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Review

New Frontiers in Therapy of Peripheral Nerve Sheath Tumors in Patients With Neurofibromatosis Type 1: Latest Evidence and Clinical Implications

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Abstract. *Almost all individuals with neurofibromatosis type 1 (NF1) develop peripheral nerve sheath tumors (PNSTs), mainly benign neurofibromas, however about 10% of PNSTs will undergo transformation to malignant peripheral nerve sheath tumors (MPNSTs). Surgical treatment of PNSTs has traditionally been regarded as a standard approach. The availability of new agents that target specific molecular pathways involved in the pathogenesis of PNST has led to a number of clinical trials, which resulted in increased chances for better survival and quality of life. This review presents the latest evidence and clinical implications for new therapies of PNSTs in patients with NF1 emphasizing the potential benefit from the use of Ras/MAPK pathway inhibitors, immunotherapy, chemotherapy or radiation therapy. We present evaluation of current knowledge on available treatment modalities.*

Neurofibromatosis type 1 (NF1) is an autosomal dominant neurocutaneous disease affecting about 1 in 3500 people worldwide (1). The hallmark clinical features of NF1 include multiple café-au-lait macules, neurofibromas, intertriginous freckling, osseous lesions, Lisch nodules and optic pathway gliomas. The disorder is typified by the presence of multisystem tumors, which carries a high risk of malignant transformation (2, 3). Nearly 100% of individuals with NF1 develop benign peripheral nerve sheath tumors (BPNSTs) and in approximately 30-50% of them atypical and plexiform neurofibromas (PNFs) are found. In about 10% of NF1 patients, neurofibromas may undergo transformation to malignant peripheral nerve sheath tumors (MPNSTs), which are highly aggressive. The differentiation between atypical neurofibroma and low grade MPNST is probably the most challenging issue in the pathology of peripheral nerve sheath tumors (PNSTs), particularly in NF1 patients. Clinically, atypical tumors often develop as extensive, slowly growing neoplasms, and pain can be a characteristic feature (4, 5). The poor response to currently available therapies underlines the need for more effective, targeted treatment methods for NF1-associated PNSTs (6, 7). In this review, we analyzed the latest evidence and clinical implications of new therapies of PNSTs in patients with NF1 emphasizing the importance of patient risk stratification to identify those who are likely to benefit from the use of Ras/MAPK pathway inhibitors, immunotherapy, chemotherapy or radiotherapy. We also analyzed the limitations of administering these therapies to all individuals with NF1-associated PNSTs together with future perspectives.

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Methodology

PubMed searches were performed to identify potentially clinically relevant English-language studies published in the last 15 years. The searches were based on a combination of indexed terms and free text terms ("peripheral nerve sheath tumors", "plexiform neurofibromas", "MPNST", "neurofibromatosis type 1", "NF1") AND ("treatment", "therapy", "resection", "surgical

treatment", "MEK inhibitors", "kinase inhibitors", "mTOR inhibitors", "immunotherapy", "anti-PD1", "chemotherapy", "radiotherapy"). We analyzed all potentially relevant full papers, and paid particular attention to patient population and applied treatment. We analyzed all publications where the variety of therapies for aggressive PNSTs in pediatric and adult NF1 patients were presented. All types of treatment, including surgery, chemotherapy, immunotherapy, radiation therapy, were considered. We also analyzed reports related to atypical treatment methods, such as diet and vaccine treatment. Our database was supplemented with abstracts from Joint Global Neurofibromatosis Conferences held in 2016 (Italy, Padova) and 2018 (France, Paris) and with information from https://clinicaltrials.gov website. We focused mainly on the results of randomized clinical trials. However, most reports were based only on a relatively small number of patients. This review includes a summary of all NF1-related PNSTs treatment methods found in available medical literature. We described and compared results obtained by the researchers and formulated conclusions, considering which method was highly effective. Each relevant paper was analyzed by two independent investigators. Overlapping data were excluded. In total, 68 papers (including conference abstracts) and 21 clinical trials were found, and qualified as possibly relevant. Finally, 29 reports and 17 clinical trials were selected as relevant to the objective of the study. On the basis of these analyses, we complemented the review with a clinical evaluation that we graded as: positive, negative, optional.

Nomenclature for NF1-associated PNSTs

PNSTs encompass a wide spectrum of benign and malignant clinicopathologic entities, whose subsets are difficult to classify. The major categories of these tumors are classified as: neurofibroma, schwannoma, perineurioma, hybrid nerve sheath tumors, and MPNSTs (8, 9). However, this classification is not appropriate for NF1, as nearly 100% of individuals with NF1 will develop PNSTs mainly in the form of neurofibromas and their atypical ambiguous subtypes. Since PNSTs required a separate description for NF1 patients, recommendations for diagnosis and classification were proposed at the meeting held at the National Institute of Health (NIH) in 2016 in Bethesda. Characteristics of NF1-associated PNSTs are shown in Table I (7).

The Ki67 index may also be useful in assessing PNSTs in NF1 individuals highlighting proliferative hot spots. While cutaneous, diffuse and atypical neurofibromas usually have low labeling indices (<2-5%), high proliferation rates (>10%) can aid in the detection of MPNST arising in a neurofibroma (7). Loss of the CDKN2A locus at 9p21, which encodes the cell cycle regulator p16, characterizes early steps in the malignant transformation of neurofibromas. Complete loss of nuclear p16 is a frequent finding in MPNSTs and may be detected in ordinary and atypical neurofibromas indicating that it can be an early modification in malignant progression, but by itself is not adequate to diagnose malignancy (7, 10).

Imaging Evaluation of PNSTs – Differentiation of Benign and Malignant Lesions

Magnetic resonance imaging (MRI) is the most useful method for evaluating the anatomical extent of the lesion before surgical planning (5, 11). However, the morphological imaging features demonstrated limited diagnostic precision for differentiation of benign and malignant PNSTs with specificities of 18-82% and sensitivities of 18-94%. In MRI, MPNSTs present specific morphological properties including irregular shapes and margins, heterogeneity within tumor and peritumoral oedema (12-14).

Ultrasound or computed tomography (CT) may be useful in some patients for image-guided biopsies and bone scintigraphy can be helpful in assessing osseous involvement (11, 15).

FDG-PET/CT-guided percutaneous biopsy is an effective procedure and the most dependable approach for untimely detection of NF1-associated MPNST (16, 17). Benign PNFs demonstrate low fludeoxyglucose (FDG) uptake, whereas MPNSTs depict moderate to high FDG accumulation. Commonly standard uptake values (SUV), the amount of FDG uptake, usually range between 1.0-3.99 in benign tumors and between 3.1-21.4 in malignant lesions. There is an overlap between BPNSTs and MPNSTs for SUV values between 2.5 to 3.5. Therefore, it seems that the symptomatic PNFs with SUV ≥3.5 should be excised and lesions with SUV 2.5-3.5 should have precise clinical evaluation. FDG-PET/CT can be useful in the diagnosis of MPNST with specificity ranging from 72% to 95% and sensitivity ranging from 91% to 100% (15, 18, 19). The optimum time for measuring SUV in patients with symptomatic PNFs is 240 min after injection of FDG (19).

Whole-body hybrid PET/MRI is a viable alternative for evaluation of the potential occurrence of MPNSTs in NF1 patients, with sensitivity similar to that of PET/CT. Furthermore, X-ray dose reduction with PET/MR approaches 50% compared to PET/CT, a vital concern in this patient population with tumor suppressor gene impairment (15, 20, 21).

Diffusion-weighted MRI (DW-MRI) without administration of intravenous contrast material improves precision compared to morphological MRI in the differentiation of malignant and benign lesions in NF1-patients. DW-MRI can be a very valuable complementary method, when borderline glucose metabolism of tumors is observed in PET imaging (12).

Table I. *Nomenclature for NF1-associated PNSTs (4, 5, 7, 8, 32, 92-94).*

Diagnosis	Characteristics	Comments
Neurofibroma	- Benign neoplasm from nonmyelinating Schwann cells - Wavy nuclei, wispy cell processes and a myxoid to collagenous matrix ("shredded carrots") - IHC: SOX10 (+), S100 (+), lattice-like CD34+ fibroblastic network	The most common are localized cutaneous neurofibromas which usually occur as a single lesion. They can result in a fusiform expansion of the large nerve trunk. Diffuse neurofibromas are characterized by a plaque-like enlargement commonly in the region of head and neck. Cutaneous or diffuse neurofibromas seldom evolve into MPNST.
Plexiform neurofibroma	- Involvement of plural adjacent nerve fascicles and/or multiple components of the nerve plexus - delineated by EMA+ perineurial cells	Can implicate skin layers, fascia, bones, muscles and penetrate the viscera. The adjacent skin may demonstrate hyperpigmentation or hypertrichosis. The hypertrophy of surrounding connective tissues and underlying bones is often observed. The most popular locations are the head, neck, trunk and extremities. PNF has a potential for malignant degeneration.
Neurofibroma with atypia	- Scattered bizarre nuclei	Atypical neurofibroma has been suggested to be premalignant lesions based on their CDKN2A loss, as is recognized in MPNST, and can transform to MPNST.
Cellular neurofibroma	- Neurofibroma with hypercellularity - Mitotic index: <1/50 HPF	There are no definitive data on risk for progression to MPNST.
Atypical neurofibromatous neoplasm of unknown biologic potential (ANNUBP)	- neoplasm from Schwann cell with ≥2/4: 1) cytologic atypia, 2) loss of neurofibroma architecture, 3) hypercellularity, 4) mitotic index: >1/50 HPF and <3/10 HPF	Possibly ANNUBPs are not malignant in most NF1 patients.
Low-grade MPNST (frequency: 15%)	- Characteristics like ANNUBP - Mitotic index: 3-9/10 HPF and no necrosis	The appearance of new, growing, or permanent pain in the area of neurofibroma is an important signal that should always be carefully evaluated. MPNST may occur at any age with the same frequency in both sexes.
High-grade MPNST (frequency: 85%)	- Mitotic index: >10/10 HPF - Mitotic index: 3-9/10 HPF and presence of necrosis	The median age for MPNST in NF1-patients is 20-40 years. Primary tumors usually occur in the extremities (45-59%), within the trunk (17-34%), or head and neck (19-24%). In most cases, the dimension of the tumor is >5 cm before starting treatment, and up to 50% of patients present with metastases, commonly to the lung. Usually aggressive, with 5-year survival rates at 34%-60%.

MPNST: Malignant peripheral nerve sheath tumor; IHC: immunohistochemistry; HPF: high power fields; PNF: plexiform neurofibroma.

Pathogenesis of PNSTs in NF1

The NF1 syndrome is the consequence of mutations in NF1 tumor suppressor gene on chromosome 17q11. More than 500 mutations have been identified, with the majority resulting in a loss of function of the neurofibromin protein, which is encoded by the *NF1* gene (22, 23). Neurofibromin is highly expressed in numerous organs, but is mostly abundant in the brain tissue, spinal cord, and peripheral nervous system. A variation in a single germline allele is sufficient to cause the NF1 syndrome, but according to Knudson's "2-hit hypothesis", tumor formation appears to require the loss of function of a second allele (22, 24). Neurofibromin also participates in the regulation of histogenesis, and cellular maintenance or repair. Accordingly, NF1 is a disorder of not only tumor predisposition, but also of dysplasia (25).

Neurofibromin is a protein that accelerates the intrinsic hydrolysis of Ras from its GTP- to inactive GDP-bound conformation (26). In healthy cells, Ras is in the inactive conformation and is responsible for correct proliferation, transformation, differentiation, and apoptosis. Upon NF1 inactivation, Ras hyperactivity and the consequent activation of various downstream proliferative and survival pathways, like the mammalian target of rapamycin (mTOR), mitogen-activated protein kinase (MAPK), or AKT (Mouse breed AK thymoma, termed protein kinase B, or PKB) pathways are observed (5, 22). Hence, by accelerating the conversion of Ras-GTP to Ras-GDP, neurofibromin negatively regulates Ras-dependent signaling cascades. In the pathophysiology of NF1, when neurofibromin is defective, Ras-GTP is constantly activated, which results in unrestrained stimulation of various pro-growth pathways (26).

Biallelic loss of neurofibromin is responsible for the development of PNSTs in patients with NF1 syndrome. However, the pathway to tumorigenesis is distinctly more complicated; *NF1* mutations are probably not sufficient to induce neoplastic change. Murine experiments have also shown the significance of haploinsufficient NF1-mast cells for accelerating PNF growth. In addition to Ras activation, maturation, recruitment and proliferation of mast cells have been demonstrated to be mediated by the stem cell factor (SCF), the ligand for the KIT receptor tyrosine kinase (RTK), suggesting SCF/KIT-dependent tumorigenic tumor-stromal interactions in PNFs. The next molecular pathway leading from benign lesion to MPNST in NF1 syndrome remains uncertain. Figure 1 depicts the multiple major nodes engaged in the pathogenesis of MPNSTs, involving angiogenesis, intracellular signaling pathways, and interactions with the environment of the tumor (5, 27).

Indications for Treatment of PNSTs

Cutaneous neurofibromas should be removed when they cause transient itching and stinging, cosmetic problems or catch on clothing. Resection of benign PNFs is usually difficult because of encroachment of the lesion on adjacent structures and its inseparable vascular nature. Surgical intervention carries a high risk of life-threatening hemorrhage, especially in cases of facial PNFs (28).

About 50% of PNFs occur in the region of the face, head, neck, and larynx. Serious controversy persists regarding the indications and timing of surgical interventions for PNFs of the head and neck. In pediatric PNFs the management is based on serial imaging studies to establish impending risk to the airway and other critical neck structures. There are definite indications for surgical resection of large tumors of the head and/or neck: 1) to exclude malignant transformation in a fast enlarging mass; 2) to increase airway patency; 3) to alleviate symptoms caused by compression of neural structures, particularly in paraspinal PNFs; 4) to achieve aesthetic results, particularly in individuals with trigeminal lesions, bearing in mind the related risk of facial nerve palsy (29).

PNFs involving the orbit, eyelid, periorbital, and facial structures are called "orbital-periorbital PNFs" (OPPNFs). The best management for newly diagnosed OPPNFs is close observation with regular ophthalmological and MRI evaluations because a lot of OPPNFs will be not symptomatic and progressing. Indications for treatment can be 1) young age of the patient; 2) rapid growth of PNFs; 3) presence of a concurrent optic pathway glioma; 4) symptomatic tumor (*i.e.*, strabismus, vision loss, glaucoma, proptosis, ptosis, amblyopia); 5) infiltration of OPPNF into other structures (*i.e.*, cavernous sinus) (30).

Based on a review of published studies, the following indications for surgical interventions for PNSTs of plexiform/diffuse type of limbs should be considered: 1) exploration/biopsy: rapidly enlarging mass and/or an unusual or novel mass with long-lasting pain are the predominant findings leading to the decision to explore the affected region; 2) nodular PNF: this tumor type has a higher risk of malignant degeneration if situated in deeper body regions; 3) superficial PNF: in the cases of not extensive involvement of the body region, when surgery and rehabilitation can be implemented; 4) invasive PNF: the surgical objectives are often limited to improvements in the outline of the body without affecting the tumor load of deeper body regions. An important distinction in this patient group is the restriction of tumor growth to the soft tissue or simultaneous tumor-associated alteration of soft tissue and bones; 5) palliative treatment: amputation of the affected limb with progressive PNF or MPNST, to increase survival chances (31, 32).

Clearly, the future of favorable control of PNFs lies in the development of effective nonsurgical modalities. MPNST tumors always require early and aggressive treatment (28). In each case of PNST, management decisions should include input from a multidisciplinary group (30).

Treatment of PNSTs

Management of PNSTs has traditionally been surgical, because these tumors are not radiosensitive and, given their slow growth rates, only limited benefit has been seen with chemotherapy (29). The accessibility of agents that target Ras signaling and other pathways involved in the pathogenesis of PNFs has led to a number of clinical trials. The development of genetically engineered mouse models of NF1-related tumors has led to preclinical trials of targeted drugs (33). The outcome of treatment of PNSTs in individuals with NF1, based on review of reported cases, is presented in subsequent sections.

Surgical treatment and other invasive methods. Surgery with complete removal of the lesion with tumor free margins is the most effective approach to treat patients with PNSTs. However, due to the large extent of many lesions, complete resection of these tumors is hardly feasible and may cause severe iatrogenic damage. Furthermore, PNFs may present in the form of diffuse enlargement of the affected body region (11, 29, 32). Current surgical experience has shown that recurrence rates for BPNSTs range from 1.3% to 54% and are higher in pediatric PNFs (29, 30, 32, 34-37). Outcome is largely influenced by tumor histopathology, type of mutation and tumor location (34, 38-40). Due to unsatisfactory results from surgical treatments, more effective and safer operating methods are sought. Callefi *et al*. have proposed a technique named compartmentalization, which is based on neurofibroma's mechanical ischemia before surgical excision, without preoperative embolization or use of sclerosing agents.

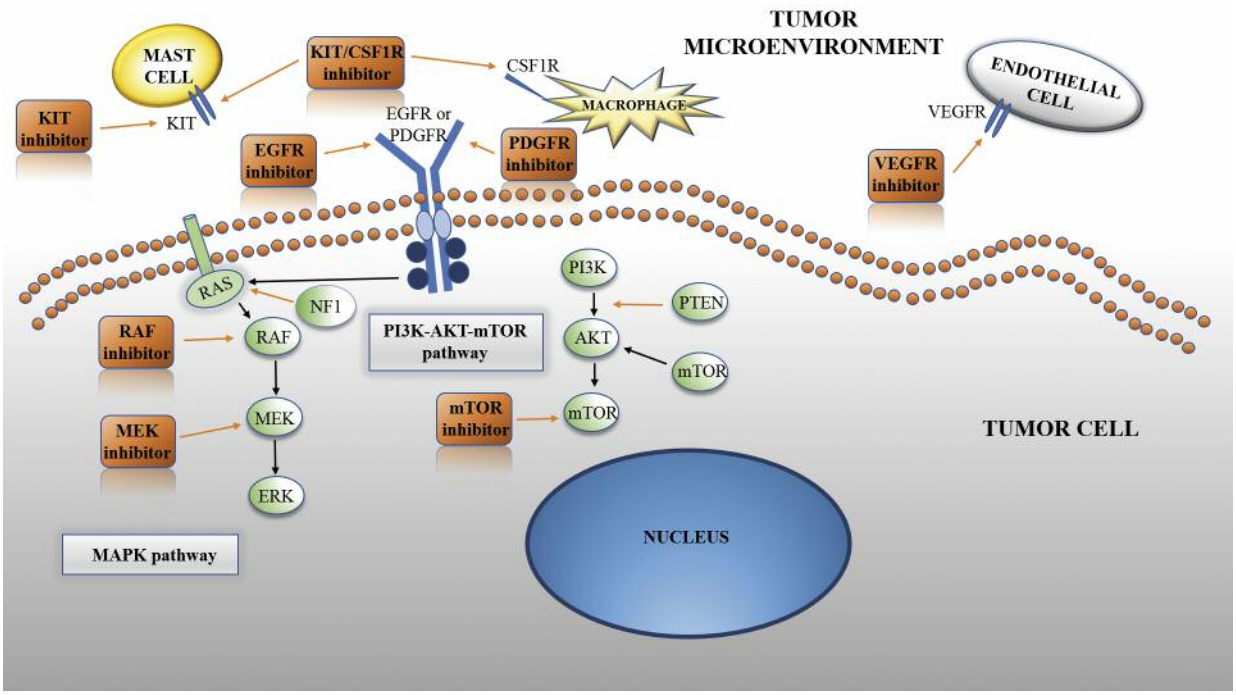

Figure 1. *Major molecular mechanisms implicated in the pathogenesis of MPNSTs, which include various KIT signaling cascades, epigenetic regulation and tumor microenvironment interactions. The mechanisms of action of potential small-molecule inhibitors targeting each of the mentioned machineries are denoted (27). KIT: Receptor tyrosine kinase; CSF1R: colony stimulating factor 1 receptor; EGFR: epidermal growth factor receptor; PDGFR: platelet-derived growth factor receptor; VEGFR: vascular endothelial growth factor receptor; RAF: rapidly accelerated fibrosarcoma; MEK: mitogen-activated protein kinase; ERK: extracellular-signal-regulated kinase; MAPK: mitogen-activated protein kinase; PI3K: phosphatidyl inositol 3-kinase; AKT: mouse strain AK thymoma; mTOR: mammalian target of rapamycin.*

This technique allows complete surgical excision of big size PNFs, otherwise inoperable, in a single surgical approach, significantly decreasing the risk of bleeding and also allows histopathological examination of PNFs (41).

In addition to expected management with routine imaging and surgical resection, possible alternative treatment options for non-cutaneous PNSTs include cryoablation, radiosurgery, microwave ablation and radiofrequency ablation. There are only single reports of percutaneous treatment of PNSTs (42-47). The treatment objective for BPNSTs within main peripheral nerves should be lesion control and not complete ablation, since most normal fibers travel within the capsule of the tumor. The management of MPNST is much more aggressive than that of BPNST, so a tissue diagnosis should be received prior to percutaneous treatment (42). Additionally, there is no proven benefit of carbon dioxide laser treatment over surgical removal of neurofibromas, but laser can be useful for some small lesions. Nevertheless, the risk of recurrence or a hypertrophic scarring after resection still exists (28). It is a crucial factor to balance the present activity of the patient with the risk of future loss of a function induced by an invasive intervention (30).

MEK inhibitors. Mitogen-activated protein kinase (MEK) is a key protein in the mitogen activated protein (MAP) kinase signal transduction pathway for many growth factor receptors that supply growth signals to tumor cells (48). Selumetinib is an inhibitor of MEK 1/2, which can mediate anti-tumor effects in PNFs by inhibiting Ras signaling (33). The phase I trial of selumetinib in 24 pediatric NF1-patients (3-17 y) with inoperable PNFs showed unprecedented activity with objective responses (PNF volume decrease ≥20%) in 71% of enrolled children. None of the patients had disease progression. However, a slow tumor regrowth was observed in several individuals who required dose reductions due to toxicity. This fact suggests that a minimal selumetinib tissue concentration may be required for anti-tumor activity. In 2019, U.S. FDA approved selumetinib for the treatment of pediatric patients (≥3 y) with NF1 symptomatic and/or progressive, inoperable PNFs (33, 48).

Only a few case reports of patients with NF1-dependent PNFs effectively treated with trametinib have been reported so far (49, 50). All currently ongoing clinical trials with MEK inhibitors for NF1-patients with PNFs or MPNST are listed in Table II (51).

Table II. *Review of current clinical trials with MEK inhibitors for patients with NF1-related PNFs/MPNST (51).*

Trial	Phase	Eligibility	Regimen tested and schedule	Objective	ClinicalTrials.gov identifier
MEK 1/2 Inhibitor Selumetinib (AZD6244 Hydrogen Sulfate) in Adults With Neurofibromatosis Type 1 (NF1) and Inoperable Plexiform Neurofibromas	2	≥18 y; NF1; inoperable PNF that causes morbidity or is growing	Selumetinib - 50 mg, orally, every 12 hours every day continuously (1 cycle=28 days)	ORR: ≥20% decrease of PNFs volume	NCT02407405
An Intermediate Access Protocol for Selumetinib for Treatment of Neurofibromatosis Type 1	2	2-18 y; NF1; inoperable progressive/ symptomatic PNF	Selumetinib (no information available about dose)	No data	NCT03259633
Intermittent Dosing of Selumetinib In Childhood NF1 Associated Tumors (INSPECT)	1/2	3-18 y; NF1; inoperable PNF and/or progressive OPG	Selumetinib – orally twice daily on 5 out of 7 days (without more data)	Phase 1: MTD Phase 2: ORR	NCT03326388
AZD6244 Hydrogen Sulfate for Children With Nervous System Tumors	1/2	12-18 y; NF1; inoperable PNF	Selumetinib – orally, every 12 hours on continuous daily schedule for cycles of 28 days until unacceptable toxicity	Phase 1: MTD Phase 2: PRR, CRR	NCT01362803
Phase II Study of Binimetinib in Children and Adults With NF1 Plexiform Neurofibromas (NF108-BINI)	2	≥18 y (Arm A) or 1-17 y (Arm B); NF1; progressive or causing significant morbidity PNF	Binimetinib – orally, every 12 hours, 45 mg/dose in adults (1 cycle – 28 days) (no information available about dose in pediatric patients)	Change from baseline target tumor volume at 12 months	NCT03231306
Trametinib for Pediatric Neuro-oncology Patients With Refractory Tumor and Activation of the MAPK/ERK Pathway.	1/2	1 m-25 y; PNF or LGG; NF1 positive or negative	Trametinib: 0.025 mg/kg/ day, up to a total of 18 cycles (1 cycle=28 days)	Phase 1: ORR Phase 2: TTP, PFS, OS, safety and tolerability of drug	NCT03363217
MEK Inhibitor PD-0325901 Trial in Adolescents and Adults With NF1 (MEK Inhibitor)	2	≥16 y; NF1; growing or symptomatic, inoperable PNF	PD-0325901 – orally, 2 mg/m^2/dose (max 4 mg), schedule: 3 week on/1 week off	Tumor volume response, toxicity, ORR, QoL	NCT02096471
Study to Investigate Safety, Pharmacokinetic (PK), Pharmacodynamic (PD) and Clinical Activity of Trametinib in Subjects With Cancer or Plexiform Neurofibromas and Trametinib in Combination With Dabrafenib in Subjects With Cancers Harboring V600 Mutations	1/2	1 m-17 y; NF1 associated PNFs or other solid tumors with BRAF V600 mutation	Trametinib – orally, once daily, dose: 0.0125-0.040 mg/kg/day; max 3 mg Dabrafenib – 3 mg/kg with dose escalation of 0.75 mg/kg/day	Safety and tolerability of the drugs; tumor volume response on trametinib and dabrafenib used as monotherapy and in combination	NCT02124772
Pediatric Long-Term Follow-up and Rollover Study	4	≥1 y; patients who received monotherapy or combination with dabrafenib and trametinib	Trametinib Dabrafenib (no information available about doses)	Evaluation of AEs and clinical benefits	NCT03975829
SARC031: MEK Inhibitor Selumetinib (AZD6244) in Combination With the mTOR Inhibitor Sirolimus for Patients With Malignant Peripheral Nerve Sheath Tumors	2	≥12 y; unresectable or metastatic, sporadic or NF1 associated MPNST	Selumetinib - orally, 50 mg twice daily continuously Sirolimus - orally, 4 mg once daily with a cycle 1 day 1 loading dose of 12 mg (1 cycle=28 days)	Evaluation of clinical benefits, toxicities, PFS, OS	NCT03433183

NF1: Neurofibromatosis type 1; PNF: plexiform neurofibroma; ORR: objective response rate; OPG: optic pathway glioma; MTD: maximum tolerated dose; PRR: partial response rate; CRR: complete response rate; LGG: low grade glioma; TTP: time to progression; PFS: progression-free survival; OS: overall survival; QoL: quality of life; AEs: adverse events; MPNST: malignant peripheral nerve sheath tumor.

Tyrosine kinase inhibitors. Imatinib is a specific inhibitor of a number of tyrosine kinase (TK) enzymes. There are many TK enzymes in the body and imatinib is specific for the TK domain in ABL, stem cell factor (c-KIT) and platelet-derived growth factor receptor (PDGF-R). The BCR-ABL pathway includes many downstream pathways such as the Ras/MAPK pathway, which stimulates proliferation in a growth factor-independent manner. In an imatinib phase II trial, PNF volume decreased from baseline by at least 20% in only 6 of 36 patients (17%) (52, 53). A phase III study that evaluated the efficacy and safety of imatinib mesylate treatment in adult patients with NF1-related MPNST was terminated early due to slow recruitment and lack of effect (NCT00427583) (51).

Nilotinib is an active TK inhibitor which targets ABL (and the oncogenic BCR-ABL), together with several other RTKs including those for c-KIT, collagen and PDGF-R. It has a number of advantages over imatinib, including a favorable toxicity profile. Wei *et al*. have demonstrated an inhibitory effect of nilotinib on viability and proliferation of PNF-derived Schwann cells and PNST-cells *in vitro* with 50% inhibitory concentration values lower than those of imatinib. In this *in vivo* model, the more potent effect of nilotinib over imatinib was also revealed. These results showing that nilotinib shows a more potent antitumor effect than imatinib *in vivo* and *in vitro*, suggest the possible clinical application of nilotinib for PNFs (54). In the early phase I clinical trial with nilotinib, 3 out of 6 adult patients with NF1-associated PNFs completed the study. In 2 patients, stabilization of the disease was observed and 1 individual had tumor progression (NCT01275586) (51).

Sunitinib malate is a multi-targeted RTK inhibitor that seems to be an exceptional candidate for the treatment of NF1-associated PNFs. Ferguson *et al*. have shown that sunitinib inhibits gain-in-functions within base cellular constituents of the PNF microenvironment including NF1-mast cells and fibroblasts, driven by hyperactive, Ras-dependent signaling. Further, they demonstrated that sunitinib malate induces growth arrest or regression of PNFs in genetic modified mice validating inhibition of various TKRs as a possible treatment for NF1-individuals with PNFs (55). Safety profile and effectiveness of sunitinib were evaluated in 19 NF1-patients (3-65 y) with PNFs through a phase I clinical trial. The study was terminated, because one patient died due to an uncertain cause, but possibly related to the drug (NCT01402817) (51).

Sorafenib is a potential inhibitor for RTK. Pre-clinical testing of sorafenib in a genetically susceptible mouse model for NF1-related PNF showed significant decreases in lesion size. Kim *et al*. have conducted a phase I trial of sorafenib in 9 children (3-18 y) with NF1 and inoperable PNFs, where no tumor shrinkage and poor tolerance of the drug was observed (56).

Cediranib is a potent inhibitor of vascular endothelial growth factor (VEGF) RTK. The phase II trial NCT00326872 included patients with NF1 and PNF and/or neurofibroma near the spine. The trial was terminated due to slow accrual prior to interim analysis (51).

Cabozatinib is a multitargeted TK inhibitor. In a phase II study (NCT02101736), cabozatinib was used in 23 subjects (≥16 y; median age 23 y) with NF1 and clinically significant PNFs. The objective response rate to drug was defined as ≥20% reduction in tumor volume at the end of 12 cycles. Among 19 eligible patients, 8 (42%) had an objective response. None of the patients had PNF progression during treatment (51, 57).

Interferons. Interferon-α is a cytokine predominantly produced by leukocytes in response to infections and has immunoregulatory, antiviral, antiproliferative and antitumor activities. The mechanisms include the activation of immunomodulatory factors (cytotoxic T-lymphocytes, NK cells, monocytes), the induction of increased cell surface expression of class I MHC antigens, and inhibition of secretion of anti-angiogenic factors (58).

Pegylated interferon-α-2B (pegIFN-α-2B) was evaluated in a phase I trial that included 17 patients (1.9-34.7 y; median age 9.3 y) with NF1-related PNFs. Five of the patients (5/17; 29.4%) showed a 15%-22% decrease in tumor volume. Five patients developed tumor progression 11-24 months after the beginning of treatment (59). In a phase II trial with pegIFN-α-2B, tumor volume decrease by at least 20% was identified in only 4 of 82 (4.9%) patients (1.6-21.4 y; median age 10 y) (58).

Kebudi *et al*. have studied 5 patients (1.1-12 y; median age 8 y) with unresectable, progressive and symptomatic PNFs. All of them had experienced relief from pain during treatment with interferon-α-2Aa (IFN-α-2A), and in one case radiologic response was observed (60).

mTOR-inhibitors. Converging evidence has demonstrated that neurofibromin regulates growth of cells by negatively influencing the mammalian target of rapamycin (mTOR) pathway. Mammalian TOR is a central integrator of a number of cellular processes, like cell proliferation, growth and survival, protein translation and angiogenesis. Furthermore, mTOR pathway activation propagates tumor proliferation in NF1 genetically engineered mouse models and human NF1-related tumor explants (61). The suppression of mTOR by rapamycin significantly inhibited the growth of NF1-related malignancies in a genetically engineered murine model. The results of these trials suggest that rapamycin (sirolimus) or its derivatives, such as temsirolimus or everolimus, might be used as a potential therapy for NF1-tumors.

In the study of the safety and efficacy of everolimus for life-threatening, surgically intractable, internal PNFs in adult

NF1-patients the drug had no effect on tumor volume (62). Hua *et al*. have presented 3 cases of young NF1-patients (8 y, 16 y, 17 y) who were treated with sirolimus for life-threatening PNFs. After 12-months follow-up, no difference from baseline in PNFs volume was demonstrated. However, in all 3 cases pain had decreased, which led to cessation of all analgesics (63). Another trial assessed sirolimus as a therapy for inoperable NF1-related internal PNFs in a pediatric population (3-17.7 y; median age 8.2 y). The time to progression (>20% increase in the sum of the volumes of all index PNFs) was significantly shorter in the placebo group (11.9 months) than in the sirolimus group (15.4 months) (61).

Drug combinations including mTOR inhibitor are being currently tested in clinical trials for MPNST: ganetespib + sirolimus (NCT02008877), bevacizumab + everolimus (NCT01661283), pexidartinib + sirolimus (NCT02584647), selumetinib + sirolimus (NCT03433183). The results have not been published yet (51).

PD1-inhibitors. Programmed death-ligand 1 (PD-L1) expression on PNFs cell membrane has been found and identified as a predictive marker correlated with the therapeutic response to anti PD-L1/anti-PD-1 checkpoint inhibitor monoclonal antibodies. The location and type of lymphocytic infiltrate have significant influence on response to immune checkpoint inhibitors. Tumors with infiltration of CD8+ cells are considered good candidates for therapy with anti-PD-1 drugs. The tumor infiltrating lymphocytes (TILs) or high expression of PD-L1 on PNF cells suggest that patients can be responsive to treatment with immune checkpoint inhibitors (64).

Currently, there are two phase II clinical trials, where adult patients with unresectable MPNST are treated with the use of humanized monoclonal IgG4 antibody directed against programmed death-1 (PD-1) cell surface receptor: The first study examines the efficacy of pembrolizumab monotherapy (NCT02691026) and the second study the combined therapy with nivolumab (anti-PD-1 agent) and ipilimumab (anti-CTLA-4 antigen monoclonal antibody) (NCT02834013). No results are available yet for these clinical trials (51).

Conventional chemotherapy. The standard of care in locally advanced MPNST is to receive local disease control, primarily using operating techniques. The primary goal is to acquire negative surgical margins. If there is an increased risk of unresectability of the tumor, neoadjuvant chemotherapy or/and radiotherapy can be applied, particularly in patients with a tumor size of >5 cm and when a quick reduction of tumor mass is necessary. Currently there are no randomized clinical trials available where chemotherapy is evaluated in MPNST. The data are limited to retrospective, single analyses of case series (65). In a few reports and clinical trials, the sensitivity of MPNST to various types of classical chemotherapeutic agents was assessed. The results of these studies are presented in Table III (66-71).

Madhankumar *et al*. have demonstrated IL13Rα2 expression in a few MPNST cell lines. IL13 conjugated liposomal doxorubicin was formulated and demonstrated cytotoxic effect following binding and internalization in a MPNST cell culture model. A sequential *in vivo* study in the MPNST sciatic nerve tumor model indicated that unconjugated liposomal doxorubicin was less efficient in inhibiting tumor progression compared to IL13 conjugated liposomal doxorubicin. This, additionally supports that IL13 receptor targeted nanoliposomes can be an important approach for treating MPNSTs (72).

Radiation therapy. There are many controversies regarding the role of radiation therapy (RT) in the management of MPNST, because it may be a malignancy-risk factor for patients with NF1. According to some of these studies, RT decreases the risk of local recurrence and improves local control (LC), however, it does not result in better survival. Most specialists recommend RT in high-risk patients: large tumor size (>5 cm or >10 cm), high grade tumors and margin positive tumors. There is also some disagreement about optimal timing of RT: preoperatively versus postoperatively. In a preoperative setting, tumor volume and its relation to adjacent organs is accurately seen in CT scanning and therefore radiation planning is more reliable. However, a large tumor pushes the critical organs and acts as a natural shield. Theoretically, tumor with intact blood supply shows a better response to RT (73, 74).

Bishop *et al*. have reviewed the medical records of 71 patients (16-88 y; median age 39 y; 37% with NF1-status) treated with RT and surgery for locally advanced MPNSTs. Preoperative RT was used in 23 individuals (32%) to a median dose of 50 (50-60) Gy, and 48 (68%) patients received postoperative RT to a median dose of 64 (45-70) Gy. Median follow-up was 118 months. The 5-year LC, disease-specific survival and distant metastasis free survival rates were 84%, 66%, and 62%, respectively. Uncertain or positive surgical margin status was the only certain factor negatively associated local relapse at 5 years (28% vs. 5% for negative margins). Therapy with the combination of surgery and RT achieved more favorable LC (75).

In a phase II clinical trial, 50 patients (≥16 y) with primary or locally recurrent paraspinal sarcomas or chordomas were evaluated. Treatment consisted of pre- and/or postoperative proton or photon RT with or without radical resection. RT median dose was 76.6 (59.4-77.4) Gy. In follow-up, the 5 and 8-year LC rates were 94% and 85% for patients with primary tumors and 81% and 74% for the entire group (76).

In a retrospective study, 11 patients (29-79 y, median age 47 y, 27% with NF1) with MPNSTs, who had been treated

Table III. *Chemotherapy available for MPNSTs (66-71).*

	References	Chemotherapy	Schedule	Patients	Outcome measures	Comments
Neoadjuvant chemotherapy	(66)	Ifosfamide (I) Doxorubicin (D) Etoposide (E)	4 cycles (21 d): 2xI/D, 2xI/E I: 1800 mg/m^2; d1-5 D: 37.5 mg/m^2; d1-2 E: 100 mg/m^2; d1-5	- NF1-MPNST: 34 (median age: 33 y; 8-66 y) - sporadic-MPNST: 14 (median age: 40 y; 13-72 y)	PR (>50% decrease of target lesions): 17.9% (NF1) *vs*. 44.4% (sporadic)	Due to the small number of patients, the study did not have sufficient statistical power.
	(71)	Ifosfamid (I) Epirubicin (Ep)	5-11 cycles I/Ep I: 1800 mg/m^2; d1-5 Ep: 60 mg/m^2; d1-2	P1: NF1, 27 y P2: NF1, 35 y P3: NF1, 59 y P4: non-NF1, 29 y P5: non-NF1, 54 y	Decrease in tumor: P1: 39% P2: 0% P3: 47% P4: 15% P5: 33%	No comments.
	(67)	Standard CTH: Ifosfamid (I) Epirubicin (Ep)	Group A: 3 cycles; I: 3000 mg/m^2; d1-3 Ep: 60 mg/m^2; d1-2	Group A: 144 (≥18 y): - MPNST: 15 (10%) - other types*:129 (90%)	4-years OS and DFS: 62% (Group A) *vs*. 38% (Group B)	Disease criteria: high-risk (high malignancy grade, size ≥5 cm, deeply located), localized STS. Study: randomized, phase III.
		Histotype-tailored chemotherapy – for MPNST: Ifosfamid (I) Etoposide (E)	Group B: 3 cycles; - for MPNST: E: 150 mg/m^2; d1-3 I: 3 g/m^2; d 1-3; - histotype-tailored chemotherapy for other types*	Group B: 142 (≥18 y): - MPNST: 12 (8%) - other types*: 130 (92%)		
Adjuvant chemotherapy	(68)	Ifosfamide (I) Epirubicin (Ep)	I: 3000 mg/m^2; d1-3 Ep: 60 mg/m^2; d1-2 Arm A: 3 preoperative cycles Arm B: 3 preoperative + 2 postoperative cycles	Arm A: 164 (≥18 y) Arm B: 164 (≥18 y)	10-years OS and RFS: 58% (Arm A) *vs*. 61% (Arm B)	Disease criteria: high-risk (grade 3, deep site, size ≥5 cm), localized STS. Study: randomized, phase III.
	(70)	Doxorubicin (D) monotherapy or combined with other CTH	D: 50-90 mg/m^2/cycle	18 RCTs: 1953 (≥18 y)	- OS: 1124/1953 (57.5%) - LR: 296/1700 (17.4%) - DR: 553/1700 (32.5%) - OR: 884/1747 (50.6%)	Meta-analysis: 18 RCTs for patients with localized, resectable STS.
	(69)	Four categories of CTH		MPNST: 175 (15.6-76.3 y; median age 42.6 y) Other types STS: 2500 (10.0-79.5 y; median age 51.5 y)	Follow-up 4.1 y (MPNST *vs*. other STS histotypes): - RR: 21% *vs*. 22% - PFS 17 *vs*. 16 weeks - OS: 48 *vs*. 51 weeks	Chemotherapy-naive STS patients treated on 12 pooled nonrandomized and randomized trials.
		1 Anthracyclines: Doxorubicin (D) or Epirubicin (Ep)	D: 75 mg/m^2 Ep: 75-150 mg/m^2	MPNST: 61 Other types STS: 940	PFS: 17 weeks	
		2 Ifosfamide (I)	I: 5-12 g/m^2	MPNST: 26 Other types STS: 383	PFS: 9.4 weeks	
		3 Doxorubicin (D) Ifosfamide (I)	D: 50-75 mg/m^2 I: 5 g/m^2	MPNST: 58 Other types STS: 789	PFS: 26.9 weeks	
		4 Cyclophosphamide (C) Vincristine (V) Adriamycin (A) Dacarbazine (Da)	No data.	MPNST: 30 Other types STS: 388	PFS: 10.4 weeks	

NF1: Neurofibromatosis type 1; MPNST: malignant peripheral nerve sheath tumor; PR: partial response; CTH: chemotherapy; OS: overall survival; DFS: disease-free survival; STS: soft tissue sarcoma; RFS: relapse-free survival; RCT: randomized controlled trial; LR: local recurrence; DR: distant recurrence; OR: overall recurrence; RR: response rate (to CTH); PFS: progression-free survival. *Other types: high-grade myxoid liposarcoma, leiomyosarcoma, synovial sarcoma, undifferentiated pleomorphic sarcoma.

Table IV. *Evaluation of current knowledge on possible clinical treatment modalities in NF1-associated PNSTs.*

Treatment	Current evaluation
Surgical treatment and other invasive methods	Positive: should be regarded as "gold standard" initial approach, if tumor localization and size are favorable
Pre-emptive pharmacological approach	Negative: no data available
Sequential pharmacological treatment after surgery	Positive: due to high rate of recurrences post surgery
Pharmacological treatment	Optional: conflicting data in severely symptomatic disease
MEK inhibitors	Positive: low rate of tumor progression
Tyrosine kinase inhibitors	Optional/negative: conflicting results, some severe failures
Interferons	Negative: negligible response to treatment
mTOR inhibitors	Optional/negative: no reduction in tumors volume was observed after monotherapy; further studies are required, including combination therapy
PD1 inhibitors	Optional: no clinical data are available, although preclinical study and data from other settings are promising
Chemotherapy	Positive: increases the chance of complete surgical resection of MPNST
Radiation therapy: preemptive	Negative: no clinical data available
Radiation therapy: pre-operational	Optional/positive: controversial due to low radiosensitivity; however, might improve final outcome
Radiation therapy: post-operational	Optional/positive: controversial due to low radiosensitivity; however accumulating data about positive outcome
Other therapeutic options	Optional: conflicting data, based on small groups of patients

with carbon C12 ion irradiation with 60 Gy cumulative dose, were analyzed. Median follow-up was 17 months (range=3-31 months) and during this time three local progressions, one distant failure and two deaths were observed (OS-75%). Carbon ion irradiation yields very promising short-term LC in patients suffering from unresectable or gross residual MPNSTs (77).

In a retrospective review, the outcomes of 33 patients with MPNSTs (18 NF1-associated, median age 15 y; 15 sporadic tumors, median age 41 y) were evaluated. Twenty patients were treated with RT in a median dose of 58.5 Gy. The median survival of all participants was 46.5 months and 43.7% 5-year OS was observed. The extent of resection, histology grade and tumor location were the most important prognostic factors. The analysis showed that RT may be an effective method to achieve local and symptomatic control with well-tolerated toxicities (78).

In a retrospective review of 15 patients (10-38 y, median age 25) with NF1-associated MPNST who underwent treatment with RT (median dose 50 Gy; 44-63), therapeutic strategies with RT resulted in satisfying LC rates and were well-tolerated by the patients. The OS was 100%, 79.2% and 53.2% at 1, 3 and 5 years, respectively. No secondary malignancies associated with radiation treatment were reported (79).

Other therapeutic options. Tipifarnib is a selective inhibitor of farnesyltransferase (a target to block Ras signaling) that has an antiproliferative effect. In a phase II trial of 62 NF1-patients (3-21.5 y; median age 9.7 y) with progressive PNFs, the time to progression (TTP), rather than tumor response, was the primary endpoint of assessment of the activity of tipifarnib. Compared to placebo, tipifarnib did not significantly prolong TTP. The largest decrease in PNF volume was 11%, in only one patient (80).

Pirfenidone is an antifibrotic drug that modulates the expression of growth factors or cytokines that are relevant to fibrosis (81). In a phase II study of 24 adults (15-67 y) with NF1-associated unresectable PNFs, pirfenidone was well-tolerated and decreased tumor size by ≥15% in 29.2% (7/24) patients. Improvement in neurologic function and reduction in pain were also observed (82). In another phase II trial of pirfenidone in 36 younger patients (3-18.8 y, median age 8.9 y) the median TTP was 13.2 months. The drug was well-tolerated, but did not demonstrate satisfactory activity to warrant further evaluation in NF1-children with progressive PNFs (81).

The oncogene MET encodes for a RTK that is involved in the progression and metastasis of most solid human cancers. Several studies implicate oncogenic MET signal activation in NF1-related MPNST disease progression. Peacock *et al*. have used a mice model to demonstrate that NF1-MET MPNSTs were sensitive to the highly selective MET inhibitor, capmatinib.

The treatment with capmatinib and trametinib led to reduction of response variability and enhanced suppression of tumor growth, and also suppressed both Ras/ERK and PI3K/AKT signaling. These data expand understanding of the role of MET signaling in MPNST progression and suggest a potential therapeutic niche for NF1-patients with MPNSTs (83).

Poly(ADP) ribose polymerase (PARP) inhibitors are primarily used in malignancies with known defects in DNA repair genes. In *in vitro* studies, it has been proven that PARP1 and PARP2 are highly expressed in MPNST tissue samples, and PARP inhibitor (Olaparib) might be an effective therapy in MPNST and should be further investigated for its potential clinical use in this type of malignancy (84).

Accumulating evidence indicates that a desmoplastic reaction involving high deposition of the glycosaminoglycan Hyaluronic Acid (HA) in extracellular matrix can lead to poor drug penetrance and efficacy. Human MRI images display large regions of poor uptake of contrasting agent, and a human tissue microarray shows 100% positivity of HA deposition trough all samples, including PNFs. Breaking down this physical barrier is a promising potential avenue to improve drug penetrance, perfusion, and efficacy. In Kellers' research combination treatment with pegylated hyaluronidase (PEGPH20) and doxorubicin was more effective as compared to monotherapy. Preliminary results also show an increase of OS when PEGPH20 is combined with a targeted MEK inhibitor. PEGPH20 shows promising therapeutic benefit in targeting physical barriers in MPNSTs. Improved drug delivery and efficacy will open avenues to further drug combinations for this currently incurable malignancy (85).

Curcumin is a turmeric-derived polyphenol that has been shown to interact with several molecular targets implicated in carcinogenesis. There are reports that after 6 months, NF1-individuals adopting a Mediterranean diet enriched with curcumin (1200 mg/day) presented a significant reduction in the volume and/or number of cutaneous neurofibromas. In one patient, a large cranial PNF presented a 28% reduction in volume (86, 87). Furthermore, it was shown that curcumin may increase the sensitivity of neurofibromin deficient MPNST cells to TRAIL (TNF-related apoptosis-inducing ligand) while downregulating anti-apoptotic proteins (88).

Viability and proliferation of some MPNST cells can be reduced by all-trans retinoic acids (ATRA), and combination of ATRA and MEK inhibitor demonstrated additive reduction in cell viability (89).

Currently research on gene therapy for the treatment of NF1 related MPNSTs is ongoing. The development of adeno-associated viruses (AAVs)-based treatment using the NF1-GAP-related domain to deactivate Ras activity in MPNSTs and in pre-cancerous cells in NF1-patients has been initiated (90).

Therapy with oncolytic Measles Virus encoding thyroidal sodium iodide symporter (MV-NIS) has significant antitumor properties in many types of cancers. Local administration of MV-NIS vaccine into MPNST-derived tumors resulted in significant reduction in tumor size and improved survival in an *in vitro* study (91). A phase I trial on vaccine therapy is currently evaluated (NCT02700230) (51).

Evaluation of Treatment Modalities

NF1 is one of the most common genetic disorders that equally affects all races and both sexes. While it is one of the most frequent diseases predisposing to development of malignancy with the preponderance of PNSTs, no effective treatment is available so far. Based on extensive review of the published data, we present an evaluation of the current knowledge on possible clinical treatment modalities (Table IV). This evaluation suggests that future studies should focus on development of pre-emptive strategies and post-surgical approaches, based on molecularly-defined targeted treatment, improved systemic/local chemotherapy or local radiotherapy. In conclusion, no effective PNSTs treatment was found except complete surgical resection, which can be performed in selected patients with NF1. It seems that the purpose of the other methods of therapy is the regression of tumor size in order to increase the chances for surgical treatment. As the clinical outcome is still not satisfactory, further studies are necessary to bring clinical benefit.

Conflicts of Interest

The Authors declare that they have no conflicts of interest regarding this study.

Authors' Contributions

AM: study concept and design, data acquisition and analysis, manuscript preparation; PG: data acquisition, data analysis and interpretation; MW: quality control of data, data analysis and interpretation, manuscript review; JS: study design, quality control of data, data analysis and interpretation, manuscript review and editing.

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