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Plexiform neurofibromas in neurofibromatosis type 1: current and emergent therapeutic strategies

Hannah Kim[1], Julia Polen[2], Gurcharanjeet Kaur[3]

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Abstract

Neurofibromatosis type 1-associated plexiform neurofibromas cause significant morbidity and carry a risk of malignant transformation. Early targeted agents failed to demonstrate efficacy, safety, or durable responses until the discovery of mitogen-activated protein kinase kinase (MEK 1/2) inhibitors. Selumetinib and mirdametinib are approved medical therapies that can potentially reduce tumor volume and symptoms, improve patient-reported outcomes, and have manageable toxicities. An indirect comparison between selumetinib and mirdametinib suggests differences in efficacy and safety, but direct confirmatory head-to-head trials are needed. Active clinical trials in the pipeline are exploring other targets in the MEK pathway, along with combination therapies. Key priorities include the impact of malignant peripheral nerve sheath tumor risk, defining long-term safety, durability off therapy, predictors of response and resistance, and implementation of multidisciplinary care.

INTRODUCTION

Neurofibromatosis type 1 (NF1) is a rare neurogenetic disorder that affects approximately 1 in 2,500 individuals worldwide[1]. This genetic defect causes a wide range of clinical manifestations, including, but not limited to, nervous system tumors, skeletal manifestations, vasculopathies, seizures, headaches, and learning disabilities. One hallmark manifestation of NF1 is the development of plexiform neurofibromas (PNs), which occurs in 30%-60% of individuals with NF1[1,2]. Although benign, PNs can cause substantial morbidity due to pain, motor or sensory impairment, disfigurement, and compression of vital anatomical structures including the spinal cord, airway, or major blood vessels. More importantly, 8%-13% of the PNs may transform into malignant peripheral nerve sheath tumors (MPNSTs), a type of aggressive sarcoma associated with high morbidity and mortality rates[1]. Historically, treatment options have been limited to surgical resection, which carries significant risk in many patients because of the location of the tumors. Recent targeted therapies have introduced a new era of pharmacologic management.

[1]William Carey University College of Osteopathic Medicine, Hattiesburg, MS 39401, USA.
[2]School of Nursing, Elon University, Elon, NC 27244, USA.
[3]Department of Neurology, Columbia University Irving Medical Center, New York, NY 10032, USA.

Correspondence to: Dr. Gurcharanjeet Kaur, Department of Neurology, Columbia University Irving Medical Center, New York, NY 10032, USA. E-mail: gk2626@cumc.columbia.edu

Table 1. Summary of drugs previously trialed, FDA-approved, and currently in the pipeline. Partial response for all trials was defined as ≥ 20% reduction

Drug name	Mechanism of action	Trial phase	Outcome	Refs.
Sirolimus	mTOR inhibitor	Phase II, completed	No significant tumor shrinkage or clinical benefit	[4]
Imatinib	Tyrosine kinase inhibitor	Phase II, completed	Partial response (PR) in 17% of intent-to-treat, and 26% in patients treated for ≥ 6 months; 30% subjective improvement in symptoms and function	[5]
Pirfenidone	Antifibrotic, anti-inflammatory, antioxidant	Phase II, completed	No objective responses (no tumor volume reduction or improvement in QoL)	[6]
Tipifarnib	Farnesyltransferase inhibitor	Phase II, completed	Improvement in QoL but no significant change in time to progression of tumor volume	[7]
Sunitinib	Multi-targeted tyrosine kinase inhibitor	Phase II, terminated	Trial terminated because of death of uncertain cause but possibly related to drug	[8]
Selumetinib	MEK 1/2 inhibitor	FDA approved (pediatrics and adults)	70% of the patients achieved PR; 48% improvement in child-reported health-related QoL 20% objective response rate; meaningful pain intensity reduction	[9,12-14]
Mirdametinib	MEK 1/2 inhibitor	FDA approved (pediatrics and adults)	52% PR in pediatrics, 41% PR in adults, defined as ≥ 20% reduction in tumor volume	[10,15]
Binimetinib	MEK 1/2 inhibitor	Phase II, completed	74% of the patients achieved PR	[19,25]
Cabozantinib	Receptor tyrosine kinase inhibitor (VEGF, MET, TAM, RET)	Phase II, completed	42% (8/19) in adolescents and adults; No significant change in global QoL scores; 3-point decrease in worst tumor-pain in the PR group	[21]
Cabozantinib + Selumetinib	Combination therapy with receptor tyrosine kinase inhibitor and MEK 1/2 inhibitor	Phase I, Ib, 2; Not yet recruiting	No data yet but assessing the synergistic effects of cabozantinib with selumetinib	[22]
Healx	Mitochondrial modulation, multi-pathway	Phase 2, recruiting	No data yet	[20]

mTOR: Mechanistic target of rapamycin; MEK 1/2: mitogen-activated protein kinase kinase; FDA: food and drug administration; QoL: qualitiy of life.

DRUGS THAT WERE PREVIOUSLY TRIALED

Developing effective treatments for NF1-associated PNs has remained an ongoing challenge[3]. Although several targeted agents showed preclinical or early-phase promise, most failed to demonstrate sufficient efficacy or acceptable safety to support regulatory approval, reflecting the complexity of PN biology and underscoring the limitations inherent to dysregulated Ras signaling[3].

For example, sirolimus, a mechanistic target of rapamycin (mTOR) inhibitor, was evaluated in a Phase II trial for patients with progressive PNs and showed no significant clinical benefit or tumor shrinkage [Table 1][4]. Imatinib, a tyrosine kinase inhibitor, showed a partial response in some patients, suggesting some therapeutic potential[5]. However, the modest and variable responses underscore tumor heterogeneity and limit generalizability, and highlight the need for biomarker-guided, personalized approaches. Pirfenidone, an antifibrotic agent with anti-inflammatory and antioxidant properties, showed no significant reduction in tumor volume or enhanced quality of life compared to placebo[6].

Other pathway-directed strategies also proved unsuccessful. Tipifarnib, a farnesyltransferase inhibitor, did not significantly prolong time to progression of PNs; however, it was well tolerated and was associated with some improvements in quality of life, suggesting a potential in supportive care[7]. Sunitinib, a multi-targeted tyrosine kinase inhibitor, was terminated early due to a patient death of uncertain cause with no meaningful response observed[8]. Given limited efficacy, safety concerns, and non-durable response, earlier agents were not adopted into practice until the recent success of mitogen-activated protein kinase kinase (MEK 1/2) inhibitors.

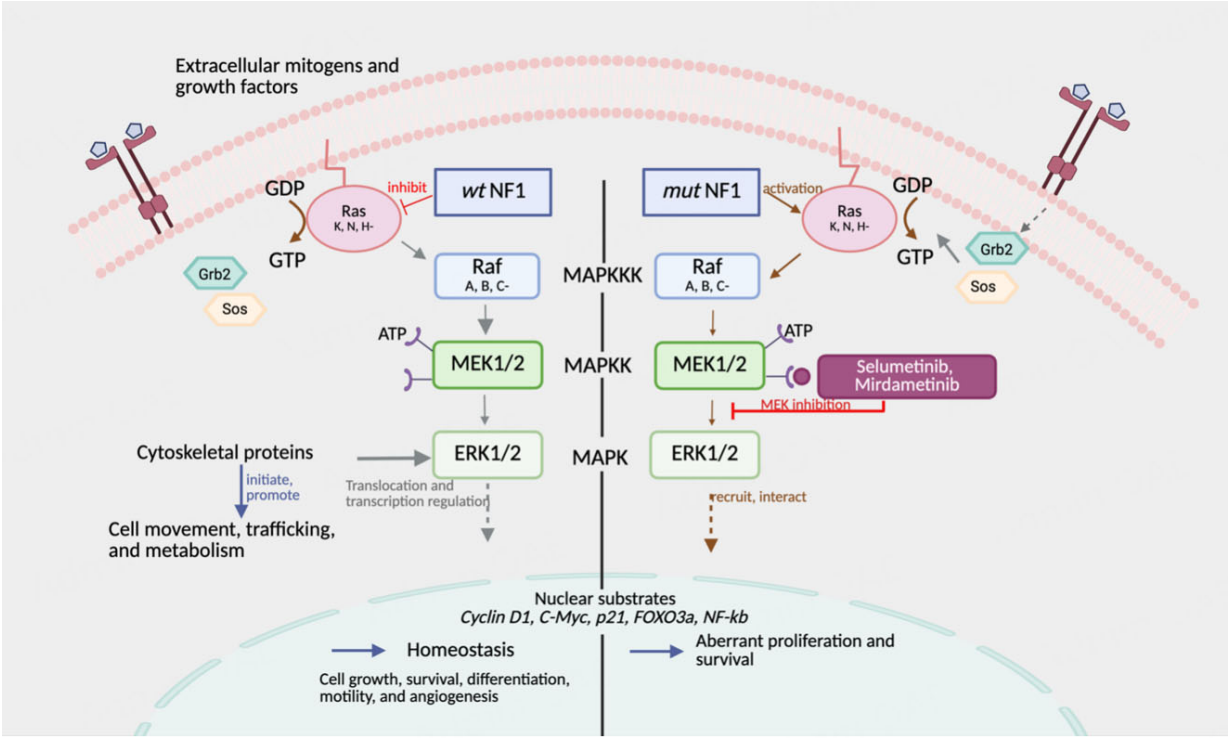

Figure 1. Mechanism of MEK inhibition by selumetinib and mirdametinib. Loss of NF1 function leads to overactive Ras signaling, promoting tumor growth. Created in BioRender. Kim, H. (2025) https://BioRender.com/796ondy. NF1: Neurofibromatosis type 1; MEK 1/2: mitogen-activated protein kinase kinase; ERK: extracellular signal-regulated kinase.

APPROVED MEK INHIBITORS

The emergence of MEK1/2 inhibitors, selumetinib and mirdametinib, has led to Food and Drug Administration (FDA)-approved therapies for patients with symptomatic, inoperable PNs [Table 1][9,10]. MEK inhibitors are allosteric inhibitors of MEK1 and MEK2. MEK1/2 function within the mitogen-activated protein kinase (MAPK) signaling cascade, referred to as the Rat sarcoma (RAS)-rapidly accelerated fibrosarcoma (RAF)-mitogen-activated protein kinase kinase (MEK)-extracellular signal-regulated kinase (ERK) pathway, which regulates cellular growth, differentiation, proliferation, and survival [Figure 1][9,11]. In NF1, Ras signaling becomes dysregulated due to loss or reduced activity of neurofibromin, leading to prolonged and uncontrolled downstream MAPK activation and growth of peripheral nerve sheath tumors in some individuals. By inhibiting MEK1/2, selumetinib and mirdametinib prevent downstream activation of ERK, thereby suppressing cell proliferation and angiogenesis and producing tumor shrinkage and disease stabilization[9,11].

Selumetinib (Koselugo), approved on April 10, 2020, was the first FDA-approved therapy for PNs for pediatric patients ≥ 2 years with symptomatic, inoperable PNs [Table 1][9]. The approval was based on results from the Phase II SPRINT trial (NCT01362803), in which 70% of the patients achieved partial response, defined as a ≥ 20% reduction in tumor volume on volumetric magnetic resonance imaging (MRI), with the median tumor volume-reduction of 27.9%[9,12]. Notably, 56% of participants had a durable response lasting ≥ 12 cycles (approximately 1 year)[12]. Progression-free survival at 3 years was substantially higher in patients taking selumetinib compared with a matched natural-history cohort from the National Cancer Institute (NCI), in which 78% of untreated individuals had ≥ 20% tumor growth with median progression-free survival of 1.3 years[12]. In addition to tumor shrinkage, there were clinically meaningful improvements in

Table 2. Most common side effects of mirdametinib and selumetinib[26]

Side effect	Selumetinib	Mirdametinib
Cardiac (decreased ejection fraction/shortening fraction)	38% (Grade 1-2); 2% (Grade 3)	Not reported to date
Diarrhea	54% (Grade 1-2); 4% (Grade 3)	Not reported to date
Fatigue	56% (Grade 1-2)	26% (Grade ≥ 2)
Nausea/vomiting	44% (Grade 1-2)	21% (Grade ≥ 2)
Ophthalmologic	No dose limiting toxicity	No dose limiting toxicity
Paronychia	38% (Grade 1-2); 6% (Grade 3)	Not reported to date
Rash/skin toxicity	52%-58% (Grade 1-2); 4%-10% (Grade 3)	53% (Grade ≥ 2)

mTOR: Mechanistic target of rapamycin; MEK 1/2: mitogen-activated protein kinase kinase; FDA: food and drug administration.

function, pain, and disfigurement in the majority of patients, highlighting the impact beyond tumor shrinkage[12]. More recently, selumetinib has been approved for adults with PNs in November 2025[13]. In the randomized KOMET study (NCT04924608), selumetinib achieved objective response rate (ORR) of 20% (95% confidence interval (CI): 11, 31) by end of cycle 16, with 86% of the responders maintaining a durable response of ≥ 6 months[13,14]. Further, individuals who had chronic pain scores of ≥ 3 reported meaningful reduction in pain[14].

Mirdametinib (Gomekli) was recently approved on February 11, 2025, for adults and pediatric patients ≥ 2 years with symptomatic, non-resectable PNs[10]. In the ReNeu clinical trial (NCT03962543), the confirmed partial response rate was 52% (29/56) in pediatrics and 41% (24/58) in adults, with 75% of individuals maintaining durable response for ≥ 12 months[10,15]. The median reduction in tumor volume was 41% (range, -90 to 13)[15]. Patient-reported outcomes showed clinically meaningful improvements in pain severity, interference, and health-related quality of life, similar to the pediatric findings with selumetinib[15].

Tolerability and safety considerations

Both drugs were generally well tolerated, but adverse events (AEs) are common[9,12,15,16]. Common AEs include gastrointestinal upset, xerosis, fatigue, muscle pain, acne, stomatitis, paronychia, and headache. Most were Grade 1-2 with the use of NCI common terminology criteria for adverse events (CTCAE) v 4/5 [Table 2][12,15]. However, about 10% of patients taking selumetinib and 9% of adults and 14% of children taking mirdametinib discontinued treatment because of toxicity[12,15], underscoring the need for proactive AE prevention and dose modification.

Comparative effectiveness and implications

In an indirect treatment comparison, using matching-adjusted indirect comparison (MAIC) and simulated treatment comparison (STC), mirdametinib demonstrated a significantly greater mean best reduction in tumor volume compared to selumetinib (MAIC: -36.0% *vs.* -22.8%; STC: -36.2% *vs.* -22.8%)[17].

Dose reductions due to treatment-related adverse events (TRAEs) were significantly lower in mirdametinib (MAIC: 12% *vs.* 28%, odds ratio [OR] = 0.355, $P = 0.048$; STC: 11% *vs.* 28%, OR = 0.309, $P = 0.028$). Several common TRAEs, including acneiform rash, diarrhea, nausea, vomiting, fatigue, stomatitis, and elevated creatine phosphokinase, occurred less frequently. No significant differences in ORR or selected safety outcomes (paronychia, alopecia, neutropenia, asymptomatic left ventricular ejection fraction (LVEF) decline) were observed[17]. Since the drugs were not tested in the same study and patient differences may bias results, the findings should be validated in head-to-head trials and could be strengthened through biomarker-informed studies.

Long-term considerations

Longer-term tolerability, resistance, and toxicity of MEK inhibitors have not been well studied. Emerging follow-up data on selumetinib demonstrate that only four participants (5.4%) experienced > 20% of tumor growth over seven years, with sustained improvements in PN-related pain intensity and reduced pain interference[18]. No new safety signals were identified during long-term follow-up; however, some known toxicities of selumetinib were observed for the first time after years of therapy, reinforcing the need for continued surveillance[9,19]. Further, little is known about tumor regrowth after treatment discontinuation and the mechanisms of primary or acquired MEK inhibitor resistance. While MEK1/2 inhibitors have marked significant advances in treatment of PNs, non-responders underscore the need for alternate RAS-pathway agents and other novel mechanisms, which are currently under investigation in clinical trials.

DRUGS IN THE PIPELINE

Several therapies are currently in clinical trials for NF1-associated PNs with efforts focused both on expanding the utility of MEK inhibitors and exploring alternative therapeutic targets. Within MEK inhibitors, binimetinib (MEK162) has shown partial responses (≥ 20% volumetric reduction) in Phase II cohorts [Table 1][20]. Healx Limited is investing in artificial intelligence (AI)-driven drug discovery approaches that target mitochondrial dysregulation to inhibit the growth of NF1 cells by modulating various pathways involved in tumor development[19]. Beyond MEK inhibition, cabozantinib, a multi-kinase inhibitor, has shown tumor-volume reduction, improved quality of life, and minimal adverse effects[21]. The results suggested that cabozantinib has clinical activity in reducing tumor burden and alleviating pain in NF1-associated PNs, particularly in adolescents and adults. Along with monotherapies, combination strategies are underway; cabozantinib in combination with selumetinib will assess the tolerability, synergy, and efficacy as a dual therapy[22].

CONCLUSIONS AND FUTURE DIRECTIONS

The therapeutic landscape for PNs has rapidly evolved since 2020, largely driven by the success of MEK1/2 inhibitors such as selumetinib and mirdametinib. These agents have redefined the standard of care for NF1-associated inoperable PNs by demonstrating clinically meaningful tumor shrinkage, disease stabilization, and improved quality of life. However, no studies to date evaluate whether MEK inhibition can prevent or delay malignant transformation.

MPNSTs are aggressive sarcomas with high morbidity and mortality, which arise from pre-existing PNs[1,2]. Although all individuals with NF1 carry a lifetime risk of approximately 8%-13%, patients with internal PNs have a 20-fold greater risk of transformation compared with other patients without internal PNs and compared to the general public without NF1[1,2]. Complete surgical resection remains the only potentially curative option, yet 5-year overall survival remains poor even after excision, and no FDA-approved systemic therapies are available for MPNSTs[1,2]. Further research is needed to understand the mechanisms driving resistance to MEK inhibitors and biomarkers that can inform individualized strategies. Emerging liquid-biopsy approaches using cell-free DNA (cfDNA) suggest that copy-number alteration-based assays can only identify MPNST, whereas fragmentomic signatures may distinguish premalignant stages from benign PNs (e.g., atypical neurofibroma) noninvasively, enabling early intervention[23]. Prospective, multicenter validation is needed to establish cfDNA as a routine surveillance tool and enable risk-adapted management of PNs.

As the pipeline for novel and targeted therapies continues to grow, development should not only be evaluated for volumetric response and symptomatic improvement, but also for the reduction in malignant transformation risk and early detection of resistance using biomarkers, such as cfDNA or fragmentomic

signatures. Finally, there is a critical need to develop therapeutic strategies beyond pharmaceutical interventions including early pain interventions, physical and occupational rehabilitation, psychosocial support groups, and integrative care models to fully address the needs of individuals with NF1-associated PNs across their life span.

Preclinical work suggests that restoring the missing neurofibromin gene could reduce PN burden and alleviate symptoms[24]. In an NF1 xenograft model, an engineered adeno-associated virus for NF (AAV-NF) (K55) vector showed reduced hepatic uptake and enhanced tumor targeting, improving intratumoral delivery bringing gene therapy a step closer to first-in-human clinical trials[24]. Sustained collaboration among patients, researchers, and philanthropic partners, such as the Children's Tumor Foundation and the Gilbert Family Foundation, will accelerate the development of these promising treatment strategies and may ultimately lead to a cure for NF1.

DECLARATIONS

Authors' contribution

Original draft preparation, reviewing, editing: Kim H
Assisted with draft preparation, reviewing and editing: Polen J
Assisted with draft preparation, supervision, reviewing, and editing: Kaur G

Availability of data and materials

Not applicable.

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During the preparation of the manuscript, the authors used ChatGPT (OpenAI) solely for language clarity and readability. After using this tool, the authors reviewed and edited the content and take full responsibility for the content of the published article.

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Conflicts of interest

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Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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