TARGETING THE PATHWAY

Evolving Roles of MEK Inhibitors in NF1-Associated PN

Supported by an independent educational grant from Alexion Pharmaceuticals.

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Oncology Nursing Practice
Symptom Management, Palliative Care, Supportive Care Treatment

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CPHON
Care Continuum
Pediatric Hematology and Oncology Nursing Practice
Symptom Management, Palliative Care, Supportive Care Treatment

AOCNP
Care Continuum
Care of the Pediatric Hematology and Oncology Patient
Disease Related Biology
Symptom Management, Palliative Care, Supportive Care Treatment

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Disclosures

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Grants—Tango

Other financial or material support—Boehringer Ingelheim

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Grants—Alexion/AstraZeneca

Speakers bureau—Alexion Pharmaceuticals Inc./AstraZeneca, Ipsen Pharma, and SpringWorks Therapeutics Inc.

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All identified conflicts of interest have been mitigated.

Assess neuro-oncologic features of neurofibromatosis type 1 (NF1), including tumor types and neurological signs, to support early recognition and guide clinical decision-making

Integrate MEK inhibitors in the management of NF1-associated plexiform neurofibromas (PNs) in adult and pediatric patients

Develop evidence-based, interprofessional care plans for patients with NF1 that reflect current clinical standards and support individualized, longitudinal management

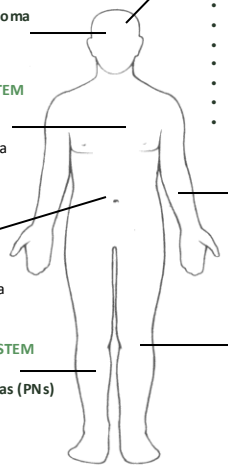
Neurofibromatosis Type 1

Clinical Features and Diagnostic Criteria

The Neurofibromatoses

NEUROFIBROMATOSIS TYPE 1 (NF1)

1 in 2,800 people worldwide



CENTRAL NERVOUS SYSTEM
- Gliomas
- Seizures
- Learning disabilities
- Attention deficit
- Autism
- Headaches
- Precocious puberty
- Vascular abnormalities (Moyamoya)
- Aqueductal stenosis
- Sleep disturbances
- Multiple sclerosis

EYES and VISION
- **Optic nerve glioma**
- **Lisch nodules**

CARDIOVASCULAR SYSTEM
- Heart valve defects
- Aortic coarctation
- Renal artery dysplasia
- Hypertension

SKIN
- **Café-au-lait macules**
- **Skinfold freckling**
- Juvenile xanthogranulomas
- Melanoma

GI SYSTEM
- GISTs

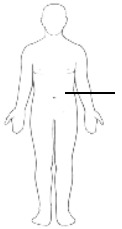
ENDOCRINE SYSTEM
- Pheochromocytoma

SKELETAL SYSTEM
- **Dysplasia of long bones**
- **Pseudarthrosis**
- **Sphenoid wing dysplasia**
- Dystrophic scoliosis
- Scalloping of vertebrae
- Pectus excavatum
- Macrocephaly
- Short stature
- Osteoporosis

PERIPHERAL NERVOUS SYSTEM
- **Neurofibromas**
- **Plexiform neurofibromas (PNs)**

NON-NF2 SCHWANNOMATOSIS

1 in 158,000 people worldwide



PERIPHERAL NERVOUS SYSTEM
- Spinal schwannomas
- Peripheral schwannomas

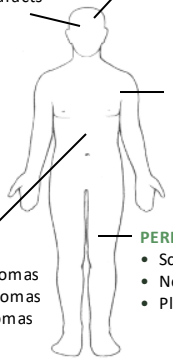
PAIN

NF2-RELATED SCHWANNOMATOSIS (NF2)

1 in 67,700 people worldwide

EYES and VISION
- Epiretinal membranes
- Retinal hamartomas
- Juvenile cataracts

CENTRAL NERVOUS SYSTEM
- Meningiomas
- Cranial nerve schwannomas



SKIN
- Schwannomas
- Café-au-lait macules

SPINE
- Schwannomas
- Ependymomas
- Meningiomas

PERIPHERAL NERVOUS SYSTEM
- Schwannomas
- Neurofibromas
- Plexiform schwannomas

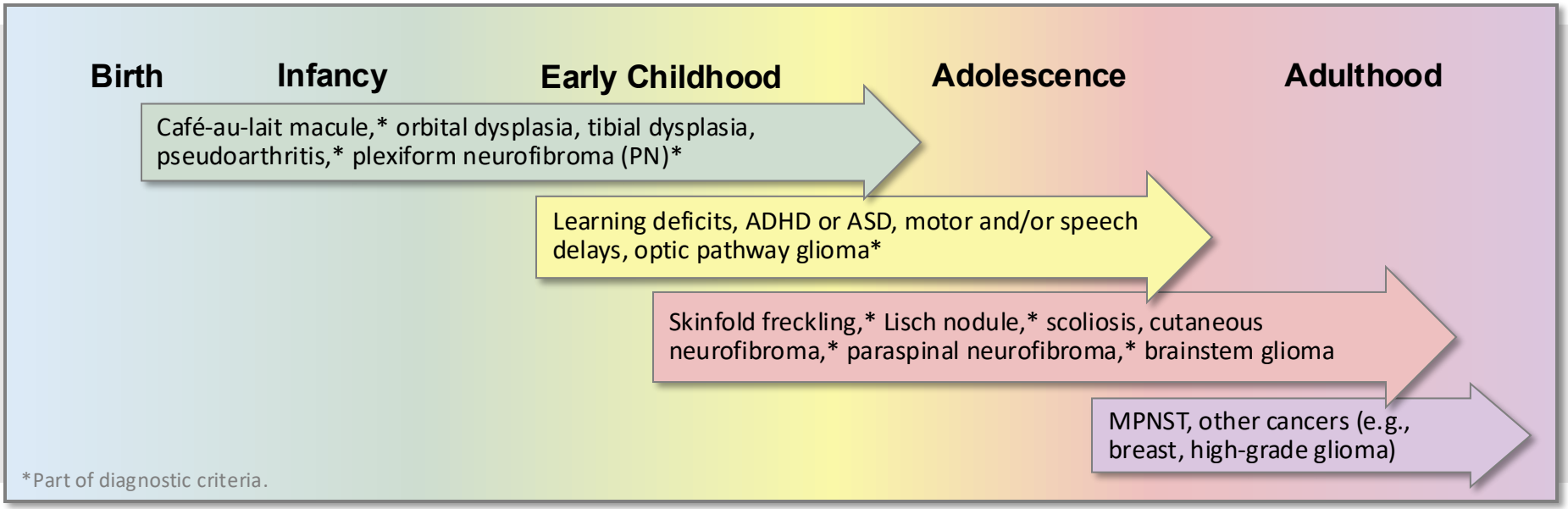
GIST, gastrointestinal stromal tumors.

Friedman JM. Neurofibromatosis 1. In: *GeneReviews*. Updated April 3, 2025. https://www.ncbi.nlm.nih.gov/books/NBK1109/.
Moodley M, et al. *Semin Pediatr Neurol*. 2024;52:101172. Lee TJ, et al. *Orphanet J Rare Dis*. 2023;18(1):292.

Development of Clinical Features of NF1

Timing and Severity Varies

Neurofibromin expression largely restricted to the nervous system and adrenal medulla, with little or no expression in other tissues



*Part of diagnostic criteria.

ADHD, attention-deficit hyperactivity disorder; ASD, autism spectrum disorder; MPNST, malignant peripheral nerve sheath tumors.

Kerashvili N, et al. *Expert Rev Neurother*. 2024;24:409–420. Botero V, et al. *J Neurodev Disord*. 2024;16:49.

NF1
Diagnostic Criteria

1988

Diagnostic criteria for NF1 are met if **two or more** of the following are found:

1. Six or more café-au-lait spots (in the greatest diameter)
   - 1.5 cm or larger after puberty
   - 0.5 cm or larger before puberty
2. Freckling in the axilla or groin
3. Two or more Lisch nodules
4. Two or more neurofibromas OR one plexiform neurofibroma
5. Optic pathway glioma
6. A distinctive osseous lesion, such as sphenoid dysplasia or thinning of long bone cortex with or without pseudoarthrosis
7. First-degree relative with NF1

2021

Diagnostic criteria for NF1 are met in an individual who **does not have a parent diagnosed with NF1** if **two or more** of the following are found:

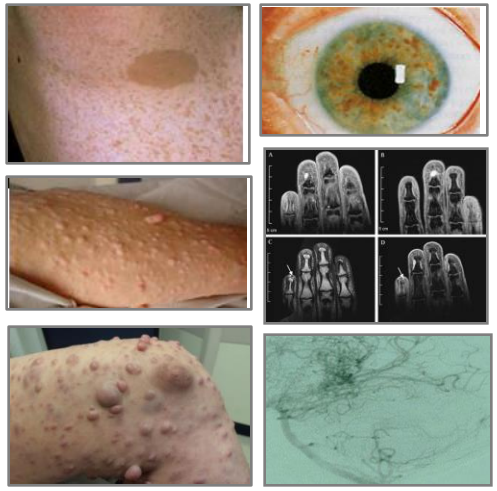
1. Six or more café-au-lait spots (in the greatest diameter)
   - 1.5 cm or larger after puberty
   - 0.5 cm or larger before puberty
2. Freckling in the axilla or groin
3. Two or more neurofibromas OR one plexiform neurofibroma
4. Optic pathway glioma
5. Two or more iris Lisch nodules OR **two or more choroid abnormalities**
6. A distinctive osseous lesion, such as sphenoid dysplasia, anterolateral bowing of tibia or pseudoarthrosis of a long bone
7. **Heterozygous pathogenic *NF1* variant with a variant allele fraction of 50% in apparently normal tissue**

If a **parent meets the above diagnostic criteria**, the individual only requires one or more of the above criteria to merit an NF1 diagnosis

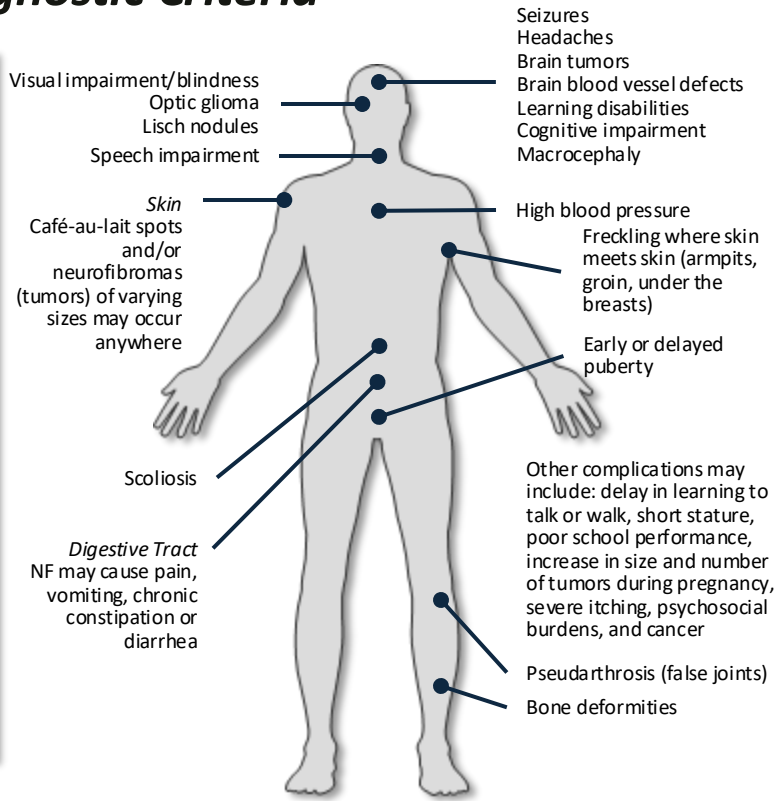
NIH Consensus Development Conference. *Neurofibromatosis.* 1988;1(3):172–178. Legius E, et al. *Genet Med.* 2021;23:1506–1513.

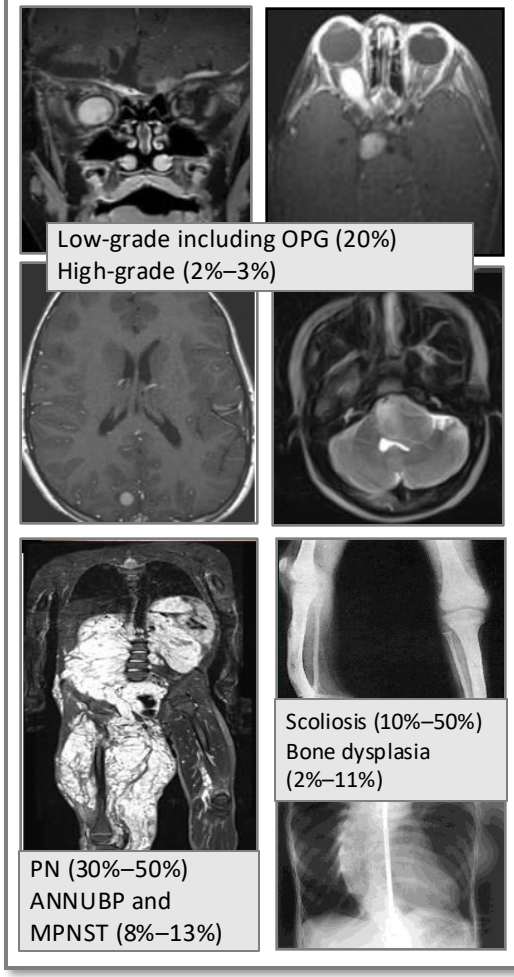
Neurofibromatosis Type 1

Manifestations and Diagnostic Criteria



Lisch nodules (>90% of adults; by 10 years)
Café-au-lait macules (~100%)
Cutaneous neurofibromas (>95%)
Cognitive manifestations (~30%–-70%)
Vascular manifestations (~2%–5%)





Carton C, et al. *EClinicalMedicine*. 2023;56:101818.
Legius E, et al. *Genet Med*. 2021;23(8):1506–1513. Toro G, et al. *Healthcare (Basel)*. 2021;9(7):881.
Well L, et al. *Sci Rep*. 2021;11(1):16889. Baudou E, et al. *Front Neurol*. 2019;10:1373.
Kim A, et al. *Sarcoma*. 2017;2017:7429697. Korf BR. *Handb Clin Neurol*. 2013;111:333–340.
Stevenson DA, et al. *J Pediatr Orthop*. 2013;33(3):269–275. Ferner RE. *Pract Neurol*. 2010;10(2):82–93.

Irene “Renie” Moss

Renie Moss
Patient Advocate and Caregiver

Renie Moss lives in Alabama with her husband of 24 years, Philip Sr., and two children, Philip Jr. (age 20) and Helen (age 17), all three of whom have NF1. Ms. Moss is an avid advocate for the neurofibromatosis patient and research communities.

- Former chair of the Children’s Tumor Foundation (CTF) Volunteer Leadership Council
- Former patient liaison to the Synodos NF1 Research Consortium
- Patient representative for Response Evaluation in Neurofibromatosis and Schwannomatosis International Collaboration (REiNS)
- Member of the University of Alabama–Birmingham (UAB) NF Clinic Patient Advisory Board
- Member of the UAB Genetic Counseling Program’s advisory board

Renie Moss. Interview with CE Concepts. August 2025.

Challenges of Accessing NF1 Care

Renie Moss

Patient Advocate and Caregiver

Renie Moss. Interview with CE Concepts. August 2025.

Case: Sam G.

Sam G. is a 7-year-old male who has experienced some mild learning difficulties and clumsiness in school, which has been attributed to behavioral issues and not formally evaluated. He has a younger brother (4 years) and sister (2 years).

At his annual physical examination, his pediatrician notes axillary freckling and small, soft cutaneous nodules. Ophthalmologic exam finds Lisch nodules. NF1 is diagnosed based on clinical criteria. Parents do not have clinical characteristics of NF1.

Examination reveals:

- 9 café-au-lait spots >0.5 cm (largest 1.5 cm, multiple smaller spots), initially referred to as "birth marks" without follow up investigation
- Bilateral axillary freckling, no neurofibromas palpable
- Mild hypotonia, coordination difficulty noted
- No scoliosis on a forward bend test; no long bone abnormalities
- Visual-spatial and processing deficits, attention and executive function concerns

Sam G. (…continued)

Recommendations

- Comprehensive ophthalmologic exam
- Baseline neurological evaluation and developmental/ behavioral monitoring and support
- Genetic counseling to discuss inheritance, family testing, reproductive planning
- Continue occupational therapy and speech therapy per IEP
- Initiate parent support via Children's Tumor Foundation and/or local NF1 support networks
- Annual follow-up appointments for NF1 surveillance: neurological exam, skin, ophthalmology, growth and development

Neurofibromatosis Type 1

MEK Inhibitors for the Treatment of Symptomatic, Inoperable Plexiform Neurofibromas in Children

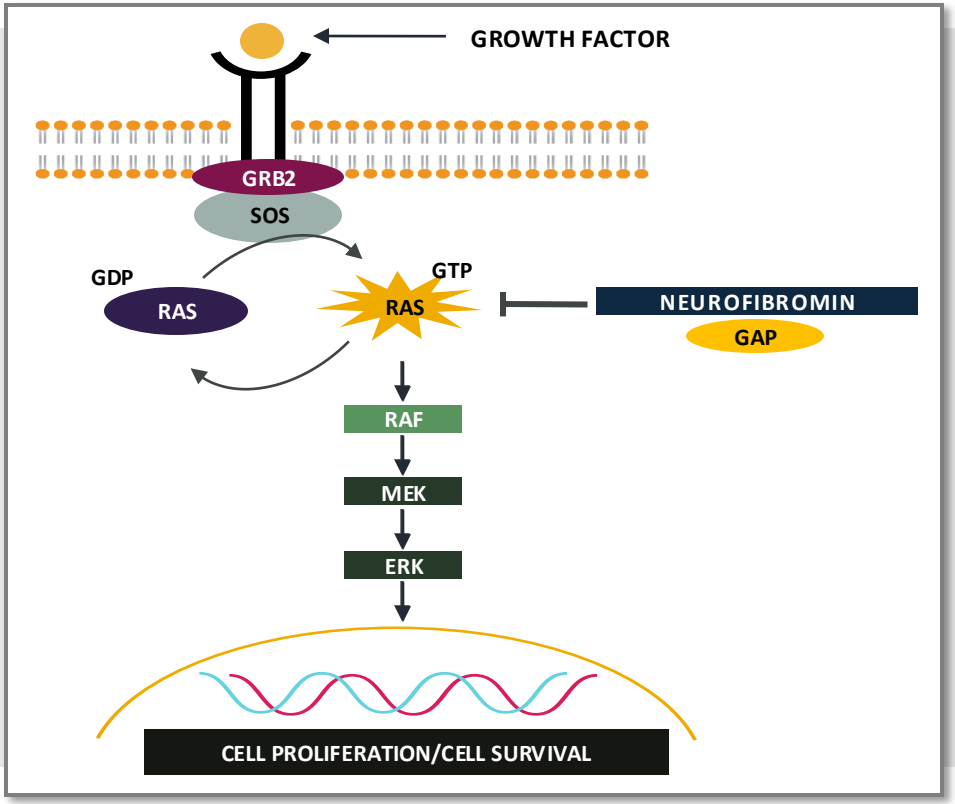
Tumors Associated with NF1

Common

- Dermal neurofibromas
- Plexiform neurofibromas (PNs)
- Optic pathway gliomas and other low-grade tumors

Rare (<10%–15% of all people with NF1)

- Malignant peripheral nerve sheath tumors (MPNSTs)
- High-grade glioma
- Breast cancer
- Gastrointestinal stromal tumors (GISTs)
- Pheochromocytoma and/or paragangliomas
- Rhabdomyosarcomas



ERK, extracellular signal-regulated kinase; GAP, GTPase-activating proteins; GDP, guanosine diphosphate; GRB2, growth factor receptor-bound protein 2; GTP, guanosine triphosphate; MEK, mitogen-activated kinase; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma; SOS, Son of Sevenless.

Lalvani S, et al. *J Multidiscip Healthc*. 2024;17:1803–1817.
Acar S, er al. *Expert Opin Investig Drugs*. 2022;31:31–40. Kerashvili N, et al. *Expert Rev Neurother*. 2024;24:409–420. Botero V, et al. *J Neurodev Disord*. 2024;16:49.

NF1-PNs

- Develop in up to 50% of patients with NF1
  - Typically, congenital or manifest in early childhood
  - Grow most rapidly in children <5 years of age
- Highly infiltrative, most frequently located in trunk or extremities
  - Can obstruct major organs, potentially life-threatening

Lalvani S, et al. *J Multidiscip Healthc*. 2024;17:1803–1817.
Acar S, er al. *Expert Opin Investig Drugs*. 2022;31:31–40. Kerashvili N, et al. *Expert Rev Neurother*. 2024;24:409–420.

NF1-PNs

- Most patients have ≥1 PN-associated morbidity
  - Most common: pain, disfigurement, and motor dysfunction
  - Other comorbidities of note: defects in vision, airway, and bowel/bladder function
- Symptomatic PNs tend to be larger than asymptomatic PNs
  - Asymptomatic and symptomatic often coexist
- Benign, but may progress to atypical neurofibromas and then undergo transformation to MPNST
  - Estimated lifetime risk of MPNST in patients with NF1 is 8%–13%

Lalvani S, et al. *J Multidiscip Healthc*. 2024;17:1803–1817. Armstrong AE, et al. *BMC Cancer*. 2023;23(1):553.
Acar S, er al. *Expert Opin Investig Drugs*. 2022;31:31–40. Kerashvili N, et al. *Expert Rev Neurother*. 2024;24:409–420.

NF1-PN Management
Observation vs Treatment

INTERTWINED CONSIDERATIONS

- Age of patient
- PN growth status
- Growth rate
- Present/impending morbidity
- Progressive nature of tumor

OBSERVATION

- Not all patients with NF1-PN require treatment
- Most stable tumors do not cause morbidity
- May not progress or cause symptoms
- Management involves regular monitoring

TREATMENT

- Goal (most cases) to improve or prevent PN-associated morbidity
- Consider when evidence shows/ suggests PN-related morbidity or tumor growth with impending morbidity

Lalvani S, et al. *J Multidiscip Healthc.* 2024;17:1803–1817.
Armstrong AE, et al. *BMC Cancer*. 2023;23(1):553. Fisher MJ, et al. *Neuro Oncol*. 2022;24:1827–1844.

NF1-PN Management
Surgery vs Medical Treatment

PRIOR TO TREATMENT

- Rule out malignant transformation of PN
- Assess change in tumor growth rate (i.e., new onset or recent change in PN-related pain)
- Biopsy if clinical concern
- Multidisciplinary input needed
- Note
  - Medical therapy for NF1-PN does not prevent transformation to MPNST
  - Treatment is different for MPNST vs NF1-PN

SURGERY

- Preferred if resection can be achieved without significant morbidity
- Complete tumor excision: ~15% of cases
- NF1-PN regrowth (post partial or subtotal resection): ~43%
- Permanent sequelae (neurologic): 5%–18% of patients

MEDICAL TREATMENT

- Preferred if specific contraindications or pre-existing conditions
- Concerns related to a therapeutic option
- Assess logistics, adverse events, formulation, compliance, long-term safety, etc.

Lalvani S, et al. *J Multidiscip Healthc.* 2024;17:1803–1817.
Armstrong AE, et al. *BMC Cancer*. 2023;23(1):553. Fisher MJ, et al. *Neuro Oncol.* 2022;24:1827–1844.

To Treat or Not to Treat NF1-PNs?

- Symptomatic, inoperable PNs
- Recent or ongoing PN growth
- Significant pain or functional impact
- PNs in high-risk locations
- Younger age or earlier in disease course

- Toxicities (skin, cardiac, gastrointestinal, ocular)
- Duration of treatment
- Long-term sequela
- Long-term data lacking for some agents

Armstrong AE, et al. *BMC Cancer*. 2023;23(1):553.

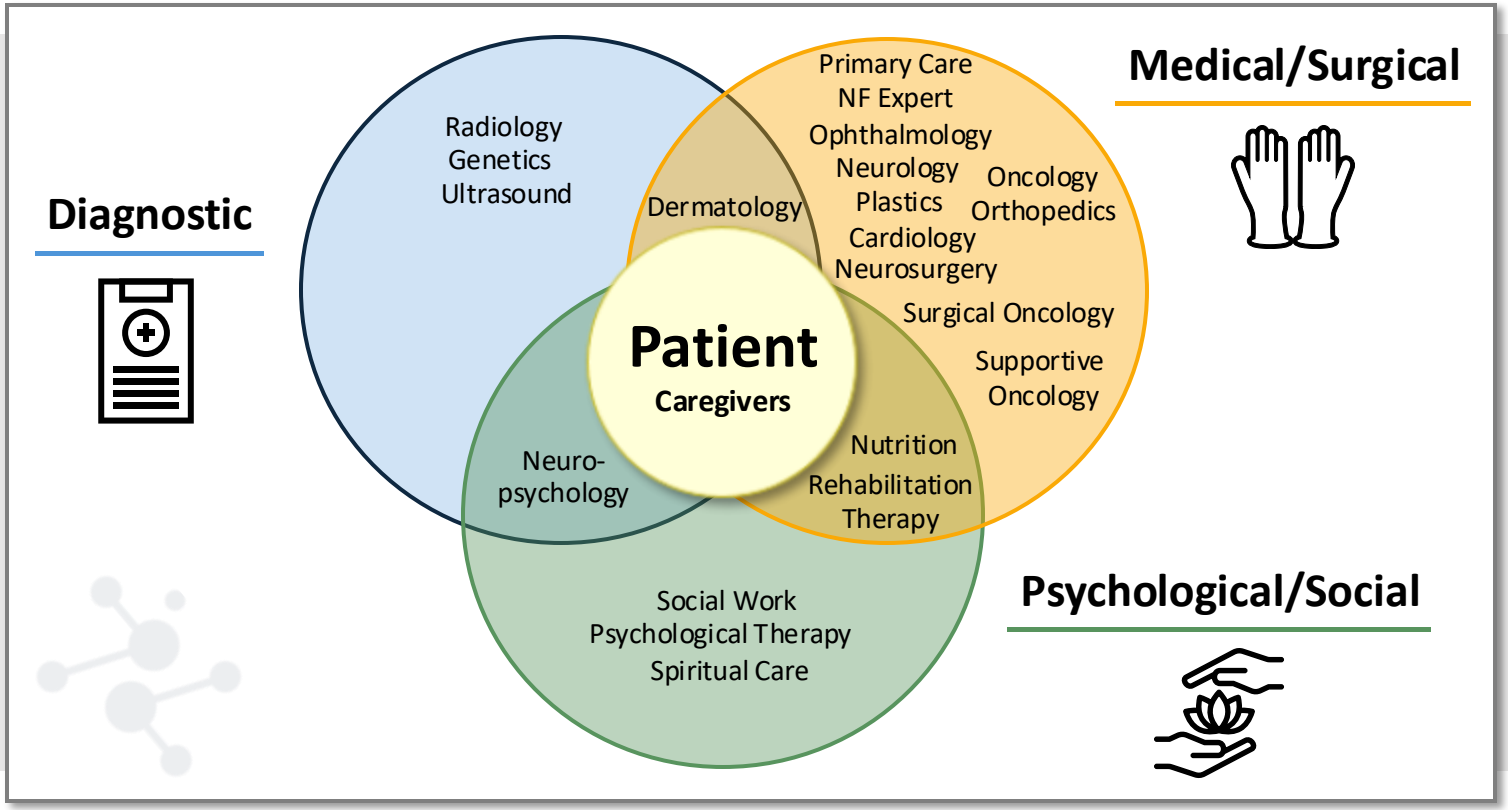
Sam G. (…continued)

At 10 years of age, he develops a slowly enlarging, diffuse swelling along the lower left jaw and neck. This area feels rubbery, is sometimes tender, and grows steadily but unpredictably. The mass is non-resectable due to its size and location and causes cosmetic deformity and periodic discomfort. MRI confirms a plexiform neurofibroma.

Over several years, the lesion causes noticeable facial asymmetry and mild difficulty with chewing and speech. He begins to experience neuropathic pain and occasional airway discomfort by age 13–14. Function and quality of life (QoL) decline, and the mass becomes increasingly prominent.

At 15 years of age, progressive pain, impaired function, and disfigurement are negatively impacting his QoL.

Multidisciplinary Care for Patients with NF1



Lalvani S, et al. *J Multidiscip Healthc*. 2024;17:1803–1817. Armstrong AE, et al. *BMC Cancer*. 2023;23(1):553.

Recommendations

- Complete resection is not possible
- In consultation with his parents, it is decided that he receive systemic therapy

Targeted Medical Therapy for NF1-PN

Several MEK inhibitors and tyrosine kinase inhibitors (TKIs) have demonstrated activity against NF1-PN.

Outcome measures in clinical trials:

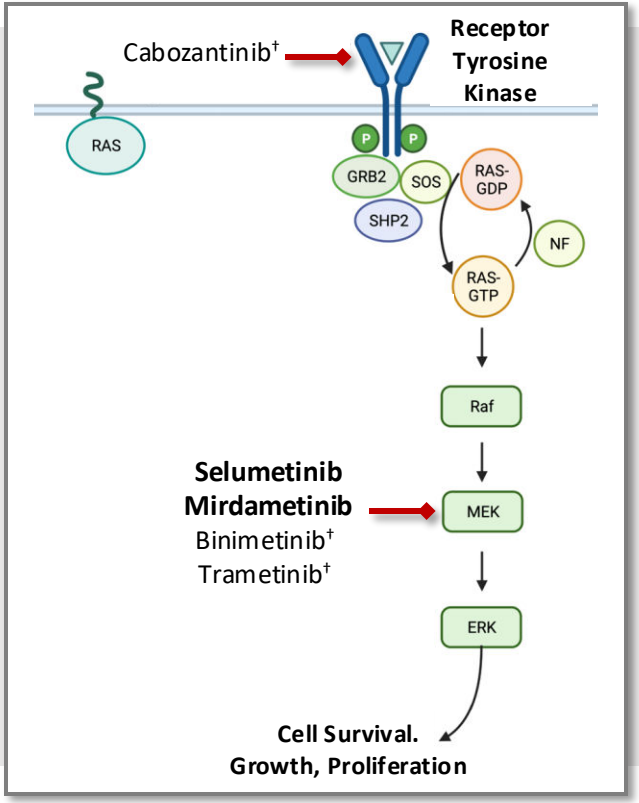
- Assessed PN growth and response via 3D volumetric analysis
- Patient-reported and functional outcome assessments

SELUMETINIB*

FDA-approved in *adult and pediatric* patients 1 year of age and older with NF1 who have symptomatic, inoperable PN

MIRDAMETINIB*

FDA-approved in *adult and pediatric* patients 2 years of age and older with NF1 who have symptomatic PN not amenable to complete resection



*Approval specifics vary by country.
NF, neurofibromin; SHP2, Src homology-2 protein tyrosine phosphatase.
Na B, et al. *Curr Oncol Rep*. 2024;26:706–713. Armstrong AE, et al. *BMC Cancer*. 2023;23(1):553.
Fischer MJ, et al. *Neuro Oncol*. 2022;24:1827–1844. de Blank PM, et al. *Neuro Oncol*. 2022;24:1845–1856.
Mirdametinib (package insert). Revised February 2025.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/219379Orig1s000lbl.pdf.
Selumetinib (package insert). Revised November 19, 2025.
https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/213756s006lbl.pdf.

†Not FDA approved for the treatment of NF1-PN.

MEK Inhibitors in Pediatric Patients

SPRINT Trial
Selumetinib in Children with Inoperable PN

- Phase 2, open-label
- Children (2–18 years of age)
- NF1 + symptomatic inoperable PN
- No evidence of MPNST, an optic glioma, malignant glioma, or other cancer requiring treatment with chemotherapy or radiation therapy

Baseline Demographics (median values)
- Age: 10 years
- Male: 60%
- Volume of target NF: 487 mL
- Progression status (progressive/not/data lacking): 42%/30%/28%
- Location of target NF
  - Neck + trunk (24%), trunk + limbs (24%), head (18%), head + neck (16%), trunk (10%), limbs (8%)
- NF-related comorbidities (median number: 3)
  - Disfigurement (88%), motor dysfunction (66%), pain (52%), airway (32%), vision (20%), bowel or bladder (20%), other (22%)

Selumetinib 25 mg/m^2 BID (n=50)
Treatment cycle: 28 days (no rest between cycles)

Up to 2 years if no drug-related toxicity or progressive disease
(≥20% volume increase in target PN)

Primary Endpoint
- Partial response (≥20% volume reduction in target PN by 3D analysis of MRI)
  - Confirmed (2 consecutive)
  - Durable (lasting ≥12 cycles)

Secondary Endpoints
- Duration of response
- Safety
- Patient-observer reported outcomes

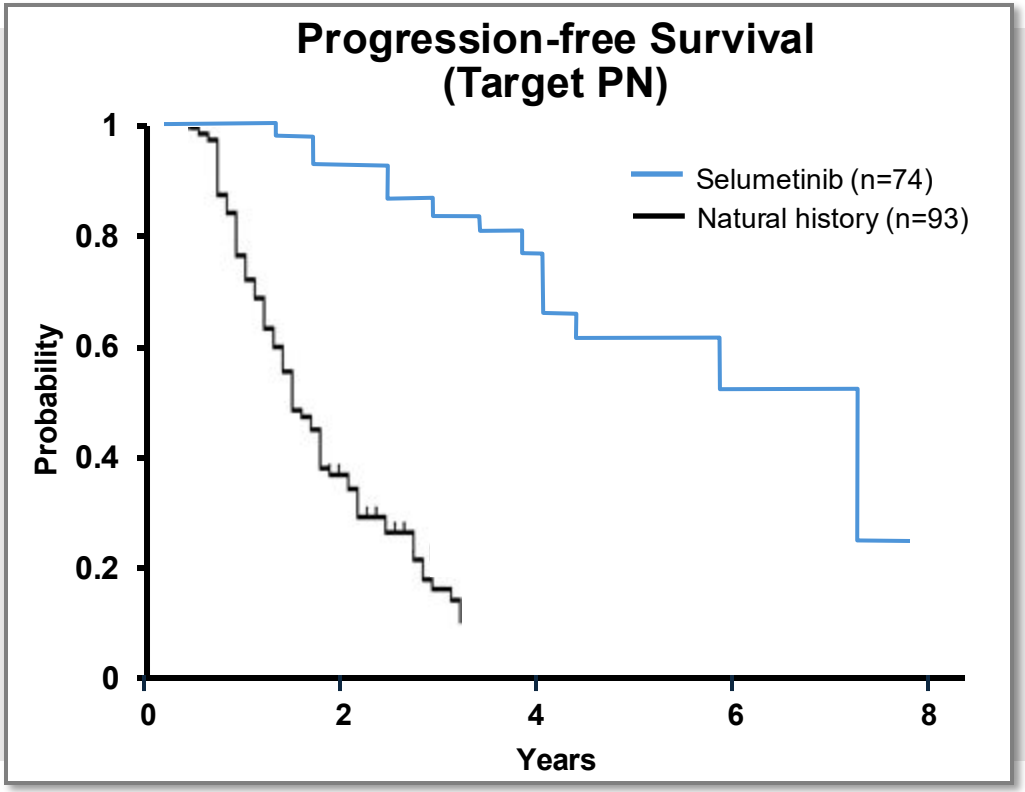
BID, twice daily.

Gross AM, et al. *N Engl J Med*. 2020;382:1430–1442.

Combined 5-Year Progression-Free Survival

SPRINT + Phase I

- Combined cohort (n=74)
  - Continuous selumetinib dosing (median duration: 57.5 cycles)
  - Remaining on treatment at data cutoff (n=31)
- Partial response
  - Confirmed and durable: 70% and 59%
- Time to response (median)
  - Initial: 8 cycles (range 4–40)
  - Best response: 18 cycles (range 4–94)
- Median PFS
  - 88 cycles (6.7 years)
- 1-year probability of being progression-free after
  - 60 cycles: 61% (95% CI, 46–73)



Gross AM, et al. *Neuro Oncol*. 2023;25:1883–1894.

Selumetinib Adverse Events

All Grade (Grade 3–4)	Gastrointestinal	Skin and Subcutaneous Tissue	Other Toxicities
≥80%	Vomiting (6%)	All rashes* (6%)	
50%–79%	Abdominal pain Diarrhea (16%) Nausea (2%) Stomatitis	Dry skin Rash acneiform (4%)	Increased CPK (7%) Musculoskeletal pain Fatigue Pyrexia (8%)
20%–49%	Constipation	Paronychia (6%) Pruritus Dermatitis (4%) Hair changes	Headache (2%) Epistaxis Hematuria (2%) Proteinuria Decreased appetite Decreased ejection fraction Sinus tachycardia Skin infection (2%) Edema

Adverse events (AEs) occurring in ≥20% of patients.
*Rash (all) includes dermatitis acneiform, rash maculo-papular, erythema, rash pustular, rash, urticaria, exfoliative rash, rash pruritic, and rash erythematous.
CPK, creatine phosphokinase.

Selumetinib (package insert). Revised November 19, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/213756s006lbl.pdf.

Selumetinib AEs of Special Interest

Ocular			
Adverse Event, n	**Grade 1**	**Grade 2**	**Grade 3**
Blurred vision	4	0	0
Cataract	1	0	0
Dry eye	1	1	0
Eye disorders (other)	2	0	0
Eye pain	1	0	0
Photophobia	1	0	0
Photosensitivity	2	1	0
Retinopathy	1	0	0
Watering eyes	1	0	0

Cardiac			
Adverse Event, n	**Grade 1**	**Grade 2**	**Grade 3**
Ejection fraction decreased	0	14	1
Hypertension	6	2	0
Sinus bradycardia	2	0	0
Sinus tachycardia	2	0	0

Safety population, N=74

No grade 4 ophthalmological or cardiac AEs reported

Gross AM, et al. *Neuro Oncol*. 2023;25:1883–1894.

Selumetinib*
Warnings and Precautions

- Ocular toxicity: blurred vision, photophobia, cataracts, and ocular hypertension
  - 15% of pediatric population (resolved in 82%)
- Cardiomyopathy
  - Decreased LVEF of ≥10% occurred in 23% of pediatric patients (all were identified during routine echocardiography); decreased LVEF resolved in 71% of these patients
- Skin toxicity
  - Rash occurred in 91% of pediatric patients (8% Grade 3); the most frequent rashes included dermatitis acneiform (54%), maculopapular rash (39%), and eczema (28%)
- Gastrointestinal toxicity
  - Diarrhea in 77% of pediatric population (15% Grade 3)
- Increased creatine phosphokinase
  - Occurred in 76% of pediatric population (9% Grade 3 or 4)
- Risk of bleeding
  - Vitamin E is excipient and can inhibit platelet aggregation and antagonize vitamin K-dependent clotting factors
- Embryo-fetal toxicity

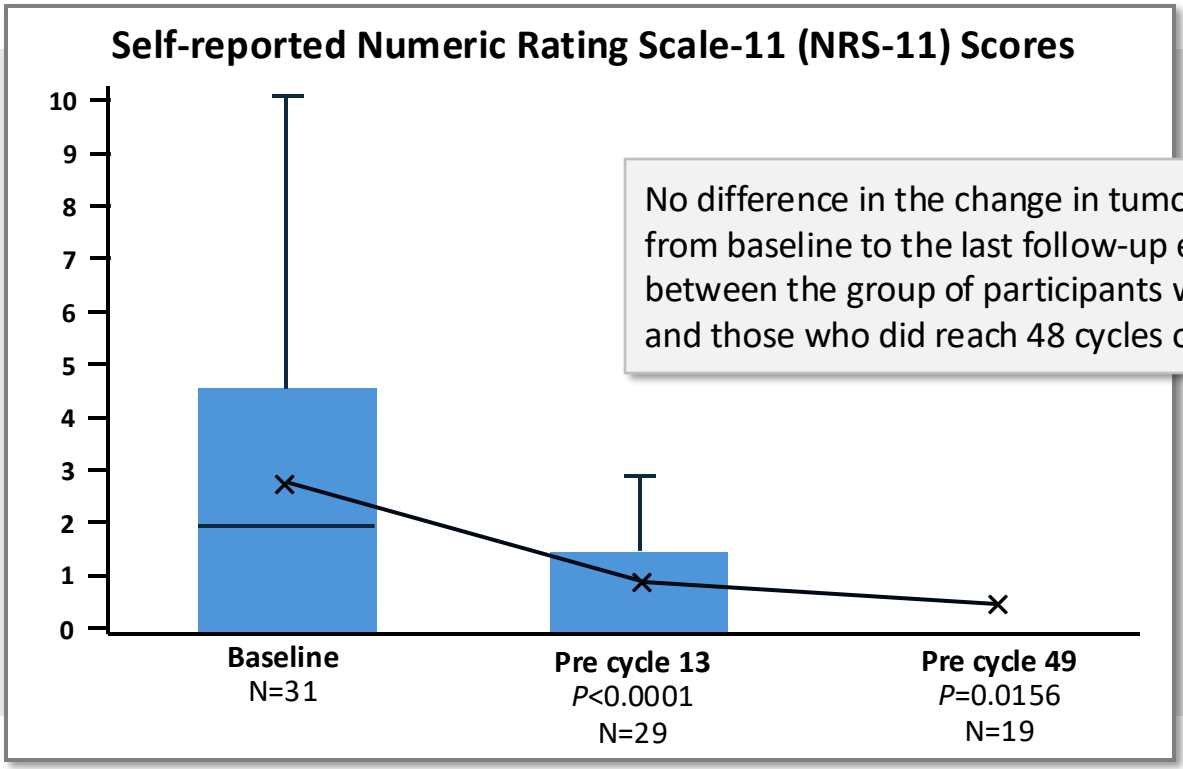
Toxicities seen in an unapproved adult population* with multiple tumor types who received selumetinib as a single agent or in combination with other anti-cancer agents:

- Retinal vein occlusion (RVO) and retinal pigment epithelial detachment (RPED)
- Intestinal perforation, colitis, ileus, and obstruction
- Cardiomyopathy (decreased left ventricular ejection fraction [LVEF])
- Severe palmar-plantar erythrodysesthesia syndrome
- Rhabdomyolysis

*Selumetinib is FDA approved in patients ≥1 year of age who have a PN; EMA approved in patients ≥3 years of age; other countries may vary.

Selumetinib (package insert). Revised November 19, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/213756s006lbl.pdf.

Selumetinib
Patient-Reported Pain



No difference in the change in tumor pain intensity from baseline to the last follow-up evaluation between the group of participants who did not reach and those who did reach 48 cycles of treatment

Gross AM, et al. *Neuro Oncol*. 2023;25:1883–1894.

ReNeu Trial

Mirdametinib in Children and Adults with Inoperable PN

- Phase 2, open-label
- Age-based cohorts
  - Pediatric (2–17 years)
  - Adults (≥18 years)
- NF1 + inoperable progressive and/or symptomatic PN

Baseline Demographics (pediatric [n=56]/adults [n=58])

- Median age: 10/58 years
- Male: 46%/36%
- Location of NF
  - Head + neck (50%/48%), lower-upper extremities (14%/29%), paraspinal (7%/9%), other (29%/14%)
- NF-related complications
  - Pain (70%/90%), disfigurement-major deformity (50%/52%), motor dysfunction or weakness (27%/40%), airway dysfunction (13%/5%), other (21%/17%)
- Target PN progressing: 63%/53%

Mirdametinib 2 mg/m² BID (max 4 mg)

Treatment cycle: 28 days (3 weeks on, 1 week off)

Up to 2 years

Primary Endpoint

- Partial response (≥20% volume reduction in target PN by volumetric MRI)

Secondary Endpoints

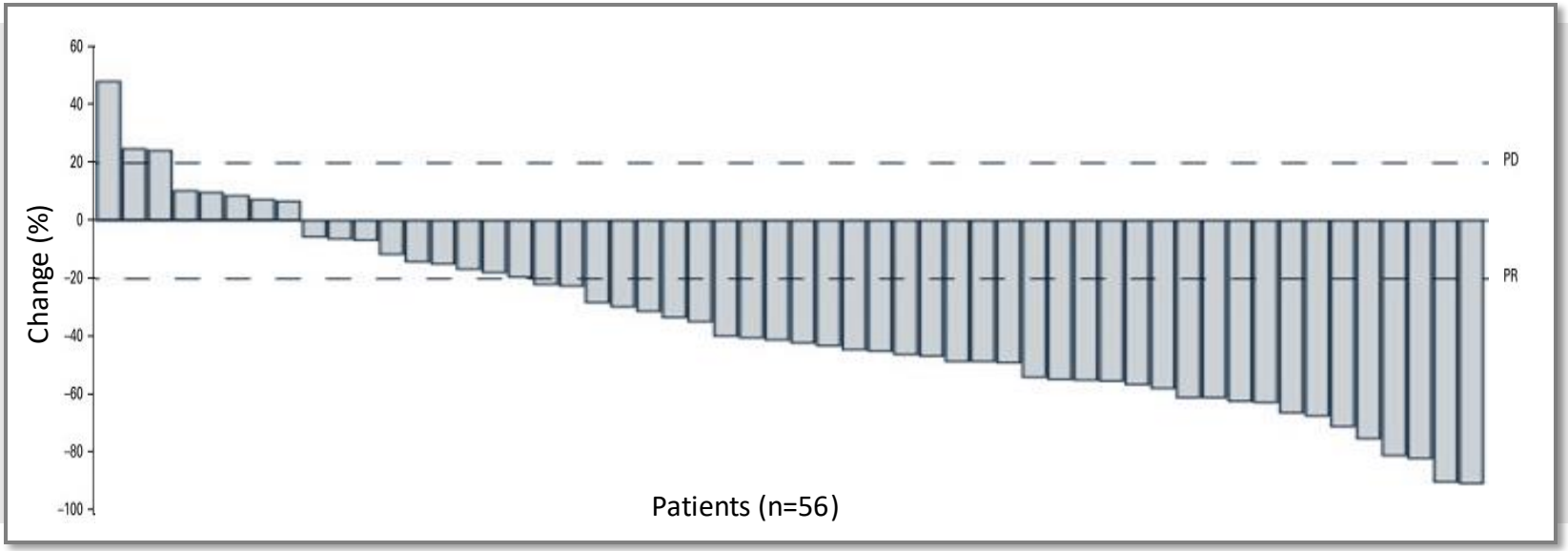
- Duration of response
- Safety
- QoL and physical functioning

Moertel CL, et al. *J Clin Oncol*. 2025;43(6):716–729.

ReNeu (Pediatrics)

Best Change from Baseline in Target PN Volume per Patient

Best Percent Change in Target PN Volume



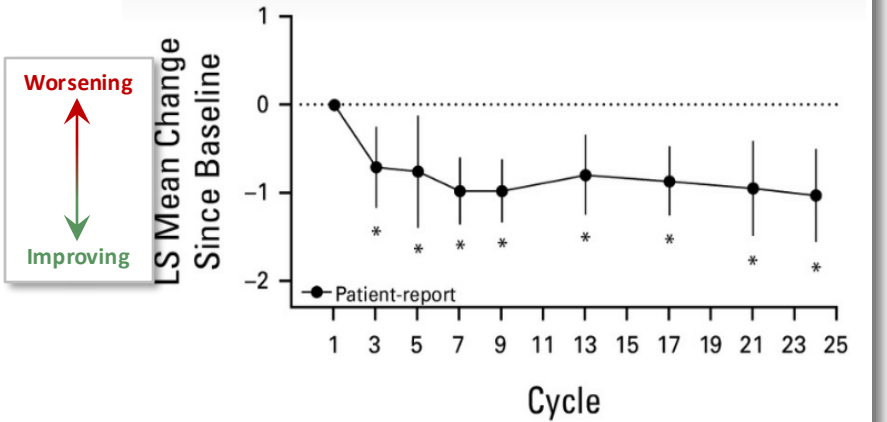
Moertel CL, et al. *J Clin Oncol*. 2025;43(6):716–729.

ReNeu (Pediatrics)

Pain and QoL

Patient-reported Pain

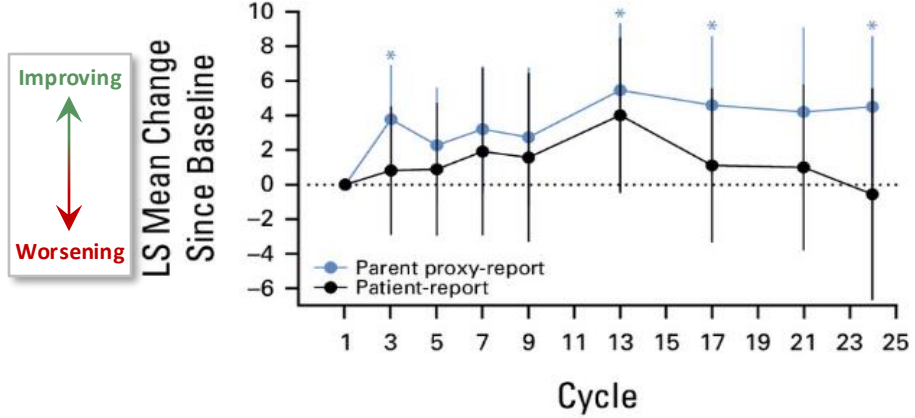
NRS-11 Score in Children



No. patients									
Patient-report	36	23	25	24	23	17	18	11	8

Patient-reported QoL

PedsQL Total Score in Children



No. patients									
Patient-report	50	48	47	41	42	38	34	32	29
Parent proxy-report	55	52	52	48	47	43	36	36	33

Moertel CL, et al. *J Clin Oncol*. 2025;43(6):716–729.

ReNeu Adverse Events (Pediatrics)

All Grade (grade 3–4)	Skin and Gastrointestinal	Other Toxicities
≥80%		
50%–79%	Rash* (4%) Diarrhea (5%)	Increased CPK (5%)
20%–49%	Nausea Vomiting Abdominal pain (4%) Stomatitis	Musculoskeletal pain (2%) Headache (2%) Paronychia Left ventricular dysfunction (2%) Increased triglycerides, creatinine, alk-phos, ALT COVID-19 Upper respiratory tract infection Decreased glucose, calcium, bicarbonate Cough Pyrexia Decreased hemoglobin, leukocytes, neutrophils, lymphocytes Increased lymphocytes

alk-phos, alkaline phosphatase; ALT, alanine aminotransferase.
AEs occurring in ≥20% of patients; data for adult patients is not included.
*Rash includes dermatitis acneiform, eczema, maculo-papular rash, pustular rash, dermatitis, erythematous rash, palmar-plantar erythrodysesthesia syndrome, exfoliative rash, skin exfoliation, pruritic rash, papule, papular rash, and macular rash.

Mirdametinib (package insert). Revised February 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/219379Orig1s000lbl.pdf.

Mirdametinib
Warnings and Precautions

- Ocular toxicity: retinal vein occlusion (RVO), retinal pigment epithelium detachment (RPED), and blurred vision
  - Occurred in 25% of patients; 20% Grade 1, 3.8% Grade 2, and 0.8% Grade 3
- Left ventricular dysfunction
  - Decreased LVEF of 10%–<20% occurred in 20%, and decreased LVEF of ≥20% occurred in 0.9% of patients (all were identified during routine echocardiography); decreased LVEF resolved in 75% of these patients
- Dermatological AEs
  - Rash occurred in 84% of patients (31% Grade 2; 6% Grade 3); the most frequent rashes (≥2%) included dermatitis acneiform (65%), rash (11%), eczema (8%), maculo-papular rash (4.5%) and pustular rash (3.8%)
- Embryo-fetal toxicity

Mirdametinib (package insert). Revised February 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/219379Orig1s000lbl.pdf.

Sam G. (…continued)

Sam is now 19 years old and has been receiving selumetinib continuously for symptomatic PN. The tumor shrank and is now stable. His pain also improved.

What would you recommend for this patient?

Which do you recommend for this patient?

A. Stop therapy

B. Switch to mirdametinib

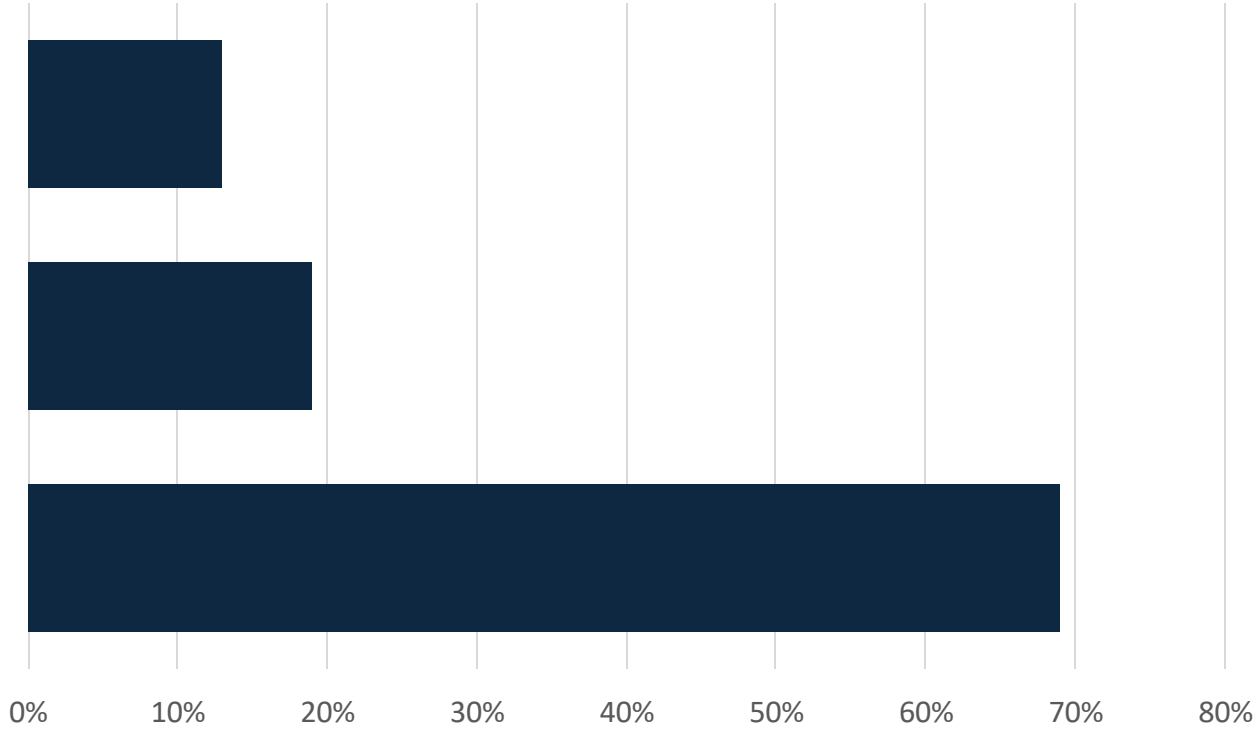
C. Stay on selumetinib

Which do you recommend for this patient?

A. Stop therapy

B. Switch to mirdametinib

C. Stay on selumetinib



Neurofibromatosis Type 1

Transition of Care

The Role of Peers in the Transition from Pediatric to Adult Care

Renie Moss

Patient Advocate and Caregiver

Renie Moss. Interview with CE Concepts. August 2025.

Clinical Perspective
Transition from Pediatric to Adult Care

Pediatric Needs

- Developmental delays
- Scholastic concerns
- Plexiform neurofibromas
- Autism/ADD
- Optic pathway gliomas
- Bone abnormalities

Adult Needs

- Dermal neurofibromas
- Malignant progression
- Pain
- Glioblastoma
- Breast cancer
- Family planning

Birth → **18 years** → **Adult**

Multidisciplinary Care Throughout the Lifespan

- Neurology
- Medical oncology
- Orthopedics
- Neurosurgery
- Plastic surgery
- Dermatology
- Psychiatry
- PT/OT

The transition of care is a process of moving from pediatric-centered to adult-centered care with or without transition to a new clinician.

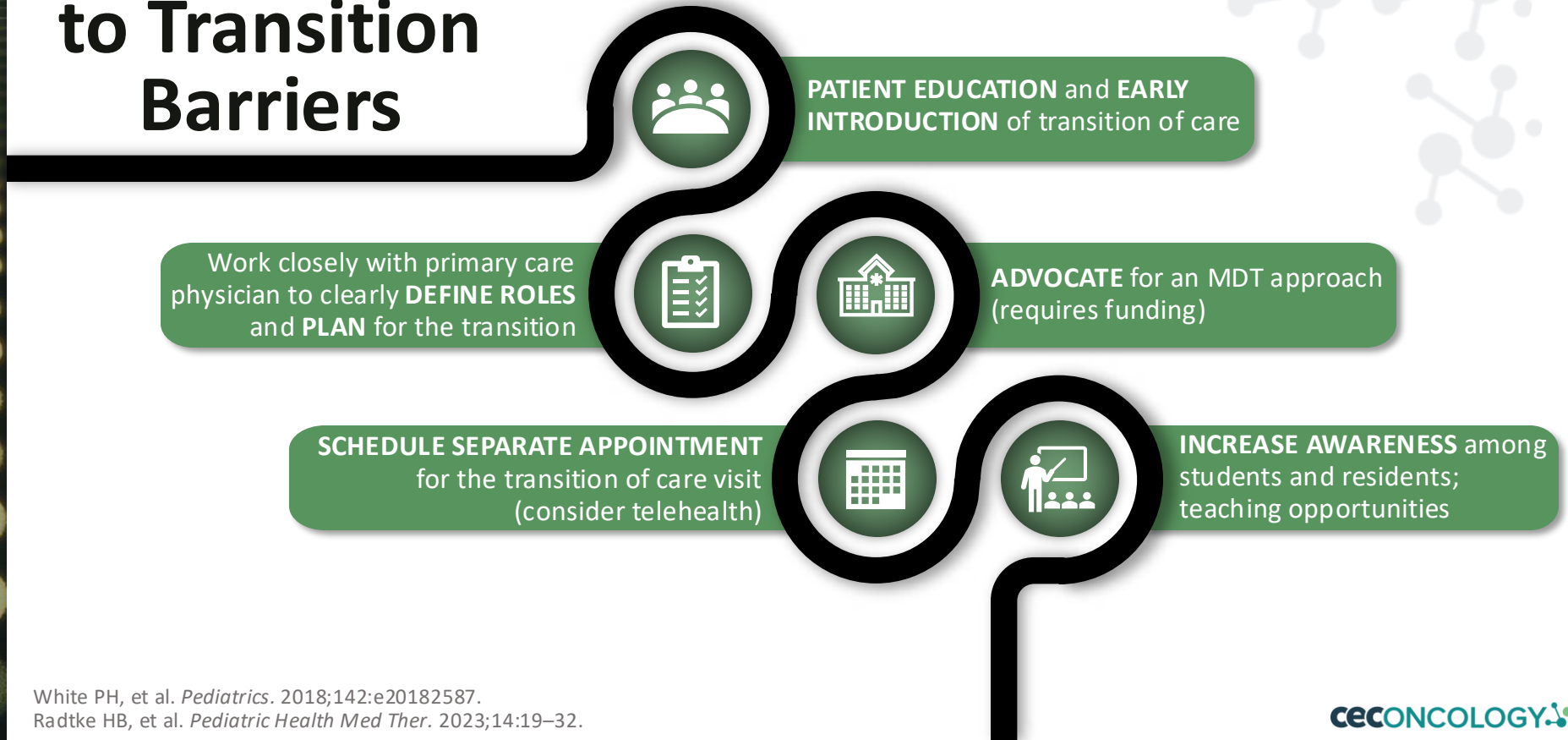
ADD, attention deficit disorder; OT, occupational therapy; PT, physical therapy.
*Based on Dr. Angela Hirbe's clinical experience and opinion.

BARRIERS to Successful NF1 Health Care Transitions

GC, genetic counselling; SW, social work.

White PH, et al. *Pediatrics*. 2018;142:e20182587.
Radtke HB, et al. *Pediatric Health Med Ther*. 2023;14:19–32.

Potential SOLUTIONS to Transition Barriers

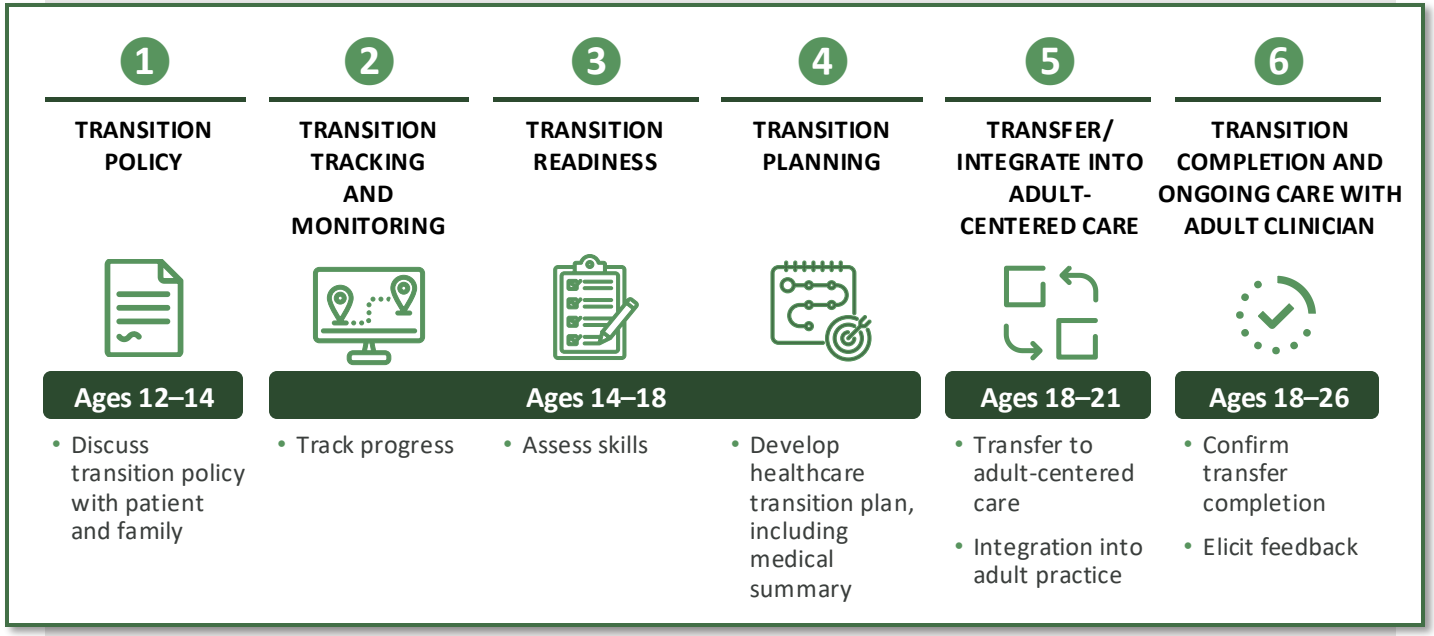


White PH, et al. *Pediatrics*. 2018;142:e20182587.
Radtke HB, et al. *Pediatric Health Med Ther*. 2023;14:19–32.

Core Elements of Health Care Transition

Key Elements for Transition to Adulthood Program

- Annual assessments to plan transition
- Establishment of yearly personal goals
- Bi-monthly adolescent and young adult transition planning meetings
- Dedicated collaborative specialists across the lifespan



White PH, et al. *Pediatrics*. 2018;142:e20182587. Radtke HB, et al. *Pediatric Health Med Ther*. 2023;14:19–32.

Tools to Aid Transition of Care

GOT TRANSITION is a national resource center on health care transition in the United States. Its aim is to “improve transition from pediatric to adult health care through the use of evidence-driven strategies for health care professionals, youth, young adults, and their families.”

Got Transition website. 2025. https://www.gottransition.org/.

Neurofibromatosis Type 1

MEK Inhibitors for the Treatment of Symptomatic, Inoperable Plexiform Neurofibromas in Adults

Case: Mary G.

Mary G. is a 45-year-old female with a painful facial PN that is also causing significant deformity. The pain is similar to what it has been for years (i.e., no new/changing pain). Her MRI does not demonstrate concerning features of the tumor.

ReNeu Trial

Mirdametinib in Children and Adults with Inoperable PN

- Phase 2, open-label
- Age-based cohorts
  - Pediatric (2–17 years)
  - Adults (≥18 years)
- NF1 + inoperable progressive and/or symptomatic PN

Baseline Demographics (pediatric [n=56]/adults [n=58])

- Median age: 10/58 years
- Male: 46%/36%
- Location of NF
  - Head + neck (50%/48%), lower-upper extremities (14%/29%), paraspinal (7%/9%), other (29%/14%)
- NF-related complications
  - Pain (70%/90%), disfigurement-major deformity (50%/52%), motor dysfunction or weakness (27%/40%), airway dysfunction (13%/5%), other (21%/17%)
- Target PN progressing: 63%/53%

Mirdametinib 2 mg/m² BID (max 4 mg)

Treatment cycle: 28 days (3 weeks on, 1 week off)

Up to 2 years

Primary Endpoint

- Partial response (≥20% volume reduction in target PN by volumetric MRI)

Secondary Endpoints

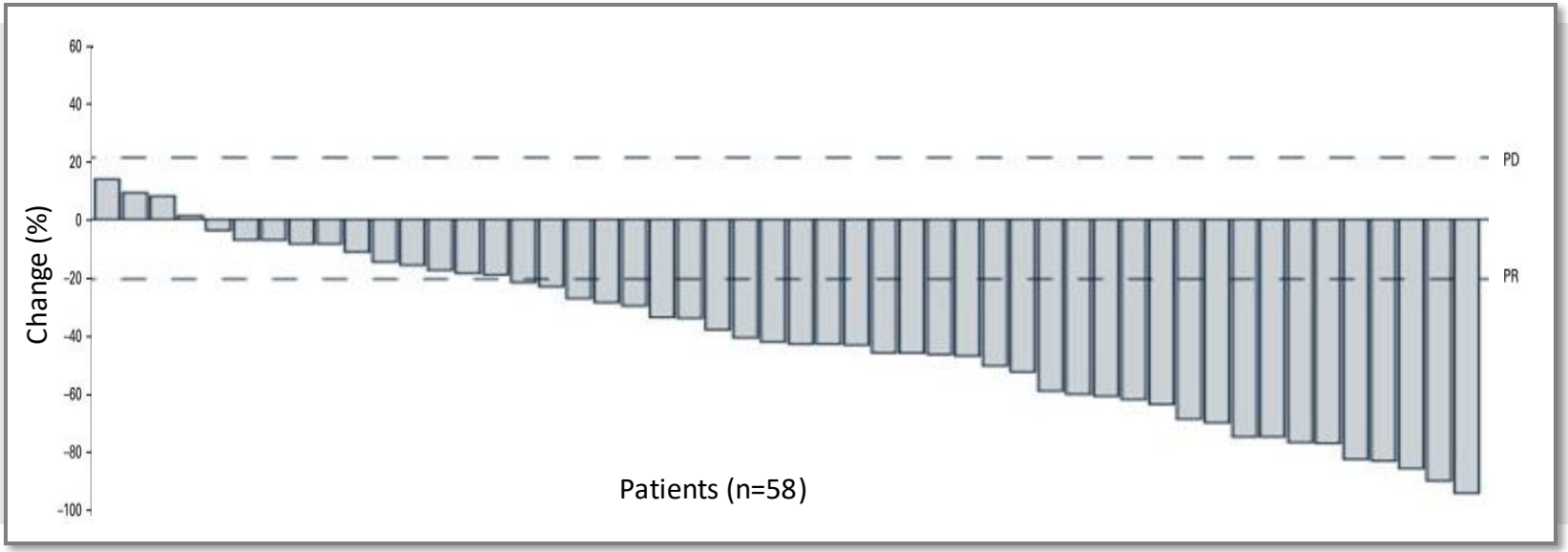
- Duration of response
- Safety
- QoL and physical functioning

Moertel CL, et al. *J Clin Oncol*. 2025;43(6):716–729.

ReNeu (Adult)

Best Change from Baseline in Target PN Volume per Patient

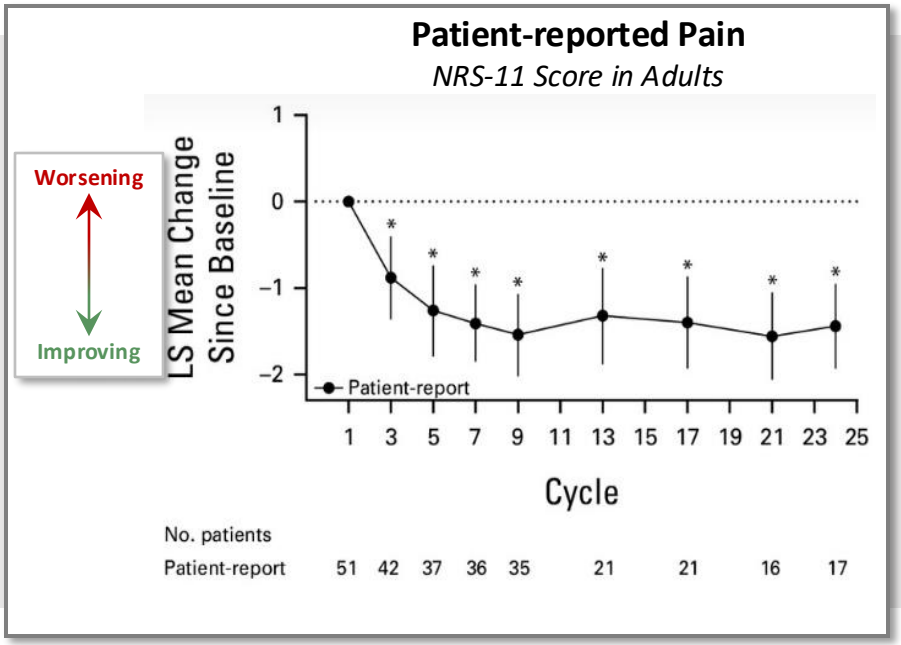
Best Percent Change in Target PN Volume

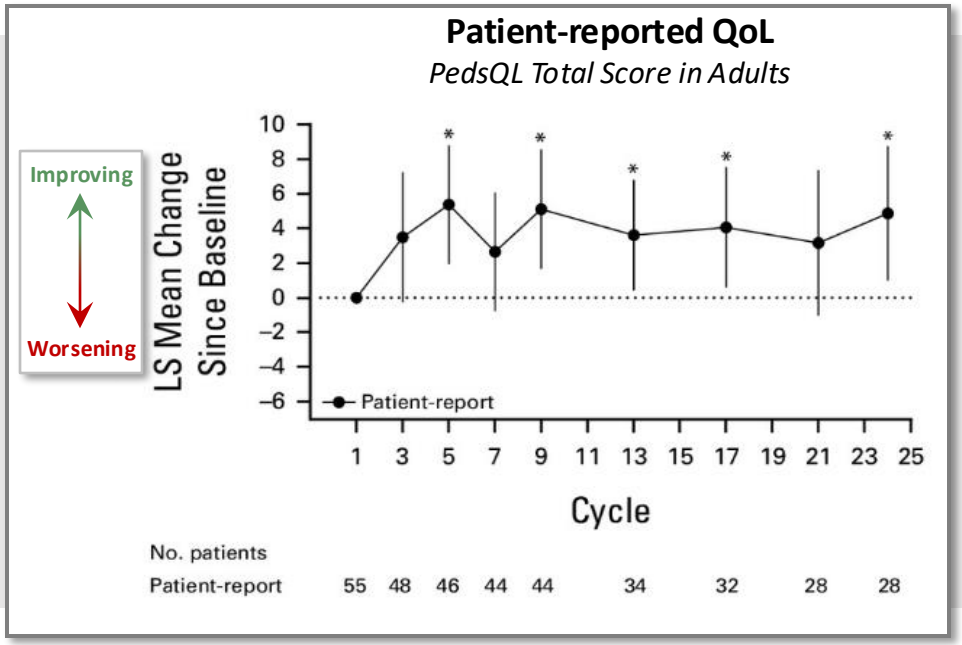


Moertel CL, et al. *J Clin Oncol*. 2025;43(6):716–729.

ReNeu (Adult)

Pain and QoL





Moertel CL, et al. *J Clin Oncol*. 2025;43(6):716–729.

ReNeu Adverse Events (Adult)

All Grade (grade 3–4)	**Skin and Gastrointestinal**	**Other Toxicities**
≥80%	Rash* (10%)	
50%–79%	Diarrhea Nausea	Increased CPK (4%)
20%–49%	Vomiting Abdominal pain (3%)	Musculoskeletal pain (5%) Headache (2%) COVID-19 (5%) Fatigue (2%) Peripheral neuropathy Increased triglycerides, cholesterol Decreased calcium Anemia Decreased hemoglobin

AEs occurring in ≥20% of patients; data for adult patients is not included.
*Rash includes dermatitis acneiform, eczema, maculo-papular rash, pustular rash, dermatitis, erythematous rash, palmar-plantar erythrodysesthesia syndrome, exfoliative rash, skin exfoliation, pruritic rash, papule, papular rash, and macular rash.

Mirdametinib (package insert). Revised February 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/219379Orig1s000lbl.pdf.

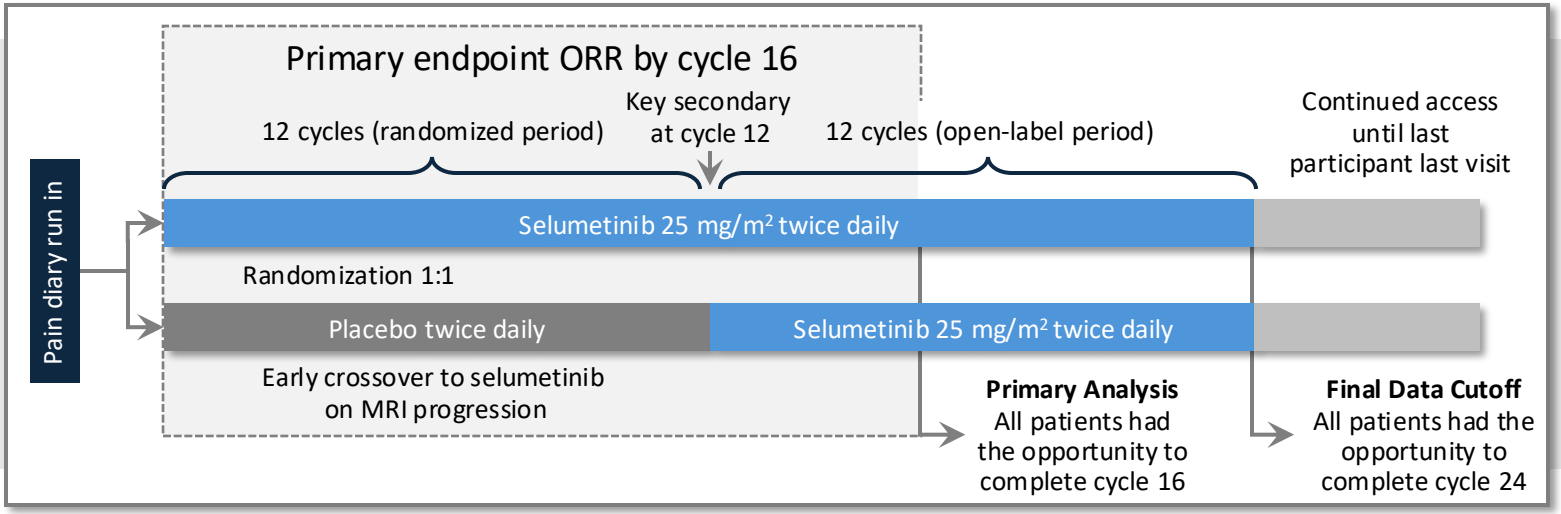
KOMET Trial

Selumetinib in Adults with Symptomatic Inoperable PN*

- Phase 3, placebo-controlled
- Adults ≥18 years of age
- NF1 + symptomatic inoperable PN
- A completed PAINS-pNF diary with a documented chronic target plexiform neurofibroma pain score on ≥4 of 7 days over ≥2 weeks during screening; stable chronic pain medication at baseline

Baseline Demographics (median values)

- Age: 29.5 years
- Male: 49%
- Volume of target PN: 92.0 mL selumetinib, 221.9 mL placebo
- Location of target PN
  - Neck + trunk (24%), trunk + limbs (24%), head (18%), head + neck (16%), trunk (10%), limbs (8%)
- Patients were stratified by chronic target plexiform neurofibroma pain score and geographical region

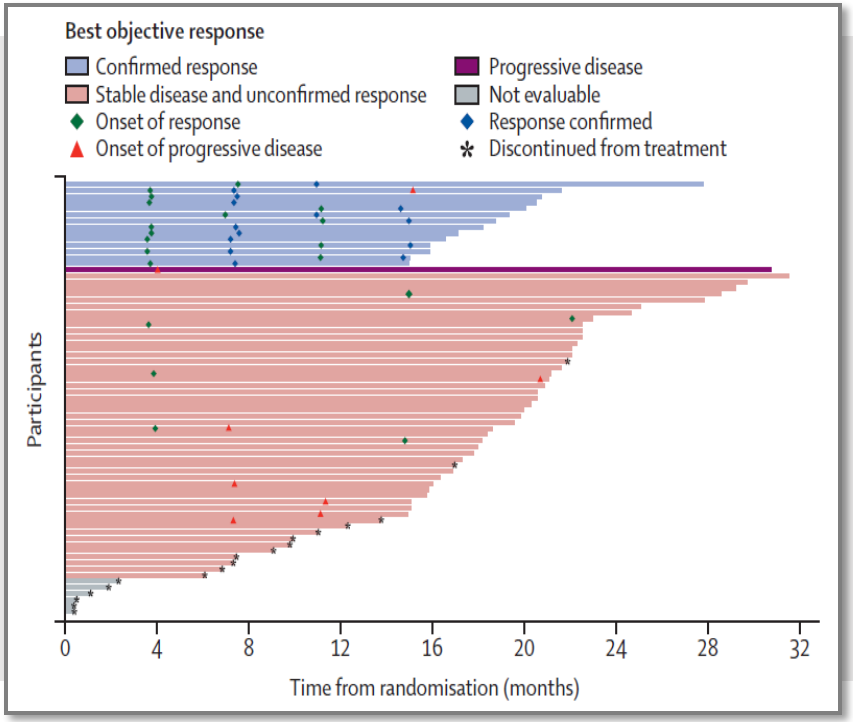


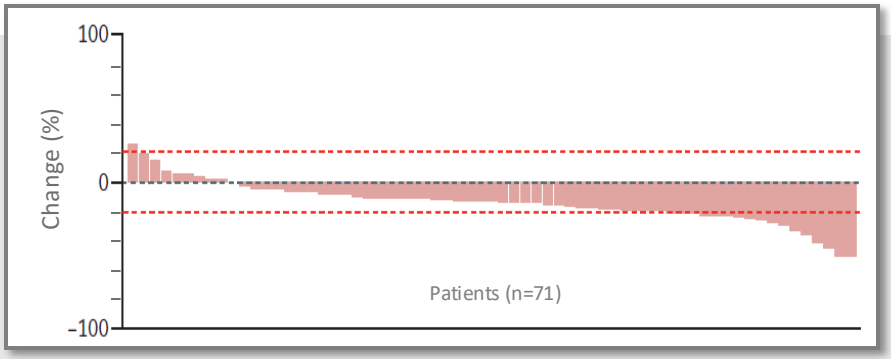
*Selumetinib is FDA approved in patients ≥1 year of age who have a PN; EMA approved in patients ≥3 years of age; other countries may vary.

Chen AP, et al. *Lancet*. 2025;405(10496):2217–2230.

KOMET Trial: Efficacy

Selumetinib in Adults with Symptomatic Inoperable PN





Participants randomly assigned to selumetinib	Target plexiform neurofibroma volume, best percentage change	
	Participants with an objective response by C16 (n=14)	Participants who had not reached an objective response by C16 (n=51)
Mean	−36·6	−9·9
Median (minimum, maximum)	−33·9 (−58·1 to −22·6)	−11·4 (−26·7 to 24·0)

Chen AP, et al. *Lancet*. 2025;405(10496):2217–2230.

KOMET Trial: Adverse Events

	Selumetinib n=71	Placebo n=74
Any AEs (grade ≥3)	100% (32%)	92% (18%)
Serious AE	14%	12%
AE leading to discontinuation	13%	7%
AE leading to dose modification	38%	14%
Any AE special interest	66%	22%
Maximum reported CTCAE grade		
1	23%	30%
2	45%	45%
3	27%	15%
4	6%	3%

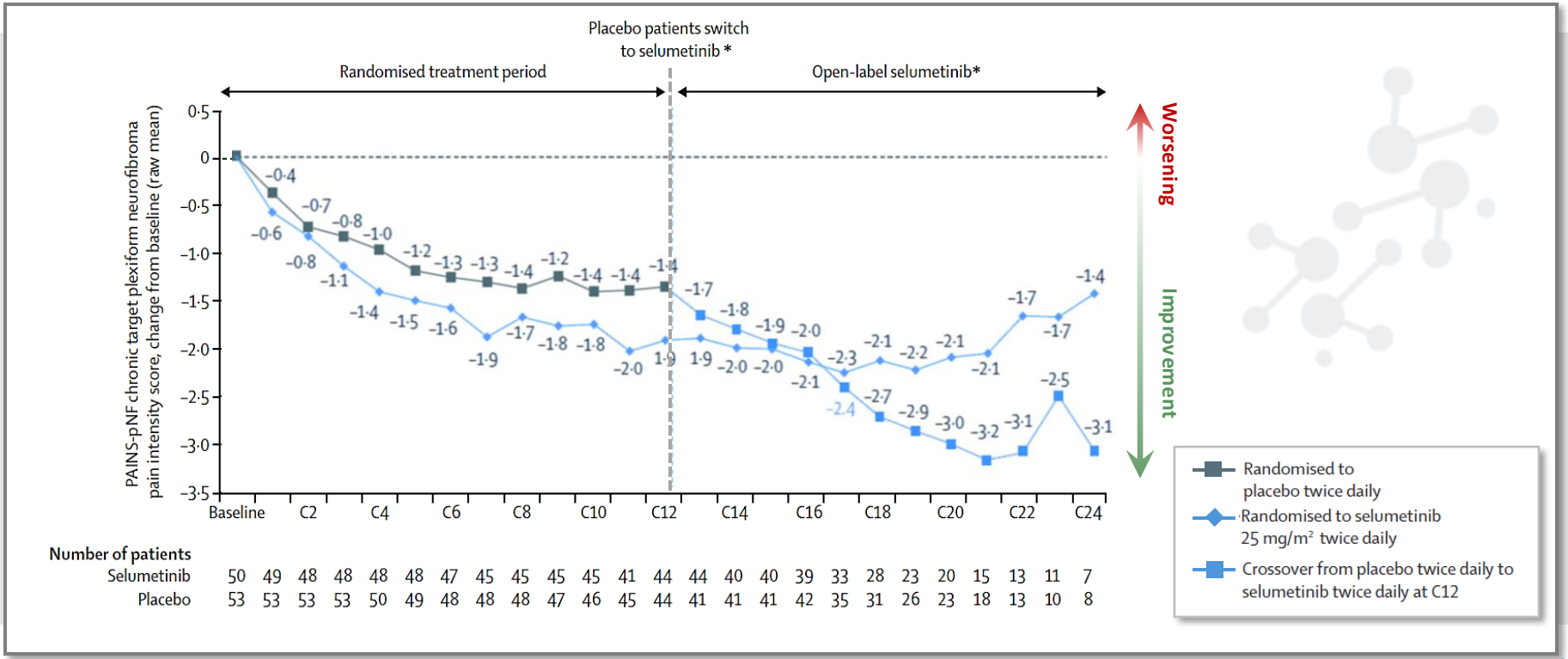
	Selumetinib n=71	Placebo n=74
Gastrointestinal disorders	75%	43%
Skin and subcutaneous tissue disorders	90%	35%
Musculoskeletal/connective tissue disorders	27%	23%
General disorders	51%	28%
Investigations	62%	28%
Infections and infestations	54%	45%
Eye disorders	17%	12%

All Grade (Grade 3–4)	Gastrointestinal	Skin and Subcutaneous Tissue	Other Toxicities
≥80%			
50%–79%	Diarrhea (12%)	Dermatitis acneiform (11%)	Increased CPK (5%)
20%–49%	Nausea (16%) Vomiting (8%)		

CTCAE, Common Terminology Criteria for Adverse Events.
Chen AP, et al. *Lancet*. 2025;405(10496):2217–2230.

KOMET Trial: Pain Scores

Selumetinib in Adults with Symptomatic Inoperable PN

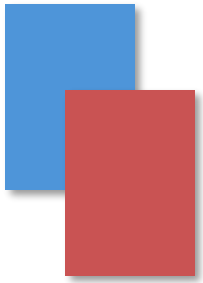


Chen AP, et al. *Lancet*. 2025;405(10496):2217–2230.

MEKi Options

SELUMETINIB

- Pediatric and adult patients
- Pill and granular (sprinkle) dosing
- Continuous therapy
- 6.2-hour serum half life
- Avoid CYP3A4 inhibitors



MIRDAMETINIB

- Pediatric and adult patients
- Capsule and dispersible tablet
- 3 weeks on, 1 week off
- 28-hour serum half life

No head-to-head comparisons
No data on MEKi switching

Selumetinib (package insert). Revised November 19, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/213756s006lbl.pdf.
Mirdametinib (package insert). Revised February 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/219379Orig1s000lbl.pdf.

Neurofibromatosis Type 1

Managing Patients Utilizing Long-Term MEK Inhibitor Therapy

Mary G. (…continued)

Mary receives mirdametinib. Her facial tumor shrinks to approximately half of its original size and the pain improves substantially. However, she develops grade 4 CPK increase.

What would you recommend for this patient?

Which do you recommend for this patient?

A. Assess for symptoms, if asymptomatic continue therapy

B. Switch to selumetinib

C. Withhold until grade ≤1 and resume at lower dose

D. Permanently discontinue treatment

E. Continue irrespective of CPK increase

Which do you recommend for this patient?

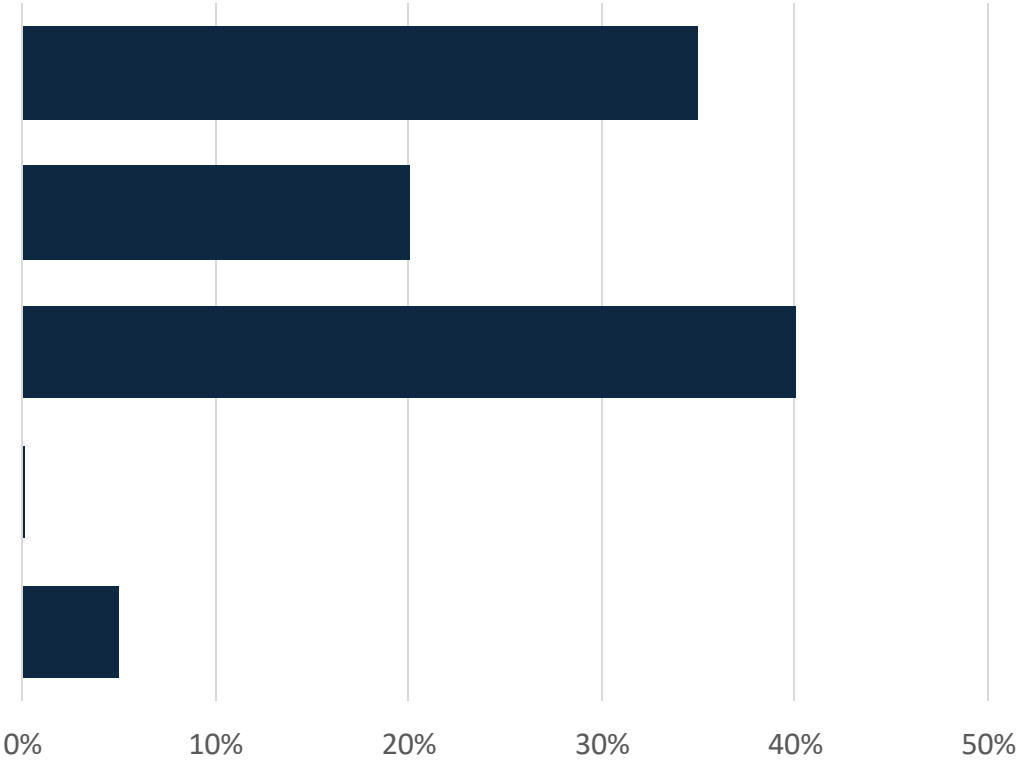
A. Assess for symptoms, if asymptomatic continue therapy

B. Switch to selumetinib

C. Withhold until grade ≤1 and resume at lower dose

D. Permanently discontinue treatment

E. Continue irrespective of CPK increase



NF1-PN and MEKi Therapy Monitoring

Exam	Monitoring
Review of systems and physical examination (including GI, vision, skin, oral mucosa, and nails)	• Every visit (generally monthly)
Ophthalmologic examination	• Baseline, then every 6–12 months • Consider increased frequency with new symptoms
Echocardiogram/ejection fraction	• Baseline, every 3–6 months
Electrocardiogram	• Baseline, then as clinically indicated
Pregnancy status	• Baseline, then per institutional standards
Laboratory examinations	• Baseline, then every 3–6 months: creatine kinase, metabolic panel, liver function tests, CBC • Baseline, then as clinically indicated: amylase, lipase

CBC, complete blood count; GI, gastrointestinal.

Friedman JM. Neurofibromatosis 1. In: Adam MP, et al., eds. *GeneReviews*. Seattle (WA): University of Washington, Seattle; 1993 (updated 2025).
Moodley M, et al. *Semin Pediatr Neurol*. 2024;52:101172. Na B, et al. *Curr Oncol Rep*. 2024;26:706–713.
Lee TJ, et al. *Orphanet J Rare Dis*. 2023;18(1):292.

General MEKi Safety Experience in Clinical Trials

Pediatric/Children

- Mild rash
- Paronychia
- Hypotonia or muscle weakness
- Retinal damage
- Impact on developmental changes are unknown

Adolescents/Adults

- Severe acne rash
- Paronychia
- Weight gain
- Fatigue
- GI problems

Gross AM, et al. *Nat Med*. 2025;31(1):105–115. Solares I, et al. *ESMO Open*. 2021;6(4):100223.
Gross AM, et al. *Neuro Oncol*. 2023;25:1883–1894. Moertel CL, et al. *J Clin Oncol*. 2025;43(6):716–729.

Summary

- Patients with NF1 are at risk for tumor and nontumor manifestations, necessitating care from a multidisciplinary team
- PNs are one of the most common tumor manifestations in patients with NF1 and carry a significant risk of malignant transformation
- PN can be managed surgically, with MEKis, or on clinical trial
- Many areas of ongoing research to improve therapy for patients with NF1-PN
- The goal of transition of care is to maintain optimal healthcare, which can only be achieved when each person, at every age, receives medically and developmentally appropriate care

Unanswered Questions

- How long is MEKi therapy needed?
- Does it help to switch between MEKi?
- What is the realistic vs optimal surveillance of a person on MEKi for PN?
- Is there a role for MEKis in preventing MPNST in people with high burden of PN?

The Future

NCT Number	Phase II Study Title	Study Status	Conditions	Primary Outcome Measures	Age Group
NCT05331105	HL-085 in Adults with Neurofibromatosis Type 1 (NF1) and Inoperable Plexiform Neurofibromas	Recruiting	NF1-PN	ORR	Adult, older adult
NCT06541847	NF119 (INSPIRE): A Phase 2, Open-Label Study to Evaluate the Safety and Effects of HLX-1502 in Patients with Neurofibromatosis Type 1	Recruiting	NF1	PN response rate	Child, adult, older adult
NCT06188741	NF114: Selumetinib for the Prevention of Plexiform Neurofibroma Growth in NF Type 1	Not yet recruiting	NF1-PN	PFS	Child
NCT06502171	Study of Cabozantinib with Selumetinib for Plexiform Neurofibromas	Not yet recruiting	NF1-PN	Dose limiting toxicity, safety	Adult (≥16 yrs)

ClinicalTrials.gov.

Put information into action!

Takeaways from this program can be implemented into your practice to improve patient care.

- *Refer patients to NF1 centers.* NF1 is a complex disease that requires support from many specialists. NF1 centers offer access to experts with experience in managing the specific needs of these patients.
- *Develop a robust multidisciplinary team for NF1 patient care.* Clinicians should have a low threshold for calling in support from specialists in neurology, cardiology, nephrology, pulmonology, genetics, and other specialties.
- *Implement strategies to improve transitions from pediatric care and integration into adult care.* Patients with NF1 are typically diagnosed in childhood and will need to transition to managing their own care as adults, which may be challenging for a young person. Remember, it is not too early to plan for the future.

Additional Resources

Visit *www.ceconcepts.com* for clinical information and certified educational activities.

Claim Credit

Scan the appropriate QR code for your mode of participation in this activity and create or log in to a Creative Educational Concepts learner account. Complete the necessary requirements (e.g., pre-test, post-test, evaluation) and then claim your credit.*

Thank you for your participation!

*To receive credit, participants must register an account and apply for credit within 10 days of the live activity. For questions or technical difficulties, please contact info@ceconcepts.com.

In-Person

Livestream

Claim ABIM MOC Credit

3 Steps to Complete

1. Actively participate in the discussion today by **responding to questions** and/or **asking the faculty questions**
   (MOC credit can be claimed even if a question goes unanswered or an incorrect response is entered)
2. Complete the post-test and evaluation at the conclusion of the webcast
3. Enter your **ABIM ID number** and **DOB** (MM/DD) on the evaluation, so credit can be submitted to ABIM

ABIM CME MOC ACCREDITED

CME for MIPS Improvement Activity

How to Claim This Activity as a CME for MIPS Improvement Activity

- Actively participate today by responding to ARS questions and/or asking the faculty questions
- Complete the post-test and activity evaluation at the link provided
- Over the next 3 months, actively work to incorporate improvements from this presentation into your clinical practice
- In approximately 3 months, complete the follow-up survey from Creative Educational Concepts

CME for MIPS IMPROVEMENT ACTIVITY

CEC will send you confirmation of your participation to submit to CMS attesting to your completion of a CME for MIPS Improvement Activity.

TARGETING THE PATHWAY

Evolving Roles of MEK Inhibitors in NF1-Associated PN

Supported by an independent educational grant from Alexion Pharmaceuticals.