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Authors

Reardon, David

Cohen, Adam

De La Fuente, Macarena

et al.

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BRAF–MEK Inhibition in Newly Diagnosed Papillary Craniopharyngiomas

P.K. Brastianos, M.D.,
Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston

E. Twohy, M.S.,
Alliance Statistics and Data Management Center, Rochester, MN

S. Geyer, Ph.D.,
Alliance Statistics and Data Management Center, Rochester, MN

E.R. Gerstner, M.D.,
Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston

T.J. Kaufmann, M.D.,
Mayo Clinic, Rochester, MN

S. Tabrizi, M.D.,
Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston

B. Kabat, B.S.,
Alliance Statistics and Data Management Center, Rochester, MN

J. Thierauf, M.D.,
Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston

M.W. Ruff, M.D.,
Mayo Clinic, Rochester, MN

D.A. Bota, M.D., Ph.D.,
UC Irvine–Chao Family Comprehensive Cancer Center, Orange, CA

D.A. Reardon, M.D.,
Dana–Farber Cancer Institute, Boston

A.L. Cohen, M.D.,
Huntsman Cancer Institute, University of Utah, Salt Lake City

M.I. De La Fuente, M.D.,
Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine, Miami

Dr. Brastianos can be contacted at pbrastianos@mgh.harvard.edu or at Massachusetts General Hospital Cancer Center, 55 Fruit St., Yawkey 9E, Boston, MA 02114. Dr. Galanis can be contacted at galanis.evanthia@mayo.edu or at Mayo Clinic, 200 1st St. SW, Rochester, MN 55905.
Drs. Barker and Galanis contributed equally to this article.

G.J. Lesser, M.D.,
Wake Forest University School of Medicine, Winston-Salem, NC

J. Campian, M.D., Ph.D.,
Washington University School of Medicine, St. Louis

P.K. Agarwalla, M.D.,
Rutgers Cancer Institute, New Brunswick, NJ

P. Kumthekar, M.D.,
Northwestern University, Chicago

B. Mann, M.B., B.S.,
the Cancer Therapy Evaluation Program, National Cancer Institute, Bethesda, MD

S. Vora, M.S.,
Ohio State University Comprehensive Cancer Center, Columbus

M. Knopp, M.D., Ph.D.,
Ohio State University Comprehensive Cancer Center, Columbus

A.J. Iafrate, M.D., Ph.D.,
Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston

W.T. Curry Jr., M.D.,
Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston

D.P. Cahill, M.D., Ph.D.,
Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston

H.A. Shih, M.D.,
Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston

P.D. Brown, M.D.,
Mayo Clinic, Rochester, MN

S. Santagata, M.D., Ph.D.,
Brigham and Women's Hospital, Harvard Program in Therapeutic Science, Dana–Farber Partners CancerCare, Boston

F.G. Barker II, M.D.,
Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston

E. Galanis, M.D.
Mayo Clinic, Rochester, MN

Abstract

BACKGROUND—Craniopharyngiomas, primary brain tumors of the pituitary–hypothalamic axis, can cause clinically significant sequelae. Treatment with the use of surgery, radiation, or both is often associated with substantial morbidity related to vision loss, neuroendocrine dysfunction, and memory loss. Genotyping has shown that more than 90% of papillary craniopharyngiomas carry *BRAF* V600E mutations, but data are lacking with regard to the safety and efficacy of

BRAF–MEK inhibition in patients with papillary craniopharyngiomas who have not undergone previous radiation therapy.

METHODS—Eligible patients who had papillary craniopharyngiomas that tested positive for *BRAF* mutations, had not undergone radiation therapy previously, and had measurable disease received the BRAF–MEK inhibitor combination vemurafenib–cobimetinib in 28-day cycles. The primary end point of this single-group, phase 2 study was objective response at 4 months as determined with the use of centrally determined volumetric data.

RESULTS—Of the 16 patients in the study, 15 (94%; 95% confidence interval [CI], 70 to 100) had a durable objective partial response or better to therapy. The median reduction in the volume of the tumor was 91% (range, 68 to 99). The median follow-up was 22 months (95% CI, 19 to 30) and the median number of treatment cycles was 8. Progression-free survival was 87% (95% CI, 57 to 98) at 12 months and 58% (95% CI, 10 to 89) at 24 months. Three patients had disease progression during follow-up after therapy had been discontinued; none have died. The sole patient who did not have a response stopped treatment after 8 days owing to toxic effects. Grade 3 adverse events that were at least possibly related to treatment occurred in 12 patients, including rash in 6 patients. In 2 patients, grade 4 adverse events (hyperglycemia in 1 patient and increased creatine kinase levels in 1 patient) were reported; 3 patients discontinued treatment owing to adverse events.

CONCLUSIONS—In this small, single-group study involving patients with papillary craniopharyngiomas, 15 of 16 patients had a partial response or better to the BRAF–MEK inhibitor combination vemurafenib–cobimetinib. (Funded by the National Cancer Institute and others; ClinicalTrials.gov number, NCT03224767.)

Craniopharyngioma, a rare but difficult-to-treat epithelial brain tumor, occurs at an age-adjusted incidence of 0.19 per 100,000 persons.[1] A locally aggressive neoplasm located at the midline in or above the sella turcica, this tumor grows adjacent to the optic chiasm and often extends to displace the hypothalamus, pituitary gland, third ventricle, brain stem, and major cerebral arteries.[2] At presentation, craniopharyngiomas are seen to cause considerable neurologic sequelae[3] by compressing these critical structures.

Surgical resection is usually attempted initially, but because these tumors often adhere to critical brain and vascular structures, partial resection is common.[4] Incompletely excised tumors almost always recur without adjuvant therapy, frequently forming cysts with firm adhesions between the recurrent tumor and the surrounding structures. Curative removal of the recurrent tumor is exceedingly difficult.[5] The cystic and solid components of craniopharyngiomas can cause substantial symptomatic mass effect. As a result, even after surgery, most patients have lifelong sequelae that can include panhypopituitarism,[3] visual defects,[3] impaired intellectual function, and wide-ranging hypothalamic dysfunction that leads to sleep disorders,[6] abnormal thermoregulation, and diabetes insipidus, as well as hyperphagia and uncontrollable obesity.[4,7,8] Radiation therapy, often used as an adjunct to improve local control after surgery, carries the risk of long-term toxic effects on adjacent normal tissues, including a high risk of vasculopathy[9,10] and hypopituitarism, which can contribute to post-treatment complications in the majority of patients.[3,11] Intracystic delivery of chemotherapy has been investigated, with minimal evidence for

benefit and with considerable toxic effects.[12] These cumulative and debilitating long-term neurologic complications can have a substantial psychosocial effect on patients, rendering many unable to work or to live independent lives.[2,4] No effective medical treatment for craniopharyngiomas is known.

Incomplete knowledge of the molecular drivers of craniopharyngiomas has historically delayed the development of effective therapies for this tumor. Two histologic subtypes of craniopharyngiomas are recognized: adamantinomatous and papillary. In a genetic analysis of craniopharyngiomas, we found clonal *BRAF* V600E mutations in papillary craniopharyngiomas from 34 of 36 patients (94%), as well as activating beta-catenin (*CTNNB1*) mutations in adamantinomatous craniopharyngiomas from 51 of 53 patients (96%).[13] Craniopharyngiomas are simple genetic tumors with a low mutation rate and no other known recurrent driver mutations.[13] The observed clinical response of *BRAF* V600E–mutant melanomas[14] and hairy-cell leukemia[15] to currently available BRAF inhibitors such as vemurafenib[14,16–20] and dabrafenib[21,22] prompted us to use BRAF and MEK inhibitor therapy in the treatment of a patient who presented with multiply recurrent *BRAF* V600E–mutated craniopharyngioma.[23] We observed a rapid and dramatic reduction in tumor volume, and others have described similar responses in case reports.[24–27] In this small phase 2, single-group study, we evaluated the combination of BRAF and MEK inhibition in patients with newly diagnosed *BRAF*-mutated papillary craniopharyngiomas. Here, we report the results of this study with regard to papillary craniopharyngiomas not previously treated with radiation.

METHODS

STUDY OVERSIGHT

This Alliance for Clinical Trials in Oncology study was designed by the principal investigators and conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines. The central institutional review board of the National Cancer Institute approved the protocol (available with the full text of this article at NEJM.org). All the patients provided written informed consent. The first author wrote the first draft of the manuscript, which was reviewed and edited by all the authors before it was submitted for publication.

PATIENTS

Eligible patients had histologically proven *BRAF* V600E–mutant papillary craniopharyngioma, as documented by central pathological review, and measurable disease, as defined by bidimensionally measurable lesions with a minimum diameter of 10 mm in orthogonal dimensions. No previous radiation or systemic therapy for craniopharyngioma was allowed for this cohort. The results of a parallel cohort of this study currently enrolling patients who had received treatment previously for craniopharyngioma are not reported here. Other key inclusion criteria were an age of 18 years or older, Eastern Cooperative Oncology Group (ECOG) performance-status score of 2 or less (on a scale of 0 to 5, with higher scores indicating greater disability), normal organ and marrow function, no evidence of intracranial hemorrhage within 4 weeks before enrollment, an interval of at least 21 days since surgery,

and no presence of congestive heart failure, unstable angina, history of long-QT syndrome, or uncontrolled arrhythmia.

STUDY TREATMENT

Treatment was administered in cycles of 28 days. Patients received vemurafenib at a dose of 960 mg orally twice daily for 28 days in combination with cobimetinib at a dose of 60 mg orally once daily for 21 days. The study prespecified that patients would receive definitive therapy with radiation or surgery after treatment with vemurafenib–cobimetinib for four cycles. The recommended radiation therapy regimen was 54 Gy at 1.8 Gy per fraction delivered daily (Monday through Friday). In selected cases, patients continued to receive vemurafenib–cobimetinib after four or five cycles with permission from the study chairs if the patients were benefiting from therapy and if definitive radiation or surgery was not recommended owing to serious concern regarding adverse outcomes or was declined by the patient. If the continuation of treatment with vemurafenib–cobimetinib was approved, the regimen was continued as prespecified until the occurrence of documented progression, unacceptable adverse events, or withholding of drug therapy for longer than 28 days.

END POINTS AND ASSESSMENTS

The primary end point of objective response was assessed by central radiologic review of prespecified volumetric criteria with the use of contrast-enhanced magnetic resonance imaging that was performed every 8 weeks (see the Supplementary Appendix, available at NEJM.org). Bidimensional measurements of lesions were used locally by site investigators to decide whether to proceed with treatment, in accordance with modified Response Assessment in Neuro-oncology (RANO) guidelines.[28] The objective response was also assessed locally according to prespecified modified RANO guidelines.

Secondary end points were progression-free survival, overall survival, response as defined by enhancing volume, response as defined by nonenhancing volume, response duration, and adverse events. In patients who had a response to therapy, response duration was defined as the period of time from the first documented objective response until the occurrence of disease progression or death. Data from patients who were event-free and alive at their last evaluation were censored at that time point, which was the last tumor assessment for the end points of progression-free survival and response duration.

STATISTICAL ANALYSIS

We evaluated the efficacy of a BRAF–MEK inhibitor combination in two separate cohorts: patients with newly diagnosed papillary craniopharyngiomas (with results reported here) and patients with craniopharyngiomas that had been previously treated with radiotherapy (a group still being enrolled at the time of this report). The study was designed separately and in parallel for each of the two cohorts with an overall family-wise type I error controlled at 0.08. A Simon’s two-stage design with one interim analysis for futility was used to evaluate the objective response on the basis of centrally reviewed volumetric data in the first 4 months. We calculated that with 16 evaluable patients, the trial would have 89% power to detect a true objective response of at least 30%, with a one-sided significance level of 0.041 against the null hypothesis that the objective response rate was no greater than 5%.

Patients could be evaluated for the primary end point if they had received at least one dose of the study treatment. If 3 or more of the first 16 evaluable patients had a complete or partial response, as measured in the first 4 months, we would consider this result to be sufficient evidence that the treatment regimen is worthy of further study. An interim futility analysis was conducted after data from 9 patients had been collected and the patients had been followed for at least 4 months; if none of these patients had a documented objective response, then we would find the regimen futile in this population. We calculated Clopper–Pearson exact binomial confidence intervals to estimate the response.[29] Progression-free and overall survival and response duration were estimated with the use of the Kaplan–Meier method, with rates at time points of interest estimated along with corresponding 95% confidence intervals for small sample sizes.[30] Given the limited incidences of progression and death, median estimates are not reported for these time-to-event outcomes.

Exploratory analyses included an assessment of whether radiation volumes would be smaller after treatment with vemurafenib–cobimetinib and an examination of cell-free DNA obtained from blood samples to assess for *BRAF* mutations in patients who consented to participate in the molecular correlative study. Exploratory analyses and methods are described in the Supplementary Appendix.

RESULTS

PATIENTS AND TREATMENT

Between February 20, 2018, and March 31, 2020, we enrolled 17 patients in the study (Table 1). One patient became ineligible after enrollment owing to the use of a concomitant medication. That patient continued to receive vemurafenib–cobimetinib therapy but was not included in the analysis for the primary end point (Fig. S1 in the Supplementary Appendix). Thus, the cohort for the primary end-point analysis consisted of 16 patients who were enrolled over the course of 25 months across nine participating institutions, with the first 9 patients included in the interim analysis enrolled in the first 7 months. The median age was 49.5 years (range, 33 to 83). A total of 15 patients had an ECOG performance-status score of 0 or 1. The median baseline tumor volume was 2.75 cm^3. Patients received a median of 8 treatment cycles (range, 0 to 19); all the cycles included at least one dose of one or both of the study drugs. The median number of cycles in which both study drugs were administered was 6 (range, 1 to 12). Patients who ended the per-protocol treatment with vemurafenib–cobimetinib went on to receive the following: radiation treatment alone as standard-of-care treatment, which was allowed according to the study design (in 6 patients); radiation followed by surgery (1 patient); radiation followed by dabrafenib (1 patient); and off-protocol vemurafenib–cobimetinib (1 patient). Seven patients received no treatment after discontinuing per-protocol vemurafenib–cobimetinib therapy.

EFFICACY

The primary end point was evaluated with the use of the volumetric measurement data from the first four cycles of BRAF–MEK inhibitor combination therapy. On the basis of central review of volumetric response criteria (Table 2) and local review of bidimensional response criteria, 15 of 16 evaluable patients (94%) were judged to have had a volumetric response

(95% confidence interval [CI], 70 to 100) (Fig. S2). The one patient who did not have a response had received treatment for 8 days before stopping therapy owing to toxic effects (grade 3 anaphylaxis and grade 2 acute kidney injury). Thus, all the patients who completed at least one cycle of therapy had a response to BRAF–MEK inhibition within 4 months after starting the combination regimen.

The median reduction in tumor volume among patients who had received per-protocol treatment with vemurafenib–cobimetinib was 91% (range, 68 to 99) (Fig. 1 and Fig. S3). Because craniopharyngiomas often have both enhancing and cystic nonenhancing imaging components, we also evaluated each volume component separately. The median reduction in enhancing tumor volume from baseline was 96% (range, 80 to 99). The median reduction from baseline in cystic nonenhancing tumor volume was 82% (range, 41 to 93). The estimated progression-free survival (as determined by volumetric measurement criteria) was 87% (95% CI, 57 to 98) at 12 months and 58% (95% CI, 10 to 89) at 24 months (Fig. 2A). Overall survival was 100% at both 12 months and 24 months (Fig. 2B).

With a median follow-up of 22 months (95% CI, 19 to 30), the estimated percentage of patients who continued to have a volumetric response at 12 months was 93% (95% CI, 80 to 100) (Fig. S4). In three patients who had a response, progressive disease developed during the follow-up period after therapy had been discontinued. In two of the patients, tumors progressed after targeted therapy had been stopped but before the patients had undergone surgery or radiation. One patient proceeded to receive treatment with dabrafenib and then to undergo radiation treatment, and the other received off-protocol vemurafenib–cobimetinib therapy followed by radiation. The third patient did not receive any treatment after disease progression (Fig. S5). Of the seven patients who received no treatment after discontinuing vemurafenib–cobimetinib, six had no evidence of tumor progression at a median follow-up of 23 months (95% CI, 19 to not reached). No patient had tumor progression while they were receiving per-protocol treatment with vemurafenib–cobimetinib (Fig. S5).

SAFETY

A total of 12 patients had a grade 3 adverse event, and 2 had a grade 4 adverse event that was determined by the treating physician to be at least possibly related to treatment (Table 3 and Tables S1 to S3). Three patients discontinued treatment owing to adverse events, with a median treatment duration of 31 days. Grade 3 adverse events that were observed in two or more patients were rash, dehydration, increase in alkaline phosphatase levels, and prolongation of the corrected QT interval. One patient had an asymptomatic grade 4 increase in the creatine kinase level, and one had grade 4 hyperglycemia that was determined to be at least possibly related to treatment.

EXPLORATORY ANALYSES

To evaluate whether radiation volumes would theoretically be smaller after treatment with vemurafenib–cobimetinib, we measured the gross tumor volumes of target tumors on scans obtained before treatment and after treatment (Tables S4 and S5). In 14 patients who were evaluated, the median gross volume before treatment was 3.8 milliliters (range, 0.2 to 23.4)

as compared with 0.3 milliliters (range, 0.0 to 3.2) after treatment. All 14 tumors abutted the optic chiasm before treatment, but only 6 did so after treatment.

A total of 32 plasma samples from 11 of the patients were evaluable for cell-free DNA analysis. Of the 11 patients, samples obtained from 4 tested positive for circulating *BRAF* V600E. Two patients had a sample positive for *BRAF* mutation at the end of treatment. Another patient had a sample positive for *BRAF* mutation before and after treatment. Finally, one patient had a positive result for *BRAF* mutation on day 1 of cycle 3 only. Two patients with *BRAF* mutations that were detected at the end of treatment had disease progression after treatment had been discontinued. Changes in levels of circulating *BRAF* were not assessed owing to the limited number of evaluable samples.

DISCUSSION

Discoveries of recurrent genomic alterations lead to meaningful precision-therapeutic strategies for patients by means of actionable clinical scenarios in which these alterations can be targeted. Although craniopharyngiomas are histologically benign tumors, they can cause profound clinical sequelae, both from mass effect at presentation and in terms of long-term complications associated with treatment.[4,7,8] To date, the two subtypes of craniopharyngioma have been managed identically with surgery followed by radiation therapy if gross total resection was not attained. Recurrence can be as high as 14 to 50%.[5,7,11,31] Even after multimodality treatment, many patients have lifelong sequelae and do not return to their prediagnosis functional status.[2,9,10,32,33] No standard effective medical treatment is recognized for craniopharyngiomas.

Our discovery that more than 90% of papillary craniopharyngiomas carry *BRAF* V600E mutations[13] led to the current precision-medicine trial of a treatment for craniopharyngiomas. In this trial, we not only showed that a national biomarker-driven trial was feasible for a rare type of brain tumor, we also found that targeted therapy led to dramatic responses in every patient in the trial who received one or more cycles of therapy. Responses were observed in both the enhancing and cystic components of the tumors, were durable, and affected subsequent treatment choices.

The availability of an effective targeted agent for craniopharyngioma supports a reconsideration of the existing clinical workflow for the treatment of this disease. A broadly effective therapy could have a transformative effect on the clinical outcomes of these patients by mitigating the known risks and long-term toxic effects of the existing standard-of-care treatments. In this study, vemurafenib and cobimetinib had a side-effect profile similar to that which has been reported among patients with other tumors who received these inhibitors. Furthermore, given that radiation therapy in this patient population is associated with a risk of long-term toxic effects, we found a substantial decrease in potential radiation volumes among patients who had received a short course of treatment with vemurafenib–cobimetinib. Consistent with this observation, only six tumors abutted the optic chiasm after therapy, whereas all the tumors abutted the optic chiasm before therapy. The smaller radiotherapy target volumes that remained after BRAF–MEK inhibitor therapy portend less

radiated normal tissues and therefore probably a lesser risk of radiotherapy-associated toxic effects.

With these data showing remarkable responses in all the patients who received one or more cycles of BRAF–MEK inhibition, a new treatment approach for newly diagnosed papillary craniopharyngiomas is feasible. Practitioners may consider less aggressive initial resection or even biopsy alone for tissue diagnosis and confirmation of a *BRAF* V600E mutation, followed by BRAF–MEK inhibitor therapy. Subsequently, definitive surgery or radiation therapy can be considered, or additional therapy or radiation may be delayed until tumor recurrence or progression. Of note, of the seven patients who had no local consolidation after BRAF–MEK inhibitor therapy, six patients have not had tumor progression.

Whether combined BRAF–MEK inhibition is indicated for therapeutic response or if single-agent BRAF inhibition might be sufficient remains an open question. Other *BRAF*-mutated tumors have high rates of developing resistance during BRAF monotherapy as compared with combination regimens.[34–36] We chose the combination, given the improved progression-free and overall survival observed with the use of combination BRAF–MEK inhibitors in other tumor types,[34,36] as well as the concerning rate of specific toxic side effects, such as proliferative skin lesions, that have been seen with BRAF monotherapy. Moreover, a case report of single-agent BRAF inhibition showed progressive regrowth in a papillary craniopharyngioma after an initial response.[37] Although other approved BRAF–MEK inhibitors are available, our trial used vemurafenib and cobimetinib because of drug availability at the time of protocol development. Case reports have described dramatic responses of papillary craniopharyngioma to treatment with dabrafenib and trametinib, which suggests that other BRAF–MEK inhibitor combinations have promise in the treatment of this disease.[24–27]

Our trial has limitations. This was a single-group study that did not include a control. However, because craniopharyngioma is a rare tumor, we sought to design a study with a small sample size for feasibility, and we powered the study appropriately to detect only a very promising response signal. The question remains regarding the ideal duration of targeted therapy in this patient population. In designing the study, we proposed four cycles of vemurafenib–cobimetinib followed by definitive surgery or radiation. Although three patients discontinued receipt of vemurafenib–cobimetinib early owing to adverse events, many patients continued to receive vemurafenib–cobimetinib beyond the prespecified four cycles because the side-effect profile was acceptable and they continued to have a response; furthermore, a subgroup of patients chose not to receive radiation therapy, and the majority continued to do well, without progressive disease. As more data are collected in long-term follow-up, further insights may be gained about the durability of response, particularly given that early relapses occur in other *BRAF*-mutated cancers, such as melanoma.[34–36] In addition, whether these findings can be extended to recurrent craniopharyngiomas is unclear. To address this question, patients with recurrent craniopharyngioma after radiation are being enrolled in a second group of this study. Future studies would benefit from comprehensive quality-of-life assessments and the use of patient-reported outcome tools in this patient population.

The finding of circulating *BRAF* in a subgroup of patients raises the intriguing possibility of noninvasive detection of disease in this patient population. However, since this was a multicenter study, the processing of plasma samples at each site was not uniform, with considerable variability in the quality of samples. Data from precise assessments of the sensitivity and specificity of detection of *BRAF* mutations in peripheral-blood samples obtained from patients with craniopharyngioma are lacking. Further studies will be needed with more plasma samples and more uniform sample processing to establish the best protocols for blood-based genomic diagnostic monitoring in this patient population.

The results of this biomarker-driven trial for papillary craniopharyngiomas showed durable partial or better responses in all patients who received at least one cycle of vemurafenib–cobimetinib.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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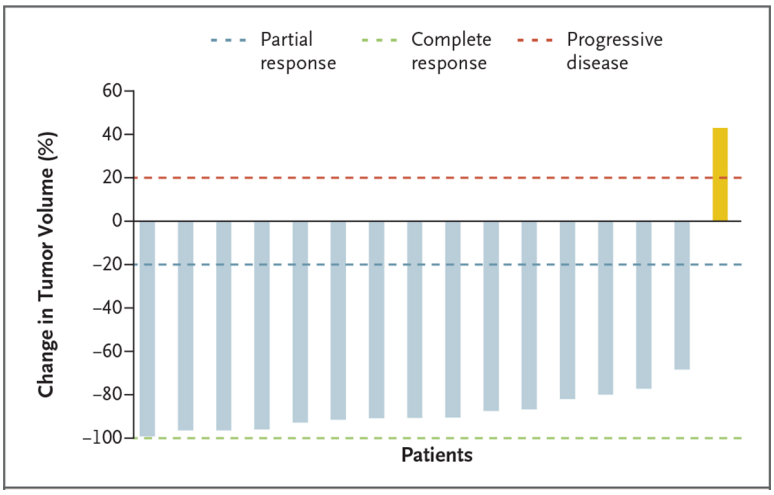

Figure 1. Change in Tumor Volume from Baseline.

The blue bars indicate the 15 patients with papillary craniopharyngiomas who had a partial response to vemurafenib–cobimetinib therapy. The yellow bar indicates 1 patient who received only 8 days of therapy before withdrawing because of toxic effects. The horizontal dashed lines indicate the corresponding measures for each type of response.

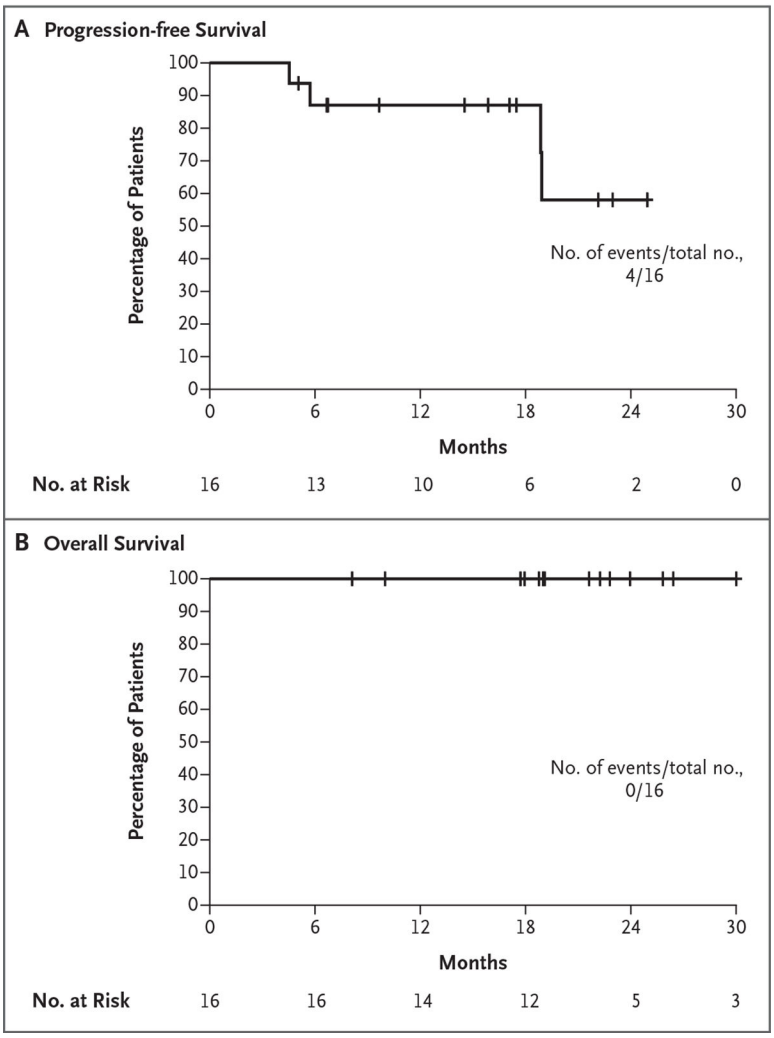

Figure 2. Estimates of Progression-free and Overall Survival.

Panel A shows the Kaplan–Meier estimates of progression-free survival as assessed by central review. Progression-free survival was estimated to be 87% (95% CI, 57 to 98) at 12 months and 58% (95% CI, 10 to 89) at 24 months. Hatch marks indicate data censoring. Panel B shows the Kaplan–Meier estimates of overall survival. The estimated percentage of overall survival was 100% at 12 months (95% CI, 69 to 100) and 24 months (95% CI, 16 to 100).

Table 1.

Characteristics of the Patients at Baseline.

Characteristic	Value (N = 16)
Age	
Mean ±SD	51.1±12.9
Median	49.5
Range	33.0–83.0
Race — no. (%) *	
White	11 (69)
Asian	3 (19)
Unknown	2 (12)
Ethnic group — no. (%) *	
Hispanic	0
Non-Hispanic	15 (94)
Not reported	1 (6)
Sex — no. (%)	
Female	9 (56)
Male	7 (44)
Age group — no. (%)	
<70 yr	15 (94)
≥70 yr	1 (6)
ECOG performance-status score — no. (%) †	
0 or 1	15 (94)
2	1 (6)
Status of primary tumor — no. (%)	
<50% subtotal resection	5 (31)
≥50% subtotal resection	4 (25)
Biopsy only	4 (25)
Complete resection with recurrence	3 (19)

* Race and ethnic group were reported by the patients.

† Eastern Cooperative Oncology Group (ECOG) performance-status score is measured on a scale of 0 to 5, with higher scores indicating greater disability.

Table 2.

Objective Response at 4 Months.*

Assessment	Value (N = 16)
Volumetric response according to central radiologic review	
Complete or partial response — no. (%)	15 (94)
95% confidence interval	70–100
Nonresponse — no. (%)	1 (6)
Bidimensional response according to local radiologic review	
Complete or partial response — no. (%)	15 (94)
95% confidence interval	70–100
Nonresponse — no. (%)	1 (6)

* The primary end point of volumetric response was determined with the use of volumetric measurement data from the first four cycles of BRAF-MEK inhibitor combination therapy. Bidimensional measurements of lesions were used locally to assess the objective response according to modified Response Assessment in Neuro-oncology (RANO) guidelines.

Table 3.

Grade 3 or 4 Adverse Events at Least Possibly Related to Treatment.

Event	Grade 3	Grade 4
	no. (%)	
Allergic reaction	1 (6)	0
Anaphylaxis	1 (6)	0
Increased creatinine kinase level	0	1 (6)
Prolonged corrected QT interval	2 (12)	0
Other general or administration-site disorder	1 (6)	0
Maculopapular rash	6 (35)	0
Other skin or subcutaneous disorder	1 (6)	0
Hypertension	1 (6)	0
Acne or acneiform rash	1 (6)	0
Dehydration	2 (12)	0
Hemorrhage involving the central nervous system	1 (6)	0
Increased alkaline phosphatase level	2 (12)	0
Hyperglycemia	1 (6)	1 (6)
Hyponatremia	1 (6)	0
Pain	1 (6)	0