Research Square

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Treatment continuity of MEK inhibitors and tumor trajectories after discontinuation in NF1 associated plexiform neurofibromas

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Abstract

Background:

MEK inhibitors have improved the management of neurofibromatosis type 1-associated plexiform neurofibromas (NF1-PNs), but the relationship between treatment continuity and post-discontinuation tumor behavior in routine practice remains unclear.

Methods:

We retrospectively analyzed 40 patients with NF1-associated PNs treated with selumetinib or luvometinib at a tertiary referral center. Patients were classified as discontinuation or no discontinuation according to treatment continuity during follow-up. Outcomes were assessed using a harmonized T0/T1/T2 framework. Pain was evaluated using the Numeric Rating Scale (NRS), and longitudinal tumor change was measured in the same predefined target lesion.

Results:

Nineteen patients discontinued treatment and 21 remained on treatment. Compared with the no-discontinuation group, the discontinuation group showed less favorable tumor trajectories, with smaller tumor shrinkage at T1 ($P = 0.0107$), tumor regrowth at T2 relative to baseline ($P < 0.0001$), and greater tumor rebound ($P < 0.0001$). In paired analyses within the discontinuation group, median tumor volume changed from − 5.0% at T1 to 5.0% at T2 ($P = 0.0003$). Pain outcomes were more heterogeneous, with no significant between-group difference in pain rebound. Among patients who discontinued treatment, cost-related interruption was the most frequent documented reason (10/19, 52.6%).

Conclusions:

In this real-world NF1-PN cohort, treatment discontinuation was common and was associated with less favorable tumor trajectories over time. The clearest post-discontinuation signal was observed in tumor rebound, whereas symptom changes were more heterogeneous. Cost-related interruption was the most frequent documented reason for discontinuation, suggesting that financial burden may represent an important practical barrier to sustained MEK inhibitor therapy.

Introduction

Plexiform neurofibromas (PNs) are among the most characteristic and clinically challenging tumors in neurofibromatosis type 1 (NF1)[1–2]. These lesions are frequently diffuse, infiltrative, and intimately associated with peripheral nerves and surrounding soft tissues, making complete surgical resection difficult or impossible in many patients[3–5]. Although some PNs remain relatively stable over time,

others are associated with substantial morbidity, including pain, functional impairment, disfigurement, and progressive local tissue involvement[6]. Accordingly, durable disease control remains a major therapeutic challenge in NF1-associated PN[7–8].

The development of MEK inhibitors has substantially changed the treatment landscape for NF1-associated PN[9]. Clinical trials and real-world studies have shown that agents such as selumetinib and luvometinib can induce tumor shrinkage and improve selected patient-centered outcomes in at least a subset of patients[10–14]. Because NF1 loss results in activation of the RAS/MAPK pathway, sustained MEK inhibition provides a biologically plausible strategy for suppressing PN growth. However, in routine practice, the clinical benefit of this treatment approach may depend not only on initial response, but also on treatment continuity over time[15].

In real-world settings, prolonged oral targeted therapy is often difficult to maintain. Treatment interruption or discontinuation may occur because of adverse events, perceived lack of benefit, personal preference, or financial burden[16–19]. Yet, compared with the growing literature describing on-treatment efficacy, much less is known about post-discontinuation tumor behavior in NF1-associated PN. In particular, it remains insufficiently characterized whether treatment interruption is associated with loss of tumor control, and whether clinically relevant symptom trajectories parallel radiographic changes in routine care.

From a practical clinical perspective, financial burden may be an especially important driver of treatment interruption, particularly when reimbursement remains incomplete and long-term out-of-pocket costs are substantial[11]. However, the relevance of economic burden in NF1-associated PN should not be viewed only as a health-services issue. Rather, economically driven interruption may represent one real-world mechanism through which sustained pathway suppression is lost, potentially altering subsequent tumor trajectory.

Therefore, the present study aimed to evaluate treatment continuity and post-discontinuation clinical trajectories in patients with NF1-associated PNs receiving MEK inhibitors in routine practice. Specifically, we examined longitudinal tumor and pain changes within a harmonized analytic framework, while also exploring the role of economic burden as a pragmatic driver of treatment discontinuation.

Methods

Study design and setting

This retrospective real-world observational study was conducted at a tertiary referral center in China between January 1, 2024 and January 31, 2026. The study was designed to evaluate how treatment continuity relates to longitudinal tumor and symptom trajectories in patients with NF1-associated PNs treated with MEK inhibitors in routine practice, with particular attention to post-discontinuation changes.

Patients

Patients were eligible if they had NF1-associated PNs and received oral MEK inhibitor therapy with either selumetinib or luvometinib, with available follow-up data on pain assessment and/or tumor volume evaluation during treatment. Patients were included regardless of whether treatment was continued or discontinued during follow-up. Patients were excluded if baseline pain or imaging data were unavailable, if follow-up data were insufficient to define the analytic T1/T2 framework, or if the reason for discontinuation could not be classified from the medical record. Treatment-related decisions, including treatment initiation, continuation, switching, dose adjustment, and discontinuation, were made by the treating physicians according to routine clinical practice and were not influenced by the study. Because the primary aim was not to directly compare individual drugs, selumetinib and luvometinib were analyzed within the same real-world treatment framework.

Data collection

Clinical data were extracted from the institutional database and medical records using a predefined case report form. Variables collected for analysis included age, sex, prior surgery, initial MEK inhibitor, treatment duration, payment method, relative dose intensity, pain scores, tumor volume change, treatment discontinuation status, and discontinuation reason. For the primary analyses, patients were categorized according to treatment continuity status during follow-up as discontinuation or no discontinuation. Detailed reasons for treatment discontinuation were additionally summarized descriptively from the medical record. Cost-related discontinuation was defined as treatment interruption or discontinuation primarily attributed to financial burden or inability to sustain treatment costs, and classification was based on the predominant documented reason for treatment interruption in the medical record.

Target-lesion approach for longitudinal tumor assessment

Tumor burden was assessed using a predefined target-lesion strategy. For each patient, longitudinal tumor evaluation was based on a single target lesion defined as the PN most closely associated with the patient's predominant symptoms at baseline. In patients with multiple lesions, the target lesion was selected according to its anatomical correspondence with the main symptom-related site, based on review of clinical documentation and imaging findings. The same target lesion was followed across all study timepoints. Tumor volume was measured in the same predefined target lesion using MRI-based slice-by-slice volumetric assessment. Tumor volume changes were expressed as percentage changes relative to baseline. This symptom-oriented target-lesion strategy was adopted to better reflect clinically meaningful disease trajectory in relation to treatment continuity.

Timepoint definition and outcome assessment

Baseline was defined as the pre-treatment assessment before MEK inhibitor initiation (T0). To improve longitudinal comparability across heterogeneous follow-up schedules, a harmonized analytic framework with pre-index (T1) and post-index (T2) assessments was used. In the discontinuation group, the index event was treatment discontinuation. In the no-discontinuation group, an analogous observation window was constructed using the last available follow-up and the assessment approximately 6 months earlier. Because follow-up timing was determined by routine clinical practice, T1 and T2 were defined using approximate rather than fixed time windows.

Pain was assessed using the Numeric Rating Scale (NRS). Pain change at T1 and T2 was calculated relative to baseline, and pain rebound was defined as the difference between T2 and T1 pain changes. Longitudinal tumor assessment was performed on the same predefined target lesion at T0, T1, and T2. Tumor volume changes at T1 and T2 were calculated relative to baseline, and tumor rebound was defined as the difference between T2 and T1 tumor volume changes.

Economic burden assessment

Economic burden was assessed pragmatically using recorded payment method and documented reasons for treatment discontinuation. Because detailed longitudinal cost data were not available for all patients, payment method was treated as a proxy indicator rather than a comprehensive measure of financial toxicity. Payment method was categorized according to the available clinical documentation as insurance or self-payment. In the present study, economic burden was examined primarily as a descriptive real-world factor related to treatment interruption.

Statistical analysis

Continuous variables are presented as median and interquartile range (IQR), and categorical variables as number and percentage. Group comparisons were performed using the Mann–Whitney U test, chi-square test, or Fisher's exact test, as appropriate. Within-group paired comparisons among patients who discontinued treatment were analyzed using the Wilcoxon signed-rank test. No formal adjustment for multiple comparisons was performed because the analyses were hypothesis-generating. A two-sided P value < 0.05 was considered statistically significant.

Ethics statement

This study was approved by the Institutional Review Board of the participating institution. Given the observational nature of the study and the use of de-identified data, the requirement for informed consent was waived.

Results

Patient disposition and treatment continuity

A total of 40 patients with NF1-associated plexiform neurofibromas were included in the study. Nineteen patients discontinued treatment and 21 remained on treatment during follow-up. Thus, treatment discontinuation was common in this real-world cohort, affecting nearly half of the included patients. The study flow and reasons for treatment discontinuation are shown in Fig. 1.

Baseline characteristics according to treatment continuity status

Baseline characteristics are summarized in Table 1. Patients in the discontinuation group were older than those in the no-discontinuation group, with median ages of 24.00 and 12.00 years, respectively (P = 0.0002). Self-payment as the primary payment method was substantially more frequent in the discontinuation group than in the no-discontinuation group (78.9% vs 19.0%, P = 0.0003). Treatment duration showed a numerical but not statistically significant difference between groups (P = 0.0760). Relative dose intensity, baseline pain score, sex distribution, prior surgery, initial selumetinib use, and the proportion of patients with maximum CTCAE grade ≥ 3 did not differ significantly between groups. These findings indicate baseline heterogeneity, particularly with respect to age and payment pattern, that should be considered when interpreting longitudinal outcomes.

Table 1
Baseline characteristics according to treatment discontinuation status

Variable	Discontinuation (n = 19)	No discontinuation (n = 21)	P value
Age, years	24.00 (16.50 to 27.00)	12.00 (7.00 to 16.00)	0.0002
Treatment duration, days	193.00 (178.00 to 338.00)	244.00 (192.00 to 475.00)	0.0760
Relative dose intensity	1.00 (0.89 to 1.00)	1.00 (1.00 to 1.00)	0.1641
Baseline pain score, NRS	1.00 (0.00 to 5.50)	3.00 (1.00 to 5.00)	0.3288
Male sex, n (%)	16 (84.2%)	12 (57.1%)	0.0888
Prior surgery, n (%)	9 (47.4%)	5 (23.8%)	0.1856
Initial selumetinib use, n (%)	12 (63.2%)	10 (47.6%)	0.3596
Self-payment as primary payment method, n (%)	15 (78.9%)	4 (19.0%)	0.0003
Maximum CTCAE grade ≥ 3, n (%)	4 (21.1%)	3 (14.3%)	0.6889

Data are presented as median (interquartile range) or n (%). NRS, Numeric Rating Scale; CTCAE, Common Terminology Criteria for Adverse Events; RDI, relative dose intensity.

Tumor trajectories according to treatment continuity status

Tumor volume trajectories are summarized in Table 2. At T1 relative to baseline, the no-discontinuation group showed greater tumor shrinkage than the discontinuation group, with median changes of -11.0% and − 5.0%, respectively (P = 0.0107). At T2, the no-discontinuation group continued to show tumor shrinkage relative to baseline, with a median change of -17.0%, whereas the discontinuation group showed a median increase of 5.0% (P < 0.0001). Tumor rebound also differed markedly between groups: the discontinuation group had a median rebound of 7.0%, while the no-discontinuation group had a median rebound of -3.0% (P < 0.0001). Overall, these results indicate that treatment discontinuation was associated with less favorable longitudinal tumor control. Longitudinal tumor volume changes are illustrated in Fig. 2.

Table 2
Pain and tumor volume trajectories according to treatment discontinuation status

Variable	**Discontinuation (n = 19)**	**No discontinuation (n = 21)**	**P value**
Change in NRS score at T1 vs baseline	0.00 (-2.00 to 0.00)	-1.00 (-2.00 to 0.00)	0.4487
Change in NRS score at T2 vs baseline	0.00 (-0.50 to 0.00)	-1.00 (-2.00 to 0.00)	0.0689
Pain rebound (T2-T1)	0.00 (0.00 to 1.00)	0.00 (0.00 to 1.00)	0.5145
Tumor volume change at T1 vs baseline	-5.0% (-11.5% to 0.0%)	-11.0% (-23.0% to -6.0%)	0.0107
Tumor volume change at T2 vs baseline	5.0% (0.0% to 12.5%)	-17.0% (-24.0% to -13.0%)	< 0.0001
Tumor volume rebound (T2-T1)	7.0% (5.0% to 11.0%)	-3.0% (-8.0% to 1.0%)	< 0.0001

Data are presented as median (interquartile range). NRS, Numeric Rating Scale.

Within-group paired analyses among patients who discontinued treatment are presented in Table 3. In the discontinuation group, median tumor volume change shifted from − 5.0% at T1 to 5.0% at T2 (P = 0.0003). This within-group pattern supports a temporal association between treatment interruption and subsequent tumor regrowth.

Table 3
Within-group paired comparisons of pain and tumor volume trajectories among patients who discontinued treatment

Group	n	T1 vs baseline	T2 vs baseline	P value
Pain trajectory in discontinuation group	19	0.00 (-2.00 to 0.00)	0.00 (-0.50 to 0.00)	0.0422
Tumor volume trajectory in discontinuation group	19	-5.0% (-11.5% to 0.0%)	5.0% (0.0% to 12.5%)	0.0003

Data are presented as median (interquartile range). T1 indicates the pre-discontinuation assessment and T2 the post-discontinuation assessment. P values were derived from paired within-patient comparisons between T1 and T2 using the Wilcoxon signed-rank test.

Pain trajectories as a secondary outcome

Pain trajectories are also summarized in Table 2. At T1 relative to baseline, median NRS change was 0.00 in the discontinuation group and − 1.00 in the no-discontinuation group (P = 0.4487). At T2 relative to baseline, median NRS change was 0.00 in the discontinuation group and − 1.00 in the no-discontinuation group (P = 0.0689). Pain rebound did not significantly differ between groups (P = 0.5145). In paired analyses within the discontinuation group, pain scores changed from 0.00 at T1 to 0.00 at T2, although this shift reached nominal statistical significance (P = 0.0422), with a relatively modest magnitude of change. Overall, pain outcomes appeared more heterogeneous and less robust than tumor outcomes. Longitudinal changes in pain scores are illustrated in Fig. 3.

Detailed reasons for treatment discontinuation

Detailed reasons for discontinuation are summarized in Table 4. Among the 19 patients who discontinued treatment, cost-related interruption was the most frequent documented reason, accounting for 10 cases (52.6%). Other recorded reasons included malignant transformation in 3 patients (15.8%), adverse events in 2 patients (10.5%), lack of efficacy in 1 patient (5.3%), and other reasons in 3 patients (15.8%). Within the discontinuation group, 15 patients (78.9%) used self-payment and 4 patients (21.1%) used insurance. These findings support the interpretation that financial burden represented an important real-world contributor to treatment interruption in this cohort.

Table 4
Detailed reasons for treatment discontinuation

Reason for discontinuation	**n**	**% among discontinuation**
Cost-related	10	52.6%
Adverse events	2	10.5%
Lack of efficacy	1	5.3%
Malignant transformation	3	15.8%
Other reasons	3	15.8%
Payment method among discontinuation	**n**	**% among discontinuation**
Insurance	4	21.1%
Self-pay	15	78.9%

Discussion

In this real-world cohort of patients with NF1-associated plexiform neurofibromas treated with MEK inhibitors, treatment discontinuation was frequent and was associated most consistently with less favorable tumor trajectories over time. Nearly half of the patients in the cohort discontinued treatment during follow-up, underscoring the practical difficulty of maintaining long-term MEK inhibitor therapy outside trial settings. The clearest signal in the study was observed in longitudinal tumor behavior: patients who remained on treatment maintained continued tumor shrinkage within the harmonized observation framework, whereas patients who discontinued treatment showed a shift from on-treatment shrinkage at T1 to regrowth at T2. This pattern was observed not only in between-group comparisons, but also in paired within-group analyses restricted to patients who discontinued treatment. Collectively, these findings suggest that treatment continuity may be relevant to maintaining tumor control during MEK inhibitor therapy in NF1-associated PN.

These findings are clinically relevant because most prior literature has focused predominantly on on-treatment efficacy, safety, and response rates, whereas post-discontinuation tumor behavior in routine practice remains less well described[20–24]. The present study therefore adds a complementary real-world perspective by focusing not simply on whether patients respond to MEK inhibition, but on whether tumor control appears to be maintained after treatment is interrupted. In this sense, the study addresses a clinically important but less visible dimension of MEK inhibitor therapy: treatment persistence and what may occur after that persistence is lost.

In the biological context of NF1-associated PN, the observed tumor pattern is plausible. MEK inhibitors suppress signaling downstream of the RAS/MAPK pathway, and durable tumor control may therefore depend, at least in part, on sustained pathway inhibition[25–27]. Our results do not establish mechanism directly, nor do they support a causal conclusion regarding tumor regrowth after discontinuation.

However, they are compatible with the possibility that interruption of MEK inhibitor therapy may be accompanied by renewed tumor growth in at least a subset of patients. From a clinical standpoint, this interpretation is important because the benefit of MEK inhibition may need to be understood not only in terms of initial shrinkage, but also in terms of continued suppression of subsequent tumor progression[28–29].

By contrast, pain trajectories were more heterogeneous[30]. In the present dataset, pain rebound did not differ significantly between the discontinuation and no-discontinuation groups, and the overall pain signal was less consistent than the tumor signal. This divergence between tumor trajectory and symptom trajectory is biologically and clinically plausible. Pain in NF1-associated PN may be influenced by multiple factors beyond tumor volume alone, including lesion location, local nerve irritation, inflammatory changes, concomitant analgesic use, and inter-individual variability in pain perception[31–32]. In addition, baseline pain burden was relatively modest in some patients, which may have limited sensitivity for detecting meaningful rebound within a retrospective NRS-based framework. Accordingly, in the present cohort, tumor trajectory appears to represent the more stable and informative longitudinal endpoint.

The economic findings remain clinically meaningful when interpreted within this treatment-continuity framework. Among patients who discontinued treatment, cost-related interruption was the most frequent documented reason, and self-payment was common in this subgroup. These observations suggest that financial burden may represent an important real-world driver of treatment interruption, thereby indirectly influencing the maintenance of sustained pathway suppression in practice. In this sense, economic burden is not only a background characteristic but also a practical barrier that may be relevant to long-term tumor control. This observation may have implications for reimbursement policy and access to long-term targeted therapy[31].

The present findings also have practical implications for clinical care. In routine management of NF1-associated PN, the relevant question may not be limited to whether a patient initially benefits from MEK inhibition, but also whether treatment can be sustained long enough to preserve disease control. Patients who discontinue treatment may warrant closer post-discontinuation monitoring, particularly with respect to imaging-based reassessment of target lesions. More broadly, these results support the view that treatment continuity should be considered part of the therapeutic strategy itself rather than merely a background treatment characteristic.

This study has several limitations. First, it was a retrospective single-center study with a relatively small sample size, which limits statistical power and generalizability. Second, although selumetinib and luvometinib were analyzed within the same therapeutic framework, the study was not designed to directly compare the efficacy of individual MEK inhibitors. Third, economic burden was assessed pragmatically through payment method and documented discontinuation reason rather than through detailed longitudinal cost or household financial toxicity data. Fourth, although the harmonized T0/T1/T2 framework improved comparability, follow-up intervals remained inherently heterogeneous under real-

world conditions. Fifth, baseline heterogeneity across groups, including differences in age and payment method, raises the possibility of residual confounding. Because of limited sample size and event counts, no multivariable adjustment was performed, and residual confounding cannot be excluded. Finally, classification of discontinuation reasons was based on retrospective chart review and may have been subject to misclassification. These findings should therefore be validated in larger multicenter cohorts.

Despite these limitations, the study has notable strengths. It integrates treatment continuity, discontinuation frequency, tumor trajectory, symptom assessment, and real-world discontinuation reasons within a single NF1-associated PN cohort and applies a harmonized longitudinal framework that permits comparison between discontinuation and no-discontinuation groups. Most importantly, the results consistently indicate that the strongest clinical signal after treatment interruption lies in loss of tumor control. Taken together, these findings support the clinical relevance of treatment continuity in NF1-associated PN and highlight the need to better understand how real-world barriers to sustained therapy may shape long-term outcomes.

Conclusions

In this real-world cohort of patients with NF1-associated plexiform neurofibromas treated with MEK inhibitors, treatment discontinuation was common and was associated with less favorable tumor trajectories over time. The clearest post-discontinuation signal was observed in tumor rebound, whereas symptom changes were more heterogeneous. Cost-related interruption was the most frequent documented reason for discontinuation, suggesting that financial burden may represent an important practical barrier to sustained MEK inhibitor therapy. Taken together, these findings support the clinical relevance of treatment continuity in NF1-associated PN and highlight the need for closer post-discontinuation monitoring and improved real-world access to long-term therapy.

Declarations

Funding

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Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

This retrospective study was approved by the Ethics Committee of Xuanwu Hospital, Capital Medical University, Beijing, China. The study was conducted in accordance with the ethical standards of the

institutional research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Given the retrospective observational design and the use of de-identified data obtained from routine clinical practice, the requirement for informed consent was waived by the Ethics Committee of Xuanwu Hospital, Capital Medical University.

Clinical trial number

not applicable.

Consent to Publish

declaration: not applicable.

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Author Contribution

Lei Zhang: study conception, data interpretation, manuscript drafting. Lei Cheng: data collection and verification. Kai Wang: imaging and clinical data review. Zhenlei Liu: statistical support and data curation. Hao Wu: supervision, study design, manuscript revision, and final approval. All authors read and approved the final manuscript.

Data Availability

The datasets generated or analyzed during the current study are not publicly available because they contain potentially identifiable clinical information, but de-identified data are available from the corresponding author on reasonable request, subject to institutional approval.

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Figures

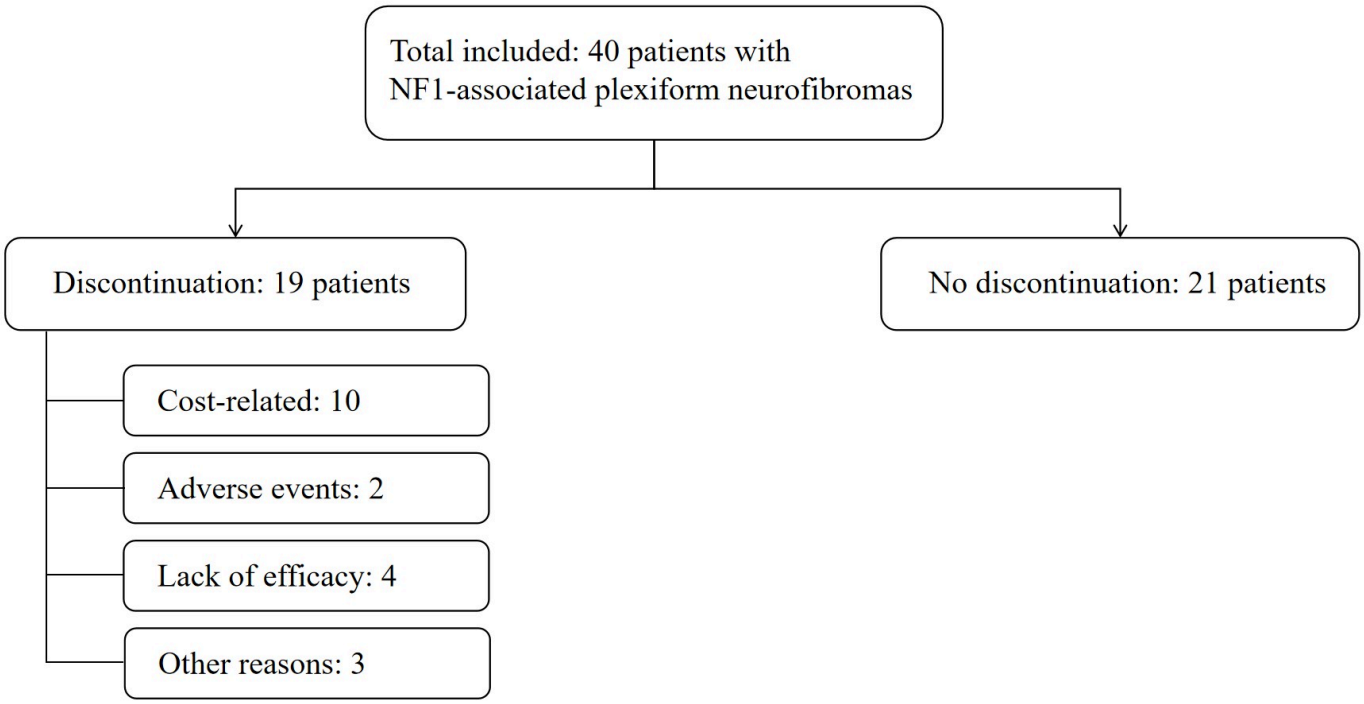


Figure 1

Study flow diagram according to treatment continuity status. A total of 40 patients with NF1-associated plexiform neurofibromas treated with MEK inhibitors were included in the study. Nineteen patients discontinued treatment during follow-up, including 10 with cost-related discontinuation, 2 with discontinuation due to adverse events, 1 with discontinuation due to lack of efficacy, 3 with discontinuation associated with malignant transformation, and 3 with discontinuation for other reasons. Twenty-one patients remained on treatment throughout follow-up.

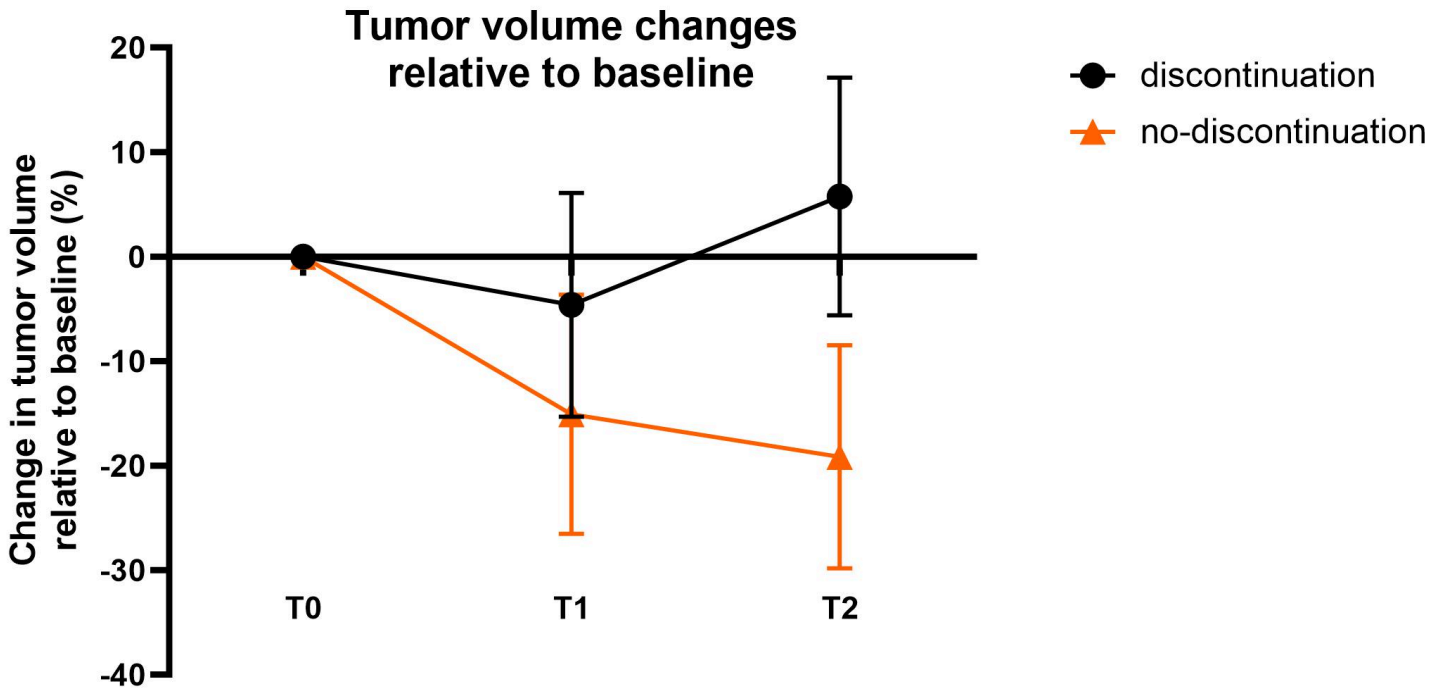


Figure 2

Longitudinal tumor volume changes relative to baseline according to treatment discontinuation status. Tumor volume changes are presented as percentage changes relative to baseline (T0) at T1 and T2. Longitudinal tumor assessment was performed using the same predefined target lesion for each patient across all timepoints.

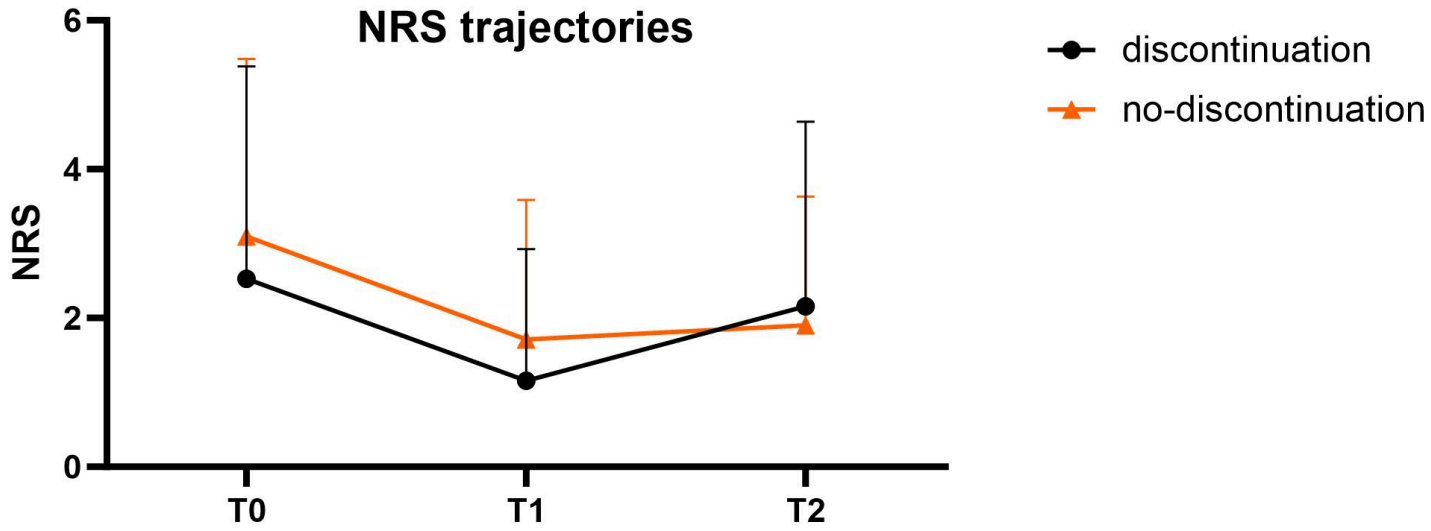


Figure 3

Longitudinal changes in pain scores according to treatment discontinuation status. Pain was assessed using the Numeric Rating Scale (NRS) at baseline (T0), pre-index follow-up (T1), and post-index follow-up

(T2).