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Therapeutic Development in Neurofibromatosis

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Abstract

Although neurofibromatosis (NF) was initially recognized in the nineteenth century, only in the past two decades we have witnessed a paradigm shift in therapeutics. This progress is driven by the increasing understanding of the natural history of the NF-associated tumors and understanding of the molecular landscape of these disorders. Multiple clinical trials have been launched evaluating non-surgical treatment modalities and more studies are in the pipeline. Recently, the NF community has adopted standardized endpoints recommended by the Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) International Collaboration established in 2011. Such collaborations among academic, regulatory and supporting communities are crucial for providing the infrastructure needed for advancing the therapeutic development in the field of NF.

Keywords: neurofibromatosis type I, neurofibromatosis type II, chemotherapy, radiotherapy, therapeutics, clinical trials, targeted therapy

1. Introduction

The neurofibromatoses are a heterogenous group of familial tumor predisposition syndromes that result from pathogenic variants in tumor suppressor genes leading to dysregulation in various cellular pathways. This dysregulation eventually leads to tumors of the central and peripheral nervous systems as well as multiorgan involvement. The incidence of Neurofibromatosis type 1 (NF1) is approximately 1 in every 2500–3500 births [1], while the incidence of neurofibromatosis type 2 (NF2) is approximately 1 in every 25,000–33,000 births [2]. Schwannomatosis (SWN) has been identified as a distinct entity with different genetic etiology and clinical phenotype from NF2, but it is difficult to assess the precise incidence of this condition. Although the tumors that develop most frequently in NF1, NF2 and SWN are histologically benign, they can cause significant neurologic disabilities and even mortality due to the involvement of the central and peripheral nervous systems. These tumors represent a unique therapeutic challenge due to the heterogeneity in severity and rate of progression among patients and hence novel therapeutic approaches are needed. In this chapter, we will review the recent studies in the field of neurofibromatosis therapeutics along with the collaborative efforts for innovative clinical trial designs.

2. The power of collaboration in neurofibromatosis research

The establishment of the NFCTC in 2006 by the Department of Defense was a landmark in the field of NF therapeutics development [3]. The consortium has been in continuous operation since inception. It provides infrastructure, and shared resources across multiple institutions to generate resource-efficient clinical trials. The REiNS working groups are another clear example of the influence of collaboration among NF experts to advance the NF drug development efforts. The Children's Tumor Foundation (CTF) has provided support to the NF community, including efforts to advance research as well as public education and patient support. In 2007, the CTF invested \$4 million to launch the Neurofibromatosis Preclinical Consortium (NFPC) to test candidate drug therapies in NF1 and NF2 models. The Neurofibromatosis Therapeutic Acceleration (NTAP) was established as a private philanthropy to accelerate the development of effective therapeutics for pNFs and cNFs. NTAP has partnered with CTF in the evaluation of potential therapeutic agents in animal models of pNFs.

The collaborative efforts among academic, federal regulatory, and private foundations have resulted in early successes in the NF therapeutic development. In February 2018, selumetinib, a MEK1/2 inhibitor co-developed by AstraZenca and Merck&Co, received breakthrough status from the FDA. Selumetinib was granted Orphan Drug Designation based on data from the phase II trial that tested selumetinib in pediatric patients with inoperable pNFs (NCT01362803) [4] and hence, selumetinib may become the first approved drug for NF. This success highlights the power of collaboration, which moved Selumetinib from a repurposed oncology drug to its current clinical success in NF patients. The funders involved for in this "MEK story" are the CTF, the National Institute of Health (NIH), the Congressionally Directed Medical Research Program (CDMRP) through NFCTC, and the NTAP at Johns Hopkins University [5].

3. Therapeutic development in neurofibromatosis type I

Understanding of the pathogenesis and molecular landscape of the NF1-associated tumors has advanced dramatically in recent years. This advancement, along with the continued collaborative approaches across the research community, has fueled therapeutic development efforts against many of the NF1 manifestations. Therapeutic development in NF1 has been tumor-specific, due to the substantial heterogeneity of the development and behavior of NF1-associated tumors across and within patients. Plexiform neurofibromas (pNFs), the source of major morbidity in NF1, has been an area of major focus for therapeutic development, followed by other NF1-associated tumors including cutaneous neurofibromas (cNF), optic pathway gliomas (OPG), and malignant peripheral nerve sheath tumors (MPNST).

3.1 NF1-associated plexiform neurofibroma

Plexiform neurofibromas (pNFs) affect up to 50% of NF1 patients and can involve any peripheral nerve [6, 7]. They occur most commonly in the trunk, followed by the extremities [6]. pNFs tend to grow most rapidly in early childhood and may increase by $\geq 20\%$ per volume per year in young children [8]. Though surgery remains the mainstay for treatment of pNF, complete resection is virtually impossible due to the frequent involvement of adjacent normal tissue, and occasionally critical structures. Moreover, surgical resection is frequently challenging since pNF can cross tissue planes and involve multiple body regions. The most common

morbidities leading to surgery are neurologic, disfigurement, and airway involvement [9]. A substantial risk of pNF regrowth after surgical resection has motivated the ongoing research to find non-invasive therapies for pNF.

There are multiple ongoing clinical trials (**Table 1**) targeting pNF which represent a rapid expansion in the pNF therapeutic landscape. Though some of the tested drugs have failed to achieve the primary endpoint, they helped establish the natural history of the growth rates of pNF [10, 11]. The therapeutic development efforts in pNFs had shifted from testing “empirically,” usually cytotoxic, agents to agents being supported by well-established transitional studies. The first agent that showed radiographic response was imatinib, with a response rate of 17% [12]. Ras-pathway targeted therapy has been of particular interest, as it provides an opportunity for treating multiple manifestations of NF1 with one drug. For example, Selumetinib, which is a MEK (mitogen-activated protein kinase) inhibitor, has shown activity in pNF and low-grade gliomas (including OPG) associated with NF1 [13].

3.2 NF1-associated gliomas

Optic pathway glioma (OPG) is the most common form of glioma seen in individuals with NF1. While 15–20% of children with NF1 will develop OPG [27, 28] only 30–50% will be symptomatic and one-third will require therapeutic intervention [29]. In those with confirmed decline in visual acuity (VA) or involvement in the hypothalamus, chemotherapy is the mainstay of treatment. First-line chemotherapeutic agents include vincristine and carboplatin [30], while second-line agents include vinblastine [31], vinorelbine [32], and temozolomide [33]. There is a report of four cases of refractory OPG (two sporadic and two NF1-associated OPG) that showed marked improvement in VA following treatment with bevacizumab [34]. These agents rarely restore the premorbid visual acuity and the aim of treatment is usually to stabilize disease and prevent further worsening [35, 36]. Radiotherapy is usually avoided in NF1-associated OPG for concern of secondary tumors [37] and moya moyo syndrome [38]. Surgical excision of OPG is not feasible due to the tumor location and is usually reserved for instances of complete loss of vision, severe proptosis, or hydrocephalus.

Recently, small molecule inhibitors have been used for refractory OPG in clinical trials (**Table 2**). Among these agents, selumetinib has shown promising results in phase II studies and was proven to be active in recurrent, refractory or progressive NF1-associated pediatric low-grade glioma [39].

Unnecessary cytotoxic therapies for OPG should be avoided, as many OPGs remain asymptomatic and some even regress over time [28]. One of the efforts to standardize the VA assessment in clinical trials for NF1-associated OPG is through using optic coherence tomography (OCT) [40, 41]. OCT provides an objective assessment of the retinal nerve fiber layer thickness. OCT is a noninvasive tool to monitor children with OPG in whom, especially the youngest ones, traditional methods of VA assessment is challenging [42]. Another objective noninvasive tool to assess VA in NF1-associated OPG is automated tractography of the optic radiation that was validated in a recent study [43].

A retrospective study that analyzed the clinical and pathological features of gliomas in 100 individuals with NF1 emphasized the wide histologic spectrum of gliomas in those with NF1 [44]. Indeed, individuals with NF1 have an increased risk of malignant gliomas compared with the general population [45], but there are confounding reports on glioblastoma prognosis in those with NF1 vs. cases without NF1 [46, 47]. A recent study analyzed the molecular landscape of gliomas in NF1 and showed that 50% of low-grade gliomas displayed an immune signature, T-lymphocytic infiltrate, and increased neoantigen load [48], findings that may influence future clinical trials in NF1-associated gliomas.

Drug	Target	Phase	Age (y)	Endpoints	Results
Thalidomide [14]	Angiogenesis	I	>5	ORR	Completed/unclear benefit
Sirolimus [15] NCT00634270	mTOR	II	>3	3D ORR, TTP	Modest increase in TTP, no objective response
Sorafenib [16] NCT00727233	Raf kinase, c-kit, PDGF, VEGFR2,3	I	3–18	3D ORR	Intolerable, decrease in QOL due to pain, no objective response
Pirfenidone [17, 18] NCT00076102	Fibroblast proliferation	I, II	3–21	3D ORR	Completed, no objective response
Cediranib NCT00326872	VEGFR-1, -2, -3	II	≥18	3D ORR	Terminated due to slow accrual
Tipifarnib [19] NCT00021541	Farnesyl transferase	I, II	3–25	TTP, 3D ORR	Completed, No difference in TTP
PEG-Interferon alpha 2b [20, 21] NCT00396019	Immune, angiogenesis	I, II	18 months–21 years in phase II	TTP, 3D ORR	Doubled TTP, 3D ORR less than 20%
Vinblastine/Methotrexate NCT00030264	Cytotoxic	II	≤25	TTP	Completed, pending results
Celecoxib; PEG-Interferon alpha 2b NCT00846430	Immune, angiogenesis	II	2–30	Symptoms improvement, ORR	Active, not recruiting
Nilotinib NCT01275586	BCR-ABL, PDGFR, c-kit	Pilot	≥18	RECIST, 3D ORR	Completed
Everolimus [22] NCT01412892	mTOR	II	18–60	3D ORR	Completed, no objective response
Everolimus NCT01365468	mTOR	II	>10	3D ORR, TTP	Terminated due to slow accrual
Imatinib [23] NCT01673009	c-kit, PDGFR	II	3–65	RECIST, 3D ORR	17% 3D ORR

Drug	Target	Phase	Age (y)	Endpoints	Results
Sunitinib NCT01402817	PDGFR, VEGFR, c-kit	II	3–65	3D ORR	Terminated (1 patient died)
Pexidartinib [24] NCT02390752	c-kit, FLT3, CSF1R	I, II	3–31	ORR	Recruiting
Cabozantinib NCT02101736	RET, c-MET, VEGFR	II	≥3	3D ORR	Recruiting
Trametinib NCT02124772	MEK	I	1 month–17 years	PK, PD, toxicity	Recruiting
PD-0325901 [25] NCT02096471	MEK	II	≥16	3D ORR	Completed, 42% 3D ORR
Selumetinib [26] NCT01362803	MEK	I, II	2–18	3D ORR	Active, not recruiting, 71% 3D ORR
Selumetinib NCT02407405	MEK	II	≥18	3D ORR	Recruiting
Binimetinib NCT03231306	MEK	II	≥1	3D ORR	Recruiting
Selumetinib (intermittent dosing) NCT03326388	MEK	I, II	3–18	Toxicity, 3D ORR	Active, not recruiting
Trametinib NCT03363217	MEK	II	1 month–25 years	3D ORR, TTP RECIST	Recruiting
Imatinib (in pNF with airway involvement) NCT03688568	c-kit, PDGFR	II	6 months–12 years	Sleep study/PFT, 3D ORR	Recruiting

Abbreviations: 3D ORR, volumetric objective radiographic response; BCR-ABL, fusion gene of breakpoint cluster region and Abl1; c-kit, kit ligand or stem cell factor; c-MET, MET proto-oncogene; CSF1R, colony stimulating factor 1 receptor; FLT3, Fms-like tyrosine kinase 11; MEK, mitogen activated protein kinase; mTOR, mammalian target of rapamycin; PD, pharmacodynamic; PDGFR platelet-derived growth factor; PFT, pulmonary function test; PK, pharmacokinetics; RECIST, Response Evaluation Criteria In Solid Tumors; RET, rearranged during transfection proto-oncogene; TTP, time to progression; VEGFR vascular endothelial growth factor receptor; ORR, objective response rate.

Table 1.
Clinical trials for neurofibromatosis type 1-associated plexiform neurofibromas.

Drug	Target	Phase	Age	Endpoints	Status
Vinblastine +/- Bevacizumab NCT02840409	Cytotoxic/VEGF	II	6 months–18 years	Response rate, OS, PFS, visual outcome measures, OCT	Recruiting
Pegylated interferon NCT02343224	Tumor microenvironment	II	3–18 years	Response rate	Recruiting
Pomalidomide NCT02415153	Angiogenesis/ immunomodulation	I	3–20 years	Toxicity, MTD	Active, not recruiting
Lenalidomide NCT01553149	Angiogenesis/ immunomodulation	II	0–21 years	Response rate	Active, not recruiting
Everolimus (RAD001) NCT01158651	mTOR	II	1–21 years	Response rate	Active, not recruiting
Binimetinib (MEK162) NCT02285439	MEK	I/II	1–18 years	MTD, response rate	Recruiting
Binimetinib (MEK162) NCT01885195	MEK	II	Older than 18 years	Response rate	Completed (pending results)
Selumetinib NCT01089101	MEK	I/II	3–21 years	Safety, MTD, Response rate	Recruiting

Abbreviations: MEK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; VEGF, vascular endothelial growth factor.

Table 2.

Clinical trials for optic pathway gliomas (OPG) and other gliomas associated with neurofibromatosis type 1.

3.3 NF1-associated malignant peripheral nerve sheath tumors

Malignant peripheral nerve sheath tumors (MPNSTs) are rare high-grade sarcomas with poor prognosis [49]. MPNSTs occur more frequently in those with NF1 compared with the general population, with a lifetime risk of 8–13% [50]. Several studies have not shown a significant difference in the molecular landscape between sporadic and NF1-associated MPNSTs [51, 52]. FDG-PET remains the gold standard noninvasive diagnostic tool for MPNSTs, with 89–100% sensitivity and 72–95 specificity [53, 54]. Surgical resection with negative margins is the mainstay of treatment [55], though that is not usually feasible. Use of adjuvant radiotherapy to induce local control in MPNSTs failed to show improvement in overall survival in NF1-associated MPNSTs [56].

There are limited chemotherapeutic options, including agents like doxorubicin, and ifosfamide [57, 58]. A phase II study of bevacizumab and everolimus that enrolled 25 individuals (17 had NF1-associated MPNST) did not show a clinical benefit (defined as complete response, partial response or stable disease for ≥ 4 months) [59]. Although preclinical studies showed EGFR amplification in MPNST [60], EGFR inhibitors did not show clinical activity against MPNST in clinical trials. A few studies have been conducted in sarcomas using targeted therapy, and these have not shown clinical activity; tested drugs included imatinib [61], dasatinib [62], sorafenib [63], and erlotinib [64]. These negative studies emphasize the importance of developing xenografts to explore new therapeutic targets and explore pathways of interest like the NF1/P53-mutant transgenic MPNST model [65–67].

Combined targeted therapy has been used to exploit cellular vulnerabilities of cancer cells, as in RAS-driven tumors which are refractory to conventional therapies. A preclinical study has shown dramatic tumor shrinkage in a transgenic MPNST mouse model in response to combined HSP90 and mTOR inhibition [68]. This promising preclinical work had led to a phase I/II study of gantespib, a novel injectable inhibitor of HSP90 and the mTOR inhibitor, sirolimus. The study enrolled 20 participants (NCT02008877) and results are pending [69]. Another novel approach undergoing phase I study utilizes the oncolytic potential of the genetically engineered injectable measles virus Edmonston vaccine strain (MVEdm) that encodes thyroid sodium iodide symporter [70] (Table 3).

3.4 NF1-associated cutaneous neurofibromas

Cutaneous neurofibromas (cNFs) are among the most common manifestations in NF1, affecting about 99% of patients with NF1 [71]. cNFs are unlikely to undergo malignant transformation or to cause fatal complications or severe neurologic disability. Nevertheless, cNFs are considered one of the greatest concerns in patients, especially adults, with NF1. These concerns are mainly due to disfigurement and dysesthesia, causing substantial psychological distress and negative body image perception [72]. There is immense variability in cNF among patients with NF1 with respect to size, location, age at first presentation, associated symptoms, and number. These factors affect the therapeutic approach to cNFs and emphasize the need for reproducible and reliable endpoints to ensure clinical success for tested agents.

Drug	Target	Phase	Age (years)	Endpoints	Status
EGFR806 CAR-T cell NCT03618381	Immunotherapy	I	1–26	Toxicity	Recruiting
Selumetinib and Sirolimus NCT03433183	MEK and mTOR	II	≥12	CBR, PFS, OS	Active, not recruiting
Injectable MVEdm vaccine strain NCT02700230	Oncolytic virotherapy	I	≥18	Toxicity, MTD, ORR	Recruiting
Pazopanib vs. Sapanisertib NCT02601209	PDGFR, VEGFR, c-kit (Pazopanib), TORC1&2 (Sapanisertib)	I (Sapanisertib), II	≥18	MTD, PFS, ORR	Active, not recruiting
Lorvotuzumab mertansine NCT02452554	CD-56 antibody	II	1–30	RECIST	Active, not recruiting
Pexidartinib and Sirolimus NCT02584647	c-kit, FLT3, CSF1R, mTOR	II	≥18	PFS, OS	Recruiting

Abbreviations: CBR, clinical benefit rate; c-kit, kit ligand or stem cell factor; c-MET, MET proto-oncogene; CSF1R, colony stimulating factor 1 receptor; FLT3, Fms-like tyrosine kinase 11; MEK, mitogen activated protein kinas; MTD, maximum tolerated dose; MVEdm; measles virus edmonston vaccine strain, OS, overall survival; PDGFR platelet-derived growth factor; PFS, progression free survival; RECIST, Response Evaluation Criteria In Solid Tumors; TORC, mammalian target of rapamycin complex; TTP, time to progression; VEGFR vascular endothelial growth factor receptor; ORR, objective response rate.

Table 3.
 Clinical trials for malignant peripheral nerve sheath tumors in neurofibromatosis type 1.

Clinical management for cNF involves surveillance or procedure-based therapy. Conventional surgical resection promotes complete removal of the lesion, but there are obstacles, including limited number of lesions that can be treated in a single session and the scarring that may be induced by surgical resection. Other alternatives include electrodesiccation, which remove cNFs through dehydration and denaturation [73]. This allows for removal of large numbers (up to thousands) of cNFs in one session, but it requires general anesthesia and may cause scarring and pigmentation changes. A retrospective study of 106 individuals with multiple, small cNFs treated with CO₂ laser ablation reported >90% patient satisfaction, yet a local infection rate was reported to be 15% [74]. Other procedure-based therapies reported in cNFs are laser photocoagulation [75] and radiofrequency ablation [76]. Another approach using local drug/device combinations is the photodynamic therapy (PDT), which is being tested in different cancers [77]. PDT in cNFs studies use a photosensitizer, 5-amino-levulinic acid, plus illumination with red light. PDT was evaluated in phase I study (NCT01682811) and a phase II study (NCT02728388) is active in a single US institution.

One of the early efforts for treatment of cNFs and their associated symptoms used ketotifen [78]. Ketotifen is a histamine 1 receptor blocker which facilitates mast cell stabilization and; its use in NF1 is based on the finding of abundant mast cells in neurofibromas. Improvement in pain and pruritis has been reported, but objective tumor shrinkage has not been documented. Three drugs have been tested in cNFs using local therapeutic approaches; the first was ranibizumab, a vascular endothelial growth factor monoclonal antibody, which was injected intralesionally (NCT00657202). The overall effect of the treatment was minimal and the variability in the tumor volume assessment (measured by a caliper) limited the interpretation of the data. The second agent was topical imiquimod, which showed minimal efficacy in tumor shrinkage compared to baseline volume (measured by a caliper) (NCT00865644). The third agent was topical rapamycin, an mTOR inhibitor, which was initially tested in Tuberous Sclerosis Complex (TSC)-associated angiofibromas (NCT01031901) [79]. The study enrolled 52 patients with TSC and NF1 and data are expected.

Due to the relatively benign histology of cNFs and the likely need for long term therapy, there are special considerations pertaining to cNF drug development [80]. The safety profile of tested drugs is a major concern to physicians, regulators, patients and their caregiver. Also, the route of administration and cost are important considerations, as individuals with cNF are more likely to require treatment (either medication or intervention) for an extended period of time. The variant phenotype among affected persons, demographic differences, and the goal of treatment are important factor determining the type and timing of treatment.

The above-mentioned considerations, especially the safety profile, make oral systemic therapies preferable for individuals with a heavy tumor burden. Everolimus, an oral mTOR inhibitor, was evaluated in a phase II study of disfiguring cNF associated with NF1 (NCT02334902). The study enrolled 22 patients and used photographic measurement of selected lesion to assess surface volume. While 5/22 patients withdrew due to adverse events, a very modest effect was reported in <20% of the participants [81]. Due to the promising results of using targeted therapies against MEK, selumetinib is being studied in NF1-associated cNFs (NCT02839720). The study is a phase II, multi-institutional, open label study with the primary outcome measure being the change in the size of cNFs assessed by digital photography and caliper measurements.

The Clinical Trial Design and Development REiNS subgroup, involving experts from different settings, has presented the priorities and challenges associated with conducting clinical trials targeting cNF in NF1 [82]. The subgroup members

reviewed key topics like natural history, assessment methods, functional endpoints, safety, and development strategies. One of the most important topics, which pose a major challenge in cNF clinical trials, is the measurement of outcomes. Methods of measurement that have been used include calipers, digital and volume photography, ultrasound, and MRI. The subgroup members support considering clinically meaningful measures of effectiveness in interpreting changes in tumor size or number. Tumor size reduction that correlates with improved pain control or discomfort is more clinically meaningful than the crude number or size of the tumors. New approaches, such as high-frequency ultrasound or optical coherence tomography, may be able to address some of the limitations of the conventional methods like MRI, photography or caliper measurement. These new approaches need to be validated through additional studies. The subgroup members recommend several key factors when designing clinical trials on cNF, including timing to initiate intervention, eligibility criteria to ensure diversity, mechanism of the intervention, route of administration, safety monitoring, and regulatory considerations.

4. Therapeutic development in neurofibromatosis type 2

NF2 is an autosomal dominant disorder that affects the central and peripheral nervous systems. NF2 has an estimated incidence of 1 in 25,000–33,000 births, making it far less common than NF1 [83]. Vestibular schwannomas (VS) are considered the hallmark of NF2, and bilateral VS fulfill the clinical diagnosis of definite NF2 [84]. The average age at diagnosis in NF2-associated VS is about 27 years [85]; diagnosis in childhood predicts a severe phenotype and unfavorable prognosis [86]. Though VS are slowly progressive tumors, they can cause significant neurologic disability, including hearing loss and eventually deafness, balance problems, and brain stem compression [87]. The other common tumor associated with NF2 is meningioma, which is the most common intracranial tumor worldwide. Up to half of individuals with NF2 develop meningiomas [88], and despite benign histology, they may lead to a shortened life expectancy [89].

The loss of the tumor suppressor protein merlin in NF2 leads to activation of pro-survival pathways via RAS modulation. Hence, NF2 shares many of the same targets identified in NF1. Merlin is absent not only in NF2-associated VS, but also in sporadic VS [90]. This observation is important as it may point to a shared therapeutic pathway between NF2-associated VS and sporadic VS [91].

Though surgery remains the mainstay of treatment in sporadic VS, or stereotactic radiosurgery (SRS) for tumors <3 cm [92], these approaches have proved to be less efficacious in NF2-associated VS, with high rate of complications, including facial nerve weakness, hearing loss, and headache [93, 94]. Moreover, there are growing concerns about utilizing radiation therapy in NF2 due to risk of late malignant transformation [95]. Some of the challenges that face NF2 clinical trials are the substantial variability in disease severity across individuals with NF2, the lack of clear association between the rate of VS growth and the rate of hearing loss, and the variable growth rates between the right and the left VS in same patient [96]. A prospective study that highlighted the lack of correlation between VS size or growth rate and rate of hearing loss was published in 2014 and included 120 individuals with NF2-associated VS (total of 200 VS) [97]. The investigators used word recognition score (WRS) as an objective measurement for hearing decline and defined radiographic tumor growth as $\geq 20\%$ increase in tumor volume compared with baseline. The study showed that the mean rate of hearing decline from diagnosis was 5% at 1 year and 16% at 3 years, while the rate of VS tumor graphic progression was 31% at 1 year and 79% at 3 years. The median time to progression

(14 months) was significantly shorter than the median time to hearing decline (62 months) [93]. This study, along with prior reports, elucidated the natural history of individuals with NF2 to help to determine the most appropriate timing for intervention [81, 83, 98].

Clinical trials for NF2 have been focused on vestibular schwannomas, since loss of hearing is often the most pressing concern in individuals with NF2. A group of 36 international researchers, physicians, representatives from the pharmaceutical industry, and patient advocates held a workshop to provide consensus recommendations to accelerate clinical trials progress in NF2 [99]. The group provided recommendations on participant selection, clinically meaningful and feasible endpoints, the clinical trials models most appropriate for NF2, and candidate therapeutic agents for NF2.

Different cellular pathways have been targeted in clinical trials for NF2-associated tumors (**Table 4**), with mixed responses. One of the most promising agents used in NF2 is bevacizumab, which was initially given on a compassionate use basis for adults with NF2-associated VS with severe disability [100, 101]. In these reports, 6 of 10 participants had $\geq 20\%$ reduction in tumor volume and significantly improved hearing. The promising results led to designing two phase II clinical trials using bevacizumab in persons with NF2 who suffered from progressive hearing loss. A preliminary report from one of these 2 trials that enrolled 22 participants showed that the overall hearing and radiographic response rates were 41 and 23% respectively, though pediatric participants appeared to benefit less compared to adults (NCT01767792) [102]. Bevacizumab was used in a dose of 10 mg/kg every 2 weeks for 6 months, followed by 5 mg/kg every 3 weeks for 18 months; this regimen was well tolerated.

Drug	Target	Phase	Age (years)	Endpoints	Status
Everolimus [104] NCT01419639	mTOR	II	≥ 3	VS: 15% volume reductions	No RR
Everolimus [105] NCT01490476	mTOR	II	≥ 15	VS: volume reduction	No RR
Everolimus NCT01345136	mTOR	II	16–65	VS: volume reduction	Active, not recruiting
Everolimus NCT01880749	mTOR	Early phase I	≥ 18	VS and MEN: tumor PK, molecular analysis	Active, not recruiting
Lapatinib [106] NCT00973739	EGFR/ErBb2	II	4–80	VS: 15% volume reduction	23.5% RR
Lapatinib NCT00863122	EGFR/ErBb2	Early phase I	≥ 18	VS: tumor PK, molecular analysis	Completed, pending results
Axitinib NCT02129647	VEGF, c-kit, PDGFR	II	≥ 18	VS: 20% volume reduction	Active, not recruiting
Nilotinib NCT01201538	PDGF, c-kit	II	≥ 18	VS: 20% volume reduction	Terminated
PTC 299 NCT00911248	VEGF	II	≥ 18	VS: Tumor volume or WRS	Terminated
Endostatin NCT02104323	Anti-angiogenic	II	16–30	Tumor volume	Completed, pending results

Drug	Target	Phase	Age (years)	Endpoints	Status
AR-42 NCT02104323	HDAC	Early phase I	≥18	VS and MEN: tumor PK, molecular analysis	Active, not recruiting
Bevacizumab [107] NCT01207687	VEGF	II	≥12	VS: hearing response measured by WRS	Completed, hearing response 36%
Bevacizumab [102] NCT01767792	VEGF	II	≥12	VS: hearing response measured by WRS	Active, not recruiting, hearing response 41%, RR 23%
Acetylsalicylic acid NCT03079999	Antiplatelet, anti-inflammatory	II, randomized, placebo-control	≥12	VS: PFS	Active
Vistusertib (AZD2014) NCT02831257	mTORC1, mTORC2	II	≥18	MEN: RR using volumetric MRI	Active, not recruiting
Selumetinib NCT03095248	MEK	II	3–45	VS, MEN, and ependymoma: hearing response measured by WRS, RR	Active

Abbreviations: *c-kit*, *kit* ligand or *stem cell factor*; *EGFR/ErBb2*, *epidermal growth factor reception*; *HDAC*, *histone deacetylase*; *MEK*, *mitogen activated protein kinas*; *MEN*, *meningioma*; *mTOR*, *mammalian target of rapamycin*; *mTORC*, *mammalian target of rapamycin complex*; *PDGFR* *platelet-derived growth factor*; *PFS*, *progression-free survival*; *PK*, *pharmacokinetics*; *VEGF*, *vascular endothelial growth factor*; *RR*, *radiographic response*; *VS*, *vestibular schwannoma*; *WRS*, *word recognition score*.

Table 4.
 Clinical trials in Neurofibromatosis type 2-associated vestibular schwannomas and meningiomas.

NF2 shares many of the same targets identified in NF1; hence, some of the therapeutic agents tested in NF1 are being tested in NF2, including everolimus (NCT01345136), sorafenib, and selumetinib (NCT03095248). The dual mTORC1 and mTORC2 inhibitor, vistusertib (AZD2014), is used in a phase II study for NF2 patients with progressive or symptomatic meningiomas (NCT02831257). While the primary outcome for this study is the radiographic response rate for meningioma using volumetric MRI scans, the secondary outcomes include response assessment for VS and non-target meningioma using volumetric MRI. The NFCTC has approved using crizotinib, a MET and ALK inhibitor, in a phase II study for children and adults with NF2-associated progressive VS. There are promising preclinical studies identifying crizotinib as a potent inhibitor of NF2-null Schwann cell proliferation in vitro and tumor growth in vivo [103]. The goal for these clinical trials is to assess the hearing response rate as a clinically meaningful endpoint and to assess tolerability and long term effects of the tested agents, as well as identify biomarkers that can predict outcomes.

5. Therapeutic development in Schwannomatosis

Schwannomatosis (SWN), as the name implies, is characterized by the development of multiple peripheral nerve schwannomas, without concomitant involvement

of the vestibular nerve, and, less commonly, meningiomas [108–110]. Since the schwannoma is the most common tumor in NF2 and SWN, there can be overlap between the two syndromes. SWN is a distinct entity with different clinical phenotype and genetic etiology from NF2. Germline mutations in SMARCB1 and LZTR1, both tumor suppressor genes, have been identified in SWN [111–113]. Unlike NF1 and NF2, pain is the most common symptom reported by individuals affected with SWN, with 68% reporting chronic pain in SWN in a retrospective study [114].

Surgical resection is considered the treatment of choice for symptomatic schwannomas for pain relief, though local recurrence is not uncommon. Patients usually require multiple surgical resections due to pain, focal neurologic deficits, or myelopathy [113]. Radiotherapy is reserved for those with life-threatening or enlarging tumors, and in rare occasions, malignant schwannomas. There are no available safety studies with respect to radiotherapy-induced malignant transformation in SWN, though theoretically it is possible given the available data from NF1, and NF2 studies.

Up to date, no clinical trials have been conducted in the setting of SWN and no known effective therapies exist. A case report was published using bevacizumab in one individual with SWN-associated refractory pain with a remarkable response in pain control [115].

6. Clinical trials endpoints in neurofibromatoses

Most early clinical trials for patients with neurofibromatoses used designs and endpoints similar to oncology trials. However, there are major differences in natural history, disease manifestations, and overall prognosis between patients with NF and those with cancers. Hence, there was an unmet need to establish standardized endpoints in NF clinical trials that will allow precise data interpretation and the ability to assess efficacy across different studies. The Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) International Collaboration was established in 2011 at the Children's Tumor Foundation (CTF) meeting to achieve consensus about the design for future clinical trials with major emphasis on endpoints. The collaboration included 7 working groups; disease biomarkers; whole-body MRI; functional, visual, patient-reported, and neurocognitive outcome; and imaging for tumor response. Later, two more working groups were added; cutaneous neurofibromas, and patient representation [116].

The REiNS Collaboration published the initial recommendations for clinical trials endpoint in 2013 [117]. MRI with volumetric analysis was recommended as the standard imaging metric for pNF and VS in NF1 and NF2 clinical trials [118]. A 20% volume change was chosen to indicate an increase or decrease in the tumor size. MRI analysis requires central review to ensure consistent results. This is a time and resource intensive tool; thus, the development of methods that can be incorporated into routine clinical practice and can be performed more easily is warranted. Whole-body MRI imaging (WB-MRI) may serve as an endpoint in clinical trials that target multiple tumors. The working group concluded that while WB-MRI is feasible for identifying tumors using both 1.5 T and 3.0 T systems, choosing a standardized image acquisition and analysis methods is crucial for applying WB-MRIs as a tool for assessing tumors in NF [119]. For clinical trials targeting NF2-associated VS, the REiNS functional outcomes group endorsed the use of maximum word recognition score as the primary endpoint for hearing. The group recommended using the measurement of improvement in lip excursion (SMILE) system for studies of facial function [120]. For clinical trials targeting NF-associated OPG, the visual outcomes working group recommended the use

of visual acuity as the primary endpoint, as opposed to measurement of tumor size [121]. The group also recommended assessing the optic disc for pallor to allow accurate interpretation of the visual acuity. Regarding the neurocognitive outcomes, the working group concluded that The Digit Span (DS) subtest from the Wechsler scales is the most appropriate performance-based outcome measure, as it provides the best psychometrics, feasibility, and utility across a wide age range, and is extensively used in previous research [122]. For similar reasons, the Conners scale achieved the highest ratings of behavioral questionnaires and is considered the most appropriate observe-rated outcome measure.

It is uncommon for pNF to cause airway compromise or pulmonary dysfunction, yet airway pNFs are clinically important. The REiNS functional outcomes group developed consensus recommendations for sleep and pulmonary outcome endpoints in airway pNFs [123]. The group endorsed using the apnea hypopnea index (AHI) as the primary sleep endpoint, and pulmonary resistance at 10 Hz (R10) of forced expiratory volume in 1 or 0.75 seconds (FEV1 or FEV 0.75) as the primary pulmonary endpoint. The group also identified secondary sleep and pulmonary outcomes. Measures of sleep and pulmonary function may be more clinically meaningful as endpoints than changes in tumor size in clinical trials targeting airway pNFs. Regarding patient-reported outcomes (PRO) of pain and physical function in NF clinical trials, the REiNS working group recommended the numeric rating scale-11 (NRS-11) to assess pain intensity for age 8 years and older [124]. To assess pain interference, the group recommended the Pain Interference Index in pediatric studies and the Patient-Reported Outcome Measurement Information System (PROMIS) Pain Interference Scale in adult studies. PROMIS Physical Function Scale was deemed the most appropriate for NF trials to assess the physical functioning domain. The REiNS disease biomarkers working group reported consensus recommendations to provide clinicians and researchers with a common set of guidelines to collect and store biospecimens and for establishment of biobanks for neurofibromatosis [125]. The group described the existing biomarkers in NF and report consensus recommendations for standard operation procedures to standardize sample collection and methodology protocols to promote comparison between studies.

Drug discovery is a very costly and lengthy process, which may take up to 10 years from first-in-human dosing to approval [126]. This process is usually preceded by years of extensive preclinical research to identify suitable targets for clinical development. The REiNS International Collaboration continues to work on developing consensus endpoints in NF clinical trials and to promote early engagement with FDA and other industry partners to accelerate the drug development and approval for NF-associated tumors.

7. Conclusion

The field of NF therapeutics is at inflection point. Several clinical trials have been conducted targeting various manifestations of NF and more studies are ongoing. The alignment of endpoints along with utilizing validated clinical outcomes measures represents a priority for therapeutic development for NF. Fortunately, there is a growing interest in NF, which is drawing the attention of pharmaceutical and biotechnology companies to grow the pipeline for NF targeted therapy. These efforts are combined with several ongoing laboratory and preclinical studies that provide unique opportunities to study the complex biology and natural history of NF-associated tumor. The US breakthrough therapy designation that was granted to Selumetinib in NF1 endorses the critical need for partnership among the major consortia and funders to accelerate the therapeutics development efforts in the NF field.

Disclosures

Mina Lobbous and Bruce Korf report no disclosures relative to the manuscript.

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