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Selumetinib in pediatric patients with neurofibromatosis type 1 and plexiform neurofibroma: Propensity score analysis of the SPRINT trial versus a Natural History control arm

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INTRODUCTION

- Neurofibromatosis type 1 (NF1) is a multisystem genetic disorder with diverse clinical features[1]
  - NF1-related plexiform neurofibromas (NF1-PN) can be associated with severe morbidities, and considerably impact quality of life[2-6]
- As of March 2023, selumetinib (ARRY-142886, AZD6244), a potent and highly selective mitogen-activated protein kinase kinase 1/2 inhibitor, is the first and only approved medical therapy indicated for the treatment of pediatric patients with NF1 and symptomatic, inoperable PN[7-9]
  - This approval was based on results from the pivotal SPRINT trial
  - As SPRINT was a single-arm trial, an external Natural History (NH) study was used to compare progression-free survival (PFS)[10]
- Propensity score analysis is a causal inference and statistical tool that balances observed baseline characteristics between treated and untreated groups[11,12]
  - Propensity score is defined as probability of treatment assignment given the observed baseline characteristics[12,13]

OBJECTIVE

- To perform propensity score analysis to account for differences in baseline prognostic factors between SPRINT study and NH external control arm
  - To estimate the reduction in the risk of NF1-PN progression with selumetinib

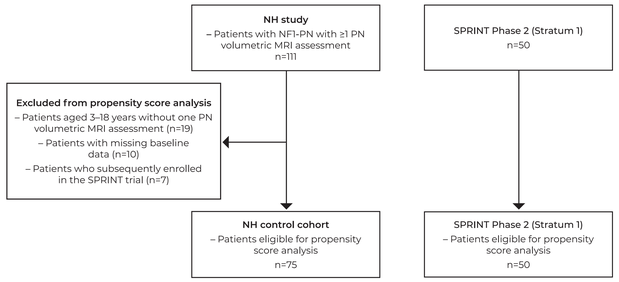
METHODS

- SPRINT is an open-label, Phase 2, single-arm study evaluating selumetinib in pediatric patients with NF1 and symptomatic, inoperable PN (NCT01362803)[10]
- The National Cancer Institute NH study is a longitudinal, observational study of pediatric and adult patients presenting with NF1-related tumor or non-tumor manifestations, regardless of current enrollment status in a treatment study[5,14]
- Baseline characteristic balance between studies was assessed by standardized differences before and after application of each propensity score method
  - Standardized differences were estimated using a previously developed SAS® macro[15]
- The propensity score for selumetinib treatment was estimated using multivariate logistic regression (study was dependent variable and all baseline covariates observed were independent variables)
  - Once the propensity score was obtained for each patient, 1:1 propensity score matching without replacement, inverse probability of treatment weighting (IPTW), and 1:2 propensity score matching with replacement were performed to incorporate the scores into balancing the baseline characteristics between the studies
    - These methods were compared to the direct comparison (no propensity score analysis)
  - After accounting for differences in baseline confounding factors, the effect of selumetinib treatment on the risk of NF1-PN progression was estimated

RESULTS

- Data included for patients in the SPRINT study are based on latest data cut-off of March 31, 2021 (median follow-up of 4.3 years)
- All 50 patients enrolled in the Phase 2 SPRINT study (Stratum 1) and 75/111 patients from the NH study were included in this analysis (**Figure 1**)
- Baseline characteristics with standardized differences are shown in **Table 1**, and were generally balanced, except for PN status and location

Figure 1. Patient disposition



MRI, magnetic resonance imaging; NF1, neurofibromatosis type 1; NH, Natural History; PN, plexiform neurofibroma.

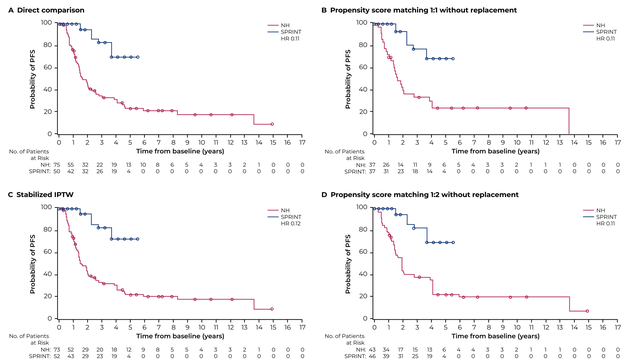
Table 1. Baseline patient demographics and PN characteristics before propensity score analysis

Characteristic	SPRINT (N=50)	NH (N=75)	Standardized difference
Sex, n (%)			
Female	20 (40.0)	27 (36.0)	0.082
Male	30 (60.0)	48 (64.0)	
Race, n (%)			
White	42 (84.0)	58 (77.3)	0.306
Asian	1 (2.0)	1 (1.3)	
Unknown/other	3 (6.0)	11 (14.7)	
Black/African American	4 (8.0)	5 (6.7)	
Recategorized race, n (%)			
White	42 (84.0)	58 (77.3)	0.169
Other	8 (16.0)	17 (22.7)	
Age, years			
Median (min, max)	10.2 (4, 17)	9.8 (3, 18)	0.058
Weight, kg			
Median (min, max)	29.6 (16, 89)	29.9 (12, 78)	0.017
Height, cm			
Median (min, max)	132.8 (100, 171)	131.5 (83, 180)	0.021
Body mass index, kg/m²			
Median (min, max)	17.6 (13, 39)	17.0 (12, 27)	0.119
Target PN location, n (%)			
Head	9 (18.0)	9 (12.0)	0.748
Head/neck	8 (16.0)	5 (6.7)	
Neck/trunk	12 (24.0)	11 (14.7)	
Trunk	5 (10.0)	29 (38.7)	
Trunk/extremity	12 (24.0)	14 (18.7)	
Extremity	4 (8.0)	6 (8.0)	
Whole body	0	1 (1.3)	
Recategorized target PN location, n (%)			
Head, head/neck, neck/trunk	29 (58.0)	25 (33.3)	0.511
Trunk, trunk/extremity, extremity, whole body	21 (42.0)	50 (66.7)	
Target PN volume, mL			
Median (min, max)	487.5 (5.6, 3820)	422 (23.5, 5759)	0.148
PN status, n (%)			
Progressive	21 (42.0)	25 (33.3)	0.597
Non-progressive	15 (30.0)	42 (56.0)	
Unknown	14 (28.0)	8 (10.7)	

Race and PN location were re-categorized for visual representation of the data.
NH, Natural History; max, maximum; min, minimum; PN, plexiform neurofibroma.

- Balance was generally achieved regardless of the propensity score method used (**Supplementary Table 1**)
  - Balance was achieved across all baseline characteristics following IPTW and 1:2 propensity score matching with replacement (standardized difference ≤20%); balance was achieved following 1:1 propensity score matching without replacement, except for NF1-PN status (standardized difference 25%)
- NF1-PN progression following selumetinib treatment in SPRINT versus NH, before and after propensity score analysis, is shown in **Figure 2**

Figure 2. Kaplan–Meier curves for PFS before and after propensity score analysis



Patients with propensity scores that were larger than the pre-specified caliper width were excluded from matching.
IPTW, inverse probability of treatment weighting; NH, Natural History; PFS, progression-free survival.

- PFS hazard ratio (HR) adjusted for covariates was 0.11 with direct comparison (**Table 2**)
  - Following 1:1 propensity score matching without replacement, IPTW, and 1:2 propensity score matching with replacement, the adjusted PFS HRs were consistent with the direct comparison: 0.11, 0.12, and 0.11, respectively, HR CI 95% values fell between 0.09 and 0.42, and p-values were consistently <0.001
- PFS HR unadjusted for covariates following 1:1 propensity score matching without replacement, IPTW, and 1:2 propensity score matching with replacement were also consistent with direct comparison (**Table 2**)

Table 2. PFS HR before and after propensity score analysis

Analysis method	HR§ (adjusted for covariates)	95% CI	P-value	HR¶ (unadjusted for covariates)	95% CI	P-value
Direct comparison	0.11	0.05, 0.25	<0.001	0.21	0.11, 0.41	<0.001
Cox model; 1:1 propensity score matching without replacement*†	0.11	0.04, 0.29	<0.001	0.22	0.11, 0.42	<0.001
Cox model; stabilized IPTW	0.12	0.06, 0.25	<0.001	0.18	0.09, 0.36	<0.001
Cox model; 1:2 propensity score matching with replacement†‡	0.11	0.06, 0.24	<0.001	0.21	0.12, 0.37	<0.001

*Greedy matching algorithm was used without replacement; †The difference in the logit of the propensity score for a match must be less than or equal to 0.2 times the pooled estimate of the common standard deviation of the logits of the propensity scores; ‡Each treated patient was matched up to two controls (matching was performed with replacement); §HR was obtained using Cox regression (including study, sex, non-White race, age, weight, height, and PN location, status and volume as covariates); ¶HR was obtained using Cox regression (including study as the only covariate).

CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting; PFS, progression-free survival; PN, plexiform neurofibroma.

CONCLUSIONS

Evaluation of standardized differences after application of different propensity score methods showed that baseline characteristics of the cohorts were mostly balanced, supporting the published SPRINT direct comparison[10]

Selumetinib use in the SPRINT cohort was associated with significantly reduced risk of NF1-PN progression compared with the NH cohort; results were aligned before and after propensity score analysis

Overall, these results further strengthen existing evidence on the clinical value of selumetinib in the treatment of pediatric patients with NF1-PN

PLAIN LANGUAGE SUMMARY

Why did we perform this research?
Neurofibromatosis type 1 (NF1) is a disorder caused by mutations in the *NF1* gene. Individuals with NF1 can develop tumors called plexiform neurofibromas (PN), which can be painful, cause other clinical problems, and lead to a reduced quality of life. Selumetinib is a drug that has been approved to treat children with symptomatic NF1-PN. Its approval was based on positive results from the SPRINT clinical trial. The SPRINT trial reported tumor shrinkage, improvements in pain and function, and acceptable safety in children with symptomatic NF1 who received selumetinib. This study did not have a control arm to compare the results of selumetinib with; however, a Natural History (NH) study evaluated patients with NF1-PN who did not receive selumetinib. Participants from the SPRINT study were matched against participants from the NH study to create an external control arm for the SPRINT trial.

How did we perform this research?
Differences in baseline characteristics (e.g. age, sex, weight, race) between the SPRINT and NH studies were identified. Then, a statistical method called propensity score analysis was performed to balance the characteristics between the studies. This allowed us to look at differences in the reduction in the risk of PN progression for patients who had received selumetinib compared with those who had not received selumetinib.

What were the findings of this research and what are the implications?
The baseline characteristics were similar in both studies, supporting the findings from the SPRINT study. Notably, the results demonstrated that PN progression significantly reduced with selumetinib compared with the NH cohort, supporting the use of selumetinib to treat children with NF1-PN.

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Disclosures
Ayo Adeyemi is an employee of, and owns stocks from, Alexion, AstraZeneca Rare Disease. Andrea M. Gross has served as unpaid scientific advisor for Alexion, AstraZeneca Rare Disease and Springworks. Andrea Baldwin declares no conflicts of interest. Eva Dombi declares an unpaid leadership or fiduciary role for the Response Evaluation in Neurofibromatosis and Schwannomatosis imaging group as a co-chair, and an unpaid leadership or fiduciary role for the Neurofibromatosis Clinical Trials Consortium as a co-chair for the imaging committee. Brigitte C. Widemann has served as an unpaid scientific advisor for Alexion, AstraZeneca Rare Disease and Springworks. Kyaw Joe Sint is an employee of and owns stocks from Alexion, AstraZeneca Rare Disease.

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