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# Long-term safety and efficacy of selumetinib in children with neurofibromatosis type 1 on a phase 1/2 trial for inoperable plexiform neurofibromas

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**Abstract**

**Background**. Selumetinib shrank inoperable symptomatic plexiform neurofibromas (PN) in children with neurofibromatosis type 1 (NF1) and provided clinical benefit for many in our previously published phase 1/2 clinical trials (SPRINT, NCT01362803). At the data cutoff (DCO) of the prior publications, 65% of participants were still receiving treatment. This report presents up to 5 years of additional safety and efficacy data from these studies.

**Methods**. This manuscript includes data from the phase 1 and phase 2, stratum 1 study which included participants with clinically significant PN-related morbidity. Participants received continuous selumetinib dosing (1 cycle = 28 days). Safety and efficacy data through February 27, 2021 are included. PN response assessed by volumetric magnetic resonance imaging analysis: Confirmed partial response (cPR) ≥20% decrease from baseline on 2 consecutive evaluations. Phase 2 participants completed patient-reported outcome measures assessing tumor pain intensity (Numeric Rating Scale-11) and interference of pain in daily life (pain interference index).

**Results**. For the 74 children (median age 10.3 years; range 3–18.5) enrolled, overall cPR rate was 70% (52/74); median duration of treatment was 57.5 cycles (range 1–100). Responses were generally sustained with 59% (44) lasting ≥ 12 cycles. Tumor pain intensity ($n = 19$, $P = .015$) and pain interference ($n = 18$, $P = .0059$) showed durable improvement from baseline to 48 cycles. No new safety signals were identified; however, some developed known selumetinib-related adverse events (AEs) for the first time after several years of treatment.

**Conclusions**. With up to 5 years of additional selumetinib treatment, most children with NF1-related PN had durable tumor shrinkage and sustained improvement in pain beyond that previously reported at 1 year. No new safety signals were identified; however, ongoing monitoring for known selumetinib-related AEs is needed while treatment continues.

## Key Points

- Plexiform neurofibroma tumor shrinkage and improvement in pain with selumetinib are generally sustained with continued treatment.
- No new safety signals have been identified, but long-term monitoring is needed.

Plexiform neurofibromas (PNs) are benign peripheral nerve sheath tumors that occur in up to 50% of patients with neurofibromatosis type 1 (NF1)[1,2] and can lead to significant clinical morbidity.[3–5] NF1-related tumors, including PNs, are characterized by double inactivation of the *NF1* gene which leads to over-activation of the *RAS* pathway.[6] Previously reported results from our phase 1 and 2 studies of selumetinib (NCT013620803), an oral selective MEK1/2 inhibitor that

## Importance of the Study

Selumetinib is the first medication approved for use in children with neurofibromatosis type 1 and inoperable, symptomatic plexiform neurofibromas (PN). To maintain tumor response, treatment with selumetinib often lasts many years and long-term safety and efficacy data have not previously been described. This report provides up to 5 years of additional safety and efficacy data for the previously published phase 1/2 trials of selumetinib for children with inoperable PN (SPRINT, NCT01362803). Overall, for those who remain on treatment, both tumor responses to selumetinib and improvements in tumor-related pain are sustained. No new safety signals were identified; however, known selumetinib-related adverse events can develop years after treatment initiation and therefore ongoing monitoring is needed while patients remain on drug. Thus, these results show that treating children with selumetinib for symptomatic, inoperable NF-related PN is safe, tolerable, and often provides durable clinical benefits.

targets a pathway downstream of RAS, for PN in children with NF1 demonstrated partial response (PR)s (PN volume shrinkage by ≥20%) in 71% and 68% of participants, respectively.[7,8] In addition, the phase 1 study established the recommended phase 2 dose of selumetinib for this population,[7] and the phase 2 study demonstrated clinical benefits for participants beyond PN shrinkage including improvement in tumor pain intensity, pain interference, quality of life, and some functional measures.[8]

The median duration of treatment on the phase 1 study at the time of data cutoff (DCO) in our prior 2016 publication was 30 cycles (1 cycle = 28 days, range 6-56), with 19 of the 24 participants remaining on treatment at that time. Similarly, the median duration of treatment in the phase 2 study at the time of the 2020 publication was 36 cycles (range 0–47), with 29 of the 50 participants remaining on treatment. With the approval of selumetinib for the treatment of children with NF1 and symptomatic, inoperable PN by the US Food and Drug Administration in 2020, and subsequently in 11 other markets worldwide in 2021, further elucidating the long-term safety and efficacy of selumetinib in this population is crucial. In addition, long-term safety and tolerability are of critical importance for the assessment of the risk: benefit profile of therapies for treatment of a non-malignant condition such as PN. In this report, we present approximately 5 and 2 years of additional safety and efficacy data from the phase 1 and 2 studies, respectively, of selumetinib in pediatric patients with NF1 and symptomatic, inoperable PN.

## Methods

### Trial Oversight

This study is a National Cancer Institute (NCI) Pediatric Oncology Branch-coordinated, Cancer Therapy Evaluation Program-sponsored trial with 4 participating sites (NCI Pediatric Oncology Branch, Children's Hospital of Philadelphia, Cincinnati Children's Hospital, and Children's National Hospital). The protocol was approved by the institutional review board at each participating site. All patients or their legal guardians provided written informed consent.

### Patients

Children with a clinical diagnosis of NF1,[9] 2 to 18 years of age, able to swallow intact capsules, and with inoperable measurable PNs[10] were eligible for both the phase 1 and phase 2 portions of the trial. For the phase 2 study, we enrolled patients on 2 strata: Stratum 1 for patients with at least one PN-related morbidity and stratum 2 for those with no clinically significant PN-related morbidity but potential for development of PN-related morbidity. This report includes updated results from phase 1 and phase 2, stratum 1 only. Results from stratum 2 were recently published in a separate manuscript.[11]

### Evaluations

All patients underwent scheduled clinical and laboratory safety evaluations, echocardiograms, ophthalmology exams, and magnetic resonance imaging for response evaluation. Children on the phase 2 study also completed patient-reported and observer-reported outcome measures and functional response evaluations, annually up to 4 years. In this report, we present subsequent results from the patient-reported outcome measures of pain, including the self-report Numeric Rating Scale-11 (NRS-11) for assessment of target tumor pain intensity (children ages ≥ 8 years)[12] and the self- and parent-report pain interference index (PII)[13,14] to evaluate the interference of pain on daily functioning (children ages ≥8 years and parents of children ≥5 years, respectively).

### Drug Administration and Safety Assessments

On both the phase 1 and phase 2 studies, selumetinib was administered twice daily on a continuous dosing schedule (1 cycle = 28 days). Starting selumetinib doses for children on the phase 1 study were either 20 mg/m$^2$ ($n$ = 12), 25 mg/m$^2$ ($n$ = 6), or 30 mg/m$^2$ ($n$ = 6) per dose. Participants on the phase 2 study were treated at the recommended phase 2 dose of 25 mg/m$^2$/dose.[7,15]

Patients with progressive disease (PD) at trial entry (≥20% increase in PN volume within 15 months before enrollment) could remain on selumetinib as long as they did not have disease progression on treatment. Patients without

disease progression at trial entry could continue treatment for a maximum of 2 years unless a PR was observed, in which case treatment could continue until meeting off-treatment criteria. Participants on phase 1 were followed until 30 days off treatment or until selumetinib-related adverse events (AEs) resolved to grade 1 or stabilized before coming off study. Participants on phase 2 remain on study for long-term safety and efficacy monitoring 7 years following initiation of treatment or 5 years after study drug discontinuation, whichever is longer. Of note, those who began treatment with a MEKi outside of the clinical trial were taken off study at the time of drug initiation.

AEs were graded using the NCI Common Terminology Criteria for AEs, version 4.0. Up to two dose reductions were allowed for most dose-limiting (phase 1) or dose-modifying (phase 2) toxicities.[7,8]

### Tumor Response Evaluations

Tumor response evaluation was performed centrally at the NCI by volumetric analysis of the MRI[10] of the PNs (non-blinded). At baseline, the most clinically relevant tumor was selected by the treating physician as the target lesion and used to determine response to treatment. Patients were considered evaluable for response after receiving at least one dose of study drug. A PR was defined as target PN volume decreases from baseline of ≥ 20%; confirmed PR (cPR) was defined as a PR on consecutive restaging exams at least 3 months apart; durable PR was a PR lasting for ≥12 cycles (approximately 1 year). PD was defined as volume increase from baseline of ≥20% from baseline volume or, if a patient had achieved a PR, an increase of ≥20% from the best response (calculated as current volume minus volume at best response divided by volume at best response multiplied by 100). Of note, in absence of alternative effective medical therapies, those participants with PD based on a ≥20% increase from best response after a PR were permitted to stay on treatment until tumor volume was ≥20% above baseline volume. The overall response rate was defined as the cPR rate based on an intention to treat analysis. Progression-free survival (PFS) was calculated as the number of cycles of treatment until disease progression or censoring at the time of coming off-treatment or most recent restaging evaluation. Duration of treatment was calculated as the number of cycles of selumetinib completed prior to DCO, including those after PD where applicable.

### Statistical Considerations

For the patient- and observer-reported outcomes measures obtained, we compared the changes in each measurement over time, primarily between baseline, after cycle 12 of treatment and after cycle 48 of treatment, using the Wilcoxon signed rank test. For this analysis of patient- and observer-reported outcomes measures, patients were considered evaluable if they had measurements completed at baseline and at the post-cycle 48 evaluation (approximately 4 years on treatment). To compare the change from baseline to the final follow-up evaluation between the group that reached cycle 48 to the group that did not, we used the Wilcoxon rank sum test. For the NRS-11 assessing pain intensity, a change of 1 to 2 points is considered clinically meaningful in a variety of pain populations[16–20]; therefore, a threshold of 2 points was applied to participants in this trial. Spearman correlations were used to assess for relationships between continuous baseline tumor and patient characteristics and PN volume. Additional comparisons between dichotomous baseline characteristics and tumor response category (responder vs. non-responder) were performed using Fisher's exact test. Analyses comparing continuous variables against tumor response category were performed using Wilcoxon rank sum test. The probability of PFS as a function of cycles was estimated using the Kaplan–Meier method.

## Results

### Patient Characteristics and Treatment Course

A total of 74 participants were enrolled on the phase 1 ($n$ = 24) and phase 2, stratum 1 ($n$ = 50) studies of selumetinib, median age of 10.3 years (range 3, 18.5) (Table 1). This report includes data collected through an updated DCO of February 27, 2021 on both the phase 1 and phase 2 studies. At the new DCO, the median durations of treatment for participants on the phase 1 and 2 studies are 75.5 cycles (range 6, 100) and 55.5 cycles (range 1,73), respectively. This report includes an additional 45.5 and 19.5 cycles of treatment and associated safety and efficacy data for phase 1 and 2, respectively, beyond what was previously published. The median duration of treatment for all participants ($n$ = 74) was 57.5 cycles (range 1, 100).

At DCO, 9 of 24 (38%) of participants on the phase 1 study remain on treatment. The treatment discontinuation reasons for the other 15 participants were: adverse event (AE) (3), PD (2), refused of further treatment (3), principal investigator discretion/best interest of patient (3), treatment period complete (2), switched to alternative treatment (1) and resistant tumor (1) (additional details in Supplementary Table 1). Of the 9 participants remaining on treatment, 3 were assigned at enrollment to the 20 mg/m$^2$/dose, 5 at 25 mg/m$^2$/dose, and 1 at 30 mg/m$^2$/dose.

For the phase 2 study, 23 of 50 (46%) of participants remain on treatment at DCO. The treatment discontinuation reasons for the other 27 participants were PD (7), AE (6), principal investigator discretion (6), refused of further treatment (3), treatment period completed (2), intercurrent illness (2) and protocol violation (1) (additional details in Supplementary Table 1). Fifteen participants who are off treatment remain on study for long-term follow-up as part of the phase 2 trial.

### Safety and Tolerability

Across both the phase 1 and 2 studies, no new or concerning safety signals were identified during the additional years of observation since the prior DCO.

**Table 1.** Characteristics of the Study Participants and Target Plexiform Neurofibromas

| Characteristic | Phase 1[7] | Phase 2, Stratum 1[8] | Total |
|---|---|---|---|
| Patients Enrolled | 24 | 50 | 74 |
| Median Age at Enrollment, years (min, max) | 10.9 (3.0, 8.5) | 10.2 (3.5, 17.4) | 10.3 (3.0, 18.5) |
| Sex (male, female) | 13, 11 | 30, 20 | 43, 31 |
| Race, *n* | | | |
| Asian | 2 | 1 | 3 |
| Black or African American | 2 | 4 | 6 |
| White | 18 | 42 | 60 |
| Unknown | 2 | 3 | 5 |
| Median baseline volume of target PN, mL (min, max) | 1205 (29, 8744) | 487 (5, 3820) | 540 (5, 8744) |
| Progression status of target PN at Study entry – *n* (%) | | | |
| Progressive | 9 (38) | 21 (42) | 30 (41) |
| Non-progressive | 8 (33) | 15 (30) | 23 (31) |
| Insufficient information | 7 (29) | 14 (28) | 21 (28) |
| Location of target PN – *n* | 4 | 9 | 13 |
| Head only | 1 | 8 | 9 |
| Head and neck | 6 | 12 | 18 |
| Neck and trunk | 4 | 5 | 9 |
| Trunk only | 8 | 12 | 20 |
| Trunk and extremity | 0 | 4 | 4 |
| Extremity only | 1 | 0 | 1 |
| Whole body | | | |

## Phase 1 (*n* = 24)

All participants had at least one toxicity possibly related to study drug, 99% were ≤ grade 2 and the most common were asymptomatic creatine phosphokinase (CPK) increase, gastrointestinal toxicity, mucositis, and fatigue. Ten participants had 1 dose reduction and 3 participants required 2 dose reductions for toxicity. Three of these dose reductions occurred since the prior DCO. Elevated CPK (asymptomatic) was the only grade 4 AE possibly related to selumetinib in this population (Supplementary Table 2). Three participants were removed from treatment due to an AE possibly related to treatment (intolerable grade 2 mucositis, fatigue/myalgias, and nausea/reflux).

## Phase 2, Stratum 1 (*n* = 50)

Most participants (*n* = 49) had ≥1 AE at least possibly related to treatment (97% grade ≤ 2). The most common AEs were gastrointestinal symptoms, asymptomatic CPK increase, paronychia, and acneiform rash. Sixteen participants had ≥1 dose reduction; 5 of these had 2 dose reductions for toxicity. Since the prior DCO, only 1 additional participant had a dose reduction. Three grade 4 AEs possibly related to study drug were reported (CPK increase, hyperuricemia, and skin ulceration) (Supplementary Table 3). Five participants were removed from treatment for an AE considered possibly related to selumetinib (grade 4 skin ulceration, grade 3 weight gain, grade 3 paronychia, grade 3 acute kidney injury, and grade 3 diarrhea).

## AEs of Special Interest

As a class, MEK inhibitors are known to have rare but potentially serious ocular and cardiac side effects.[21,22] In this cohort, there was only one documented event of central serous retinopathy. The participant was on the phase 1 study and developed shallow bilateral central serous retinopathy, diagnosed via ocular coherence tomography only (not present on clinical exam), on their post-cycle 94 evaluation without any vision changes. Study drug was continued, and repeat evaluation 3 weeks later showed resolution of the central serous retinopathy. There were no episodes of retinal vein occlusion.

For cardiac toxicities, there were 16 participants with asymptomatic left ventricular ejection fraction (LVEF) decrease (15 grade 2 (10%–19% drop from baseline), 1 grade 3 (>20% drop from baseline)). The median number of cycles to the first episode of decreased LVEF for a participant was 20 (range 4, 95). Only 3 participants had their first episode of decreased LVEF occur after the prior DCO. The majority of those with decreased LVEF at any point (14/16, 88%) had recovery or stability of LVEF which did not progress or require any further intervention without a drug hold. Five participants had a decrease in LVEF below 53% (lower limit of normal) which, though still asymptomatic, led to dose interruption and dose reduction for 2 of them. The other 3 participants recovered back to baseline LVEF without dose interruption. All 5 of these participants had their LVEF recover to within normal limits and were able to safely continue selumetinib. Eight participants had at least one episode of hypertension (6 grade 1, 2 grade 2), all of which resolved without medical therapy. Of note, all participants who had a CPK ≥ grade 2 (between 2.5 and 5 times above the upper limit of normal) had CPK isoenzymes checked at the first occurrence, and no one had a concerning elevation in CK-MB, indicating there was no significant cardiac component to the elevated CPK.

A summary of all AEs with at least possible attribution to selumetinib in both phase 1 and phase 2, stratum 1 is available in the supplement (Supplementary Table 4).

## Tumor Volumetric Response

For phase 1, the median best tumor response was –32% (range –47%, –6%) with cPR in 18 of the 24 participants (75%) (Figure 1A). There was one additional confirmed PR after the originally reported DCO and this occurred at cycle 28 of treatment. The most recent response at each participant's last restaging visit prior to DCO was cPR in 33% ($n$ = 8), stable disease in 21% ($n$ = 5), and PD in 46% ($n$ = 11) (Figure 2A). Median time to best response was 22 cycles and responses were durable in 16 participants (67%). There were 11 participants who developed PD, all after the prior DCO. Of those, 4 had a prior dose reduction and 8 remained on treatment after PD. Only 2 participants had tumor growth >20% above baseline volume. For those with PD, median time to progression was 46 cycles (range 28, 88); for the entire phase 1 cohort, median PFS was 52 cycles (Figure 3A).

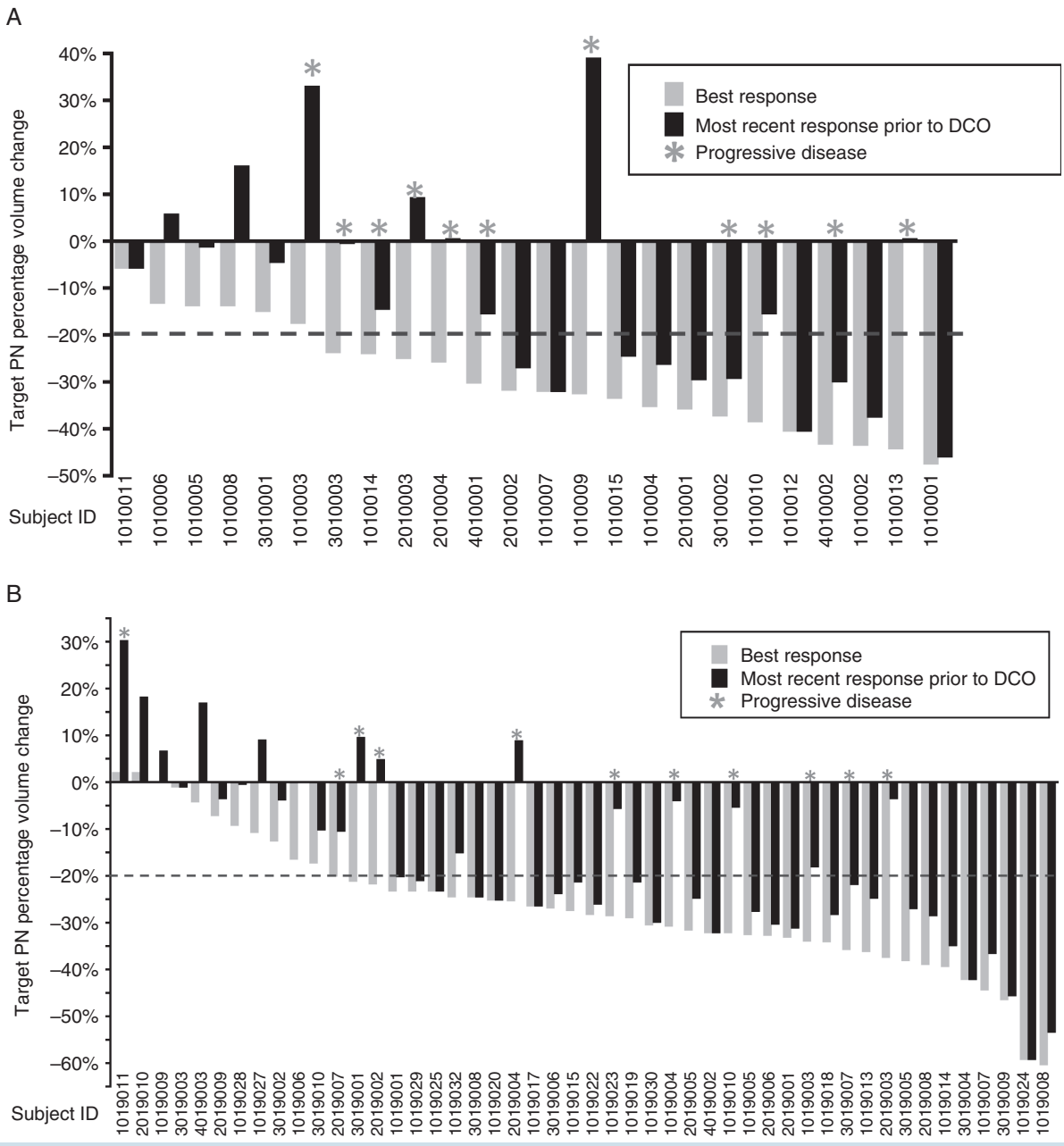


**Figure 1.** Waterfall plots for phase 1 and phase 2, stratum 1 with data cutoff (DCO) of February 27, 2021. Includes each participant's best tumor volumetric response (gray bar) and most recent response prior to DCO (black bar). Partial response (PR) was defined as >20% tumor shrinkage from baseline (dashed line) and progressive disease (PD) was defined as >20% increase from baseline OR from best response if there was a prior PR (marked by asterisks). (A) phase 1, (B) phase 2, Stratum 1.

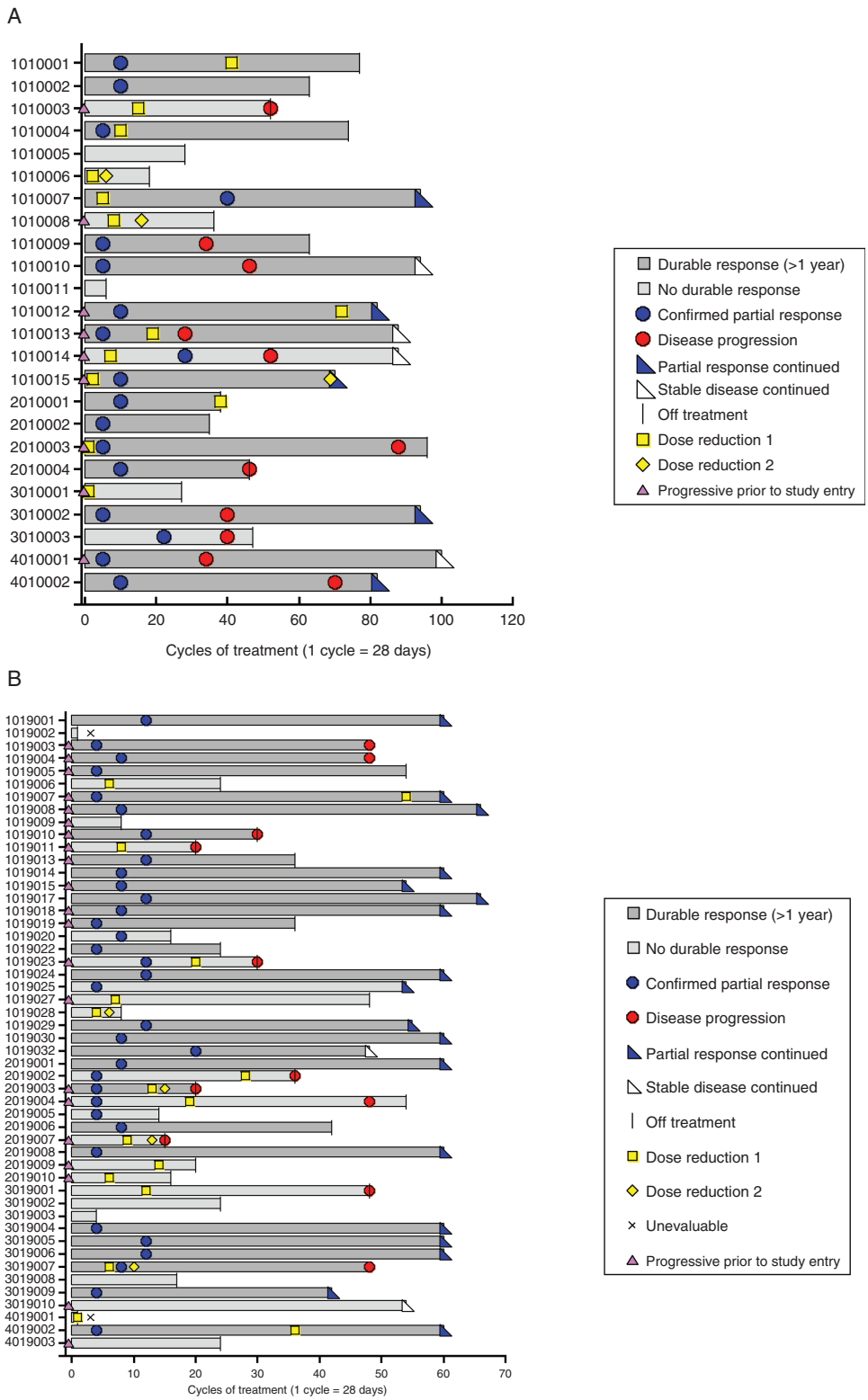


**Figure 2.** Swimmers plots of treatment course for phase 1 (A) and phase 2, stratum 1 (B) through data cutoff (DCO). Each participant's duration of treatment is illustrated by the bars above. The cycle at which the participant began a confirmed partial response (cPR) (blue dot) or had progressive disease (PD) (red dot) are marked as applicable. The dark gray bars indicate those who had a durable tumor response response (≥ 12 cycles). Participants with progressive tumors at study entry (≥20% increase in plexiform neurofibromas volume within 15 months before enrollment) are marked with purple triangles at the beginning of each bar. The participant's tumor and treatment status as of the last restaging evaluation prior to DCO is indicated at the end of each bar, including: off treatment (black line), on treatment with stable disease (white triangle), or on treatment with continued partial response (blue triangle). Dose reductions are marked with yellow squares (first dose reduction) and diamonds (second dose reduction). Data included through first-time participants were taken off treatment. (A) phase 1 ($n = 24$), (B) phase 2, stratum 1 ($n = 50$).

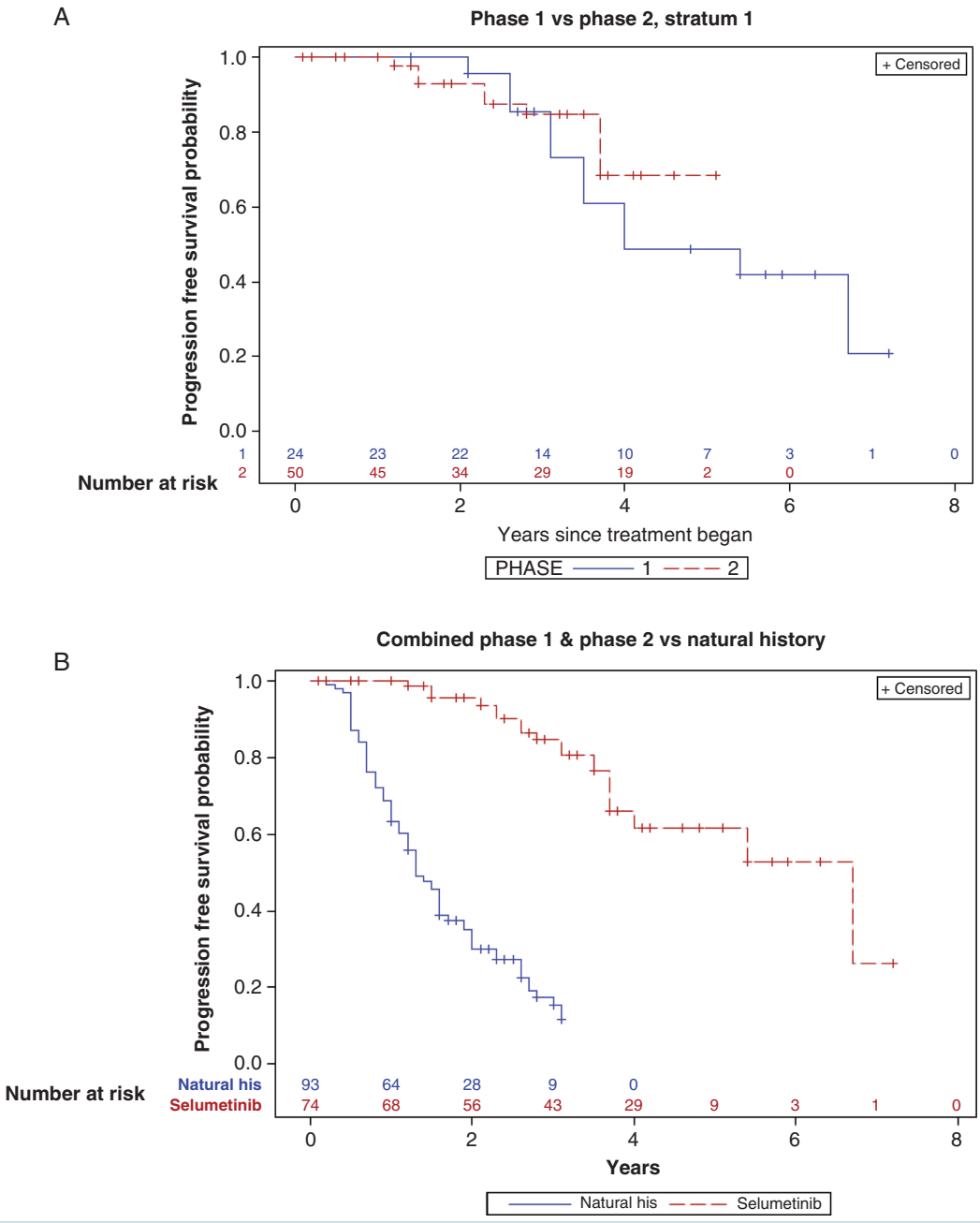


**Figure 3.** Progression-free survival (PFS) on selumetinib: Individual phase 1 and phase 2 (stratum 1) PFS curves (3A) and combined curve (3B). Median PFS for phase 2, stratum 1 not reached. Median PFS for phase 1 was approximately 4 years (52 cycles of treatment). Median PFS for the combined phase 1 and 2 cohort was approximately 6.7 years (88 cycles of treatment), significantly longer than the previously published age-matched natural history cohort with median PFS of 1.3 years.

In phase 2, the median best tumor response was –27.2% (range –60.3%, 2.2%) with cPR in 68% ($n$ = 34) (Figure 1B). There were no additional confirmed PRs after the prior DCO. The most recent response at each participant's last restaging visit prior to DCO is 50% with cPR ($n$ = 25), 24% stable disease ($n$ = 12), 22% with PD ($n$ = 11), and 4% unevaluable ($n$ = 2). Median time to best response was 16 cycles (range 4, 94) and responses were durable in 28 (56%) participants (Figure 2B). For those with PD, median time to progression was 36 cycles (range 16, 48) with 6 additional participants having PD since the prior DCO; median PFS for the entire phase 2 cohort has not been reached (Figure 3A). Of 11 participants with PD, 8 had ≥1 prior dose reduction for toxicity and 4 remained on treatment; 2 participants had tumor growth >20% above baseline volume while on treatment.

Across both studies, the median time to initial response was 8 cycles (range 4, 40) and median time to best

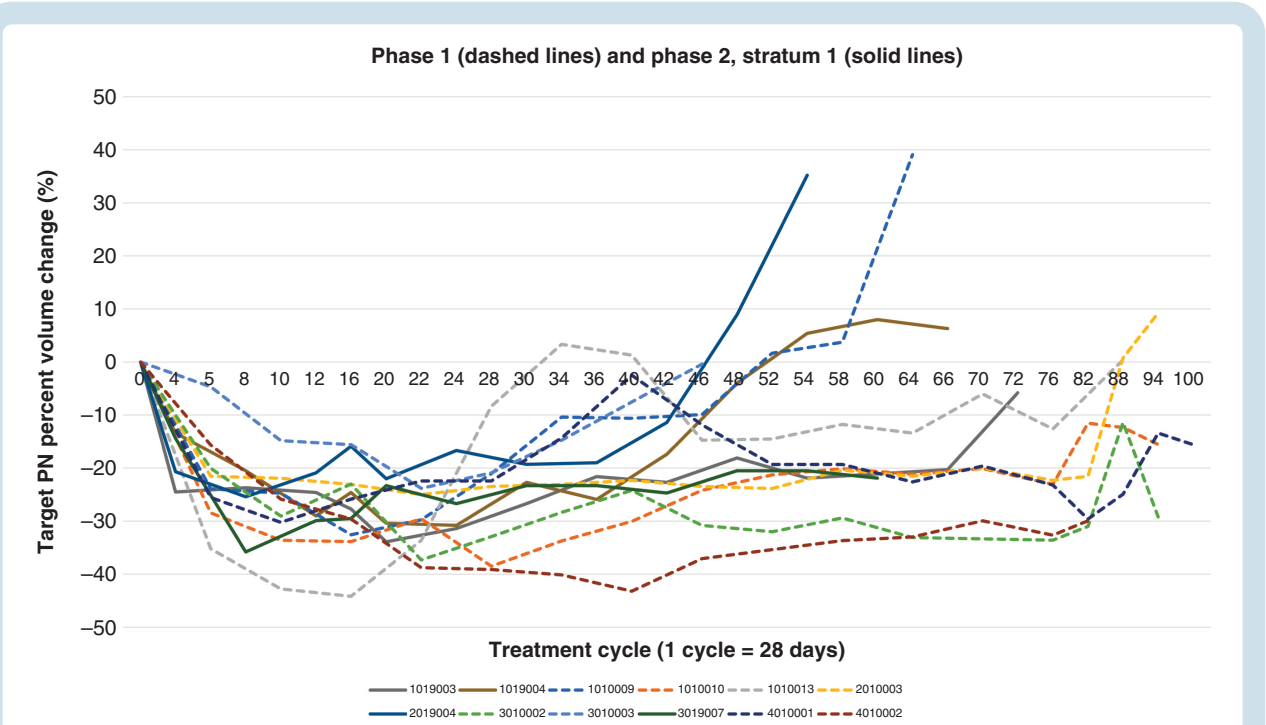


**Figure 4.** Target plexiform neurofibroma percent volume change for participants who achieved a partial response but then had disease progression (≥ 20% volume increase from best response) and remained on treatment ($n = 12$).

response was 18 cycles (range 4, 94). The median duration of the first confirmed PR was 34.5 cycles (min 4, max 77). The median age at enrollment for those with tumors that were progressive prior to initiation of treatment (median 7.6 years, $n = 30$) was significantly less than those with non-progressive tumors (median 12 years, $n = 30$, $P = .002$). However, there was no difference in the best response of tumors between those with progressive and non-progressive tumors at baseline (–28.0% and –31.1%, respectively, $P = .47$). Twelve participants remained on treatment after having PD with ≥20% increase above their best response. Of these, 2 participants went on to have tumor volume growth > 20% above baseline and were removed from treatment for this reason; 3 had tumor volumes that qualified for PR (<20% below baseline) and the remaining 7 had PN volumes between –20% and +20% of their baseline volume (Figure 4). There was no apparent difference in the imaging or participant characteristics that we could identify to explain the variations in growth behavior across these tumors. Median PFS for all 74 participants was 88 cycles, with 61.2% probability (95% CI: 46.3%–73.2%) of being progression-free after 60 cycles (Figure 3B).

## Predictors of Tumor Response

Across both studies ($n = 74$) we assessed whether baseline patient or tumor characteristics including sex, age at enrollment, baseline tumor volume, tumor type (nodular vs. typical appearing), tumor progression status at baseline, or PN location were associated with achieving a PR or correlated with the degree of tumor response. There was no association between any of these factors and tumor response ($P > .10$ for all).

## Patient-and Observer-Reported Outcome Measures of Pain (Phase 2, Stratum 1 only)

For participants completing the pain measures through 48 cycles (approximately 4 years) of treatment, there was a significant decrease in self-reported tumor pain intensity ($n = 19$) and pain interference ($n = 18$) from baseline to post-cycle 12 (NRS-11: $P = .001$, means = 2.21 to 0.68; PII: $P = .019$, means = 0.93 to 0.40), which both remained lower than baseline at post-cycle 48 (NRS-11: $P = .015$, post-cycle 48 mean = 0.58; PII: $P = .0059$, post-cycle 48 mean = 0.38) (Figure 5). Of note, there was no difference in the change in tumor pain intensity from baseline to the last follow-up evaluation between the group of participants who did not reach 48 cycles of treatment ($n = 12$) and the group that did reach 48 cycles ($n = 19$) ($P = .7997$). In examining individual change in the NRS-11 tumor pain intensity scores, 10 participants (out of 19) had a decline of ≥2 points (53%) from baseline to 48 cycles, indicating clinically meaningful improvement, while 8 participants remained stable (scores of 0 [no pain] or decline of 1 point) and only 1 participant rated an increase in tumor pain intensity. For the parent-report PII ($n = 24$), a similar pattern of decrease was found in pain interference from baseline to post-cycle 12 ($P = .010$; means = 1.11 to 0.35) and post-cycle 48 ($P = .002$; 48-cycle mean = 0.26).

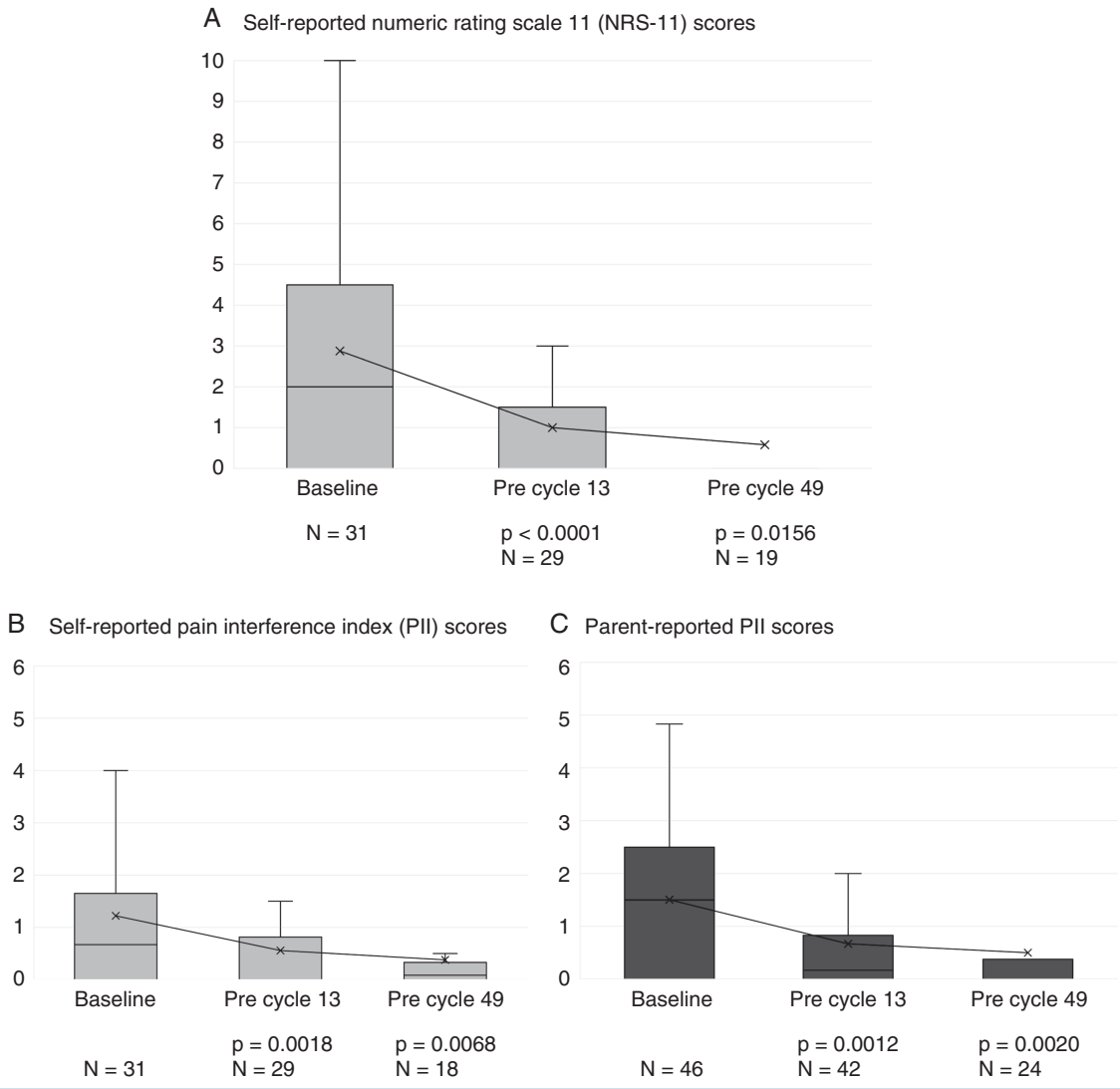


**Figure 5.** Patient-and observer-reported outcome measures of pain through 48 cycles of treatment on selumetinib show continued improvement in tumor-related pain intensity and pain interference for those who remained on treatment. (A) Self-reported numeric rating score-11 (NRS-11) Scores, (B) Self-reported pain interference index (PII) Scores, (C) Parent-reported PII Scores.

## Discussion

With up to 5 years of additional data on the safety, tolerability, and efficacy of selumetinib in children enrolled on the phase 1 and 2 clinical trials for NF1-related inoperable PN we found that tumor responses and improvements in patient- and observer-reported outcome measures of pain were durable in those participants who stayed on treatment, and no new safety signals were identified. Overall, the tumor volumetric responses on the phase 1 and phase 2 study were similar, with 75% and 68% achieving a confirmed PR, respectively, and a similar median degree of tumor shrinkage at best response (–32% and –27.2%, respectively). At DCO, 32 of the 74 participants (43%) remain on treatment with selumetinib. These responses were generally sustained, with 59% (44) lasting ≥ 12 cycles and for those with a cPR, a median duration of initial response of 34.5 cycles.

The median PFS of the combined cohort was 88 cycles, or approximately 7 years, which contrasts sharply with the previously published age-matched control cohort of children with PN not treated with selumetinib where the median PFS was just over 1 year.[8] Of note, unlike the control cohort where PD was defined as >20% increase from baseline volume, the vast majority of participants on the selumetinib trial, including those with PD, remained at or below their baseline tumor volume, with only 4 participants (5.4%) having tumor growth >20% above baseline at any time. These findings confirm that selumetinib treatment not only causes PN shrinkage in most children, but also dramatically slows PN growth in comparison to historical controls.

One unique subset of participants within this analysis were those who had disease progression (>20% above

best response) but remained on treatment. As seen in Figure 4, only 2 of 12 continued to have significant PN growth on treatment leading to drug discontinuation. On imaging, all 12 of these tumors were typically appearing PN. While there were some issues with treatment compliance after prolonged therapy, the two participants who had continued growth of their tumors >20% above baseline did not report a significant number of missed doses and appeared to have developed resistance to treatment. One of these two participants (2019004) did have a dose reduction at cycle 19, though they did not have initial PD until cycle 48. Reassuringly, there has been no evidence of atypical or malignant transformation in either of these target lesions with PD >20% above baseline since discontinuing therapy; however, the reason they stopped responding to selumetinib is not known.

Two of the most clinically meaningful improvements for participants from the phase 2, stratum 1 trial were a decrease in PN-related tumor pain intensity as well as a decrease in overall pain interference in daily life throughout the first year of treatment. With this follow-up long-term analysis, we were able to demonstrate that in those participants who remained on treatment, the substantial improvement in pain was maintained at least through 48 cycles of treatment, approximately 4 years.

No new or concerning safety signals were identified during the additional years of observation on either study. However, nearly all the children on selumetinib (73 of the 74, 99%) had at least one treatment-related AE on study. In addition, 29 of the 74 participants (39%) required at least one dose reduction due to a selumetinib-related AE, including 8 participants (11%) who were eventually removed from treatment for selumetinib-related toxicity. Of note, there have been no additional participants taken off treatment for a drug-related toxicity since the prior DCO on either the phase 1 or 2 study. However, though no new signals were identified, several participants developed known AEs, such as asymptomatic decreased LVEF, for the first time after being on treatment for several years. These findings highlight that though generally tolerated, treatment with selumetinib is not without potential toxicities, and that long-term monitoring for AEs, such as cardiac and ophthalmologic toxicities, is indicated. On this trial, echocardiogram monitoring was done every 4 months for the first 2 years and then every 6 months while on treatment. Ophthalmologic evaluation was done after 4 months and 12 months of treatment for the first year and then annually. While our data do not provide sufficient evidence to select monitoring intervals, this frequency of evaluation, along with appropriate patient education regarding any concerning signs or symptoms of possible toxicities (eg, exercise intolerance or blurred vision), appeared to be adequate for safely monitoring this population. Families should be educated about these risks as well as the need for ongoing safety monitoring and mitigating therapies before initiation and during treatment.

One of the main limitations of both the phase 1 and phase 2 studies is that they were not randomized controlled trials. However, when comparing the PN growth data to the previously reported age-matched control cohort, it is clear that selumetinib is altering the natural course of PN growth. A similar comparison against a control cohort was not feasible for the patient-reported outcome measures, thus, one cannot rule out other possible causes, such as a placebo effect, although there was sustained improvement in these clinical outcomes over time. Interestingly, when some patients required a drug hold, even temporarily, they reported that their pain returned or increased, also suggesting a relationship between pain and selumetinib. In addition, one of the challenges of this trial has been determining when children may be able to stop selumetinib treatment once they have achieved and maintained a confirmed PR for several years. Many patients started treatment as teenagers and are now young adults in their early 20s. The natural history of PN is to grow most rapidly in young children.[23] While tumor regrowth has been seen in pediatric patients who have stopped therapy, it is not known if this same regrowth will be seen in older patients who come off treatment. The appropriate duration of MEKi treatment for PN as well as its effect on pain in children as they develop into adulthood needs to be further investigated in future clinical trials.

Overall, the data presented here show that the majority of children with inoperable, symptomatic NF1-related PN achieved PN shrinkage that was durable for years in most cases as long as selumetinib was continued. In addition, the results demonstrate that previously reported improvements in tumor-related pain were sustained for a prolonged period with continued treatment. Reassuringly, no new safety signals were identified in this cohort; however, long-term safety monitoring is ongoing.

## Supplementary material

Supplementary material is available online at *Neuro-Oncology* (http://neuro-oncology.oxfordjournals.org/).

## Keywords:

MEK Inhibitors | Neurofibromatosis type 1 | Plexiform Neurofibromas

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## Conflict of interest statement

Dr. Michael J Fisher and Dr. Jaishri O Blakeley have been paid advisors for Springworks Therapeutics. The authors report no other financial conflicts of interest. Dr. Miriam Bornhorst has been a paid advisor for Alexion, AstraZeneca Rare Disease.

## Authorship statement

BCW, ED, MJF, AK, BW and JOB conceived of and designed the trial. AMG and PLW drafted, and subsequently all authors revised, the manuscript. All authors approved the documents for submission.

## Data Availability

De-identified data will be made available to researchers upon reasonable request.

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