Emerging Treatments in Neurofibromatosis Type 1-Associated Inoperable Plexiform Neurofibromas: a Systematic Review and Recommendations

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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 current treatment landscape in NF1 inoperable-PN and recommendations for prospective reimbursement are provided.

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.
- The 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. Only selumetinib has achieved reimbursement in NF1-inoperable PN.
- It is recommended that Phase 3 trials are designed to include quality of life measures, and for manufacturers to utilise reimbursement pathways which expedite appraisals for drugs with the same mechanism of action.

BACKGROUND & AIMS

- Neurofibromatosis type-1 (NF1) is a rare, complex, autosomal-dominant genetic disorder caused by germline mutations in the NF1 tumour suppressor gene.[1]
- Although NF1 has a range of manifestations, nearly all individuals with NF1 develop benign nerve sheath tumours 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 objective of this study is to create an overview of the current treatment landscape of MEK inhibitors and targeted anti-cancer agents in NF1 inoperable-PN and provide recommendations for future reimbursement.

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.
- Two reviewers independently screened records for inclusion according to prespecified criteria at title/abstract and full text stage and performed data extraction. Any discrepancies between reviewers were resolved through consensus or third reviewer adjudication.
- Extracted data items included study identifier, trial status, treatment arms, trial design, inclusion/exclusion criteria, study endpoints, and reimbursement status. Data was summarised using text and accompanying tables and figures.

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 Targeted cancer therapies	Studies investigating non-novel treatments
Outcome	Study background information	Studies not reporting any outcomes of interest
Study design	Clinical trials of all phases (ongoing or completed)	Study designs not of interest

RESULTS

- Of 178 records identified, 21 unique studies reporting on 11 emerging therapies were selected for inclusion.

Figure 1. PRISMA flow diagram.

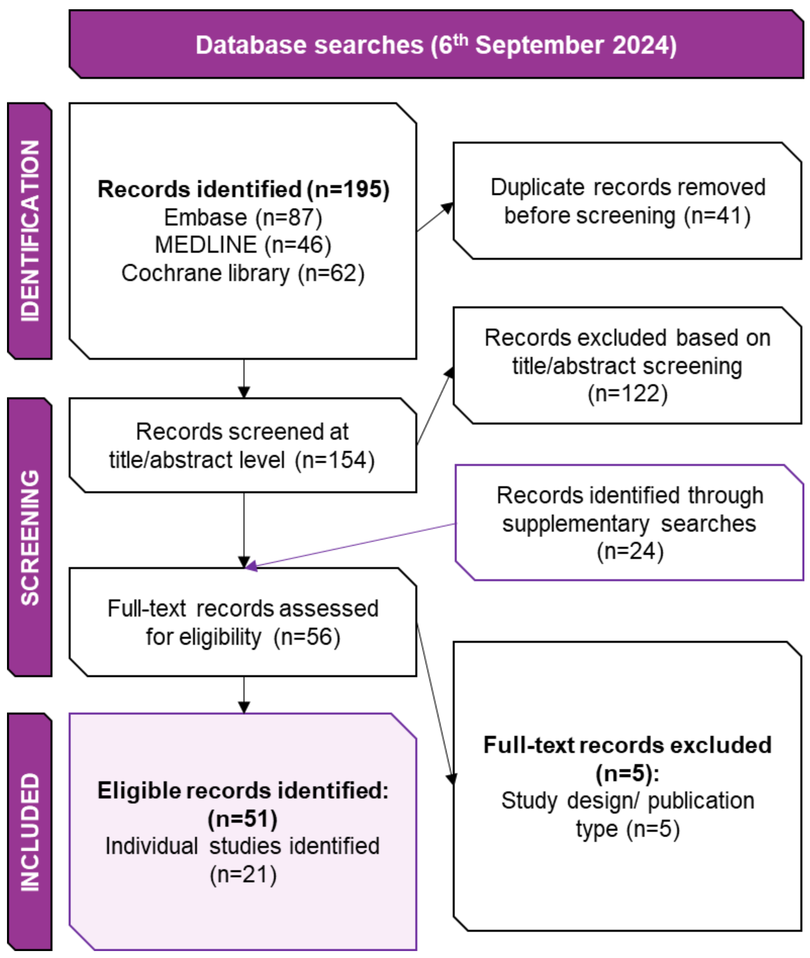

Table 2. Emerging treatment landscape in NF1 inoperable-PN.

Drug	Route	Trial(s)	Sponsor	Key endpoint(s)
FCN-159[a]	Oral	NCT05913037	Fosun Pharma	Objective Response Rate
Tunlametinib[a]	Oral	NCT05331105	KeChow Pharma	Objective Response Rate
Selumetinib[a]	Oral	NCT04924608, NCT01362803, NCT02407405, NCT02644512, NCT04590235, NCT04495127, NCT05309668, NCT03326388	AstraZeneca	Objective Response Rate Partial and Complete Response Rate
Binimetinib[a]	Oral	NCT03231306	Pfizer	Objective Response Determination
Mirdametinib[a]	Oral	NCT03962543, NCT02096471	SpringWorks Therapeutics	Partial or Complete Response Rate
Trametinib[b]	Oral	NCT03363217, EudractCT-2019-001317-16, NCT02124772	Novartis	Objective Response Rate
Cabozantinib[b]	Oral	NCT02101736	Exelixis	Objective Response Rate
Tipifarnib[b]	Oral	NCT00021541	Kura Oncology	Time to Progression
Sorafenib[b]	Oral	NCT00727233	Bayer	Maximum tolerated dose
Sirolimus[b]	Oral	NCT00634270	Pfizer	Time to Progression
Everolimus[b]	Oral	NCT01412892, NCT01365468	Novartis	≥30% tumour reduction

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

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. To accelerate access further, cost-comparison approaches to technology appraisals could be considered in England, if equivalent efficacy is demonstrated in trials. These strategies can help address the unique challenges posed by NF1 and facilitate more expeditious approval and reimbursement processes for novel therapies.
- Given the differing key endpoints for emerging treatments, if cost-comparison is not possible, endpoint surrogacy may be required for economic modelling to demonstrate the relationship between trial endpoints and the reduction in long-term risks.

References

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