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NF1 Plexiform Neurofibroma Trial

A Phase 2b Trial of the MEK Inhibitor Mirdametinib in Patients With Neurofibromatosis Type 1-Associated Plexiform Neurofibromas (ReNeu) – NCT03962543 – Interim Results

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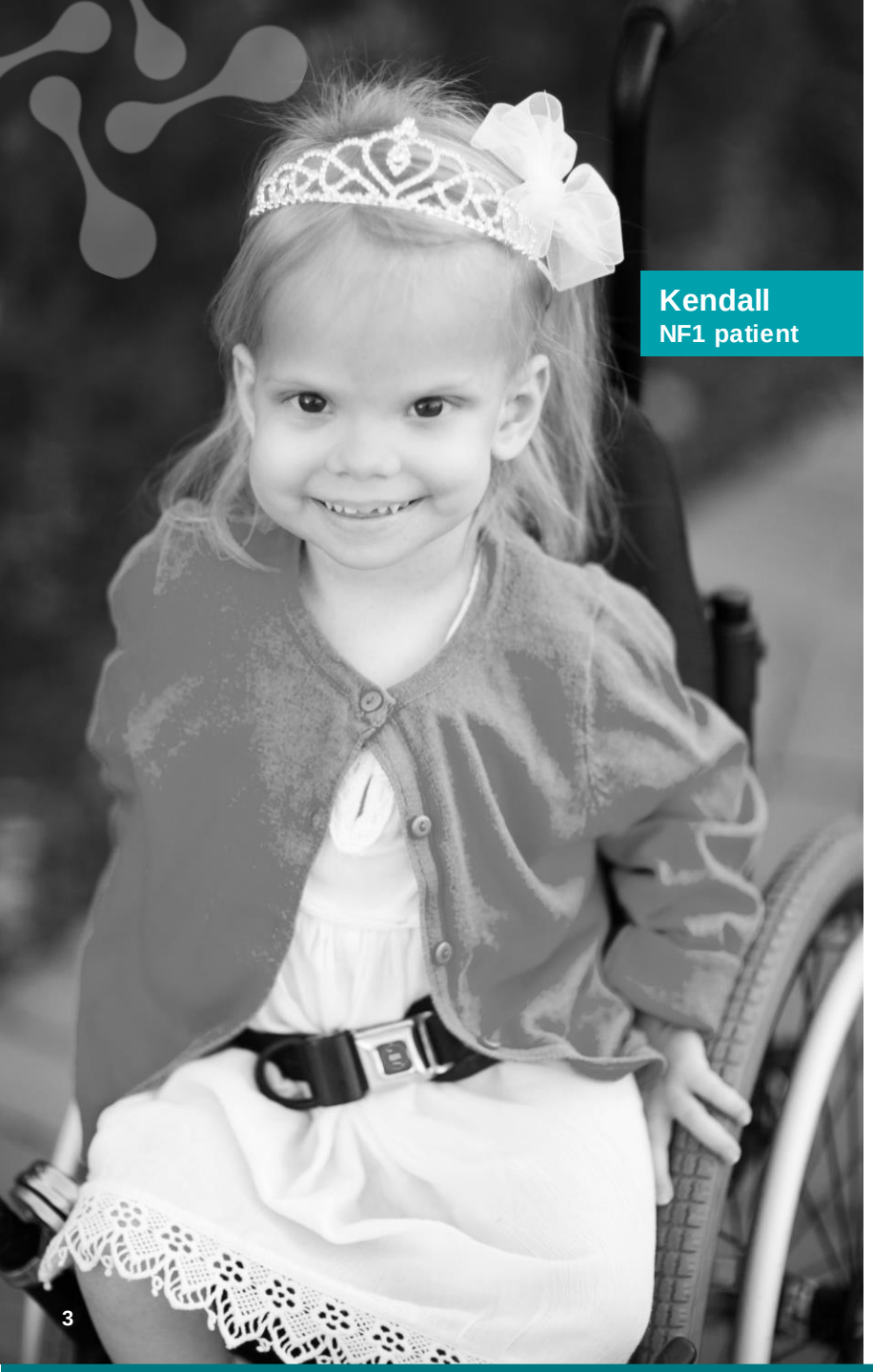
For the ReNeu investigators

SpringWorks THERAPEUTICS



Plexiform Neurofibromas Are Painful, Disfiguring Tumors That Grow Along Peripheral Nerve Sheaths

NF1-associated plexiform neurofibromas (NF1-PN) patients present with significant morbidities

- NF1 mutations cause loss of neurofibromin, a key MAPK pathway repressor, leading to uncontrolled tumor growth across the body
- NF1-PN grow along nerves and can lead to extreme pain and disfigurement
- NF1 patients can experience neurocognitive deficits and developmental delays

MEK inhibitors have emerged as a validated class for NF1-PN treatment

- Surgical resection is challenging due to the infiltrative tumor growth pattern along nerves and can lead to permanent nerve damage and disfigurement

~100,000 NF1 patients in the United States

- ~30-50% lifetime risk of developing plexiform neurofibromas in NF1 population
- NF1-PN can malignantly transform into MPNST, a diagnosis that has a 12-month survival rate of under 50%

Source: Kim et al., *Sarcoma*, 2017.
MPNST = malignant peripheral nerve sheath tumor

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Mirdametinib: An Emerging Therapy for Patients with NF1-PN

- Activation of MAPK pathway (RAS-RAF-MEK-ERK signaling pathway) is frequently observed in human tumors, including NF1-PN, and MEK inhibition has been clinically validated for NF1-PN patients

- Mirdametinib is a potent, oral, allosteric, brain penetrant, small molecule MEK1/2 inhibitor with clinical validation and over 250 subjects exposed to date

- Encouraging safety and anti-tumor activity observed in Phase 2 investigator-initiated trial in adolescents and adults with NF1-PN that was conducted prior to initiation of ongoing ReNeu trial

- Compound potency, optimized dose/schedule, and preclinical data indicating BBB penetrance may allow for a potentially differentiated profile compared to other MEK inhibitors

- Lack of food effect and development of pediatric formulation provide opportunities to reduce overall patient burden

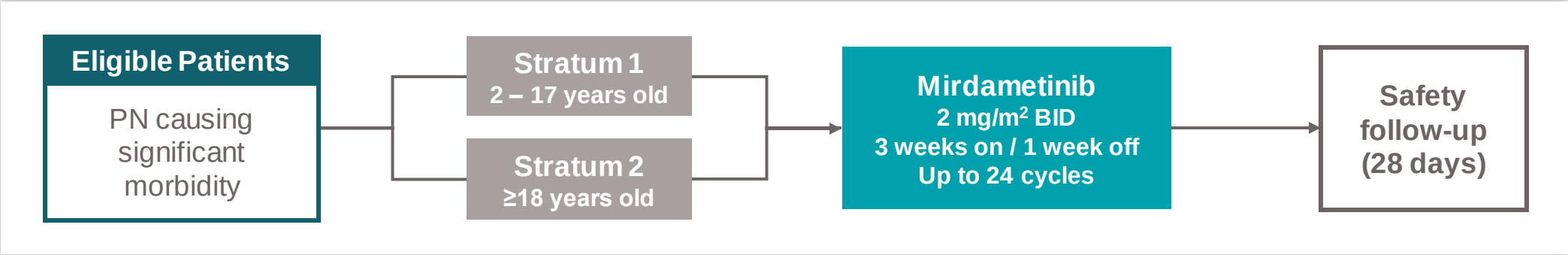
ReNeu Study Design

Trial Summary

- Enrolling ~100 patients in 2 strata (pediatrics, adults)
- 2 mg/m^2 BID dosing with intermittent course (4-week cycles of 3 weeks on, 1 week off) for up to 24 cycles
  - Maximum dose of 4 mg BID
  - Treatment duration designed to evaluate longer-term benefit of mirdametinib in NF1-PN

Summary of Endpoints

- Primary Endpoint: Objective response rate
- Secondary Endpoints: Safety and tolerability, duration of response, and quality of life assessments



Enrollment is ongoing at 47 centers across the US and total enrollment has exceeded 70%

Baseline Demographics and Patient Disposition

Characteristic	n (%)
Patients enrolled	20
Median age at enrollment [range] - yr	33.5 [19 – 69]
Sex	
Male	4 (20)
Female	16 (80)
Location of target neurofibroma	
Head and Neck	9 (45)
Lower Extremities	6 (30)
Chest Wall	1 (5)
Paraspinal	1 (5)
Upper Extremities	1 (5)
Other	2 (10)
Type of neurofibroma-related complication	
Pain	20 (100)
Major Deformity	10 (50)
Motor Dysfunction/Weakness	10 (50)
Lower Extremity	7 (35)
Upper Extremity	3 (15)
Progression of PN at Entry	6 (30)
Optic Glioma	2 (10)
Airway Dysfunction	1 (5)
Other	3 (15)

Disposition	n (%)
Patients enrolled	20
Treated	20 (100)
Duration of mirdametinib exposure (days)	
Median	359.5
Range	238, 469
On study at time of data cutoff	16 (80)
Discontinued treatment	4 (20)
Adverse Event (1)	1 (5)
Progressive Disease	1 (5)
Participant Decision	1 (5)
Other (2)	1 (5)

As of the March 23, 2021 data cutoff, median time on therapy for first 20 patients enrolled was 13 cycles (~12 months)

(1) Due to Grade 1 diarrhea.
(2) Patient unable to undergo required MRI imaging due to titanium rod implant from non-treatment related worsening of scoliosis.
Note: Data are from the first 20 adult patients enrolled in the Phase 2b ReNeu trial (data cutoff: March 23, 2021), representing a database snapshot, and may change based on ongoing routine data monitoring. The ReNeu trial is ongoing, and these results may not be predictive of future data presentations or the final study results.

Safety Summary: Treatment-Emergent and Treatment-Related AEs

	Treatment-Emergent AEs (≥15% of patients)			Treatment-Related AEs	
	All Grades	Grade 3	Grade 4	Grade 3	Grade 4
Adverse Event	n (%)	n (%)	n (%)	n (%)	n (%)
At least 1 AE	20 (100)	3 (15)	-	1 (5)	-
Dermatitis acneiform/Rash maculopapular	18 (90)	1 (5)	-	1 (5)	-
Nausea	12 (60)	-	-	-	-
Diarrhea	10 (50)	-	-	-	-
Abdominal Pain	6 (30)	-	-	-	-
Fatigue	6 (30)	-	-	-	-
Vomiting	5 (25)	-	-	-	-
Dry skin	4 (20)	-	-	-	-
Ejection fraction decreased	4 (20)	-	-	-	-
Constipation	3 (15)	-	-	-	-
Dyspnea	3 (15)	1 (5)	-	-	-
Gastroesophageal reflux disease	3 (15)				
Arthralgia	3 (15)				
Ear pain	3 (15)				
Urinary tract infection	3 (15)				
Coronavirus infection	-	1 (5)	-	-	-
Coronavirus test positive	-	1 (5)	-	-	-
Headache	-	1 (5)	-	-	-
Non-cardiac chest pain	-	1 (5)	-	-	-
Scoliosis	-	1 (5)	-	-	-

- Mirdametinib has been generally well tolerated
- Potentially attenuated MEK inhibitor class toxicities observed (lack of significant paronychia or elevated creatine phosphokinase)
- Most adverse events (AEs) have been Grade 1 or 2
- Only one Grade 3 treatment-related AE (rash) and no Grade 4 or Grade 5 AEs
- One patient had a dose reduction required due to Grade 3 rash

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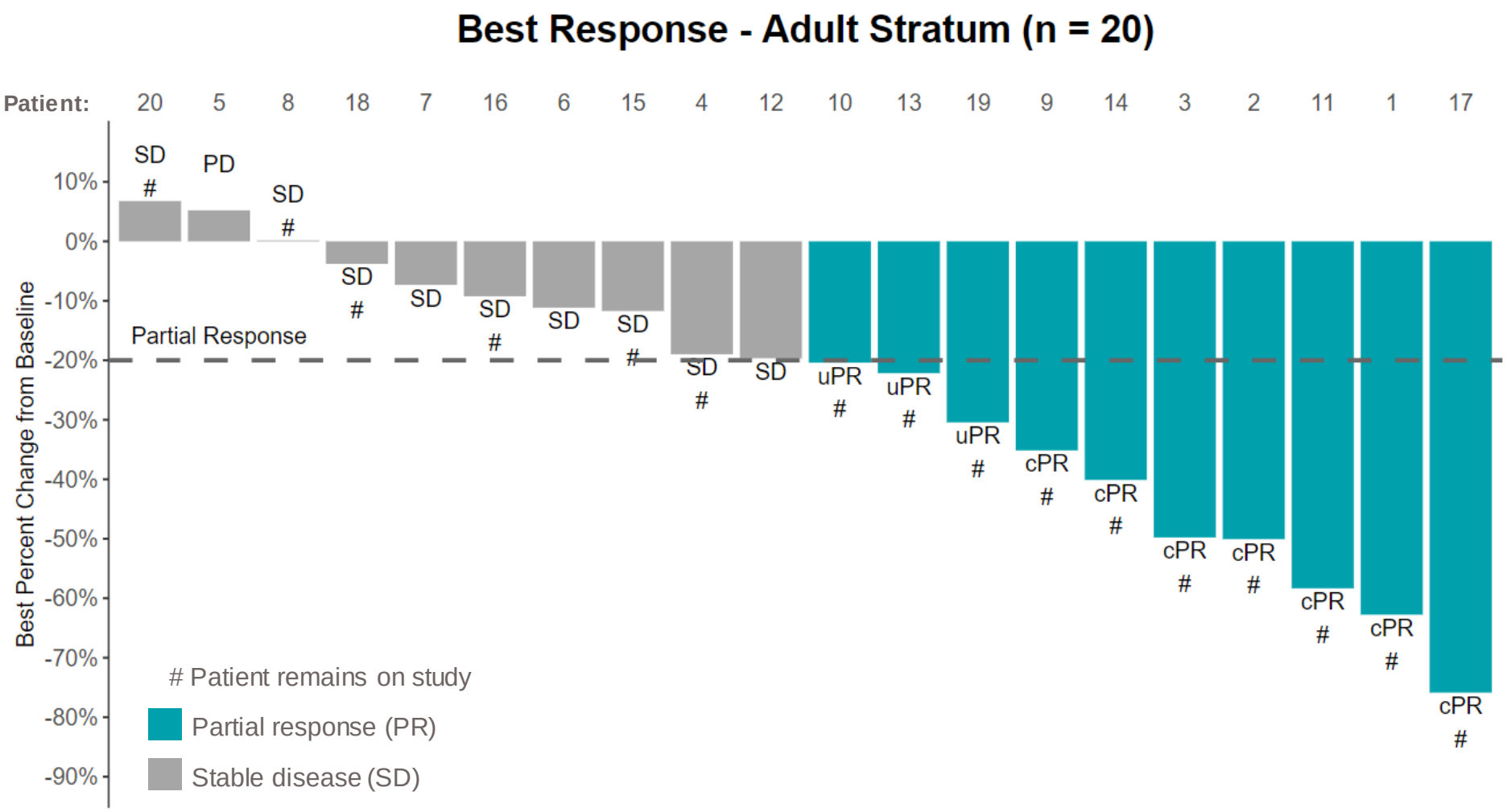
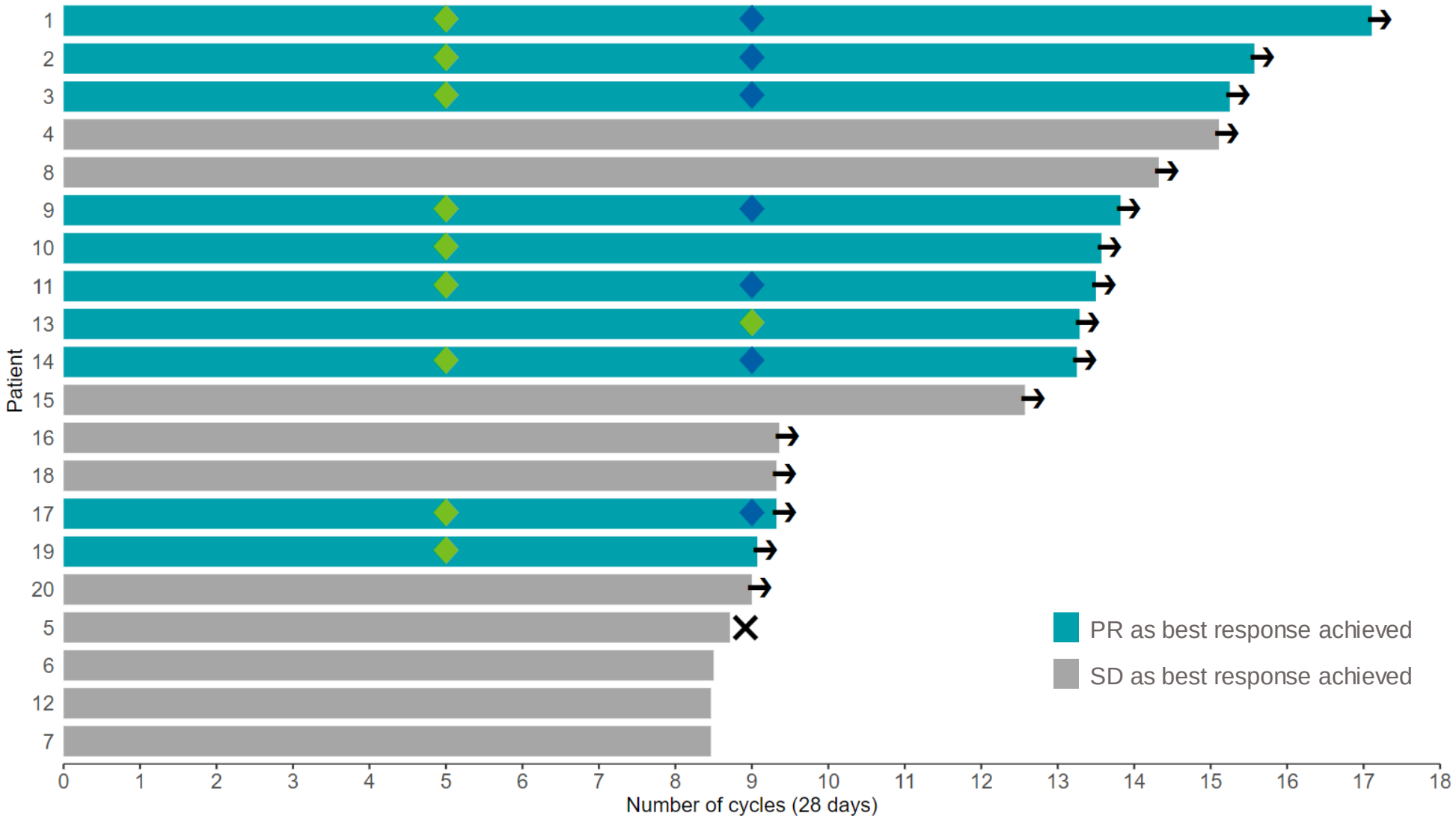
50% of Patients Have Achieved an Objective Response by BICR



- 10 of the first 20 patients enrolled have achieved a PR by BICR
- 7/10 patients had their PRs confirmed
- Responders had a median tumor volume reduction of 45%

BICR: Blinded Independent Central Review ; cPR: confirmed partial response; PD: progressive disease; PR: partial response (defined as a ≥20% reduction in tumor volume); SD: stable disease; uPR: unconfirmed partial response
Note: Data are from the first 20 adult patients enrolled in the Phase 2b ReNeu trial (data cutoff: March 23, 2021), representing a database snapshot, and may change based on ongoing routine data monitoring. The ReNeu trial is ongoing, and these results may not be predictive of future data presentations or the final study results. Confirmed PR means subsequent scan confirmed (20%) reduction in tumor volume.

Treatment Duration and Response



- Patient on study as of Mar 23, 2021
- Partial response achieved
- Partial response confirmed
- Progressive disease

- 80% of patients remain on study
- All patients with objective responses continue on study
- Reason for patients discontinuing therapy include: (1) PD, (1) participant decision, (1) AE [1] and (1) other [2]

(1) Due to Grade 1 diarrhea.
(2) Patient unable to undergo required MRI imaging due to titanium rod implant from non-treatment related worsening of scoliosis.
AE: adverse event; PD: progressive disease; PR: partial response (defined as a ≥20% reduction in tumor volume); SD: stable disease
Note: Data are from the first 20 adult patients enrolled in the Phase 2b ReNeu trial (data cutoff: March 23, 2021), representing a database snapshot, and may change based on ongoing routine data monitoring. The ReNeu trial is ongoing, and these results may not be predictive of future data presentations or the final study results. Scans occur following cycle 5, 9 and 13.

Key Takeaways

- On track to achieve full enrollment in 2H 2021
- Interim data from first 20 adult patients enrolled in ongoing Phase 2b trial reaffirm mirdametinib as a potentially differentiated therapy for NF1-PN
  - As of the March 23, 2021 data cutoff, median time on therapy was 13 cycles (~12 months)
  - 10/20 (50%) of patients have achieved objective response by blinded central review; 16/20 (80%) of patients remain on study
  - Generally well tolerated safety profile – majority of AEs were Grade 1 or 2, with only one Grade 3 TRAE reported; no Grade 4 or 5 AEs
- Availability of pediatric formulation (dispersible tablet) and lack of food effect, eliminating the requirement of daily fasting, may improve treatment satisfaction and reduce overall patient burden

AE: adverse event
Note: Data are from the first 20 adult patients enrolled in the Phase 2b ReNeu trial (data cutoff: March 23, 2021), representing a database snapshot, and may change based on ongoing routine data monitoring. The ReNeu trial is ongoing, and these results may not be predictive of future data presentations or the final study results. An objective response is defined as a ≥20% reduction in tumor volume.

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Sheila
NF1-PN Patient

Sincere thanks to the patients, families, caregivers, and the investigators for their commitment to NF1-PN patients and for their contributions to the ReNeu trial and the results presented today

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