ReNeu: A Pivotal Phase 2b Trial of Mirdametinib in Adults and Children with Neurofibromatosis Type 1 (NF1)-Associated Symptomatic Inoperable Plexiform Neurofibroma (PN)

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Financial and Competing Interests and Disclosure

Christopher L. Moertel, MD: Employment with OX2 Therapeutics; leadership role: OX2 Therapeutics; equity interest: OX2 Therapeutics; consultancy/advisory role: SpringWorks Therapeutics Inc, Alexion Pharmaceuticals; patents, royalties, or other intellectual property: OX2 Therapeutics; travel expenses: SpringWorks Therapeutics Inc, Alexion Pharmaceuticals

The ReNeu trial was sponsored by SpringWorks Therapeutics Inc.

Background

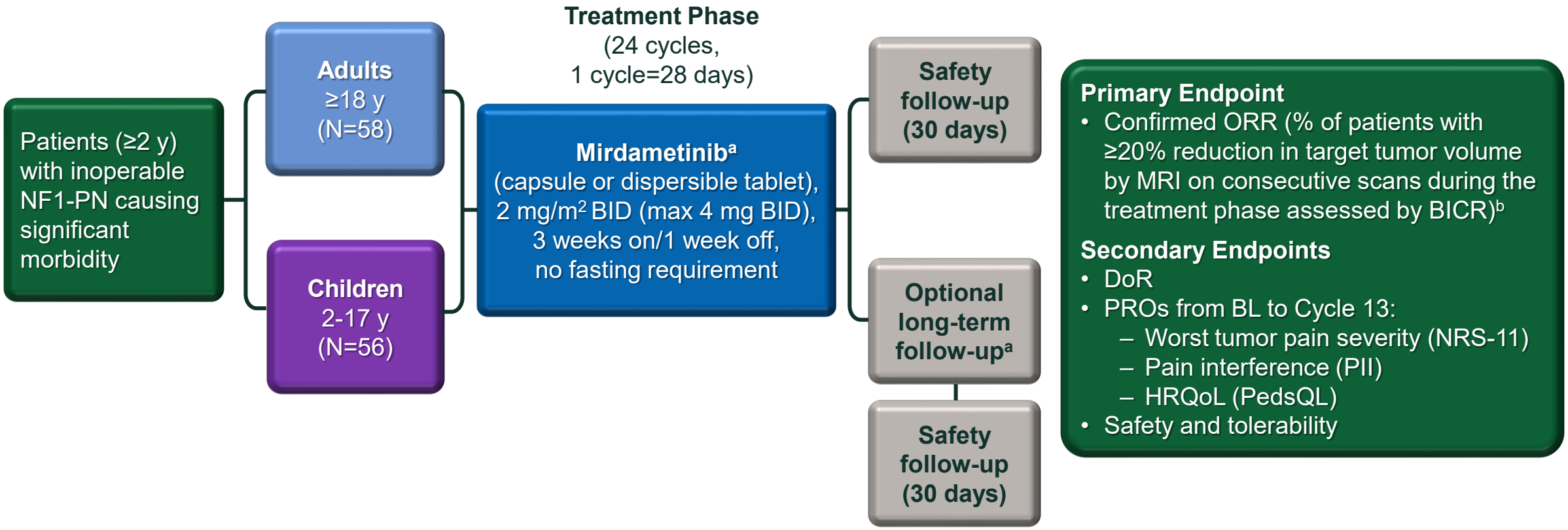
- Plexiform neurofibromas (PNs) are nonmalignant nerve sheath tumors reported in 30% to 50% of people with neurofibromatosis type 1 (NF1)[1,2]
  - PN often cause morbidities, including pain, impaired HRQoL, disfigurement, and increased risk of malignant transformation[3,4]
- No pharmacologic therapies are approved for adults; one MEK inhibitor is FDA-approved for children (≥2 years)[5]
- Mirdametinib is an investigational, oral, highly-selective, CNS-penetrant, small-molecule MEK1/2 inhibitor[a]
  - A phase 2 trial (NF106) of mirdametinib demonstrated efficacy and a manageable safety profile in adults and adolescents (≥16 years) with NF1-PN[6]

[a]Mirdametinib is an investigational product that has not been approved by any regulatory authority; the safety and efficacy of mirdametinib have not been established.

CNS, central nervous system; **FDA**, US Food and Drug Administration; **HRQoL**, health-related quality of life; **MEK**, mitogen-activated protein kinase kinase; **NF1**, neurofibromatosis type 1; **PN**, plexiform neurofibroma.

1. Prada CE, et al. *J Pediatr*. 2012;160:461-467. **2.** Miller DT, et al. *Pediatrics.* 2019;143:e20190660. **3.** Gutmann DH, et al. *Nat Rev Dis Primers*. 2017;3:17004. **4.** Fisher MJ, et al. *Neuro Oncol*. 2022;24:1827-44. **5.** KOSELUGO [Prescribing Information]. AstraZeneca Pharmaceuticals LP; 2024. **6.** Weiss BD, et al. *J Clin Oncol*. 2021;39(7):797-806.

ReNeu: A Multicenter, Open-label, Pivotal, Phase 2b Trial of Mirdametinib in Adults and Children With NF1-PN (NCT03962543)



[a]In the LTFU, patients continue on mirdametinib at the last dose assigned in the treatment phase. [b]Per REiNS criteria. Consecutive scans for confirmation of objective response had to occur within 2-6 months. BICR with 2 reviewers and 1 adjudicator. High concordance of tumor volumes between readers (R=0.9907).

BICR, blinded independent central review; **BID**, twice a day; **BL**, baseline; **DoR**, duration of response; **LTFU**, long-term follow-up phase; **MRI**, magnetic resonance imaging; **NRS-11**, Numeric Rating Scale-11; **ORR**, objective response rate; **PedsQL**, Pediatric Quality of Life Inventory; **PII**, Pain Interference Index; **PRO**, patient-reported outcomes; **REiNS**, Response Evaluation in Neurofibromatosis and Schwannomatosis.

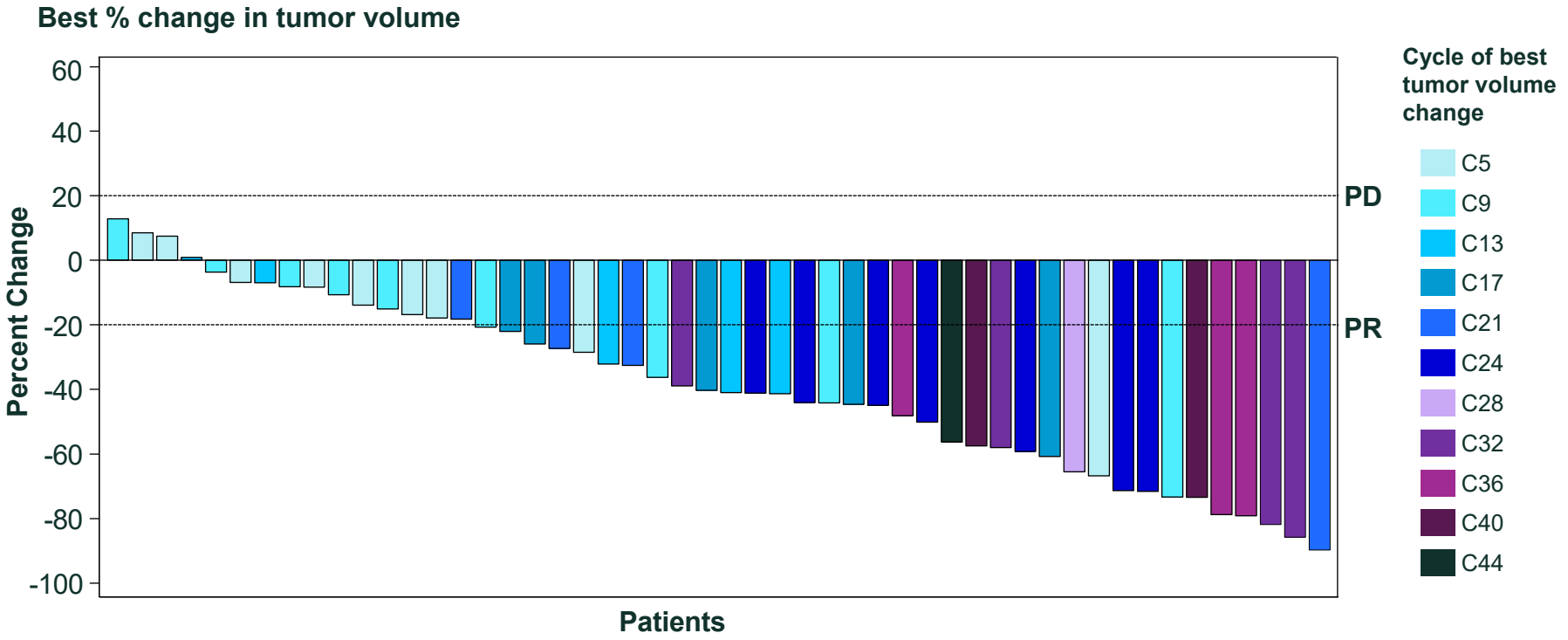
1. ClinicalTrials.gov. https://www.clinicaltrials.gov/study/NCT03962543. Accessed May 9, 2024.

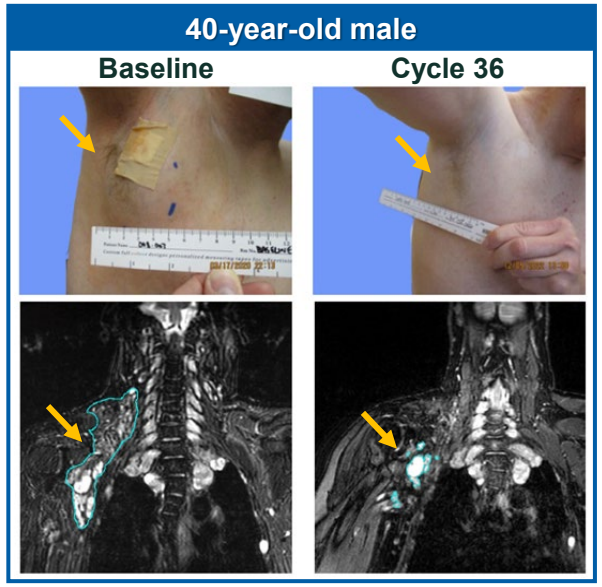
Baseline Demographics and Characteristics

	Adults (N=58)	Children (N=56)
Age, median (range), years	**34 (18 to 69)**	**10 (2 to 17)**
Sex, n (%)		
Female	37 (64)	30 (54)
Male	21 (36)	26 (46)
Volume of target PN, median (range), mL	**196 (1 to 3457)[a]**	**99 (5 to 3630)**
Target PN progressing at trial entry, n (%)	**31 (53)**	**35 (62)**
Location of target PN, n (%)		
Head and neck	28 (48)	28 (50)
Lower/upper extremities	17 (29)	8 (14)
Paraspinal	5 (9)	4 (7)
Torso[b]	5 (9)	8 (14)
Other	3 (5)	8 (14)
Type of PN-related morbidity, n (%)		
Pain	52 (90)	39 (70)
Disfigurement or major deformity	30 (52)	28 (50)
Motor dysfunction/weakness	23 (40)	15 (27)
Airway dysfunction	3 (5)	7 (12)
Other	10 (17)	12 (21)

[a]A target PN volume of ≥5 mL was an inclusion criterion. The patient enrolled with a target PN of 1 mL was a protocol deviation.
[b]Includes chest wall, mesentery and pelvis, and abdominal wall.

Mirdametinib Demonstrated Significant cORR by BICR and Deep and Durable Tumor Volume Reductions in Adults



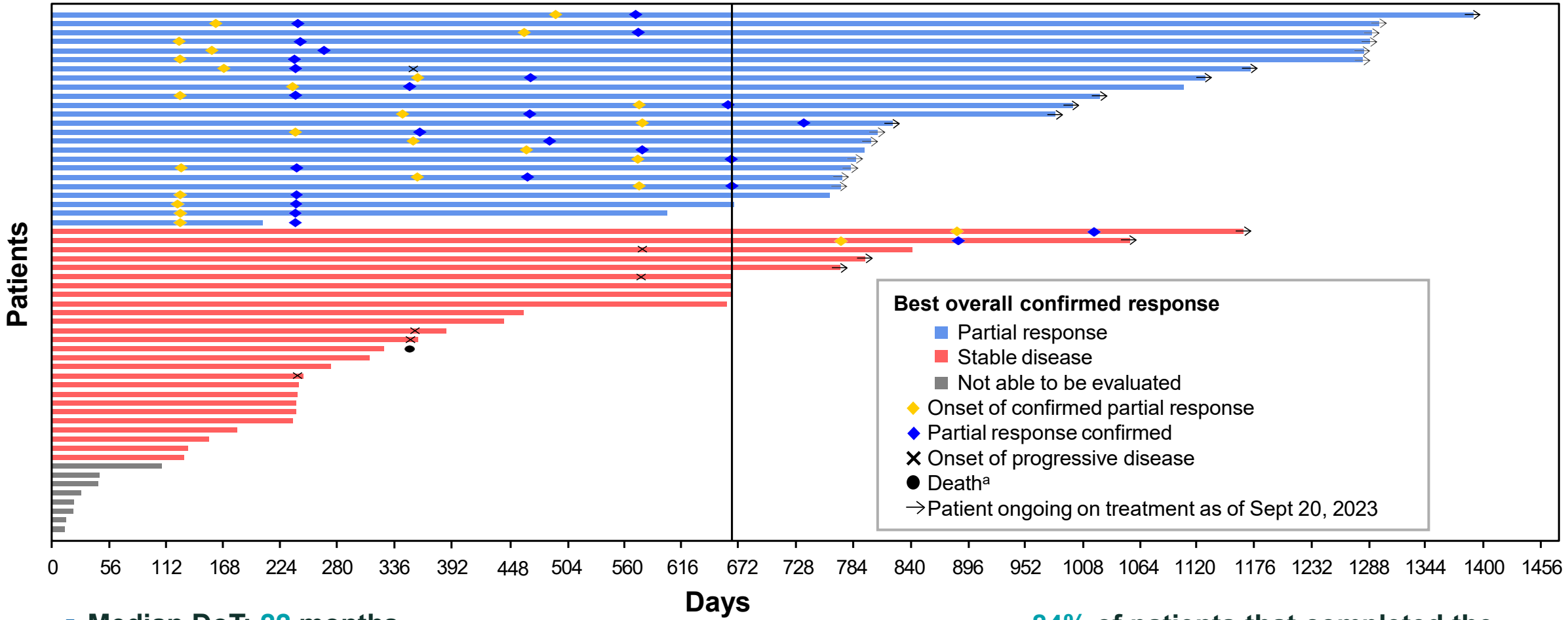


Target PN volume change from baseline[c] at Cycle 36: –79%

- Confirmed ORR: 41%[a] (24/58; *P*<.001 vs null hypothesis[b])
  - Two additional adults achieved a confirmed PR in the LTFU
- Median best change in tumor volume: –41% (range, –90 to 13)
- 62% of adults with confirmed objective response achieved a deep response (>50% tumor volume reduction)

[a]Confirmed ORR defined as proportion of patients with ≥20% reduction of target PN volume from baseline assessed by BICR on ≥2 consecutive scans within 2 to 6 months during the treatment phase.
[b]The minimum clinically relevant ORR (null) was defined as 23% for adults. [c]MRI images are 2D visual representation for presentation and may not represent the total volumetric changes observed. Additional/alternative sequences may have been utilized to best analyze the volumetrics of the target lesion.
cORR, confirmed objective response rate.

Mirdametinib Demonstrated Significant cORR by BICR and Deep and Durable Tumor Volume Reductions in Adults

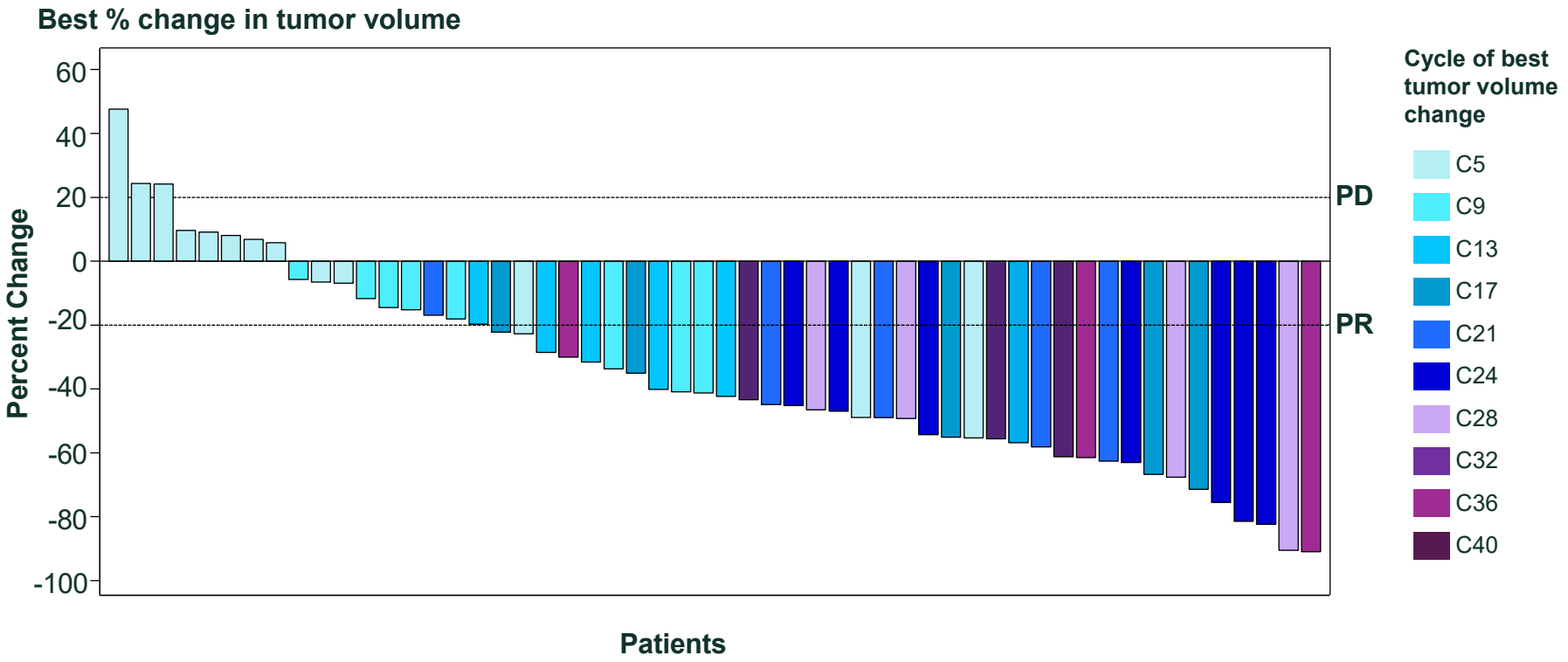


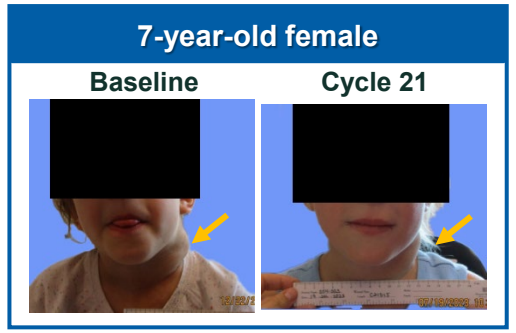
- **Median DoT: 22 months**
- **Median time to onset of response: 7.8 months (range, 4 to 19)**
- **Median DoR: not reached**

- **84% of patients that completed the treatment phase chose to continue in the LTFU**

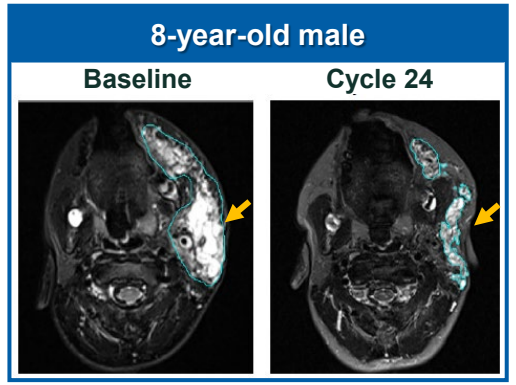
The vertical line corresponds to the per-protocol date of the end-of-treatment phase on Cycle 24, Day 21. Two adults achieved a confirmed PR in the LTFU.
[a]There was one death due to COVID-19 in an adult within 30 days of discontinuing mirdametinib (not considered to be treatment-related).
DoT, duration of treatment; **LTFU,** long term follow-up.

Mirdametinib Demonstrated Significant cORR by BICR and Deep and Durable Tumor Volume Reductions in Children





Target PN volume change from BL at Cycle 21: –49%

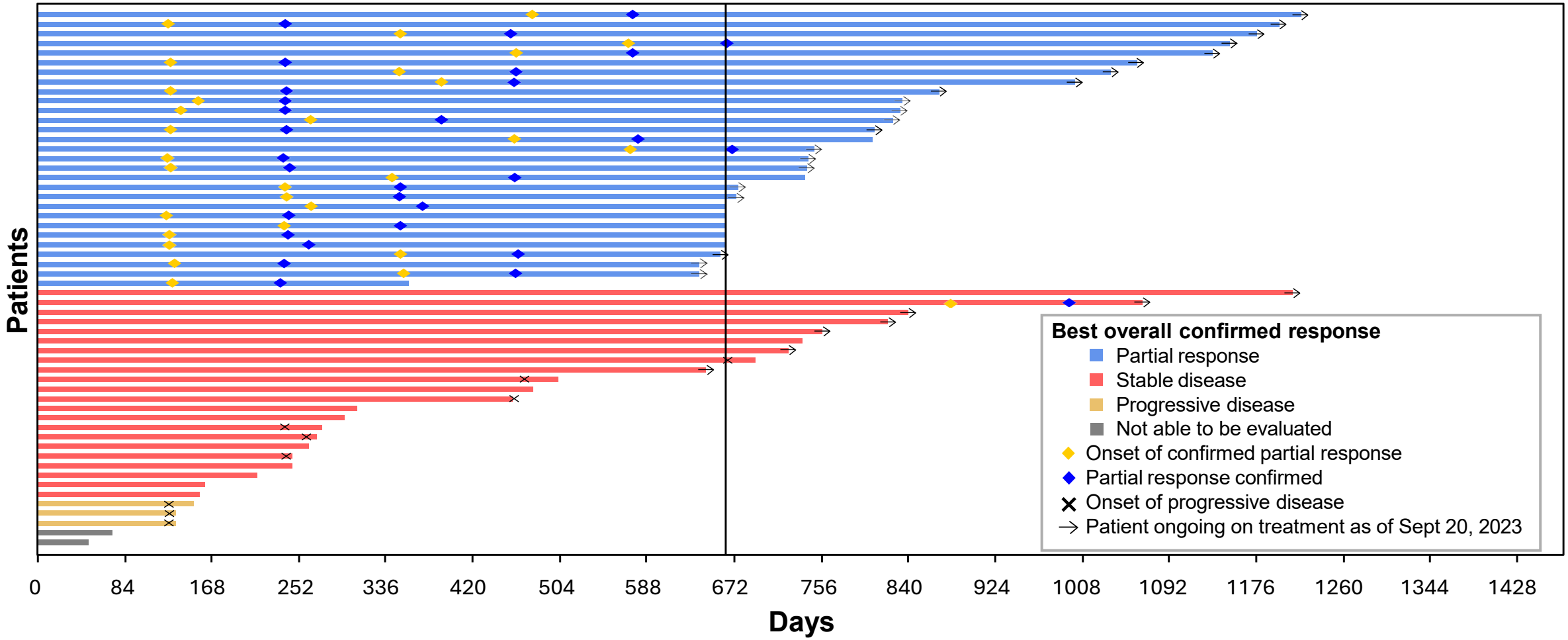


Target PN volume change from BL[c] at Cycle 24: –82%

- Confirmed ORR: 52%[a] (29/56; *P*<.001 vs null hypothesis[b])
  - An additional child achieved a confirmed PR in the LTFU
- Median (range) best change in tumor volume: –42% (range, –91 to 48)
- 52% of children with confirmed objective response achieved a deep response (>50% tumor volume reduction)

[a]Confirmed ORR defined as proportion of patients with ≥20% reduction of target PN volume from baseline assessed by BICR on ≥2 consecutive scans within 2 to 6 months during the treatment phase.
[b]The minimum clinically relevant ORR (null) was defined as 20% for children. [c]MRI images are 2D visual representation for presentation and may not represent the total volumetric changes observed. Additional/alternative sequences may have been utilized to best analyze the volumetrics of the target lesion.

Mirdametinib Demonstrated Significant cORR by BICR and Deep and Durable Tumor Volume Reductions in Children



- **Median DoT: 22 months**
- **Median time to onset of response: 7.9 months (range, 4 to 19)**
- **Median DoR: not reached**

- **85% of patients that completed the treatment phase chose to continue in the LTFU**

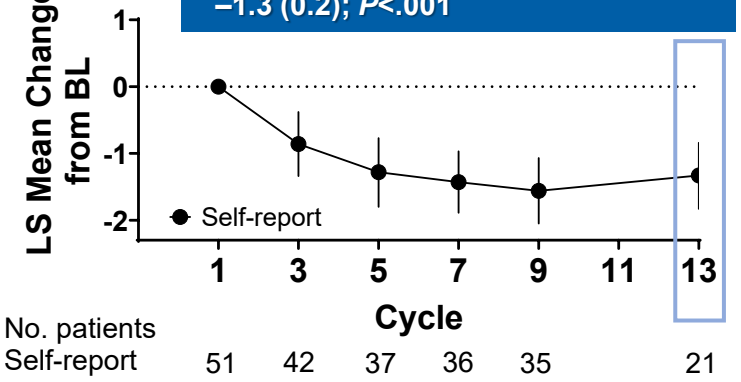
The vertical line corresponds to the per-protocol date of the end-of-treatment phase on Cycle 24, Day 21. One child achieved a confirmed PR in the LTFU.
LTFU, long term follow-up.

Mirdametinib Treatment Demonstrated Improvements in Pain

Worst tumor pain severity *(NRS-11 score)*

ADULTS

LS mean (SE) change from BL[a] at C13
–1.3 (0.2); *P*<.001

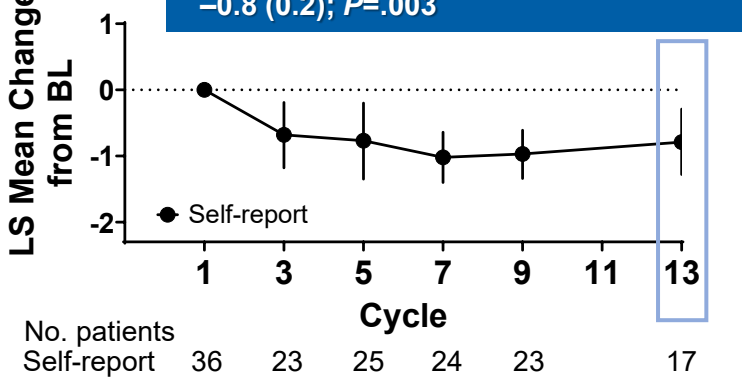


Worsening ↕ Improvement

No. patients						
Self-report	51	42	37	36	35	21

CHILDREN

LS mean (SE) change from BL[a] at C13
–0.8 (0.2); *P*=.003

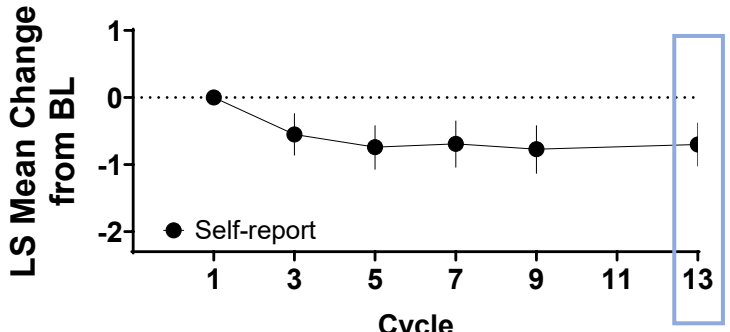


Worsening ↕ Improvement

No. patients						
Self-report	36	23	25	24	23	17

Pain Interference *(PII score)*

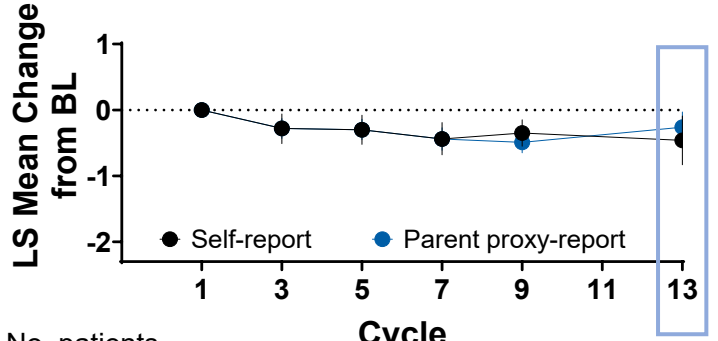
LS mean (SE) change from BL[a] at C13
–0.7 (0.2); *P*<.001



Worsening ↕ Improvement

No. patients						
Self-report	52	43	38	37	36	22

LS mean (SE) change from BL[a] at C13
–0.5 (0.2); *P*=.017 (self-report)
–0.3 (0.1); *P*=.025 (parent proxy-report)



Worsening ↕ Improvement

No. patients						
Self-report	45	29	32	33	31	22
Parent proxy-report	44	27	26	28	26	20

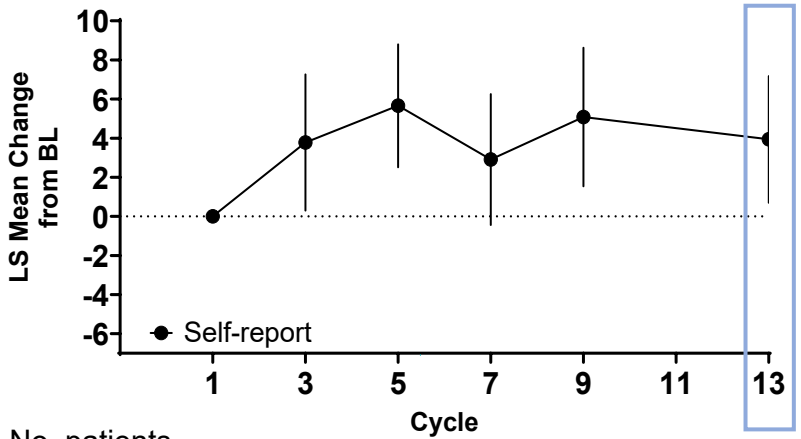
[a]PROs were recorded at Cycle 1 Day 1 (Baseline) and at Day 15 of subsequent cycles, and Cycle 13 was the prespecified endpoint.
NRS-11 scores range from 0 (no pain) to 10 (worst pain imaginable); higher scores indicate worse pain. PII scores range from 0 (not at all) to 6 (completely); higher scores indicate greater pain interference (worsening).
C, Cycle; **LS**, least-squares; **No.**, number; **SE**, standard error.

Mirdametinib Treatment Demonstrated Improvements in HRQoL

HRQoL
(PedsQL Total Score)

ADULTS

LS mean (SE) change from BL[a] at C13
3.9 (1.6); *P*=.018

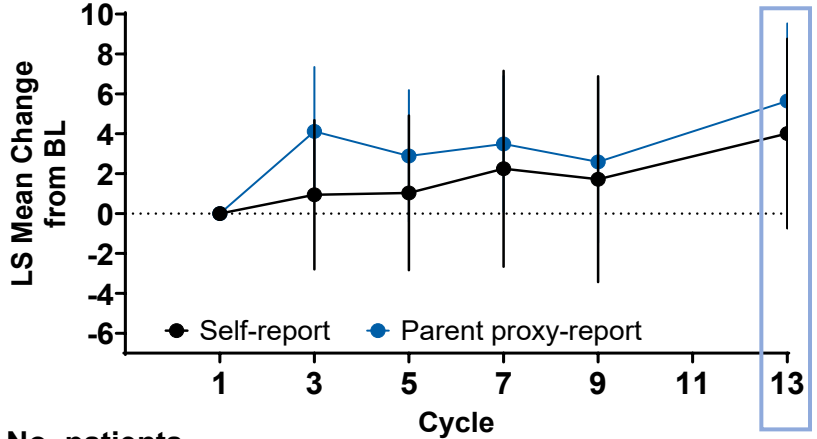


Improvement
Worsening

No. patients						
Self-report	55	48	46	44	44	34

CHILDREN

LS mean (SE) change from BL[a] at C13
4.0 (2.4); *P*=.096 (self-report)
5.6 (1.9); *P*=.005 (parent proxy-report)



Improvement
Worsening

No. patients						
Self-report	50	48	47	41	42	38
Parent proxy-report	55	52	52	48	47	43

[a]PROs were recorded at Cycle 1 Day 1 (Baseline) and at Day 15 of subsequent cycles, and Cycle 13 was the prespecified endpoint.
PedsQL items are assessed on a Likert scale from 0 (never a problem) to 4 (almost always a problem); these are reverse scored and linearly transformed to a 0 to 100 scale (0=100; 1=75; 2=50; 3=25; 4=0). Total PedsQL score is the mean of all item scores; higher scores indicate better HRQoL.

Mirdametinib Safety Profile

Treatment-related adverse events (TRAEs) Safety population, n (%)	Adults (N=58)[a]		Children (N=56)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any TRAE	**57 (98)**	**9 (16)**	**53 (95)**	**14 (25)**
TRAEs of any grade reported in ≥20% of patients in either cohort				
Dermatitis acneiform	45 (78)	5 (9)	24 (43)	1 (2)
Diarrhea	28 (48)	0 (0)	21 (38)	1 (2)
Nausea	21 (36)	0 (0)	12 (21)	0 (0)
Vomiting	16 (28)	0 (0)	8 (14)	0 (0)
Fatigue	12 (21)	1 (2)	5 (9)	0 (0)
Ejection fraction decreased	7 (12)	0 (0)	11 (20)	1 (2)
Blood creatinine phosphokinase increased	6 (10)	1 (2)	11 (20)	4 (7)
Paronychia	1 (2)	0 (0)	17 (30)	0 (0)
Serious TRAEs[b]	1 (2)		0 (0)	
Interruptions due to TRAEs	5 (9)		8 (14)	
Dose reductions due to TRAEs	10 (17)		7 (12)	
Discontinuations due to TRAEs[c]	12 (21)		5 (9)	

[a]There was one death due to COVID-19 in an adult (not considered to be treatment-related). [b]One treatment-related SAE in adult cohort, grade 3 RVO with confounding factors (hormonal contraception and COVID-19 vaccination). No treatment-related SAEs or RVO in pediatric cohort. [c]TRAEs leading to treatment discontinuation in >1 patient included dermatitis acneiform (4 adults, 1 child), diarrhea (4 adults, 1 child), nausea (4 adults), rash (1 adult, 1 child), and urticaria (2 children). The presence of more than 1 AE may have led to treatment discontinuation in a patient.
RVO, retinal vein occlusion; **SAE**, serious adverse event; **TRAE**, treatment-related adverse event.

Summary

Mirdametinib demonstrated deep and sustained tumor volume reductions and improvement in patient- (and parent proxy-) reported pain and HRQoL in adults and children

- Largest multicenter NF1-PN trial to date, prospectively utilized BICR to confirm target tumor response
- Primary endpoint of confirmed ORR (per REiNS criteria) of 41% in adults and 52% in children, median DoR not reached
  - An additional 2 adults and 1 child achieved a confirmed response in the LTFU phase
- Largest median reduction in PN volume reported to date in published clinical trials of targeted agents in NF1-PN[1-6]
  - including deep responses >50% tumor volume reduction
- Improvement in pain (NRS-11, PII) and HRQoL (PedsQL) from baseline
- Manageable safety profile, majority of TRAEs were grade 1/2
  - Rates of interruptions, reductions, and common MEK inhibitor-related AEs were lower vs previously published phase 2 MEK inhibitor studies in pediatric NF1-PN[1,2,7,a]
- Dispersible tablet formulation for children and adults with difficulty swallowing, and no fasting requirement

[a]No head-to-head studies have been conducted between mirdametinib and other MEK inhibitors.

1. Gross AM, et al. *Neuro Oncol*. 2022;24(11):1978-1988. **2.** Gross AM, et al. *N Engl J Med*. 2020;382(15):1430-42. **3.** Gross AM, et al. *Neuro Oncol.* 2023;25(10):1883-94. **4.** Suenobu S, et al. *Neurooncol Adv*. 2023;5(1);vdad054. **5.** Dombi E, et al. *N Engl J Med*. 2016;375(26):2550-60. **6.** Fisher MJ, et al. *Nat Med*. 2021;27(1):165-73. **7.** KOSELUGO [Prescribing Information]. AstraZeneca Pharmaceuticals LP; 2024.

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