

Assessing the Feasibility of Indirect Comparison of Luvometinib versus Selumetinib in the Treatment for Pediatric Patients with Neurofibromatosis Type 1 in China

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BACKGROUND

- Neurofibromatosis type 1 (NF1) is an autosomal-dominant neoplastic rare genetic disorder with the global prevalence of approximately 1:3000¹, mainly featured by café-au-lait macules (CALMs), multiple neurofibromas, and axillary or inguinal freckles. Most patients typically onset, and afterwards experience rapid progression in early childhood.
- Plexiform neurofibromas (PNs) are reported in about 30%-60% of NF1 patients, usually growing along nerves with multiple branches involved^{2,3}.
- **Deterioration risk:** NF1-PNs patients have an 8-13% lifetime risk of transformation to malignant peripheral nerve sheath tumors (MPNSTs), which exhibit poor prognosis and are associated with a high mortality risk^{3,4}.
- **Impaired quality of life:** PNs can cause pain, disfigurement, bone destruction, and compression of vital structures
- NF1-PN remains incurable so far, conventional treatments still face with great challenges⁵.
- Surgical resection is the most common option, while it is difficult to resect completely, and high risk of postoperative complications follows.
- Medication therapies are limited; only two MEK inhibitor (MEKi) have been approved with NF1-PN indication in China.
- Selumetinib is the first approved MEKi for pediatric NF1 patients with symptomatic and inoperable PNs (≥ 3 to <18 years old) in China; Luvometinib is the second approved MEKi with treatment for NF1 children with symptomatic and inoperable PNs (≥ 2 to <18 years old) in China.
- **There is no published clinical evidence regarding the comparative efficacy and safety of selumetinib versus luvometinib.**

OBJECTIVE

- To examine studies of interest for selumetinib in pediatric NF1-PNs patients via a targeted systematic literature search.
- To investigate the most feasible indirect treatment comparison (ITC) method between luvometinib and selumetinib according to the characteristics of available trails.

METHODOLOGY

Targeted systematic literature searching

- The searching strategy was developed by referring to the PICOS frame (Table 1).
- The systematic literature search was conducted in PubMed (latest searching date: 1st July 2025), according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines⁵.

Table 1 The PICOS frame and searching strategy used in systematic searching

Population (P)	Neurofibromatosis type 1 patients with unresectable plexiform neurofibromas
Intervention (I)	Selumetinib
Comparator (C)	No restrictions
Outcomes (O)	No restrictions
Study design (S)	Clinical trials
Information sources	PubMed database
Searching strategy	(selumetinib*[Title/Abstract]) AND ((Neurofibromatosis type 1[Title/Abstract]) OR (NF1[Title/Abstract])) AND ((Plexiform Neurofibromas[Title/Abstract]) OR (PN[Title/Abstract])) AND (clinicaltrial[Filter])

- Given the study objective, study design, and the population, explicit eligibility criteria were applied to the searching results to identify suitable clinical evidence which included pediatric NF1 patients with symptomatic and inoperable PNs for selumetinib.

Feasibility assessment of an in direct comparison^{7,8}

- Considering the individual patient data (IPD) for the pivotal phase II trial (NCT04954001)⁶ on luvometinib is available, matching-adjusted indirect comparison (MAIC) is considered a better choice when indirectly comparing the effectiveness of luvometinib and selumetinib.
- MAIC is an ITC methodology used to compare two treatments without head-to-head studies comparing these treatments directly and has focused on accounting for trial dissimilarities. MAIC corrects for baseline differences in patient populations, allowing indirect comparison with limited bias when IPD are available for at least one study. Where IPD is available, baseline characteristics can be adjusted and reweighted to match summary statistics based on the comparator population's aggregate data (AgD).
- Besides, the MAIC approach can be divided into two types (Figure 1). Anchored MAIC, in which there is a connected network of clinical trials that include the interventions of interest that exist, and unanchored MAIC, which means the same comparator between interventions of interest is not necessary. An anchored MAIC purpose is to correct the bias that occurs from patients being different in the two trials and, therefore, likely to show different treatment effects for reasons other than the intervention being studied. The logic for unanchored MAIC is similar; the only difference is that we adjust the relative effect of single arms instead of relative effects in each trial.

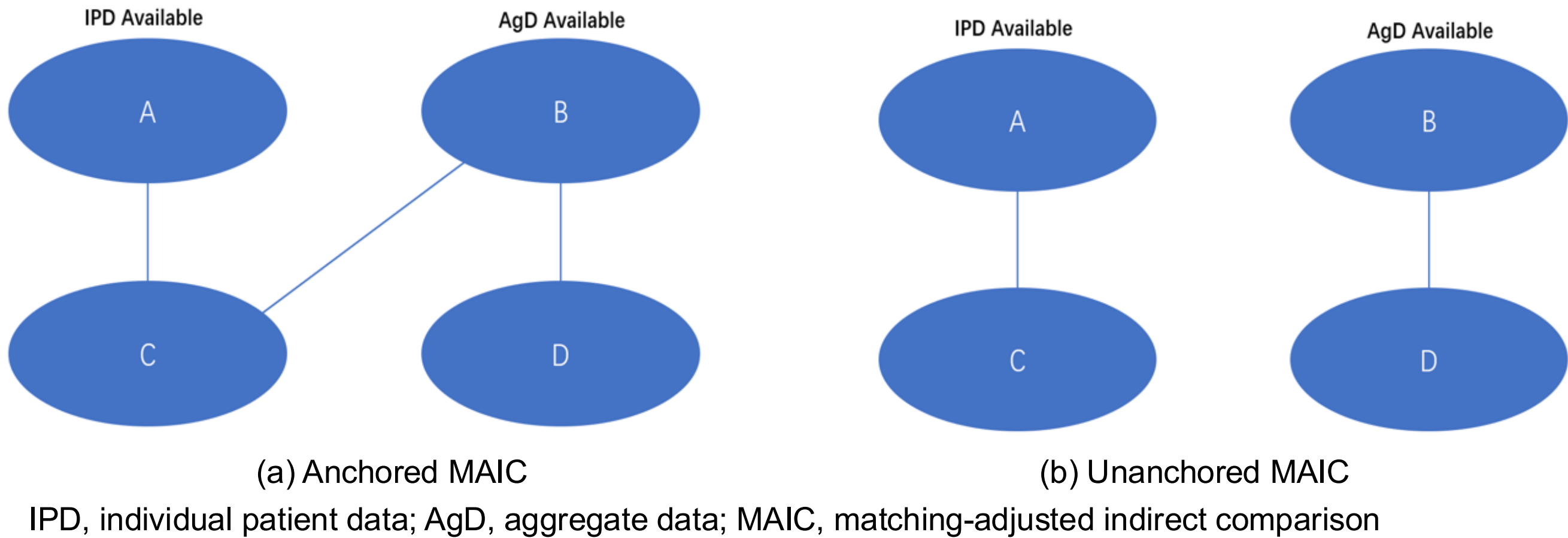


Figure 1 Two types of MAIC

- The characteristics of all the available clinical trials on selumetinib were summarized. Comparison on trial design, administration and outcome measures between luvometinib phase II trial (NCT04954001)⁶ and each retrieved selumetinib study was conducted.

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RESULTS

- Figure 2 shows the PRISMA flow diagram of the 10 retrieved records from literature searching and reference tracking. The full-text of 7 articles were examined for eligibility after sifting through reviewing the title and abstract. Two published summary trials were figured out, a single-arm, single-center phase II trial in Korea⁹, and the international pivotal clinical trial (SPRINT, NCT01362803)¹⁰, were ultimately included.

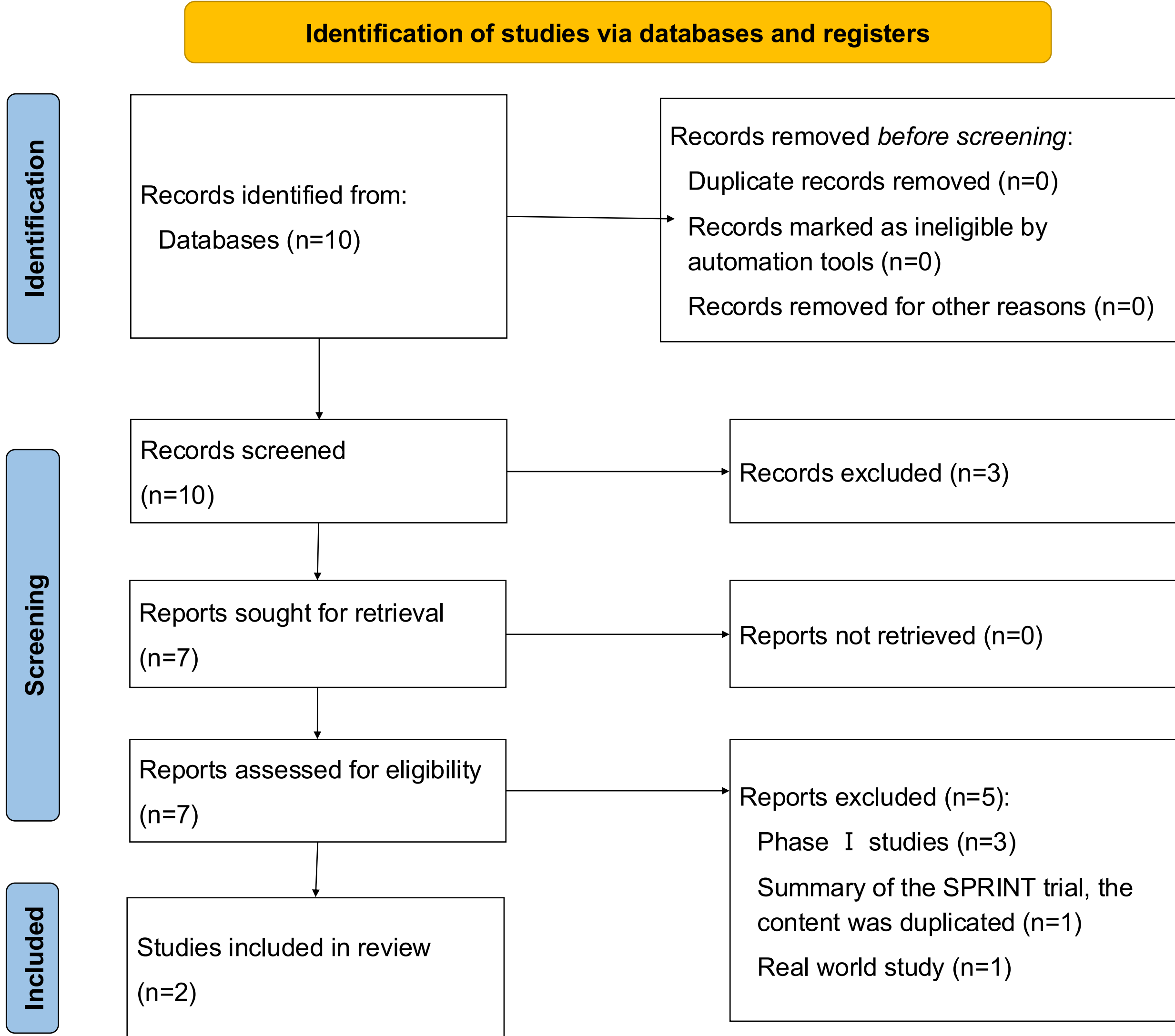


Figure 2 The PRISMA flow diagram

- Comparison details between the luvometinib study and the two selumetinib trials are shown in Table 2.

Table 2 Characteristics of the Luvometinib and Selumetinib trials

	Luvometinib NCT04954001 ⁶	Selumetinib KCT0003700 ⁹	Selumetinib NCT01362803 ¹⁰
Trial design	Multicenter, single-arm, phase II	Single-center, single-arm, phase II	Multicenter, single-arm, phase II
No. patients	43 pediatric patients	30 adult patients; 60 children patients	50 children patients
Study duration	Median FU: 25.1 months	2 years	3.2 years
Key inclusion criteria	• 2≤age<18 • Inoperable NF1-PN • PN causing significant morbidity	• 3≤age≤18 • ≥1 measurable PN • With NF1 having significant symptoms/comorbidities or inoperable PN with the potential to develop symptoms/comorbidities	• 2≤ages≤18 • ≥1 measurable PN • Inoperable NF1-PN • PN causing significant morbidity
Treatment group and drug administration	Oral luvometinib 5 mg/m ² QD	Adult patients • Oral selumetinib 25 mg/m², BID (N=20) • Oral selumetinib 50 mg/m², BID (N=10) Pediatric patients • Oral selumetinib 25 mg/m², BID (standard dose group, N=30) • Oral selumetinib 20 mg/m², BID (lower dose group, N=30)	Oral selumetinib 25 mg/m ² BID
Key outcome measures	ORR assessed by investigators, ORR assessed by BIRC, CBR, DCR, DOR, PFS, safety, quality of life (PedsQL™ Generic Core Scales), overall tumor pain (NRS-11)	PR rate, safety, PN volume change, quality of life (The PedsQL 4.0 Generic Core Scales), pain score (10-point scale NPS/WBS), etc.	cPR, cCR, DOR, PFS, quality of life (PedsQL scales, Global Impression of Change scale, PROMIS Mobility and Upper Extremity scales), pain score (NRS-11), safety, etc.

BID, twice daily; BIRC, blinded independent review committee; CBR, clinical benefit rate; cCR, confirmed complete response; cPR, confirmed partial response; DCR, disease control rate; DOR, duration of response; FU, follow-up; mITT, modified intent-to-treat; NF1, Neurofibromatosis type 1; NPS, numeric pain rating scale; NRS-11, the 11-item Numerical Rating Scale; ORR, objective response rate; PedsQL, Pediatric Quality of Life Inventory; PFS, progression-free survival; PN, plexiform neurofibromas; PR, partial response; PROMIS, Patient-Reported Outcomes Measurement Information System; WBS, Wong-Baker Faces Pain Rating Score.

Comparison on trial design

The Korea trial employed a single-center design and enrolled both pediatric and adult NF1 patients, whereas the SPRINT trial is a multicenter study restricted to pediatric patients, which is consistent with the luvometinib trial.

Comparison on treatment arms

Patients in SPRINT were administered at the standard dose (25mg/m², BID), while the Korea trial divided patients into two dosing group, a lower-dose group (20mg/m², BID) and a standard-dose group.

Comparison on reported outcomes

Only PR rate, safety data and a few patient-reported outcomes (PROs) were reported in Korea trial, without PFS nor clinical benefit data being collected.

CONCLUSION

- Given that both two retrieved trials on selumetinib were single-arm design, non-anchored MAIC is identified as the most appropriate ITC method for the comparison between luvometinib and selumetinib.
- The SPRINT trial was preferable as the data source for selumetinib in ITC with trial design, treatment regimen and outcome measures taken into consideration.