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Target Product Profile for Cutaneous Neurofibromas: Clinical Trials to Prevent, Arrest, or Regress Cutaneous Neurofibromas

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Cutaneous neurofibromas (cNFs) are benign tumors of the skin that affect >95% of adults with neurofibromatosis type 1. Despite their benign histology, cNFs can significantly impact QOL due to disfigurement, pain, and pruritus. There are no approved therapies for cNFs. Existing treatments are limited to surgery or laser-based treatments that have had mixed success and cannot be readily applied to a large number of tumors. We review cNF treatment options that are currently available and under investigation, discuss the regulatory considerations specific to cNFs, and propose strategies to improve cNF clinical trial design and standardize clinical trial endpoints.

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INTRODUCTION

Cutaneous neurofibromas (cNFs) are benign tumors that form in the dermal layer of the skin and involve multiple cell types, including Schwann cells and neurons. Despite their benign histology, they are frequently reported as the most burdensome aspect of neurofibromatosis type 1 (NF1) because they frequently cause significant disfigurement and are associated with pain and pruritus (Bergqvist et al., 2020; Cannon et al., 2018; Ehara et al., 2018; Guiraud et al., 2019; Ortonne et al., 2018; Page et al., 2006; Wolkenstein et al., 2003). Several studies have consistently shown the negative impact of cNFs on QOL (Guiraud et al., 2019; Page et al., 2006; Wolkenstein et al., 2003).

cNFs typically appear in late childhood or early adolescence and increase in number and size over a person's lifetime (Duong et al., 2011). By adulthood, >95% of adults with NF1 have cNFs (Ehara et al., 2018; Huson et al., 1988). The efficacy of current therapies for cNFs, including laser-based treatments or radiofrequency ablation, is highly variable, and surgical resection remains the standard of care. These treatments have several limitations. First, none of the current therapies are specifically approved by regulatory agencies for cNF treatment, thereby limiting insurance coverage and patient access to treatment. Indeed, access to the few options available for cNFs is limited to a few specialty clinics, and only a select number of tumors can be treated per session. These limitations lead to an increased burden on affected patients, who frequently have to locate the few centers that offer treatment and travel for multiple consultations and treatment sessions. Furthermore, all of the current treatments result in new skin changes and are only sought after cNFs have already become symptomatic and affected patient QOL. To improve QOL outcomes, treatments that prevent cNF development altogether or stop cNF growth when they are in their early stages are urgently needed.

cNFs vary in morphology, and it is unknown whether this reflects different stages of a single tumor or different biologic subtypes (Figure 1) (Ortonne et al., 2018). In the nascent/latent stage, tumors are not apparent by visual inspection or palpation but can be detected using imaging techniques such as high-resolution ultrasound and optical coherence tomography. Flat cNFs are visible, have a slightly raised surface, and range in size from 0.5 to 12 mm. Sessile cNFs are more raised and have an apex, ranging from ~1 to 10–12 mm. Globular cNFs are even more apparent and taller in height (20–30 mm). Finally, pedunculated cNFs have a distinct stalk that connects the tumor above and below the skin surface (Ortonne et al., 2018).

cNF appearance varies across the lifespan, and in older adults, it is common for different cNF morphologies to coexist within one individual (Figure 1). Awareness of the variability in cNF appearance and its potential evolution over time is important for therapeutic development because these

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Abbreviations: 3D, three-dimensional; ALA, aminolevulinic acid; cNF, cutaneous neurofibroma; CO_2, carbon dioxide; ERK, extracellular signal–regulated kinase; FDA, Food and Drug Administration; HFUS, high-frequency ultrasound; MEK, mitogen-activated protein kinase kinase; NF1, neurofibromatosis type 1; PD, pharmacodynamic; PK, pharmacokinetic; pNF, plexiform neurofibroma; PRO, patient-related outcome

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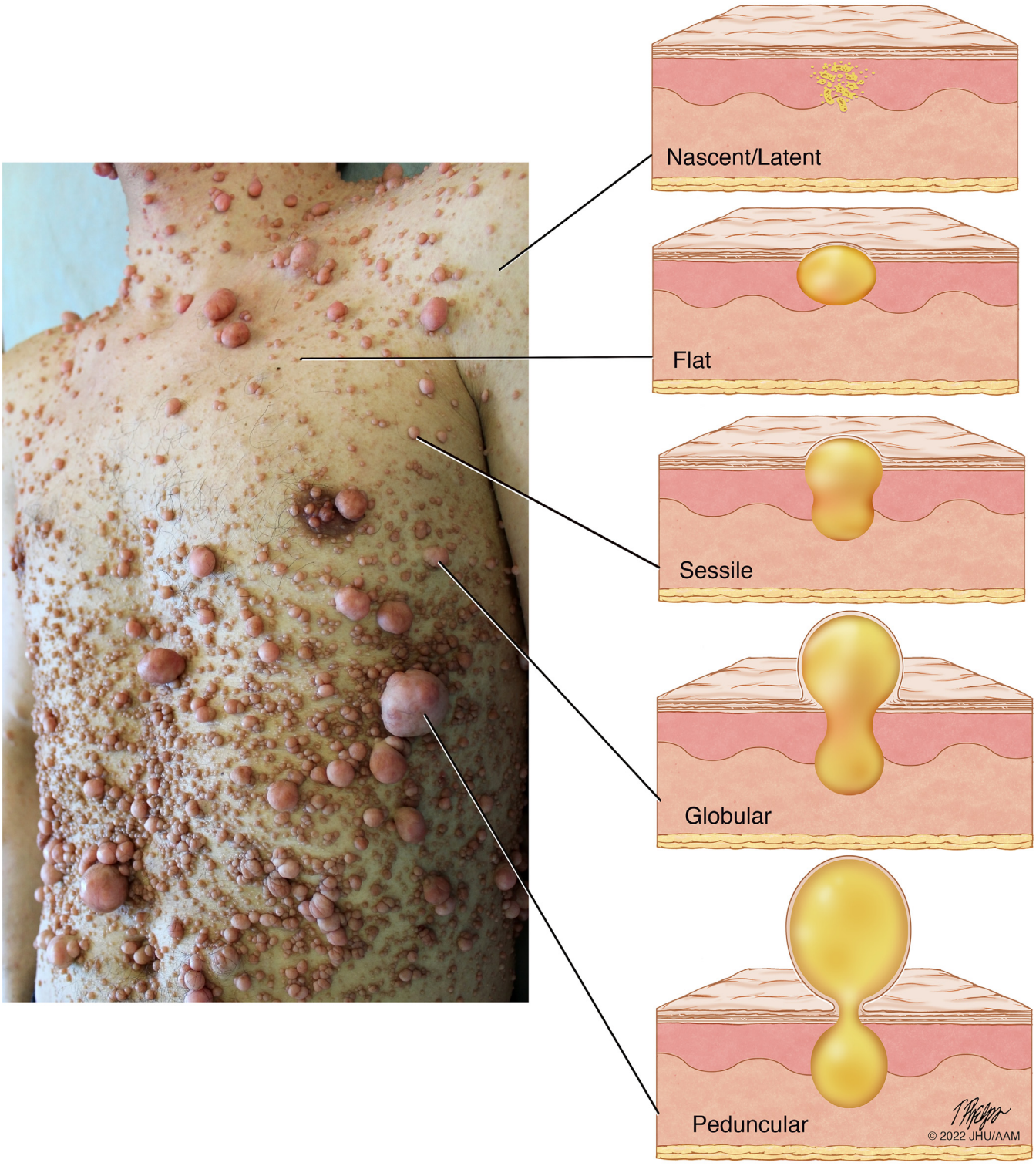

Figure 1. Variable appearances of cNFs. Example of an individual with NF1 and a heavy burden of cNFs that vary in their appearance. Illustration: Tim Phelps © 2022 JHU AAM Department of Art as Applied to Medicine the Johns Hopkins University School of Medicine. AAM, Art as Applied to Medicine; cNF, cutaneous neurofibroma; JHU, Johns Hopkins University; NF1, neurofibromatosis type 1.

factors and patient characteristics (skin type, tumor symptoms, and location) directly influence the optimal therapeutic approach. For example, smaller, flat tumors may be amenable to topical therapies, whereas the height of globular and pedunculated cNF may prevent adequate tissue penetration of topical treatments. Nascent/latent tumors are the predominant morphology in young children. In these individuals, the treatment goal is to prevent cNF development and growth, with the overall objective of preventing them from becoming clinically apparent and symptomatic.

By contrast, flat and sessile cNFs typically emerge in adolescents and young adults. Given the small number and size of the tumors, the therapeutic goal would be to intervene early to arrest and potentially reverse tumor growth. Finally, globular and pedunculated tumors are most frequently seen in older adults. For these patients, treatment goals include preventing the growth of existing tumors, preventing new tumor development, providing symptomatic relief, and decreasing the size and number of existing tumors.

Thus, given the high prevalence and morbidity of cNFs, effective and accessible interventions to treat existing cNFs and prevent cNFs from developing and causing morbidity are needed.

CURRENT TREATMENT OPTIONS

Surgical excision

Physical removal is the mainstay of treatment for cNFs, primarily focused on surgical excision with primary closure by dermatologists or general and plastic surgeons. However, this method may be inaccessible to a majority of the global NF1 population because of the need for surgical expertise, a sterile field, and general anesthesia in some cases (Bromley et al., 1982; Onesti et al., 2010; Pailheret, 1990). Simpler surgical approaches using local anesthesia are feasible for lesions <1 cm and can be performed in the outpatient setting by family practitioners, physician assistants, and nurse practitioners using inexpensive medical equipment and a nonsterile technique (Chamseddin et al., 2019). cNF removal under local anesthesia could be implemented as a low-risk therapy for both symptomatic and disfiguring tumors in patients with a limited number of cNFs. A critical consideration for resection of cNF is complete removal of the mass within the deeper dermis. Without this, recurrence is likely. Although one study reported the removal of a median of 330 cNFs in a single treatment session (megasession) (Onesti et al., 2010), the standard practice is limited to five cNFs per session to avoid general anesthesia and due to the risk of wound healing and reimbursement limitations.

In general, patients report favorable cosmetic results and improved QOL after surgical excision (Guiraud et al., 2019). Scars associated with surgery may be more acceptable than those after laser ablation, which are often hyper- or hypopigmented (Chamseddin and Le, 2020). Potential complications of surgical excision include hypertrophic scarring, keloid formation (especially in African American individuals and those with a history of keloid formation), and postinflammatory pigmentation. Although surgical excision is an effective approach to removing a small number of cNFs per treatment session, it is not feasible for patients with a severe cNF burden except for the removal of larger, dominant tumors. Surgical excision does not address nascent/latent cNFs and thus cannot be used as a preventive strategy.

Device-based treatments

Tumor ablation with carbon dioxide (CO_2) or Erbium:YAG lasers (Méni et al., 2015), radiofrequency ablation (Kim et al., 2016, 2013), and Neodymium:Yttrium Aluminum Garnet tumor photocoagulation are used as local therapies to treat cNFs (Table 1). Electrodessication is a technique that involves tissue desiccation through tumor dehydration and denaturation and enables the removal of hundreds to thousands of cNFs in a single session (Levine et al., 2008; Lutterodt et al., 2016). However, the general limitations of these techniques include the ability to only treat small, visible tumors; pain; scarring; skin-specific pigmentary changes (hypopigmentation or hyperpigmentation); and infection. In addition, electrodessication requires the use of general anesthesia. Furthermore, these techniques typically result in incomplete tumor removal and do not prevent cNF progression in the region, so repeat interventions may be required.

Topical photodynamic therapy using aminolevulinic acid (ALA) and 633 nm red light has also been studied for cNFs (Dolmans et al., 2003; Quirk et al., 2021). However, this has not translated to regular use in clinical practice, partly because of tumor size and the limited penetration of ALA as well as the pain associated with the procedure when large skin regions require treatment. Ablative fractional laser-assisted drug delivery to improve drug penetration and uptake has been explored for other skin diseases (Fredman et al., 2022; Hendel et al., 2021) and may be a strategy for cNFs.

Several efforts are underway to optimize device-based treatments for cNF. An ongoing study is evaluating the performance of four U.S. Food and Drug Administration (FDA)–approved device-based treatments: 980 nm laser, Alexandrite laser, radiofrequency needle coagulation, and deoxycholic acid (Kybella) injections (NCT04730583). Preliminary data showed that all modalities are safe and partially effective in reducing cNF size, although there are differences in tolerability and operator skill requirements (Anderson et al., 2022). Another study is investigating the safety and efficacy of high-intensity focused ultrasound to ablate cNF (NCT05119582), assessing tumor resolution of the full body with both 20 MHz ultrasound imaging and punch biopsy.

Currently, device-based strategies only address clinically visible tumors. In addition to the limitations mentioned earlier, the optimal timing of these interventions is unclear. Identifying areas of quiescent or early-developing cNFs and subsequent large-field therapy may provide improved outchytomes. Spatial frequency domain imaging and optical coherence tomography could potentially be used in the future to map large areas, identify areas of interest, and guide treatment (Li et al., Current and emerging imaging techniques for neurofibromatosis type 1–associated cutaneous neurofibromas. Forthcoming 2023).

Systemic treatments

There is significant interest in targeting key signaling pathways involved in cNF formation with systemic therapies that may both prevent cNF formation and reduce the number and size of existing tumors. Everolimus, an mTOR inhibitor, has been evaluated in a single-arm study (NCT02332902), but only 13% of tumors in 19% of participants showed reduced surface volume after treatment. Furthermore, the rate of adverse effects was high (Slopis et al., 2018). Selumetinib, an oral mitogen-activated protein kinase kinase (MEK) inhibitor, has shown significant activity in plexiform neurofibromas (pNFs), resulting in radiographic overall response rates of 66% (Gross et al., 2020). This led to the approval of

Table 1. Summary of Therapies that Have Been Evaluated or Are Currently under Investigation for cNF

Intervention	n	Target	Endpoint	Results
Surgical excision				
• **Treatment goal**: shrinkage, cure; consider biopsies for PK/PD studies in early intervention studies				
• **Target tumors**: flat, sessile, globular, and pedunculated cNFs				
Device-based treatments				
• **Treatment goal**: early intervention, shrinkage, and cure				
• **Target tumors**: flat and sessile cNFs, limited application for globular and pedunculated tumors				
Electrodessication for multiple cNFs (Levine et al., 2008)	97	Small- to medium-sized tumors	Patient satisfaction (cosmesis)	High patient satisfaction, minimal scarring
Electrodessication in treating cNFs (Lutterodt et al., 2016)	6	Small- to medium-sized tumors	Patient satisfaction (cosmetic and functional)	High patient satisfaction, minimal scarring
Laser photocoagulation (surface and interstitial) (Elwakil et al., 2008)	12	<5 mm thick (surface); >5 mm thick (interstitial)	Lesion regression Patient satisfaction (cosmesis)	For surface-treated cNF: 76–100% regression in 43% of treated cNF For interstitial-treated cNF: 76–100% regression for 36% of treated cNF High overall patient satisfaction
CO_2 laser (Méni et al., 2015)	106	Small to medium size (<1 cm)	Patient satisfaction (cosmesis) Pain	High patient satisfaction (90%) No pain in 52% during treatment Pain in 44% 2 days after treatment
Radiofrequency ablation (Kim et al., 2016)	20	Not reported	Safety, efficacy, patient satisfaction (cosmesis)	Complete reduction in 48% >75% reduction in 54% High patient satisfaction
Radiofrequency ablation (Kim et al., 2013)	16	Small to large (4 mm–10 cm)	Patient satisfaction (cosmesis)	High patient satisfaction
Radiofrequency ablation + vitamin D3 ointment (Yoshida et al., 2007)	8	Small to medium size (<1 cm)	Grade of clearance (photographic)	Good clearance (>50%) Poor clearance (<25%)
Robust surgical removal (Chamseddin et al., 2019)	12	Average of 1 cm	Patient satisfaction (Dermatology Life Quality Index)	Significant improvements across multiple domains
Photodynamic therapy (NCT02728388)	30	Activation of ALA	Phases 1: photosensitizer uptake and MTD Phase 2: time to progression	Phase 1: Established uptake of photosensitizer and MTD Phase 2: Ongoing
Kybella and several devices (980 nm laser, 755 nm Alexandrite laser, radiofrequency) (NCT04730583) (Anderson et al., 2022)	20	Kybella (cytolytic agent): targets adipose cells	Safety and tolerability	Safe, pain most significant with 980 nm laser, variable effectiveness
TOOsonix System (NCT05119582)	20	Ultrasound	Safety	N/A
Systemic treatments				
• **Treatment goal**: prevention, early intervention, shrinkage, and cure				
• **Target tumors**: nascent, flat, and sessile cNFs, limited application for globular and pedunculated cNFs				
Selumetinib (NCT02839720)	24	MEK	Tumor shrinkage	N/A
Topical treatments				
• **Treatment goal**: prevention (in small and visible areas), early intervention, shrinkage, and cure				
• **Target tumors**: all types of cNFs				
Rapamycin (Koenig et al., 2012)	28	mTOR	Safety	Safe but no clear change in tumor volume
Ranibizumab (NCT00657202)	11	VEGF angiogenesis	PD	Highly variable responses
Imiquimod (NCT00865644)	20	TLR7/8	Tumor shrinkage	Few patients with a minor decrease in tumor volume; responses highly variable
Diclofenac sodium (Oliveira et al., 2021)	7	COX-1, COX-2	Efficacy	N/A
NFX-179 gel (Sarin et al., 2021)	35	RAS pathway	Safety and tolerability; tumor shrinkage	Tumor volume change with 0.15% and 0.5% gel but high SD

Abbreviations: ALA, aminolevulinic acid; cNF, cutaneous neurofibroma; CO2, carbon dioxide; MEK, mitogen-activated protein kinase kinase; MTD, maximum tolerated dose; N/A, not available; PD, pharmacodynamic; PK, pharmacokinetic; TLR, toll-like receptor.

selumetinib for the treatment of symptomatic, inoperable pNFs in 2020. Given the success in pNFs, a clinical trial of selumetinib for the treatment of cNFs (NCT02839720) was initiated. Although selumetinib appeared to decrease cNF volume, preliminary data also showed that selumetinib-associated adverse effects in adults with cNFs were not tolerable. Final data on the effect of selumetinib on tumor volume have not been published yet.

The adverse effects encountered with systemic drugs highlight the therapeutic challenges for cNFs. Unlike pNFs or cancers, cNFs are not life threatening and may require repeated or lifelong treatment. Therefore, the side effects seen with pNFs and cancer therapies may not be tolerable to patients treated for cNFs. Alternative dosing schedules utilizing the minimum effective dose for cNF treatment or prevention and selecting drugs with better adverse effect profiles for cNF treatment are needed.

Topical and intralesional treatments

Topical treatments consist of the direct application of drugs to the skin, whereas intralesional therapies are directly injected into the tumor. Owing to their local application, they are attractive treatment strategies to mitigate the side effects of systemic therapies. However, these treatments have shown limited success in cNFs to date. cNF microporation using a laser device followed by topical application of diclofenac in six patients (NCT03090971) did not meet its endpoints (Oliveira et al., 2021). Direct injections of ranibizumab, an anti-VEGF mAb, resulted in variable responses (NCT00657202). Topical application of imiquimod (a toll-like receptor 7/8 agonist) in the form of a 5% cream was also assessed in a pilot study (NCT00865644), but results have not yet been reported.

Topical MEK inhibitors are currently undergoing evaluation in clinical trials, based on data that these agents have activity in cNF mouse models (Mo et al., 2021). Phase 1 and 2a data on NFX-179, a topical gel, showed a favorable safety and tolerability profile and potential therapeutic benefit, as evidenced by a 47% reduction in phosphorylated ERK levels in target tumors treated with the highest dose (0.5% gel). There was a trend toward tumor size reduction by a mean of 17% in the group treated with the 0.5% gel compared with an 8% reduction in the vehicle group ($P = 0.073$) (Sarin et al., 2021). No significant local or systemic toxicities were observed. A phase 2b study is ongoing (NCT05005845).

Treatment of early cNFs

There has been considerable interest in identifying and treating early cNFs before they are clearly visible. However, no studies have been conducted to assess the efficacy of treating nascent lesions, and we therefore do not yet know the durability of such early interventions. However, experience with techniques commonly used to treat cNFs, such as CO2 lasers, indicates that cNFs that are completely removed do not regrow. This is true even for globular or pedunculated lesions (Peltonen et al., 2022). Hence, it is reasonable to hypothesize that nascent and flat lesions that are completely treated will not recur. However, this hypothesis requires further investigation. Furthermore, new cNFs can develop across the lifespan. Cannon et al. (2018) showed that in a subset of 14 adult patients (mean age of 50 years) with NF1, the number of new cNF over 8 years was roughly three new lesions on the back, two new lesions on the abdomen, and <1 new lesion on an extremity. This suggests that successful treatment of early lesions may have long-term benefits for an individual with NF1-associated cNFs.

MINIMUM CRITERIA TO SELECT THERAPIES FOR ADVANCEMENT TO EFFICACY STUDIES

cNFs pose unique challenges for the therapeutic development process. First, the non–life-threatening nature of cNFs and the likely need for repeated or chronic treatment warrant special consideration for toxicity and treatment duration thresholds. Therapeutics for cNFs must show an excellent safety and tolerability profile. Patients and clinicians may not be willing to accept treatments that have significant side effects or require frequent monitoring. For instance, selumetinib almost universally causes an acneiform rash and requires surveillance echocardiograms and ophthalmologic exams (FDA, 2020), which may be too burdensome for some patients. The benign histology of cNFs also warrants a reasonable time-to-response interval that is acceptable to both patients and clinicians. The time to radiographic and functional response for selumetinib in pNFs was as long as 12 months (Gross et al., 2020), which may be similarly long for cNFs. Finally, treatment duration (single treatment session vs. chronic treatment) needs to be well defined and matched to treatment goals (prevention vs. regression). For example, depending on their symptoms and tumor burden, patients may have a strong preference for a few treatment sessions per year or a daily topical or systemic treatment. Guidance for defining frameworks for toxicity profile, time-to-response, and treatment duration may be gleaned from other dermatologic diseases. For instance, regulatory approval of ixekizumab for psoriasis was based on the assessment of endpoints at 12 weeks (Gordon et al., 2016). Although time-to-response in inflammatory skin conditions will invariably differ from that of a neoplastic skin disease based on differences in disease biology, defining potential time-to-response or treatment duration for tumor prevention is an important step to launching therapeutic trials for cNFs.

Second, therapeutic development strategies will differ based on treatment goals, which depend on the patient and tumor phenotype. Preventive therapy for clinically undetectable or small cNFs will differ from a curative treatment aimed at reversing or resolving existing tumors. Accordingly, efficacy endpoints must be clearly defined. Traditional drug efficacy endpoints such as changes in tumor size and biomarkers are important to show the biologic effect of a treatment. However, given the psychosocial impact of cNFs, endpoints that measure the effect on symptom burden (pain, pruritus, and disfigurement) and the impact of treatment on QOL should also be incorporated into trials.

Third, pharmacokinetic (PK) and pharmacodynamic (PD) studies are needed to inform drug advancement to later-phase trials. For instance, tumor depth is an important consideration for topical drugs or regional devices because drug penetration may be insufficient in large globular and pedunculated cNFs. For systemic treatments, it will be important to determine the plasma concentrations of drugs to achieve adequate skin and tumor penetration. Animal models (Staedtke et al.,

Existing and developing preclinical models for neurofibromatosis type 1–related cutaneous neurofibromas. Forthcoming 2023) may be appropriate to study these questions (Juluru et al., 2012; Schnetz and Fartasch, 2001).

REGULATORY CONSIDERATIONS

Because approved therapies for cNF do not exist, there is no regulatory precedent for a path towards approval. Treatment goals include preventing tumor development, reducing and reversing the size of existing tumors, and reducing tumor-associated morbidity and symptoms. The FDA provides guidance on the type of evidence required to establish therapeutic effectiveness (FDA, 2019). Two adequate and well-controlled investigations or one adequate and well-controlled large multicenter trial that can provide substantial evidence of effectiveness are generally required to meet the substantial evidence standard. The substantial evidence standard can also be met on the basis of an adequate and well-controlled clinical investigation and confirmatory evidence. Confirmatory evidence can be derived from data showing strong mechanistic support for the therapy (e.g., PD data or compelling nonclinical data) or from natural history data. Given that NF1 is a rare disease, conducting a large, randomized, placebo-controlled trial with equal allocations may not be feasible. Thus, for cNF therapeutic development, providing confirmatory evidence may be needed to accelerate and obtain regulatory approval. In this regard, the approval of selumetinib for pNFs is an informative tool to help guide studies for cNF treatments.

A key element for the approval of selumetinib for pNFs was the natural history data for pNFs (Gross et al., 2020). Understanding the natural history of a disease, including how and over what time period it progresses, is crucial for adequate drug development and clinical trial design. Without this knowledge, the selection of endpoints and the timing for measurement of these endpoints are very difficult. For pNFs, a natural history study was initiated in 2008 (NCT00924196). For cNFs, the natural history has not been fully described. A key challenge has been the variable burden of cNFs within and across individuals. However, some preliminary data are available to help guide clinical trial endpoints. A prospective study of 22 adults over 8 years showed that both cNF size and number increased slowly over time and occurred at different rates across body regions (Cannon et al., 2018). Other studies have shown that the greatest number of cNFs are on the trunk, followed by the head and neck, upper limbs, and lower limbs (Ehara et al., 2018; Fijałkowska and Antoszewski, 2020). However, many questions remain unanswered, including the natural history in non-Caucasian individuals, genetic modifiers of cNF development, the change in the histologic composition of cNFs over a person's lifetime, and whether or not environmental factors (e.g., trauma, diet, sun exposure, endogenous and exogenous hormone exposure) modify cNF development. Several efforts aim to comprehensively define the natural history of cNF. In an ongoing prospective study at Johns Hopkins University (Baltimore, MD), correlative studies between tumor burden and demographic factors (age, skin type), patient-reported outcomes, and NF1 genotype are underway to assess 500 NF1 patients of all ages with three-dimensional (3D) digital imaging annually over a 5-year period. In addition, GWAS to identify genetic modifiers of cNF burden are in progress (NCT04941027).

As outlined earlier, confirmatory evidence may also consist of preclinical and clinical data that provide strong mechanistic support for a therapy. This requires a detailed understanding of the treatment's mechanism of action. For instance, ERK phosphorylation status has been incorporated as an endpoint in the clinical trial of the topical MEK inhibitor NFX-179 (Sarin et al., 2021). Furthermore, recent epigenetic studies in cNFs have shown distinct methylation signatures across cNFs of different size categories (Grit et al., 2021). Future research is needed to establish the validity and predictive reliability of such biomarkers for cNF growth behavior.

CONSIDERATIONS FOR CLINICAL TRIALS AND CLINICAL TRIAL ENDPOINTS

Endpoints for clinical trials should be valid, reliable, measurable, meaningful to patients, and appropriate for the treatment population and treatment goals. For cNFs, therapeutic efficacy should be measured using both quantitative (objective) and qualitative (subjective) endpoints. An assessment of tumor burden based on the size, number, shape, and color of existing and new tumors is a reasonable quantitative measure. These tumor-based metrics should constitute the primary endpoint in clinical trials. Of note, there is currently no consensus on whether the goal of treatment includes size reduction of a subset of cNFs but not complete clearance (as seen in pNFs and cancers). In addition, there is no agreement or recommendation on the optimal method to count, measure, and longitudinally track cNFs. Several devices are available to measure cNF size, including calipers, 3D photography, and high-frequency ultrasound (HFUS) (Thalheimer et al., 2021). Each device has advantages and disadvantages with regard to cost, operator training required, reliability, reproducibility, and suitability for small versus large tumors (Li et al., unpublished data). For instance, HFUS is suitable for small tumors and can detect nascent tumors below the skin surface. HFUS and 3D photography allow for central review, which makes them particularly attractive for clinical trials. Artificial intelligence–based quantification methods using, for instance, deep learning may greatly improve the efficiency and accuracy of measuring tumor burden and could be explored in the future.

In addition to tumor-based metrics, including QOL measures as an endpoint in cNF clinical trials is critical. Several patient-related outcomes (PROs) are available to assess QOL; however, these target NF1 or dermatologic diseases in general and do not measure cNF-specific concerns (Wolters et al., 2021). For cNF clinical trials, the coprimary or secondary endpoint should be a tool that measures a change in appearance in response to treatment. To address this, the Skindex has recently been adapted to assess cNF-specific PROs, but further evaluation of its responsiveness to treatment and cross-cultural validation is required (Fertitta et al., 2022). In addition to an appearance-specific tool, a global impression of change based on the physician's and patient's assessment should also be included as a coprimary or

secondary endpoint. The global impression of change is a measure of whether a change is clinically meaningful.

Secondary or exploratory endpoints should also be incorporated in cNF clinical trials because they may provide confirmatory evidence of a drug's effectiveness, which can facilitate regulatory approval. Such endpoints include validated biomarkers of response such as prognostic, predictive, and PK/PD biomarkers (Wallis et al., 2021). Prognostic biomarkers assess the outcome of disease independent of the treatment provided. Predictive biomarkers serve as surrogates for drug activity and therefore measure the outcome of treatment. Finally, PK/PD biomarkers assess target engagement, provide information about drug metabolism, and help with dose selection to limit adverse effects (Wallis et al., 2021). For instance, currently approved therapies that inhibit RAS (which is upregulated in NF1) are available, but these drugs were developed for cancer indications and have a side effect profile that is inappropriate for patients with cNFs. Using PK/PD studies in animal models, it may be possible to define lower doses with biologic activity that result in an acceptable toxicity profile for cNF treatment.

Pathologic complete response is an additional endpoint that should be considered for cNFs. A pathologic complete response is achieved when there is no evidence of tumor cells after therapeutic exposure. This has been an increasingly important endpoint in breast cancer in the last decade and has been used in that setting to support accelerated regulatory approval (National Archives, 2014). Given that the process of discovery, development, and approval of a therapy takes 7–10 years from first-in-human dosing to approval (Hay et al., 2014), incorporating endpoints such as pathologic complete response and other markers of biologic activity is important to expedite the discovery of active therapies for cNFs.

Furthermore, innovative and more efficient clinical trial strategies are needed, such as basket trials, umbrella trials, and platform trials. A basket trial examines multiple diseases treated with a common intervention. An umbrella trial examines a single disease and assesses multiple interventions. A platform trial also examines multiple interventions but is more dynamic because treatment arms may be added or removed on the basis of what is found during specific interim analyses or new data emerging in the field. This allows for flexibility and efficiency (FDA, 2022).

Finally, early and continuous engagement with health authorities can lead to improved clinical trial design, shared learning, and an overall faster path to the identification and validation of effective therapies for cNFs. This should include a discussion on appropriate endpoints in cNF clinical trials and can be done through mechanisms such as a Special Protocol Assessment with the FDA. This process enables the investigative team to proceed with a clinical trial using a protocol that is considered adequate and acceptable by the FDA (FDA, 2018).

CONCLUSION

cNFs are a cause of significant morbidity in individuals with NF1, and effective therapies are urgently needed to both prevent and treat these skin tumors. cNFs pose unique challenges to the development of therapeutics and the design of clinical trials because of their heterogeneity within and across affected individuals. Several active initiatives are underway to address knowledge gaps and increase the accuracy and efficiency of cNF clinical trials, including natural history studies as well as efforts to dissect the similarities and differences across cNFs and between cNFs and other tumors. As our understanding of cNF growth behavior over time and in response to treatment improves, consensus recommendations on clinically meaningful clinical trial endpoints are needed. Given the heterogeneity of cNFs, treatment options and goals (prevention vs. early intervention vs. regression vs. cure) will need to be tailored toward predefined patient populations. Finally, the field requires a shift in how clinical trials are conducted and how clinical care is delivered for cNFs. This includes designing innovative clinical trials to accelerate the path to regulatory approval, training clinicians across subspecialties (e.g., dermatology, genetics, and neurology) who provide care to patients with NF1 to acquire additional skills (e.g., procedural skills) to treat cNFs, and better outreach strategies to individuals with NF1 and their caregivers to enhance cross-talk about the goals of early intervention and the availability of novel therapeutics.

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CONFLICT OF INTEREST

IL, CGR, SYL, SRD, VS, MRS, and JOB receive support from the Neurofibromatosis Therapeutic Acceleration Program (NTAP) at Johns Hopkins University. MRS, JOB, and IL receive funding from the Department of Defense. IL and JOB are consultants for SpringWorks Therapeutics. KMK is a consultant for Sciton, IQVIA, and FDZJ; has research contracts with Biophotas, Orlucent, and Michaelson Diagnostics; receives equipment to her clinic from Sciton and Michaelson Diagnostics; and serves as a Board Member for the American Society for Laser Medicine and Surgery. The remaining authors state no conflict of interest.

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Conceptualization: IL, CR, JOB, PW; Formal Analysis: IL, CR, JOB, PW; Writing - Original Draft Preparation: IL, CR, SG, KMK, DK, ZY, SYL, JOB, PW; Writing - Review and Editing: IL, CR, SG, KMK, DK, ZY, SYL, SDR, VS, MS, JOB, PW

Disclaimer

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