

SpringWorks THERAPEUTICS

ReNeu Trial Update

February 25, 2021

Agenda

ReNeu
1Q 2021 Update

Topic	Speaker
Opening Remarks	Saqib Islam *Chief Executive Officer*
ReNeu Trial Update and Interim Data Review	L. Mary Smith, Ph.D. *Chief Development Officer*
Key Takeaways and Future Program Updates	Badreddin Edris, Ph.D. *Chief Operating Officer*
Q&A	All

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This presentation contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995 relating to our business, operations, and financial conditions, including but not limited to current beliefs, expectations and assumptions regarding the future of our business, future plans and strategies, our development plans, our preclinical and clinical results, the interim data of the ReNeu clinical trial, including its interim primary efficacy, safety and tolerability data, and other future conditions. Words such as, but not limited to, "look forward to," "believe," "expect," "anticipate," "estimate," "intend," "plan," "would," "should" and "could," and similar expressions or words, identify forward-looking statements. New risks and uncertainties may emerge from time to time, and it is not possible to predict all risks and uncertainties. Any forward-looking statements in this presentation are based on management's current expectations and beliefs and are subject to a number of risks, uncertainties and important factors that may cause actual events or results to differ materially from those expressed or implied by any forward-looking statements contained in this presentation, including, without limitation, risks relating to: (i) the success and timing of our ongoing DeFi and ReNeu clinical trials, (ii) the fact that interim data from a clinical study may not be predictive of the final results of such study or the results of other ongoing or future studies, (iii) the success and timing of our product development activities and initiating clinical trials, (iv) the success and timing of our collaboration partners' ongoing and planned clinical trials, (v) our ability to obtain and maintain regulatory approval of any of our product candidates, (vi) our plans to research, discover and develop additional product candidates, (vii) our ability to enter into collaborations for the development of new product candidates, (viii) our ability to establish manufacturing capabilities, and our and our collaboration partners' abilities to manufacture our product candidates and scale production, (ix) our ability to meet any specific milestones set forth herein, and (x) uncertainties and assumptions regarding the impact of the COVID-19 pandemic on SpringWorks' business, operations, clinical trials, supply chain, strategy, goals and anticipated timelines.

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SpringWorks Overview

Saqib Islam – *Chief Executive Officer*

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SpringWorks Therapeutics is a Clinical-Stage Targeted Oncology Company

- **Two late-stage rare oncology programs** in potentially registrational trials, each supported by strong clinical data
- **Seven programs addressing large opportunities in genetically defined cancers** in collaboration with industry leaders
- Leveraging **strong development capabilities** and **shared-value partnerships** to enhance portfolio value and become a partner of choice
- Led by an **experienced management team** with deep expertise in drug development and commercialization
- Well-capitalized to execute **important value-driving milestones** across both standalone and partnered programs

Our ambition is to ignite the power of promising science to unleash new possibilities for patients

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Pipeline Provides Multiple Opportunities for Value Creation Across Three Distinct Oncology Segments

1 Late-Stage Rare Oncology

Two registrational trials ongoing, each supported by strong Phase 2 data and with best-in-class potential

Nirogacestat
Desmoid Tumors
Phase 3 topline data: 2H21

Nirogacestat
Pediatric Desmoid Tumors
Phase 2 trial initiated: 3Q20

Mirdametinib
NF1-PN
Phase 2b full enrollment: 2H21

2 BCMA Combinations in Multiple Myeloma

Advancing nirogacestat as a cornerstone of BCMA combination therapy across three modalities

Nirogacestat + BLENREP
BCMA ADC
Phase 1b initial clinical data: 2021

Nirogacestat + ALLO-715
BCMA Allogeneic CAR-T
Phase 1 trial initiated: 1Q21

Nirogacestat + Teclistamab
BCMA-CD3 Bispecific
Phase 1 trial initiated: 1Q21

Nirogacestat + Elranatamab
BCMA-CD3 Bispecific
Phase 1b/2 trial initiation: 1H21

Nirogacestat + PBCAR269A
BCMA Allogeneic CAR-T
Phase 1 trial initiation: 1H21

3 Biomarker-Defined Metastatic Solid Tumors

Precision oncology approach to highly prevalent cancers with near-term clinical POC readouts

Mirdametinib + Lifirafenib
RAS/RAF Mutant Solid Tumors
Phase 1b/2 initial clinical data: 2021

BGB-3245
RAF Mutant Solid Tumors
Phase 1 initial clinical data: 2021

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Successful Clinical and Operational Execution in 2020 Has Positioned SpringWorks for Multiple Important Data Readouts in 2021

	2020	2021
1 Late-Stage Rare Oncology	✓ Fully enrolled nirogacestat Ph3 DeFi trial ✓ Launched nirogacestat Ph2 trial with COG in pediatric desmoid tumors	✓ Mirdametinib Ph2b ReNeu trial update *(1Q21)* ❑ Nirogacestat Ph3 DeFi trial topline readout *(2H21)*
2 BCMA Combinations in Multiple Myeloma	✓ Signed 4 additional industry collaborations ✓ Achieved FPFD in GSK Ph1b combo trial ✓ Signed collaboration with Fred Hutchinson Cancer Research Center	✓ Ph1 combo trials with Allogene and Janssen initiated *(1Q21)* ❑ Ph1 trial initiations for 2 additional BCMA combo studies *(1H21)* ❑ Initial Ph1b combo data with GSK *(2021)*
3 Biomarker-Defined Metastatic Solid Tumors	✓ Achieved FPFD in BGB-3245 Ph1 trial ✓ Published AACR preclinical combination data from mirdametinib + lifirafenib	❑ Initial Ph1b/2 mirdametinib + lifirafenib data with BeiGene *(2021)* ❑ Initial Ph1 BGB-3245 data with BeiGene *(2021)*

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ReNeu Trial Update and Interim Data Review

Saqib Islam – *Chief Executive Officer*

L. Mary Smith, Ph.D. – *Chief Development Officer*

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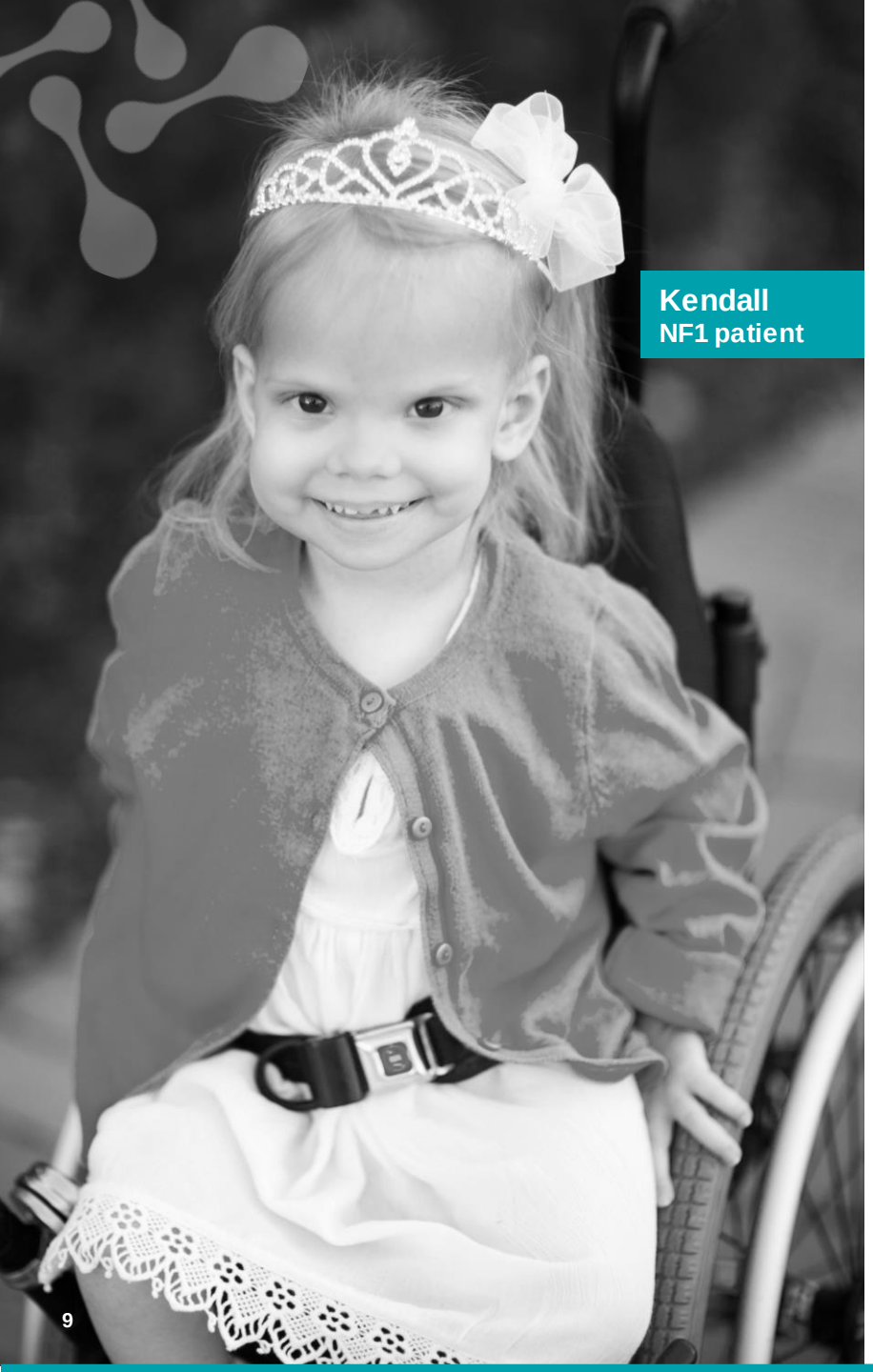

Plexiform Neurofibromas Are Painful, Disfiguring Tumors That Grow Along Peripheral Nerve Sheaths

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: A Potentially Best-in-Class Therapy for Patients with NF1-PN

- Mirdametinib is a potent, oral, allosteric 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

- Granted Orphan Drug Designation for NF1 by FDA and European Commission and Fast Track Designation for NF1-PN by FDA

- Compound potency, optimized dose/schedule, and lack of food effect may allow for a potentially differentiated profile compared to other MEK inhibitors

Potentially Registrational Pediatric and Adult Phase 2b ReNeu Trial in Progress

PHASE 2 | PHASE 2B

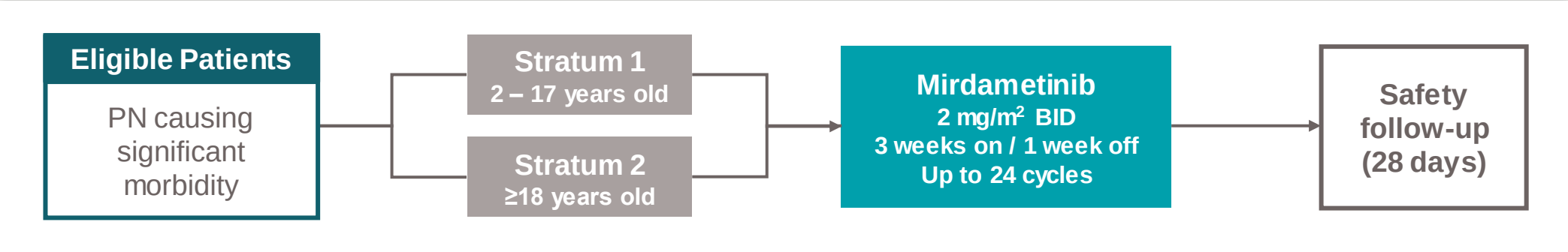
ReNeu

Trial Summary

- Enrolling ~100 patients in 2 strata (pediatrics, adults) across ~50 sites in the US
- 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



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Enrollment Status

- The ReNeu trial began enrolling patients in November 2019 and has reached ~70% of its final enrollment target – we anticipate completing enrollment in 2H 2021
- Enrollment of adult stratum is ahead of pediatric stratum due to a planned safety analysis after the first 5 pediatric patients (9-17 years of age) were administered at least 2 cycles of mirdametinib
  - Safety analysis was conducted in April 2020 and DMC concluded that in these 5 pediatric patients, mirdametinib's safety profile was comparable to adults
  - The DMC then recommended that the study should proceed, fully opening the pediatric stratum to enroll patients ≥2 years of age aided by the availability of a pediatric mirdametinib formulation
- Robust clinical infrastructure is in place
  - Over 40 sites activated in the US (targeting ~50 sites in total)
  - Broad site distribution helps to raise awareness and experience with mirdametinib

Note: Data are from the first 20 adult patients enrolled in the Phase 2b ReNeu trial (data cutoff: January 22, 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.

Interim Data Summary from Adult Stratum

- Safety and efficacy analysis is of the first 20 adult patients treated in the ongoing study
  - Data cutoff of January 22, 2021
  - Median time on treatment for these 20 patients was 10.1 cycles (approximately 10 months)
- Blinded Independent Central Review (BICR) was used for tumor assessments
  - BICR was implemented to both reduce potential effect of bias as well as ensure consistency in how tumor measurements were conducted across study
- Objective responses are defined as ≥ 20% reduction in tumor volume
  - Objective response definition has been endorsed by REiNS (Response Evaluation in Neurofibromatosis and Schwannomatosis), has been discussed with the FDA for the ReNeu trial and has previously been used to support FDA approval in the indication

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Baseline Demographics and Patient Disposition

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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)
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)

(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: January 22, 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.

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50% of Patients Have Achieved an Objective Response by BICR

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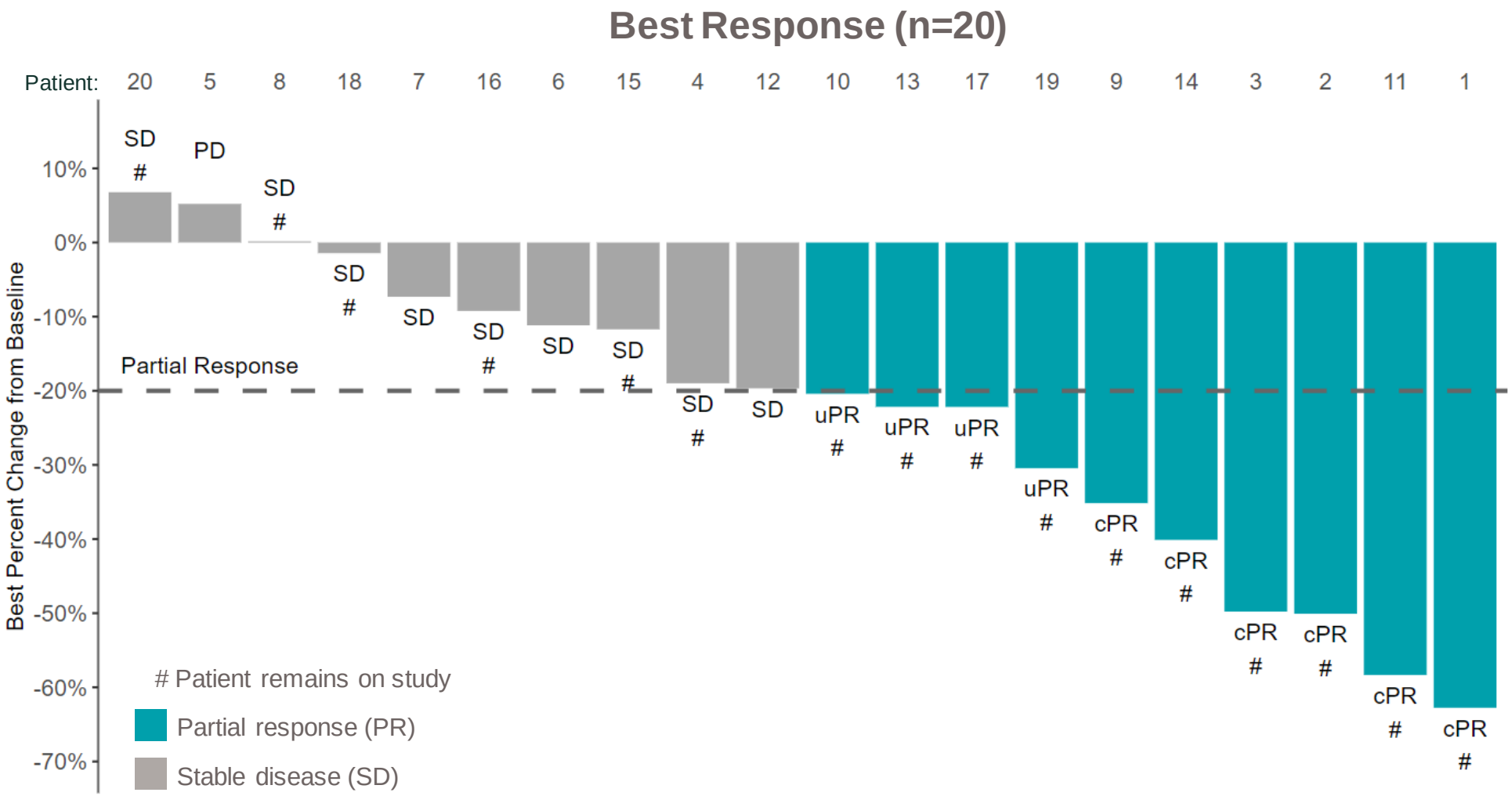

- 10 of the first 20 patients enrolled have achieved a PR by BICR
- 7 patients had a scheduled scan after achieving their PR – of these, 6/7 had their PR confirmed (1 SD)

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

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Treatment Duration and Response

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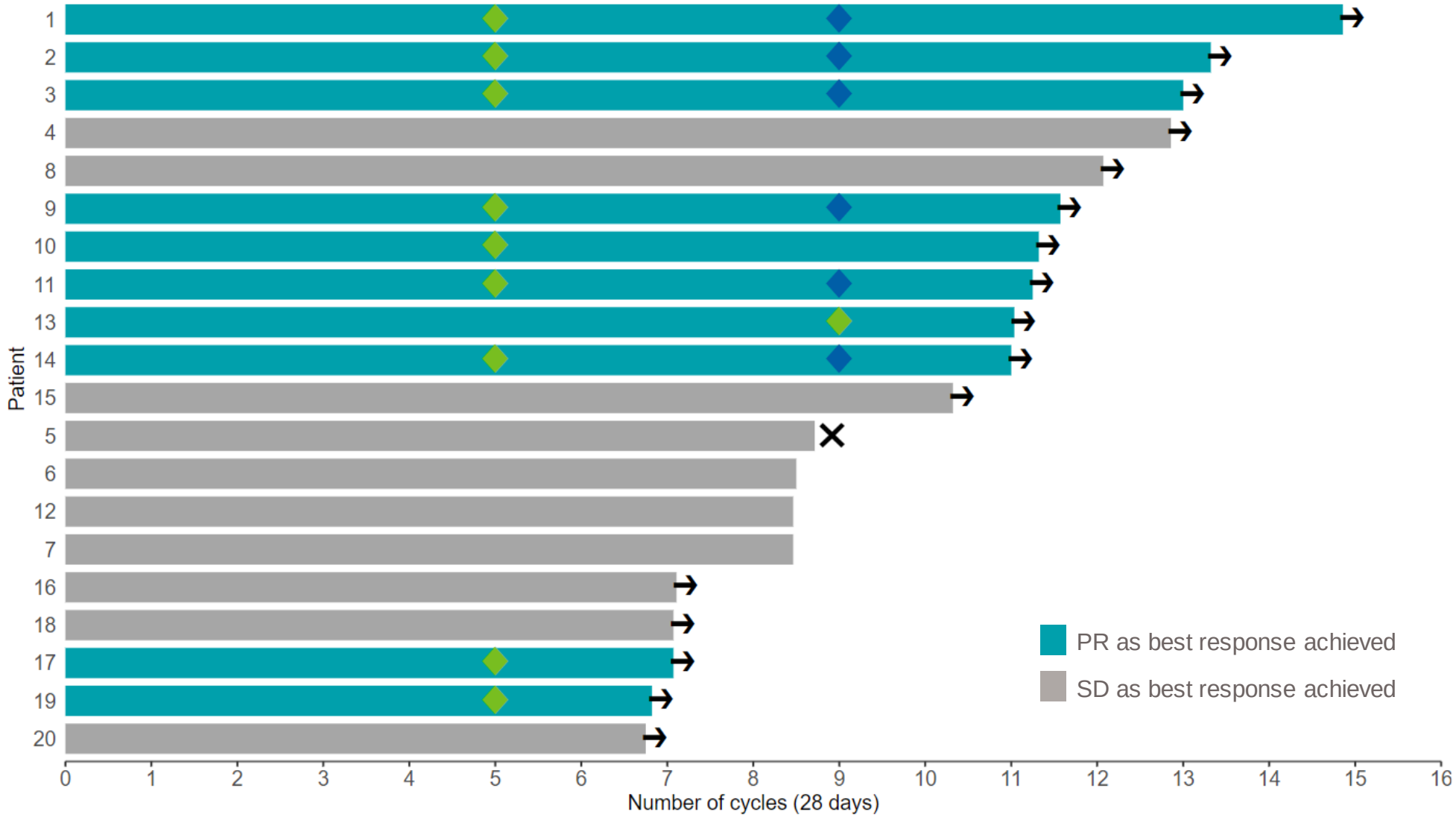

- Patient on study as of Jan 22, 2021
- Partial response achieved
- Partial response confirmed
- Progressive disease

- 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: January 22, 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.

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Safety Summary: Treatment-Emergent and Treatment-Related AEs

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	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/ Rash maculopapular	18 (90)	1 (5)	-	1 (5)	-
Nausea	10 (50)	-	-	-	-
Diarrhea	9 (45)	-	-	-	-
Vomiting	5 (25)	-	-	-	-
Abdominal Pain	5 (25)	-	-	-	-
Fatigue	5 (25)	-	-	-	-
Dry skin	4 (20)	-	-	-	-
Ejection fraction decreased	4 (20)	-	-	-	-
Dyspnea	3 (15)	1 (5)	-	-	-
Hypertension	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
- 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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Key Takeaways and Future Program Updates

Badreddin Edris, Ph.D. – *Chief Operating Officer*

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Key Takeaways and Future Updates

- Interim data in 20 adult patients from ongoing Phase 2b trial reaffirm mirdametinib as a potentially best-in-class therapy for NF1-PN
  - As of the January 22, 2021 data cutoff, median time on therapy was 10.1 cycles (~10 months)
  - 10/20 (50%) of patients have achieved objective response by BICR
  - 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 and no Grade 4 or 5 AEs
- On track to achieve full enrollment in 2H 2021
  - Trial is ~70% enrolled (target: 100 patients)
  - 40+ sites activated in the US (target: 50 sites)
  - Update on overall program timelines to be provided upon achieving full enrollment
- Additional data from the ReNeu trial to be shared at future medical conference in 2021

AE: adverse event; BICR: Blinded Independent Central Review
Note: Data are from the first 20 adult patients enrolled in the Phase 2b ReNeu trial (data cutoff: January 22, 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.

Sheila
NF1-PN Patient

Thank You

SpringWorks wishes to thank the patients, families, caregivers, and dedicated researchers for their commitment to NF1-PN patients and for their contributions to the ReNeu trial and the results presented today

Q&A

Saqib Islam – *Chief Executive Officer*

L. Mary Smith, Ph.D. – *Chief Development Officer*

Badreddin Edris, Ph.D. – *Chief Operating Officer*

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