Short-term efficacy assessment of brigatinib for the treatment of neurofibromatosis type 2: A retrospective study

ZHI LIN[1*], WEI YU[2*], FANGFANG JING[1], ZONGYI XU[3], MINGLU LIU[4] and SHUNCHANG JIAO[1]

[1]Department of Oncology, The First Medical Center of Chinese PLA General Hospital, Beijing 100853, P.R. China;
[2]Department of Radiation Oncology, The First Medical Center of Chinese PLA General Hospital, Beijing 100853, P.R. China;
[3]Department of Emergency, The Eighth Medical Center of Chinese PLA General Hospital, Beijing 100091, P.R. China;
[4]Outpatient Department, Southern Medical Branch of Chinese PLA General Hospital, Beijing 100089, P.R. China

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Abstract. Neurofibromatosis type 2 (NF2) is a genetic disorder caused by mutations in the NF2 tumor suppressor gene. This disease causes the growth of multiple schwannomas and meningiomas. There are currently no Food and Drug Administration-approved treatments for these malignancies. Due to their continuous development, these tumors cause a high rate of morbidity and mortality. The aim of the present study was to observe the short-term efficacy of brigatinib in treating NF2. Patients diagnosed with NF2 at The First Medical Center of Chinese PLA General Hospital (Beijing, China) between June 2021 and April 2024 were retrospectively enrolled and treated with 90 mg oral brigatinib once daily, with changes in the size of meningiomas and vestibular schwannomas, as well as hearing, emotional state and pain, measured before and after treatment. Adverse reactions to medication administration were also seen and documented. Changes in markers before and after therapy were investigated using repeated-measures ANOVA. Patients were stratified into two age groups (<18 and ≥18 years), with disease progression evaluated by longitudinal changes in meningioma maximal diameter on magnetic resonance imaging. The log-rank test was used to determine the difference in time between drug delivery and illness development. A total of 12 patients were enrolled. After 12 months of oral brigatinib therapy, the meningioma volume significantly decreased ($P<0.05$) at both the 6 and 12th month. There was a significant difference in time to illness development between individuals aged <18 and ≥18 years ($P=0.049$). The symptom checklist-90 and visual analogue scale scores were considerably reduced at 6 and 12 months ($P<0.05$). However, no significant improvement was seen in acoustic neuroma volume or the mean hearing threshold (both $P>0.05$). In conclusion, brigatinib may relieve meningiomas and pain and improve emotional well-being in patients with NF2.

Correspondence to: Dr Shunchang Jiao, Department of Oncology, The First Medical Center of Chinese PLA General Hospital, 28 Fuxing Road, Haidian, Beijing 100853, P.R. China
E-mail: jiaosc@vip.sina.com

Dr Minglu Liu, Outpatient Department, Southern Medical Branch of Chinese PLA General Hospital, 8 Dongdajie Road, Fengtai, Beijing 100089, P.R. China
E-mail: mingluliu21@gmail.com

*Contributed equally

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Introduction

Neurofibromatosis type 2 (NF2) is an autosomal dominant condition resulting from mutations in the NF2 gene located on chromosome 22, and it is marked by the presence of multiple neurological tumors (1). The main manifestations of NF2 include the presence of bilateral vestibular schwannomas (also known as bilateral acoustic neuromas), meningiomas, spinal tumors and various neoplasms affecting both the central and peripheral nervous systems. These may result in hearing loss, balance issues, headaches, facial nerve paralysis, impaired vision and various neurological symptoms (2,3).

The management of NF2 generally requires a comprehensive strategy, which encompasses the surgical removal of tumors, radiation treatment, medication-based therapies and supportive rehabilitation services. The surgical resection method is frequently employed to remove tumors that are accessible; however, it entails certain risks, particularly when dealing with tumors located in sensitive areas. Radiation therapy is effective in managing tumor growth; however, it can also lead to negative side effects. At present, there are limited effective treatments for NF2 available. The effectiveness of pharmaceutical agents in addressing NF2-associated tumors is constrained, thus surgical intervention continues to be the primary approach for managing NF2 progression (4,5). For individuals with NF2 who are unable or opt against surgical intervention, pharmacological treatments play a vital role in disease management. Currently, there are no specific medications that demonstrate high efficacy in the treatment of tumors associated with NF2.

NF2 is linked to various intracellular signaling pathways, including Hippo, protein kinase A, PI3K/AKT,

Rac/p21 activated kinases/JNK, WNT/β-catenin, receptor tyrosine kinase, Ras, MAPK, Yes-associated protein, p21-activated kinase, CD44 and Rac/Rho (6,7). Inactivation of NF2 leads to the activation of these cellular pathways, which are crucial in the pathological development of NF2-associated tumors. Focusing on these pathways may prove beneficial in the treatment of the tumors (8). Protein tyrosine kinase inhibitors have demonstrated the ability to decelerate tumor growth and prolong progression-free survival in clinical trials (9,10). The potential of these inhibitors as a treatment for NF2 tumors warrants further investigation. Brigatinib represents an advanced class of tyrosine kinase inhibitors that has received approval for the treatment of anaplastic lymphoma kinase/ROS proto-oncogene 1 (ALK/ROS1)-positive non-small cell lung cancer (NSCLC). It effectively inhibits ALK and ROS1 fusion proteins, obstructing downstream pro-survival pathways including MAPK/ERK and PI3K/AKT. This combined approach effectively diminishes tumor growth and spread, particularly in individuals with central nervous system involvement (11,12). In NF2, the absence of the Merlin protein resulting from mutations in the NF2 gene causes the hyperactivation of various tyrosine kinases, such as focal adhesion kinase 1 (FAK1) and Ephrin type-A receptor 2 (EphA2). The activity of these kinases is a significant factor in the proliferation of schwannomas and meningiomas. A preclinical study showed that brigatinib inhibits FAK1 and EphA2 activity without relying on ALK/ROS1, leading to a reduction in NF2-deficient tumors in mouse models (13). This multi-targeted approach highlights brigatinib as a compelling candidate for tumors associated with NF2. Currently, there is a limited number of clinical studies validating its short-term efficacy for NF2. The present study assessed the immediate efficacy of brigatinib for NF2, with the goal of introducing a novel therapeutic option for the condition.

Patients and methods

Study design. Twelve patients with NF2 were retrospectively identified from the hospital medical information database at The First Medical Center of Chinese PLA General Hospital (Beijing, China), covering the period from June 2021 to April 2024. Inclusion criteria included age ≥6 years, clinical diagnosis of NF2. Exclusion criteria included medical conditions incompatible with brigatinib, and tumors not amenable to volumetric MRI analysis. The present study adhered to the STROBE guidelines (https://www.strobe-statement.org/). All 12 patients received medical consultation and treatment at the First Medical Center of Chinese PLA General Hospital (Beijing, China). Their surgical histories involved multiple medical centers, including the First Medical Center of Chinese PLA General Hospital (Beijing, China), Xuanwu Hospital of Capital Medical University (Beijing, China), Beijing Tiantan Hospital (Beijing, China) and Huashan Hospital Affiliated to Fudan University (Shanghai, China).

The hypothesis of the present study posits that brigatinib will lead to a substantial reduction in meningioma volume and delay disease progression. The primary outcome measure of this study was the change in meningioma after vs. before treatment. Secondary outcomes included changes in patients' hearing, emotional state, pain level and the occurrence of adverse events.

Participants. Inclusion criteria were defined as patient age >6 years, a clinical diagnosis of NF2 between the ages of 14 and 16 years (14-16) and no prior treatment with tyrosine kinase inhibitors. Individuals were excluded from the study if they met any of the following criteria: Prior treatment with tyrosine kinase inhibitors, surgical procedures necessitated by tumor progression during the trial, medical conditions that are not compatible with brigatinib treatment and tumors that are not amenable to measurement via magnetic resonance imaging (MRI). Brigatinib was administered for the treatment of NSCLC at a dosage of 180 mg once daily, following a 7-day lead-in period at 90 mg once daily (17). To ensure safety and tolerability in evaluating the potential effects of brigatinib on NF2, a dose of 90 mg was chosen for the intervention. Participants received a daily dosage of 90 mg of brigatinib, provided by Takeda Pharma. Written informed consent was obtained from the patient's parents or guardians to allow the patient to receive the treatment.

Variables. The primary outcome was change in meningioma volume and secondary outcomes included changes in the size of vestibular schwannomas, as well as hearing, emotional state and pain, measured before and after treatment. The change in the maximum diameter of meningiomas on MRI was employed to assess disease progression, following the RECIST criteria (18). Disease progression was defined as a ≥20% increase in the maximum meningioma diameter on MRI. Patients without progression by the end of follow-up (censored data) were those who either completed the 12-month follow-up without meeting the progression criteria or were lost to follow-up. The time from starting medication to disease progression was assessed and patients were divided into two age groups (<18 and ≥18 years) to compare progression times. Secondary endpoints included changes in the volume of vestibular schwannomas, changes in hearing, emotional state and pain. Adverse effects during the study were also observed and recorded.

Data sources and data measurement. Brain MRIs were performed at baseline, as well as 6 and 12 months during treatment. For scans, sagittal and coronal positions were used and scanning sequences Spin Echo (SE), Fast SE (FSE) and Fast Recovery FSE for multi-angle T1-weighted imaging (T1WI) and T2WI imaging were measured. The MRI scans included post-contrast images of the internal auditory canal and the entire brain. The physician selected the largest meningioma and vestibular schwannoma to assess tumor volume. The measurements in the MRI examination were carried out by two board-certified neuroradiologists with >8 years of work experience and these two neuroradiologists received training before the study was launched. The tumor's maximum diameter was measured in the coronal plane (a), axial plane (b) and sagittal plane (c) using the Siemens Picture Archiving and Communication System (version 4.5; Siemens Healthineers), with the tumor volume calculated as a x b x c.

Hearing levels were assessed using pure-tone audiometry (PTA) for air conduction thresholds. Initially, patients were guided into the auditory evaluation chamber to ensure a tranquil testing setting for accurate results. Using standard headphones, audiologists gradually increased the sound

volume until the participants could hear it and then decreased it until they could no longer hear it. This meticulous procedure allowed accurate recording of the minimum sound thresholds at which participants could hear different frequencies. PTA was measured at the frequencies 0.25, 0.5, 1.0, 2.0, 4.0 and 8.0 kHz in each ear and the average of the thresholds at four frequencies was used to assess hearing loss (19).

Quantitative variables. The patients' emotional state was assessed using the Symptom Checklist-90 (SCL-90) (20). A total score of 150 indicated a poor emotional state. The SCL-90 is a widely used psychological appraisal instrument to assess an individual's psychological well-being and emotional disposition. This measure includes 90 items that explore various psychological symptoms and emotions, including but not limited to anxiety, depression, hostility, obsession and fear. Participants rate each item based on their experiences over the past month, providing a detailed view of their psychological landscape.

A visual analog scale (VAS) was used to measure the patient's pain levels (21). The VAS is a common tool for assessing the intensity of pain or other attributes based on individual experiences. The VAS consists of a line of adjustable length, with numerical values at each end representing diametrically opposed sensations, denoted as 0 and 10. Patients indicate their pain levels along this continuum to create a gradient of ratings. Types and severity of adverse reactions are carefully recorded. Regular follow-ups were conducted through outpatient clinics or by phone for 12 months.

Research studies assessed patients' overall health status and functional capacity using the Eastern Cooperative Oncology Group (ECOG) performance score (22).

The hearing levels, pain and emotional states of the patients were evaluated by the same two board-certified neuroradiologists who conducted the MRI imaging assessment.

Statistical analysis. Data were statistically analyzed using SPSS software (version 25.0; IBM Corp.) and the R programming language (version 4.3.2; The R Project for Statistical Computing; www.r-project.org). Continuous variables were expressed using means and standard deviations and categorical data were presented as counts and percentages. Repeated-measures ANOVA was used to compare the changes over time (pre- and post-medication). The normality of the data distribution was tested using the Shapiro-Wilk test before conducting the analysis. Non-parametric tests, like the Friedman non-parametric repeated-measures ANOVA test, were used to compare the change before and after the medication if the data didn't follow a normal distribution assumption. Kaplan-Meier curves were generated to visualize time-to-progression differences between age groups, as previously described in studies analyzing tumor growth dynamics (17). For the comparison of the time to disease progression between patients aged <18 and ≥18 years, the log-rank test was initially used. However, considering the potential issue of survival curves crossing, an alternative analysis using the Fleming-Harrington test family was also conducted. Categorical variables were compared with Fisher's exact test. In this study, multiple hypotheses were tested. To address the potential increase in Type I error probability, the Bonferroni correction method was applied for the post-hoc tests. $P<0.05$ was considered to indicate statistical significance.

Results

Patient characteristics. A total of 12 participants were enrolled with a median age of 22 years (range, 14-32 years) and a median body mass index of 21.02 kg/m^2 (range, 17.6-26.8 kg/m^2). The cohort included nine men (75%) and three women (25%). The median follow-up time was 20.58 months (range, 12-40 months) (Table I). A total of nine participants had previous surgeries. The median time from diagnosis to receiving brigatinib was 13 months (range, 3-30 months). All participants had bilateral vestibular nerve schwannomas and spinal meningiomas; nine participants had cranial meningiomas and seven participants had subcutaneous tumors. The number of participants reporting hearing loss, pain, impaired motor function, visual impairment and poor emotional states was, respectively, 10, 5, 6, 7 and 6 (Table I).

Tumor size. The average size of the meningioma in the brain was 13.00±4.86 mm^3 at the start, 12.14±4.12 mm^3 at 6 months and 11.58±3.89 mm^3 at 12 months, indicating a significant decrease ($P<0.05$; Fig. 1A). The time to disease progression was significantly different between patients aged <18 years and those aged ≥18 years ($P=0.049$; Fig. 1B), but there was no significant difference between patients with a low ECOG score (<2) and high ECOG score (>2) ($P>0.05$ according to the log-rank test) (Fig. 1C). By contrast, the volume of vestibular nerve schwannomas showed little change during drug treatment (Fig. 2).

Hearing function, emotional state and pain. Median PTA thresholds of participants who had hearing loss (n=10) were 39.90±15.34 dB (left ear) and 38.30±19.37 dB (right ear). After 12 months of treatment, the thresholds were 40.2±16.19 dB (left ear) and 37.80±20.10 dB (right ear). Hearing did not significantly improve ($P>0.05$; Fig. 3). The VAS (Fig. 4) and SCL-90 (Fig. 5) scores were significantly lower at 6 and 12 months compared to the baseline ($P<0.05$).

Safety. At the 6 months, 17 adverse events were reported: Hypertension (n=1), diarrhea (n=5), liver dysfunction (n=1), arrhythmia (n=1), skin rash (n=4) and fatigue (n=5). At 12 months, 19 adverse events were reported: Hypertension (n=2), diarrhea (n=4), liver dysfunction (n=1), arrhythmia (n=2), skin rash (n=5) and fatigue (n=5) (Table II).

Discussion

NF2 is marked by the presence of numerous tumors within the nervous system that progressively deteriorate over time. Even though tumors may be classified as histologically benign, they can lead to significant complications, including hearing and vision loss, motor function impairment, paralysis, pain and epilepsy, which are substantial contributors to mortality and disability (23). Bilateral vestibular schwannomas are the most prevalent tumors associated with NF2, occurring in ~90% of cases. Furthermore, it is observed that 45-58% of individuals with NF2 present with intracranial meningiomas, while 20% exhibit spinal meningiomas.

Table I. Demographics and clinical characteristics of participants at baseline.

Participant no.	Age, years	Sex	BMI, kg/m^2	Previous surgical excision	Time before brigatinib, years	Follow-up time, months	Type of tumor[a]	Symptoms[b]
1	30	Male	23.1	Yes	20	24	1, 2, 3	1, 3, 4, 5
2	32	Male	19.4	Yes	30	24	1, 2, 3, 4	1, 2, 3, 4, 5
3	14	Female	17.8	Yes	13	16	1, 2, 3	1, 5
4	19	Male	22.7	Yes	3	38	1, 2, 3	1, 2, 4, 5
5	26	Female	20.4	Yes	21	18	1, 2, 3	1, 2, 4, 5
6	32	Male	22.3	Yes	17	24	1, 2, 3	1, 3, 4, 5
7	17	Male	20.1	No	3	13	1, 3	
8	15	Male	19.1	No	3	12	1, 2, 3	1, 2
9	30	Male	17.6	Yes	10	13	1, 3	1, 2
10	15	Male	24.2	Yes	12	40	1, 3, 4	3, 4
11	14	Female	18.7	No	10	13	1, 2, 3, 4	1, 3
12	20	Male	26.8	Yes	14	12	1, 2, 3, 4	1, 3, 4

[a]1, Bilateral vestibular nerve schwannomas; 2, cranial meningioma; 3, spinal meningioma; 4, subcutaneous tumor. [b]1, Hearing loss; 2, pain; 3, impaired motor function; 4, visual impairment; 5, poor emotional states. BMI, body mass index.

Meningiomas frequently present as multiple benign tumors that exert pressure on surrounding brain tissue and cranial nerves, potentially leading to seizures and cerebral edema (24).

To date, no effective treatment for NF2 has been established. Surgery and stereotactic radiosurgery are employed in the management of tumors; however, their effectiveness is typically limited to short-term relief. The long-term outlook for patients continues to be unfavorable (25). Currently, there is no medication authorized for the treatment of NF2 tumors. Investigations indicate that bevacizumab, a vascular endothelial growth inhibitor, has the potential to impede the growth of NF2-induced acoustic neuromas and may lead to some enhancement in hearing (26-29). However, the impact on meningiomas and cutaneous neurofibromas remains ambiguous.

Chang *et al* (13) discovered that cells from NF2-related meningioma and schwannoma do not exhibit ALK expression. In contrast to NSCLC, where ALK inhibition is applied, brigatinib demonstrates the ability to inhibit multiple tyrosine kinases, such as EphA2 and FAK1. Brigatinib has demonstrated the ability to inhibit the activity of NF2 gene knockout cells and decrease the volume of meningioma and schwannoma in mice, suggesting its potential as a treatment for NF2 tumors (13). Building upon the foundation established by Chang *et al* (13), the present investigation involved a follow-up of 12 patients receiving oral therapy with brigatinib. While brigatinib is mainly focused on targeting tyrosine kinases in NSCLC, emerging evidence indicates its possible application in NF2. A phase II trial indicated a 25% tumor response rate and a 35% improvement in hearing among patients with NF2 receiving brigatinib at a dosage of 180 mg daily (30). However, the effectiveness regarding the meningioma volume and non-auditory symptoms is still uncertain, necessitating additional research. The present investigation built upon previous findings by showcasing its efficacy against meningiomas, underscoring a wider scope of therapeutic possibilities.

NF2 represents an autosomal dominant genetic disorder resulting from mutations in the NF2 gene. The gene is responsible for encoding and expressing the Merlin protein *in vivo*, predominantly located in Schwann cells, meningeal cells, lens fiber cells and nerve cells (30). Merlin plays a crucial role in inhibiting cell proliferation through the regulation of cell-cell adhesion. Consequently, the loss of Merlin due to mutations in the NF2 gene results in tumor growth. Merlin engages with various intracellular signaling pathways, such as receptor tyrosine kinases. Certain tyrosine kinase inhibitors have shown efficacy in NF2-deficient mice (31), indicating that these inhibitors may represent a viable treatment option for NF2.

Brigatinib demonstrates inhibitory effects on several receptor tyrosine kinases, such as ALK, ROS1, insulin-like growth factor-1 receptor and EGFR. However, there is a lack of studies regarding its application in the treatment of NF2. The study by Plotkin *et al* (30) evaluated the efficacy and safety of brigatinib in the treatment of NF2-related schwannomatosis. Their results showed that with brigatinib, significant radiological responses were achieved in multiple types of tumors. Of the target tumors, 10% (95% CI, 3-24%) showed shrinkage and 23% (95% CI, 16-30%) of all tumors showed a response. In addition, ~35% (95% CI, 20-53%) of patients experienced improved hearing and there was a reduction in self-reported pain severity. This present study involved the observation and evaluation of brigatinib's short-term effectiveness in treating NF2, revealing its potential to reduce the volume of meningioma. Meningiomas present a range of histological features and genetic irregularities. Research shows that between 45 and 58% of individuals with NF2 present with intracranial meningiomas, while ~20% exhibit spinal meningiomas (32). NF2-related meningiomas predominantly arise in the supratentorial areas, encompassing the frontal, parietal and temporal lobes, along with the cerebral falx. The MRI scans conducted on the patients in this study revealed the presence of meningiomas in the conventional cranial regions. The mean volume decreased from baseline. Although the volume change was not significant, the patient's pain and emotional

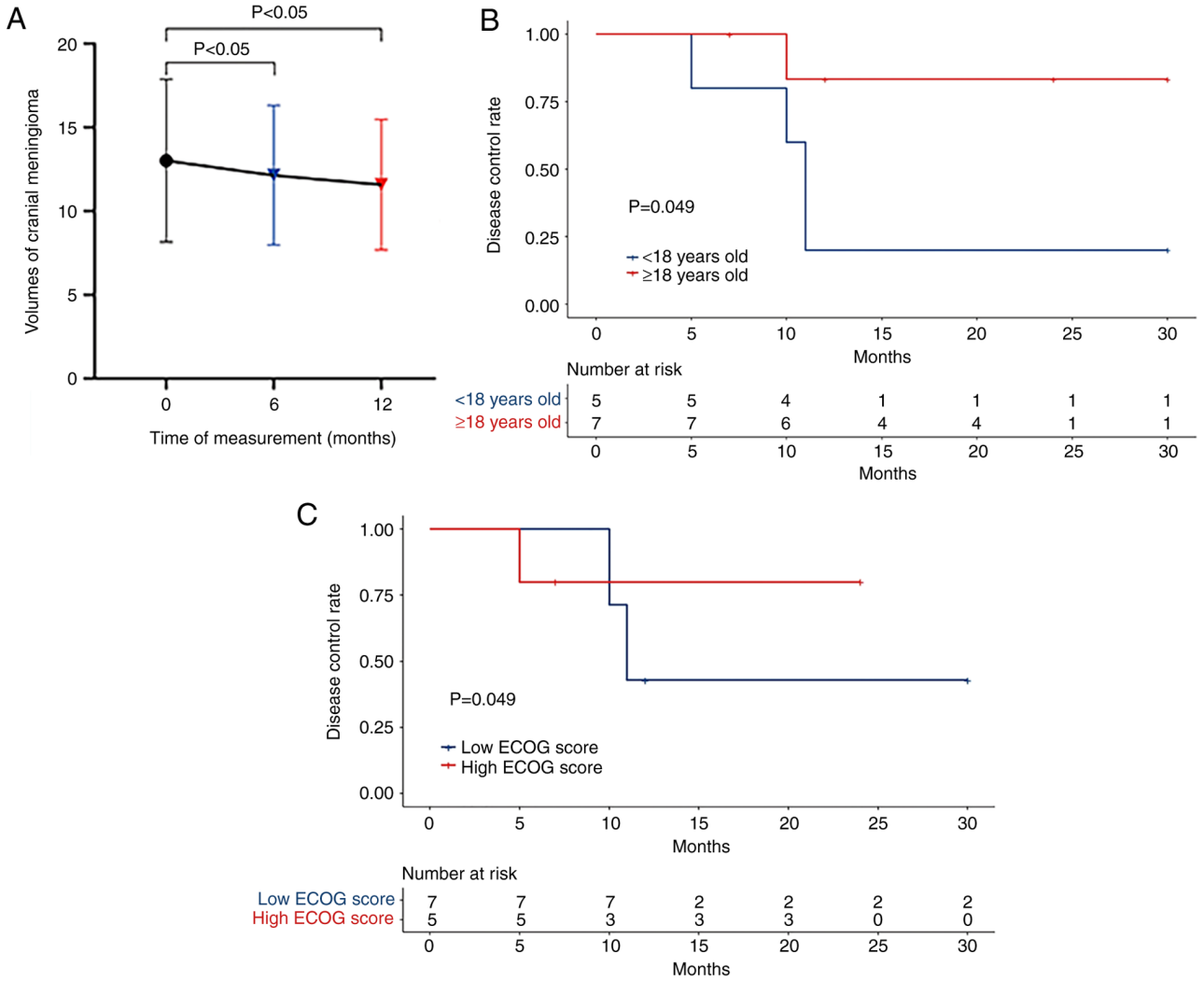

Figure 1. (A) Line graph showing the marginal mean of volumes of cranial meningioma, with a significant difference between the baseline, 6 and 12th-month values. (B) Comparison of disease progression by Kaplan-Meier curves. The time from medication administration to disease progression was longer in patients aged ≥18 years than in those aged <18 years (P<0.05 by the log-rank test). (C) Comparison of disease progression based on ECOG scores. No discernible difference was observed between low ECOG score (<2) and high ECOG score (≥2) (P>0.05 by the log-rank test). ECOG, Eastern Cooperative Oncology Group.

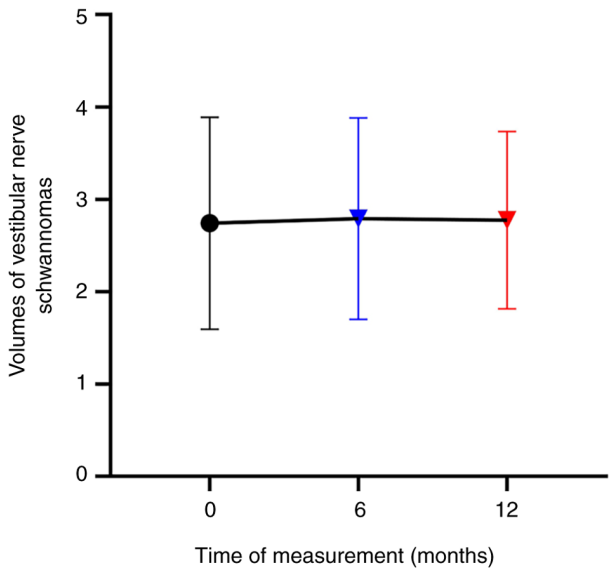

Figure 2. Line graph showing the marginal mean volume of vestibular nerve schwannomas. There was no significant difference between the baseline, 6 and 12th-month values.

state improved significantly. Younger patients (aged <18 years) exhibited a shorter disease progression time in comparison to their older counterparts (≥18 years). This may be associated with accelerated tumor growth in younger individuals (15).

NF2 may lead to peripheral neuropathy, ophthalmic abnormalities and cutaneous lesions. Patients with NF2 frequently present with cutaneous lesions; however, these lesions are generally less pronounced compared to those seen in patients with NF1. Schwannomas cause significant pain in individuals with NF2. While the precise mechanisms underlying NF2-related pain remain incompletely understood, it is suggested that this pain may be linked to tumor activation and/or the sensitization of primary sensory afferents through several pathways, such as mechanical compression of nerves, direct cell-cell signaling and the release of secretory factors (33). Currently, surgical resection is recognized as the most effective and safe approach for addressing pain associated with NF2 peripheral nerve schwannoma (34). Nonetheless, pain associated with schwannomas frequently continues after tumor removal and does not seem to have a direct relationship with the size of the tumor. This indicates that pain could arise from factors beyond nerve compression (35).

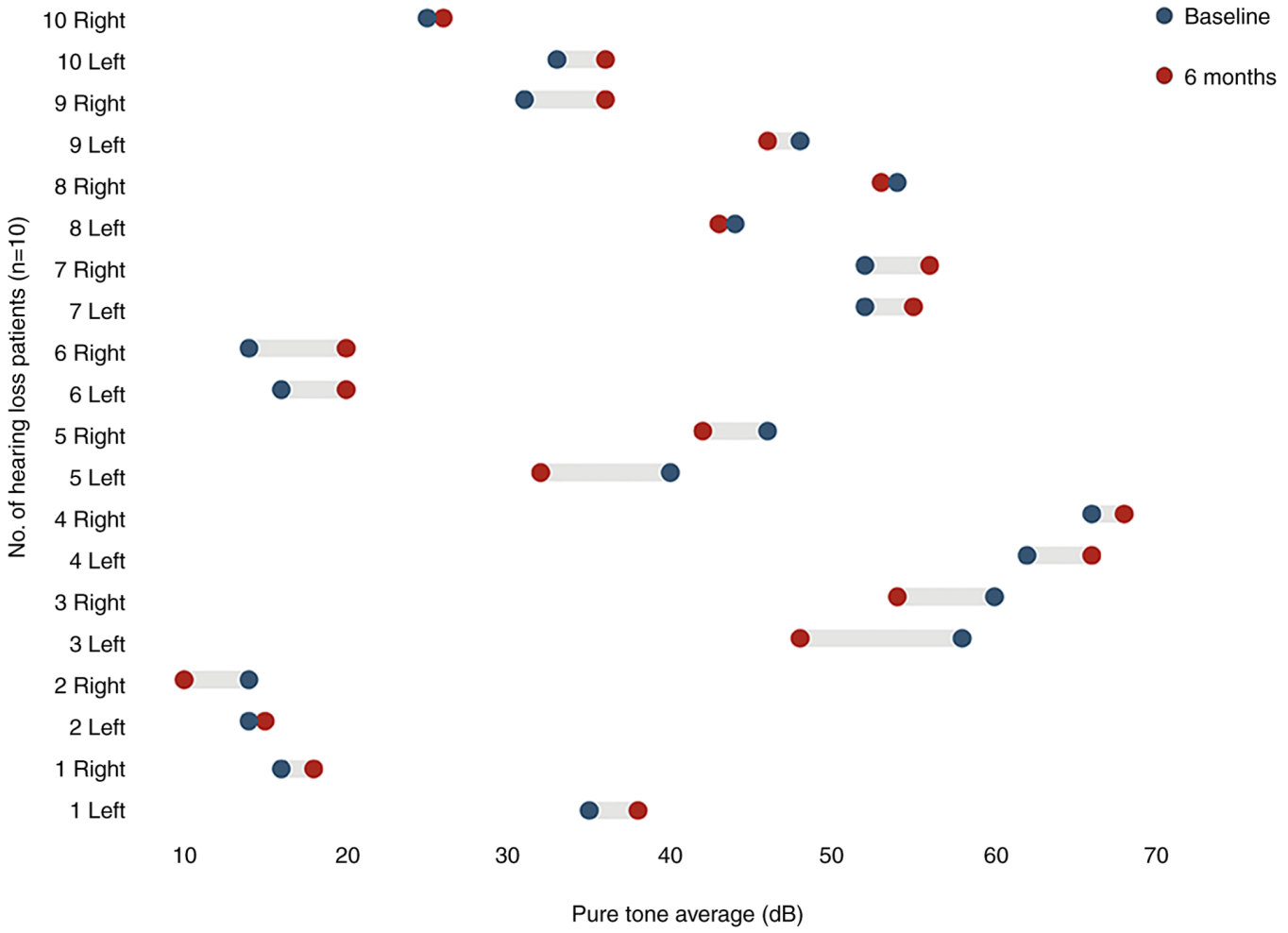

Figure 3. Pure tone average of patients with hearing loss. Every horizontal line represents one patient's left or right ear. The blue dots represent the pure tone average at baseline, while the red dots represent that at 12 months of receiving brigatinib.

The present investigation evaluated the short-term effectiveness of brigatinib in the treatment of NF2. An important advantage of brigatinib is its ability to enhance patients' pain management and emotional well-being. Follow-up feedback revealed notable pain relief within 24 h of initiating brigatinib treatment. Brigatinib primarily focuses on tumor cells by engaging multiple pathways to impede their growth and dissemination, particularly in the context of NSCLC. This investigation indicates that brigatinib may also alleviate tumor-associated pain symptoms through a reduction in tumor burden. Furthermore, brigatinib has the potential to offer swift pain relief via additional mechanisms, warranting further exploration.

The findings suggest that blocking tyrosine kinase activity may serve as an effective strategy for managing NF2 symptoms and enhancing clinical outcomes. This facilitates further investigation into tyrosine kinase inhibitors as a possible treatment for NF2. Nonetheless, there was no observed enhancement in acoustic neuroma and hearing, likely attributable to the challenges of addressing all symptoms in patients with NF2 with a singular pharmacological intervention.

The majority of individuals diagnosed with vestibular schwannomas demonstrate a reduction in Merlin expression. Investigations into the associated cellular pathways triggered by the loss of Merlin have examined these as possible therapeutic targets for addressing vestibular schwannomas. Merlin's interaction with ErbB2 facilitates the activation of downstream MAPK/ERK and PI3K/Akt signaling pathways (36). Activation of ErbB receptors occurs in both sporadic and NF2-related vestibular schwannomas, with EGF expression showing an increase in NF2-related cases. This indicates the potential effectiveness of EGFR inhibitors in the treatment of NF2-related vestibular schwannomas. Clinical studies indicate that the EGFR inhibitor erlotinib does not have a significant impact on hearing or tumor size in patients with progressive vestibular schwannoma (37).

Tyrosine kinase inhibitors that target EGFR/ErbB2 show variable efficacy in reducing tumor size and enhancing hearing in NF2-related vestibular schwannomas, presenting challenges in their role as effective treatment options. The levels of VEGF and its receptors are increased in schwannomas, showing an association with tumor growth and volume. VEGF inhibitors, such as bevacizumab, have demonstrated encouraging outcomes in vestibular schwannomas, notably enhancing hearing and decreasing tumor size. Nonetheless, the administration of bevacizumab poses several challenges, such as the requirement for regular parenteral delivery, potential side effects, noticeable drug resistance and the possibility of rebound tumor progression (38). Numerous investigations into the use of bevacizumab for vestibular schwannomas depend on brief follow-up periods

Table II. Adverse events occurring in patients receiving brigatinib.

Adverse Event	Total no. of events (n=36)	6 months (n=17)	12 months (n=19)
Hypertension	3	1	2
Diarrhoea	9	5	4
Liver dysfunction	2	1	1
Arrhythmia	3	1	2
Skin rash	9	4	5
Fatigue	10	5	5

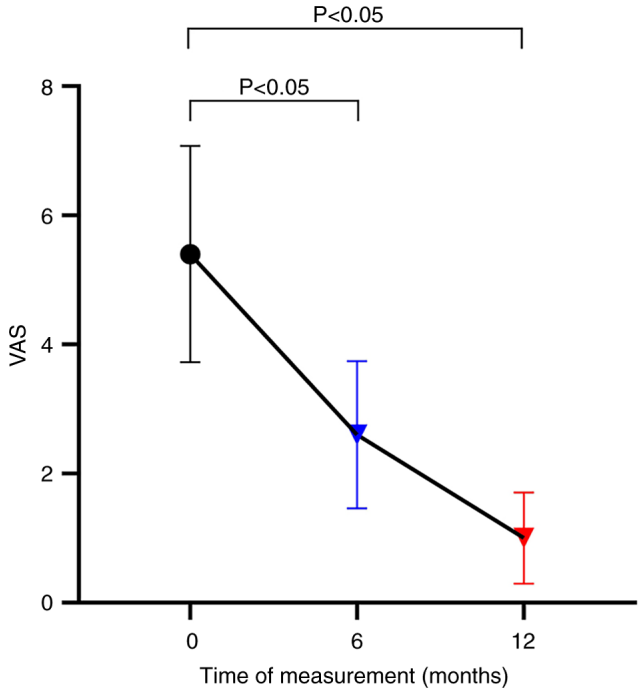

Figure 4. Line graph showing the VAS score, with a significant difference between the baseline and the 6 and 12th-month values. VAS, visual analog scale.

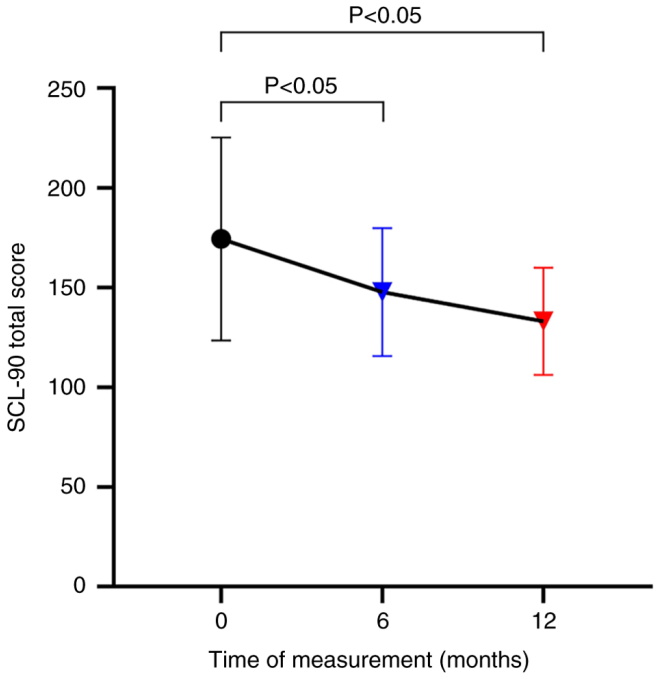

Figure 5. Line graph showing the SCL-90 total score, with a significant difference between the baseline, 6 and 12th-month values. SCL-90, symptom checklist-90.

and are deficient in long-term findings. Brigatinib engages in distinct pathways compared to those that have demonstrated efficacy in reducing tumor size and enhancing hearing in NF2-related vestibular schwannomas. This may clarify the absence of observed improvements in acoustic schwannoma size or hearing in the present study. Besides, the study by Plotkin *et al* (30) observed a certain degree of hearing improvement, but in the present study, there was no significant improvement in the volume of acoustic neuroma or the average hearing threshold (P>0.05). This difference may be, to a certain extent, attributed to the variation in sample size.

The small cohort of patients with NF2 and the elevated expense of brigatinib constrained the sample size of the present study, complicating the evaluation of brigatinib's impact on spinal tumors in NF2. This may clarify the absence of progress in vestibular schwannomas and auditory function. In the interim, additional clinical observation is required to assess the long-term efficacy of brigatinib in the treatment of NF2.

The main adverse effects noted during the trial included fatigue, skin rash and diarrhea, none of which resulted in the cessation of the medication. No significant adverse reactions were observed; however, one patient experienced severe anemia. Given the patient's history of anemia, which showed improvement following treatment, anemia may not be associated with brigatinib. No instances of anemia were reported in other studies involving brigatinib (39,40).

Of note, the present study has several limitations. NF2 exhibits a wide range of clinical manifestations that differ significantly from one individual to another, complicating the development of a universal treatment that can effectively address all patient symptoms. Tailored approaches that involve collaboration across various disciplines could prove to be a promising strategy in the management of NF2. In addition, further clinical drug studies are essential to generate evidence and explore new therapeutic possibilities for NF2. The limited sample size (n=12) restricts the statistical power of the findings. Although selection bias was minimized by continuously enrolling all eligible patients, as this study was based on a retrospective dataset, selection bias may still exist. Certain patients may not have been included in the study due to milder

or more severe conditions, which may result in the sample of the present study not fully representing the entire NF2 patient population. It is essential to validate these findings through larger, multicenter trials. Although both the log-rank test and Cox model indicated a significant relationship between age and progression risk, it is essential to interpret these findings with caution and validate them in larger cohorts.

In conclusion, the present findings indicate that brigatinib has a notable impact on reducing meningioma volume in individuals with NF2, while also enhancing their emotional health and relieving pain. Nonetheless, the effect on vestibular schwannoma volume and hearing thresholds is not significant.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

ZL and WY were involved in the conception and design of the study and analyzed data. FJ and ZX collected the data and helped with the data analysis. ML and SJ helped with the data analysis, drafted and proofread the manuscript, performed final editing and are guarantors of the study. ML and SJ confirm the authenticity of the raw data. All authors have checked and approved the final version of the manuscript.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki (2013) and approved by the Institutional Review Board (IRB) of The First Medical Center of Chinese PLA General Hospital (Beijing, China; IRB approval no. S2021-409-01). Informed consent was obtained from all adult participants and written parental consent was secured for minors, consistent with ethical guidelines for pediatric research.

Patient consent for publication

Not applicable.

Competing interests

All authors declare that they have no competing interests.

References

1. Rouleau GA, Merel P, Lutchman M, Sanson M, Zucman J, Marineau C, Hoang-Xuan K, Demczuk S, Desmaze C, Plougastel B, *et al*: Alteration in a new gene encoding a putative membrane-organizing protein causes neuro-fibromatosis type 2. Nature 363: 515-521, 1993.
2. Asthagiri AR, Parry DM, Butman JA, Kim HJ, Tsilou ET, Zhuang Z and Lonser RR: Neurofibromatosis type 2. Lancet 373: 1974-1986, 2009.
3. Slattery WH: Neurofibromatosis type 2. Otolaryngol Clin North Am 48: 443-460, 2015.
4. Evans DG, Baser ME, O'Reilly B, Rowe J, Gleeson M, Saeed S, King A, Huson SM, Kerr R, Thomas N, *et al*: Management of the patient and family with neurofibromatosis 2: A consensus conference statement. Br J Neurosurg 19: 5-12, 2005.
5. Plotkin SR, Messiaen L, Legius E, Pancza P, Avery RA, Blakeley JO, Babovic-Vuksanovic D, Ferner R, Fisher MJ, Friedman JM, *et al*: Updated diagnostic criteria and nomenclature for neurofibromatosis type 2 and schwannomatosis: An international consensus recommendation. Genet Med 24: 1967-1977, 2022.
6. Okada T, You L and Giancotti FG: Shedding light on Merlin's wizardry. Trends Cell Biol 17: 222-229, 2007.
7. Zhang N, Bai H, David KK, Dong J, Zheng Y, Cai J, Giovannini M, Liu P, Anders RA and Pan D: The Merlin/NF2 tumor suppressor functions through the YAP oncoprotein to regulate tissue homeostasis in mammals. Dev Cell 19: 27-38, 2010.
8. Apra C, Peyre M and Kalamarides M: Current treatment options for meningioma. Expert Rev Neurother 18: 241-249, 2018.
9. Angus SP, Oblinger JL, Stuhlmiller TJ, DeSouza PA, Beauchamp RL, Witt L, Chen X, Jordan JT, Gilbert TSK, Stemmer-Rachamimov A, *et al*: EPH receptor signaling as a novel therapeutic target in NF2-deficient meningioma. Neuro Oncol 20: 1185-1196, 2018.
10. Mohanty A, Pharaon RR, Nam A, Salgia S, Kulkarni P and Massarelli E: FAK-targeted and combination therapies for the treatment of cancer: An overview of phase I and II clinical trials. Expert Opin Investig Drugs 29: 399-409, 2020.
11. Markham A: Brigatinib: First global approval. Drugs 77: 1131-1135, 2017.
12. Hoy SM: Brigatinib: A review in ALK-inhibitor Naïve advanced ALK-positive NSCLC. Drugs 81: 267-275, 2021.
13. Chang LS, Oblinger JL, Smith AE, Ferrer M, Angus SP, Hawley E, Petrilli AM, Beauchamp RL, Riecken LB, Erdin S, *et al*: Brigatinib causes tumor shrinkage in both NF2-deficient meningioma and schwannoma through inhibition of multiple tyrosine kinases but not ALK. PLoS One 16: e0252048, 2021.
14. Mulvihill JJ, Parry DM, Sherman JL, Pikus A, Kaiser-Kupfer MI and Eldridge R: NIH conference. Neurofibromatosis 1 (Recklinghausen disease) and neurofibromatosis 2 (bilateral acoustic neurofibromatosis). An update. Ann Intern Med 113: 39-52, 1990.
15. Evans DG, Huson SM, Donnai D, Neary W, Blair V, Newton V and Harris R: A clinical study of type 2 neurofibromatosis. Q J Med 84: 603-618, 1992.
16. Baser ME, Friedman JM, Wallace AJ, Ramsden RT, Joe H and Evans DGR: Evaluation of clinical diagnostic criteria for neurofibromatosis 2. Neurology 59: 1759-1765, 2002.
17. Camidge DR, Kim HR, Ahn MJ, Yang JCH, Han JY, Hochmair MJ, Lee KH, Delmonte A, Garcia Campelo MR, Kim DW, *et al*: Brigatinib versus crizotinib in ALK inhibitor-naive advanced ALK-positive NSCLC: Final results of phase 3 ALTA-1L trial. J Thorac Oncol 16: 2091-2108, 2021.
18. Walia A, Tuia J and Prasad V: Progression-free survival, disease-free survival and other composite end points in oncology: Improved reporting is needed. Nat Rev Clin Oncol 20: 885-895, 2023.
19. Carl AC, Hohman MH and Cornejo J: Audiology pure tone evaluation. [2023 Mar 1]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing, 2025.
20. Kostaras P, Martinaki S, Asimopoulos C, Maltezou M and Papageorgiou C: The use of the symptom checklist 90-R in exploring the factor structure of mental disorders and the neglected fact of comorbidity. Psychiatry Res 294: 113522, 2020.
21. McCormack HM, Horne DJ and Sheather S: Clinical applications of visual analogue scales: A critical review. Psychol Med 18: 1007-1019, 1988.
22. Azam F, Latif MF, Farooq A, Tirmazy SH, AlShahrani S, Bashir S and Bukhari N: Performance status assessment by using ECOG (eastern cooperative oncology group) score for cancer patients by oncology healthcare professionals. Case Rep Oncol 12: 728-736, 2019.
23. Grossen A, Gavula T, Chrusciel D, Evans A, McNall-Knapp R, Taylor A, Fossey B, Brakefield M, Carter C, Schwartz N, *et al*: Multidisciplinary neurocutaneous syndrome clinics: A systematic review and institutional experience. Neurosurg Focus 52: E2, 2022.

24. Mautner VF, Lindenau M, Baser ME, Hazim W, Tatagiba M, Haase W, Samii M, Wais R and Pulst SM: The neuroimaging and clinical spectrum of neurofibromatosis 2. Neurosurgery 38: 880-886, 1996.
25. Coy S, Rashid R, Stemmer-Rachamimov A and Santagata S: An update on the CNS manifestations of neurofibromatosis type 2. Acta Neuropathol 139: 643-665, 2020.
26. Blakeley JO, Ye X, Duda DG, Halpin CF, Bergner AL, Muzikansky A, Merker VL, Gerstner ER, Fayad LM, Ahlawat S, *et al*: Efficacy and biomarker study of bevacizumab for hearing loss resulting from neurofibromatosis type 2-associated vestibular schwannomas. J Clin Oncol 34: 1669-1675, 2016.
27. Lu VM, Ravindran K, Graffeo CS, Perry A, Van Gompel JJ, Daniels DJ and Link MJ: Efficacy and safety of bevacizumab for vestibular schwannoma in neurofibromatosis type 2: A systematic review and meta-analysis of treatment outcomes. J Neurooncol 144: 239-248, 2019.
28. Tamura R, Fujioka M, Morimoto Y, Ohara K, Kosugi K, Oishi Y, Sato M, Ueda R, Fujiwara H, Hikichi T, *et al*: A VEGF receptor vaccine demonstrates preliminary efficacy in neurofibromatosis type 2. Nat Commun 10: 5758, 2019.
29. Plotkin SR, Allen J, Dhall G, Campian JL, Clapp DW, Fisher MJ, Jain RK, Tonsgard J, Ullrich NJ, Thomas C, *et al*: Multicenter, prospective, phase II study of maintenance bevacizumab for children and adults with NF2-related schwannomatosis and progressive vestibular schwannoma. Neuro Oncol 25: 1498-1506, 2023.
30. Plotkin SR, Yohay KH, Nghiemphu PL, Dinh CT, Babovic-Vuksanovic D, Merker VL, Bakker A, Fell G, Trippa L and Blakeley JO; INTUITT-NF2 Consortium: Brigatinib in NF2-related schwannomatosis with progressive tumors. N Engl J Med 390: 2284-2294, 2024.
31. den Bakker MA, Vissers KJ, Molijn AC, Kros JM, Zwarthoff EC and van der Kwast TH: Expression of the neurofibromatosis type 2 gene in human tissues. J Histochem Cytochem 47: 1471-1480, 1999.
32. Paldor I, Abbadi S, Bonne N, Ye X, Rodriguez FJ, Rowshanshad D, Itzoe M, Vigilar V, Giovannini M, Brem H, *et al*: The efficacy of lapatinib and nilotinib in combination with radiation therapy in a model of NF2 associated peripheral schwannoma. J Neurooncol 135: 47-56, 2017.
33. Coy S, Rashid R, Stemmer-Rachamimov A and Santagata S: Correction to: An update on the CNS manifestations of neurofibromatosis type 2. Acta Neuropathol 139: 667, 2020.
34. Kukutla P, Ahmed SG, DuBreuil DM, Abdelnabi A, Cetinbas M, Fulci G, Aldikacti B, Stemmer-Rachamimov A, Plotkin SR, Wainger B, *et al*: Transcriptomic signature of painful human neurofibromatosis type 2 schwannomas. Ann Clin Transl Neurol 8: 1508-1514, 2021.
35. Peyre M, Tran S, Parfait B, Bernat I, Bielle F and Kalamarides M: Surgical management of peripheral nerve pathology in patients with neurofibromatosis type 2. Neurosurgery 92: 317-328, 2023.
36. Mohammed N, Hung YC, Xu Z, Chytka T, Liscak R, Tripathi M, Arsanious D, Cifarelli CP, Perez Caceres M, Mathieu D, *et al*: Neurofibromatosis type 2-associated meningiomas: An international multicenter study of outcomes after Gamma Knife stereotactic radiosurgery. J Neurosurg 136: 109-114, 2021.
37. Fernandez-Valle C, Tang Y, Ricard J, Rodenas-Ruano A, Taylor A, Hackler E, Biggerstaff J and Iacovelli J: Paxillin binds schwannomin and regulates its density-dependent localization and effect on cell morphology. Nat Genet 31: 354-562, 2002.
38. Plotkin SR, Halpin C, McKenna MJ, Loeffler JS, Batchelor TT and Barker FG II: Erlotinib for progressive vestibular schwannoma in neurofibromatosis 2 patients. Otol Neurotol 31: 1135-1143, 2010.
39. Tamura R, Tanaka T, Miyake K, Yoshida K and Sasaki H: Bevacizumab for malignant gliomas: Current indications, mechanisms of action and resistance, and markers of response. Brain Tumor Pathol 34: 62-77, 2017.
40. Camidge DR, Kim HR, Ahn MJ, Yang JC, Han JY, Lee JS, Hochmair MJ, Li JY, Chang GC, Lee KH, *et al*: Brigatinib versus crizotinib in ALK-positive non-small-cell lung cancer. N Engl J Med 379: 2027-2039, 2018.