# Novel therapies for neurofibromatosis type 1-associated inoperable plexiform neurofibromas: A systematic literature review

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*Study sponsored by Initiate Consultancy Ltd.*

## SUMMARY

### OBJECTIVES

- Neurofibromatosis type-1 (NF1) commonly manifests benign nerve sheath plexiform neurofibromas (PNs) which cause high morbidity.
- As multiple or infiltrating tumours are surgically intractable, medical treatment to shrink these benign tumours and reduce the risk of malignant transformation is highly valuable for NF1-inoperable PN treatment.
- The clinical outcomes of MEK inhibitors and targeted anti-cancer agents in NF1 inoperable-PN patients are described.

### METHODS

- A comprehensive systematic review involving electronic databases and supplementary sources was conducted.
- Trials that investigated emerging therapies in NF1-inoperable PN and were published before September 2024, were included.
- Cochrane collaboration methods and PRISMA guidelines for SLRs were followed.
- The study protocol was registered (PROSPERO registration: **CRD42024588717**).

### FINDINGS

- In total, 6 MEK inhibitors and 5 targeted anti-cancer therapies evaluated for the treatment of inoperable-PN associated with NF1 were identified. Selumetinib and mirdametinib were found to have significant evidence which suggested their clinical efficacy in treating NF1-inoperable PN.

### RECOMMENDATIONS

- In 2020, selumetinib was approved by the United States Food and Drug Administration (FDA) to treat paediatric NF1 symptomatic, inoperable-PN and in 2024, the FDA granted a priority review to mirdametinib in paediatric and adult patients with NF1 inoperable-PN.
- Despite the successful inhibition of MEK for patients, significant progress has not been made in increasing the novel therapeutic options available to paediatric and adult patients with NF1-inoperable PN.
- Following regulatory approval, when seeking reimbursement for these products, manufacturers should design their Phase 3 trials to include quality of life measurements. These can subsequently be used in health economic models, because health-state utilities tend to be a significant source of uncertainty in rare conditions.

## BACKGROUND & AIMS

- Neurofibromatosis type-1 (NF1) is a rare, complex, autosomal-dominant genetic disorder caused by germline mutations in the NF1 tumor suppressor gene.[1]
- Although NF1 has a range of manifestations, nearly all individuals with NF1 develop benign nerve sheath tumors i.e., plexiform neurofibromas (PNs), which cause significant morbidity and humanistic burden when surgery is not a viable treatment option.
- The establishment of the Neurofibromatosis Clinical Trial Consortium in 2006 bolstered clinical research for new treatments in NF1-PN including mitogen-activated protein kinase (MEK) inhibitors and targeted anti-cancer therapies.[2]
- The aim of this review was to identify and summarise the clinical outcomes of MEK inhibitors and targeted anti-cancer agents in NF1-PN.

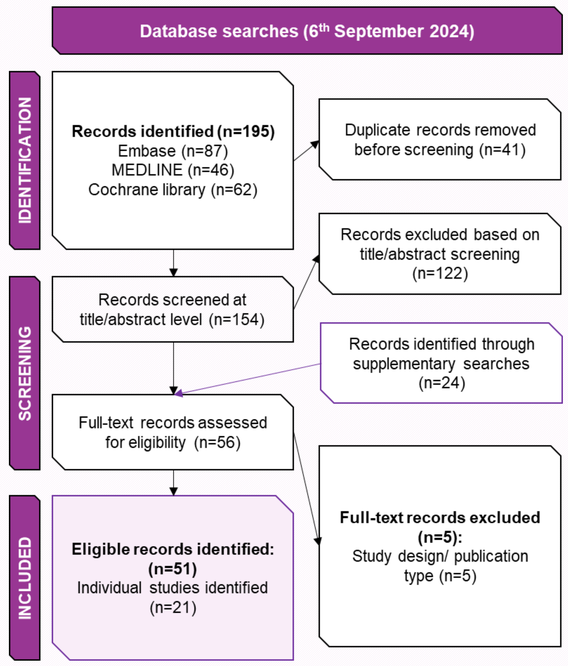
## METHODS

- A PRISMA-adherent systematic review[3] following recommendations from the Cochrane Handbook for Systematic Reviews of Interventions[4] included an electronic database search on 6th September 2024 of Embase, MEDLINE(R) ALL and the Cochrane Central Register of Controlled Trials (CENTRAL) to identify ongoing or completed clinical studies in NF1 inoperable-PN, without language or publication limits.
- Other resources searched included conference proceedings from the American Society of Clinical Oncology Annual Meeting and the European Society for Medical Oncology, clinical trial registries including ClinicalTrials.gov, World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) and European Union (EU) Clinical Trials Register, and nice.org.uk. The study protocol was registered with PROSPERO: CRD42024588717.
- Two reviewers independently screened records for inclusion according to prespecified criteria (**Table 1**) at title/abstract and full text stage, performed data extraction and risk of bias assessments. Any discrepancies between reviewers were resolved through consensus or third reviewer adjudication.
- Extracted data items included study status, patient characteristics, and clinical outcomes, including change in tumour volume and response outcomes. Data was summarised using text and accompanying tables and figures.
- Risk of bias of included trials was assessed using the Cochrane RoB-2 or ROBINS-I tool.

## RESULTS

- Of 178 records identified through database and supplementary searches, 21 unique clinical studies reporting on 11 emerging therapies were selected for inclusion within this review (**Figure 1**).
- Of the 11 emerging NF1 inoperable-PN therapies (**Table 2**), six were MEK inhibitors (selumetinib, mirdametinib, trametinib, binimetinib, FCN-159, and tunlametinib), and five were targeted anti-cancer agents (cabozantinib, tipifarnib, sorafenib, sirolimus, and everolimus).
- Clinical evidence was found to suggest significant efficacy of MEK inhibitors selumetinib (**Figure 2**) and mirdametinib in treating patients with NF1-inoperable PN.
- No evidence was found to suggest a significant clinical benefit of anti-cancer agents tipifarnib, sorafenib, sirolimus or everolimus in treating NF1-inoperable PN.

**Figure 1. PRISMA flow diagram.**




## CONCLUSIONS

- There is evidence to suggest that selumetinib and mirdametinib therapies may have clinically beneficial effects in patients with NF1 inoperable-PN.
- For other MEK inhibitors and targeted anti-cancer agents, current evidence does not indicate significant clinical effectiveness in treating NF1 inoperable-PN.
- Published data on efficacy outcomes of MEK inhibitors and targeted anti-cancer agents in treating NF1 inoperable-PN is still very limited, with only 21 relevant clinical studies identified through this systematic review, of which 19 were either phase 1 or 2.

**Figure 2. Response rate outcomes for selumetinib**

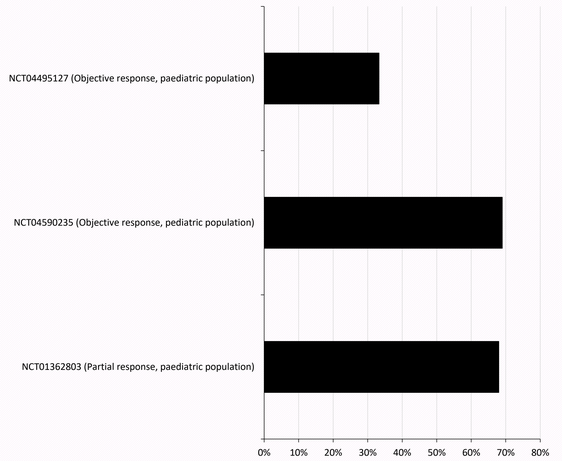



**Table 2. Emerging treatment landscape in NF1 inoperable-PN.**

| Drug | Trials (phase) | Key endpoint(s) |
|---|---|---|
| **FCN-159**[a] | NCT05913037 (phase 3) | Objective Response Rate |
| **Tunlametinib**[a] | NCT05331105 (phase 2) | Objective Response Rate |
| **Selumetinib**[a] | NCT04924608 (phase 3), NCT01362803 (phase 1/2), NCT02407405 (phase 2), NCT04590235 (phase 1), NCT04495127 (phase 1), NCT05309668 (phase 1/2), NCT03326388 (phase 1/2) | Objective Response Rate<br>Partial and Complete Response Rate |
| **Binimetinib**[a] | NCT03231306 (phase 2) | Objective Response Determination |
| **Mirdametinib**[a] | NCT03962543 (phase 2), NCT02096471 (phase 2) | Partial or Complete Response Rate |
| **Trametinib**[b] | NCT03363217 (phase 2), EudractCT-2019-001317-16 (phase 2), NCT02124772 (phase 1/2) | Objective Response Rate |
| **Cabozantinib**[b] | NCT02101736 (phase 2) | Objective Response Rate |
| **Tipifarnib**[b] | NCT00021541 (phase 2) | Time to Progression |
| **Sorafenib**[b] | NCT00727233 (phase 1) | Maximum tolerated dose |
| **Sirolimus**[b] | NCT00634270 (phase 2) | Time to Progression |
| **Everolimus**[b] | NCT01412892 (phase 2), NCT01365468 (phase 2) | ≥30% tumour reduction |

***Note: [a]MEK Inhibitor; [b]Targeted anti-cancer agent.***

**Table 1. Inclusion/exclusion criteria.**

| Criteria | Inclusion | Exclusion |
|---|---|---|
| **Population** | People with neurofibromatosis type 1-associated inoperable/unresectable plexiform neurofibromas | Patients with a condition other than NF1 inoperable-PN |
| **Intervention/Comparator** | MEK inhibitors<br>Targeted cancer therapies | Studies investigating non-novel treatments |
| **Outcome** | Study background information and efficacy outcomes | Studies not reporting any outcomes of interest |
| **Study design** | Clinical trials of all phases (ongoing or completed) | Study designs not of interest |

## References

1. *Gutmann et al. (2017). Neurofibromatosis type 1. Nature Reviews Disease Primers, 3(1), 1-17*
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3. *Page et al. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. bmj, 372.*
4. *Chandler et al. (2019). Cochrane handbook for systematic reviews of interventions. Hoboken: Wiley.*

*Presented at ISPOR, 13 – 16 May 2025*

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