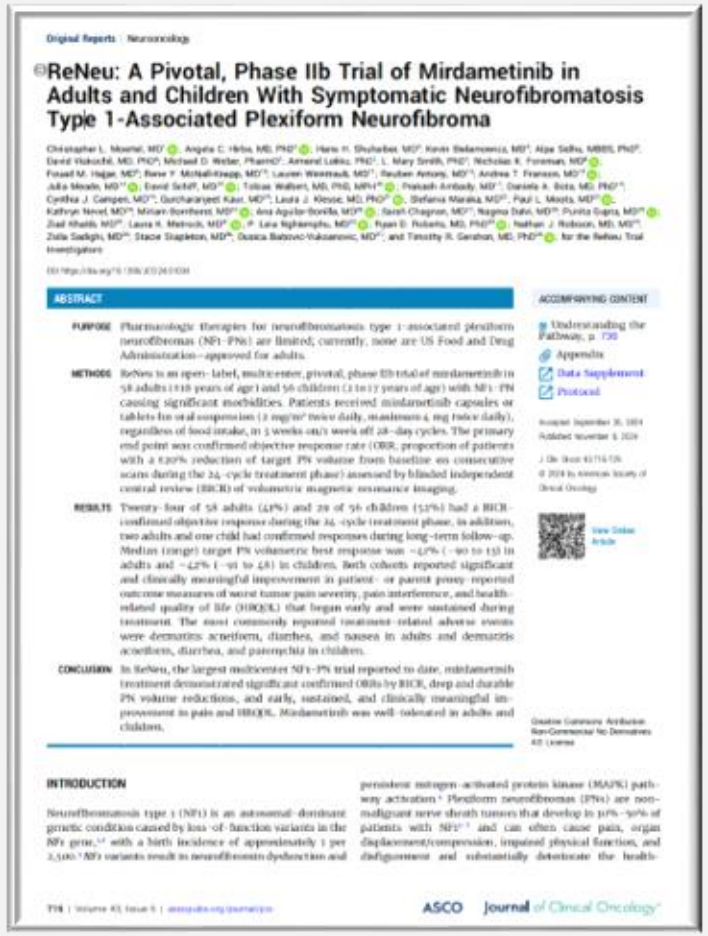
RENEU: A Pivotal, Phase IIb Trial of Mirdametinib in Adults and Children With Symptomatic Neurofibromatosis Type 1-Associated Plexiform Neurofibroma



Original Reports · Neurooncology

ReNeu: A Pivotal, Phase IIb Trial of Mirdametinib in Adults and Children With Symptomatic Neurofibromatosis Type 1-Associated Plexiform Neurofibroma

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ABSTRACT

PURPOSE Pharmacologic therapies for neurofibromatosis type 1–associated plexiform neurofibromas (NF1-PNs) are limited; currently, none are US Food and Drug Administration–approved for adults.

METHODS ReNeu is an open-label, multicenter, pivotal, phase IIb trial of mirdametinib in 58 adults (≥18 years of age) and 56 children (≥2 to <18 years of age) with NF1-PN causing significant morbidities. Patients received mirdametinib capsules or tablets for oral suspension (2 mg/m² twice daily, maximum 4 mg twice daily), regardless of food intake, in 3 weeks on/1 week off 28-day cycles. The primary end point was confirmed objective response rate (ORR; proportion of patients with a ≥20% reduction of target PN volume from baseline on consecutive scans during the 24-cycle treatment phase) assessed by blinded independent central review (BICR) of volumetric magnetic resonance imaging.

RESULTS Twenty-four of 58 adults (41%) and 29 of 56 children (52%) had a BICR-confirmed objective response during the 24-cycle treatment phase. In addition, two adults and one child had confirmed responses during long-term follow-up. Median (range) target PN volumetric best response was −41% (−90 to 15) in adults and −42% (−91 to 48) in children. Both cohorts reported significant and clinically meaningful improvement in patient- or parent proxy-reported outcome measures of worst tumor pain severity, pain interference, and health-related quality of life (HRQOL) that began early and were sustained during treatment. The most commonly reported treatment-related adverse events were dermatitis acneiform, diarrhea, and nausea in adults and dermatitis acneiform, diarrhea, and paronychia in children.

CONCLUSION In ReNeu, the largest multicenter NF1-PN trial reported to date, mirdametinib treatment demonstrated significant confirmed ORRs by BICR, deep and durable PN volume reductions, and early, sustained, and clinically meaningful improvement in pain and HRQOL. Mirdametinib was well-tolerated in adults and children.

ACCOMPANYING CONTENT

Understanding the Pathway, p. 730

Appendix

Data Supplement

Protocol

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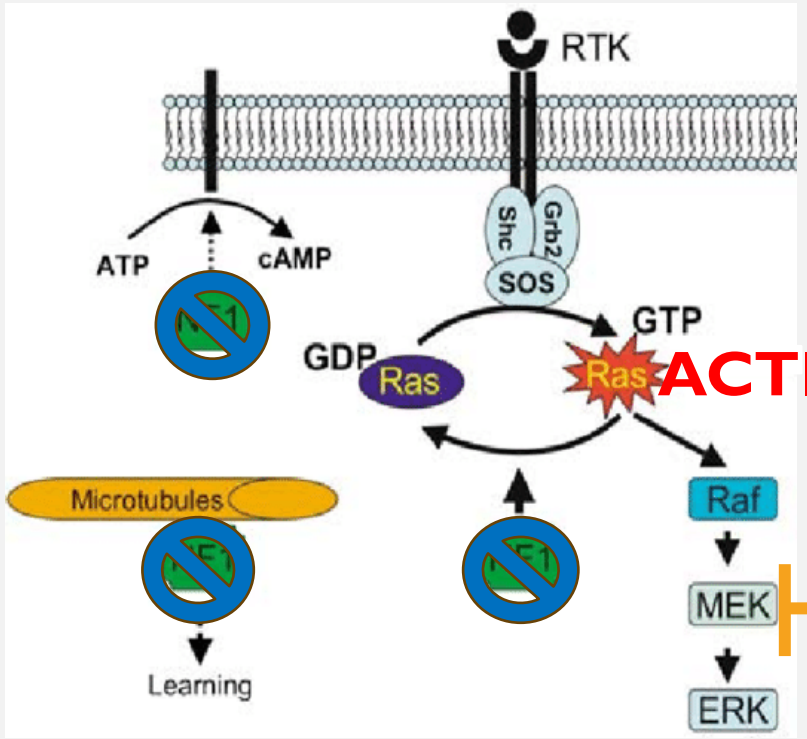
View Online Article

INTRODUCTION

Neurofibromatosis type 1 (NF1) is an autosomal-dominant genetic condition caused by loss-of-function variants in the *NF1* gene,[1,2] with a birth incidence of approximately 1 per 2,500.[3] *NF1* variants result in neurofibromin dysfunction and persistent mitogen-activated protein kinase (MAPK) pathway activation.[4] Plexiform neurofibromas (PNs) are non-malignant nerve sheath tumors that develop in 30%-50% of patients with NF1[5-7] and can often cause pain, organ displacement/compression, impaired physical function, and disfigurement and substantially deteriorate the health-

- Moertel CL et al., J Clin Oncol 2024
- NCT03962543 | Data cutoff: Sept 20, 2023
- DOI https://doi.org/10.1200/JCO.24.01034

Rationale & Study Design



Mirdametinib– Phase II trial (adults / adolescents only)
Phase IIb trial: Larger adult trial, children, tablet-for-suspension formulation for patients with swallowing difficulties

Trial Design

Participants: Children (2–17 y, n=56), Adults (≥18 y, n=58) and 24 treatment cycles

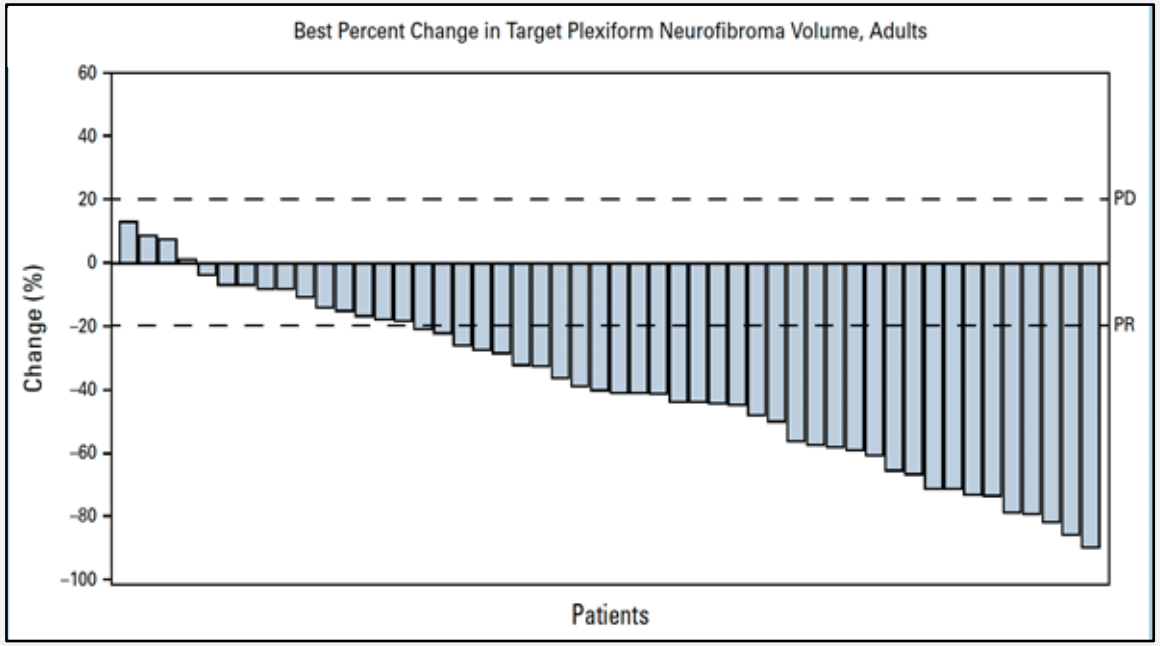
Mirdametinib dose:
2mg/m² PO BID (max 4 mg BID), 3 weeks on/ 1 week off; PROs at cycle 13

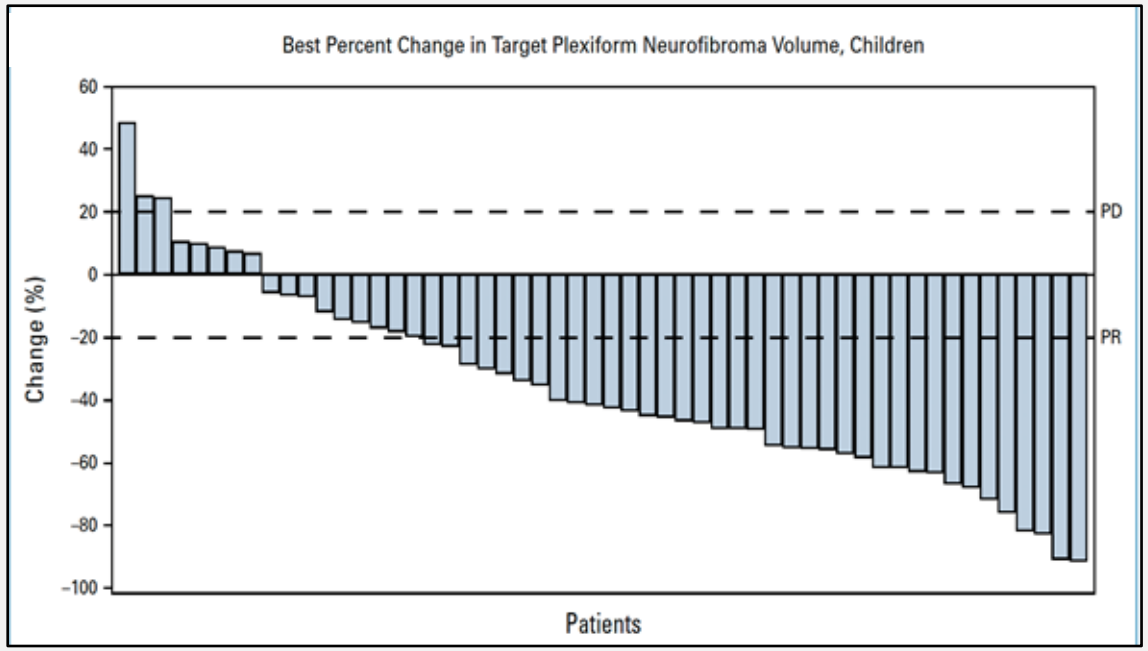
Primary end point: BICR-confirmed ORR (≥20% volumetric reduction
Key secondary end point: DoR, PFS (children vs matched historical), PROs

30-day safety follow-up after treatment discontinuation

Le LQ, Parada LF.Tumor microenvironment and neurofibromatosis type I: connecting the GAPs. Oncogene. 2007;26(32):4609-4616. doi:10.1038/sj.onc.1210261
NF1,Neurofibromatosis type1; PN, plexiform neurofibromatosis; BICR, blinded independent central review; ORR, objective response rate; DoR, duration of response; PFS, progression-free survival; PROs, patient-reported outcomes.

Mirdametinib-treated Adults and Children Achieved Significant Confirmed Objective Response Rate





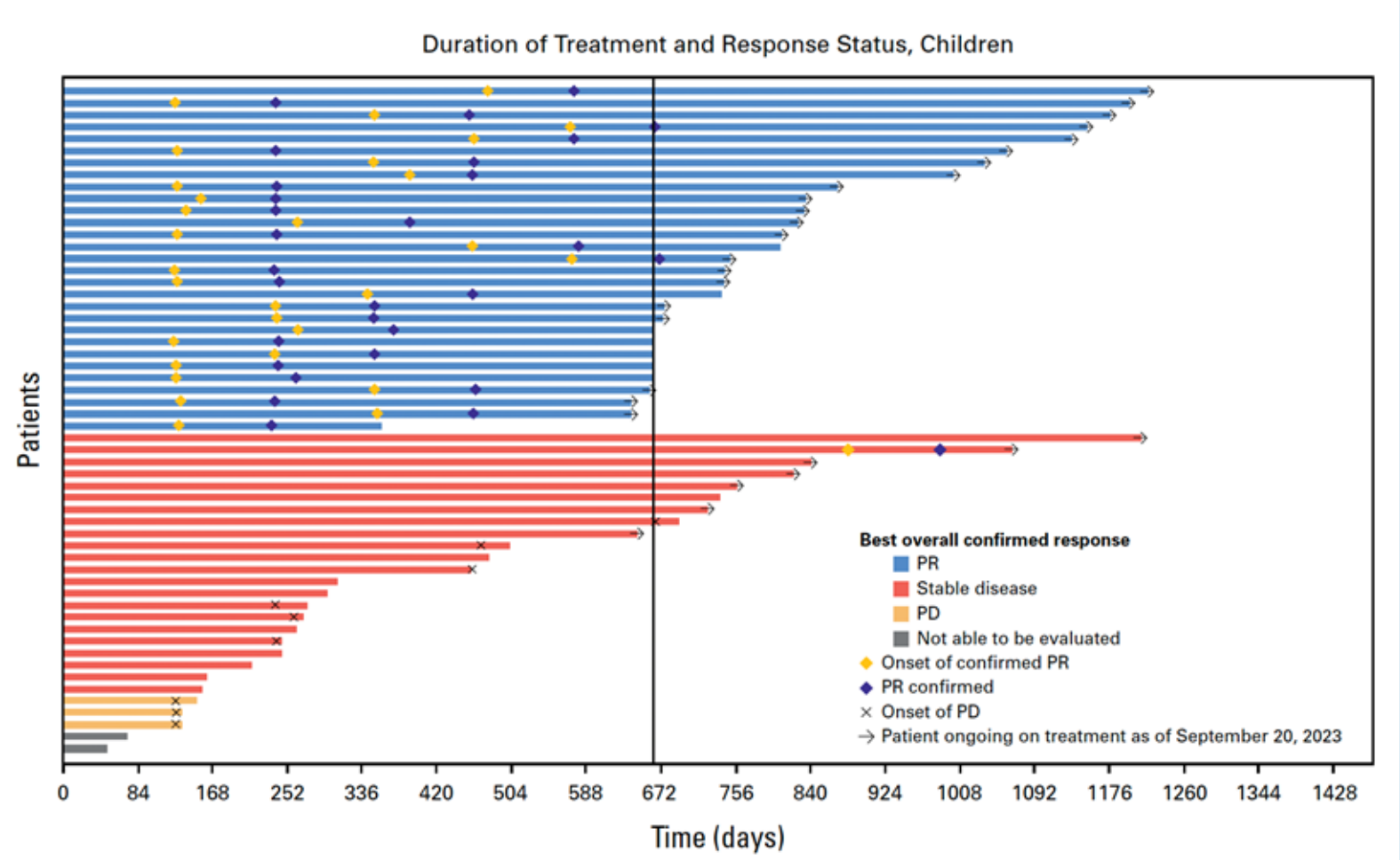
Primary end point confirmed ORR (adults): 41% (24/58); (95% CI, 29 to 55); *(P < .001)*

Primary end point confirmed ORR (children): 52% (29/56); (95% CI, 38 to 65); *(P < .001)*

Key Findings: Majority of responders achieved >50% tumor volume reduction (62% adults, 52% children)

PD, progressive disease; PN, plexiform neurofibroma; PR, partial response; ORR, objective response rate. Moertel et al., J Clin Oncol 2024

Mirdametinib-treated Adults and Children Achieved Deep and Durable Response



Adults:

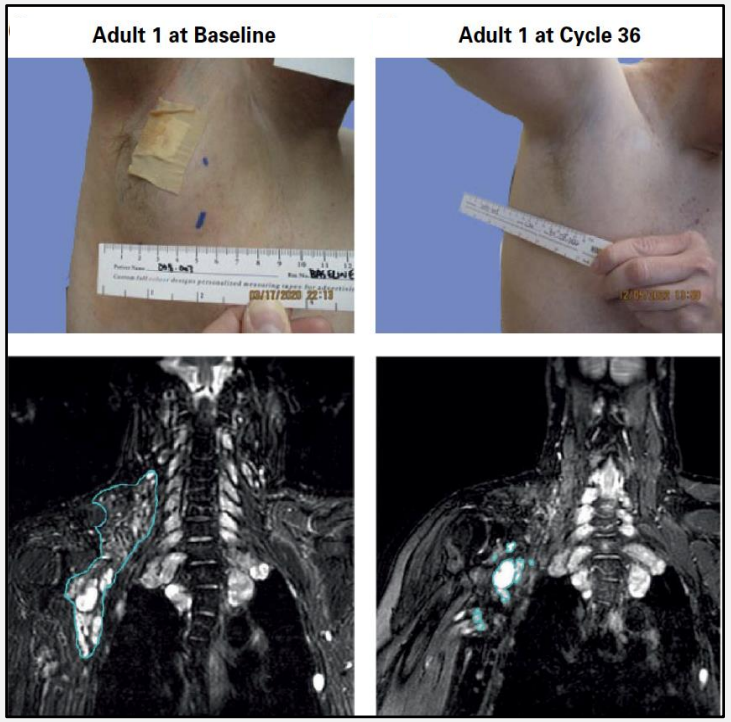
- Median time to confirmed response: 7.8 months (range, 4.0–19.0)
- Median treatment duration: 21.8 months (range, 0.4–45.6)
- The median time to best volumetric percentage change:15.2 months (range, 4.0–40.0)

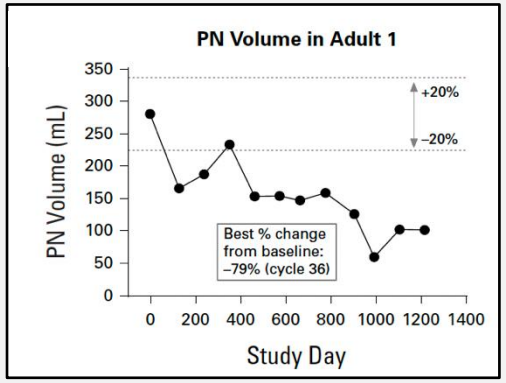
Children:

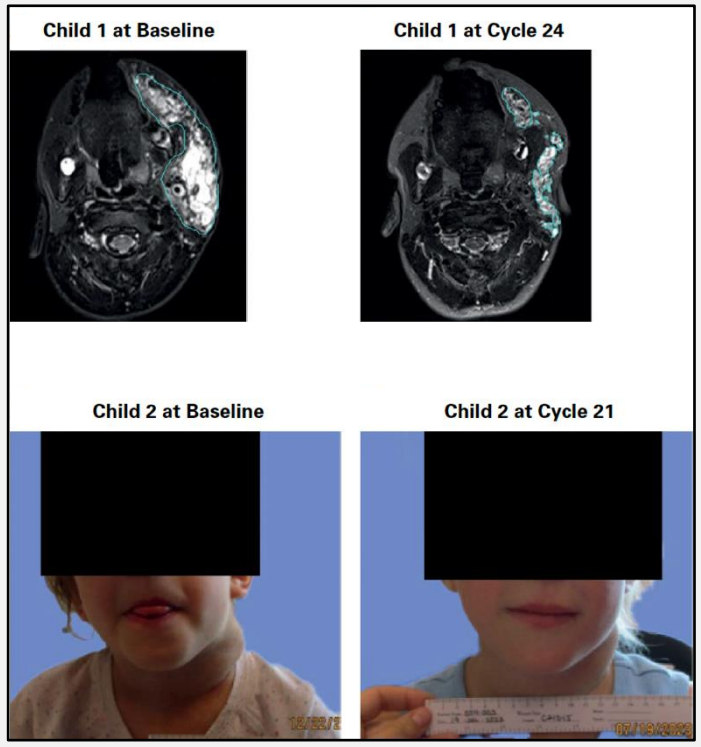
- Median time to confirmed response: 7.9 months (range, 4.1–18.8)
- Median treatment duration: 22.0 months (range, 1.6–40.0)
- The median time to best volumetric percentage change: 13.4 months (range, 4.0–32.7)

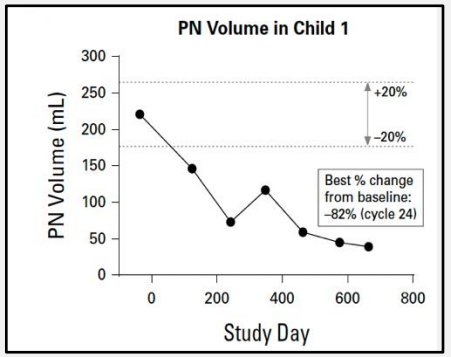
PD, progressive disease; PN, plexiform neurofibroma; PR, partial response; ORR, objective response rate; DCO, data cutoff date (Sept 20, 2023). Moertel et al., J Clin Oncol 2024

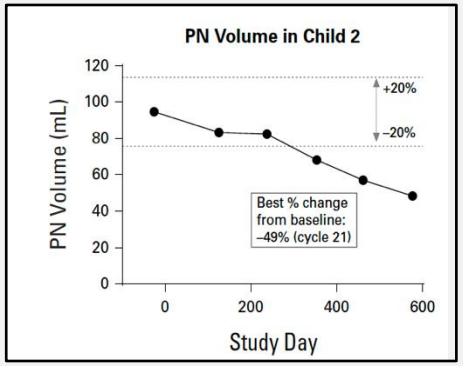
Adult and Children Case Studies









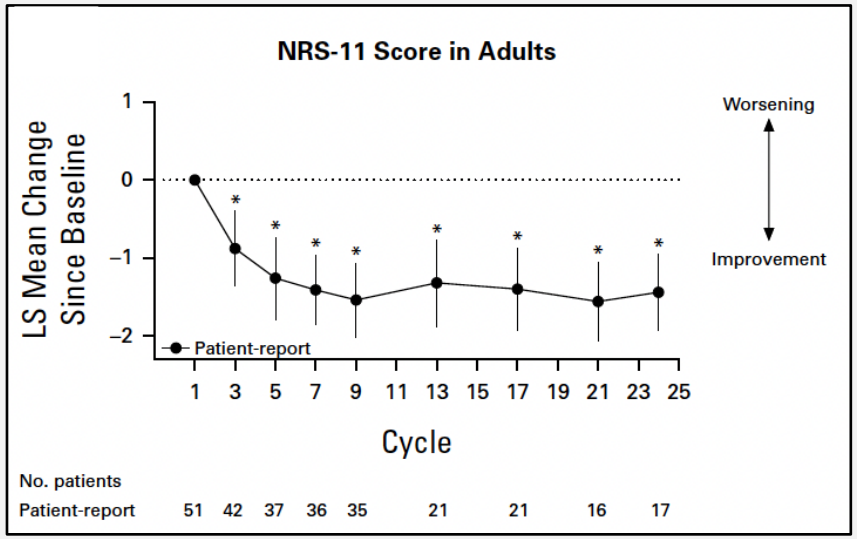


Adult 1: Baseline volume 281 mL → 60mL (-79%) at cycle 24

Child 1: Baseline volume 221 mL → 39 mL (-82%) at cycle 24
Child 2: Baseline volume 95 mL → 48 mL (-49%) at cycle 21

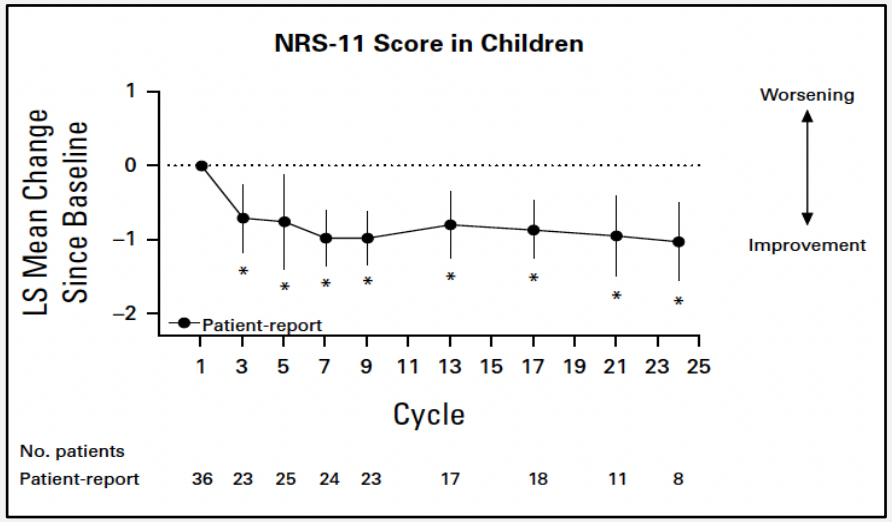
The study team obtained consent for use of patient images through the institutional informed consent process. Moertel et al., J Clin Oncol 2024

Mirdametinib Significantly Improved (Reductions) Patient Reported Outcomes



NRS-11 Score: LS mean change, -1.3; SE, 0.2; *P* < .001

- PII Score: LS mean change, -0.7; SE, 0.2; *P* < .001
- HRQOL Score: LS mean change, +3.9; SE, 1.6; *P* = .02

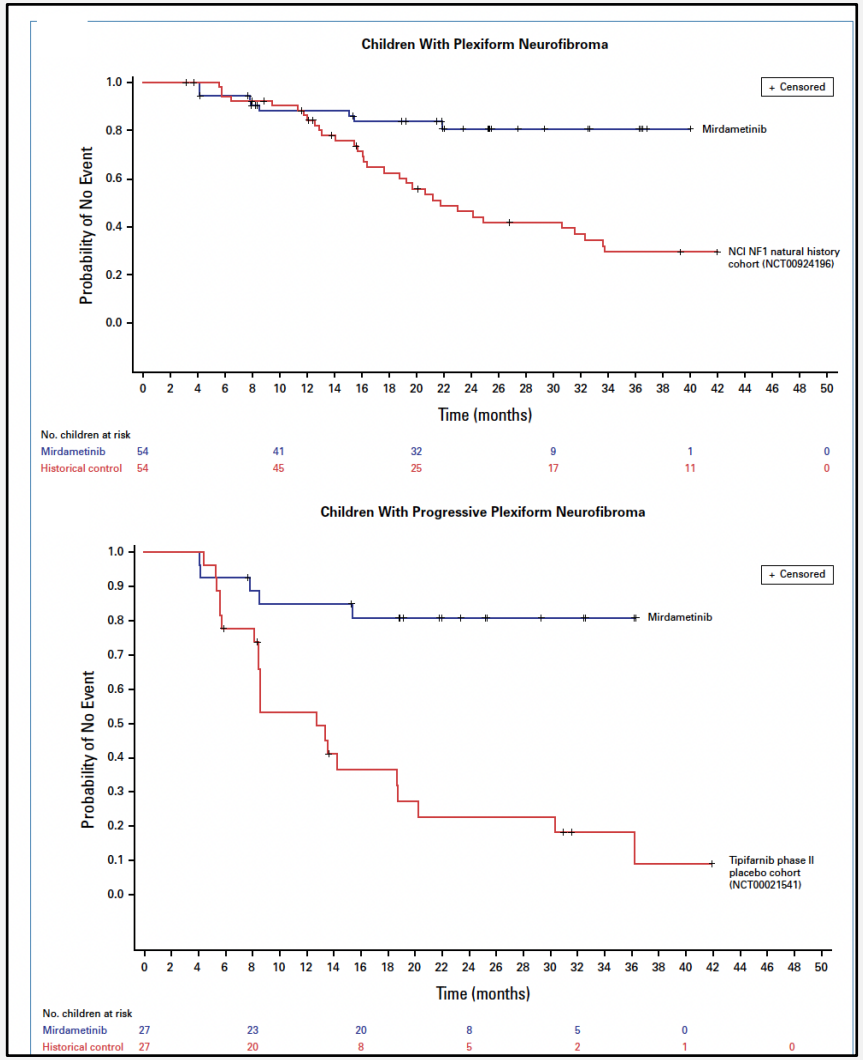


NRS-11 Score: LS mean change, -0.8; SE, 0.2; *P* = .003

- PII Score: LS mean change, -0.5; SE, 0.2; *P* < .02)
- Parent proxy-reported pain interference (PII): LS mean change, -0.3; SE, 0.1; *P* = .03
- HRQOL (PedsQL)Total Score: LS mean change, +5.6; SE, 1.9; *P* = .005

LS, least-squares; PRO, patient-reported outcome, NRS 11,numeric rating scale-11; PII, pain interference (Pain interference Index [PII]); HRQOL, health-related quality of life; PedsQL 4.0, pediatric quality of life inventory, version 4.0. Moertel et al., J Clin Oncol 2024

Mirdametinib Significantly Improved Pediatric PN Tumor Volume and PFS vs Historical Controls



In target PN volume

- Mirdametinib-treated children: LS mean difference, -41% %; *P* < .001
- Mirdametinib-treated children with PD at baseline: LS mean difference, -44%; *P* < .001

- Pediatric PFS mirdametinib-treated vs NCI natural history, HR 0.24 (*P* <.001)
- Pediatric PFS mirdametinib-treated vs tipifarnib placebo, HR 0.14 (*P* <.001)

LS, least square means; PD, progressive disease; PFS, progression free survival; HR, hazard ratio. Moertel et al., J Clin Oncol 2024. Comparison data: NCI NF1 Natural History (NCT00924196) and Tipifarnib Phase II (NCT00021541)

Mirdametinib Demonstrated a Manageable Safety Profile Enabling Long-Term Dosing and Clinical Benefits

Safety: Adverse effects common but mostly grade 1–2

- In adults: Acneiform dermatitis 78%, Diarrhea 48%
- In children: Dermatitis 43%, Diarrhea 38%, Paronychia 30%
- Asymptomatic LVEF decrease in 12% of adults and 20% of children; one adult with grade 3 retinal vein occlusion (serious TRAE)

Conclusion: Mirdametinib demonstrated robust, durable tumor reduction and clinically meaningful improvements in pain/HRQOL across both cohorts.

HRQOL, health-related quality of life. LVEF, left ventricular ejection fraction; TRAE, treatment related adverse effects. Moertel et al., J Clin Oncol 2024.