events was noted between independent and investigator assessments in the two trial groups (30 vs. 9 events with dabrafenib plus trametinib and 22 vs. 9 with chemotherapy). However, the hazard ratios were similarly favorable, which suggests that the observed treatment benefit was maintained. The independently determined efficacy results presented here reflect up-to-date RANO criteria, which incorporate the results of T2 FLAIR imaging.[26,27] Strict interpretation of the RANO criteria by the independent reviewer may have contributed to the higher number of progression events reported as compared with investigator review, because the criteria for progressive disease are sensitive to increases relative to nadir, regardless of changes from baseline. In our trial, 10 patients who had a response continued to receive dabrafenib plus trametinib after independently assessed progression, which suggests that these children continued to derive clinical benefit according to the investigator's opinion.

The safety profile of dabrafenib plus trametinib was consistent with that observed in adults across other indications, with pyrexia and fatigue among the most common adverse events.[19-21] However, weight gain as an adverse event or an increase of at least 2 BMI-for-age percentiles was reported in 32 of 73 patients who received dabrafenib plus trametinib. Abnormal weight gain has been observed in patients with pediatric low-grade glioma and may be a result of hormonal effects of tumors located near the hypothalamic or pituitary axis.[33] Our analysis suggests that tumor location does not appear to be associated with the weight gain observed with dabrafenib plus trametinib, findings that support other reports that suggest weight gain as a safety signal with MAPK-targeted therapy in this patient population.[34]

Fewer patients in the group receiving dabrafenib plus trametinib than in the chemotherapy group had adverse events of grade 3 or higher (47% vs. 94%) and fewer discontinued therapy because of adverse events (4% vs. 18%). Nevertheless, potential toxic effects with dabrafenib plus trametinib and the risk–benefit ratio should be evaluated on an individual basis, particularly because indefinite treatment may be required and the long-term safety of dabrafenib plus trametinib in this population is unknown.[31] A rollover trial to assess the long-term effects of therapy with dabrafenib, trametinib, or a combination of both drugs in pediatric patients (NCT03975829) is ongoing.[35] Future studies are needed to evaluate functional outcomes (e.g., visual acuity), further molecular characterization, and most effective treatment duration.

This randomized trial shows the superiority of dabrafenib plus trametinib as first systemic therapy for pediatric patients with low-grade glioma with *BRAF* V600 mutations as compared with carboplatin plus vincristine, the standard chemotherapy approach. This benefit was evident in the higher independently determined response, longer progression-free survival, and better side-effect profile as reflected in the lower frequency of treatment discontinuation because of toxicity. Overall, these findings show

Table 3. Adverse Events (Safety Population).

Category	Dabrafenib plus Trametinib (N=73)		Chemotherapy (N=33)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Adverse event				
Any	73 (100)	34 (47)	33 (100)	31 (94)
Treatment related*	67 (92)	19 (26)	32 (97)	29 (88)
Leading to discontinuation	3 (4)	2 (3)	6 (18)	3 (9)
Leading to dose adjustment or interruption	58 (79)	27 (37)	26 (79)	19 (58)
Requiring additional therapy	72 (99)	22 (30)	32 (97)	22 (67)
Serious adverse event				
Any	29 (40)	20 (27)	13 (39)	7 (21)
Treatment related*	10 (14)	4 (5)	8 (24)	4 (12)
Adverse events occurring in ≥15% of patients in either group				
Any	73 (100)	34 (47)	33 (100)	31 (94)
Pyrexia	50 (68)	6 (8)	6 (18)	1 (3)
Headache	34 (47)	1 (1)	9 (27)	1 (3)
Vomiting	25 (34)	1 (1)	16 (48)	1 (3)
Fatigue	23 (32)	0	10 (30)	0
Diarrhea	21 (29)	0	6 (18)	2 (6)
Dry skin	19 (26)	0	1 (3)	0
Nausea	18 (25)	0	15 (45)	0
Epistaxis	15 (21)	0	1 (3)	0
Rash	14 (19)	1 (1)	3 (9)	1 (3)
Abdominal pain	12 (16)	0	7 (21)	0
Anemia	11 (15)	0	20 (61)	8 (24)
Upper respiratory tract infection	11 (15)	0	2 (6)	0
Increased weight	11 (15)	5 (7)	0	0
Increased alanine aminotransferase	10 (14)	4 (5)	9 (27)	3 (9)
Neutropenia	10 (14)	7 (10)	10 (30)	10 (30)
Decreased neutrophil count	10 (14)	4 (5)	16 (48)	16 (48)
Constipation	9 (12)	0	12 (36)	0
Increased aspartate aminotransferase	8 (11)	2 (3)	5 (15)	0
Oropharyngeal pain	8 (11)	0	6 (18)	0
Decreased white-cell count	8 (11)	0	12 (36)	5 (15)
Decreased appetite	4 (5)	0	8 (24)	0
Decreased lymphocyte count	4 (5)	0	5 (15)	2 (6)
Decreased platelet count	4 (5)	0	10 (30)	3 (9)
Stomatitis	4 (5)	0	5 (15)	0
Alopecia	2 (3)	0	8 (24)	0
Anxiety	1 (1)	0	5 (15)	1 (3)
Hypomagnesemia	1 (1)	0	6 (18)	1 (3)

Table 3. (Continued.)

Category	Dabrafenib plus Trametinib (N=73)		Chemotherapy (N=33)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Pain in jaw	1 (1)	0	6 (18)	0
Hypersensitivity	0	0	5 (15)	1 (3)
Infusion-related reaction	0	0	5 (15)	1 (3)
Peripheral motor neuropathy	0	0	5 (15)	1 (3)
Peripheral sensory neuropathy	0	0	6 (18)	1 (3)

* The determination that an adverse event was related to a trial therapy was made by the investigator.

the value of early molecular testing in children with low-grade glioma to determine the presence or absence of *BRAF* V600 mutations.

The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the National Health Service, the National Institute for Health and Care Research (NIHR), or the Department of Health.

Supported by Novartis. Dr. Hargrave is supported by funding from the NIHR Great Ormond Street Hospital Biomedical Research Centre.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the patients and their families, as well as all the investigators and site personnel, for making this trial possible; and Christina Kim, Pharm. D., and Amy Ghiretti, Ph.D., of Articulate Science, a part of Nucleus Global, an Inizio Company, for providing medical writing and editorial assistance with an earlier version of the manuscript.

APPENDIX

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