Matching-adjusted 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 1:3000[1], 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 challenges[5].
  - 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 comprehensive evidence regarding the comparative efficacy and safety of selumetinib versus luvometinib due to the absence of head-to-head clinical trials.

OBJECTIVE

- To compare the efficacy and safety of luvometinib with selumetinib in pediatric NF1-PNs patients aged over 2 years through a matching-adjusted indirect comparison (MAIC) method.

METHODOLOGY

Data Source

- Individual patient data (IPD) from the pivotal phase II trial (NCT04954001), a multicenter, open-label, single-arm study were used for luvometinib[6].
- A systematic literature search was performed in March 2025 to examine the clinical evidence for selumetinib in PubMed. Two summary trials[7,8] were figured out, and the SPTINT trial[8] (NCT01362803) was finally chosen as the most appropriate data source for selumetinib after taking trial design and reported data into account.

Identification of matching variables

- Six common baseline characteristics were reported in both trials, and the comparison before matching is shown in **Table 1**.

Table 1 Comparison of Common Baseline Characteristics before adjustment

Baseline characteristics	Luvometinib (N=43)	Selumetinib (N=50)	RD	*P*-value
Age, years (mean±SD)	8.49±4.32	10.30±3.92	-1.81	0.008*
Male, % (mean)	46.5%	60.0%	-13.5%	0.087
Volume of target neurofibroma, ml (mean±SD)	135.9±210	837.11±925	-701.21	<0.001*
Location of the target neurofibroma† (%)				
Neck	16.3%	40.0%	-23.7%	<0.001*
Trunk	34.9%	58.0%	-23.1%	0.003*
Limbs	18.6%	32.0%	-13.4%	0.031*
Head	30.2%	34.0%	-3.8%	0.598
Number of neurofibroma-related complications (mean, range)	0.7 (1-3)	3 (1-5)	-2.3	<0.001*
Type of neurofibroma-related complication (%)				
Disfigurement	69.8%	88.0%	-18.2%	0.014*
Motor dysfunction	4.7%	66.0%	-61.4%	<0.001*
Pain	65.1%	52.0%	13.1%	0.082
Vision	2.3%	20.0%	-17.7%	<0.001*
Other	11.6%	22.0%	-10.4%	0.042*

SD, standard deviation; RD, relative difference; A p-value < 0.05 suggests a statistical significance has been reached.
†, Luvometinib trial only listed the most related neurofibroma location for each patient, while the SPRINT trial had listed all the neurofibroma locations and classified patients as, neck and trunk (n=12), trunk and limbs (n=12), head and neck (n=8); limbs only (n=4), head only (n=9), trunk only (n=5). Naïve summation was applied in the SPRINT data for consistence in classification.

- Given that the great between-group difference in the target neurofibroma volume and the number of complications led to a >90% sample size loss in matching, neither of them were included in weighting adjustment. The different classifying criteria for tumor location and complication also limited matching variable selection. With attempts in different combinations of investigational matching variables, age and sex were finally included in the weighting adjustment.

Endpoints

- The following efficacy outcomes were assessed:
  - **Partial response assessed by investigators (INV-assessed PR)**, defined as a target neurofibroma volume decrease from baseline of at least 20%, in accordance with Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) criteria
  - **Objective response rate assessed by investigators (INV-assessed ORR)**, defined as the percentage of patients with PR lasting for over 3 months.
  - **Progression-free survival (PFS)**, defined as time from the date of initial dose until progressive disease or death due to any cause, whichever occurred first.
- Safety endpoints included grade ≥ 3 treatment-related adverse events (TRAEs) rate.

Statistical analysis

- An unanchored MAIC approach was chosen due to the absence of a common comparator for luvometinib trial and the SPRINT trial. All analyses were performed in accordance with the UK National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) 18[9] and methods described by Signorovitch et al[10].

RESULTS

Response outcomes

- INV-assessed ORR and INV-assessed PR for luvometinib and selumetinib before and after adjustment are displayed in **Table 2**.
- Before MAIC, the INV-assessed ORR and PR were relatively lower in the luvometinib group than in the selumetinib group, with a RD of -7.5% in INV-assessed ORR (p=0.605) and -4.2% in INV-assessed PR (p=0.554) respectively.
- After population adjustment, the response outcomes in luvometinib group shows a slight decrease, while results still suggested no statistically significant difference compared to selumetinib group.

Table 2 Response and Survival Outcomes for Luvometinb vs. Selumetinib

Outcomes	Luvometinib	Selumetinib	Relative effects	
Before MAIC				
			RD	***P*-value**
INV-assessed ORR	60.5%	68.0%	-7.5%	0.605
INV-assessed PR	69.8%	74.0%	-4.2%	0.554
	Median, months (95% CI)		**HR (95% CI)**	***P*-value**
INV-assessed PFS	NA	NA	2.87 (0.74-11.17)	0.128
After MAIC				
			RD	***P*-value**
INV-assessed ORR	60.2%	68.0%	-7.8%	0.296
INV-assessed PR	69.6%	74.0%	-4.4%	0.535
	Median, months (95% CI)		**HR (95% CI)**	***P*-value**
INV-assessed PFS	NA	NA	3.29 (0.81-13.37)	0.096

RD, rate difference HR, hazard ratio; NA, not achieved; PFS, progression-free survival; CI, confidential interval; A p-value < 0.05 suggests a statistical significance has been reached.

Survival outcomes

- The results of time-to-event outcomes are presented in **Table 2**, and Kaplan-Meier (KM) curves are plotted in **Figure 1**.
- The median PFS for both luvometinib and selumetinib group was not reached until the cut-off date, and the HR indicates no significant difference observed in PFS between the two treatments (HR= 3.29, 95%CI 0.81-13.37, *p* = 0.096) after adjustment.

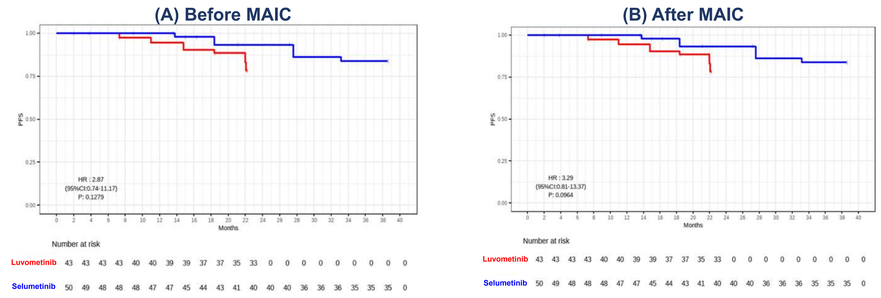

Figure 1 Kaplan-Meier plots of PFS results before and after adjustment

Safety outcomes

- **Table 3** gives the comparison results in TRAEs grade ≥ 3 with a ≥ 5% incidence specifically.
- Compared with selumetinib, luvometinib was associated with a significantly lower incidence in certain TRAEs after weighting, including diarrhea (RD -14.00%, p<0.001), dermatitis acneiform (RD -6.00%, p<0.001), and weight gain (RD -6.00%, p<0.001), while the folliculitis incidence was higher (8.70% vs. 0%, p=0.048).

Table 3 Safety Outcomes for Luvometinb vs. Selumetinib

TRAEs	Incidence before MAIC (%)				Incidence after MAIC (%)			
	Luvometinib	Selumetinib	RD	*P*-value	Luvometinib	Selumetinib	RD	*P*-value
Diarrhea	0%	14.00%	-14.00%	**<0.001***	0%	14.00%	-14.00%	**<0.001***
Dermatitis acneiform	0%	6.00%	-6.00%	**<0.001***	0%	6.00%	-6.00%	**<0.001***
Paronychia	2.33%	6.00%	-3.67%	0.122	2.87%	6.00%	-3.13%	0.224
Folliculitis	4.65%	0%	4.65%	0.160	8.70%	0%	8.70%	**0.048***
Weight gain	0%	6.00%	-6.00%	**<0.001***	0%	6.00%	-6.00%	**<0.001***
Blood CPK increased	4.65%	4.00%	0.65%	0.842	5.18%	4.00%	1.18%	0.728

MAIC, matching-adjusted indirect comparison; TRAEs, treatment-related adverse events; CPK, creatine phosphokinase; RD, rate difference; A p-value < 0.05 suggests a statistical significance has been reached.

CONCLUSION

- This study suggested similar efficacy and survival outcomes between luvometinib and selumetinib in pediatric NF1 patients with unresectable and symptomatic PN. Luvometinib demonstrated comparable or superior safety for most grade ≥ 3 TRAEs compared to selumetinib, except for a higher rate of folliculitis.
- The evidence was limited due to differences in some specific patient baseline characteristics, and the estimation is considered exploratory only. Nevertheless, the MAIC results could still provide valuable information for clinicians in practice in the future.

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DISCLOSURES

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