ORIGINAL ARTICLE

Selumetinib in Children with Inoperable Plexiform Neurofibromas

A.M. Gross, P.L. Wolters, E. Dombi, A. Baldwin, P. Whitcomb, M.J. Fisher, B. Weiss, A.R. Kim, M. Bornhorst, A.C. Shah, S. Martin, M.C. Roderick, D.C. Pichard, A. Carbonell, S.M. Paul, J. Therrien, O. Kapustina, K. Heisey, D.W. Clapp, C. Zhang, C.J. Peer, W.D. Figg, M. Smith, J. Glod, J.O. Blakeley, S.M. Steinberg, D.J. Venzon, L.A. Doyle, and B.C. Widemann

ABSTRACT

BACKGROUND

No approved therapies exist for inoperable plexiform neurofibromas in patients with neurofibromatosis type 1.

METHODS

We conducted an open-label, phase 2 trial of selumetinib to determine the objective response rate among patients with plexiform neurofibromas and to assess clinical benefit. Children with neurofibromatosis type 1 and symptomatic inoperable plexiform neurofibromas received oral selumetinib twice daily at a dose of 25 mg per square meter of body-surface area on a continuous dosing schedule (28-day cycles). Volumetric magnetic resonance imaging and clinical outcome assessments (pain, quality of life, disfigurement, and function) were performed at least every four cycles. Children rated tumor pain intensity on a scale from 0 (no pain) to 10 (worst pain imaginable).

RESULTS

A total of 50 children (median age, 10.2 years; range, 3.5 to 17.4) were enrolled from August 2015 through August 2016. The most frequent neurofibroma-related symptoms were disfigurement (44 patients), motor dysfunction (33), and pain (26). A total of 35 patients (70%) had a confirmed partial response as of March 29, 2019, and 28 of these patients had a durable response (lasting ≥1 year). After 1 year of treatment, the mean decrease in child-reported tumor pain-intensity scores was 2 points, considered a clinically meaningful improvement. In addition, clinically meaningful improvements were seen in child-reported and parent-reported interference of pain in daily functioning (38% and 50%, respectively) and overall health-related quality of life (48% and 58%, respectively) as well as in functional outcomes of strength (56% of patients) and range of motion (38% of patients). Five patients discontinued treatment because of toxic effects possibly related to selumetinib, and 6 patients had disease progression. The most frequent toxic effects were nausea, vomiting, or diarrhea; an asymptomatic increase in the creatine phosphokinase level; acneiform rash; and paronychia.

CONCLUSIONS

In this phase 2 trial, most children with neurofibromatosis type 1 and inoperable plexiform neurofibromas had durable tumor shrinkage and clinical benefit from selumetinib. (Funded by the Intramural Research Program of the National Institutes of Health and others; ClinicalTrials.gov number, NCT01362803.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Gross at the Pediatric Oncology Branch, National Cancer Institute, National Institutes of Health, 9000 Rockville Pike, Bldg. 10, Rm. 1-5742, Bethesda, MD 20892, or at andrea.gross@nih.gov.

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Neurofibromatosis type 1, an autosomal dominant genetic disorder characterized by multiple progressive tumor and nontumor manifestations, has limited treatment options.[1] In patients with the disorder, dysfunction of the guanosine triphosphatase–activating protein neurofibromin leads to overactivation of the RAS pathway.[2] Therefore, targeted inhibition of the RAS pathway with mitogen-activated protein kinase (MAPK) kinase (MEK) inhibition is a logical treatment approach[3] that has been successful in a preclinical model of neurofibromatosis type 1.[4] Plexiform neurofibromas are histologically benign peripheral-nerve sheath tumors that occur in up to 50% of persons with neurofibromatosis type 1[5,6] and can cause substantial complications.[7,8]

In a phase 1 trial of the oral selective MEK inhibitor selumetinib (AZD6244 or ARRY-142886) involving 24 children with inoperable neurofibromatosis type 1–related plexiform neurofibromas, we found a median change in tumor volume of −31% (range, −47 to −6), a confirmed partial response in 17 children (71%), and anecdotal evidence of clinical improvement[9] but no complete responses. Therefore, assessment of whether selumetinib treatment can result in clinically meaningful improvement is critical in order to accurately gauge the benefit–risk ratio of selumetinib treatment in patients with neurofibromatosis type 1. Determining clinical benefit in this population is a challenging task, given that neurofibromas occur in various locations, patients have a wide variety of neurofibroma-related symptoms, and few validated patient-reported or functional outcome measures for neurofibromatosis type 1 exist. The goal of this phase 2 trial was to confirm the objective response rate of plexiform neurofibromas to selumetinib (primary objective) and to assess whether treatment was associated with clinical benefit (key secondary objectives).

METHODS

TRIAL OVERSIGHT

This trial was coordinated by the National Cancer Institute (NCI), Center for Cancer Research, Pediatric Oncology Branch (POB), and sponsored by the Cancer Therapy Evaluation Program (CTEP). The trial was conducted at four participating sites: NCI POB, Children's Hospital of Philadelphia, Cincinnati Children's Hospital, and Children's National Hospital. The trial protocol (available with the full text of this article at NEJM.org) was designed and written by the NCI investigators. AstraZeneca provided selumetinib for the trial, approved the trial protocol, and provided financial support for the analysis of selumetinib in plasma samples and for the conduct of the clinical trial through a Cooperative Research and Development Agreement with the NCI CTEP. AstraZeneca did not have a role in patient recruitment, data analysis, or manuscript preparation but participated in the review and approval of the manuscript for submission. The protocol was approved by the institutional review board at each participating site. All the patients or their legal guardians provided written informed consent. The authors vouch for the accuracy and completeness of the data reported and for the fidelity of the trial to the protocol.

PATIENTS

Children 2 to 18 years of age who had received a clinical diagnosis of neurofibromatosis type 1,[10] who had inoperable, measurable plexiform neurofibromas,[11] and who were able to swallow intact capsules were eligible to participate. We enrolled patients in two strata: stratum 1 for patients with at least one neurofibroma-related complication and stratum 2 for those with no clinically significant neurofibroma-related complications but with the potential for development of a neurofibroma-related complication (complete eligibility criteria and other details are provided in the trial protocol). This report includes the results from stratum 1 only. All the patients underwent scheduled clinical and laboratory safety evaluations, echocardiography, ophthalmology examinations, magnetic resonance imaging (MRI), patient-reported and observer-reported outcome assessments, and evaluations of functional response (Table 1).

DRUG ADMINISTRATION AND SAFETY ASSESSMENTS

Selumetinib was administered at the recommended phase 2 dose (25 mg per square meter of body-surface area)[9,12] approximately every 12 hours in 28-day cycles on a continuous dosing schedule. Medication adherence was assessed by review of patient diaries and capsule counts (see Section A in the Supplementary Appendix, available at NEJM.org).

Patients with progressive disease at trial entry (≥20% increase in neurofibroma volume

Table 1. Trial Evaluations.*

Evaluation	Category of Plexiform Neurofibroma–Related Complications	Baseline	Time Point after Baseline†
Safety and disease evaluations			
History taking and physical examination, safety laboratory studies	All	Yes	Before cycles 2, 3, 4, 5, 7, 9, 11, 13, 17, 21, and 25, then every 6 cycles
Echocardiography, plexiform neurofibroma disease evaluation (MRI)‡	All	Yes	Before cycles 5, 9, 13, 17, 21, and 25, then every 6 cycles
Ophthalmologic examination	All	Yes	Before cycles 5 and 13, then every 12 cycles
Patient diary and capsule count	All	No	Before cycles 3, 5, 9, 13, 17, 21, and 25, then every 6 cycles
Pharmacokinetics and pharmacodynamics			
Selumetinib and N-desmethyl selumetinib	All	Yes	Before cycle 2 or 3
Cytokines and bone marrow–derived precursor cells	All	Yes	Before cycles 3, 5, 9, and 13 and at the time of progression
Patient-reported outcome measures			Before cycles 3, 5, 9, and 13, then every 12 cycles
Pain intensity (NRS-11)‡	All ≥8 yr of age	Yes	
Pain Interference Index‡	All ≥5 yr of age§	Yes	
PedsQL quality-of-life scales‡	All§	Yes	
Global Impression of Change scale‡	All ≥5 yr of age§	No	
PROMIS Mobility and Upper Extremity scales	Motor§	Yes	
Functional measures			Before cycles 5, 9, and 13, then every 12 cycles
Photography and videography	All visible plexiform neurofibromas	Yes	
Strength evaluation (manual muscle testing using the MRC scale)‡	Motor	Yes	
Range of motion‡	Motor	Yes	
Leg length evaluation, grooved pegboard test	Motor	Yes	
6-Min walk test	Motor, airway¶	Yes	
Polysomnography‡	Airway¶	Yes	
Pulmonary-function tests (spirometry, impulse oscillometry)‡	Airway¶	Yes	
Exophthalmometry‡	Orbital	Yes	
Visual acuity‡	Orbital	Yes	
Bowel and bladder questionnaire‡	Bowel and bladder	Yes	
Audiologic and otolaryngology examination	Other	Yes	
Speech evaluation, swallow study	Other	Yes	

* At baseline, all the patients were assigned to one or more categories of plexiform neurofibroma–related complications on the basis of the location of the target neurofibroma and the clinical presentation. This assignment then determined the patient-reported outcome, observer-reported outcome, and functional evaluations that the patient would complete for the duration of the trial. MRC denotes Medical Research Council, MRI magnetic resonance imaging, NRS-11 the 11-item Numerical Rating Scale, PedsQL Pediatric Quality of Life Inventory, and PROMIS Patient-Reported Outcomes Measurement Information System.
† One cycle equals 28 days.
‡ Shown are key outcome measures.
§ For all scales, child-reported scores are for children 8 years of age or older, and parent-reported scores are for children 5 years of age or older, except for the PedsQL, in which parent-reported scores are for children 2 years of age or older.
¶ Patients with tracheostomy or other invasive airway support were not required to complete these functional evaluations.

≤15 months before enrollment) could continue to receive selumetinib as long as they did not have disease progression during treatment. Patients without disease progression at trial entry could continue treatment for a maximum of 2 years unless a partial response was observed, in which case treatment could continue until criteria for discontinuation of trial therapy were met. A complete list of criteria for discontinuation of trial therapy and discontinuation of trial participation are provided in Section B in the Supplementary Appendix.

Adverse events were graded with the use of the NCI Common Terminology Criteria for Adverse Events, version 4.0. Definitions of dose-modifying toxic effects are included in Section C in the Supplementary Appendix. Up to two dose reductions were allowed for selumetinib-related toxic effects (see Section D in the Supplementary Appendix).

EVALUATION OF TUMOR RESPONSE

Tumor-response evaluation was performed centrally at the NCI by (nonblinded) volumetric analysis of the MRI[11] of the plexiform neurofibroma. At baseline, the most clinically relevant tumor was selected by the treating physician as the target lesion and was used to determine response to treatment. (For details on tumor volumetric MRI assessment, see Section E in the Supplementary Appendix.)

ASSESSMENT OF CLINICAL BENEFIT

We conducted comprehensive, prospective, standardized clinical evaluations of functional, patient-reported, and observer-reported outcome measures that were tailored to the location of the target neurofibromas. Children of sufficient age, their parents, or both completed patient-reported outcome measures that have been validated in pediatric populations. The evaluations assessed pain intensity (11-point Numerical Rating Scale [NRS-11][13]), interference of pain in daily functioning (Pain Interference Index[14,15]), health-related quality of life (Pediatric Quality of Life Inventory [PedsQL] Generic Core Scales[16,17]), and perceived changes with treatment (Global Impression of Change scale[18]). NRS-11 scores range from 0 (no pain) to 10 (worst pain imaginable). Scores on the Pain Interference Index range from 0 to 6, with higher scores indicating greater pain interference. PedsQL scores range from 0 to 100, with higher scores indicating better health-related quality of life. Scores on the Global Impression of Change scale range from 1 (very much improved) to 7 (very much worse). For patients with a neurofibroma-related motor complication, children and parents also completed the Patient-Reported Outcomes Measurement Information System (PROMIS) Mobility and Upper Extremity short forms[19,20] to assess physical functioning. PROMIS T scores have a mean of 50 and a standard deviation of 10, with higher scores indicating better physical function. (For details on patient- and observer-reported measures, see Section F in the Supplementary Appendix.)

On the basis of the location of the target plexiform neurofibroma and the clinical presentation, each patient was assigned to one or more categories of neurofibroma-related complications (disfigurement, airway impairment, bowel or bladder dysfunction, motor dysfunction, pain, vision, and other). The presence or absence of disfigurement as a neurofibroma-related complication was the subjective decision of the trial team and was based on whether the neurofibroma was visible and distorted normal anatomical features.

Each patient underwent standardized functional evaluations according to the relevant category or categories of neurofibroma-related complications (Table 1). Key measurements were chosen from each complication category to assess for change over time (see Section G in the Supplementary Appendix).

RESPONSE CRITERIA

Patients were considered able to be evaluated for response after receiving at least one dose of selumetinib. A partial response was defined as a target neurofibroma volume decrease from baseline of at least 20%; a confirmed partial response was defined as a partial response on consecutive restaging examinations at least 3 months apart; and a durable partial response was defined as a partial response lasting for at least 12 cycles (approximately 1 year). Progressive disease was defined as a volume increase from baseline of at least 20% or, if a patient had had a partial response, an increase of at least 20% from the best response. The overall response rate was defined as the percentage of patients with a confirmed partial response in an intention-to-treat analysis.

EFFECT OF SELUMETINIB ON THE NATURAL HISTORY OF NEUROFIBROMA GROWTH

To assess whether selumetinib alters the natural history of neurofibroma growth, we compared changes in the size of neurofibromas in patients who received selumetinib in this trial with the growth of neurofibromas in age-matched patients in the NCI natural-history study of neurofibromatosis type 1, who did not receive selumetinib (ClinicalTrials.gov number, NCT00924196) (see Section I in the Supplementary Appendix).

PHARMACOKINETIC AND PHARMACODYNAMIC MARKERS

The pharmacokinetics of selumetinib in plasma were assessed at baseline and at a steady state, and the pharmacodynamics of selumetinib were assessed by measuring levels of circulating hematopoietic stem cells and progenitor cells. Methods for and results of these analyses are available in Sections J, T, and U in the Supplementary Appendix.

STATISTICAL ANALYSIS

The sample size for the primary objective of tumor response was based on a target response rate to rule out a 15% response rate with a lower two-sided 95% confidence boundary (see Section H in the Supplementary Appendix). For most patient- and observer-reported outcomes and functional measures obtained, no validated thresholds for clinically meaningful change exist in the pediatric population with neurofibromatosis type 1; therefore, we described the changes in each measurement over time, primarily between baseline and after cycle 12 of treatment, using descriptive statistics including the reporting of 95% confidence intervals where appropriate. For the patient- and observer-reported outcomes and functional measures, patients were considered able to be evaluated if they had measurements completed at baseline and at the evaluation after cycle 12. Where published literature provided guidance for defining clinically meaningful changes in children with neurofibromatosis type 1 or a clinically similar pediatric population, we applied those criteria (see Sections F and G in the Supplementary Appendix). For those measures with no neurofibromatosis type 1–specific definitions of clinically meaningful change, a minimal clinically important difference (MCID) was calculated with the use of a standardized distribution-based method of greater than 0.5 SD.[21-23] Spearman correlations were used to assess for relationships between changes in clinical measures and neurofibroma volume.

RESULTS

PATIENT CHARACTERISTICS

A total of 50 patients (median age, 10.2 years; range, 3.5 to 17.4) were enrolled in stratum 1 from August 2015 through August 2016 (Table 2). Data as of March 29, 2019, are reported here (median total number of treatment cycles, 36; range, 0 to 47). The median target neurofibroma volume at baseline was 487 ml (range, 5 to 3820). A total of 21 patients (42%) had progressive neurofibromas at enrollment. Patients had a median of three neurofibroma-related complications (range, one to five), the most common being disfigurement (44 patients), motor dysfunction (33), and pain (26). (For details on neurofibroma-related complications, see Section K in the Supplementary Appendix.)

TUMOR VOLUMETRIC RESPONSE

A total of 37 of 50 patients (74%; 95% confidence interval [CI], 60 to 85) had a partial response, 35 (70%) had a confirmed partial response, and 28 (56%) had a durable response. The median time to initial response was 8 cycles (range, 4 to 20), and the median time to best response was 16 cycles (range, 4 to 36). The median change in neurofibroma volume at best response was –27.9% (range, –55.1 to 2.2). (For details on tumor response, see Section L in the Supplementary Appendix.) The median duration of response and median progression-free survival were not reached, with progression-free survival of 84% as of 3 years since the start of treatment (Fig. 1). Age at enrollment, the volume and progression status of the target neurofibroma at baseline, and the location of the target neurofibroma did not distinguish patients who had a partial response from those who did not (data not shown).

At the time of data cutoff, 23 patients (46%) continued to have a partial response, 6 (12%) had stable disease, and 21 (42%) had discontinued treatment. Reasons for discontinuation were progressive disease (5 patients), stable disease (nonprogressive at baseline) (2), toxic effects (5), and

Table 2. Characteristics of the Patients and Target Plexiform Neurofibromas at Baseline.

Characteristic	Value
Patients enrolled — no.	50
Median age at enrollment (range) — yr	10.2 (3.5–17.4)
Sex — no.	
Male	30
Female	20
Median volume of target neurofibroma (range) — ml	487 (5–3820)
Progression status of target neurofibroma at trial entry — no.	
Progressive	21
Nonprogressive	15
Insufficient data	14
Location of the target neurofibroma — no.	
Neck and trunk	12
Trunk and limbs	12
Limbs only	4
Head only	9
Head and neck	8
Trunk only	5
No. of neurofibroma-related complications per patient (range)	3 (1–5)
Type of neurofibroma-related complication — no. (%)	
Disfigurement	44 (88)
Motor dysfunction	33 (66)
Pain	26 (52)
Airway	16 (32)
Vision	10 (20)
Bowel or bladder	10 (20)
Other	11 (22)

other reasons (discretion of the site principal investigator [4 patients], patient declined further treatment [2], nonadherence [1], and development of intercurrent illness [malignant peripheral-nerve sheath tumor] [2]). One patient who discontinued treatment because of a toxic effect was found to have progressive disease at the time of off-treatment assessment 24 days later. Of the 6 patients with progressive disease, 5 had previous dose reductions.

In contrast to the patients receiving selumetinib, 73 of 93 age-matched controls (78%) in the NCI natural-history study of neurofibromatosis type 1 had a neurofibroma volume increase of at least 20% over the same period of time as this treatment trial (3.2 years), with a median progression-free survival of 1.3 years (95% CI, 1.1 to 1.6) and a progression-free survival of 15% at 3 years (Fig. 1). No patients in the natural-history study had tumor shrinkage of more than 20% during this time period. (For details on results in age-matched controls, see Section M in the Supplementary Appendix.)

PATIENT-REPORTED, OBSERVER-REPORTED, AND FUNCTIONAL OUTCOME MEASURES

Overview of Results

We collected serial patient-reported outcomes and functional measures in most patients, with very few missing evaluations (Section N in the Supplementary Appendix). A majority of patients (68%) had some degree of improvement in at least one of the various functional, patient-reported, and observer-reported outcome measures over time (Fig. 2A and Sections O and P in the Supplementary Appendix). For data on MCIDs, see Section Q in the Supplementary Appendix.

Pain

A total of 29 children had data on tumor pain intensity (physician-selected target tumor) that could be evaluated, and 29 children and 42 parents had data on pain interference that could be evaluated. After 12 months of treatment with selumetinib, there were substantial decreases in child-reported tumor pain intensity (mean change in the NRS-11 score, –2.14 points; 95% CI, –3.14 to –1.14) and child-reported and parent-reported pain interference (mean change in the Pain Interference Index score, –0.62 points [95% CI, –1.02 to –0.21] and –0.81 points [95% CI, –1.32 to –0.31], respectively), with a decrease occurring as early as 2 months after initiation of treatment for pain intensity and 4 months for pain interference (data not shown). Of 19 patients with a baseline NRS-11 score of more than 0 (physician-selected target tumor), 14 (74%) had a decrease of at least 2 points in the score, which is considered a clinically meaningful improvement.[24,25] Of the 17 patients who had a decrease in the NRS-11 score, 16 (94%) had either no change or a decrease in the number of pain medications they were taking. The Pain Interference Index scores of 38% of the children and 50% of the parents decreased substantially (greater than the distribution-based MCID of 0.53 points and 0.81 points, respectively).

Quality of Life

A total of 29 children and 45 parents had data on health-related quality of life that could be evaluated. The mean total quality-of-life score on the PedsQL increased, indicating improvement, on child-reported measures (mean change, 6.7 points; 95% CI, 0.1 to 13.3) and parent-reported measures (mean change, 13.0 points; 95% CI, 8.1 to 17.8). A total of 48% of children and 58% of parents reported clinically meaningful increases (greater than the distribution-based MCID of 8.7 points and 8.1 points, respectively) in the score after 1 year of treatment. The mean child-reported score on the physical-functioning domain increased (improved) from baseline to 1 year (mean change, 6.7 points; 95% CI, 0 to 15.6), and the mean parent-reported scores increased on the physical, emotional, and social scales (mean changes, 13.8 points [95% CI, 7.8 to 19.8], 17.4 points [95% CI, 11.1 to 23.8], and 11.7 points [95% CI, 5.0 to 18.5], respectively) over this time period.

Global Impression of Change

The mean child-reported and parent-reported scores on the Global Impression of Change scale at 1 year indicated that the child's "tumor-related problems other than pain" were "much improved" (median score, 2 in children and parents). After 12 cycles, 72% of children and 86% of parents reported some level of improvement with respect to the child's tumor-related problems (Fig. 2B). Only 1 of 29 children and 1 of 43 parents reported changes as being in the "minimally worse" rating category, and no children or parents reported the changes as being "much worse" or "very much worse."

Motor Dysfunction

A total of 33 patients had motor dysfunction at baseline. Of 18 patients with motor dysfunction and data on strength that could be evaluated, 14 (78%) improved their strength, with a median increase in the total strength score of 4.8% (95% CI, 1.1 to 11.1) with the use of manual muscle testing between baseline and after cycle 12. A total of 10 patients (56%) had a clinically meaningful increase in strength (greater than the distribution-based MCID of 4.6%). Range of motion also increased over time, with a median increase of 3.9% (95% CI, 2.9 to 9.6), and 10 of 26 patients (38%) had a clinically meaningful increase in range of motion (greater than the distribution-based MCID of 7.6%). An example of a patient with clinically meaningful improvement in both strength and range of motion is shown in Figure 3A through 3C.

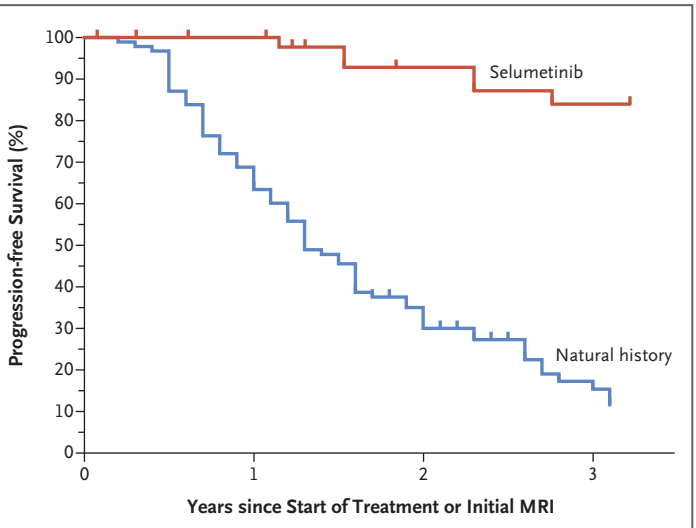


Figure 1. Target Plexiform Neurofibroma Progression–free Survival during Selumetinib Treatment as Compared with Natural History of Neurofibromatosis Type 1.

At 3 years of follow-up, the progression-free survival was 15% in the natural-history group and 84% in the selumetinib group.

Between baseline and after cycle 12, the mean T scores for the child-reported scores on the PROMIS Mobility scale (20 children) and Upper Extremity scale (19 children) did not change substantially. The mean T scores of 15 of 28 parents (54%) showed a clinically meaningful increase (greater than the distribution-based MCID of 2.2 points) from baseline to 1 year in the child's mobility (mean change, 3.0 points; 95% CI, 1.3 to 4.7), but fewer of the parents' scores showed a meaningful increase in the child's shoulder, arm, and hand function.

Airway Impairment

A total of 16 patients had airway impairment at baseline. One of 5 patients with a tracheostomy at baseline was able to be decannulated after 12 cycles of therapy owing to neurofibroma shrinkage by 25.8%. For the remaining 11 patients with spirometry testing, the median forced expiratory volume in 1 second (FEV_1) increased during treatment. A total of 7 patients met the literature-defined threshold for clinically meaningful improvement of at least 12%,[26] and 3 had a similar

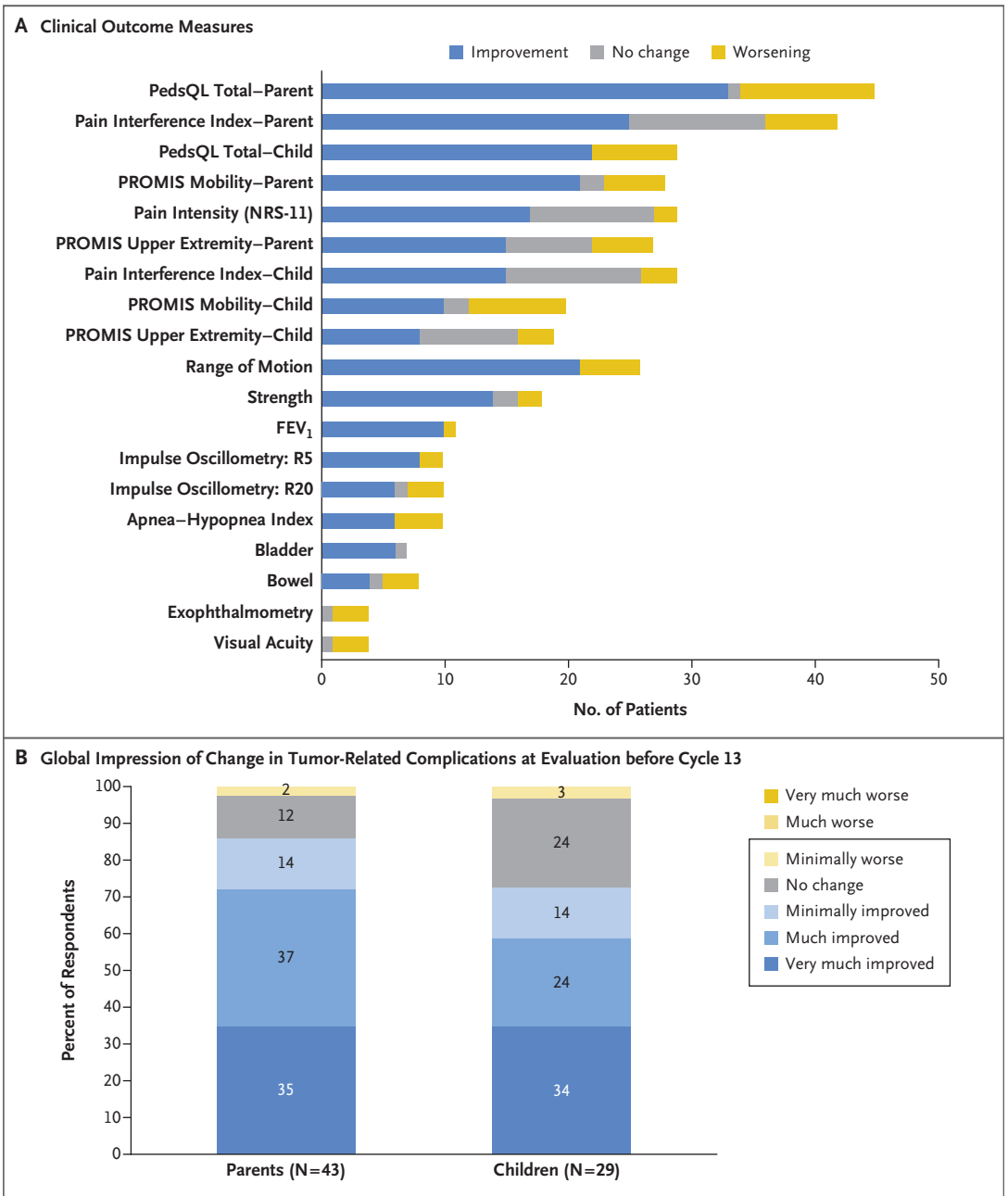
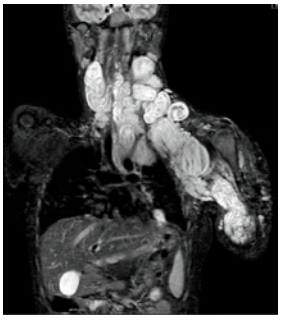


Figure 2. Change in Plexiform Neurofibroma–Related Complications between Baseline and the Evaluation before Cycle 13 of Treatment with Selumetinib.

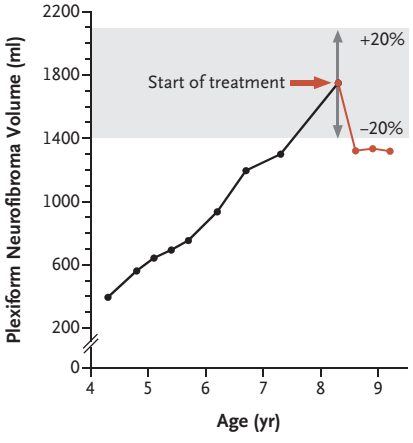
Most patients had some degree of improvement or no change and few had any worsening in functional, patient-reported, and observer-reported outcome measures of plexiform neurofibroma–related symptoms (Panel A). FEV_1 denotes forced expiratory volume in 1 second, NRS-11 the 11-item Numerical Rating Scale, PedsQL the Pediatric Quality of Life Inventory, PROMIS Patient-Reported Outcomes Measurement Information System, R5 airway resistance at 5 Hz, and R20 airway resistance at 20 Hz. On the Global Impression of Change scale (Panel B), 86% of parents (37 of 43) and 72% of children (21 of 29) (blue shaded areas) who completed the form reported some level of improvement with respect to the child's plexiform neurofibroma–related complications (other than pain) at the evaluation before cycle 13. Percentages may not total 100 because of rounding.

degree of improvement in the percentage of predicted FEV_1 based on age, sex, and height, which confirms that at least some of the improvements were not simply related to the patients' linear growth.[26] There was a clinically meaningful improvement in airway resistance as measured by impulse oscillometry (resistance at 5 Hz) in 5 patients. Among 10 patients with data on polysomnography that could be evaluated, no meaningful change in airway obstruction during sleep was noted. However, none of the patients had a baseline score on the Apnea–Hypopnea Index of more

A MRI of Patient 1



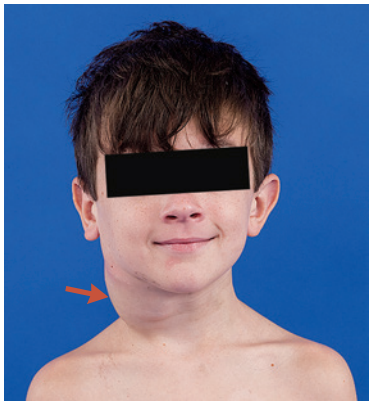
B Tumor Volume in Patient 1



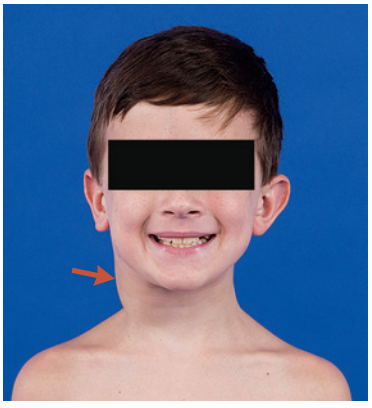
C Clinical Outcomes in Patient 1

Outcome Measure	Baseline	Evaluation before Cycle 13
Tumor volume — ml	1748	1318
NRS-11 score	3	0
Pain Interference Index		
Child-reported	2	1
Parent- or guardian-reported	3.7	0.8
Score on strength scale	9.5	10.0
Range of motion — degrees	649	977
Neck extension — degrees	42	72
Neck lateral flexion, left — degrees	10	47
Shoulder abduction, left — degrees	75	180
Internal rotation, left — degrees	46	90
External rotation, left — degrees	42	90

D Patient 2 at Baseline



E Patient 2 before Cycle 13



F Tumor Volume in Patient 2

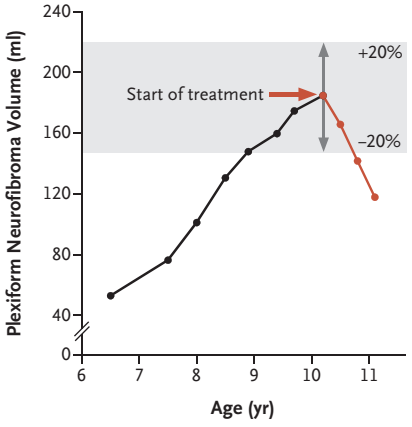


Figure 3. Examples of Specific Patients.

Panels A through C relate to an 8-year-old boy (Patient 1) with a large plexiform neurofibroma in the left neck, arm, and trunk (Panel A) that had a baseline volume of 1748 ml (Panel B). The patient received ibuprofen daily for tumor pain, and the tumor caused limitations in range of motion and strength at baseline (Panel C), with values marked in red indicating range of motion more than 2 SD below age- and sex-matched expected normal values. He had a 24.6% decrease in plexiform neurofibroma volume (Panel B) at the evaluation before cycle 13 with resolution of pain, allowing him to discontinue ibuprofen. In addition, the strength and range of motion of the muscles and joints in the body quadrant of the target plexiform neurofibroma increased by 5.3% and 50.5%, respectively, with normalization of his neck and shoulder movement (Panel C). NRS-11 scores range from 0 (no pain) to 10 (worst pain imaginable). Scores on the Pain Interference Index range from 0 to 6, with higher scores indicating greater interference of pain in daily functioning. Scores on the strength scale reflect the average strength of muscles in the quadrant of the target plexiform neurofibroma; scores range from 0 to 10, with higher scores indicating greater strength. The value for range of motion is the sum of degrees of motion in the joints in the body quadrant of the target plexiform neurofibroma. Panels D through F relate to a 10-year-old boy (Patient 2) with a plexiform neurofibroma in the right neck (baseline volume, 185 ml). The tumor shrank 36.2% after 12 cycles of treatment (Panel F), with a visible decrease in the disfigurement caused by the neurofibroma (Panels D and E). MRI denotes magnetic resonance imaging.

than 5, which is considered to be the lower limit necessary to see a meaningful effect of treatment.[26]

Other Outcomes

A total of 10 patients had visual impairment at baseline. Among these patients, no significant changes in visual acuity or exophthalmometry measurements over time were noted. A total of 10 patients had bowel dysfunction, bladder dysfunction, or both at baseline. Bowel incontinence resolved in 3 of 5 patients, and daytime urinary incontinence resolved in 2 of 6 patients. A total of 44 patients had disfigurement at baseline. Many patients and parents reported subjective improvement in appearance, with 24 parents and 11 children describing improved appearance on the Global Impression of Change Scale at 1 year. An example of a patient with a decrease in neurofibroma-related disfigurement with treatment is shown in Figure 3D through 3F.

CORRELATION BETWEEN CLINICAL EVALUATIONS AND VOLUMETRIC RESPONSE

No moderate or strong correlations were noted between changes in functional or patient-reported outcome assessments and percentage change in tumor volume. (For scatter plots of correlation, see Section R in the Supplementary Appendix.)

SAFETY AND ADVERSE-EVENT PROFILE

Patients received a median of 36 cycles (range, 0 to 47) of selumetinib, with medication adherence of more than 95% for most according to pill count for the first 12 cycles (see Section N in the Supplementary Appendix). The most common toxic effects were grade 1 and 2 gastrointestinal symptoms (nausea, vomiting, or diarrhea), an asymptomatic increase in the creatine phosphokinase level, acneiform rash, and paronychia (see Section S in the Supplementary Appendix). A total of 14 patients (28%) had dose reductions for toxic effects. Five of these patients (10%) discontinued treatment owing to toxic effects considered by the investigators to be possibly related to selumetinib: grade 3 diarrhea (cycle 3), grade 3 weight gain (cycle 9), grade 3 paronychia (cycle 15), grade 4 skin ulceration (cycle 19), and grade 4 elevated creatinine level (cycle 8). None of the patients had symptomatic changes in the left ventricular ejection fraction or had retinal serous detachment or another vision-threatening ocular effect.

DISCUSSION

We previously reported evidence of shrinkage of plexiform neurofibromas in children who received selumetinib, with confirmed partial responses in 71% of the children, but that phase 1 trial did not assess clinical benefit.[9] Demonstration of clinically meaningful benefit with an acceptable safety profile is required for long-term use of an antineoplastic agent in children with neurofibromatosis type 1. Therefore, in addition to confirming the response rate and duration of response (primary objective), our current trial assessed whether selumetinib treatment could provide clinical benefit (key secondary objectives).

Patients with substantial neurofibroma-related complications were enrolled, and we obtained near-complete scheduled patient-reported outcome assessments and functional evaluations. We confirmed our previously reported response rate (70% in the current trial) and found clinically meaningful benefit from treatment with selumetinib. Most responses were durable, lasting more than 1 year.[7,27] Only a small number of patients had progressive disease during the trial, and most of these patients (five of six) had dose reductions before progression. In addition to tumor shrinkage, 68% of the patients had some degree of improvement with respect to at least one plexiform neurofibroma–related complication such as pain or a limitation in physical functioning (Fig. 2A). It is notable that the decrease in neurofibroma-related pain intensity reached clinically meaningful levels in 74% of the patients.[24,25] Furthermore, 38% of the children and 50% of the parents reported a clinically meaningful decrease in pain interference, and 48% and 58%, respectively, reported a clinically meaningful increase in health-related quality of life. The majority of the children and parents (72% and 86%, respectively) reported improvements as compared with baseline on the Global Impression of Change scale, and the few who reported minor worsening noted that these were primarily due to selumetinib-related toxic effects, all of which were reversible with treatment interruption.

Overall, plexiform neurofibroma–related functional deficits generally remained stable or improved during treatment (Fig. 2A). Improvements in strength and airway function reached clinical significance in a subgroup of patients. These re-

sults differ from existing natural-history data showing that neurofibroma-related complications worsen over time.[7,8]

The tumor shrinkage and lack of progression in this trial are in stark contrast to the findings of the NCI natural-history study, in which most patients had disease progression (Fig. 1) and none had shrinkage of more than 20% during a matching period of observation. These results also differ from those of previous clinical trials[28-31] involving patients with progressive plexiform neurofibromas in which volume decreases of at least 20% were rare.

In the current trial, toxic effects of selumetinib were similar to those reported previously, including an asymptomatic increase in the creatine phosphokinase level, gastrointestinal symptoms, paronychia, and rash. No irreversible or cumulative toxic effects were noted, with no decreased cardiac ejection fraction resulting in dose interruption or retinal serous detachment.[32-34] Long-term safety evaluations are under way as part of this trial.

A limitation of our trial is that, with the exception of the Pain Interference Index[15] and the measurements of visual acuity,[35] the other outcome measures that were used have not yet been validated for the population with neurofibromatosis type 1. We also did not find a direct correlation between change in neurofibroma size and patient-reported outcomes or functional responses. This relationship is probably influenced by multiple factors, including neurofibroma location, growth rate, and the degree of neurofibroma-related pain. Even small tumors (e.g., orbital tumors) can result in considerable symptoms, so there was not a direct relationship between neurofibroma volume and degree of symptoms even at baseline. Similarly, even small reductions in volume can yield benefit in some situations (e.g., in patients with spinal cord compression). In addition, the fact that most patients had some decrease in neurofibroma volume and very few had volume increases makes the establishment of any correlation statistically challenging.

Recently, other MEK inhibitors have also resulted in partial responses in patients with neurofibromatosis type 1–related neurofibroma,[36-38] and selumetinib treatment resulted in shrinkage in neurofibromatosis type 1–related gliomas in the optic pathway.[39] These findings confirm MEK inhibition as a rational treatment strategy for neurofibromatosis type 1–related tumors.

In this phase 2 trial of selumetinib in children with neurofibromatosis type 1 and symptomatic plexiform neurofibroma, selumetinib resulted in sustained neurofibroma shrinkage in the majority of patients and provided clinically meaningful benefit. The toxicity level and absence of cumulative toxic effects permit long-term treatment.

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APPENDIX

The authors' full names and academic degrees are as follows: Andrea M. Gross, M.D., Pamela L. Wolters, Ph.D., Eva Dombi, M.D., Andrea Baldwin, P.N.P., Patricia Whitcomb, R.N., Michael J. Fisher, M.D., Brian Weiss, M.D., AeRang Kim, M.D., Ph.D., Miriam Bornhorst, M.D., Amish C. Shah, M.D., Ph.D., Staci Martin, Ph.D., Marie C. Roderick, Psy.D., Dominique C. Pichard, M.D., Amanda Carbonell, R.N., Scott M. Paul, M.D., R.M.D., Janet Therrien, B.S., Oxana Kapustina, M.L., Kara Heisey, B.S., D. Wade Clapp, M.D., Ph.D., Chi Zhang, Ph.D., Cody J. Peer, Ph.D., William D. Figg, Pharm.D., Malcolm Smith, M.D., Ph.D., John Glod, M.D., Ph.D., Jaishri O. Blakeley, M.D., Seth M. Steinberg, Ph.D., David J. Venzon, Ph.D., L. Austin Doyle, M.D., and Brigitte C. Widemann, M.D.

The authors' affiliations are as follows: the Pediatric Oncology Branch (A.M.G., P.L.W., E.D., P.W., S.M., M.C.R., D.C.P., A.C., J.T., O.K., J.G., B.C.W.) and the Clinical Pharmacology Program (C.J.P., W.D.F.), Center for Cancer Research, National Cancer Institute, and the Rehabilitation Medicine Department, Clinical Center (S.M.P), National Institutes of Health, Bethesda, the Clinical Monitoring Research Program Directorate, Frederick National Laboratory for Cancer Research, National Cancer Institute, Frederick (A.B., K.H.), the Cancer Therapy Evaluation Program (M.S., L.A.D.) and the Biostatistics and Data Management Section, Center for Cancer Research

(S.M.S., D.J.V.), National Cancer Institute, National Institutes of Health, Shady Grove, and Johns Hopkins University School of Medicine, Baltimore (J.O.B.) — all in Maryland; Children's Hospital of Philadelphia, Philadelphia (M.J.F., A.C.S.); Cincinnati Children's Hospital, Cincinnati (B.W.); Children's National Hospital, Washington, DC (A.K., M.B.); and Indiana University School of Medicine, Indianapolis (D.W.C., C.Z.).

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