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Neurofibromatosis in the Era of Precision Medicine: Development of MEK Inhibitors and Recent Successes with Selumetinib

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Abstract

Purpose of Review—Patients with neurofibromatosis type 1 (NF1) are at increased risk for benign and malignant neoplasms. Recently, targeted therapy with the MEK inhibitor class has helped address these needs. We highlight recent successes with selumetinib while acknowledging ongoing challenges for NF1 patients and future directions.

Recent Findings—MEK inhibitors have demonstrated efficacy for NF1-related conditions, including plexiform neurofibromas and low-grade gliomas, two common causes of NF1-related morbidity. Active investigations for NF1-related neoplasms have benefited from advanced understanding of the genomic and cell signaling alterations in these conditions and development of sound preclinical animal models.

Summary—Selumetinib has become the first FDA-approved targeted therapy for NF1 following its demonstrated efficacy for inoperable plexiform neurofibroma. Investigations of combination therapy and the development of a representative NF1 swine model hold promise for translating therapies for other NF1-associated pathology.

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Keywords

Neurofibromatosis; MEK inhibitor; Selumetinib; Plexiform neurofibroma; Low-grade glioma; Optic pathway glioma; Malignant peripheral nerve sheath tumor; Combination therapy

Introduction

Neurofibromatosis type 1 (NF1) is an autosomal dominant neurocutaneous and tumor predisposition syndrome with well-defined clinical features developed by a National Institutes of Health (NIH) convened expert panel in 1987 [1]. The underlying genetic alteration is in the neurofibromin 1 gene, *NF1*, located on chromosome 17 that encodes neurofibromin. *NF1* is among the largest genes, and many inactivating, loss of function, and germline mutations have been described. Nonetheless, genetic testing is sensitive, can help differentiate neurocutaneous syndromes, and can confirm a suspected diagnosis, including mosaic disease, before full clinical features develop [2•]. While fully penetrant, there is great variation in disease manifestations, even within families, but morbidity results from multisystem pathology including benign and malignant tumors [3]. A deeper understanding of neurofibromin's role in the core mitogen-activated protein kinase (MAPK) cell signaling pathway has led to success with disease directed therapy in recent years. This is exemplified by the first FDA-approved therapy for patients with NF1 with selumetinib, for inoperable NF1- associated plexiform neurofibromas in children this year [4•]. The continued development of representative preclinical models and exploration of combination therapy for other neoplastic manifestations of NF1 hold promise to continue improving health outcomes for people with NF1.

Genomic Alterations and Cell Signaling Dysregulation in NF1-Associated Pathology

The Mitogen-Activated Protein Kinase Pathway

Tumorigenic cells develop homeostatic imbalances leading to cell proliferation and to resisting cell death [5]. Ten cell signaling pathways controlling cell growth and cell death are altered in most human cancer [6]. The mitogen-activated protein kinase (MAPK) pathway, first discovered in 1988, is initiated by autophosphorylation of receptor tyrosine kinases (RTKs) leading to sequential downstream activation of RAS GTPases, RAF kinases, MEK kinases, MAPKs ERK1 and ERK2, and finally transcription factors such as ELK1 [7]. The product of the *NF1* gene encodes neurofibromin, a protein with a central GTPase activating protein (GAP) domain that interacts with RAS-GTP, dramatically increasing its intrinsic GTPase activity and thereby causing its conversion to RAS-GDP, thus reducing levels of RAS-GTP, the active species of RAS. Thus, neurofibromin functions to reduce RAS-GTP mediated activation of its effector pathways, including the MAPK and phosphoinositide 3-kinase (PI3K) pathways. Dysregulation of these pathways results from biallelic loss of *NF1*, as occurs in neoplasms in NF1 patients [8]. Congenital alterations of genes involved in the interrelated MAPK and PI3K pathways, collectively called RASopathies, lead to an increased incidence of neoplasms [9, 10].

The discovery of the MAPK pathway and its key role in tumorigenesis spurred the development of targeted therapy for sporadic tumors, in which alterations in genes encoding RTKs, RAS proteins, and RAF and MEK kinases contribute to malignancy. Examples of specific alterations leading to drug development include $EGFR^{T790M}$, $BRAF^{V600E}$, and $KRAS^{G12C}$ mutations [11]. In these settings, acquired drug resistance is common. Drug resistance can occur due to increased activation of upstream kinases as well as mutations in the targeted receptor or kinase itself. Altered cross-talk to engender resistance can involve alternative MEK activators. Also, cells can use various MEK isoforms, of which at least seven are known, and activate different nuclear transcription factors [7, 12]. The ERK1/2 kinases, in contrast, are specifically activated by MEK1/2. This specific function of MEK1/2 makes them an attractive target given the diverse cellular proliferation and survival responses induced by ERK, especially in NF1 where mutations of upstream kinases and RTKs are not present constitutionally [12].

NF1-Associated Neurofibromas

Neurofibromas are benign tumors that arise from neoplastic Schwann cells [13]. They usually show biallelic loss of *NF1*, do not express neurofibromin, and demonstrate activated RAS-GTP compared to controls [8]. Cutaneous neurofibromas (cNF) are discrete tumors involving the dermis or epidermis. Virtually all individuals with NF1 develop cNFs during their lifetime, and cNF contribute to disfigurement, dysesthesia, psychosocial distress, and quality of life impairment [14]. Plexiform neurofibromas (pNF) arise internally within virtually any peripheral nerve sheath, grow along nerve tracts, and can invade adjacent tissues. Compression of organs and structures and asymmetric or rapid growth lead to disfigurement and morbidity, with pain and motor morbidities most common [15•]. Children and adolescents with pNF demonstrate significantly worse measures in psychosocial and functional domains [16•].

In contrast to cNF, pNF are less prevalent with 25–50% of NF1 individuals affected. They arise early in life, are possibly congenital, and show peak growth during childhood [13]. Importantly, pNF are at risk of malignant degeneration to malignant peripheral nerve sheath tumors (MPNST), distinct from cNF. While histologically similar, the clinical differences between cNF and pNF suggest underlying biologic differences. In a methylation analysis, differential gene expression was observed between each group, with cNF epigenetically reinforced for RAS/MEK3/p38 and pNF for RAS/ERK [12, 17•].

NF1-Associated Gliomas

Individuals with NF1 are at increased risk for central nervous system tumors, which are mainly indolent low-grade neoplasms but can include aggressive infiltrating disease and develop in an estimated 15–20% of patients. Low-grade gliomas (LGG) are more common in children and most frequently affect the optic pathway. The incidence of high-grade gliomas (HGG) increases with age, with more than 50-fold increased relative risk compared to the general population [18•]. Pediatric LGGs invariably involve upregulation of the MAPK signaling pathway. They are distinct from adult LGG, which are characterized by chromosome 1 and 19 losses and *IDH1* mutations and which frequently degenerate into HGG over time [19••]. Of all pediatric LGG, an estimated 14% occur in individuals with

NF1, highlighting their shared biology [19••]. NF1-associated LGG have excellent (>95%) 20-year overall survival, but progression-free survival is lower at 41–58%, and morbidity due to tumor location and adverse effects of treatment are significant concerns [19••, 20].

NF1-Associated Malignant Neoplasms

MPNST are the leading cause of mortality in adults with NF1 [21]. They typically arise from prior pNF and have frequently metastasized before diagnosis [13]. Compared to sporadic MPNST, NF1-associated MPNST arise at a younger age and are less responsive to chemotherapy [13]. The progression of pNF to MPNST appears to start with the development of pre-malignant lesions, namely, atypical neurofibroma and atypical neurofibromatous neoplasm of uncertain biological potential (ANNUBP), which commonly acquire loss of *CDKN2A/B* [13, 22•, 23]. MPNST contain many additional genomic rearrangements; amplification of *PDGFR*, *KIT*, and *EGFR*; and mutations/deletions in *SUZ12*, *EDD*, *TP53*, and/or *PTEN* along with additional complex RAS-activating mutations [24, 25•].

HGG and breast cancer are additional important causes of neoplasia-related mortality in adults with NF1. Like pNF and MPNST, the biological complexity is distinct between LGG and HGG. LGGs in patients with NF1 are enriched for expression of proteins in the MAPK pathway, and there is a subset (up to 50%) characterized by lymphocyte infiltration, which may contribute to tumor senescence often observed with LGG [26••]. In contrast, when patients with NF1 develop HGG, additional mutations including those in *ATRX*, *TP53*, and *CDKN2A* are acquired, the PI3K pathway is activated, and tumors have low immune infiltration [26••, 27, 28]. The development of breast cancer in females with NF1 occurs earlier than the general population and is linked with poorer outcomes due to an increased proportion of triple negative and HER2 positive subtypes [29]. Somatic acquisition of mutations in *TP53*, *KMT2C*, *KMT2D*, and *PIK3CA* has been observed [30].

Precision Medicine in NF1—Development of MEK Inhibitors Including Selumetinib

The first MEK inhibitor (MEKi) was discovered in 1995, and subsequent generations of this class saw improved pharmacological properties [12]. These compounds were developed and tested for prevalent cancers such as melanoma and lung cancer, and now they are used for diverse indications [31]. The application of MEKi for NF1, a rare disease, has been accelerated by a remarkable collaboration between the NF community, researchers, funding agencies, and pharmaceutical company stakeholders (Table 1). The Children's Tumor Foundation and other funding agencies including the NIH, Congressionally Directed Medical Research Programs (CDMRP), NF clinical trials consortium, Gilbert Family Foundation, and the Neurofibromatosis Therapeutics Acceleration Program (NTAP) all support NF research and have contributed to the advancement of research and therapeutics for NF1 patients. Together, these organizations have supported the development of >20 clinical trials for MEKi for NF-related conditions [32–35].

Selumetinib (AZD6244; ARRY-142886) is a second-generation allosteric MEKi with an active metabolite that is itself a highly selective kinase inhibitor. Cells treated with the inhibitor show reduced ERK phosphorylation, *in vitro* and *in vivo* [36]. It has favorable pharmacokinetics (PK) with a half-life of 12 h and is metabolized by CYP and UGT enzymes [37–39]. The development of genetically engineered mouse NF1 models helped demonstrate the importance of the MAPK pathway in NF1-associated neurofibromas, and the MEKi PD-0325901 was shown to be active in plexiform-like neurofibromas and MPNSTs [40]. Further work demonstrated that even low dose exposure to PD-0325901 reduced tumor volume in neurofibroma-bearing mice [41]. These studies in a murine pNF model were repeated using selumetinib. Neurofibroma-bearing mice showed a sustained decrease in phosphorylated ERK and maximal tumor shrinkage of 30% as determined by volumetric magnetic resonance imaging (MRI) [42, supp appendix]. These preclinical studies provided a rationale for evaluating MEKi in clinical trials for NF1-associated neoplasms.

Clinical Advancements with Selumetinib for NF1

Challenges in Clinical Trial Design for NF

NF1 alterations can be associated with significant neurodevelopmental, neurologic, cardiovascular, and musculoskeletal abnormalities [2•, 43]. Consequently, quality of life can be impacted across psychosocial and health-related domains [43, 44]. Neoplasms, both benign and malignant, may develop at any age and grow with variable kinetics. In some cases, medical therapies must be tolerated for a long duration, be able to reduce tumors of large volume, or treat malignant tumors [45]. Additional challenges for the NF patient population are the relative rarity of the disorder leading to slow clinical trial enrollment, variable disease kinetics among individuals with similar pathology, and variation in disease penetrance and presentation [46•].

The NF community is exemplary for its innovation and collaboration in addressing these challenges. Firstly, the National Cancer Institutes (NCI) natural history study of NF1 has advanced understanding of NF-related morbidities and has been used as a benchmark for clinical study interpretation [46•, 47•]. Secondly, clinical trial design has benefited from standardization of outcome measures by The Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) working groups, created in 2011 [48]. As an illustrative example, historical trials for treatment of pNF were limited by imaging techniques to monitor disease response; REiNS standardized the use of volumetric MRI, which is now incorporated into clinical trials for plexiform neurofibroma [45, 46•, 48–50]. For optic pathway gliomas, visual acuity as an endpoint has surpassed tumor reduction, and other functional outcomes (e.g., motor and respiratory function) in addition to patient-reported outcomes (PRO) of pain inform effectiveness of therapy [48]. While challenges exist in implementation, defining and standardizing clinical trial endpoints precedes clinical trial design that incorporates the reality of NF as a multisystem, lifelong disease state [51].

Efficacy of Selumetinib in Plexiform Neurofibroma

Historically, pNF have been difficult to treat. Agents tested to slow or reverse pNF progression in clinical trials include the farnesyl transferase inhibitor tipifarnib, the antifibrotic agent pirfenidone, the mTOR inhibitor sirolimus, and pegylated interferon alfa-2b. Of these, only pegylated interferon alfa-2b prolonged time to progression with 65% of patients in this trial demonstrating stable disease for 12 months. However, only a minority of patients (5%) achieved tumor volume reduction ≥ 20% [13, 47•, 52]. Imatinib mesylate achieved a 17% rate of ≥ 20% volume reduction primarily in patients with small baseline tumor volumes, and 30% reported symptom improvement [53].

Following promise for MEKi in the treatment of pNF in preclinical models, selumetinib was evaluated in a phase I trial including children with inoperable pNFs. The trial established a maximum tolerated dose of 25 mg/m^2/dose that was tolerable for an extended duration (median 30 cycles). In contrast to prior trials, selumetinib showed remarkable success with every patient achieving volume reduction of their pNF after a median of 20 cycles and 71% achieving ≥ 20% volume reduction [42]. Common adverse events of MEKi include dermatologic reactions, gastrointestinal side effects, and cardiotoxicity. Dose-limiting toxicities within the 20 mg/m^2 and 25 mg/m^2 dosing groups were common at 39%, compared with 25% dose-limiting toxicities in the pegylated interferon trial [42].

A subsequent phase II trial of selumetinib in children with inoperable pNF, SPRINT, evaluated PROs and functional measures (N = 50). Patients were age-matched to 93 patients in the NCI natural history study of NF1 [54••]. After a follow-up of 3 years, 84% of patients had progression-free survival compared to 15% in the controls. Six patients (12%) experienced disease progression, but only two patients failed to have tumor volume reduction as best response. Overall, 70% achieved a tumor volume reduction of ≥ 20%. The median duration to best response was 16 cycles. Seventy-four percent of patients had meaningful improvement of pain, 48% had improvement of health-related quality of life, and improvements in strength and range of motion were reported by 56% and 38% of children, respectively. Adverse events were again common with 38% of patients experiencing dose-limiting toxicity, including 10% who discontinued therapy. All toxicities (Klesse, et al. have reviewed management of MEK inhibitor toxicities) in SPRINT were reversible, but tumor regrowth after discontinuing therapy was common [54••, 55••]. A decreased ratio of circulating proangiogenic hematopoietic stem/progenitor cell populations compared to non-angiogenic circulating cells was identified as a candidate bio-marker to discriminate, early in treatment, those attaining partial response from those with stable/progressive disease [54••, supp appendix].

In comparison to historical trials and untreated patients on the NCI natural history study, the use of selumetinib achieved remarkable success with regard to tumor response and patient-reported outcomes. Selumetinib is generally safe with no irreversible toxicity and can be tolerated for long durations, with 58% of patients remaining on therapy at the time of data cut off in the phase two SPRINT trial. These results led to selumetinib being the first FDA-approved therapy for NF1-associated inoperable pNF.

Other MEKi are currently in clinical trials for pNF including trametinib (GSK-1120212), mirdametinib (PD-0325901), and binimetinib (ARRY-162) [4, 56], but many unanswered questions and challenges remain. For pNFs, adherence to prolonged therapy that commonly causes side effects is required because pNF resume growth if therapy is discontinued. Additionally, there have been no complete responses to therapy. There is a lack of information regarding late toxicities of MEKi therapy. There are no ongoing trials comparing different MEKi head-to-head, nor direct comparisons of MEKi with agents in different classes. Finally, two patients in the SPRINT trial suffered malignant degeneration to MPNST—a reminder of the disease burden carried by patients with NF1 [54••]. Nonetheless, MEK inhibition with selumetinib represents a major advance in the treatment of pNF.

Promise of Selumetinib in NF1 Low-Grade Glioma

Optic pathway gliomas account for up to 75% of NF1-related LGG and occur at a mean age of 2.7–5.4 years [57, 58]. Due to their variable clinical behavior, treatment is reserved for the 30–50% of individuals experiencing decreased visual acuity or symptoms of hypothalamic dys-function [59, 60•, 61]. Given the potential morbidity of surgery and elevated risk of secondary malignancy from radiation therapy, first-line treatment often entails carboplatin-based chemotherapy [62, 63]. The combination of carboplatin and vincristine (CV) leads to improved vision in one-third of patients, while another third will have deterioration of vision, and the remainder has stable vision [13]. Symptomatic non-optic tract gliomas not amenable to complete resection are treated with similar regimens. Historically, partial response to therapy for LGG has been defined as tumor shrinkage of 50% or more, while progressive disease is defined as a greater than 25% increase.

With advances in the understanding of LGG biology, clinical trials using targeted agents have been performed. Selumetinib was first used in a phase I trial for patients with recurrent or refractory LGG. Selumetinib was tolerable at 25 mg/m^2/dose with three dose-limiting toxicities. Across all dosing levels (25 mg/m^2, 33 mg/m^2, and 43 mg/m^2), 57% of patients remained on therapy for 1 year or longer. Four out of five patients with NF1 in this trial completed 20 or more cycles [64•]. Twenty-five patients with NF1 were enrolled in the subsequent phase II trial (NCT01089101) for patients with recurrent or refractory LGG, 13 of which had an optic pathway glioma. Nine patients achieved sustained partial response, 15 had stable disease, and one had progressive disease (Figure 1). Sixty-four percent completed all 26 cycles of treatment, and the 2-year progression-free survival in this subgroup was 96%. No patient with optic glioma had worsening of vision, and 20% had improvement [65••].

These trials of selumetinib demonstrate that LGG in NF1 can be stabilized without excess toxicity. Currently, other targeted agents are being evaluated in clinical trials including trametinib (NCT03363217), binimetinib (NCT02285439, phase I/II and NCT01885195, phase II), everolimus (NCT01158651, phase II), and anti-angiogenesis agents [66•]. To date, no targeted agents have accrued long-term outcome data. The Children's Oncology Group (COG) Protocol A9952 enrolled 127 patients with NF1-related LGG and assigned them to therapy with CV. Compared to children with sporadic LGG, those with NF1 had superior

5-year event free survival (69% vs 39%) and overall survival (98% vs 87%) [67, 68]. Given that LGG are generally indolent and exhibit progression for up to 10 years from diagnosis, it is unknown whether the favorable responses reported thus far with MEKi therapy will be durable [19••]. Thus, for now, MEKi therapy for NF1-related LGG is promising for treatment of these lesions without the use of radiation or alkylating therapy, which are both associated with second malignant neoplasms in this setting [67]. These results in a refractory population have led to the first phase III trial (NCT03871257) for targeted therapy in NF1 comparing selumetinib vs. CV for previously untreated LGG [69].

Challenges and future direction

Through improvements in the understanding of NF1 biology, collaborations between funding agencies, and thoughtful implementation of clinical trial design, therapeutic advancement of MEK inhibition for the most common causes of morbidity for patients with NF1 has been achieved, leading to FDA approval of the MEKi selumetinib for inoperable pNF.

Despite successes, significant challenges in treating patients with NF1 persist. Their life expectancy is 15 years less than the general population, a consequence of malignant neoplasms [21, 70]. Malignant pathology can arise throughout life, with juvenile myelomonocytic leukemia and rhabdomyo-sarcoma prevalent in infancy and MPNST, breast cancer, high-grade glioma, and gastrointestinal stromal tumor prevalent in young adults [44, 56].

Future Treatment Approaches and Paradigms for Preclinical Investigation

In sporadic cancers, MEKi resistance commonly develops by activation of alternative oncogenic pathways (e.g., dysregulation of the RB axis through loss of CDKN2), MEK and ERK reactivation by altered RAS proteins, and activation of receptor tyrosine kinases in response to MEK inhibition [12]. Like observations in sporadic cancer, and in mouse models of MPNST, MEKi monotherapy in malignant NF-associated lesions is not expected to lead to durable treatment response [25•].

Combining targeted agents has the potential to overcome resistance and therapeutic failures for benign and malignant lesions. Agents potentially beneficial for combination therapy in NF1-related malignancy include those targeting other signaling pathways (e.g., mTOR inhibitors) and epigenetic changes in malignant lesions (e.g., CDK4/6 and BET inhibitors) [71••, 72••]. Immunotherapy represents another promising modality for treatment of NF1-associated malignancy. *NF1* mutations have broad effects on the immune system and cytokine signaling, driven by hyperactive MAPK signaling [73, 74•]. Programmed death ligand 1 (PDL-1) is expressed in some NF1-related tumors, and tumor infiltrating lymphocytes have been observed in gliomas, neurofibromas, and MPNST [26, 75]. Currently, checkpoint inhibitor therapy is being evaluated in trials for MPNST [72••]. Immunotherapy for NF1 neoplasms may be synergistic with targeted therapy, including MEK inhibitors, or be enhanced by the application of oncolytic viruses or radiation therapy, which can serve to expose neoantigens and enhance immune infiltration in the tumor microenvironment [72••, 74•, 76, 77]. Like targeted therapy, success in treatment of NF1-

associated malignant lesions with immunotherapy may be best achieved with combination approaches.

Critical to the design of precision medicine applications for advanced NF1 pathology are the development of accurate preclinical models. As described above, the *NF1*$^{flox/flox}$;*DhhCre* murine model illustrates the potential for pNF MEKi therapy [40, 78]. Induced pluripotent stem cells reprogrammed from tumor cells have been developed and banked, and high-throughput drug screening techniques have been successfully applied to NF1 cell lines [79–81]. Cre-Lox technology has also been used to develop an optic pathway glioma model in a germline *NF1*+/− mouse model, and MPNST and high-grade gliomas have been modeled by codeletion of *NF1* with *PTEN* or *TP53* [18•, 22•, 26••, 58, 82]. However, these models may not capture the full context of NF1-related malignancies, such as epigenetic alterations, so there is interest in expanding patient-derived xenograft (PDX) models [22•]. PDX models permit application of combination agents but lack an immune microenvironment. Investigations of immunotherapy can be assessed in immunocompetent animal models engrafted with syngeneic tumor cell lines.

Genetically engineered mice have additional limitations in the study of cancer, as reviewed by Watson, et al. [83]. In addition to fundamental differences at the molecular and cellular level, limitations include anatomical differences limiting disease modeling, variations in pharmacokinetic and pharmacodynamic (PD) properties making therapeutic translation challenging, and small size limiting investigations into novel imaging or surgical techniques [83]. Swine (*Sus scrofa*) models provide solutions to many of these issues. Swine have greater genetic homology with humans and are more anatomically representative. Genetically engineered swine have been established to model NF1, and these minipigs phenotypically display clinical features of NF1 present in patients, which is unique compared to other NF1 models. These pigs develop café au lait macules, neurofibromas, and optic pathway gliomas. Importantly, tumor cells undergo spontaneous loss of heterozygosity mimicking the “second-hit” phenomenon that occurs in humans [84••].

Swine models of NF1 present many opportunities for developing therapies to treat NF1. First, the cutaneous manifestations provide an opportunity to address cNF. Active trials include oral selumetinib for adults with cNF (NCT02839720) and the topical MEKi NFX-179 (NCT04435665) to assess PD changes in adults with cNF. Further development of topical therapies will be of great benefit for patients to address this lifelong complication. For systemic therapy, MEKi can be administered orally, as in human patients, and selumetinib has shown PK properties that reflect what is seen in human patients (publication pending). Second, the size of the pig allows for eloquent studies of PK/PD in target tissues. For example, we have been able to successfully characterize the PK/PD of selumetinib in target tissues, including optic nerve and sciatic nerve. Thus, these types of studies can also inform investigators as too the ability of a drug to cross the blood-brain barrier. Additionally, the faithful development of NF1 features and the long lifespan of the pig permits the study of prophylactic interventions for NF1 pathology.

Many significant challenges exist in developing combination therapies, including determining whether drug combinations are safe and effective [85]. Swine models have

great potential to address these challenges, as PK, PD, and toxicity can all be measured in a human-sized animal that shows the clinical features of NF1. On a final note, while the focus for NF1 therapy has been on kinase inhibitors, advancements in gene therapy for NF1 are underway, and the NF1 swine model will likely serve as a critical preclinical model, to establish appropriate delivery measures, as well as preclinical safety and efficacy prior to clinical trials [86].

Conclusions

Over the past three decades, advancements in the understanding of NF1 started with the discovery of the *NF1* gene and have culminated with the first precision medicine approval for NF1-related pathology, specifically selumetinib for inoperable plexiform neurofibroma. The success of MEKi therapy in NF1 has been spurred by coordinated funding and research for this rare disease and development of relevant endpoints for clinical trial design. NF1 is a multisystem disease and tumor predisposition syndrome, and numerous challenges remain. Malignant neoplasms remain the leading cause of mortality in NF1. To continue improving outcomes, the recent development of sound preclinical models holds promise to translate targeted and combination approaches, taking advantage of advanced understanding of the molecular and immunologic landscape of these diseases.

Declarations

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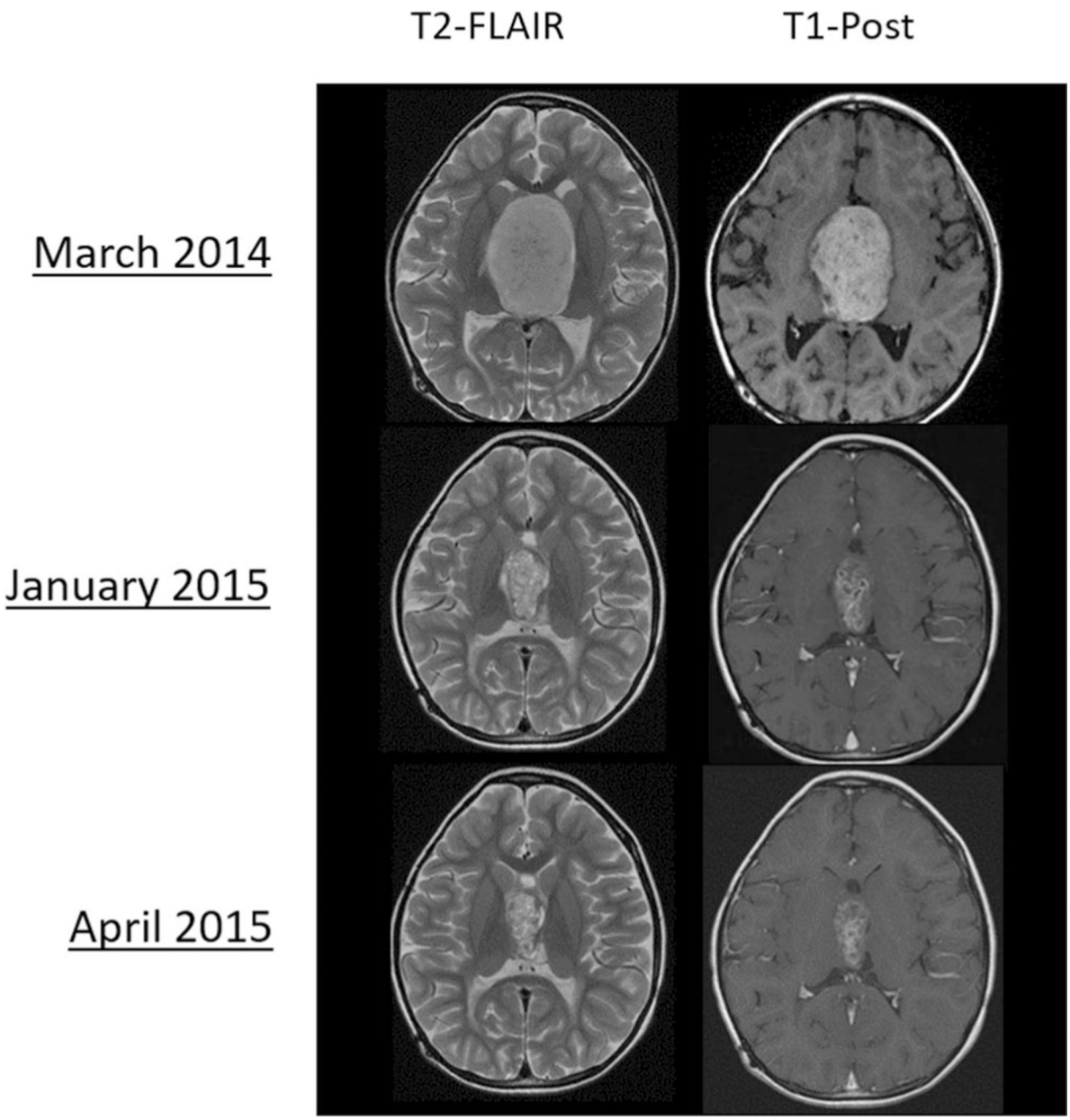

Fig. 1.

PBTC-029 phase 2, stratum 3 (recurrent NF1-associated low-grade glioma): Example of radiographic response with selumetinib monotherapy. Reproduced with permission by Dr. Jason Fangusaro and the Pediatric Brain Tumor Consortium

Table 1

Active clinical trials listed on clinicaltrails.gov (as of Oct 2020) involvingMEK inhibitors, for which NF1-related indications are eligible. This list is organized by NF1 focus. *cNF* cutaneous neurofibroma, *HGG* high-grade glioma, *JMML* juvenile myelomonocytic leukemia, *LGG* low-grade glioma, *MPNST* malignant peripheral nerve sheath tumor, *OPG* optic pathway glioma, *pNF* plexiform neurofibroma

Trial identifier	Drug(s)	Indication	Phase	Population	NF specific focus
NCT03433183	Selumetinib, sirolimus	MPNST	II	≥12 years	Yes
NCT03962543	Mirdametinib	Inoperable pNF	II	≥2 years	Yes
NCT03190915	Trametinib	Relapsed/refractory JMML	II	≥1 months	Yes
NCT02124772	Trametinib	Refractory pNF	I/II	≥1 month to ≤17 years	Yes
NCT03326388	Selumetinib	Inoperable pNF, progressive OPG	I/II	≥3 years to ≤18 years	Yes
NCT03231306	Binimetinib	Symptomatic pNF	II	≥1 years	Yes
NCT01089101	Selumetinib	Relapsed/refractory LGG	I/II	≥3 to ≤21 years	Yes
NCT02839720	Selumetinib	Symptomatic cNF	II	≥18 years	Yes
NCT02285439	Binimetinib	Advanced solid tumors and relapsed/refractory LGG	I/II	≥1 to ≤18 years	Yes
NCT04201457	Trametinib, dabrafenib, hydroxychloroquine	Recurrent LGG or HGG	I/II	≥1 to ≤30 years	Yes
NCT02407405	Selumetinib	Inoperable pNF	II	≥18 years	Yes
NCT04435665	NFX-179 (topical)	cNF	II	≥18 years	Yes
NCT03741101	Trametinib	pNF	II	≥1 to <18 years	Yes
NCT03871257	Selumetinib	NF1-associated LGG	III	≥2 to ≤21 years	Yes
NCT03363217	Trametinib	pNF and relapsed/refractory LGG	I/II	≥1 month to ≤25 years	Yes
NCT04216953	Cobimetinib, atezolizumab	Advanced soft tissue sarcoma	I/II	≥6 months	No
NCT03516123	CS3006	Advanced solid tumors	I	≥18 years	No
NCT03875820	RO5126766, VS-6063	Advanced solid tumors	I	≥18 years	No
NCT03905148	Mirdametinib, BGB-283	Advanced solid tumors	I	≥18 years	No
NCT02079740	Trametinib, navitoclax	Advanced solid tumors	I/II	≥18 years	No
NCT01364051	Selumetinib, cediranib	Advanced solid tumors	I	≥18 years	No
NCT03736850	CS3006	Advanced solid tumors	I	≥18 years	No
NCT03976050	HL-085	Advanced solid tumors	I	≥18 years	No
NCT01586624	Selumetinib, vandetanib	Advanced solid tumors	I	≥18 years	No
NCT03839342	Binimetinib, encorafenib	Advanced solid tumors	II	≥18 years	No
NCT02070549	Trametinib	Advanced solid tumors	I	≥18 years	No

Trial identifier	Drug(s)	Indication	Phase	Population	NF specific focus
NCT04485559	Trametinib, everolimus	Relapsed/refractory LGG		≥1 to ≤25 years	No
NCT03108131	Cobimetinib, atezolizumab	Advanced solid tumors	II	≥18 years	No
NCT03434262	Trametinib, ribociclib (stratum B)	Recurrent/refractory HGG	I	≥1 to ≤39 years	No
NCT01827384	Trametinib	Advanced solid tumors	II	≥18 years	No