Pivotal, Phase 2b ReNeu Trial of Mirdametinib in Children and Adults With Neurofibromatosis Type 1-Associated Plexiform Neurofibroma (NF1-PN): A Spotlight on Patients Achieving Deep Response

POSTER #CTNI-21

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INTRODUCTION

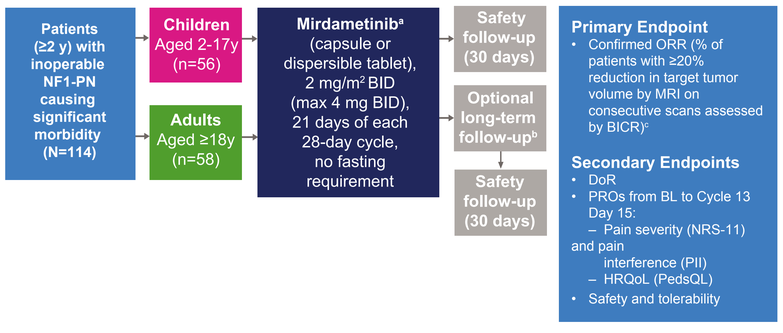
- Plexiform neurofibromas (PN) are nonmalignant peripheral nerve sheath tumors that can cause significant morbidity and develop in 30% to 50% of patients with neurofibromatosis type 1 (NF1)[1-5]
- No pharmacologic therapies are approved for adults with NF1-PN; one mitogen-activated protein kinase (MAPK) kinase (MEK) inhibitor is approved by the US Food and Drug Administration for children (≥2 years of age) with symptomatic, inoperable NF1-PN[6]
- Mirdametinib is an investigational, oral, allosteric, highly selective, potent, central nervous system-penetrant, small-molecule inhibitor of MEK1/2[7-9]
- ReNeu is an open-label, multicenter, pivotal, phase 2b trial (NCT03962543) that evaluated the efficacy, pain, health-related quality of life (HRQoL), and safety of mirdametinib in adults (≥18 years of age) and children (2 to 17 years of age) with NF1-PN
  - In ReNeu, confirmed objective response rate (ORR) among patients receiving mirdametinib during the 24-cycle treatment phase was 41% (24/58) in adults and 52% (29/56) in children[10]
  - Mirdametinib had a tolerable and manageable safety profile with early, sustained, and clinically meaningful improvements in worst tumor pain severity, pain interference, and HRQoL, which may contribute to patients' willingness to stay on therapy[10,11]
- The goal of treatment in patients with symptomatic NF1-PN is improvement of PN-associated morbidity by reducing tumor size through surgical debulking or systemic therapies[5,12]
  - Symptomatic PNs are generally larger than asymptomatic PNs, and PN growth is associated with increases in pain and functional decline[13, 14]
  - NF experts have noted a need for new therapies that improve depth of response[5]

OBJECTIVES

- To evaluate deep tumor reductions with mirdametinib in the ReNeu trial, deep response was defined as a best PN volume reduction >50% from baseline among patients with a confirmed response
  - A best PN volume reduction of >50% is more than double the threshold for a confirmed response (≥20%) based on the Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) criteria and greater than the median best PN volume reduction observed in the ReNeu trial (adults, -41% [-90, 13]; children, -42% [-91, 48])[10, 15]
- This post hoc analysis was conducted to understand whether specific patient characteristics were associated with deep responses to mirdametinib treatment
- To evaluate the percentage of adults and children with NF1-PN receiving mirdametinib who achieved both a confirmed response during the 24-cycle treatment phase and a deep response while receiving mirdametinib treatment (data cutoff: September 20, 2023)

METHODS

Figure 1. ReNeu (NCT03962543) Trial Design



[a]Capsules were administered unless a patient requested the use of the dispersible tablet formulation. [b]In the optional, ongoing long-term follow-up phase, patients continue receiving mirdametinib at the last dose assigned in the treatment phase until a withdrawal criterion is met or until commercial availability of mirdametinib. [c]Per REiNS criteria; primary endpoint assessed in 24-cycle treatment phase. In cases where 2 measurements represented different tumor response statuses, as defined above, an independent adjudicator made the final decision on which response category was recorded at that visit. BICR, blinded independent centralized review; BID, twice a day; BL, baseline; DoR, duration of response; HRQoL, health-related quality of life; NF1-PN, neurofibromatosis type 1 plexiform neurofibromas; NRS-11, Numeric Rating Scale-11; ORR, objective response rate; PedsQL, Pediatric Quality of Life Inventory; PII, Pain Interference Index; PRO, patient-reported outcome; REiNS, Response Evaluation in Neurofibromatosis and Schwannomatosis.

- The primary endpoint of ReNeu was the confirmed ORR (**Figure 1**), defined as the percentage of patients with ≥20% reduction on magnetic resonance imaging (MRI) of the target PN volume from baseline to cycle 24 (treatment phase) assessed by blinded independent central review (BICR) on 2 or more consecutive scans within 2 to 6 months
  - Adjudication is the average PN volume measurement independently calculated by 2 BICR readers or the measurement selected by an adjudicator when response category was not agreed upon
- Patients were categorized into 3 subgroups based on best percent reduction from baseline in target PN volume (**Table 1**)

Table 1. Patient Subgroups for Post Hoc Analyses

SUBGROUP	DEFINITION	ADULTS (n=58)	CHILDREN (n=56)
Subgroup A	Confirmed response and best PN reduction of >50% (deep response)	15 (26%)	15 (27%)
Subgroup B	Confirmed response and best PN reduction of ≥20% to ≤50%	9 (16%)	14 (25%)
Subgroup C	Best PN reduction of <20%	15 (26%)	17 (30%)
Not included	Unconfirmed response with a best PN volume reduction of ≥20%[a]	11 (19%)	8 (14%)
Missing	Missing postbaseline assessments were not included	8 (14%)	2 (4%)

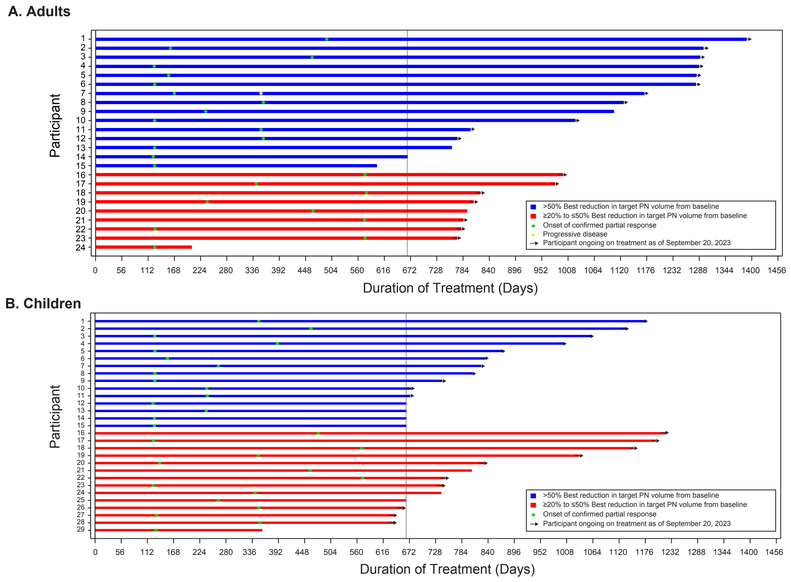
[a]No confirmed MRI. MRI, magnetic resonance imaging; PN, plexiform neurofibroma.

- Analyses of baseline characteristics, duration of mirdametinib treatment, and time to best percentage change from baseline were conducted to compare patients across subgroups
- Duration of treatment was defined as the time from first mirdametinib exposure to the date of last dose as of the data cutoff (September 20, 2023)
- Pearson correlation analyses were performed to assess the linear relationship between best percentage change from baseline in target PN volume and their baseline target PN volume for Subgroups A and B

RESULTS

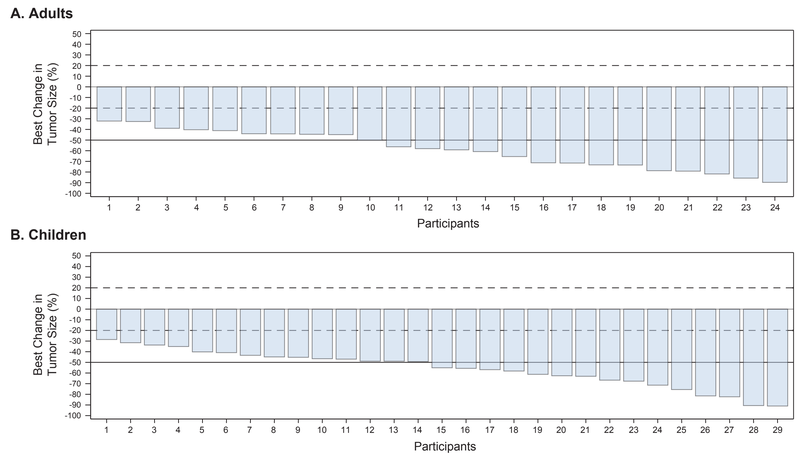
- Deep responses were observed in 62% (15/24) of adults and 52% (15/29) of children with a confirmed response treated with mirdametinib (Subgroups A and B)
- In total, 75% (18/24) of adults and 72% (21/29) of children with a confirmed response remained on treatment as of the data cutoff (**Figure 2A** and **2B**)

Figure 2. Duration of Mirdametinib Treatment and Response Status for (A) Adults and (B) Children With Confirmed Responses



Vertical lines indicate the per-protocol date of the end-of-treatment phase on cycle 24, day 21. PN, plexiform neurofibroma.

Figure 3. Waterfall Plots of Best Percentage Change From Baseline in Target PN Volume With Mirdametinib in (A) Adults and (B) Children With Confirmed Responses



Horizontal dotted lines indicate partial response (≥20% reduction in target PN volume from baseline) and progressive disease (≥20% increase in target PN volume from baseline). Horizontal solid lines indicate a deep response (>50% reduction in target PN volume from baseline).

- There was no clear trend across baseline characteristics for age, sex, progression status, or tumor location for the three analyzed subgroups among adults (**Table 2**) and children (**Table 3**)
- In adults, median baseline target PN volume in Subgroup A was less than Subgroups B and C (**Table 2**)
- Patients achieving a deep response (Subgroup A) had a longer median duration of mirdametinib treatment than those in Subgroups B or C (**Tables 2** and **3**)
- Adults and children in ReNeu with a deep response experienced an onset of confirmed response earlier than those who did not achieve a deep response (**Tables 2** and **3**)
- Median time to best percentage change from baseline in target PN volume was greater among adults and children in Subgroup A than those in Subgroups B or C (**Tables 2** and **3**)

Table 2. Baseline Characteristics and Duration of Treatment for Adults by Response Subgroup

BASELINE CHARACTERISTICS AND DURATION OF TREATMENT	SUBGROUP A: >50% (n=15)	SUBGROUP B: ≥20% TO ≤50% (n=9)	SUBGROUP C: <20% (n=15)
Age, years, median (range)	38 (18-69)	39 (24-51)	34 (19-68)
Sex, n (%)			
Male	5 (33)	4 (44)	6 (40)
Female	10 (67)	5 (56)	9 (60)
Baseline target PN volume, mL, median (range)	126 (1-449)	216 (37-2518)	184 (17-2852)
Target PN progressing at study entry, n (%)[a]			
Progressive	6 (40)	5 (56)	10 (67)
Nonprogressive	9 (60)	4 (44)	5 (33)
Target PN location, n (%)			
Head and neck	5 (33)	7 (78)	8 (53)
Extremity	5 (33)	2 (22)	5 (33)
Trunk	2 (13)	0 (0)	1 (7)
Paraspinal	3 (20)	0 (0)	1 (7)
Duration of treatment, months, median (range)[b]	37 (20-46)	26 (7-33)	9 (4-28)
Time to confirmed response, months, median (range)	5 (4-16)	15 (4-19)	—
Time to best PN volume reduction from baseline, months, median (range)	25 (8-40)	19 (8-29)	8 (4-19)

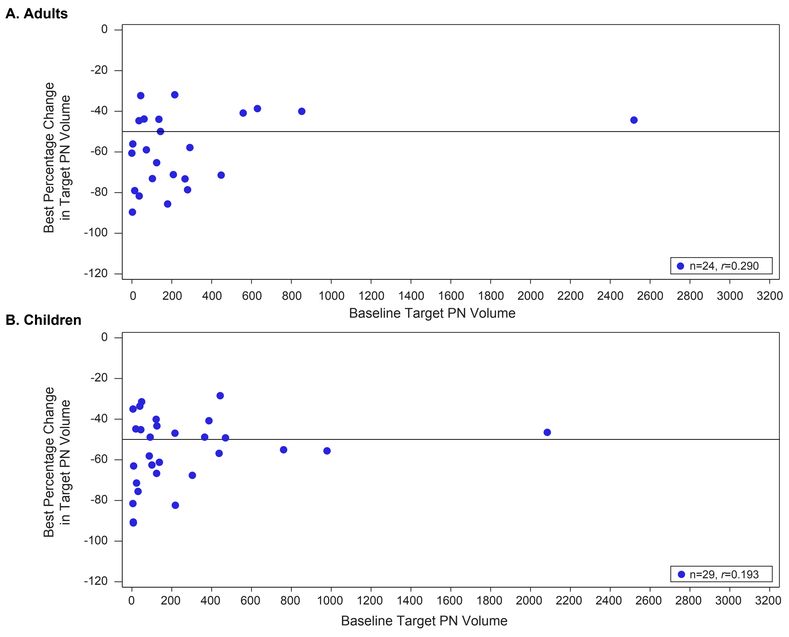
[a]Target PN progression status at study entry was determined by individual study sites. [b]Duration of treatment was defined as the time from first mirdametinib exposure to the date of last dose as of the data cutoff (September 20, 2023). Nineteen adults were not included in this analysis: 11 adults did not achieve a confirmed response but did have a best PN volume reduction of ≥20%; 8 adults had missing results. PN, plexiform neurofibroma.

Table 3. Baseline Characteristics and Duration of Treatment for Children by Response Subgroup

BASELINE CHARACTERISTICS AND DURATION OF TREATMENT	SUBGROUP A: >50% (n=15)	SUBGROUP B: ≥20% TO ≤50% (n=14)	SUBGROUP C: <20% (n=17)
Age, years, median (range)	9 (2-17)	10 (2-17)	12 (4-17)
Sex, n (%)			
Male	5 (33)	7 (50)	10 (59)
Female	10 (67)	7 (50)	7 (41)
Baseline target PN volume, mL, median (range)	103 (8-981)	126 (9-2086)	79 (5-427)
Target PN progressing at study entry, n (%)[a]			
Progressive	10 (67)	11 (79)	8 (47)
Nonprogressive	5 (33)	3 (21)	9 (53)
Target PN location, n (%)			
Head and neck	8 (53)	7 (50)	9 (53)
Extremity	2 (13)	2 (14)	2 (12)
Trunk	5 (33)	4 (29)	4 (24)
Paraspinal	0 (0)	1 (7)	2 (12)
Duration of treatment, months, median (range)[b]	27 (22-39)	25 (12-40)	9 (4-27)
Time to confirmed response, months, median (range)	5 (4-15)	11 (4-19)	—
Time to best PN volume reduction from baseline, months, median (range)	22 (11-33)	17 (4-28)	4 (4-19)

[a]Target PN progression status at study entry was determined by individual study sites. [b]Duration of treatment was defined as the time from first mirdametinib exposure to the date of last dose as of the data cutoff (September 20, 2023). Ten children were not included in this analysis: 8 children did not achieve a confirmed response but did have a best PN volume reduction of ≥20%; 2 children had missing results. PN, plexiform neurofibroma.

Figure 4. Baseline Target PN Volume and Best Percentage Change From Baseline in Target PN Volume Correlation in Adjudicated Confirmed Responses for (A) Adults and (B) Children



Horizontal solid lines indicate a deep response (>50% best reduction in target PN volume from baseline). PN, plexiform neurofibroma.

- In this post hoc analysis of patients with an adjudicated confirmed response, correlation coefficients between baseline and best percentage change from baseline in target PN volume were as follows:
  - Adults (n=24): r=0.290
  - Children (n=29): r=0.193

DISCUSSION

- In these post hoc analyses, we have used a definition of deep response that will need further validation for clinical significance
- Adults and children in Subgroup A (deep response) reached a confirmed response earlier than patients in Subgroup B and reached a best PN volume reduction later than patients in Subgroups B or C, suggesting that patients with a deep response reached a confirmed response quickly and continued to experience tumor reductions over time
- There was little to no correlation identified between baseline and best percentage change from baseline in target PN volume in adults or children
- One limitation of these analyses is that some patients were excluded because they did not meet the criteria defining the subgroups in this analysis, contributing to small patient populations in the subgroups
- Individual treatment goals should be considered for patients with NF1-PN, and symptom management associated with their NF1-PN may be more important for some patients than target PN volume decrease
- With longer duration of mirdametinib treatment, additional patients from the ReNeu trial still may experience deep response

CONCLUSION

- The majority of adults and children in ReNeu who had a confirmed response achieved a deep response (>50% best reduction from baseline in target PN volume) with mirdametinib
- There was no clear trend across baseline characteristics for age, sex, progression status, or tumor location, and no pattern was observed with regard to response; there was little to no correlation between baseline target PN volume and response
- Patients with a deep response were treated for a longer duration with mirdametinib than patients who did not achieve a deep response
- Although the time to a confirmed response in those with a deep response tended to be rapid, the best tumor volume response in those with a deep response was achieved at about 2 years of mirdametinib therapy
- On the basis of the safety and tolerability profile of mirdametinib and other clinical benefits of treatment, adults and children with NF1-PN receiving mirdametinib may be able to adhere to treatment longer, improving their likelihood of achieving a deep response

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ACKNOWLEDGMENTS

The study was sponsored by SpringWorks Therapeutics, Inc. Medical writing and editing assistance were provided by Jonathan Mitchell, PharmD, and Stephen Bublitz, ELS, of MedVal Scientific Information Services, LLC (Princeton, NJ) and were funded by SpringWorks Therapeutics, Inc.

DISCLOSURES

TG: Research funding: SpringWorks Therapeutics, Inc. **CM:** Employment: OX2 Therapeutics; leadership role: OX2 Therapeutics; equity interest: OX2 Therapeutics; consultant/advisory role: Alexion Pharmaceuticals; patents, royalties, or other intellectual property: OX2 Therapeutics; travel expenses: Alexion Pharmaceuticals. **RYM-K:** Research funding: AstraZeneca, Incyte, Jazz, Pfizer, and SpringWorks Therapeutics paid to institution. **HHS:** Research funding: AstraZeneca, NFlection, Recursion Pharma, and SpringWorks paid to institution; other relationship(s): Children's Tumor Foundation (funding). **LW:** No relevant disclosures. **FMH:** Research funding: Incyte Corporation. **MN, UI, and MDW:** Employment: SpringWorks Therapeutics, Inc; equity interest: SpringWorks Therapeutics, Inc. **AL:** Contractor: SpringWorks Therapeutics, Inc. **DB-V:** Employment: Mayo Clinic; consultant/advisory role: Alexion Pharmaceuticals; research funding: Alexion Pharmaceuticals, Recursion, and SpringWorks Therapeutics, Inc. **AH:** Consultant/advisory role: Alexion Pharmaceuticals, AstraZeneca, Intellisphere, LLC, and SpringWorks Therapeutics, Inc; patents, royalties, or other intellectual property: Boehringer Ingelheim RCV GmBH & Co KG- Licensing- T-019044 Development of a Preclinical NF1-MPNST Platform Suitable for Precision Oncology Drug Discovery and Evaluation, paid through institution; Deutsches Krebsforschungszentrum-licensing agreement for PDX cell lines, paid through institution; travel expenses: Alexion Pharmaceuticals and SpringWorks Therapeutics, Inc.

Presented at the 29th Annual Meeting of the Society for NeuroOncology, November 21-24, 2024, Houston, TX, USA