

SpringWorks® THERAPEUTICS

Corporate Presentation

December 2021

NASDAQ: SWTX

Forward-Looking Statements

Note: Unless otherwise indicated, the information presented herein is as of December 2021 and made publicly available on December 22, 2021.

This presentation may contain "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 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 product development activities, including the initiation and completion of SpringWorks' 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 collaboration partners' ongoing and planned clinical trials, (iv) our ability to obtain and maintain regulatory approval of any of our product candidates, (v) our plans to research, discover and develop additional product candidates, (vi) our ability to enter into collaborations for the development of new product candidates, (vii) our ability to establish manufacturing capabilities, and our and our collaboration partners' abilities to manufacture our product candidates and scale production, (viii) our ability to meet any specific milestones set forth herein, and (ix) uncertainties and assumptions regarding the impact of the COVID-19 pandemic on SpringWorks' business, operations, clinical trials, supply chain, strategy, goals and anticipated timelines.

Except as required by applicable law, we do not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise. Although we believe the expectations reflected in such forward-looking statements are reasonable, we can give no assurance that such expectations will prove to be correct. Accordingly, readers are cautioned not to place undue reliance on these forward-looking statements.

For further information regarding the risks, uncertainties and other factors that may cause differences between SpringWorks' expectations and actual results, you should review the "Risk Factors" section(s) of our filings with the Securities and Exchange Commission.

Certain information contained in this presentation relates to or is based on studies, publications, surveys and other data obtained from third-party sources and our own internal estimates and research. While SpringWorks believes these third-party sources to be reliable as of the date of this presentation, we have not independently verified, and make no representation as to the adequacy, fairness, accuracy or completeness of, any information obtained from third-party sources. In addition, all of the market data included in this presentation involves a number of assumptions and limitations, and there can be no guarantee as to the accuracy or reliability of such assumptions. Finally, while we believe our own internal research is reliable, such research has not been verified by any independent source.

SpringWorks® THERAPEUTICS

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
- **Nine 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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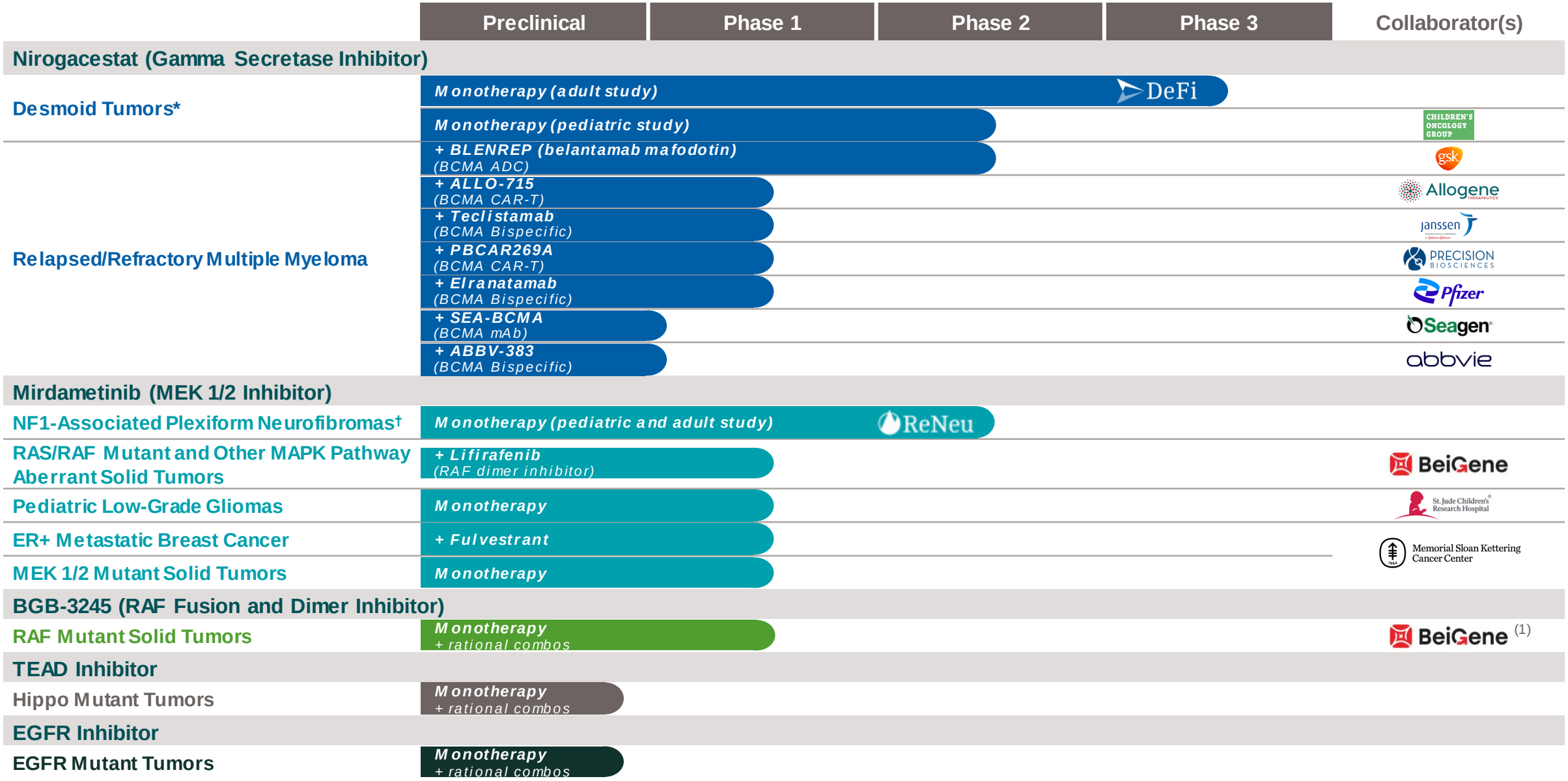
Advancing Diversified Clinical Pipeline of Targeted Oncology Programs



Note: Nirogacestat = PF-03084014 and Mirdametinib = PD-0325901 (both in-licensed from Pfizer).

* Received Orphan Drug, Fast Track and Breakthrough Therapy Designations. † Received Orphan Drug and Fast Track Designations.

(1) Being developed by MapKure, LLC, jointly owned by SpringWorks and BeiGene.

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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: 4Q21 / early 2022

Nirogacestat
Pediatric Desmoid Tumors
Phase 2 trial initiated: 3Q20

Mirdametinib
NF1 Plexiform Neurofibromas
Phase 2b full enrollment achieved: 4Q21

Mirdametinib
Pediatric Low-Grade Gliomas
Phase 1/2 FPFD: 2H21

2 BCMA Combinations in Multiple Myeloma

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

Nirogacestat + BLENREP
BCMA ADC
Phase 2 expansion cohort initiated: 3Q21

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

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

Nirogacestat + PBCAR269A
BCMA Allogeneic CAR-T
Phase 1 trial initiated: 2Q21

Nirogacestat + Elranatamab
BCMA-CD3 Bispecific
Phase 1b/2 trial initiated: 4Q21

Nirogacestat + SEA-BCMA
BCMA Monoclonal Antibody
Phase 1 trial initiation: 1Q22

Nirogacestat + ABBV-383
BCMA-CD3 Bispecific
Phase 1b trial initiation: 1H22

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: R&D day

Mirdametinib + Fulvestrant
ER+ Metastatic Breast Cancer
Phase 1/2 trial initiated: 3Q21

Mirdametinib
MEK 1/2 Mutant Solid Tumors
Phase 1/2 trial initiated: 3Q21

BGB-3245
RAF Mutant Solid Tumors
Phase 1 initial clinical data: R&D day

TEAD Inhibitor
Hippo Mutant Tumors
DC nomination: 2022

EGFR Inhibitor
EGFR Mutant Tumors
DC nomination: 2023

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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	✓ Fully enrolled mirdametinib Ph2b ReNeu and presented interim data from adult stratum ✓ FPFD in Ph1/2 mirdametinib monotherapy study for pediatric low-grade gliomas ❑ Nirogacestat Ph3 DeFi trial topline readout *(4Q21 / early 2022)*
2 BCMA Combinations in Multiple Myeloma	✓ Signed 4 additional industry collaborations ✓ Achieved FPFD in GSK Ph1 combo trial ✓ Signed collaboration with Fred Hutchinson Cancer Research Center	✓ Ph1 combo trials with Allogene, Janssen, Precision and Pfizer initiated ✓ GSK combo randomized Ph2 expansion cohort initiated & new sub-studies added ✓ Signed collaboration with AbbVie
3 Biomarker-Defined Metastatic Solid Tumors	✓ Achieved FPFD in BGB-3245 Ph1 trial ✓ Published AACR preclinical combination data from mirdametinib + lifirafenib	✓ TEAD + EGFR portfolio in-licenses ✓ Initiated mirdametinib Ph1/2 basket study in ER+ mBC and MEK 1/2 mutant solid tumors ❑ Initial Ph1b/2 mirdametinib + lifirafenib and initial Ph1 BGB-3245 data with BeiGene *(upcoming R&D day)*

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Late-Stage Rare Oncology

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Desmoid Tumors are Highly Morbid Soft Tissue Tumors that are Poorly Responsive to Surgical Interventions and Off-Label Therapies

Desmoid tumor patients present with significant morbidities

- Can manifest throughout the body including in the extremities, the head and neck region, intra-abdominally, and the thoracic region
- Patients can experience long-lasting pain due to nerve compression or tumor pressure, disfigurement, and restricted range-of-motion

No currently approved therapies and limited treatment options

- Post-surgical resection recurrence in up to 70%
- Off-label systemic therapies are poorly tolerated with inconsistent efficacy
- Physicians often adopt a watchful waiting approach

~1,000-1,500 newly incident patients per year in US

- Young patient population, with tumors more commonly diagnosed in the third and fourth decades of life
- ~5,500-7,000 patients actively receiving treatment in the US in any given year

Source: Penel et al., *European Journal of Cancer*, 2017; Tsagozis et al., *Annals of Medicine & Surgery*, 2017; SpringWorks market research.

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Nirogacestat: A New Paradigm for Patients With Desmoid Tumors

- Nirogacestat is an oral, selective gamma secretase inhibitor with over 10 years of clinical experience (approximately 300 subjects exposed)
- Clinical activity observed in Phase 1 and Phase 2 trials in desmoid tumors independent of prior lines of therapy and underlying mutation
- Generally well tolerated compound with evidence of being suitable for multi-year daily dosing
- Received Fast Track and Breakthrough Therapy Designations from FDA and Orphan Drug Designation from both FDA and European Commission
- US Composition of Matter and Method of Use patents provide protection to 2039

Phase 3 DeFi trial fully enrolled and topline data anticipated in 4Q21 / early 2022

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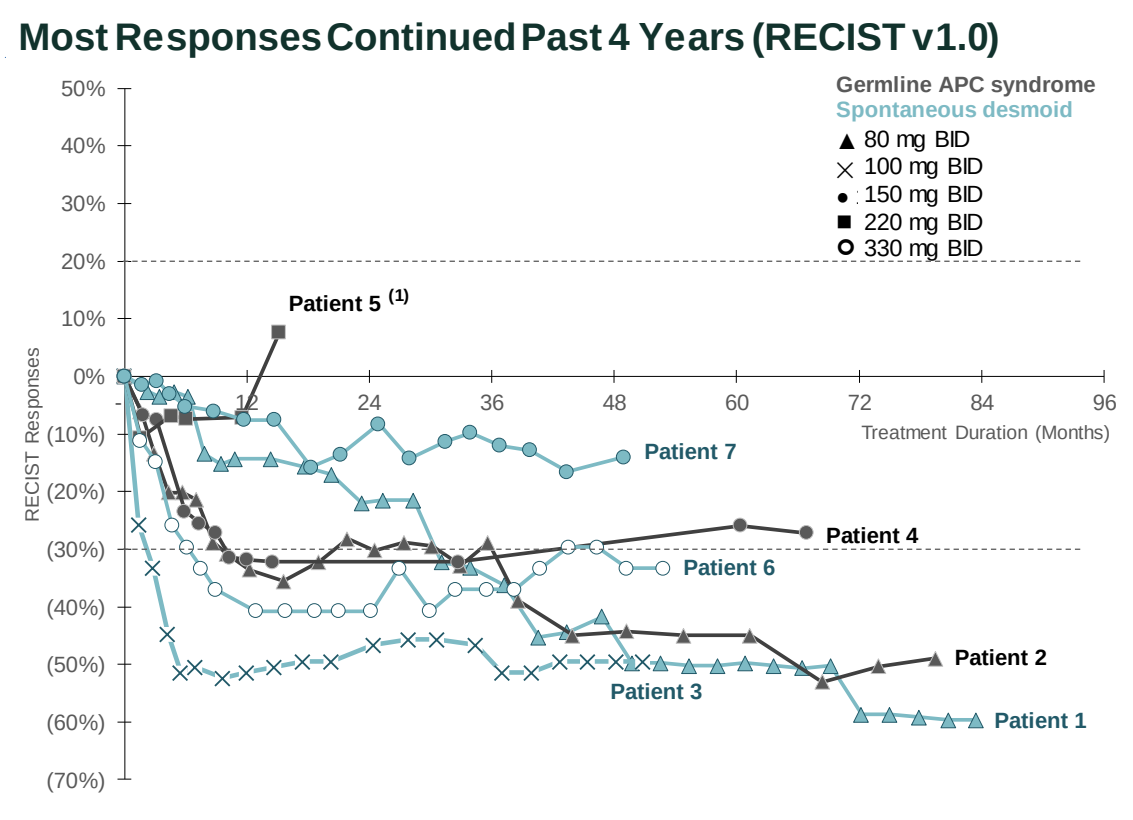
Initial Clinical Activity of Nirogacestat Observed in Desmoid Tumors

PHASE 1 | PHASE 2 | PHASE 3



- **All evaluable desmoid tumor patients in the study responded to nirogacestat treatment (1)**
  - Disease Control Rate (DCR): 100%
  - Objective Response Rate (ORR): 71.4% (5/7 evaluable desmoid patients)
  - Median PFS (mPFS): Not reached by publication date due to lack of tumor progression events
- **Median Duration of Treatment was 49.5 months at publication**
  - Of the 7 evaluable desmoid patients on study, none discontinued due to AEs (2)

Note: Disease control rate is percentage of patients experiencing objective response or stable disease on therapy as measured by RECIST v1.0.
Source: Villalobos, *Annals of Surgical Oncology*, 2018; Messersmith, *Clinical Cancer Research*, 2015.
(1) Per investigator "the only patient with clinical progression received PF-03084014 (220 mg BID) for 15.2 months and exhibited significant clinical improvement on therapy."
(2) Across the entire 64 patient Ph1 there were four discontinuations due to treatment-related AEs with a majority occurring during cycle 1.

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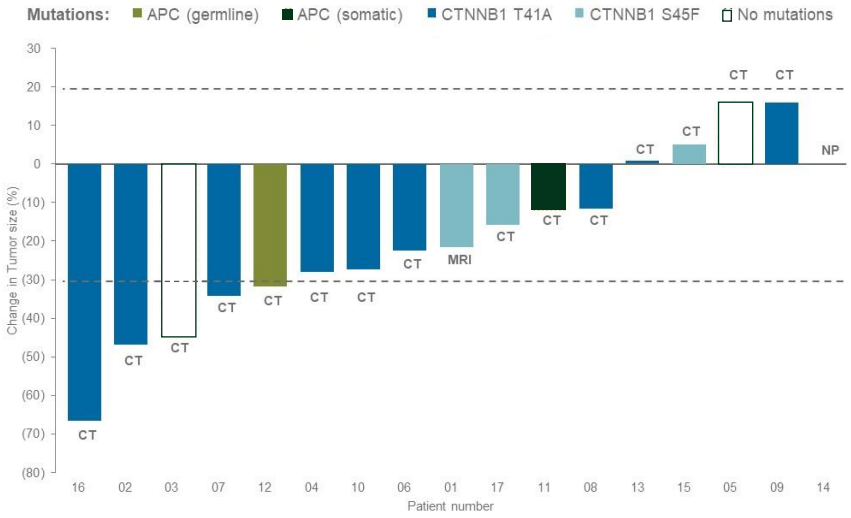
Encouraging Clinical Activity and Tolerability Observed in NCI-Conducted Phase 2 Trial in a Heavily Pre-Treated and Progressing Patient Population

PHASE 1 | **PHASE 2** | PHASE 3

Clinical Responses by RECIST v1.1



Durability and Tolerability with Long-Term Dosing

- **mPFS: Not reached by publication date due to lack of tumor progression events**
  - At time of enrollment, all patients had progressing tumors
  - Patients failed a median of 4 prior lines (1-9) of systemic therapy (1)
  - ORR of 29.4% (5/17) with no Progressive Disease

- **59% of patients remained on treatment >2 years and 71% of patients stayed on drug for >1 year**
  - Median Duration of Treatment was >25 months at publication, with 5 patients continuing as of January 2021 (treatment duration of 5+ years in these patients)
  - Well tolerated; only 1 discontinuation due to AE (2)

Note: Per RECIST 16/17 patients were evaluable. One treatment cycle = 150 mg BID continuously for 21 days. Patient #1 had a missing baseline measurement (but had MRI). Patient #14 was not evaluable per protocol, withdrew from study after cycle 1 due to travel requirements.
Source: Kummar et al., *Journal of Clinical Oncology*, 2017.
(1) 71% had received chemotherapy, 65% NSAIDs, and 59% TKIs; 4/5 partial responses had previously failed imatinib or sorafenib.
(2) Discontinuation due to grade 2 urticaria not responsive to dose reduction. No grade 4 events, all grade 3 events related to hypophosphatemia, a known class effect easily reversible with oral supplements.

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Double-Blind, Placebo-Controlled Phase 3 DeFi Trial Is Fully Enrolled

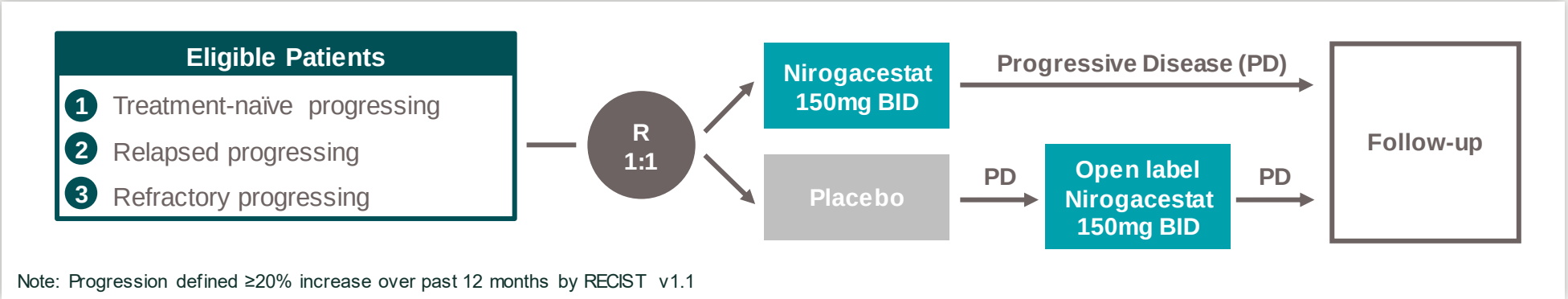
PHASE 1 | PHASE 2 | **PHASE 3**

Trial Summary

- ~140 patients at ~50 sites in North America and Europe
- Open label extension for patients progressing on placebo
- 90% powered to show ~12 month PFS difference between nirogacestat and placebo (1)

Summary of Endpoints

- Primary Endpoint: Progression-free survival (2)
  - ~50% of placebo patients expected to progress by 8 months (3)
- Secondary: Safety and tolerability, ORR, duration of response, volumetric tumor change (MRI), patient-reported outcomes



Note: Progression defined ≥20% increase over past 12 months by RECIST v1.1

Full enrollment achieved in July 2020 and topline data anticipated in 4Q21 / early 2022

(1) A total of 51 events will provide 90% power and a 1-sided type 1 error rate of 0.025 (1-side hypothesis) to detect a difference between nirogacestat and placebo, assuming the median PFS is 20 months in the nirogacestat group and 8 months in the placebo group.
(2) PFS is defined as the time from randomization until the date of assessment of radiographic progression as determined using RECIST v1.1, the date of assessment of clinical progression or death by any cause. Radiographic or clinical progression will be determined by blinded independent central review.
(3) Assumption based on placebo arm from sorafenib Phase 3 trial (Gounder et al., *New England Journal of Medicine*, 2018), literature review and chart review.

Nirogacestat Clinical Activity Also Demonstrated in Pediatric and Young Adult Desmoid Tumor Patients

EXPANDED ACCESS PROGRAM

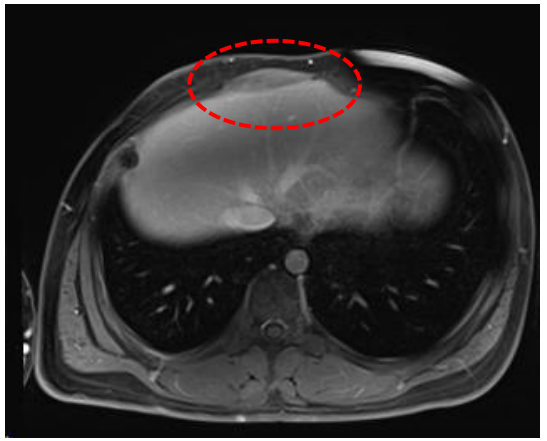
- **Clinical benefit shown in four pediatric and young adult desmoid tumor patients who received nirogacestat (1 CR, 2 PR, and 1 SD)**

	Patient 1	Patient 2	Patient 3	Patient 4
Age / Sex	17 yo male	4 yo male	19 yo female	2.5 yo female
APC Mutation	No	Yes	Yes	Yes
Prior Treatments	▪ Complete resection at 12 years old ▪ Sorafenib	▪ Celecoxib	▪ None	▪ 8 prior lines incl. sorafenib, pazopanib, chemo, cryo
Tumor Response	CR	PR	SD	Initial PR; subsequent PD
Duration of Benefit	18 months(1)	17 months(1)	10 months(1)	6 months

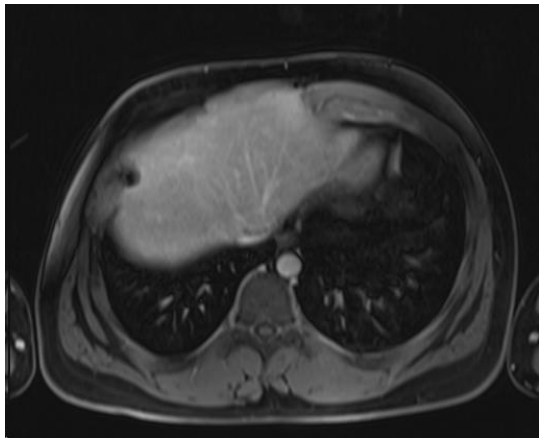
- **Nirogacestat was well tolerated; no grade 3 or 4 AEs**
  - 90 mg/m^2 per dose BID (max. 150 mg per dose BID)

Patient 1: 17-year-old male with Complete Response

Baseline MRI



After 9 months on nirogacestat



- Prior treatments include complete resection at 12 years old (experienced recurrence) and sorafenib (intolerable AEs and PD after discontinuation)
- Tumor volume regressed by 15% on MRI within 6 months of starting nirogacestat; **tumor undetectable on imaging by 9 months**

Announced collaboration with Children's Oncology Group in September 2020;
Patients being enrolled in single arm Phase 2 trial to evaluate nirogacestat in pediatric desmoid tumors

Source: Takahashi et al., *Pediatr Blood Cancer*, 2020.
(1) Ongoing at time of publication.

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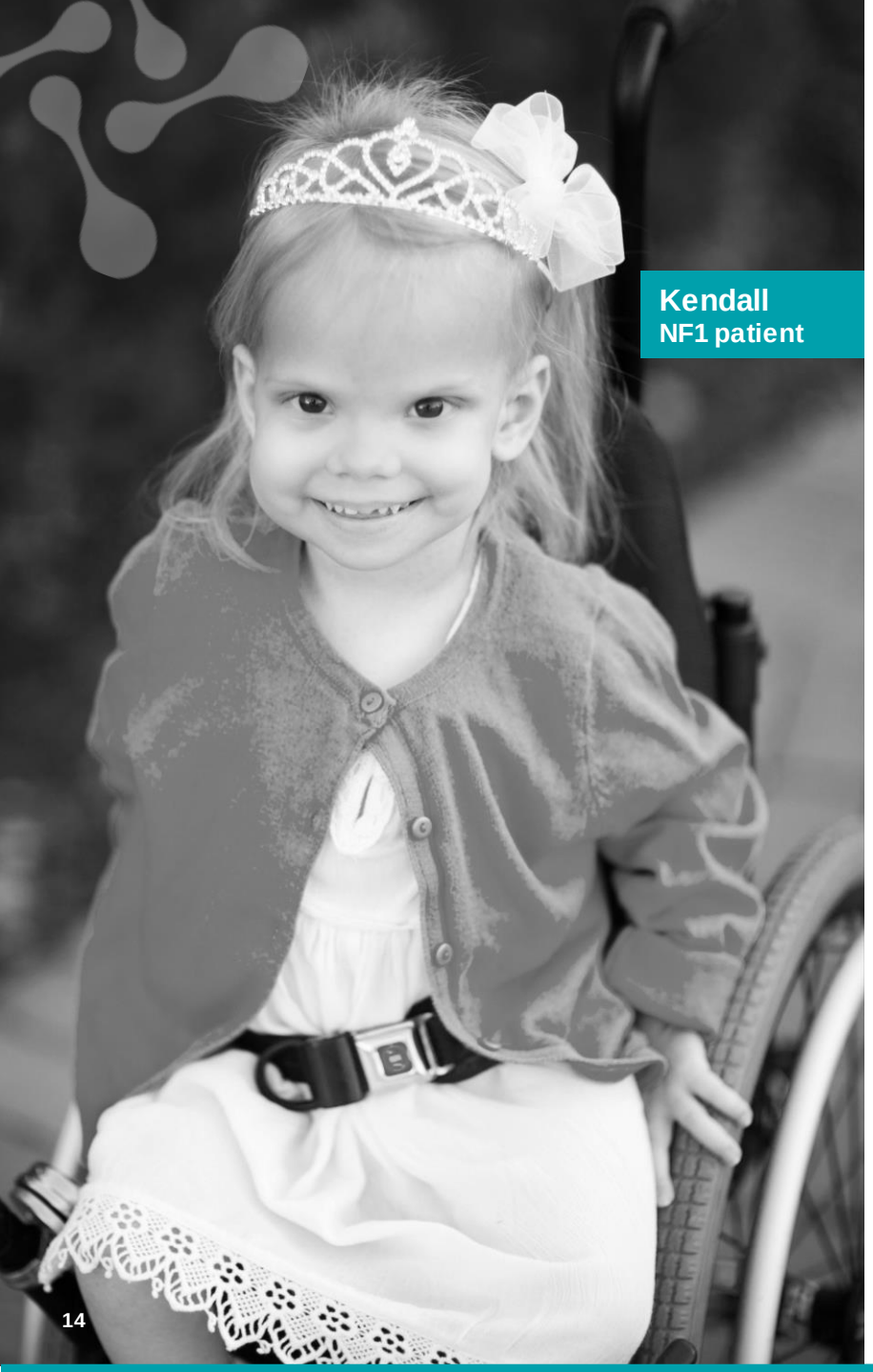

Plexiform Neurofibromas Are Painful, Disfiguring Tumors That Grow Along Peripheral Nerve Sheaths

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

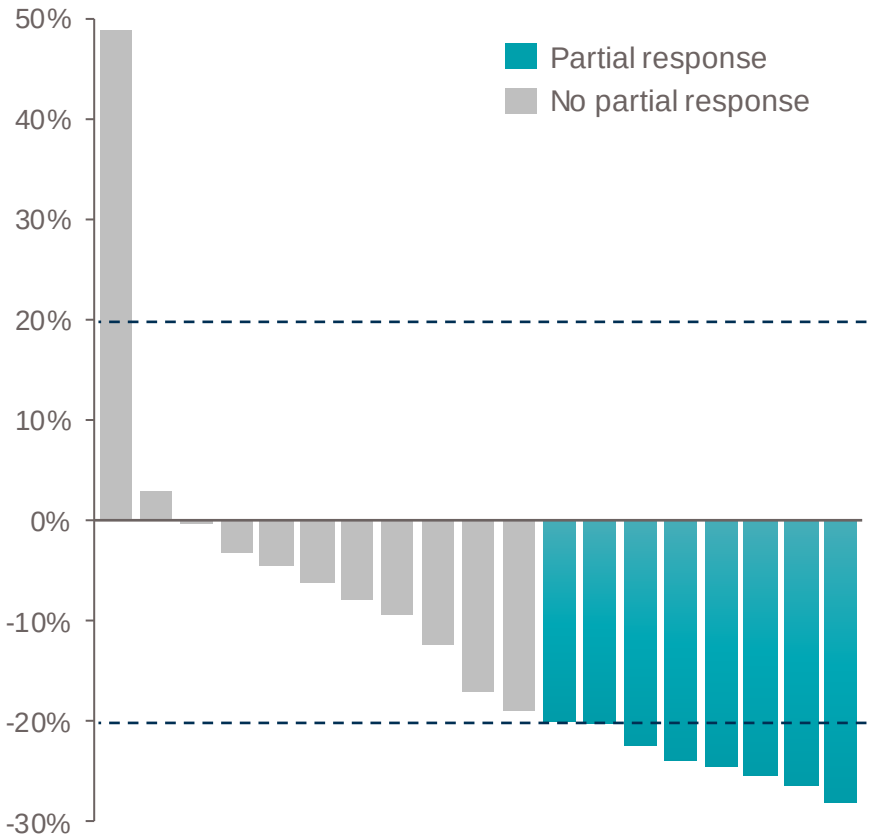
- Mirdametinib is a potent, oral, allosteric small molecule MEK 1/2 inhibitor with clinical validation and over 250 subjects exposed to date
- Encouraging safety and anti-tumor activity observed in Phase 2 investigator-initiated trial in adolescents and adults with NF1-PN
- Granted Orphan Drug Designation 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
- US Composition of Matter patents provide protection to 2041

Phase 2b ReNeu trial achieved full enrollment in 4Q21

Mirdametinib: Encouraging Phase 2 Results with Potentially Differentiated Safety Profile vs. Other MEK Inhibitors

PHASE 2 | PHASE 2B

Maximum Tumor Volume Change from Baseline



Trial Design and Clinical Activity

NEUROFIBROMATOSIS CONSORTIUM

- N = 19 patients with inoperable and symptomatic or growing PNs, aged 16-39 years (median age: 24)
- 2 mg/m^2 (up to 4 mg) BID without regard to food dosed intermittently (3 weeks on/1 week off) for maximum 24 cycles(1)
- 8 patients (42%) achieved a PR(2) by cycle 12; 10 patients (53%) had SD
- PRO measures(3) showed statistically significant improvement with mirdametinib treatment in the following areas:
  - Pain reduction for all patients on treatment by cycle 4
  - Cognitive function improvement for all patients on treatment at cycle 8
  - QoL improvement for patients who achieved a PR by cycle 8

Safety and Tolerability

- Dose and schedule minimized historical class toxicities
  - Most common adverse events were Gr1 and Gr2 acneiform rash, fatigue, and nausea
  - No Gr4 or Gr5 events; two Gr3 treatment-related events reported (pain events occurring in the same patient)
- 5 patients required dose reductions; no patient discontinued due to dose limiting toxicity
  - Gr1 rash (n = 2), Gr2 nausea (n = 1), Gr2 fatigue (n = 1), and Gr3 abdominal and/or back pain (n = 1)

Source: Weiss et al., *Journal of Clinical Oncology*, 2021.
(1) Patients without at least 15% reduction in target tumor volume after 8 courses or at least 20% reduction after 12 courses were removed from therapy.
(2) Partial response (PR) defined as a ≥20% reduction in the volume of the target plexiform neurofibroma lesion for ≥4 weeks.
(3) Patient-reported outcome (PRO) measures include the Numerical Rating Scale-11 to assess pain intensity, Brief Pain Inventory Pain Interference subscale to assess impact of pain on daily functioning, and the Pediatric Quality of Life (QoL) Inventory NF1 module to assess disease-specific health-related QoL measures.

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

PHASE 2 | PHASE 2B

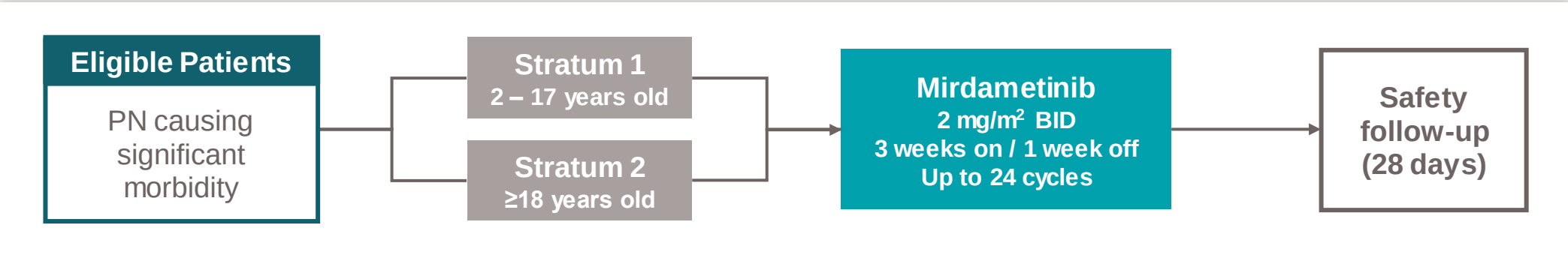
ReNeu

Trial Summary

- ~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



Achieved full enrollment in 4Q21, further updates to come at upcoming SpringWorks R&D day

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ReNeu Trial Interim Data Summary from Adult Stratum Presented at CTF

ReNeu
2Q21 CTF Presentation

- An updated safety and efficacy analysis of the first 20 adult patients treated in the ongoing study was presented at the Children's Tumor Foundation (CTF) Conference on June 15, 2021
  - Data cutoff of March 23, 2021
  - Median time on treatment for these 20 patients was 13 cycles (approximately 12 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

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.

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Baseline Demographics and Patient Disposition

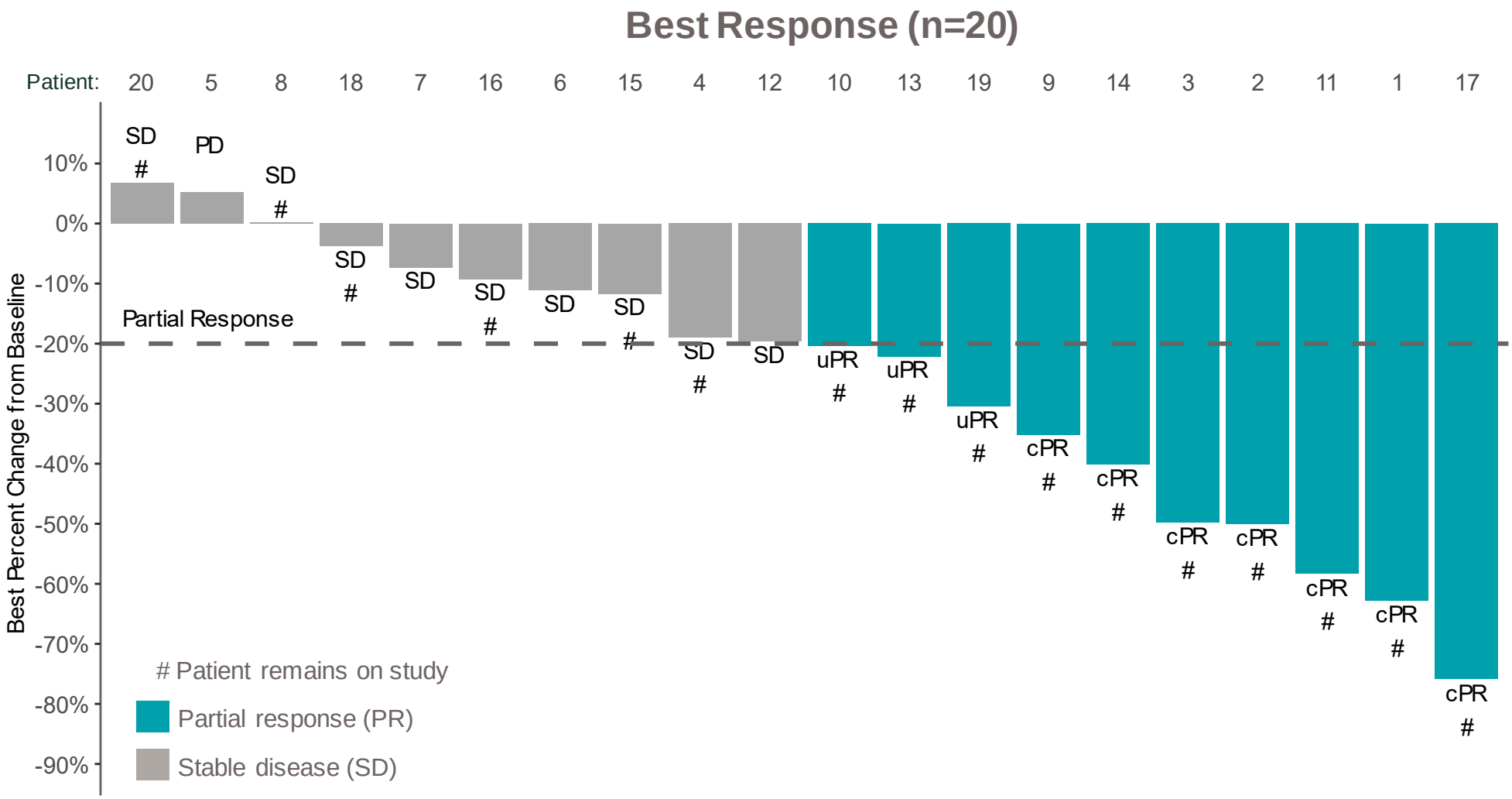
Characteristic	n (%)
Patients enrolled	20
Median age at enrollment [range] - yr	33.5 [19 – 69]
Sex	
Male	4 (20)
Female	16 (80)
Location of target neurofibroma	
Head and Neck	9 (45)
Lower Extremities	6 (30)
Chest Wall	1 (5)
Paraspinal	1 (5)
Upper Extremities	1 (5)
Other	2 (10)
Type of neurofibroma-related 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)
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: 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.

50% of Patients Have Achieved an Objective Response by BICR

ReNeu
2Q21 CTF Presentation



- 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.

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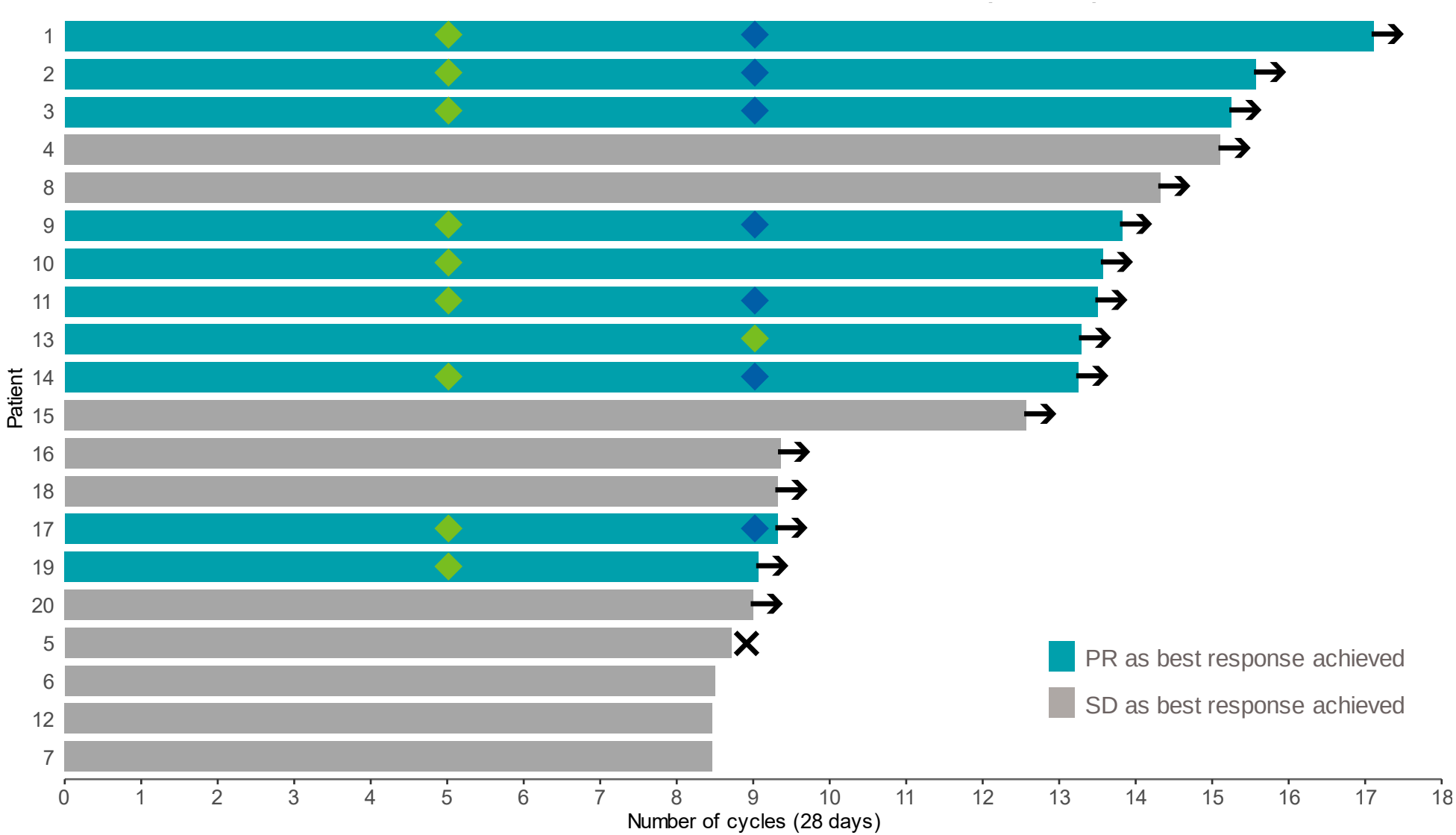
Treatment Duration and Response



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.

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
- 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

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.

Phase 2 Trial in Pediatric Low-Grade Glioma Provides Additional Expansion Opportunity for Mirdametinib

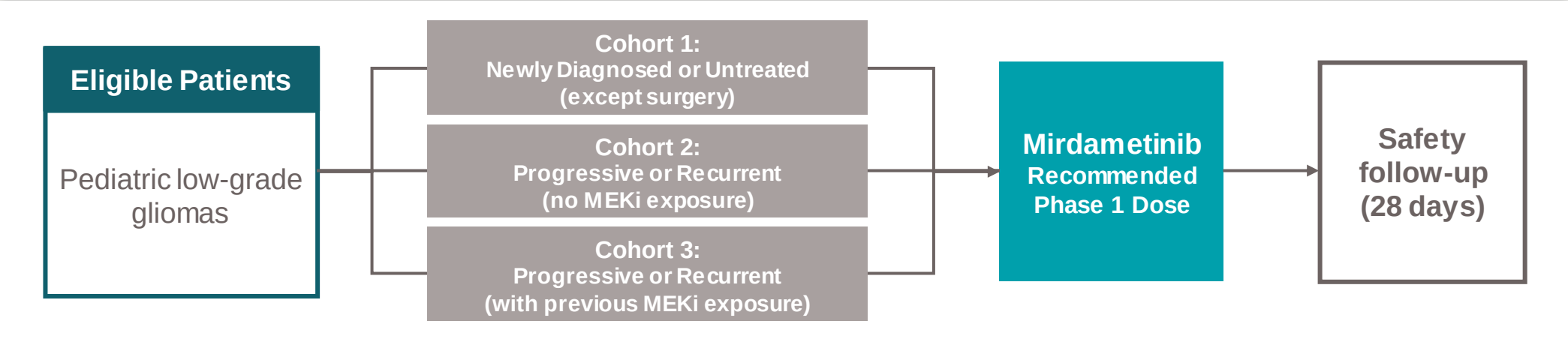
PHASE 1 | PHASE 2

Trial Summary

- Open-label, multi-center study evaluating single agent mirdametinib, a brain penetrant MEK 1/2 inhibitor, in pediatric low-grade gliomas
- Recommended dose from Phase 1 dose-finding/dose-escalation study will be used (2-4 mg/m^2, BID continuous)

Summary of Endpoints

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



Favorable safety profile and blood-brain barrier penetration properties set the stage for a potential best-in-class profile for pediatric low-grade gliomas

SpringWorks THERAPEUTICS

BCMA Combinations in Multiple Myeloma

SpringWorks® THERAPEUTICS

Nirogacestat in Multiple Myeloma: A Potentially Best-in-Class Potentiator of BCMA Therapies

Nirogacestat has the potential to be a cornerstone of BCMA combination therapy

- Significant unmet need in multiple myeloma (MM), with ~27,000 new patients in the relapsed/refractory setting in the US each year
- Gamma secretase directly cleaves membrane-bound BCMA, a clinically validated multiple myeloma target across modalities (ADC, CAR T, bispecific, mAb)
- Strong preclinical results and emerging clinical data support combining gamma secretase inhibitors with BCMA therapies
- Pursuing broad collaboration strategy with industry-leading BCMA developers to advance potentially best-in-class combinations using nirogacestat
- Sponsoring translational research with leading scientists at Fred Hutchinson Cancer Research Center and Dana-Farber Cancer Institute
- US Composition of Matter patents provide protection to 2039

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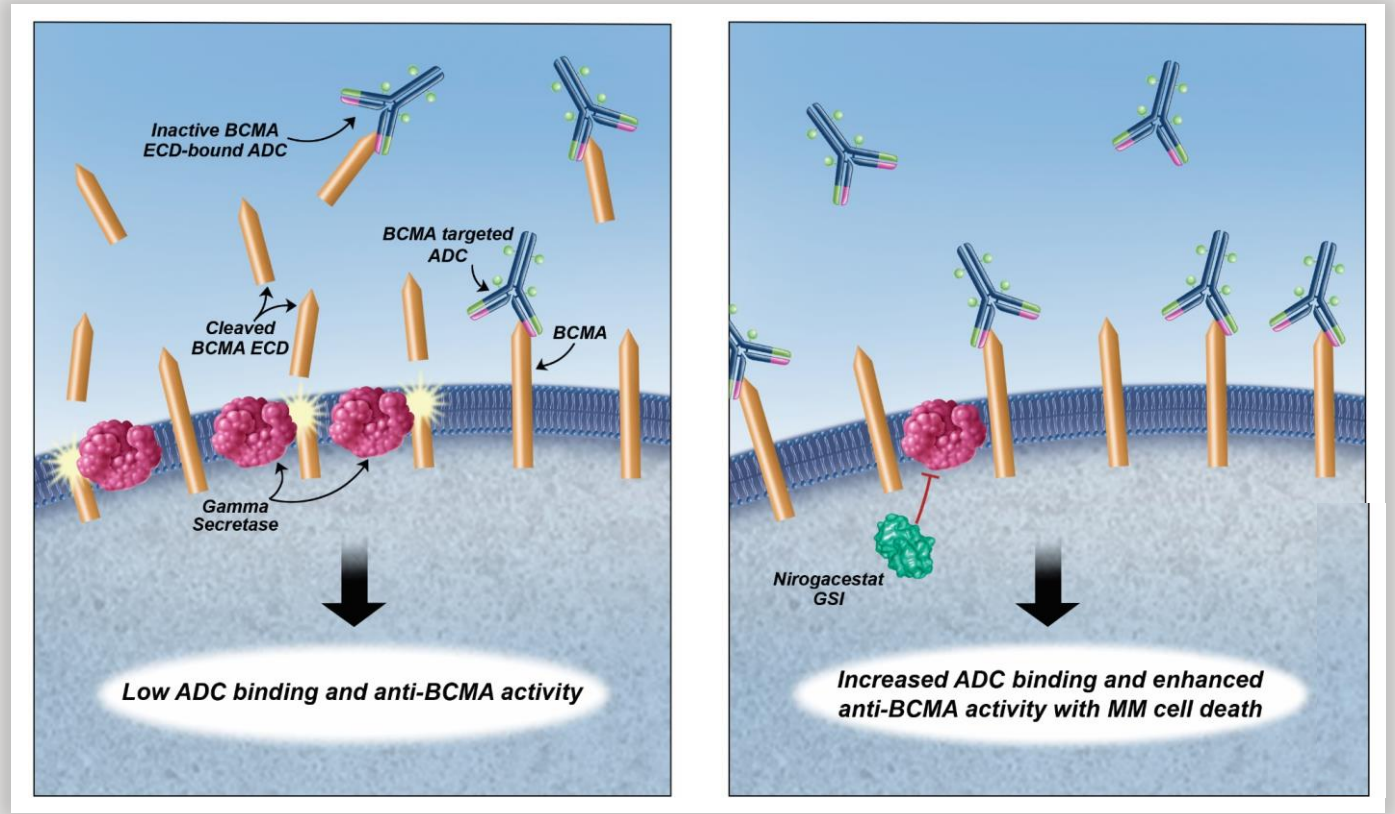
Gamma Secretase Inhibition is Emerging as a Clinically Validated Mechanism to Potentiate BCMA Therapies

- **Gamma secretase directly cleaves membrane-bound BCMA**
  - BCMA has emerged as a promising target in multiple myeloma across modalities
- **GSI can reduce cleavage of BCMA to improve activity of BCMA-directed therapies**
  - GSI can limit soluble BCMA levels, which can interfere with the activity of BCMA-directed therapies
  - GSI can dramatically increase levels of BCMA expression on the cell surface, including in patients that have failed prior BCMA-directed therapies
- **Preclinical and clinical data support combination approach**

MECHANISM OF ACTION OF NIROGACESTAT + BCMA THERAPY (ADC SHOWN)



Source: Cowan et al., Abstract #204 "Efficacy and Safety of Fully Human BCMA CAR T Cells in Combination with a Gamma Secretase Inhibitor to Increase BCMA Surface Expression in Patients with Relapsed or Refractory Multiple Myeloma", ASH 2019; Eastman et al., Abstract #4401 "Synergistic Activity of Belantamab Mafodotin (anti-BCMA immuno-conjugate) with Nirogacestat (PF-03084014, gamma-secretase inhibitor) in BCMA-Expressing Cancer Cell Lines", ASH 2019; Green et al., Abstract #1856 "Response to BCMA CAR-T Cells Correlates with Pretreatment Target Antigen Density and Is Improved By Small Molecule Inhibition of Gamma Secretase", ASH 2019; Laurent et al., *Nat. Comm.*, 2015; Pont et al., *Blood*, 2019.

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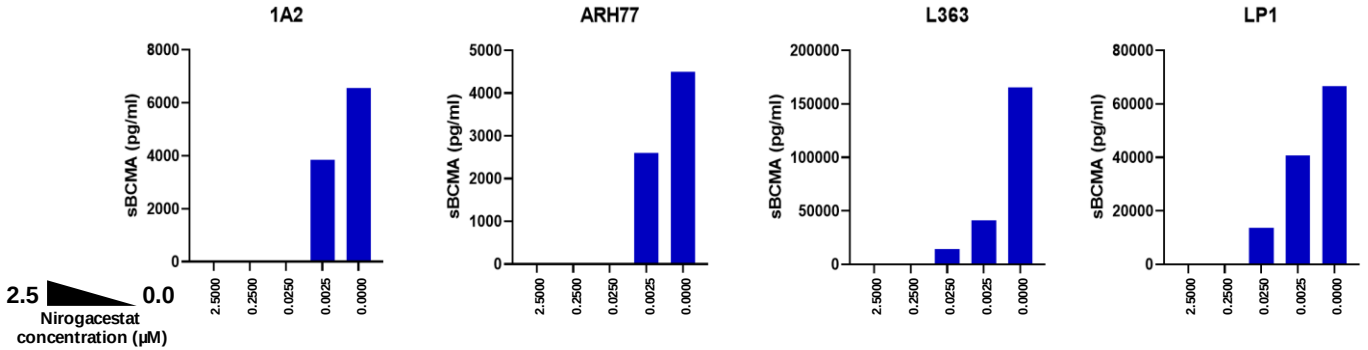
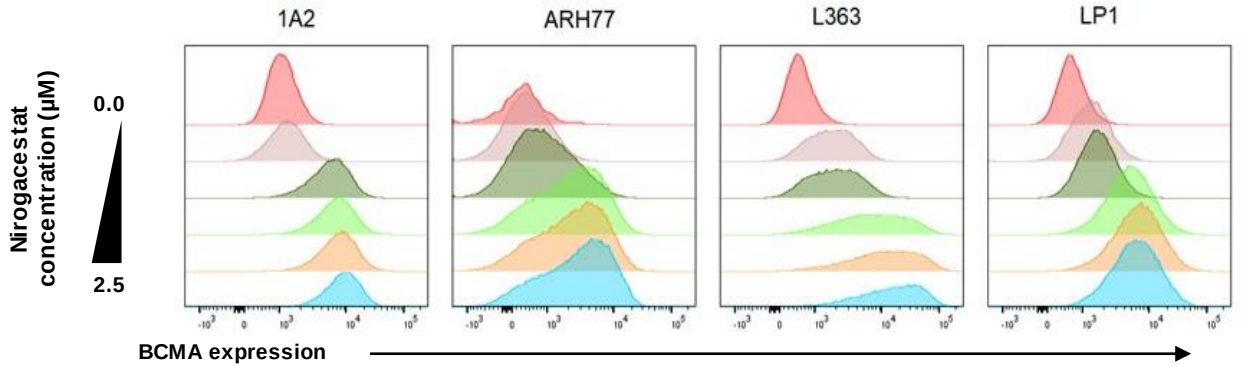
Nirogacestat Inhibited BCMA Shedding, Upregulated BCMA Expression, and Enhanced Activity of BCMA ADC Up to ~3,000-Fold

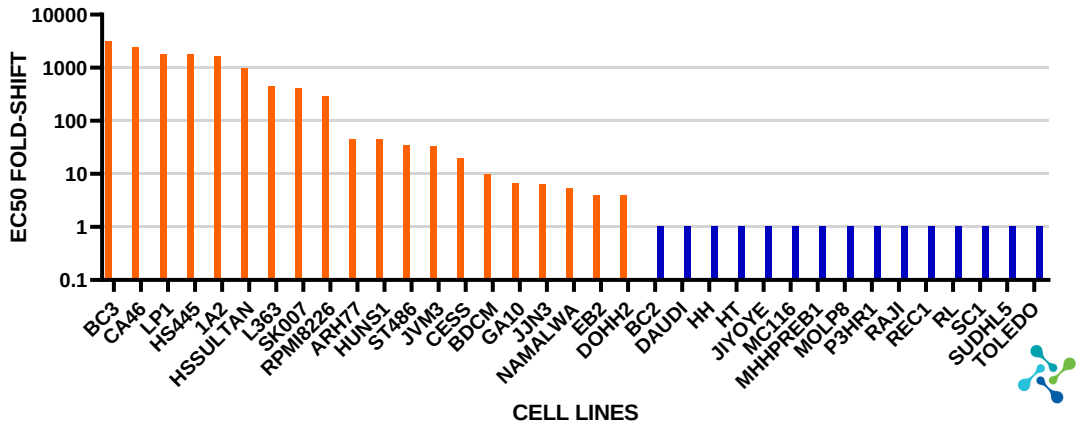
1 Nirogacestat inhibited cleavage of membrane-bound BCMA and shedding of soluble BCMA ECD



2 Nirogacestat rapidly and significantly upregulated BCMA cell surface expression levels



3 Nirogacestat enhanced multiple myeloma cell killing activity of BCMA ADC by up to ~3,000-fold



Note: ECD = extracellular domain; ADC = antibody-drug conjugate; MM = multiple myeloma.
Source: Eastman et al., Abstract #4401 "Synergistic Activity of Belantamab Mafodotin (anti-BCMA immuno-conjugate) with Nirogacestat (PF-03084014, gamma-secretase inhibitor) in BCMA-Expressing Cancer Cell Lines", ASH 2019.

SpringWorks THERAPEUTICS

Seven Clinical Collaborations Across All Key BCMA-Targeted Modalities

SpringWorks THERAPEUTICS — **Nirogacestat (GSI)**

+

Antibody-Drug Conjugate

BLENREP* (belantamab mafodotin)

- Clinical collaboration signed in June 2019
- Phase 1 combo study initiated in June 2020 as part of GSK's DREAMM-5 trial
- Randomized Phase 2 expansion cohort initiated in 3Q21 and additional sub-studies announced in 4Q21

Monoclonal Antibody

SEA-BCMA

- Clinical collaboration signed in June 2021
- Expected Seagen-sponsored Phase 1 trial initiation: 1Q22

Bispecific Antibodies

Teclistamab

- Clinical collaboration signed in September 2020
- Janssen-sponsored Phase 1 trial initiated in 1Q21

Elranatamab

- Clinical collaboration signed in October 2020
- Pfizer-sponsored Phase 1b/2 trial initiated in 4Q21

ABBV-383

- Clinical collaboration signed in December 2021
- Expected AbbVie-sponsored Phase 1b trial initiation: 1H22

CAR T-Cell Therapies

ALLO-715

- Clinical collaboration signed in January 2020
- Allogene-sponsored Phase 1 trial initiated in 1Q21

PBCAR269A

- Clinical collaboration signed in September 2020
- Precision-sponsored Phase 1 trial initiated in 2Q21
- Initial clinical data expected in mid-2022

* BLENREP is the first FDA approved BCMA-targeted therapy.

Initial Low-Dose Blenrep + Nirogacestat DREAMM-5 Cohort Has Advanced to Randomized Phase 2 Expansion Cohort – Additional Sub-Studies with SoC Agents Planned

June 2020: Phase 1 Commenced

October 2021: Randomized Phase 2 Expansion and Additional Sub-studies Announced

Phase 1
Cohort Exploration

Cohort 1:
0.95 mg/kg Blenrep Q3W
+ nirogacestat

Additional Cohorts:
Blenrep + nirogacestat

Phase 2
Randomized Cohort Expansion

2.5 mg/kg Blenrep Q3W
(monotherapy arm)

vs.

0.95 mg/kg Blenrep Q3W +
nirogacestat

Potential for other cohorts to be expanded based on efficacy

Additional Planned Sub-studies with SoC Agents

Blenrep + nirogacestat +
pomalidomide + dexamethasone

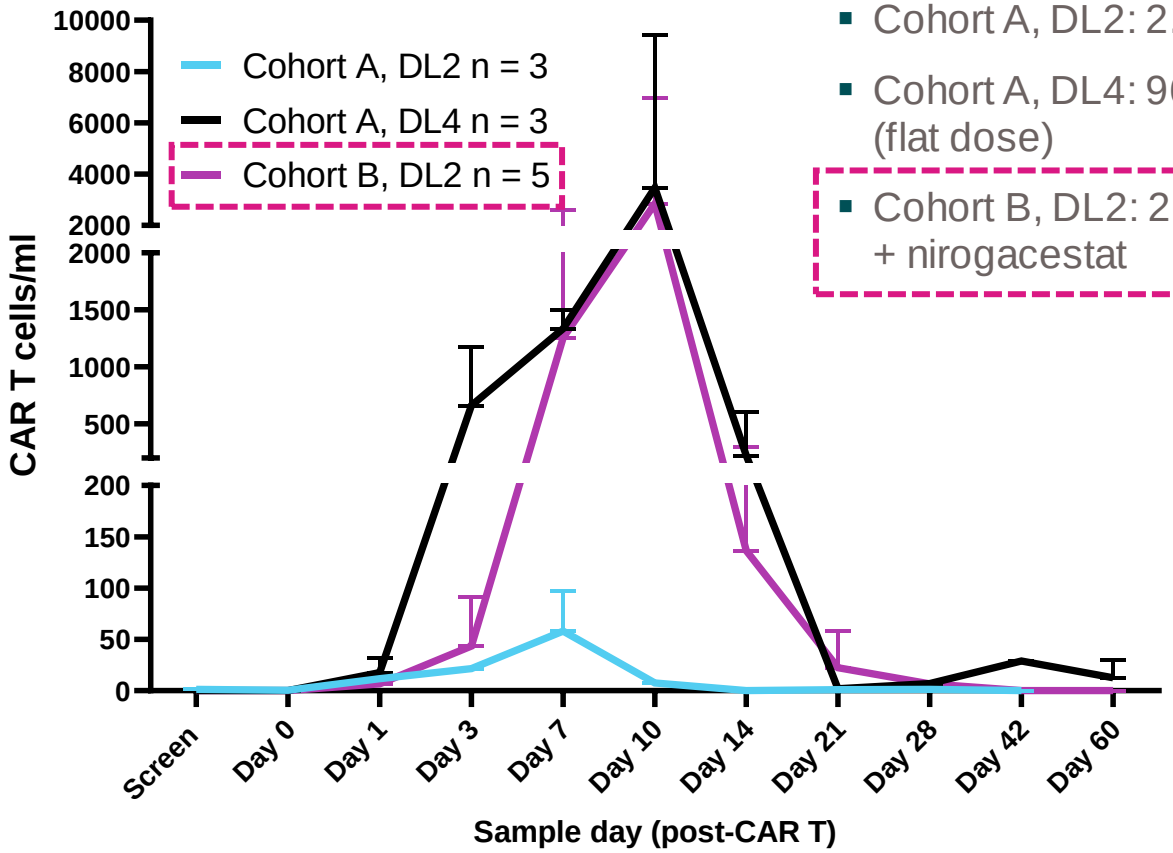
Blenrep + nirogacestat +
lenalidomide + dexamethasone

Based on encouraging preliminary data observed, first dose level advanced to randomized Ph2 expansion cohort vs. Blenrep monotherapy and additional sub-studies planned with SoC agents to potentially enable studies in earlier lines of MM

Note: SoC = standard of care.

Preliminary Clinical Data Demonstrate That Nirogacestat Treatment Can Lead to Profound Expansion of BCMA CAR-T Cells in Multiple Myeloma Patients

- Nirogacestat dosed from Day -3 to Day 60 and BCMA CAR-T (PBCAR269A) cells dosed on Day 0 in relapsed/refractory multiple myeloma patients
- Study designed in two cohorts
  - Cohort A: CAR-T cells only
  - Cohort B: CAR-T cells + nirogacestat



- Cohort A, DL2: 2.0 x 10^6 cells/kg
- Cohort A, DL4: 960 x 10^6 cells (flat dose)
- Cohort B, DL2: 2.0 x 10^6 cells/kg + nirogacestat

When combined with nirogacestat, a low dose of allogeneic BCMA CAR-T cells (PBCAR269A) achieved a similar level of expansion and persistence as a 7-fold higher dose of CAR-T cells administered as a monotherapy

Note: DL: dose level. Dose assumption based on an average weight of 70 kg per patient.
Source: Precision BioSciences investor materials (presented December 11, 2021); preliminary data from ongoing Precision-sponsored trial (NCT04171843).

SpringWorks THERAPEUTICS

Biomarker-Defined Metastatic Solid Tumors

SpringWorks® THERAPEUTICS

Mirdametinib in *RAS/RAF* Mutant Solid Tumors: Advancing Potentially Best-in-Class MEK/RAF Dimer Inhibitor Combination in Collaboration with BeiGene

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+

BeiGene

Mirdametinib + Lifirafenib

MEKi + RAF dimer inhibitor

RAS/RAF Mutant and Other MAPK Pathway Aberrant Solid Tumors

- Significant area of unmet need in cancer patients with *RAS/RAF* mutations and other MAPK pathway aberrations (approximately 25% of solid tumors)
- Lifirafenib possesses potentially best-in-class profile among RAF dimer inhibitors
- Combination synergy demonstrated across preclinical models harboring a variety of *KRAS* and *NRAS* mutations
- Phase 1b/2 trial is ongoing in Australia and the US; over half of enrolled patients remain on therapy with the longest patient on therapy for over two years (1)
- Focused investment until significant clinical validation achieved

Expect to report initial clinical data at upcoming SpringWorks R&D Day

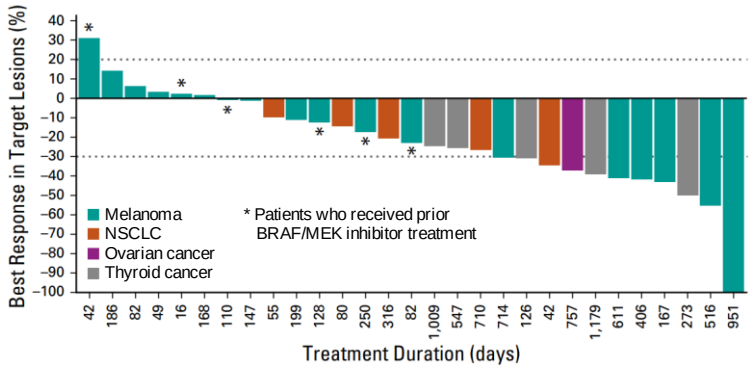
(1) Data as of September 8, 2021 and represent a snapshot that may change based on ongoing routine data monitoring. This trial is ongoing, and these results may not be predictive of future data presentations or final study results.

Mirdametinib + Lifirafenib: Encouraging Monotherapy Clinical Activity and Strong Preclinical Combination Data

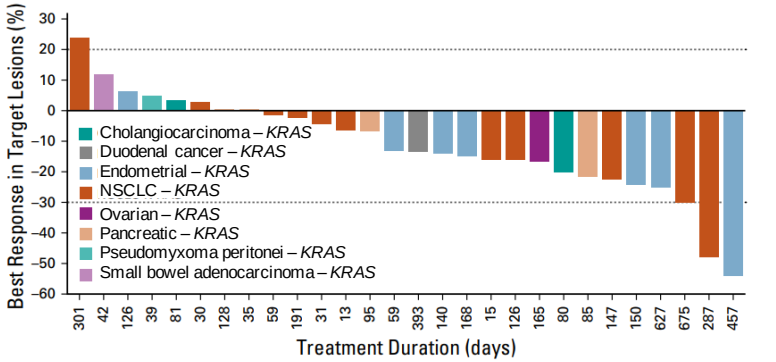
1 Lifirafenib monotherapy clinical activity in *BRAF* and *KRAS* mutant cancers

2 Preclinical synergy demonstrated with mirdametinib and lifirafenib *in vitro* across *RAS* mutations and *in vivo* at clinically relevant doses

BRAF^{mut} Cancers: P1a/b Best Objective Response

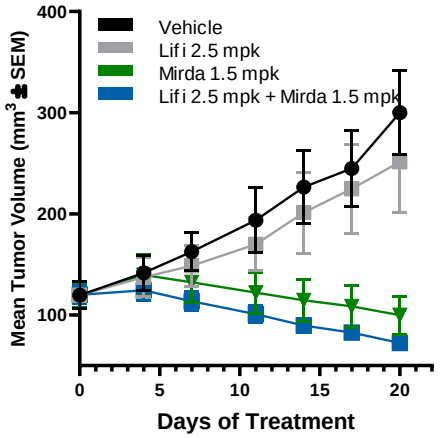


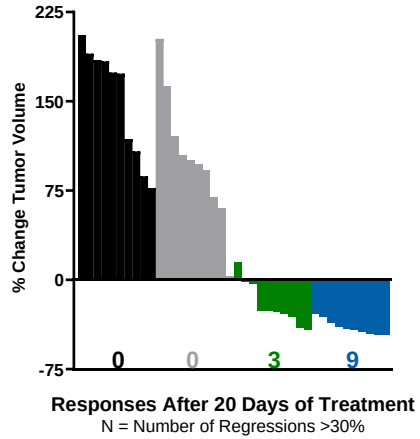
KRAS^{mut} Cancers (ex-CRC): P1a/b Best Objective Response



NSCLC Cell Line	RAS Mutation	Max EC_{50} shift with mirdametinib combo
Calu-6	K-RAS Q61K	59 fold ↓
SW1573	K-RAS G12C	97 fold ↓
NCI-H23	K-RAS G12C	22 fold ↓
NCI-H2122	K-RAS G12C	21 fold ↓
NCI-H358	K-RAS G12C	18 fold ↓
Calu-1	K-RAS G12C	No shift
Sk-Lu-1	K-RAS G12D	32 fold ↓
A549	K-RAS G12S	11 fold ↓
NCI-H1299	N-RAS Q61K	16 fold ↓

Mirdametinib + Lifirafenib *In Vivo* Activity (NCI-H358)





Source: Desai et al., *J Clin Oncol*, 2020; Tang et al., *Mol Cancer Ther*, 2015; Yuan et al., *Molecular Oncology*, 2020; Yuan et al., Abstract #6415, AACR 2020 Virtual Annual Meeting II.

SpringWorks THERAPEUTICS

Mirdametinib: Potential Expansion Opportunities in MAPK Pathway Aberrant Solid Tumor Types

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+

Memorial Sloan Kettering Cancer Center

Mirdametinib

Potent, oral, allosteric small molecule MEK 1/2 inhibitor

MAPK Aberrant Solid Tumors

- Mirdametinib is being investigated in a Phase 1/2 open-label platform study sponsored by Memorial Sloan Kettering Cancer Center and supported by SpringWorks
- The first cohort will explore mirdametinib combined with fulvestrant in the up-to-15% of ER+ metastatic breast cancers that harbor MAPK pathway alterations, including *NF1* loss-of-function mutations
- The second cohort will explore mirdametinib monotherapy in solid tumors harboring *MEK 1/2* mutations, which are present in ~2% of solid tumors
- Study builds upon promising data providing preclinical proof-of-concept for each cohort

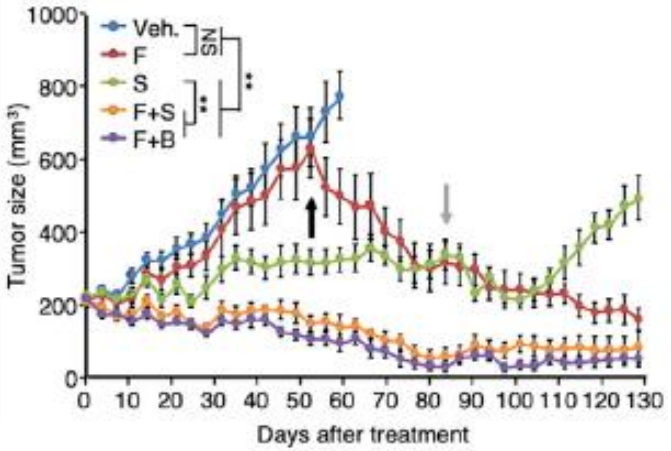
Initiated Phase 1/2 study in 3Q21

MEK Inhibitors Have Demonstrated Promising Activity in Hormone-Resistant ER+ Breast Cancer and MEK 1/2 Mutant Preclinical Models

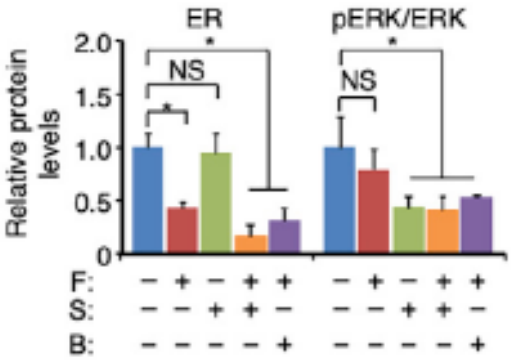
Hormone-Resistant ER+ mBC

MAPK mutations in ER+ mBC cells can lead to fulvestrant resistance, which can be reversed with MEK inhibition

NF1-Deficient ER+ BC PDX: Durable Tumor Growth Inhibition with MEKi + Fulvestrant



MEKi + Fulvestrant Modulates ER and MAPK Signaling

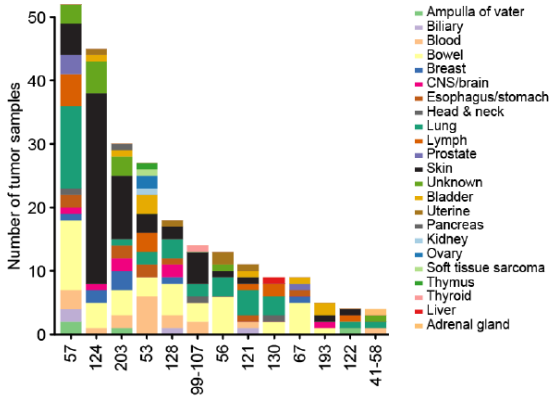


- ~25% of ER+ mBC patients progress on endocrine therapy
- *NF1* deficiency has been shown to enhance ER transcriptional activity leading to hormone resistance
  - Up to 15% of mBC harbor MAPK pathway mutations, including *NF1* LoF

MEK 1/2 Mutations

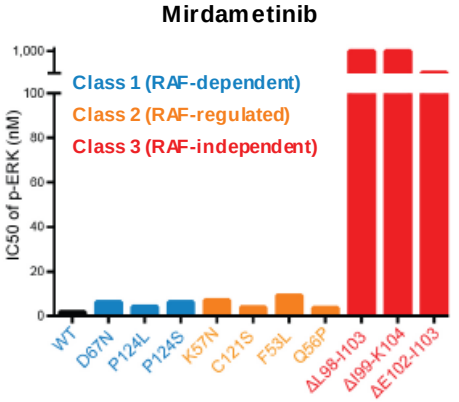
Mirdametinib shows potent preclinical activity against Class 1 and Class 2 mutations in MEK1 and MEK2

MEK 1/2 Mutants Occur Across Tumor Types



Supplementary Figure S1. Tumor type distribution of *MAP2K1* hotspot mutations.
Tumor type incidence per hotspot *MAP2K1* missense or in-frame deletion mutant.

Class 1 and 2 MEK Mutants Are Sensitive to Mirdametinib *in vitro*



- *MEK1* and *MEK2* have been validated as oncogenic targets with mutations present in ~2% of solid tumors
- Clinical case reports with allosteric MEK inhibitors also support utility of mirdametinib in tumors driven by MEK mutations

Note: B: buparlisib (PI3K inhibitor); F: fulvestrant; mBC: metastatic breast cancer; S: selumetinib (MEK inhibitor); SoC: standard of care; V: vehicle.
Source: Gao et al., 2018; Sokol et al., 2018; Hanrahan et al., 2020; Zheng et al., 2020.

SpringWorks THERAPEUTICS

BGB-3245: Potentially Differentiated Program for Currently Unaddressed *BRAF* Driver Mutations and Fusions

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+

BeiGene

BGB-3245

Mutant BRAF monomer, dimer, and fusion inhibitor

***BRAF* Mutant Solid Tumors**

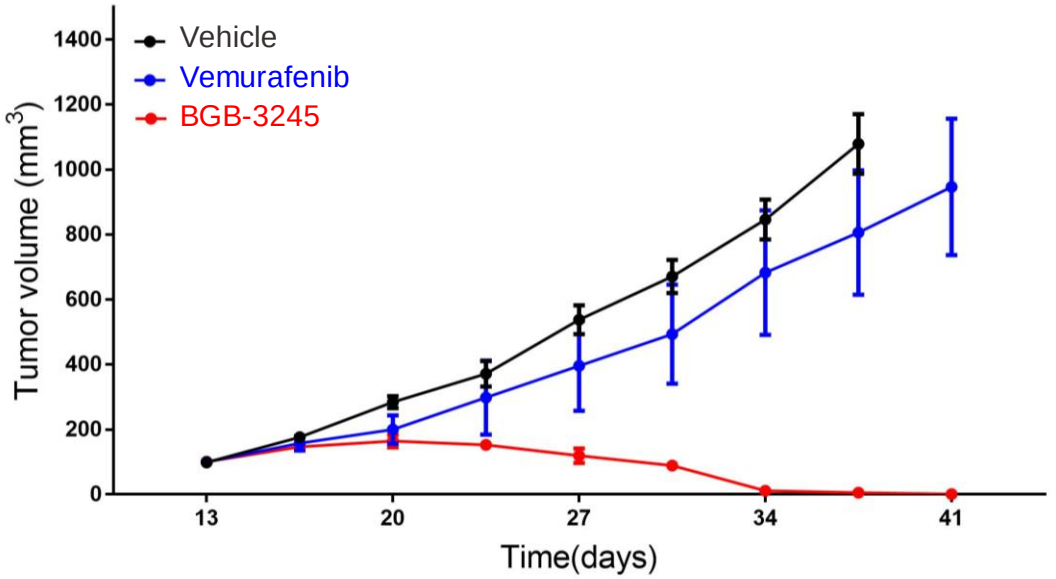
- MapKure is a joint venture between SpringWorks and BeiGene that is advancing BGB-3245, a novel BRAF inhibitor
- BGB-3245 could address *BRAF* alterations that currently lack targeted therapeutic options (non-V600 *BRAF* mutations and fusions)
- BGB-3245 has shown preclinical activity against resistance mutations to first generation *BRAF* V600 inhibitors
- Phase 1 trial initiated in 2020 and dose escalation ongoing in Australia and the US
- Industry-leading Scientific Advisory Board chaired by Dr. Neal Rosen of Memorial Sloan Kettering Cancer Center

Expect to report initial clinical data at upcoming SpringWorks R&D Day

BGB-3245 Has Demonstrated Encouraging Preclinical Activity

1 BGB-3245 is active in patient-derived xenografts driven by *BRAF* fusions and non-V600 mutations, where approved BRAF inhibitors do not work

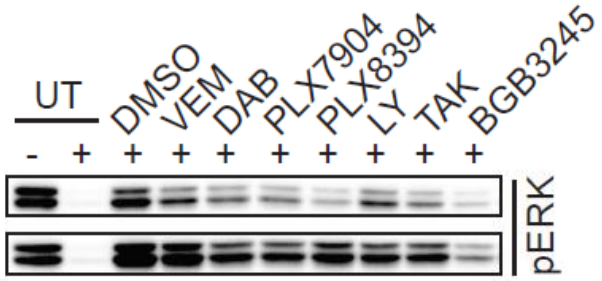
***BRAF* Fusion PDX: *In Vivo* Tumor Growth Inhibition**



- Driver mutations and fusions potentially uniquely targetable by BGB-3245 could account for up to ~5% of all solid tumors
- BGB-3245 also active preclinically against mutant *BRAF* monomers (e.g., V600)

2 BGB-3245 is active against resistance mutations that arise in *BRAF* V600 patients treated with approved BRAF inhibitors

pERK Activity in *BRAF* V600E/L514V Cell Line



- *BRAF* V600E/L514V is a dabrafenib resistance mutation
- BGB-3245 showed strongest *in vitro* activity versus other first- and second-generation BRAF inhibitors tested

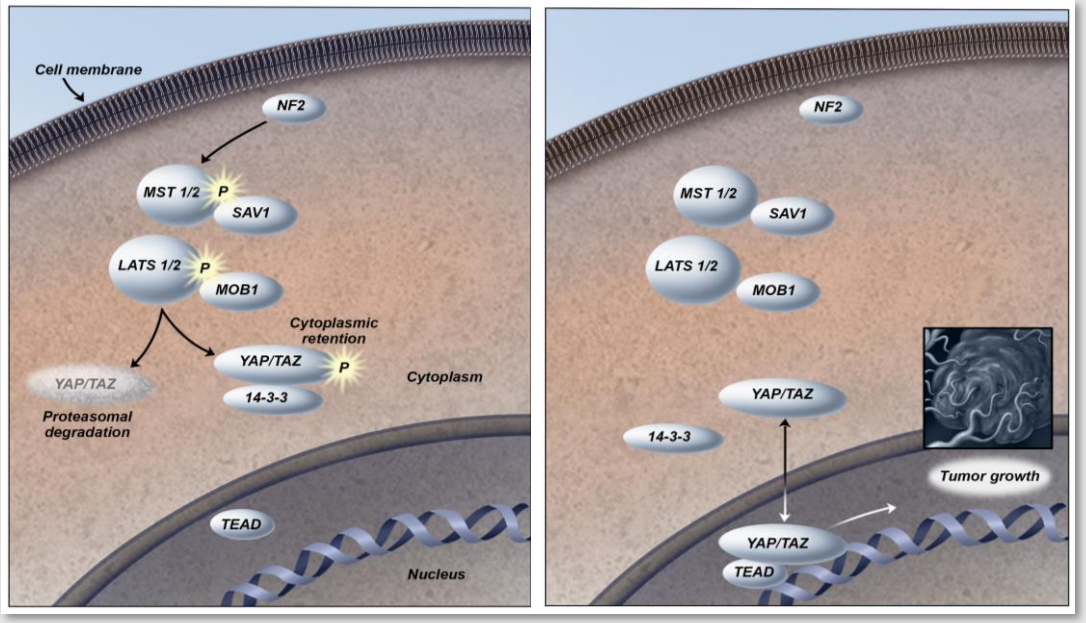
Source: Rosen presentation, Sixth International RASopathies Symposium: Precision Medicine – From Promise to Practice, 2019; Dankner et al., *Oncogene*, 2018; Ross et al., *IJC*, 2016; Dimitriadis et al., *J Neurooncol*, 2013; Garnett et al., *Molecular Cell*, 2005; Siegel et al., *CA A Cancer J Clin*, 2019; Wang et al., *Cancer Discovery*, 2018.

SpringWorks THERAPEUTICS

TEAD Inhibitor: Biomarker-Guided Approach for Tumors Driven by Aberrant Hippo Pathway Signaling

Hippo Pathway Active
YAP Inactive

Hippo Pathway Inactive
YAP Active



- Hippo pathway is genetically altered in approximately 10% of cancers and is generally associated with poor patient outcomes
- TEAD inhibition represents rational target given its central position in integrating Hippo pathway signaling
- TEAD palmitoylation is required for transcriptional activity and can be inhibited with potent and selective small molecules
- Multiple monotherapy and combination therapy opportunities guided by biomarker-driven development approach
- Program is currently in lead optimization with competitive *in vitro* and *in vivo* activity demonstrated

Expect to nominate DC and commence IND-enabling studies in 2022

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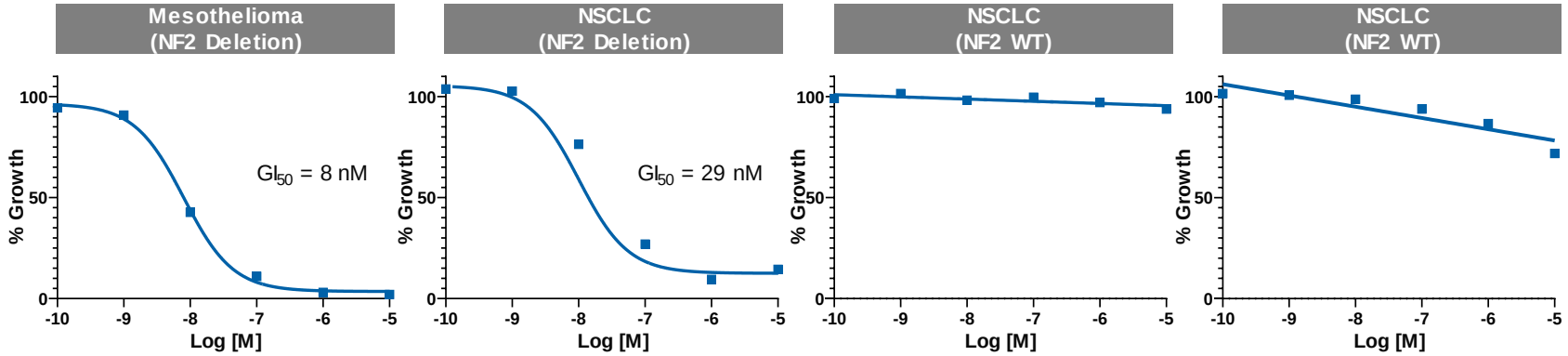
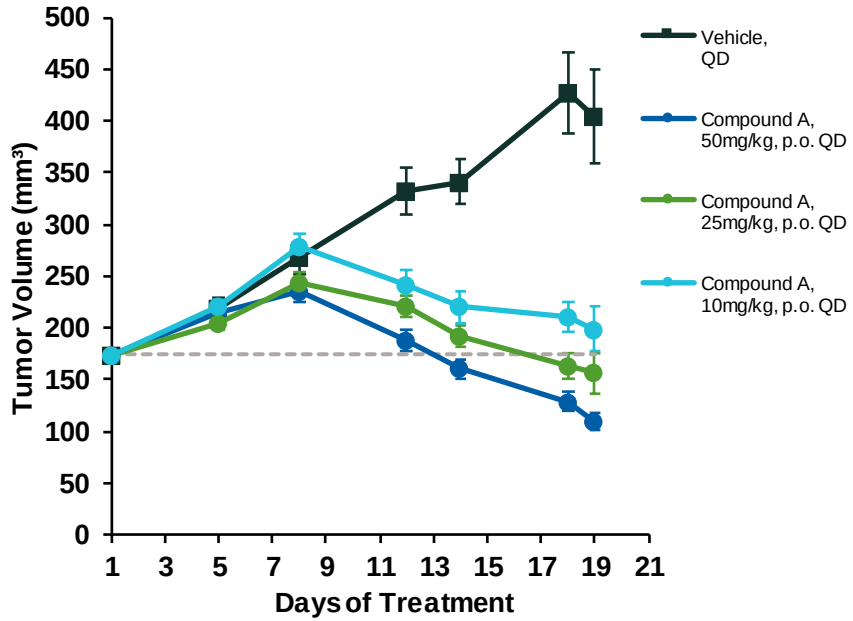
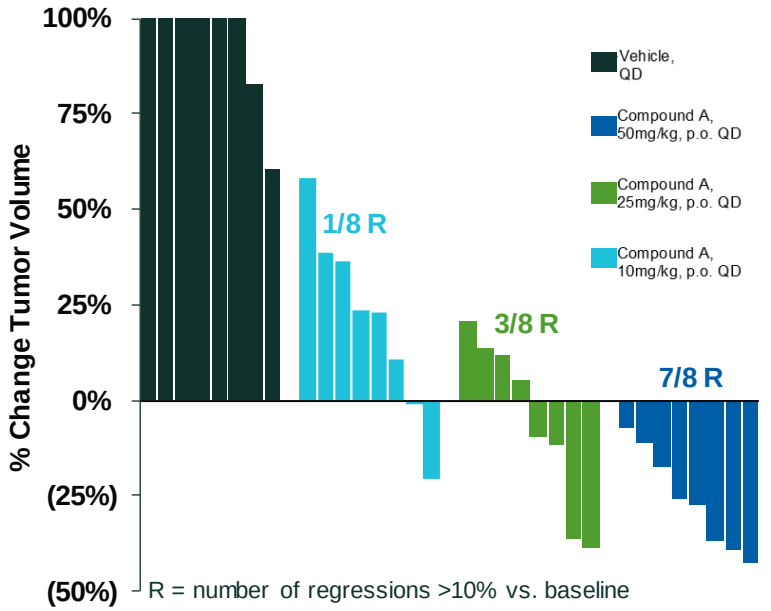
Program is in Lead Optimization with Selectivity, Potency and *In Vivo* Tumor Growth Inhibition Demonstrated

1 TEAD inhibitors potently and selectively inhibit growth of cancer cell lines driven by Hippo pathway mutations



2 Compounds have shown good tolerability and oral bioavailability *in vivo,* with dose dependent tumor growth inhibition in *NF2*-deficient xenografts





Note: GI_{50} = drug concentration producing 50% maximal growth inhibition; P.O. = by mouth; QD = once a day.

EGFR Inhibitor Portfolio Includes Several Novel Targeting Approaches to Address *De Novo* Oncogenic Drivers and Resistance Mechanisms

SpringWorks THERAPEUTICS

Three EGFR Inhibitors

First program targeting C797S mutants
Two additional first-in-class approaches

EGFR Mutant Tumors

- EGFR inhibition is a validated therapeutic approach – limitations of existing agents center on development of resistance and subgroups with suboptimal responses
- SpringWorks is working with Dana-Farber Cancer Institute and Stanford on a portfolio of next-generation EGFR inhibitors
- Most advanced program is addressing EGFR C797S-mediated osimertinib resistance utilizing a novel chemical strategy and is currently in lead optimization
- Additional strategies being advanced to address *de novo* EGFR driver and resistance mutations through first-in-class targeting approaches
- Research will be conducted in collaboration with Dr. Nathanael Gray (Stanford) and Drs. Pasi Janne, Michael Eck, and Jarrod Marto (Dana-Farber)

Expect to nominate first EGFR inhibitor DC from this portfolio in 2023

The SpringWorks Opportunity

SpringWorks THERAPEUTICS

Multiple Milestones Anticipated Across Our Pipeline in 2021

	Indication	Program		Expected Milestone	Timing
Late-Stage Rare Oncology	Desmoid Tumors	Nirogacestat		Report Phase 3 DeFi topline data in adult desmoid tumor patients	4Q 2021 / early 2022
	NF1-Associated Plexiform Neurofibromas	Mirdametinib		Achieved Phase 2b ReNeu full enrollment	4Q 2021
	Pediatric Low-Grade Gliomas	Mirdametinib		Achieved Phase 1/2 trial FPFD	2H 2021
BCMA Combinations	Relapsed / Refractory Multiple Myeloma	Nirogacestat	+ BLENREP	Initiated randomized Phase 2 expansion cohort with GSK	3Q 2021
			+ ALLO-715	Initiated Phase 1 trial with Allogene	1Q 2021
			+ Teclistamab	Initiated Phase 1 trial with Janssen	1Q 2021
			+ PBCAR269A	Initiated Phase 1 trial with Precision	2Q 2021
			+ Elranatamab	Initiated Phase 1b/2 trial with Pfizer	4Q 2021
			+ SEA-BCMA	Phase 1 trial initiation with Seagen	1Q 2022
			+ ABBV-383	Phase 1b trial initiation with AbbVie	1H 2022
Biomarker-Defined Metastatic Solid Tumors	RAS/RAF Mutant and Other MAPK Pathway Aberrant Solid Tumors	Mirdametinib	+ Lifirafenib	Report initial Phase 1b/2 data with BeiGene	R&D Day
	RAF Mutant Solid Tumors	BGB-3245		Report initial Phase 1 data	R&D Day
	ER+ Metastatic Breast Cancer	Mirdametinib	+ Fulvestrant	Initiated Phase 1/2 trial	3Q 2021
	MEK 1/2 Mutant Solid Tumors	Mirdametinib			
	Hippo Mutant Tumors	TEAD inhibitor		DC nomination	2022
	EGFR Mutant Tumors	EGFR inhibitor		DC nomination	2023

SpringWorks THERAPEUTICS

Well Capitalized to Execute on Important Value-Driving Milestones

$480.6M

Cash, Cash Equivalents & Marketable Securities(1)

No Debt

NASDAQ: SWTX

49.2M

Common Shares Outstanding(2)

(1) As of September 30, 2021.
(2) Basic common shares outstanding as of October 29, 2021.

SpringWorks THERAPEUTICS

Strategic Priorities and Building Blocks for Substantial Value Recognition in 2021

- Execute **two ongoing potentially registrational trials** in rare oncology indications
- Develop nirogacestat as a **cornerstone of BCMA combinations**
- Continue disciplined investments in **high-value early pipeline programs**
- Drive **portfolio expansion** through additional in-licenses and clinical collaborations
- Expand capabilities and **scale the organization** with talented employees

17 programs in development

2 potentially registrational trials fully enrolled

9 collaborations in large cancer indications

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