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# MEK inhibitors for neurofibromatosis type 1 manifestations: Clinical evidence and consensus

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**Abstract**

The wide variety of clinical manifestations of the genetic syndrome neurofibromatosis type 1 (NF1) are driven by overactivation of the RAS pathway. Mitogen-activated protein kinase kinase inhibitors (MEKi) block downstream targets of RAS. The recent regulatory approvals of the MEKi selumetinib for inoperable symptomatic plexiform neurofibromas in children with NF1 have made it the first medical therapy approved for this indication in the United States, the European Union, and elsewhere. Several recently published and ongoing clinical trials have demonstrated that MEKi may have potential benefits for a variety of other NF1 manifestations, and there is broad interest in the field regarding the appropriate clinical use of these agents. In this review, we present the current evidence regarding the use of existing MEKi for a variety of NF1-related manifestations, including tumor (neurofibromas, malignant peripheral nerve sheath tumors, low-grade glioma, and juvenile myelomonocytic leukemia) and non-tumor (bone, pain, and neurocognitive) manifestations. We discuss the potential utility of MEKi in related genetic conditions characterized by overactivation of the RAS pathway (RASopathies). In addition, we review

practical treatment considerations for the use of MEKi as well as provide consensus recommendations regarding their clinical use from a panel of experts.

**Keywords**

low-grade glioma | MEK inhibitors | neurofibromatosis type 1 | plexiform neurofibromas | RASopathy

Neurofibromatosis type 1 (NF1) is a common autosomal dominant tumor predisposition syndrome occurring in approximately 1:3000 individuals.[1] It is caused by haploinsufficiency of the *NF1* gene, which results in RAS pathway overactivation and contributes to tumor formation as well as other conditions associated with NF1, including neurocognitive deficits and bony changes.[2,3] NF1 follows the classic tumor suppression paradigm in tumorigenesis with benign and advanced cancers invariably showing somatic inactivation of the normal allele. Inhibition of the mitogen-activated protein kinase kinase (MEK), downstream of RAS, has recently been shown to shrink NF1-associated plexiform neurofibromas (PN), leading to the regulatory approvals of selumetinib specifically for symptomatic and inoperable PN in children. The recent success of selumetinib and evidence of efficacy from other MEK inhibitors (MEKi) has led to questions of how MEKi can best be used to ameliorate the varied manifestations of NF1. Clinical features of NF1 may differ in underlying pathogenesis, and many non-tumor manifestations may be the result of *NF1* haploinsufficiency rather than complete *NF1* loss which may impact treatment approaches.[4,5] We assembled an international, multidisciplinary panel of experts to review the existing evidence for the use of MEKi in NF1-associated tumor and non-tumor manifestations and develop consensus-based, evidence-driven recommendations for their use and monitoring (see Supplementary Material). (Consensus recommendations from this group are summarized Consensus Recommendations for the Use of MEK Inhibitors for NF1 Manifestations).

## Comparison of Different MEKi

Available MEKi are derived from the same chemical scaffold and share many pharmacologic properties. Five MEKi are compared in Table 1, all of which are orally available with similar metabolism and excretion, but variable half-lives. All five agents have a similar side effect profile that includes rash, paronychia, decreased cardiac function, and laboratory abnormalities (including creatine kinase [CK] elevation and liver dysfunction). Although the results of preclinical brain penetrance studies vary between MEKi, these studies have not reliably predicted activity against central nervous system tumors.

While MEKi have been extensively explored in adults with BRAF-driven melanoma and other malignancies, experience in children and in individuals with NF1 is limited. Clinical trials in these populations frequently use doses below the recommended adult dose for cancer, making a direct comparison with adult cancer data difficult. Recent evidence also suggests that MEKi alter the tumor immune environment which may contribute to their efficacy in addition to direct tumor effect.[31–33] Despite chemical similarities, different MEKi may have important clinical differences. While most MEKi show promise for NF1-associated indications, there have been no attempts yet to directly compare the clinical efficacy, toxicities, and effect on tumor immune microenvironment among MEKi. Currently, formulation (particularly child-appropriate versions), availability (both from regulatory bodies and through insurance coverage), and specific clinical experience in NF1 indications may be the most important distinguishing features among these MEKi.

## Tumor-specific Uses of MEKi

### Plexiform Neurofibromas

Benign peripheral nerve sheath tumors known as PNs are one of the most common tumor-related manifestations of NF1 and can cause significant morbidity.[34] Somatic inactivation of the normal *NF1* allele in Schwann cells,[35,36] leading to RAS pathway activation, is thought to be a key initiating event in PN pathogenesis. Targeted inhibition of the RAS pathway has resulted in tumor shrinkage in murine models of NF1 neurofibromas treated with either mirdametinib or selumetinib.[20,37]

Preclinical models have supported clinical trials of several MEKi in NF1-associated PN. Selumetinib showed a partial response (PR; >20% decrease by volumetric MRI) in 17 of 24 (71%) participants in a phase 1 trial[20] and 34 of 50 (68%) participants in the subsequent phase 2 study.[22] Selumetinib also prolonged progression-free survival, as no participants in the phase 2 trial had tumor progression in the first year of treatment despite 21 participants having tumors that were known to be growing at the time of study entry. Individuals receiving selumetinib showed a clinically meaningful improvement in outcome measures, such as patient-reported pain, as well as improvements in pulmonary function testing, strength, and range of motion. Though most participants receiving selumetinib had at least one treatment-related adverse event, the majority of these were mild (grade 1-2) and did not result in dose modification or drug discontinuation.[22] Results of this study led to the regulatory approvals of selumetinib for pediatric patients with NF1 and inoperable PN.

## Consensus Recommendations for the Use of MEK Inhibitors for NF1 Manifestations

### Tumor Manifestations

- MEKi are approved for the treatment of symptomatic, inoperable PN in children; their use in asymptomatic, growing, inoperable PN may be appropriate based on the clinical situation.
- There is no evidence to suggest that monotherapy with MEKi will prevent or successfully treat MPNST.
- MEKi are effective in treating NF1-LGG but are best used in the context of a clinical trial or for relapsed disease since their effect on functional outcomes and long-term tumor control are unknown.

### Non-tumor Manifestations

- Little clinical data are available for the impact of MEKi on bony manifestations of NF1 and careful monitoring of skeletal manifestations during treatment and in future clinical trials is recommended.
- PN-associated pain may be a potential indication for MEKi treatment but should be monitored systematically with validated pain measures.
- Based on current data, there is no evidence of neurotoxicity with MEKi treatment in children and young adults. Further studies are needed to evaluate any potential neurocognitive benefit.

### Practical Treatment Issues

- PN and LGG response may be gradual, but patients that respond to MEKi generally show clinical or radiographic response within 1 year.
- Most studies have been treated for 2 years or more for PN or LGG. PN growth often resumes after treatment is suspended, but response may be more durable in LGG.
- MEKi are overall well tolerated with regular screening and management of toxicities but should be held for clinically significant toxicities and can be restarted at a lower dose once the toxicity improves. Long-term safety is still being evaluated.

While selumetinib is the only currently approved treatment for this indication in children, evidence suggests that other MEKi are also likely to be similarly effective. In a phase 1/2A study, trametinib showed a PR in 12 of 26 (46%) children with NF1-associated PN.[27] Interim results of a phase 2 trial of binimetinib (NCT03231306) for progressive or symptomatic PN show a similar response rate in children (70%)[38] and adults (65%).[6] In participants ≥16 years old with progressive or symptomatic PN, the response rate to mirdametinib was 42% (8 of 19 participants).[16] While not directly comparable, interim results of a phase 2 trial of selumetinib (NCT02407405) in adults with symptomatic, inoperable PN show a 69% response rate.[39] Results of ongoing clinical trials of mirdametinib (NCT03962543) in children and adults with PN have yet to be reported. The use of MEKi for symptomatic PN in adults or for asymptomatic but growing and inoperable PN may be appropriate, but results from prospective studies are needed.

## Atypical Neurofibromas

Atypical neurofibromas (AN) are defined based on histopathological features including increased cellularity and cellular atypia in the absence of malignant features. Many AN demonstrate deletion of *CDKN2A/B*.[40] While less common than PN, AN are important in NF1 because they may be precursor lesions for transformation to malignant peripheral nerve sheath tumors (MPNST).[41] Many AN show increased avidity on 18F-fluorodeoxyglucose PET scans relative to PN, and frequently appear as distinct nodular lesions (DNL) on MRI.[42]

Mouse models of AN have explored the role of MEKi alone and in combination with other agents.[43,44] Clinical trials have also evaluated responses of DNL and AN to MEKi, suggesting that some DNL or AN may respond to MEKi.[45] However, prospective studies are needed to define the response rate and compare efficacy to PN and other tumors.[16,20,22,39] If surgery is not feasible, treatment of AN/DNL with a MEKi can be considered given the possibility of response based on this preliminary data. Prior to initiating therapy, ruling out MPNST is imperative, and patients should be closely monitored to assess response to therapy.

## Malignant Peripheral Nerve Sheath Tumors

MPNST occur in roughly 10% of individuals with NF1, often arise from preexisting PN or AN, and are the leading cause of death for people with NF1.[46,47] Multiple MPNST preclinical models have evaluated treatment with MEKi alone and in combination with other agents. Despite inhibition of cell growth in MPNST cell lines with MEKi,[48,49] xenograft and genetically engineered mouse models of MPNST treated with single-agent MEKi produced limited or no growth

**Table 1.** Comparison of Dosing, Pharmacologic Characteristics, and Clinical Trial Experience of Five MEK Inhibitors

| Agent | Available Formulations | Dosage in NF1 | Adult Cancer Dosage | Available Literature and Use in NF1 | Dosage Forms | CNS Penetration | Grade 3/4 AEs (>5%) | Half-life | Metabolism | Excretion | Distinguishing Features | Availability and Approval |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Binimetinib (MEK162, ARRY-162) | Tablet; pharmacy-prepared suspension | 32 mg/m$^2$/dose BID continuous (max dose 45 mg PO BID) (For adults with PN, max dose 30 mg PO BID[6]) | 45 mg PO BID (melanoma) | Adult trials in colorectal cancer (>200 pts treated with binimetinib in combination)[7] Pediatric phase 1 (19 pts, 17 with LGG)[8] | 15 mg | Diffuse penetration (brain and tumor) in rodent model[8] | Anemia, fatigue, dyspnea[9] | 3.5 hours[10] | UGT1A1 glucuronidation. Active metabolite produced by CYP1A2 and CYP2C19.[10] | Feces and urine[10] | Transient muscle weakness may be a common drug-specific and pediatric-specific toxicity | FDA and EMA approved in combination with encorafenib for BRAF-mutant melanoma |
| Cobimetinib (GDC-0973, XL-518) | Tablet | 60 mg PO QD (21 days on, 7 days off) | 60 mg PO QD (21 days on, 7 days off) (melanoma) | Adult trials in melanoma (>200 pts received cobimetinib in combination)[11,12] | 20 mg | Brain to plasma ratio (Kp) at 6-hour post-dose was 0.3 in WT mice[13] | Diarrhea, rash, fatigue[14] | 43.6 hours[15] | CYP3A4, also by direct glucuronidation via UGT2B7[15] | Feces via biliary excretion[15] | | FDA and EMA approved in combination with vemurafenib for metastatic melanoma |
| Mirdametinib (PD-0325901) | Capsule and liquid formulations available | 2 mg/m$^2$/dose bid (max 4 mg) 3 weeks on, 1 week off | 15 mg BID, 5 days on/2 days off, 3 weeks on, 1 week off (NSCLC) | Phase 2 (19 with NF1-PN)[16] | 1 mg | Excellent penetration at clinically relevant doses[17] | Lymphopenia, dehydration, fatigue, diarrhea, rash, confusion, dyspnea, hallucination, alkaline phosphatase abnormality, hyponatremia, hypocalcemia[18] | 8.6 hours[19] | Glucuronidation and oxidation[19] | Feces via biliary excretion[19] | Can be administered with food, excellent CNS penetration | Not FDA or EMA approved |
| Selumetinib (AZD6244, ARRY-142886) | Capsule | 25 mg/m$^2$ PO BID continuous (max dose 50 mg PO BID) | 75 mg PO BID (melanoma) | Phase 1 (38 with LGG, 24 with NF1-PN)[20,21] Phase 2 (50 LGG [25 with NF1] and 50 NF1-PN)[22,23] Ongoing studies in NF1-LGG, non-NF1 LGG, and NF1-PN | 10 mg 25 mg | Poor CSF penetration in primate model; effective in clinical trials of low-grade glioma[24] | CK increase, rash, neutropenia, paronychia, diarrhea, weight gain[22,23] | 5.3-7.2 hours[25] | CYP3A4, also by direct glucuronidation via UGT1A1 and -1A3[25] | Feces and urine[25] | Extensively studied in NF1 | FDA and EMA approved for children with symptomatic, inoperable NF1 plexiform neurofibroma |
| Trametinib (GSK1120212) | Tablet; suspension as compassionate use | 0.032 mg/kg (<6 years old) 0.025 mg/kg (>6 years old) (max 2 mg) various schedules | 2 mg PO QD (melanoma) | Adult studies in melanoma (in combination)[26] Phase 1 in children (78 pts including at least 26 with NF1)[27,28] | 0.5 mg 1 mg 2 mg | Brain to plasma ratio (Kp) in WT mice = 0.15[29] | Hypertension, rash[30] | 4-5 days[30] | Deacetylation alone or in combination with hydroxylation[30] | Feces and urine[30] | Suspension available as compassionate use | FDA and EMA approved for BRAF-mutant melanoma, and (in combination with dabrafenib) for BRAF-mutant NSCLC |

**Abbreviations:** AEs, adverse events; BID, twice daily; CNS, central nervous system; CSF, cerebrospinal fluid; EMA, European Medicines Agency; FDA, US Food and Drug Administration; LGG, low-grade glioma; NF1, neurofibromatosis type 1; NSCLC, non-small cell lung cancer; PN, plexiform neurofibroma; PO, by mouth; pts, patients; QD, daily; WT, wild type.

suppression.[37,49–52] Tumor growth inhibition was transient and resulted in resistance and reactivation of target pathways.[48] Combination therapy of MEKi with other targets of interest in MPNST pathogenesis (mTOR, MNK, BRD, MET) in preclinical models demonstrated tumor regression with synergistic responses.[50–53]

To date, there is no evidence that single-agent MEKi is effective to treat MPNST. Anecdotal evidence also suggests that MEKi do not prevent the development of MPNST, as the development of MPNST has been reported in patients receiving MEKi.[22] Ongoing (NCT03433183) and future clinical trials for MPNST will investigate combination therapies with MEKi.

## Cutaneous Neurofibroma

Cutaneous neurofibromas (CN) are tumors of the skin that affect >95% of adults with NF1 and are major detractors from quality of life, representing a substantial unmet need for people with NF1.[54] Recent efforts have discovered a putative cell of origin for CN, uncovered shared developmental pathways between PN and CN, and developed multiple preclinical models that allow testing of therapeutic agents in various stages of CN formation in both ex vivo and in vivo models.[55–59] Concurrently, a clinical trial of selumetinib for the treatment of CN (NCT02839720) is ongoing, and early reports show that all evaluable participants (n = 6) demonstrate at least 20% decrease in average CN volume compared to baseline.[60] However, participants have also experienced a number of systemic toxicities, including rash, hypertension, and skin infection that have limited the treatment duration. A phase 1 study evaluating three gel concentrations of the topical MEKi NFX-179 has recently reported early clinical results showing good tolerability, leading to a larger phase II study (NCT04435665).[58] Although MEKi show preliminary activity against CN, a great deal of work remains to determine the extent of response, optimal delivery, dosing, timing, and duration of treatment to maximize the therapeutic benefit of MEKi for CN.

## Low-grade Gliomas

Most NF1-associated pediatric low-grade glioma (LGG) harbor loss of both *NF1* alleles only, without the *BRAF* aberrations which are common in sporadic cases.[61] Older children and young adults with NF1-associated LGG (NF1-LGG) may have concomitant *CDKN2A/B* and *ATRX* mutations, and other concurrent alterations may yet be discovered. Tumors with *CDKN2A/B* and *ATRX* mutations, although maintaining some pilocytic features, also have anaplastic components and a more aggressive natural history.[62]

Preclinical studies of MEKi in non-NF1 associated LGG have focused on *BRAF*-altered models. In these models, treatment with selumetinib, trametinib, or cobimetinib has led to decreased phosphorylation of extracellular signal-regulated kinase (ERK) and reduced cell viability.[63–65] In xenograft models of *BRAF*-altered LGG, selumetinib resulted in decreased tumor volume and longer progression-free survival, while cobimetinib delayed tumor growth.[37] Similarly, treatment with mirdametinib led to decreased tumor volume and proliferation or prevented tumor formation in two mouse models of NF1-LGG.[66,67]

A phase 2 clinical study of selumetinib included a stratum of children with recurrent, refractory or progressive NF1-LGG.[23] Of the 25 children in this stratum, 10 (40%) achieved a sustained PR (≥50% reduction in tumor cross-product) to selumetinib at the recommended phase 2 dose of 25 mg/m$^2$/dose twice daily, although one participant later developed progressive disease while on therapy. The remaining 15 participants (60%) demonstrated stable disease. Two-year progression-free survival was 96%. Other MEKi have also been explored in NF1-associated and sporadic LGG. Among three NF1-LGG participants in a phase 1 trial of binimetinib, the best radiographic response included one major response, one minor response, and one stable disease.[8]

For NF1-LGG that occur in the optic pathway, vision outcomes are as important as tumor progression.[68] Among 88 previously untreated patients with NF1-associated optic pathway glioma receiving carboplatin-based therapy, visual acuity improved in 32%, was stable in 40%, and worsened in 28%.[69] In comparison, among 10 children with recurrent, refractory, or progressive NF1-associated optic pathway glioma treated in the phase 2 selumetinib study visual acuity improved in two (20%) and remained stable in eight (80%).[23]

These studies have led to the development of a phase 3 study comparing selumetinib with carboplatin and vincristine in untreated NF1-LGG (ACNS1831, NCT03871257), as well as phase 2 trials of trametinib (NCT03363217, ACTRN12620001229965) and binimetinib (NCT02285439) that specifically investigate NF1-LGG, intermittent MEKi dosing schedules (NCT03326388), and strategies to overcome MEKi resistance (NCT04201457).

These prospective trials may ultimately alter the standard of care for patients diagnosed with NF1-LGG; however, there is still much that is unknown about MEKi therapy. Factors associated with lack of response or acquired resistance are poorly understood, and the effect of MEKi on tumor senescence must be studied to inform questions regarding therapy duration and durability of response.[70] Finally, as the majority of these patients will survive their tumors, treatment efficacy must be defined not only by tumor response/stability, but also functional outcomes such as vision and quality of life, which have been poorly documented in prior studies.[68]

## Juvenile Myelomonocytic Leukemia

Children with NF1 at are increased risk of developing juvenile myelomonocytic leukemia (JMML),[71] a uniquely RAS-dependent leukemia cured only by stem cell transplantation. Although approximately 10% of JMML patients will have secondary mutations in the RAS pathway at diagnosis and at relapse, all patients have persistence of their initiating RAS pathway mutation at high allelic frequency.[72] This unique dependence on activated RAS

signaling has led to extensive testing of MEKi as a potential therapy.

Preclinical studies have investigated the role of MEKi in genetically engineered mouse models of JMML driven by *Kras*, *Nras*, or *Nf1*. Mice treated with mirdametinib or selumetinib demonstrated significantly longer survival, lower leukocyte count, higher hemoglobin levels, and smaller spleens compared to controls.[73] Interestingly, there was no difference in the *Kras*- or *Nf1*-mutant allele burden in the bone marrows of treated mice, and functional studies provided evidence that MEKi treatment induces disease regression by rebalancing cell proliferation and differentiation.[73] To determine if acquired resistance could be treated with combination therapies, selumetinib was combined with a JAK/STAT inhibitor (AZD1480) in a JMML mouse model. The combination of selumetinib and AZD1480 more effectively corrected most hematologic parameters to levels seen in control mice.[74]

These data led to the first-in-human trial of trametinib in patients with relapsed/refractory JMML (NCT03190915). This study is ongoing and response data are not yet available. Future directions for JMML trials will include using a clinically actionable DNA methylation assay to risk-stratify patients and guide treatment strategies.[75]

## MEKi for Non-Tumor Manifestations of NF1

### Bone

Characteristic skeletal abnormalities are frequently observed in patients with NF1, and some are included in the NF1 diagnostic criteria. In addition to the rare findings of long bone dysplasia and sphenoid wing dysplasia, many patients have relatively short stature, generalized low bone mineral density, increased fracture risk, and a propensity for both dystrophic and non-dystrophic scoliosis.[76–79]

Several preclinical studies have investigated the impact of MEKi to rescue bony manifestations of NF1 seen in mouse models.[80] Rescue of osteogenic differentiation of cultured *Nf1*-deficient bone-derived stromal cells was only achieved with the addition of a MEKi (U0126) and recombinant human BMP2 (rhBMP2).[81] Similarly, co-treatment of mice with mirdametinib and rhBMP2 resulted in improved fracture healing following the deletion of *Nf1* at the fracture site, although improved healing was evident with rhBMP2 alone as well.[80]

Clinical evidence for a direct effect of MEKi on the skeleton is limited to case reports. One report describes two advanced melanoma patients without NF1 who developed osteopenia and spontaneous fractures following long-term MEKi therapy.[82] In contrast, in 9 NF1 patients receiving selumetinib for PN, DEXA imaging did not reveal any difference in bone mineral density after 1 year of treatment.[83] Abnormal fracture healing has not been reported in association with MEKi, but has been seen in some but not all MEKi-treated mouse models.[81,84] Temporary interruption of MEKi treatment may be advisable for slow-healing fractures or those at risk for slow healing.

Currently, there is no robust clinical evidence to implicate a direct clinical benefit or harm of MEKi therapy on skeletal manifestations of NF1. Future studies, including careful monitoring of skeletal manifestations in patients receiving MEKi, may yield valuable information regarding their potential impact on bone health.

### Pain

Pain is common in NF1, yet the mechanisms are poorly understood.[85] Emerging preclinical data suggest that pain pathways may be potentiated by MEK/ERK upregulation,[86–89] and MEK inhibition has been shown to reduce pain behaviors in animal models of nociceptive, neuropathic, inflammatory, and visceral pain.[87–90]

The effect of MEKi on reducing the need for pain medications or sustaining long-term pain relief in NF1 has not been studied systematically. However, clinical trials and case studies consistently have observed decreased PN-related pain.[16,22] Improvement in pain may not correlate with tumor shrinkage as pain relief has been described soon after starting treatment,[91] and clinical trials often show a dissociation between pain relief and tumor response.[22,91] In a phase 2 trial of selumetinib in children with PN, 74% had a clinically meaningful decrease in tumor pain score with stable or decreased pain medication, and pain relief was recorded as early as 2 months following treatment initiation.[22] A similar pattern was found among NF1 adults with PNs receiving selumetinib.[39] In older adolescents and adults treated with mirdametinib,[16] tumor pain intensity decreased in the first 4 months of therapy and remained decreased for 12 months among individuals whose tumors responded to therapy.

Since multiple clinical trials indicate that MEKi reduces PN-related pain intensity and pain interference in daily life, intolerable PN-related pain may be a potential indication for initiating treatment with MEKi. Reliable and consistent pain measures such as the Numeric Rating Scale-11 and the Pain Interference Index[92] are essential to prospectively evaluate pain, and should be incorporated in clinical trials focused on reducing the need for pain medications or sustaining long-term pain relief.

### Neurocognition

NF1-associated cognitive deficits have been well documented across multiple domains of functioning that affect daily activities and quality of life, including increased prevalence of attention-deficit/hyperactivity disorder and learning disabilities when compared to the general population.[93,94] Suggested mechanisms include disrupted neurotransmission and impaired synaptic plasticity in key brain structures, including the hippocampus and prefrontal cortex, due to RAS hyperactivation, raising the question whether MEKi may be beneficial in the treatment of cognitive NF1 manifestations.

Preclinical studies of neurocognitive effects of MEKi in *Nf1* models have had conflicting results. Two studies involving transient MEK inhibition in neonatal mouse pups suggested treatment may prevent and rescue NF1-associated developmental defects.[95,96] In contrast, prolonged MEK suppression to prevent the natural

progression of pluripotent stem cells resulted in irreversible cellular changes that impeded development.[97] These studies highlight the complexity of neurodevelopment, drug penetration, and prevention strategies in NF1.

Recently, the first human trial examining the impact of MEKi treatment on cognition provided proof of concept that MEKi may improve executive function and working memory in children and young adults with NF1 without significant neurotoxicity.[98] Additional cognitive studies are underway, one examining treatment with selumetinib vs carboplatin/vincristine on cognitive functions in children with previously untreated NF1-LGG (NCT03871257), and another investigating the effects of trametinib vs no-treatment on cognitive and behavioral functioning in NF1 patients with optic pathway gliomas or PN (ACTRN12620001229965).

If MEKi treatment is shown to improve NF1-associated cognitive deficits, the ideal age to initiate treatment is still unknown. Early intervention has been important for behavioral therapies, but the potential for MEKi neurotoxicities in very young children is unknown. Currently, there are not enough data about the impact of MEKi on neurodevelopment and cognitive functions to make specific recommendations regarding their use in NF1. However, ongoing clinical studies will allow for comparison of MEKi-treated participants to treated and untreated control participants, provide longer follow-up, and offer additional safety information in young children with NF1.

## Practical Treatment Questions of MEKi

### Dosing

Initial dosing of specific MEKi has been established by early phase clinical trials as shown in Table 1. In some cases, the recommended phase 2 dose of MEKi for patients with NF1 is lower than the corresponding dose for oncologic indications due to differences in tolerability and treatment duration.[6,20] Dose reductions of selumetinib due to toxicity do not appear to impact response in NF1-LGG,[23] suggesting the effective treatment dose may be lower in this population. There is more variability in PN trials. Selumetinib dose reductions have affected efficacy in a portion of trial subjects[20,22]; however, those undergoing mirdametinib dose reductions never achieved a subsequent PR.[16] Given the frequency of dosing interruptions or the need for supportive care for adverse events in MEKi trials, as well as the need for prolonged treatment for PN, there is interest in evaluating alternate dosing schedules, such as intermittent, non-continuous dosing, to understand if such schedules may improve tolerability while maintaining efficacy. Future and ongoing trials (NCT03326388) will address these unanswered questions.

### Time to Response

Tumor response to MEKi may be gradual, but if a MEKi is going to benefit a patient, initial clinical and/or radiographic response is usually evident within 1 year of starting treatment. Median time to PR for LGG[23] and PN[22] in children treated with selumetinib was 3.6 months and 7.4 months, respectively. Given the slower growth rate of PN in adults, it is possible that tumor responses may occur later: the median time to response is presently 11 months among adults with PN.[39] Clinical benefit (eg, improvement in pain, airway or motor function in PN, or vision in OPG) may occur earlier and may not correlate with radiographic PR.[22]

### Duration of Treatment and Durability of Response

The ideal treatment duration for PN or LGG with MEKi is still unknown. Recent and current clinical protocols for LGG have established 2 years of therapy as an accepted duration. Durability of response appears variable after 2 years of MEKi for LGG.[23] In contrast, most PN trials have been treated for 2 years or more, and regrowth of PN has been observed in patients upon treatment discontinuation. In the phase 2 trial of selumetinib, younger age at treatment discontinuation was correlated with more subsequent tumor growth.[99] Future and ongoing clinical trials will determine these patterns more clearly.

### Treatment Failure, Resistance, Re-treatment, and Rotation of MEKi

Although most NF1-PN or -LGG patients respond to MEKi treatment, tumor responses vary in magnitude and may be clinically insufficient for some patients. Predictors of response to MEKi are unknown but would be important to inform the biological mechanisms for tumorgenesis and growth in NF1. Ras activation in NF1 may activate multiple pathways of cell proliferation and tumor growth, and it is not yet clear why MEKi were more successful than prior therapies targeting these pathways such as mTOR inhibitors which resulted in much less robust responses in PN and LGG than MEKi have.[100–102] Understanding the mechanism of NF1 tumor response and resistance may help lead to rational combinations of MEKi with other targeted inhibitors or cytotoxic therapies to improve response.

In patients who initially respond to MEKi, acquired resistance in NF1-associated tumors appears to be infrequent. Prior to assuming resistance, patient adherence and the possibility of malignant transformation (for PN) should be evaluated. Some PN that responded to MEKi therapy have responded again after an interruption in therapy. Similar data for LGG are emerging.[103]

Some practitioners have rotated from one MEKi to another in patients with NF1-associated tumors who have already benefited from MEKi therapy (clinical or radiographic) in hopes of reducing or eliminating intolerable, non-serious toxicities that cannot be managed with optimal supportive care.[104] Although there is only anecdotal information to support this strategy, it is not unreasonable to consider trying a different MEKi in these circumstances. In contrast, for patients that have not benefited (clinically and/or radiographically) from MEKi treatment, there are no data to recommend switching to a different MEKi.

### Common Adverse Events and Management

Although generally well tolerated, MEKi can cause substantial, intolerable toxicities. The toxicity profile for MEKi is considerably different from traditional cytotoxic chemotherapy and requires careful screening and management. Recently, detailed supportive care guidelines have been published.[105] Most NF1 patients treated with MEKi will develop laboratory abnormalities and skin and/or gastrointestinal (GI) toxicity.[16,20–23] The most commonly reported skin toxicities include acneiform rash (particularly in post-pubertal patients), eczematous dermatitis (particularly in pre-pubertal patients and those with known eczema), chronic paronychia, mucositis, photosensitivity, hair lightening, and alopecia.[106,107] Rashes can be intolerable, and 25%-40% of study participants have required dose reductions due to this concern.[20,22] GI toxicities are also common, including diarrhea, nausea, and weight gain.[22,23] Ongoing trials in patients with NF1 suggest increased incidence of skin and GI toxicities in adults compared with children. The most frequent laboratory abnormality is asymptomatic elevation of CK, which rarely requires dose modification if clinical symptoms are absent.[22]

Cardiac and ophthalmologic evaluations are recommended throughout treatment, although toxicities are seen more commonly in adults. Decreased left ventricular ejection fraction associated with MEKi appears to be reversible upon dose modification or drug hold, and screening echocardiograms are recommended.[108] In adult melanoma trials of MEKi, ocular toxicities, including subretinal fluid collection, retinal vein occlusion, and retinal detachment, were reported.[109] In contrast, significant ocular toxicities have not been observed in pediatric patients with NF1.[22]

Preclinical models indicate that MEKi may affect wound healing, although their clinical impact on wound healing has not been established. It may be appropriate to hold the drug preoperatively and then postoperatively until adequate wound healing has occurred, typically at least 2 weeks.[105]

Toxicity management for MEKi requires careful surveillance, and the development of long-term toxicities is being monitored in children and adults with NF1. Recommended screening for MEKi-treated NF1 patients is found in Table 2.

## Use in Other RASopathies

NF1 belongs to a group of syndromes called RASopathies that are characterized by germline RAS pathway activation.[110] RASopathies, such as Noonan, Costello, and cardiofaciocutaneous syndromes have significant overlap in phenotypic features and cancer predisposition, raising the possibility that MEKi may ameliorate or prevent worsening of disease manifestations.

Animal models of RASopathies have been used to examine the effect of MEKi on these syndromes. Intrauterine treatment in Noonan syndrome mouse models has rescued the craniofacial abnormalities associated with this syndrome,[111] while cardiac defects and growth deficits have been reduced by post-natal treatment.[112,113] Enamel defects in models of Costello syndrome have also been rescued with MEKi treatment.[114] In a zebrafish model of cardiofaciocutaneous syndrome, lower doses of MEKi rescued developmental phenotypes, while higher doses led to severe developmental consequences.[115] Cognitive deficits and abnormal behavior have also been ameliorated in some models of Costello and Noonan syndrome.[116,117]

Lessons learned from animal models have led to anecdotal experience treating life-threatening conditions associated with RASopathies in humans when no other therapies are available. Noonan-associated hypertrophic cardiomyopathy is associated with dismal outcomes when it presents in early infancy, often without any effective treatments. Trametinib has been used in two infants with this condition and was associated with rapid decrease in left ventricular mass, improved valve stenosis,

**Table 2.** Recommended Surveillance for Patients Receiving MEK Inhibitor Therapy

| Evaluation | Monitoring Recommendation[a] |
|---|---|
| Physical examination with careful evaluation of the skin, oral mucosa, and nails | Every visit, generally monthly |
| Review of systems, including GI, vision, and skin | Every visit |
| Ophthalmological examination | Baseline, then every 6-12 months, and for new symptoms. May consider increased frequency for adults |
| Echocardiogram/ejection fraction | Baseline, then every 3-6 months |
| Electrocardiogram | Baseline, then as clinically indicated |
| Pregnancy status | Baseline, then per institutional standards for patients on cytotoxic therapy |
| Laboratory evaluations | Creatine kinase, metabolic panel[b], liver function tests[b], complete blood count at baseline, every month for the first several months and then every 3-6 months.<br>Amylase, lipase at baseline, and then as clinically indicated |

[a]Adapted from Klesse et al.[105]
[b]Metabolic panel to include electrolytes, creatinine, glucose; liver function tests to include aspartate aminotransferase and alanine aminotransferase.

and normalization of laboratory values.[118] However, the safety and efficacy of MEKi in targeting other RASopathies are unknown, and any clinical benefit should be explored in clinical trials.

## Conclusion

MEKi are the first effective targeted therapy for individuals with symptomatic, inoperable NF1 PN and hold the potential to revolutionize care for other NF1 tumor and non-tumor manifestations. Further investigations into the biologic mechanisms for NF1 manifestations, the downstream impact of MEKi on Ras effector pathways, and windows of opportunity for intervention are needed to help guide clinical trial development. Similarly, additional data for MEKi regarding clinical efficacy in treating the diverse manifestations of NF1 and long-term safety data are needed to guide clinical care. Prospective trials, continued molecular discoveries, and increased clinical experience will provide a broader understanding of the role of MEKi in NF1 and other RASopathies.

## Supplementary Material

Supplementary material is available at *Neuro-Oncology* online.

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