40th Annual J.P. Morgan Healthcare Conference

Saqib Islam, Chief Executive Officer

January 11, 2022

SpringWorks THERAPEUTICS

Forward-Looking Statements

Note: Unless otherwise indicated, the information presented herein is as of January 2022 and made publicly available on January 11, 2022.

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.

THE FULL POTENTIAL
OF TARGETED ONCOLOGY
IS WAITING TO BE UNLOCKED.

LET'S GO

SpringWorks is a clinical-stage biopharmaceutical company applying a precision medicine approach to acquiring, developing and commercializing life-changing medicines for patients with devastating cancers.

- Multiple late-stage opportunities with **first approval expected in 2023** and **two marketed products expected by 2025**
- **Deep pipeline of 17 R&D programs** with steady cadence of near-term and long-term value-creating milestones
- **End-to-end resident expertise** spanning therapeutic identification, clinical development, manufacturing and commercialization
- Expanding portfolio with several **pipeline-in-a-product molecules** and **collaborative relationships** to continually unlock new opportunities
- **Durable intellectual property portfolio** and **robust balance sheet** with disciplined approach to capital allocation

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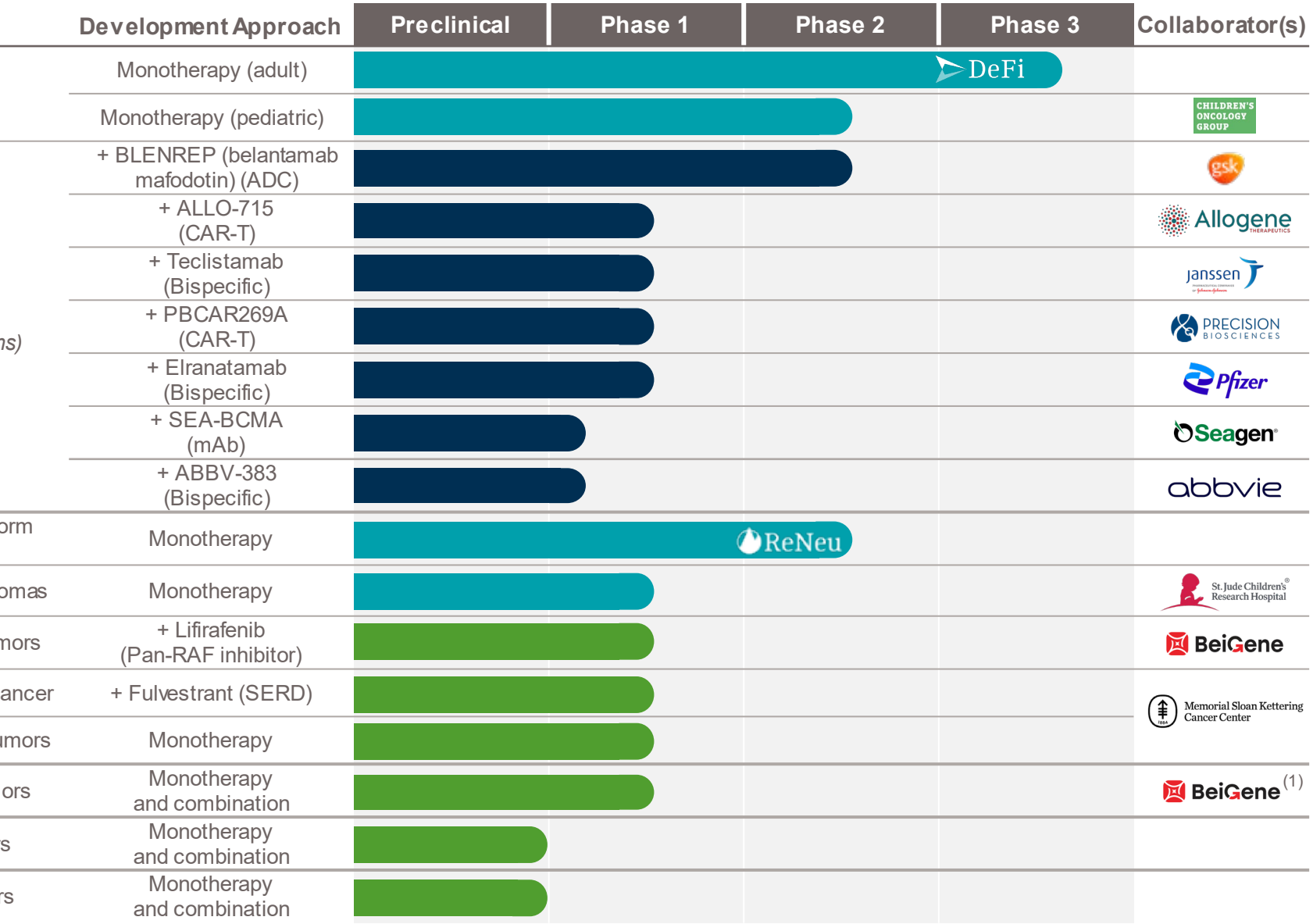
Diversified Targeted Oncology Pipeline Spanning Solid Tumors and Hematological Cancers

Compound	Indication	Development Approach	Collaborator(s)
Nirogacestat Gamma Secretase Inhibitor	Desmoid Tumors*	Monotherapy (adult)	DeFi
		Monotherapy (pediatric)	Children's Oncology Group
	Multiple Myeloma *(BCMA Combinations)*	+ BLENREP (belantamab mafodotin) (ADC)	GSK
		+ ALLO-715 (CAR-T)	Allogene Therapeutics
		+ Teclistamab (Bispecific)	Janssen
		+ PBCAR269A (CAR-T)	Precision Biosciences
		+ Elranatamab (Bispecific)	Pfizer
		+ SEA-BCMA (mAb)	Seagen
		+ ABBV-383 (Bispecific)	AbbVie
Mirdametinib MEK Inhibitor	NF1-Associated Plexiform Neurofibromas†	Monotherapy	ReNeu
	Pediatric Low-Grade Gliomas	Monotherapy	St. Jude Children's Research Hospital
	MAPK Mutant Solid Tumors	+ Lifirafenib (Pan-RAF inhibitor)	BeiGene
	ER+ Metastatic Breast Cancer	+ Fulvestrant (SERD)	Memorial Sloan Kettering Cancer Center
	MEK 1/2 Mutant Solid Tumors	Monotherapy	Memorial Sloan Kettering Cancer Center
BGB-3245 RAF Fusion and Dimer Inhibitor	RAF Mutant Solid Tumors	Monotherapy and combination	BeiGene (1)
TEAD Inhibitor Program	Hippo Mutant Tumors	Monotherapy and combination	
EGFR Inhibitor Program	EGFR Mutant Tumors	Monotherapy and combination	



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.

Rare Oncology | BCMA Combos | Biomarker-Defined Solid Tumors

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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
- **Nirogacestat**
  Pediatric Desmoid Tumors
- **Mirdametinib**
  NF1 Plexiform Neurofibromas
- **Mirdametinib**
  Pediatric Low-Grade Gliomas

2 BCMA Combinations in Multiple Myeloma

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

- **Nirogacestat + BLENREP**
  BCMA ADC
- **Nirogacestat + ALLO-715**
  BCMA Allogeneic CAR-T
- **Nirogacestat + Teclistamab**
  BCMA-CD3 Bispecific
- **Nirogacestat + PBCAR269A**
  BCMA Allogeneic CAR-T
- **Nirogacestat + Elranatamab**
  BCMA-CD3 Bispecific
- **Nirogacestat + SEA-BCMA**
  BCMA Monoclonal Antibody
- **Nirogacestat + ABBV-383**
  BCMA-CD3 Bispecific

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
- **Mirdametinib + Fulvestrant**
  ER+ Metastatic Breast Cancer
- **Mirdametinib**
  MEK 1/2 Mutant Solid Tumors
- **BGB-3245**
  RAF Mutant Solid Tumors
- **TEAD Inhibitor**
  Hippo Mutant Tumors
- **EGFR Inhibitor**
  EGFR Mutant Tumors

Value-Driving Data Readouts and Program Updates Anticipated Across the Pipeline in 2022

Milestone	Expected Timing
Nirogacestat: Phase 3 DeFi topline readout in desmoid tumors	Early 2022
Nirogacestat + SEA-BCMA: Phase 1 trial initiation in RRMM with Seagen	1Q
Nirogacestat + ABBV-383: Phase 1 trial initiation in RRMM with AbbVie	1H
Nirogacestat + BCMA therapies: Clinical data from various combo trials in RRMM	Starting in 1H
Mirdametinib + Lifirafenib: Phase 1b/2 initial data readout in RAS/RAF-mutant solid tumors	R&D Day
BGB-3245: Phase 1 initial data readout in RAF-mutant solid tumors	R&D Day
TEAD inhibitor program: DC nomination	2H
Potential for additional data readouts and updates from other programs ▪ ReNeu trial for mirdametinib in NF1-PN ▪ Other ongoing mirdametinib trials in pediatric LGG, ER+ breast cancer and MEK-mutant solid tumors ▪ Preclinical EGFR inhibitor program	Full year

RRMM = relapsed/refractory multiple myeloma; LGG = low-grade glioma.

Nirogacestat

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Nirogacestat: A Potentially Best-in-Class Gamma Secretase Inhibitor Being Evaluated Across Multiple Indications

- Nirogacestat is an oral, selective gamma secretase inhibitor with over 10 years of clinical experience
- Fast Track and Breakthrough Therapy Designations received from FDA and Orphan Drug Designation received from both FDA and European Commission (1)
- Near-term commercial opportunity in desmoid tumors; ongoing Phase 3 DeFi trial builds on consistent clinical activity observed in two earlier studies
- Potential to become cornerstone of BCMA combination therapy in multiple myeloma with seven current collaborations representing all major modalities
- Expansion opportunities in additional indications expected to be announced at R&D Day

Phase 3 DeFi Topline Readout:	**Early 2022**
Clinical Trials Ongoing or On Track for 2022 Initiation:	**9**
BCMA Collaborations:	**7**
US Composition of Matter and Method of Use patent protection:	**2039**

(1) Orphan Drug, Fast Track and Breakthrough Therapy Designations received from FDA for desmoid tumors and Orphan Drug Designation received from European Commission for soft tissue sarcoma.

Dana
Desmoid tumor patient

Desmoid Tumors Are Highly Morbid Soft Tissue Tumors That Are Often Poorly Responsive to Surgical Interventions and Off-Label Therapies

Disease Characteristics

- Desmoid tumors can lead to significant morbidities and manifest throughout the body including in the extremities, the head and neck region, intra-abdominally and the thoracic region
- Disease can be multifocal with patients potentially having multiple lesions
- DTs can lead to severe negative outcomes and symptoms including lesion ulceration, organ dysfunction, amputation, long-lasting pain due to nerve compression or tumor pressure, disfigurement and restricted range-of-motion
- Post-surgical resection recurrence in up to 70% with physicians often adopting an active surveillance approach; follow-on treatments include chemo, radiation and off-label TKIs

- 1,000-1,500 newly incident patients per year in US
- 5,500-7,000 patients actively receiving treatment in the US in any given year

- No currently approved therapies and limited treatment options
- Off-label systemic therapies are poorly tolerated with inconsistent efficacy

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

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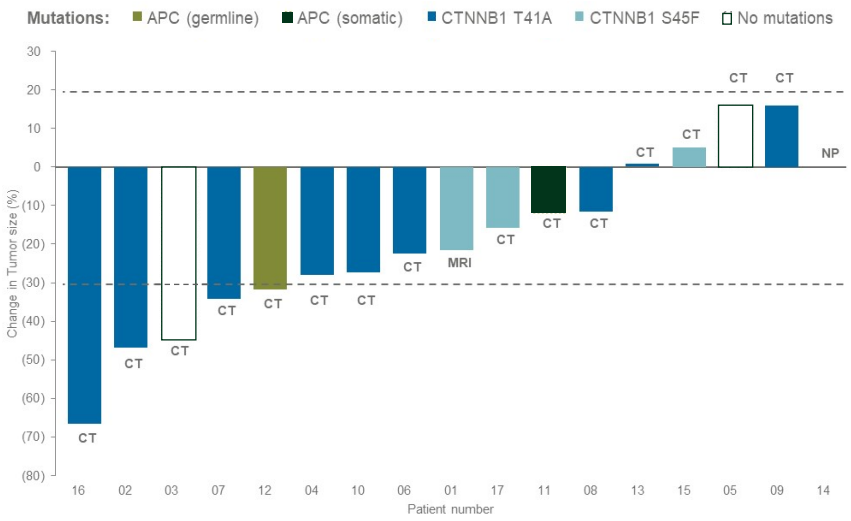
Encouraging Phase 2 Data in Actively Progressing Patients Set the Stage for Phase 3 DeFi Trial

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.

Expecting to Report Topline Data From Phase 3 DeFi Trial in Early 2022

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

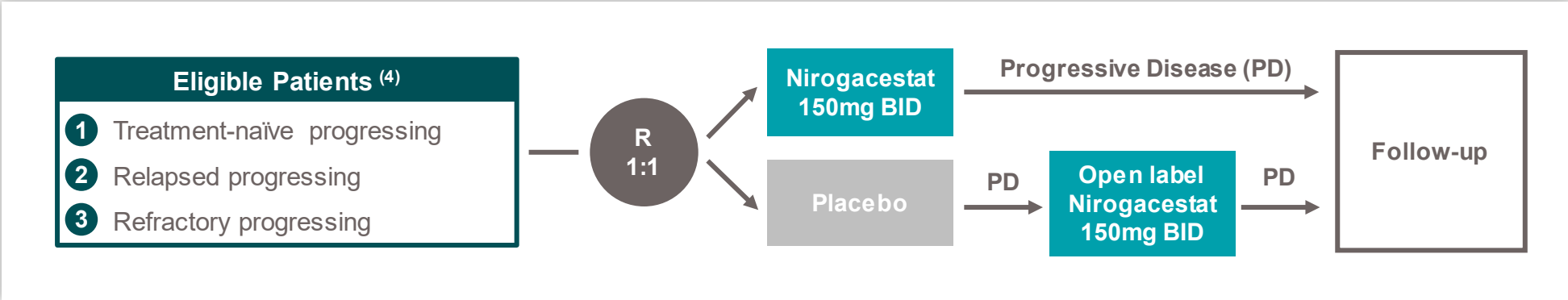
Trial Summary

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

Summary of Endpoints

DeFi

- 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



(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.
(4) Progression defined ≥20% increase over past 12 months by RECIST v1.1.

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Physicians and Patients Are Eager for a Safe and Effective Systemic Therapy for Desmoid Tumors

~5,500 to 7,000 DT patients
actively treated each year in the US

No FDA-approved therapies for DT

Physician propensity to treat remains high and willingness to utilize surgery is declining

1. Over 90% of DT patients in the US receive an active intervention
   - Physicians estimate that ~50% of patients will require a next-line treatment regardless of initial intervention selected
2. Surgery is being used as initial intervention less frequently due to high rates of post-surgical recurrence (up to 70%) and changes in treatment guidelines
   - Decreasing preference for surgery further increases the opportunity for nirogacestat
3. Healthcare resource utilization by patients remains substantially elevated for 3+ years following a DT diagnosis, underscoring significant morbidities
   - Opioid usage is high in both surgically and non-surgically treated patients
   - Increased inpatient and outpatient visits and days in the hospital persist for at least 3 years after initial diagnosis
4. Awareness of nirogacestat is high among DT physicians
   - Majority of HCPs have indicated a willingness to prescribe or switch to nirogacestat for most of their systemically-treated DT patients based on blinded drug profile

Source: SpringWorks market research; Hooda et al., CTOS 2021; Penel et al., 2017; White et al., DTRF 2021.

Nirogacestat in Multiple Myeloma: A Potentially Best-in-Class Combination Backbone for BCMA-Directed Therapies

Nirogacestat is positioned to be a potential cornerstone of BCMA combination therapy

Rationale and Development Strategy

- Gamma secretase directly cleaves membrane BCMA, a clinically validated multiple myeloma target across modalities (ADC, CAR T, mAb, bispecific)
- Emerging clinical data and strong preclinical synergy support combining gamma secretase inhibitors across BCMA modalities
- Pursuing broad collaboration strategy with leading BCMA therapy developers to generate a diverse dataset to position nirogacestat as the “go-to” GSI for MM

- ~40,000 multiple myeloma patients receiving 1L and 2L therapy annually in the US
- ~15,000 relapsed/refractory multiple myeloma patients receiving 3L+ therapy annually in the US

- Combination use being investigated across all BCMA-targeted therapy modalities
- Potential for use alongside SoC MM therapies across lines of treatment

Source: DRG market research.

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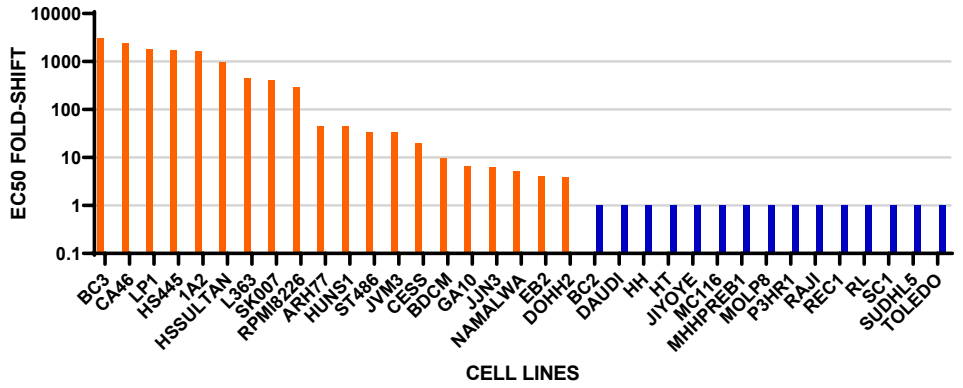
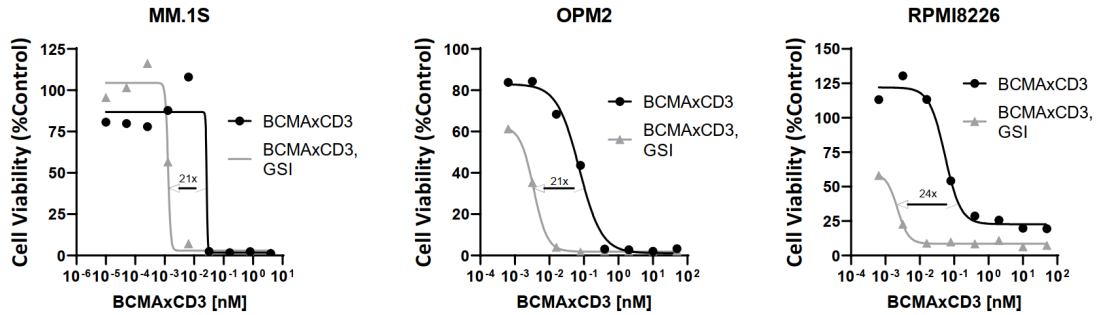
Gamma Secretase Inhibition Has Been Shown to Prevent BCMA Shedding and Increases Cell-Surface BCMA Levels, Thereby Potentiating the Activity of BCMA-Directed Therapies

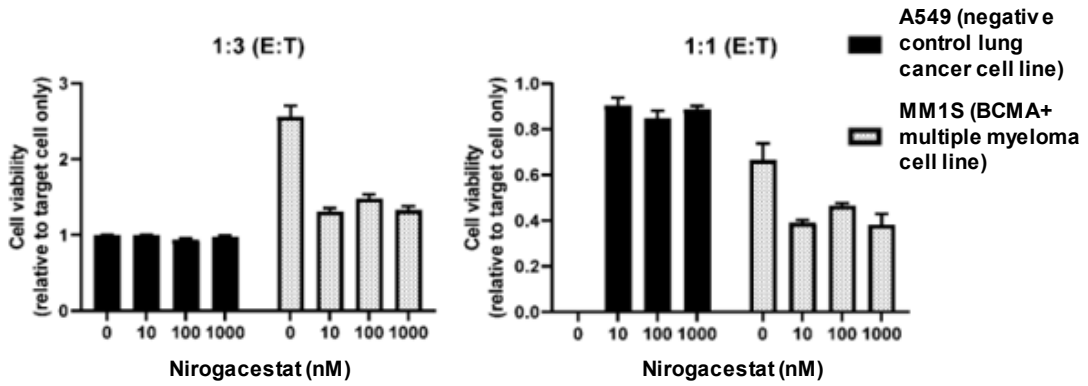
BCMA ADC



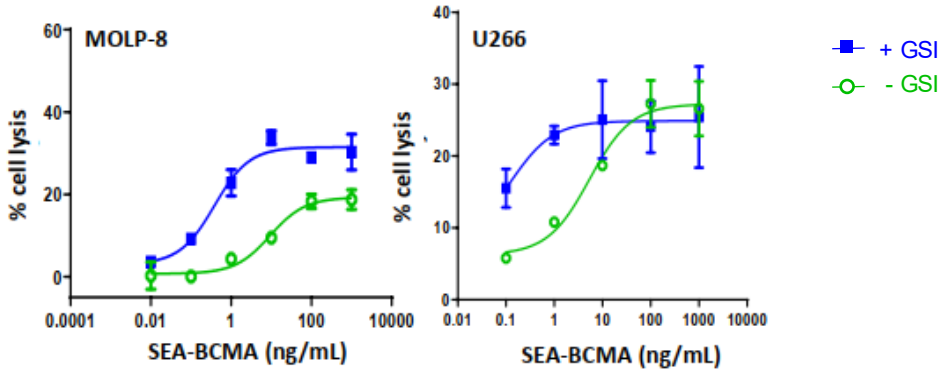
BCMA-CD3 Bispecific



BCMA CAR-T



BCMA mAb



Nirogacestat has been validated preclinically in combination with BCMA therapies representing all key modalities

Sources: Eastman et al., ASH 2019; Karwacz et al., AACR 2020; Balakumaran, A. et al., "Combination therapies of chimeric antigen receptors targeting B-cell maturation antigen and gamma secretase inhibitors", World patent WO2021146604A1, 2021 July 22; Yu et al., EHA 2021.

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Seven Clinical Collaborations Ongoing Covering All Key BCMA Therapeutic Modalities

Collaborator	Program	Modality				Collaboration Signed	Current Status
		ADC	Bispecific	CAR-T	mAb		
gsk	Blenrep (belantamab mafodotin)	✓				June 2019	Advanced into randomized Phase 2 trial
Allogene THERAPEUTICS	ALLO-715			✓		January 2020	Phase 1 trial ongoing
janssen PHARMACEUTICAL COMPANIES OF Johnson & Johnson	Teclistamab		✓			September 2020	Phase 1 trial ongoing
PRECISION BIOSCIENCES	PBCAR269A			✓		September 2020	Phase 1 trial ongoing
Pfizer	Elranatamab		✓			October 2020	Phase 1b/2 trial ongoing
Seagen®	SEA-BCMA				✓	June 2021	Phase 1 trial initiation expected 1Q22
abbvie	ABBV-383		✓			December 2021	Phase 1b trial initiation expected 1H22

Expecting significant clinical data releases across our BCMA collaboration trials throughout 2022

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

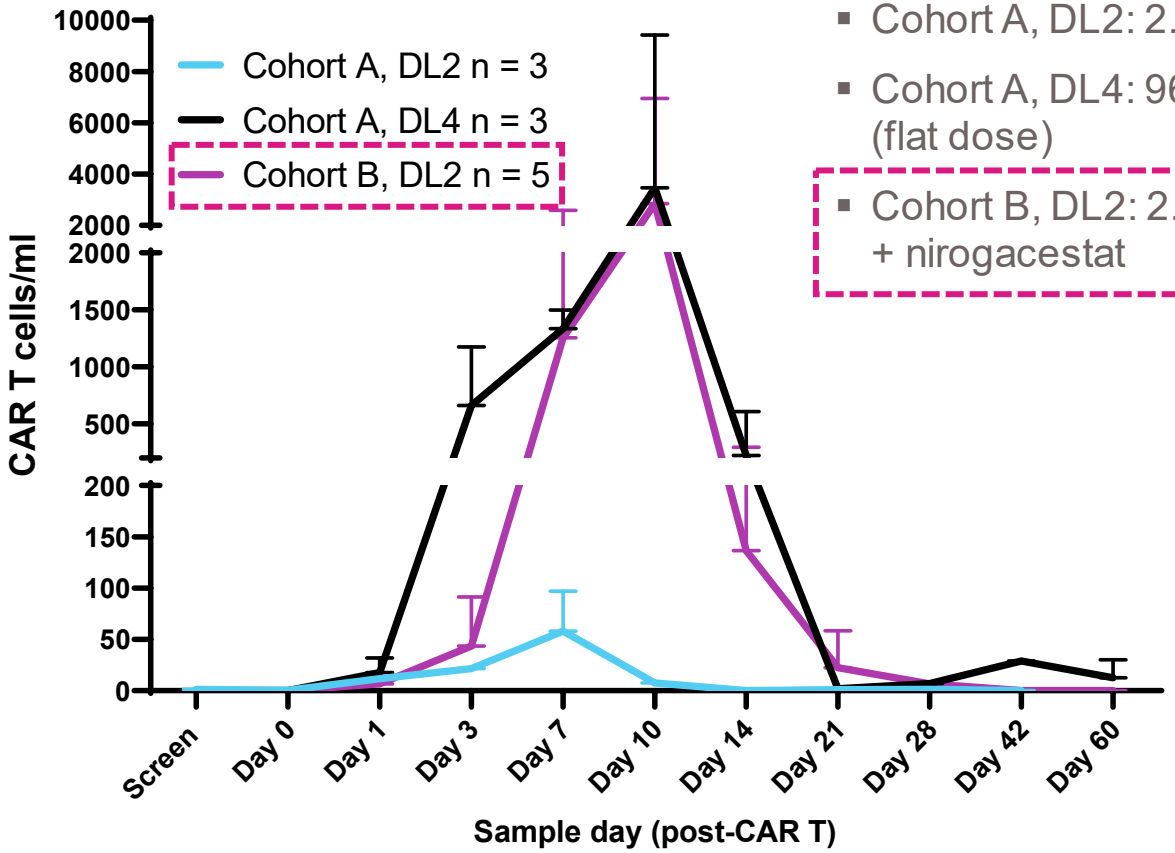
Blenrep + nirogacestat +
lenalidomide + dexamethasone

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 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.
Source: Precision BioSciences investor materials (presented December 11, 2021); preliminary data from ongoing Precision-sponsored trial (NCT04171843).

Mirdametinib

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Mirdametinib: Potent and Selective MEK Inhibitor With Differentiated Safety Profile

- Mirdametinib is an oral, allosteric MEK1/2 inhibitor with over 10 years of clinical experience
- Granted Orphan Drug Designation for NF1 by FDA and European Commission and Fast Track Designation for NF1-PN by FDA
- Ongoing Phase 2b ReNeu trial in NF1-PN is fully enrolled; NF1 is one of the largest genetic tumor predisposition syndromes with ~100k patients in the US today
- Compound potency, optimized dose/schedule, lack of food effect, limited DDI potential, and CNS exposure may allow for potentially differentiated development settings
- Monotherapy and combination studies ongoing in NF1-PN, low-grade glioma, breast cancer, RAS/RAF-mutated solid tumors and other indications

Pediatric and Adult NF1-PN Patients Enrolled on ReNeu	**100+**
Initial Clinical Data in Combination with Lifirafenib:	**R&D Day**
Clinical Trials Ongoing or On Track for 2022 Initiation:	**5**
US Composition of Matter patent protection:	**2041**

Biomarker-Guided Pipeline-in-a-Molecule Development Strategy for Mirdametinib

Indication	Development Approach	Preclinical / Phase 1 / Phase 2 / Phase 3	Collaborator(s)	Potential Annual Patient Population[1]	Biomarker(s)
NF1-PN	Monotherapy	ReNeu		~40,000 [2]	NF1
MAPK Mutant Solid Tumors	+ Lifirafenib (Pan-RAF inhibitor)		BeiGene	70,000+ [3]	RAS, RAF
Pediatric Low-Grade Gliomas	Monotherapy		St. Jude Children's Research Hospital	~15,000 [4]	MAPK Mutations
ER+ Metastatic Breast Cancer	+ Fulvestrant (SERD)		Memorial Sloan Kettering Cancer Center	~12,000 [5]	NF1 and Other MAPK Mutations
MEK 1/2 Mutant Solid Tumors	Monotherapy			~12,500 [6]	MEK1/2 Mutations

Mirdametinib has a potential total addressable population of 150,000+ patients annually and data are expected across studies in 2022

Sources: (1) Estimates are rounded and based on incidence reported by American Cancer Society Cancer Facts & Figures 2021 (US) and other sources as noted. (2) Rasmussen et al., 2000; Ferner et al., 2007; 2020 U.S. Census data. (3) Includes KRAS-mutant NSCLC and NRAS-mutant melanoma among other indications. Westcott et al., 2013; Munoz-Couselo et al., 2017. (4) Ostrom et al., 2020. Note addressable population includes prevalent population in addition to incident patients. (5) Razavi et al., 2018. (6) Hanrahan et al., 2020.

Kendall
NF1 Patient

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

Disease Characteristics

- 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

- ~100,000 patients living with NF1 in the US
- NF1 patients have a ~30-50% lifetime risk of developing NF1-PN

- MEK inhibitors are 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

Source: Kim et al., 2017.

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

ReNeu

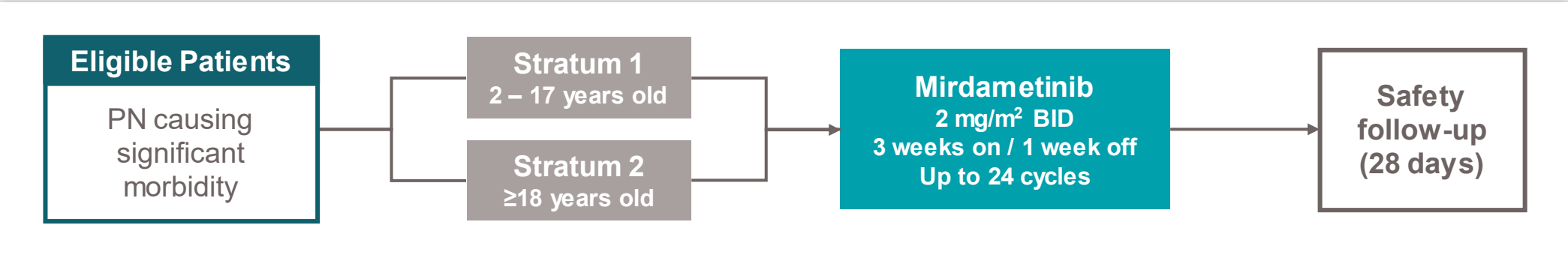
PHASE 2B

Trial Summary

- Enrolled ~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 (≥20% reduction in tumor volume)
  - Blinded Independent Central Review (BICR) used for tumor assessments
- Secondary Endpoints: Safety and tolerability, duration of response, and quality of life assessments



Full enrollment achieved in 4Q 2021

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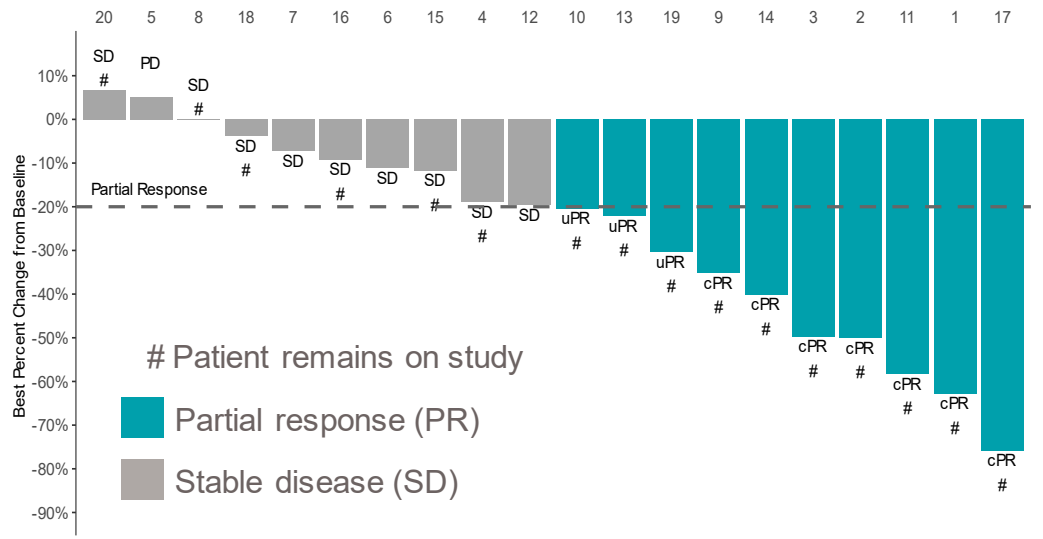
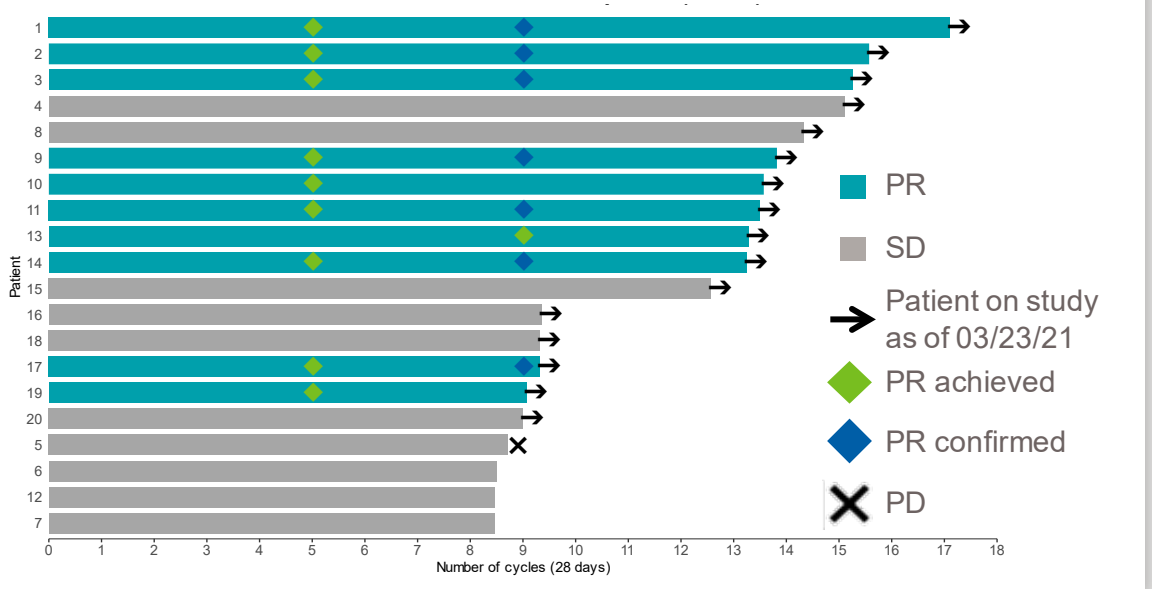
Interim Data Update From ReNeu Trial Adult Stratum Presented at CTF in June 2021

PHASE 2B

Best Tumor Responses



Treatment Duration and Response



- **50% of patients have achieved an objective response by BICR (n = 20)**
  - 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%
- **Median time on treatment for these 20 patients was 13 cycles (approximately 12 months)**
  - 80% of patients remain on study as of data cutoff
  - 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]

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.

(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.

Safety Summary From Interim Update: Treatment-Emergent and Treatment-Related AEs

ReNeu

PHASE 2B

	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.

SpringWorks THERAPEUTICS

Biomarker-Defined Metastatic Solid Tumors

SpringWorks® THERAPEUTICS

Expanding Early-Stage Pipeline to Target Range of Solid Tumor Types

	Compound	Development Approach	Indication	Preclinical	Phase 1/2	Pivotal	Collaborator(s)
Vertical MAPK Inhibition	**Mirdametinib**	+ Lifirafenib (Pan-RAF inhibitor)	MAPK Mutant Solid Tumors				BeiGene
	BGB-3245	Monotherapy and combination	RAF Mutant Solid Tumors				BeiGene (1)
Mirdametinib Expansion	**Mirdametinib**	+ Fulvestrant (SERD)	ER+ Metastatic Breast Cancer				Memorial Sloan Kettering Cancer Center
	Mirdametinib	Monotherapy	MEK 1/2 Mutant Solid Tumors				
Preclinical Portfolio: TEAD and EGFR inhibitors	**TEAD Program**	Monotherapy and combination	Hippo Mutant Tumors				
	EGFR Program	Monotherapy and combination	EGFR Mutant Tumors				

Ongoing maturation and expansion of targeted oncology portfolio with multiple data readouts expected in 2022-2023

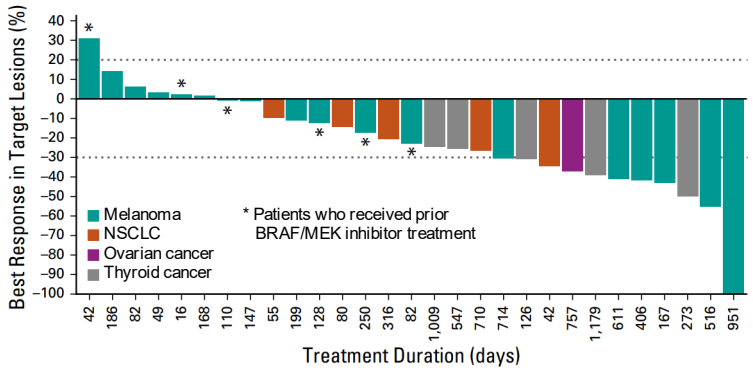
(1) Being developed by MapKure, LLC, jointly owned by SpringWorks and BeiGene.

Mirdametinib + Lifirafenib: Strong Preclinical Combination Data Builds on Encouraging Monotherapy Clinical Results

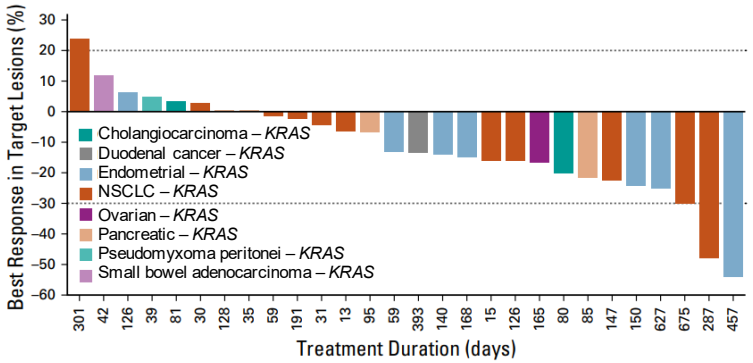
1 Lifirafenib monotherapy clinical activity in *BRAF* and *KRAS* mutant cancers

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

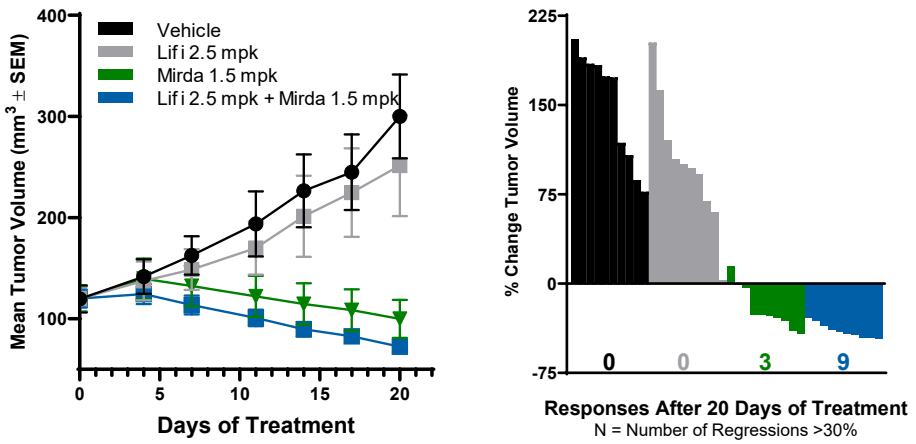


KRAS^{mut} Cancers (ex-CRC): P1a/b Best Objective Response



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)



Initial data from ongoing Phase 1/2 study expected at upcoming SpringWorks R&D Day

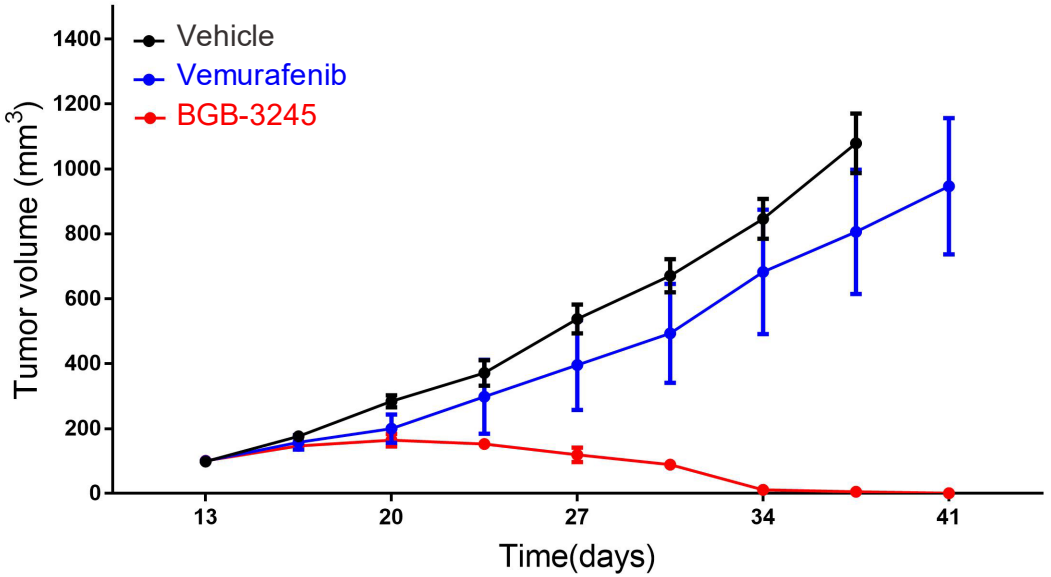
Source: Desai et al., *J Clin Oncol*, 2020; Tang et al., *Mol Cancer Ther*, 2015; Yuan et al., *Molecular Oncology*, 2020; Yuan et al., Abstract #6415, AACR 2020 Virtual Annual Meeting II.

SpringWorks THERAPEUTICS

BGB-3245: Preclinical Activity in BRAF Fusions and BRAF V600 Resistance Mutations Sets Up Multiple Monotherapy and Combination Therapy Development Avenues

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

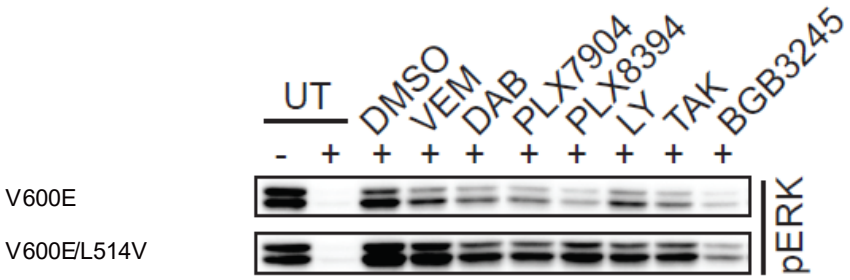
***BRAF* Fusion PDX: *In Vivo* Tumor Growth Inhibition**



- 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

Initial data from ongoing Phase 1 study expected at upcoming SpringWorks R&D Day

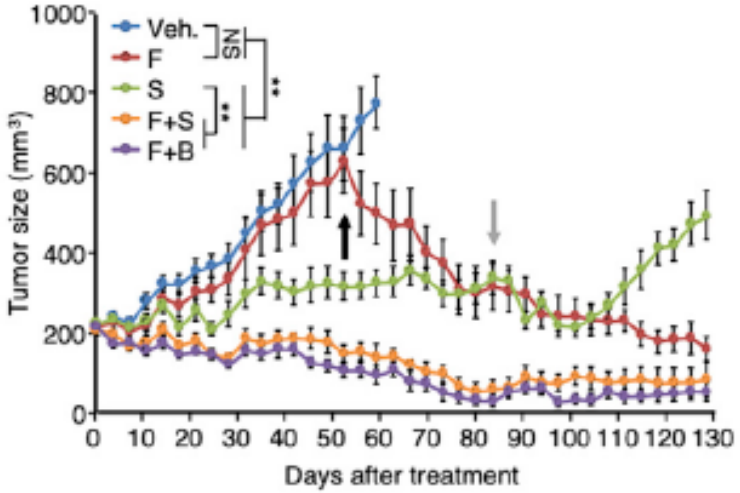
Source: Rosen presentation, Sixth International RASopathies Symposium: Precision Medicine – From Promise to Practice, 2019; Dankner et al., *Oncogene*, 2018; Rosset al., *IJC*, 2016; Wang et al., *Cancer Discovery*, 2018.

SpringWorks THERAPEUTICS

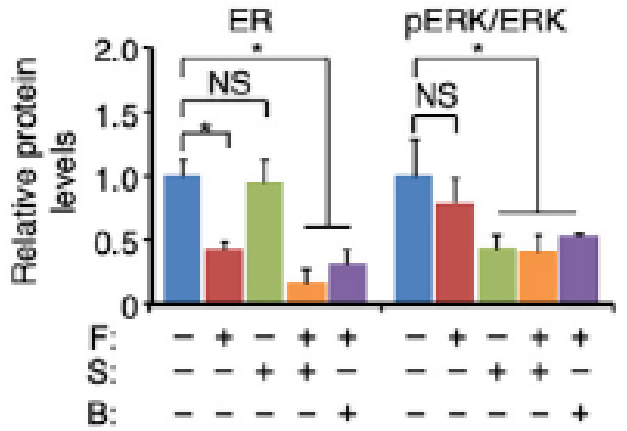
Mirdametinib: MEK Inhibitors Can Potentially Address Endocrine Therapy Resistance Due to MAPK Mutations in ER+ Breast Cancer

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

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



MEKi + Fulvestrant Modulates ER and MAPK Signaling



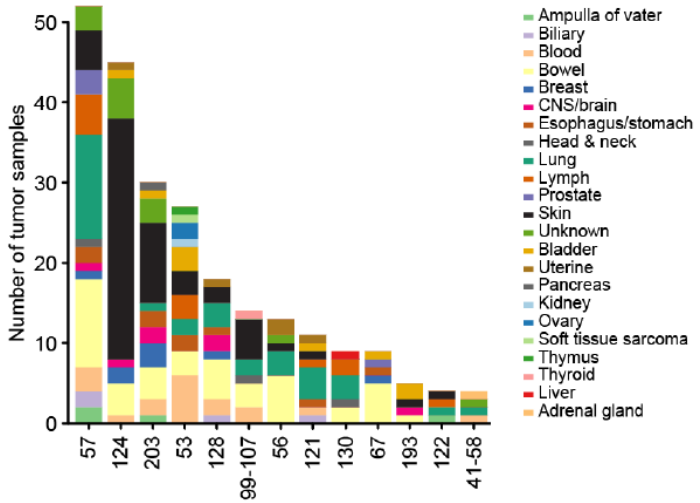
Phase 1 trial ongoing for mirdametinib + fulvestrant in ER+ breast cancer patients with MAPK-mediated resistance

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

Mirdametinib: Preclinical Activity Demonstrated in Preclinical Models Driven by Activating Mutations in MEK1 and MEK2

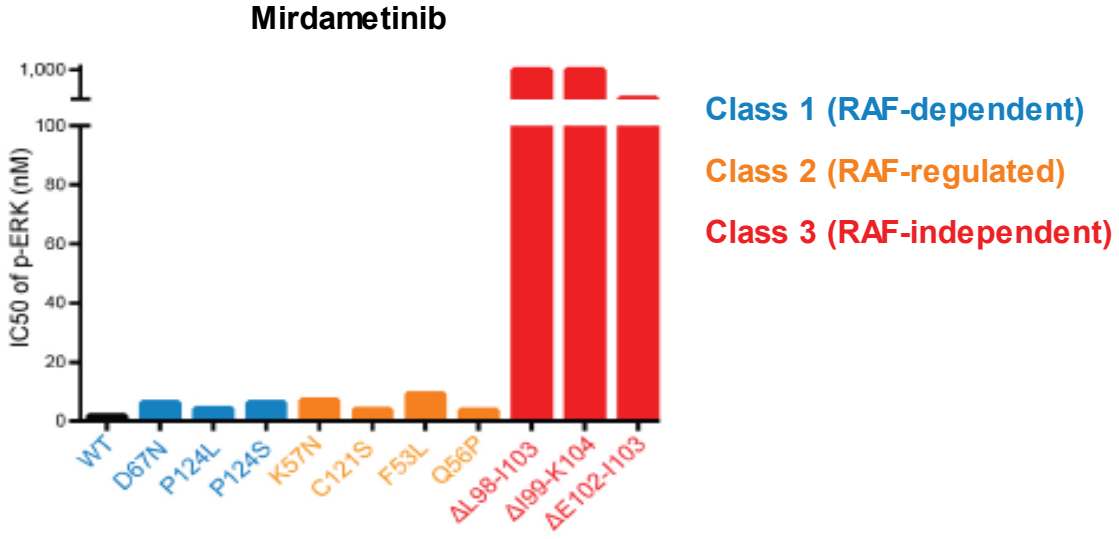
- Mirdametinib shows potent preclinical activity against Class 1 and Class 2 mutations in *MEK1* and *MEK2*
- *MEK1* and *MEK2* have been validated as oncogenic targets with mutations present in ~2% of solid tumors
- Clinical case reports with allosteric MEK inhibitors also support utility of mirdametinib in tumors driven by MEK mutations

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*

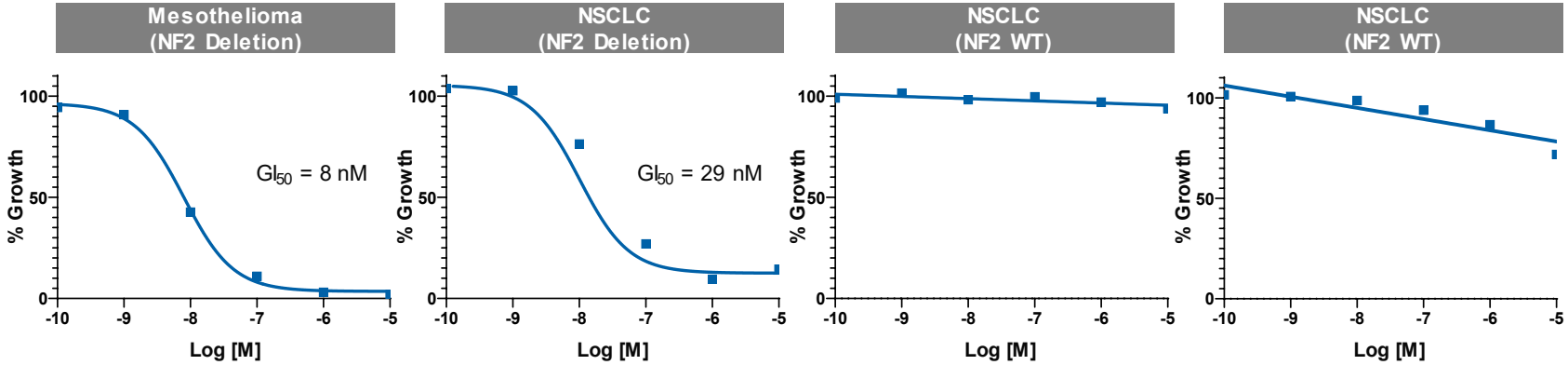


Phase 1 trial ongoing for mirdametinib in patients with MEK1/2-mutant solid tumors

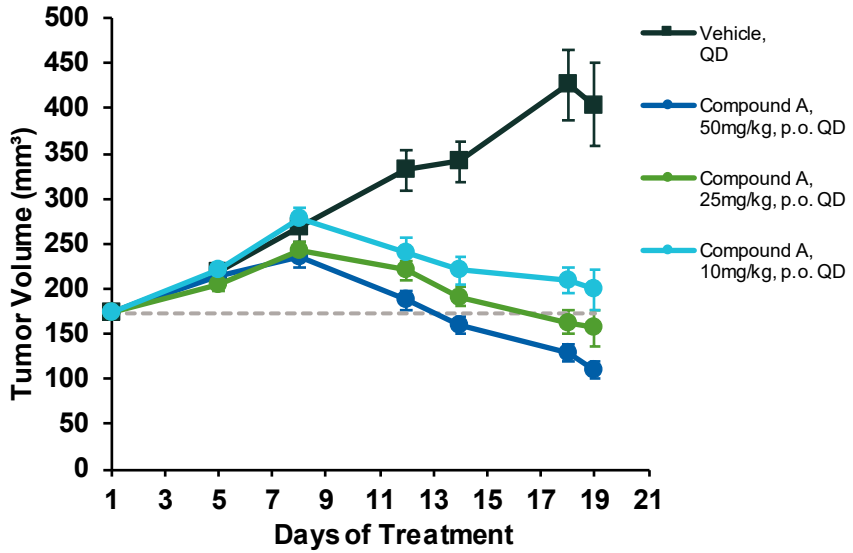
Source: Gao et al., 2018; Hanrahan et al., 2020.

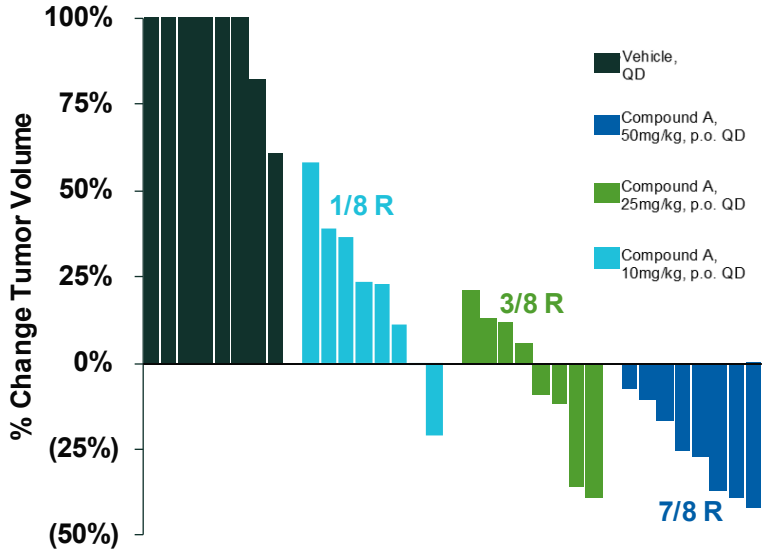
TEAD Inhibitor: Program in Lead Optimization With Selectivity, Potency and *In Vivo* Tumor Growth Inhibition Demonstrated in Hippo-Driven Models

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





TEAD inhibitor portfolio in-licensed in May 2021 with DC nomination expected in 2H 2022

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

The SpringWorks Opportunity

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

Value-Driving Data Readouts and Program Updates Anticipated Across the Pipeline in 2022

Milestone	Expected Timing
Nirogacestat: Phase 3 DeFi topline readout in desmoid tumors	Early 2022
Nirogacestat + SEA-BCMA: Phase 1 trial initiation in RRMM with Seagen	1Q
Nirogacestat + ABBV-383: Phase 1 trial initiation in RRMM with AbbVie	1H
Nirogacestat + BCMA therapies: Clinical data from various combo trials in RRMM	Starting in 1H
Mirdametinib + Lifirafenib: Phase 1b/2 initial data readout in RAS/RAF-mutant solid tumors	R&D Day
BGB-3245: Phase 1 initial data readout in RAF-mutant solid tumors	R&D Day
TEAD inhibitor program: DC nomination	2H
Potential for additional data readouts and updates from other programs ▪ ReNeu trial for mirdametinib in NF1-PN ▪ Other ongoing mirdametinib trials in pediatric LGG, ER+ breast cancer and MEK-mutant solid tumors ▪ Preclinical EGFR inhibitor program	Full year

RRMM = relapsed/refractory multiple myeloma; LGG = low-grade glioma.

Foundation in Place to Drive Sustainable Growth and Value Creation in 2022+

Focus Areas 2022+

- **Executing** late-stage development programs for nirogacestat and mirdametinib, with positive DeFi readout expected to yield first FDA-approved therapy for DT patients
- **Advancing** nirogacestat as a cornerstone of BCMA combination therapy across modalities with data readouts expected throughout 2022
- **Building** commercial infrastructure to support first potential commercial launch in 2023
- **Bolstering** R&D capabilities to advance preclinical portfolio into the clinic
- **Enhancing** exclusivity position through regulatory designations and IP portfolio development
- **Expanding** portfolio of opportunities as a partner of choice to industry and academia
- **Maintaining** strong financial position with disciplined capital allocation strategy and multi-year cash runway

Thank you

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