# Corporate Presentation

June 2022

SpringWorks® THERAPEUTICS

# Forward-Looking Statements

Note: Unless otherwise indicated, the information presented herein is as of June 2022 and made publicly available on June 5, 2022.

This presentation may contain “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, 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, our plans to report additional data from the Phase 3 DeFi clinical trial at an upcoming medical conference, the potential for the results of the Phase 3 DeFi clinical trial to support an NDA submission, the timing of our planned NDA submission for nirogacestat, and our plans for seeking regulatory approval for and making nirogacestat available to desmoid tumor patients, if approved, as well as relating to 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 topline or interim data from the Phase 3 DeFi trial or other clinical studies may not be predictive of the final or more detailed 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) the timing of our planned regulatory submissions and interactions, including the NDA for nirogacestat planned for the second half of 2022 and the timing and outcome of decisions made by the U.S. Food and Drug Administration (FDA) and other regulatory authorities, investigational review boards at clinical trial sites and publication review bodies; (v) whether FDA or other regulatory authorities will require additional information or further studies, or may fail or refuse to approve or may delay approval of our drug candidates, including nirogacestat and mirdametinib, (vi) our ability to obtain and maintain regulatory approval of any of our product candidates, (vii) our plans to research, discover and develop additional product candidates, (viii) our ability to enter into collaborations for the development of new product candidates, (ix) our ability to establish manufacturing capabilities, and our and our collaboration partners’ abilities to manufacture our product candidates and scale production, (x) our ability to meet any specific milestones set forth herein, and (xi) 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 18 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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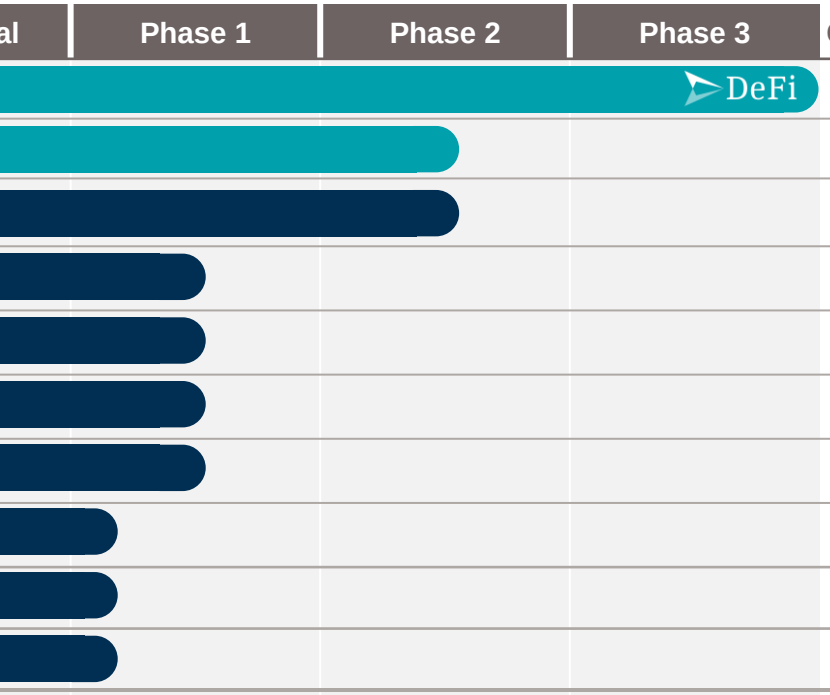
# Diversified Targeted Oncology Pipeline Spanning Solid Tumors and Hematological Cancers

| 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 |
| | | + REGN5458 (Bispecific) | REGENERON |
| **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

# Multiple Opportunities for Value Creation Across Three Distinct Oncology Segments

## 1 Rare Oncology

*Two registrational trials with best-in-class potential in areas of high unmet need*

- **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
- **Nirogacestat + REGN5458**
  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 | ✓ |
| Long-term data from NCI-Sponsored Phase 2 study in desmoid tumors | ASCO 2022 |
| Announce new monotherapy indication opportunity | R&D Day |
| Additional DeFi data at medical conference | 2H 2022 |
| Planned NDA filing in desmoid tumors | 2H 2022 |
| **Nirogacestat + BCMA therapies** | |
| Initial clinical data from combo trial with GSK (BLENREP) | ASCO 2022 |
| Additional combo trial initiations and data presentations | 2H 2022 |
| **Mirdametinib** | |
| Phase 1b/2 initial data readout in pediatric low-grade glioma (pLGG) | 2Q 2022 |
| **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** | |
| Preclinical data at AACR | ✓ |
| DC nomination | 2H 2022 |
| Potential for additional data readouts and updates from other programs<br>▪ ReNeu trial for mirdametinib in NF1 plexiform neurofibroma (NF1-PN)<br>▪ Preclinical EGFR inhibitor program | Full year |

# Nirogacestat

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

- Nirogacestat is an investigational 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]
- Achieved statistical significance on primary and all key secondary endpoints in Phase 3 DeFi trial in adult patients with progressing desmoid tumors
- Potential to become cornerstone of BCMA combination therapy in multiple myeloma with eight current collaborations representing all major modalities

| | |
|---|---|
| **Anticipated NDA Filing in Desmoid Tumors:** | **2H 2022** |
| **Clinical Trials Ongoing or On Track for 2022 Initiation:** | **11** |
| **BCMA Collaborations:** | **8** |
| **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; the disease can be multifocal with patients potentially having multiple lesions
- Desmoid tumors can lead to severe negative outcomes including lesion ulceration, organ dysfunction, amputation, long-lasting pain due to nerve compression or tumor pressure, disfigurement and in rare cases when vital organs are impacted, they can be life-threatening[1]
- Recurrence can be up to 70% post-surgery, making the approach much less favored in clinical practice today[1,2]; follow-on treatments include chemo, radiation and off-label TKIs

- 1,000-1,650 newly incident patients per year in US[3]
- 5,500-7,000 patients actively receiving treatment in the US in any given year[3]

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

Sources: (1) Penel et al., *European Journal of Cancer*, 2017; (2) Tsagozis et al., *Annals of Medicine & Surgery*, 2017; (3) Van Broekhoven et al., *Annals of Surgical Oncology,* 2015; Reitamo et al., *J Clin Path,* 1982; SpringWorks market research.

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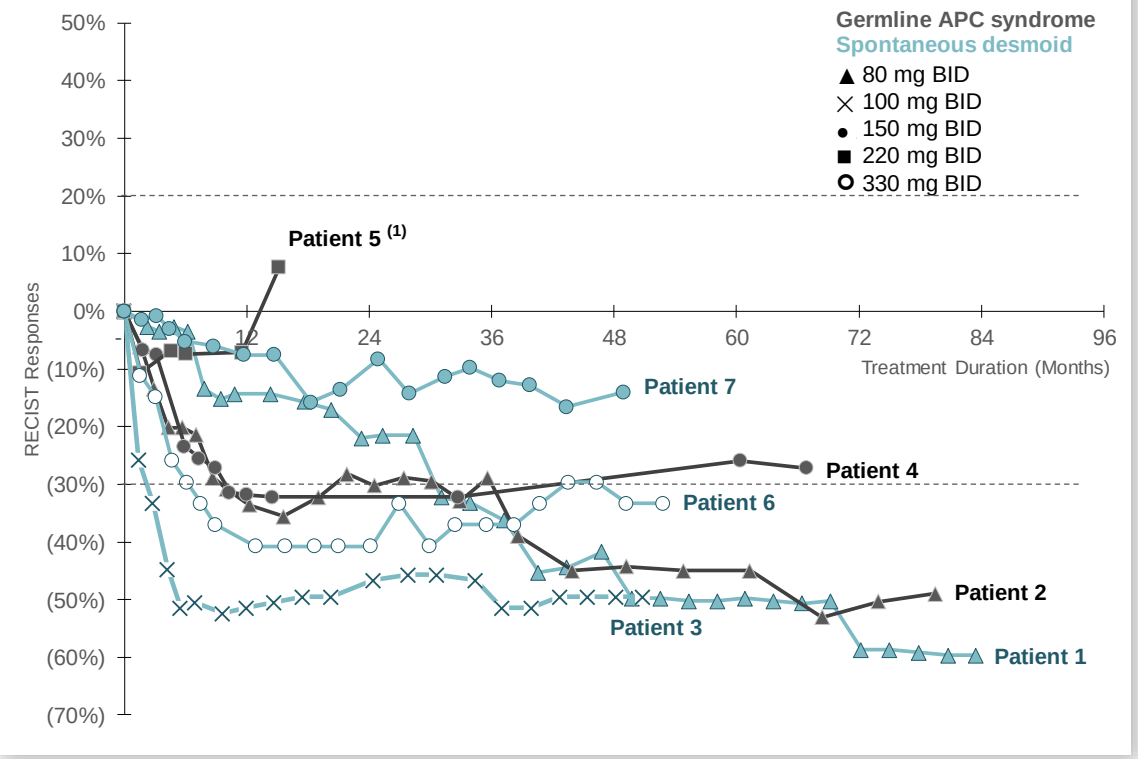
# Initial Clinical Activity of Nirogacestat Observed in Desmoid Tumors

PHASE 1 | PHASE 2 | PHASE 3

## Most Responses Continued Past 4 Years (RECIST v1.0)[1]




- **All evaluable desmoid tumor patients in the study responded to nirogacestat treatment [1,2,3]**
  - 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[1]**
  - Of the 7 evaluable desmoid patients on study, none discontinued due to AEs[4]

Note: Disease control rate is percentage of patients experiencing objective response or stable disease on therapy as measured by RECIST v1.0.
Sources: (1) Villalobos, *Annals of Surgical Oncology*, 2018; (2) Messersmith, *Clinical Cancer Research*, 2015.
Notes: (3) 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."; (4) 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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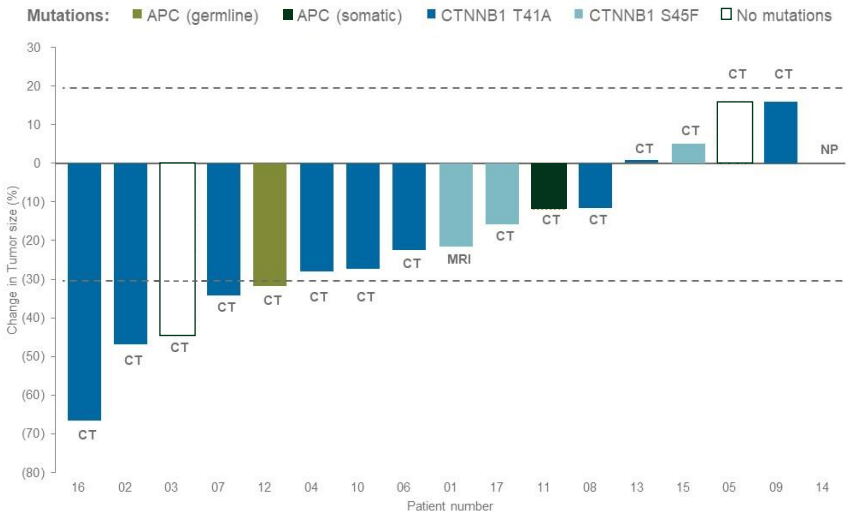
# Encouraging Phase 2 Data in Actively Progressing Patients Set the Stage for Phase 3 DeFi Trial

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.



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# Phase 3 DeFi Trial Design

PHASE 1 | PHASE 2 | PHASE 3

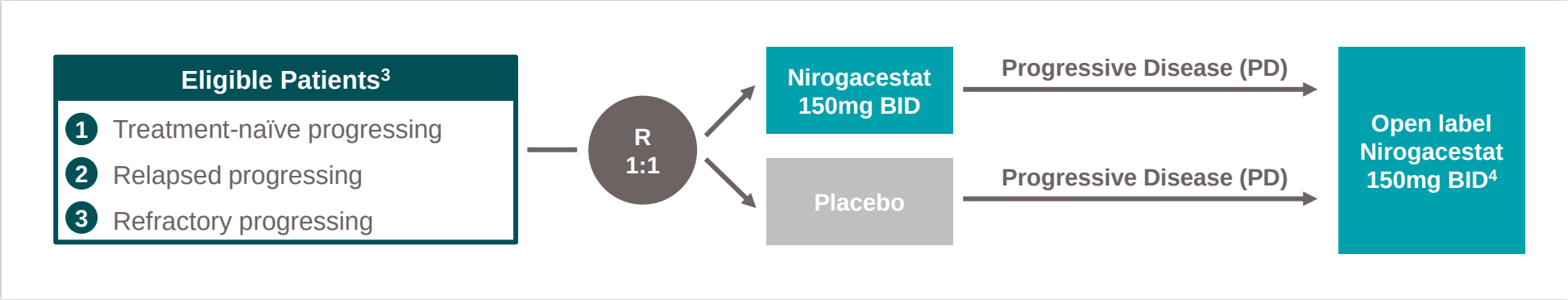
DeFi

## Trial Summary

- Global (North America and Europe), randomized (1:1), double-blind, placebo-controlled study
- 142 patients randomized with open label extension available upon radiographic disease progression
- 90% powered to show ~12-month median PFS difference between nirogacestat and placebo[1]

## Summary of Endpoints

- Primary Endpoint: Progression-free survival[2]
- Secondary and Exploratory Endpoints: Safety and tolerability, objective response rate (ORR), duration of response, volumetric tumor change assessed by MRI, patient-reported outcomes (PROs)




(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 determined by blinded independent central review.
(3) Progression defined ≥20% increase over past 12 months by RECIST v1.1.
(4) Once the end of double-blind phase notification had been issued and the primary PFS analysis had been completed, patients remaining on study that had not achieved a radiographic progression could enroll in the OLE.



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# Nirogacestat Achieved Primary and All Key Secondary Endpoints in Phase 3 DeFi Trial

| | Hazard Ratio (HR) | P-value |
|---|---|---|
| **Progression-Free Survival (PFS)** | 0.29 (95% CI: 0.15, 0.55) | < 0.001 |

- Results demonstrated a statistically significant improvement for nirogacestat over placebo, with a 71% reduction in risk of disease progression as assed by blinded independent central review (hazard ratio (HR) = 0.29; P < 0.001)
- Statistical significance was achieved on all key secondary endpoints, including objective response rate (ORR) and patient-reported outcomes (PROs)
- Nirogacestat was generally well tolerated with a manageable safety profile
  - The majority of women of child-bearing potential had adverse events consistent with ovarian dysfunction
  - Other adverse events were generally consistent with previously reported data
- Additional data are expected to be presented at an upcoming medical conference in 2H 2022

**NDA filing for nirogacestat in desmoid tumors under the FDA's Real-Time Oncology Review (RTOR) program expected 2H 2022**



Note: Topline data from Phase 3 DeFi trial were announced 05/24/22.

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

**EXPANDED ACCESS PROGRAM**

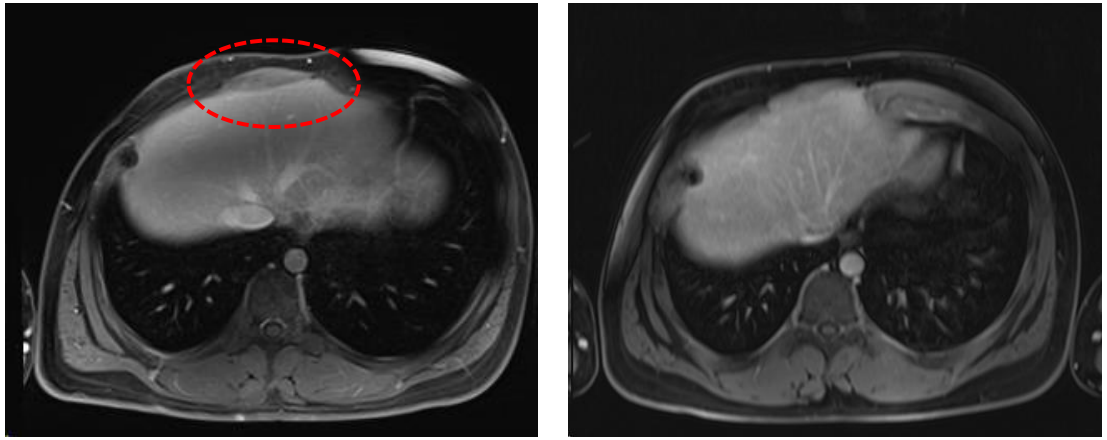
- Clinical benefit shown in four pediatric and young adult desmoid tumor patients who received nirogacestat (1 CR, 2 PR, and 1 SD)

| | 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<br>▪ 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.

# 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[1]**

**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[3,4]
   - 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[2,4]
   - 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



Sources: (1) Van Broekhoven et al., *Annals of Surgical Oncology*, 2015; Reitamo et al., *J Clin Path*, 1982; SpringWorks market research; (2) Anneberg et al., *Cancer Epidemiology*, 2022; (3) Penel et al., *European Journal of Cancer*, 2017; (4) White et al., DTRF 2021; SpringWorks market research.

# 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[1]
- ~15,000 relapsed/refractory multiple myeloma patients receiving 3L+ therapy annually in the US[1]

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

Source: (1) Siegel et al., 2022; DRG market research.



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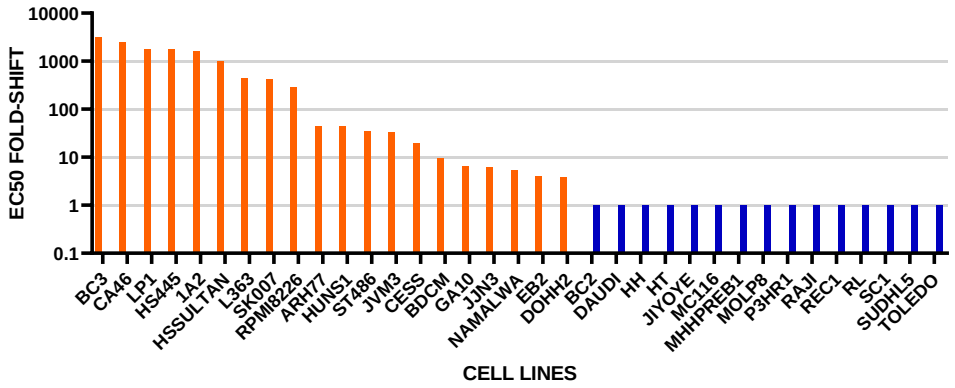
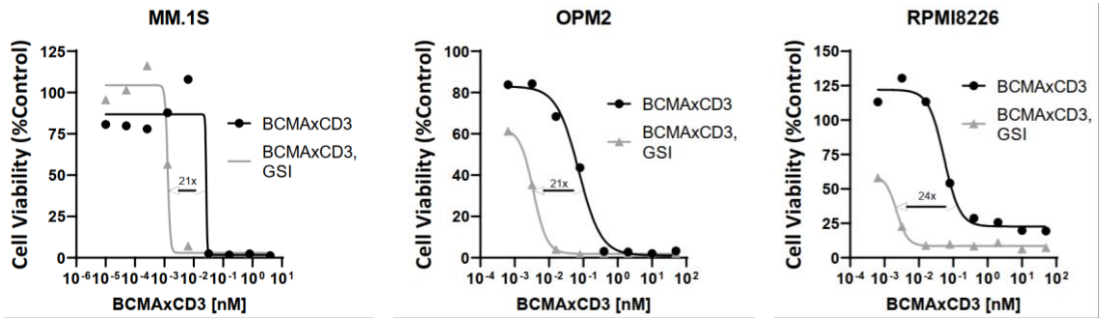
# Gamma Secretase Inhibition Has Been Shown to Prevent BCMA Shedding and Increases Cell-Surface BCMA Levels, Thereby Potentiating the Activity of BCMA-Directed Therapies

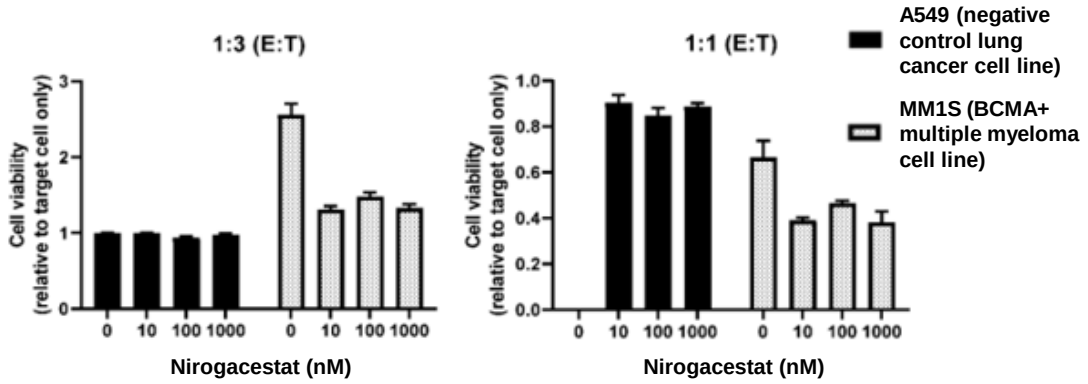
## BCMA ADC[1]



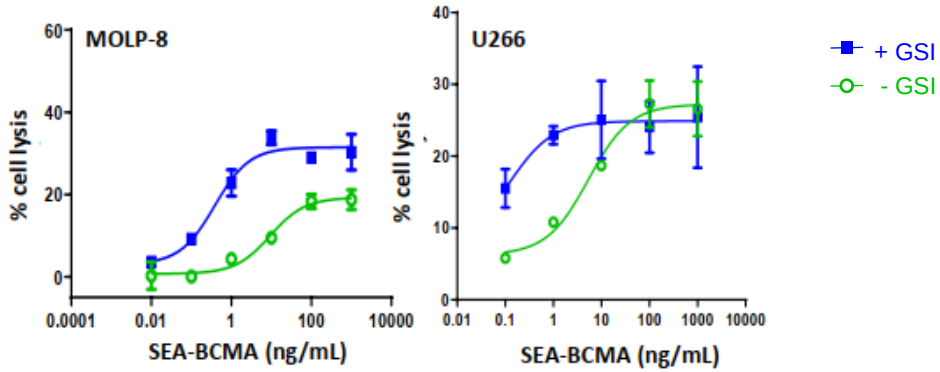

## BCMA-CD3 Bispecific[2]




## BCMA CAR-T[3]




## BCMA mAb[4]




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



Sources: (1) Eastman et al., ASH 2019; (2) Karwacz et al., AACR 2020; (3) 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; (4) Yu et al., EHA 2021.

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# Eight Clinical Collaborations Ongoing Covering All Key BCMA Therapeutic Modalities

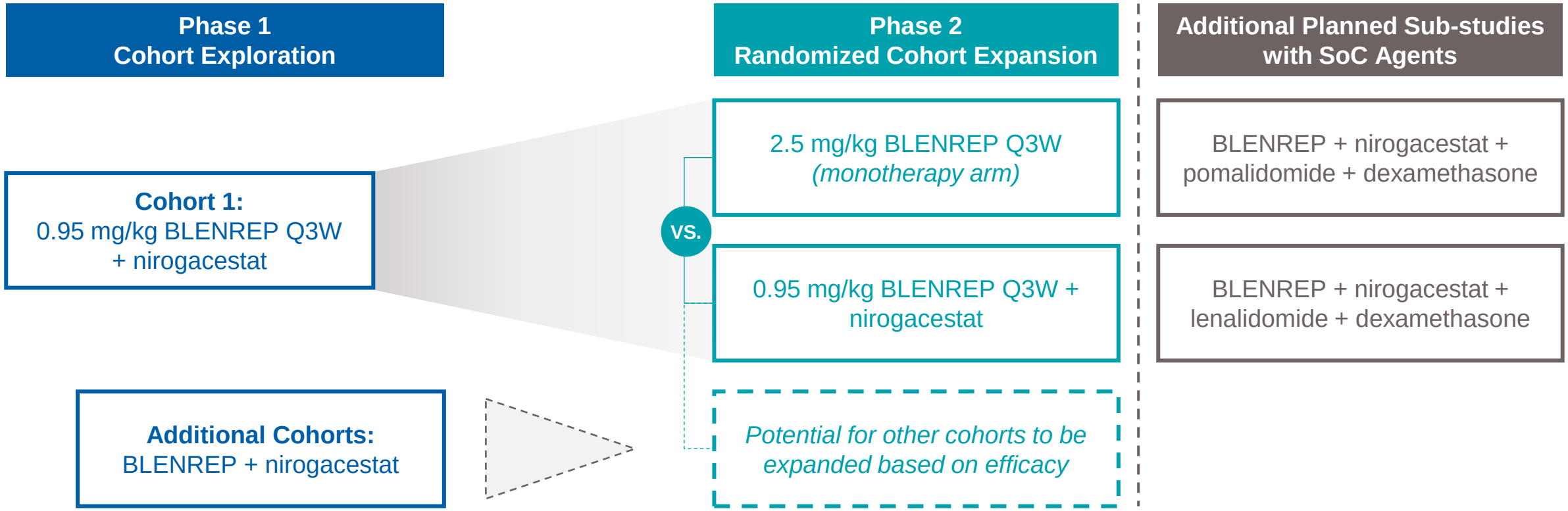
| Collaborator | Program | Modality | | | | Collaboration Signed | Current Status |
|---|---|---|---|---|---|---|---|
| | | ADC | Bispecific | CAR-T | mAb | | |
| gsk | BLENREP (belantamab mafodotin) | ✓ | | | | June 2019 | Advanced into randomized Phase 2 trial |
| Allogene Therapeutics | ALLO-715 | | | ✓ | | January 2020 | Phase 1 trial ongoing |
| Janssen | 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 planned |
| abbvie | ABBV-383 | | ✓ | | | December 2021 | Phase 1b trial initiation expected 1H22 |
| REGENERON | REGN5458 | | ✓ | | | April 2022 | Phase 1b trial planned |

**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*



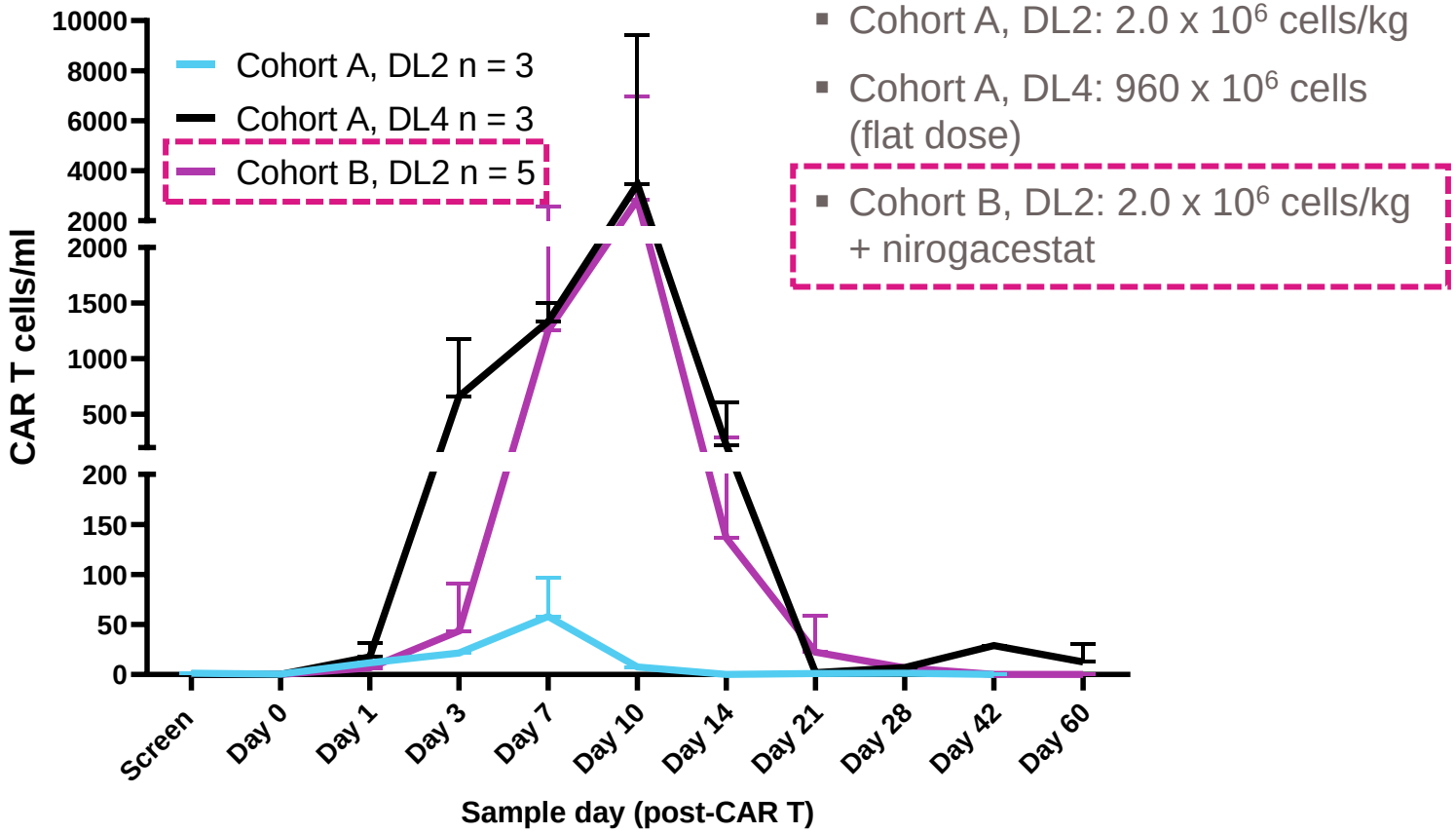

**Based on encouraging preliminary data observed, first dose level advanced to randomized Ph2 expansion cohort vs. BLENREP monotherapy and additional sub-studies planned with SoC agents to potentially enable studies in earlier lines of MM**



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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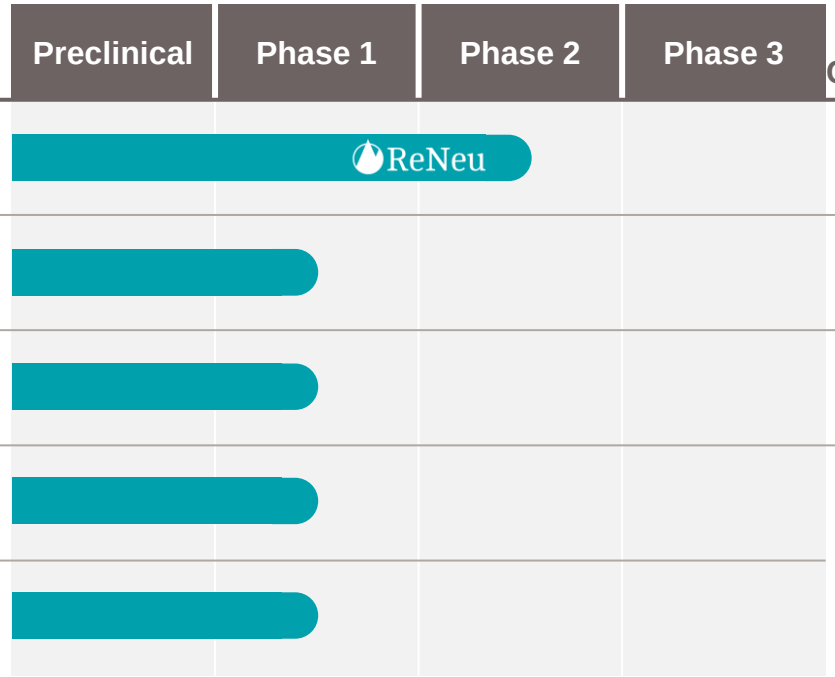
# Mirdametinib: Potent and Selective MEK Inhibitor With Differentiated Safety Profile

- Mirdametinib is an investigational, 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 | Collaborator(s) | Potential Annual Patient Population[1] | Biomarker(s) |
|---|---|---|---|---|
| NF1-PN | Monotherapy | | ~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.



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**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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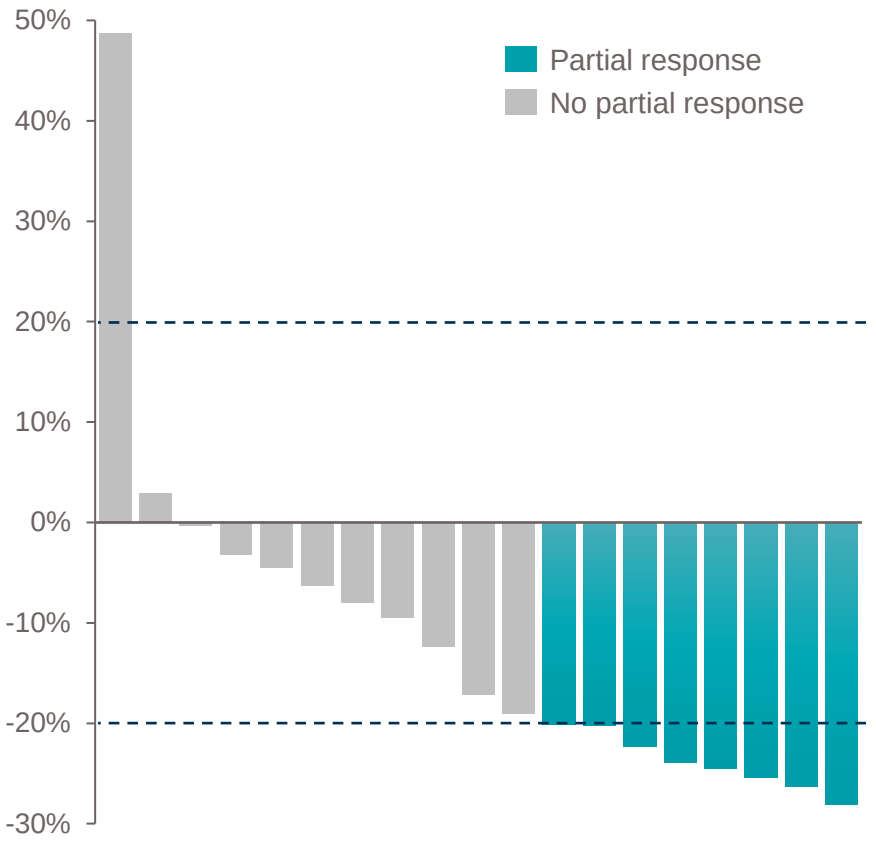
# ReNeu Trial Builds Upon Encouraging Phase 2 Results, Which Demonstrated Initial Clinical Activity, QoL Improvement for NF1-PN Patients and a Differentiated Safety Profile vs. Other MEK Inhibitors

PHASE 2 | PHASE 2B

## Maximum Tumor Volume Change from Baseline




## Trial Design and Clinical Activity

- 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.

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

ReNeu

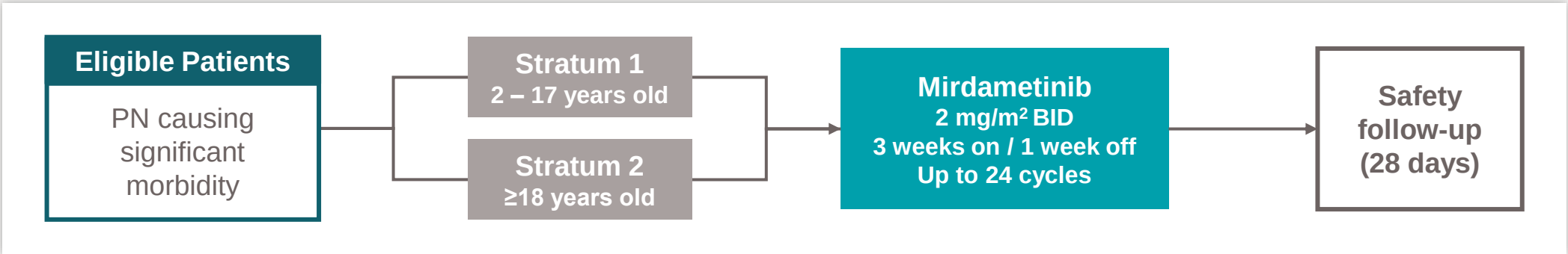
PHASE 2 | PHASE 2B

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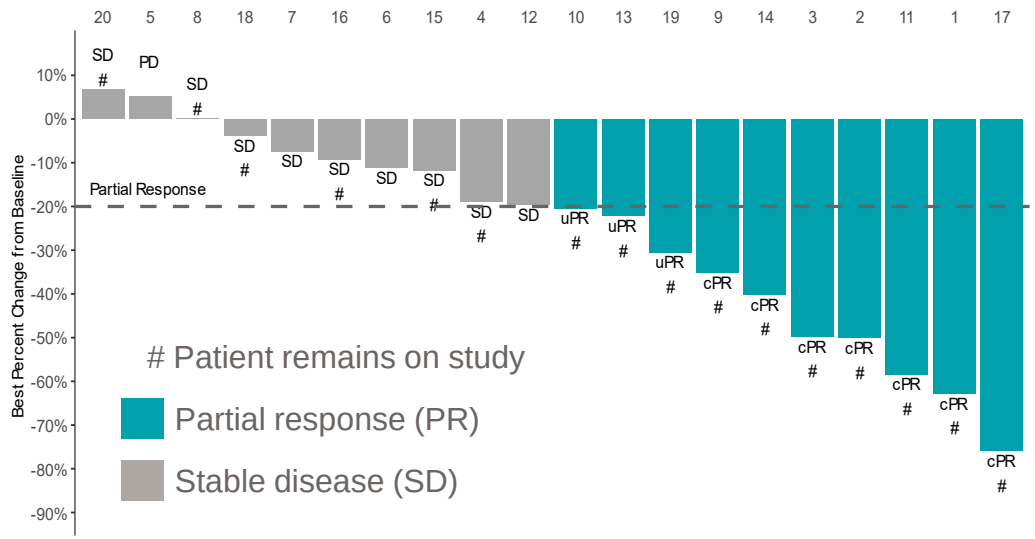
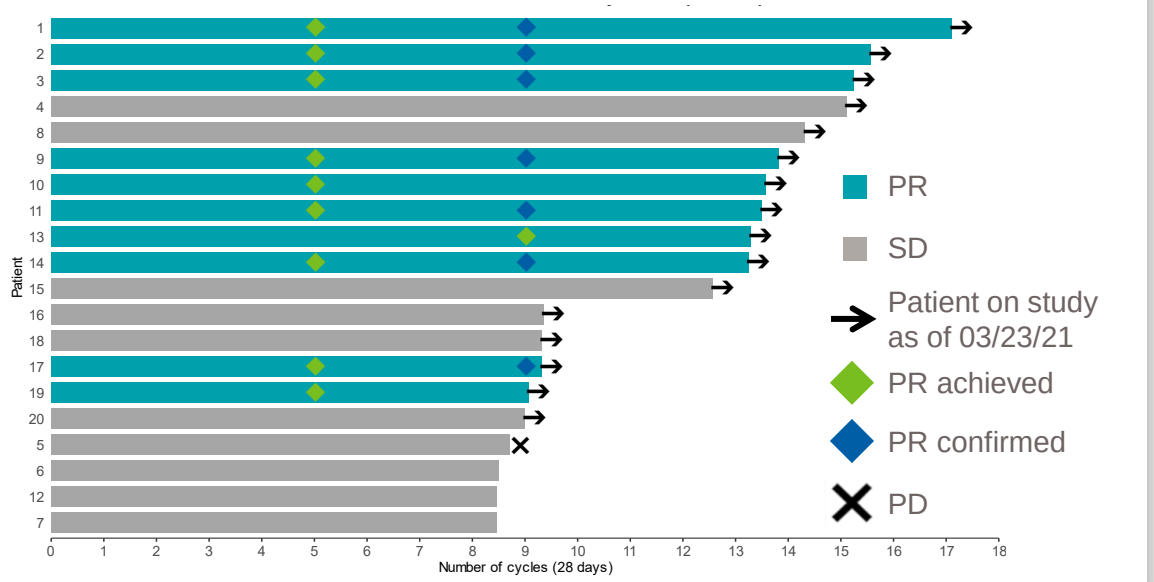
# Interim Data Update From ReNeu Trial Adult Stratum Presented at CTF in June 2021

PHASE 2 | 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

PHASE 2 | 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.

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

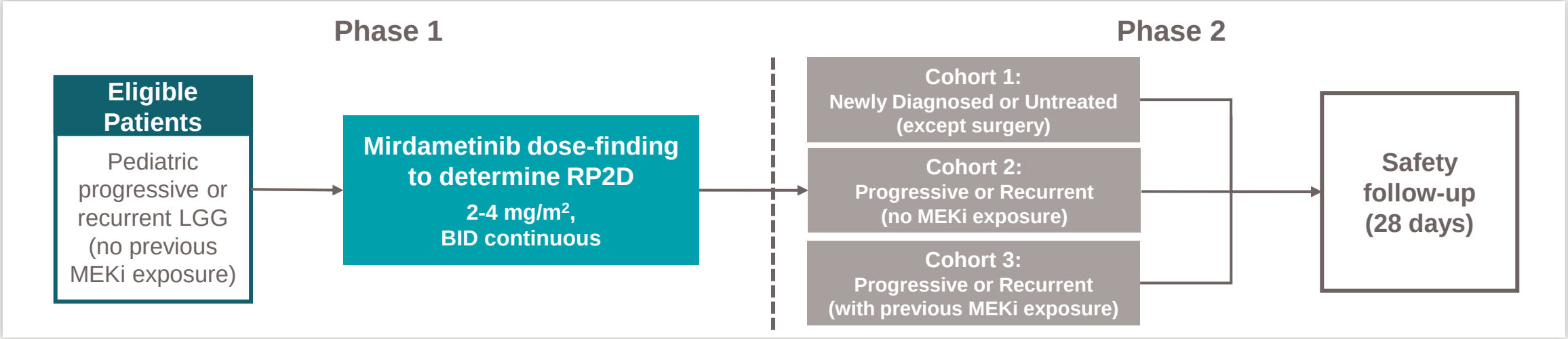
PHASE 1 | PHASE 2

## 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 with initial data in 2Q 2022**



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# Biomarker-Defined Metastatic Solid Tumors

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# 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**



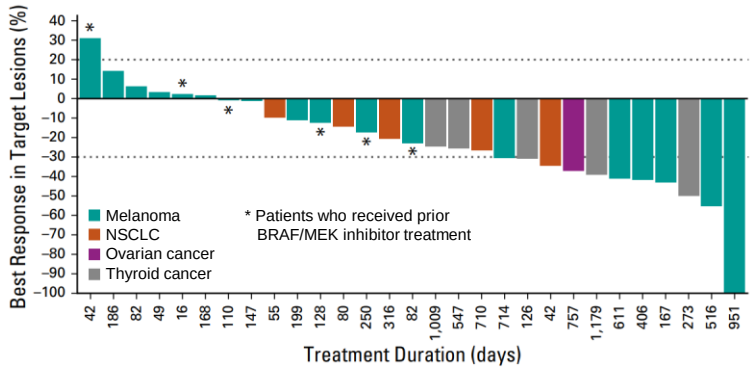
(1) Being developed by MapKure, LLC, jointly owned by SpringWorks and BeiGene.

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

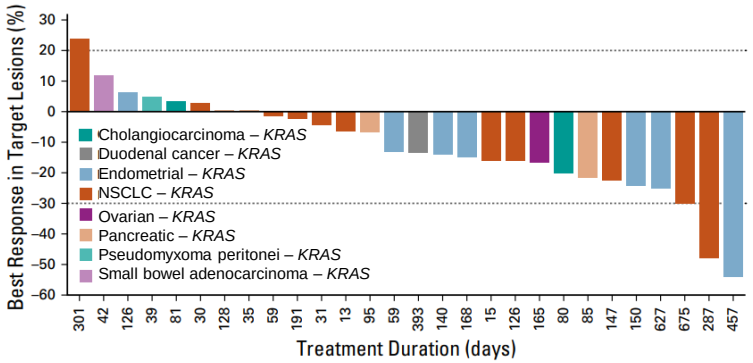
**1** Lifirafenib monotherapy clinical activity in *BRAF* and *KRAS* mutant cancers[1]

**2** Preclinical synergy demonstrated with mirdametinib and lifirafenib *in vitro* across *RAS* mutations and *in vivo*[2,3] at clinically relevant doses

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

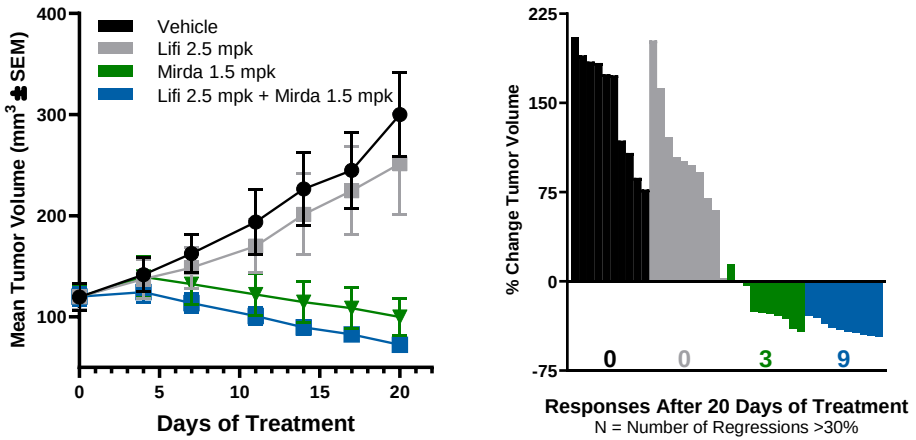



## KRAS$^{mut}$ Cancers (ex-CRC): P1a/b Best Objective Response




| 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**



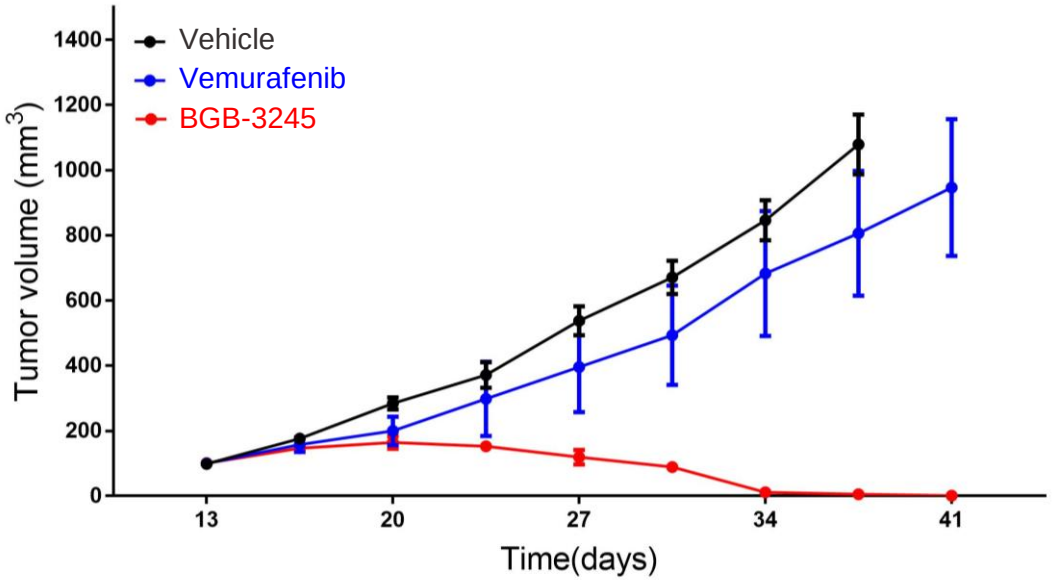
Sources: (1) Desai et al., *J Clin Oncol,* 2020; (2) Yuan et al., *Molecular Oncology*, 2020; (3) Yuan et al., Abstract #6415, AACR 2020 Virtual Annual Meeting II.

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

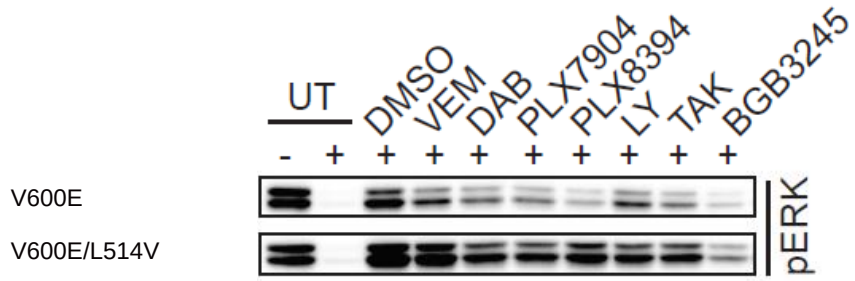
***BRAF* Fusion PDX: *In Vivo* Tumor Growth Inhibition[1]**




- Driver mutations and fusions potentially uniquely targetable by BGB-3245 could account for up to ~5% of all solid tumors[2,3]
- 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[4]**




- *BRAF* V600E/L514V is a dabrafenib resistance mutation[4]
- 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**



Sources: (1) Rosen presentation, Sixth International RASopathies Symposium: Precision Medicine – From Promise to Practice, 2019; (2) Dankner et al., *Oncogene*, 2018; (3) Ross et al., *IJC*, 2016; (4) Wang et al., *Cancer Discovery*, 2018.

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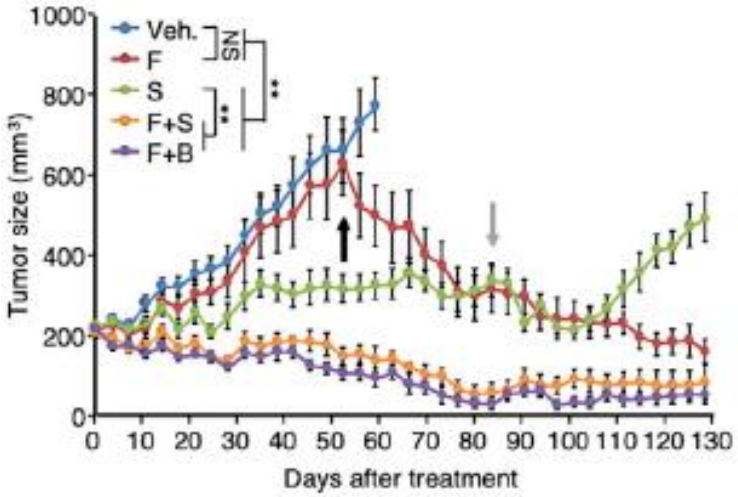
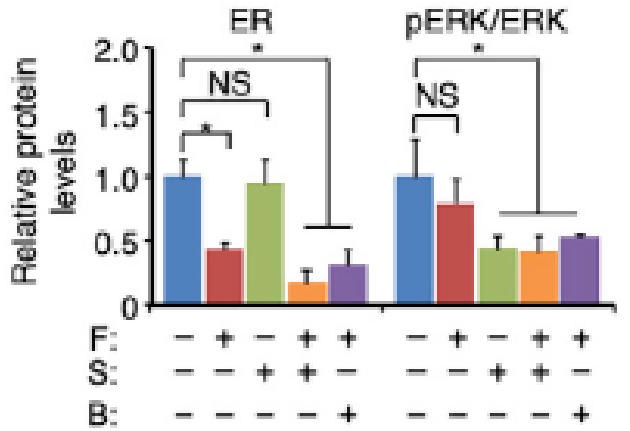
# Mirdametinib: MEK Inhibitors Can Potentially Address Endocrine Therapy Resistance Due to MAPK Mutations in ER+ Breast Cancer

- MAPK mutations in ER+ mBC cells can lead to fulvestrant resistance, which can be reversed with MEK inhibition[2]
- ~25% of ER+ mBC patients progress on endocrine therapy
- *NF1* deficiency has been shown to enhance ER transcriptional activity leading to hormone resistance[1]
  - Up to 15% of mBC harbor MAPK pathway mutations, including *NF1* LoF

## *NF1*-Deficient ER+ BC PDX: Durable Tumor Growth Inhibition with MEKi + Fulvestrant[2]




## MEKi + Fulvestrant Modulates ER and MAPK Signaling[2]




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

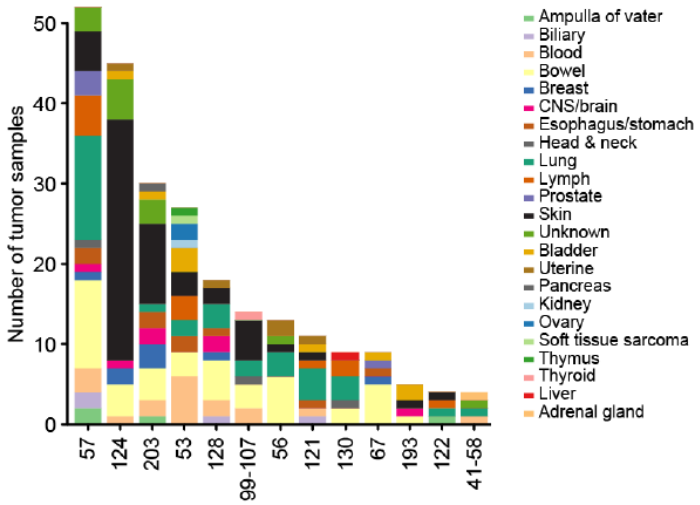


Note: B: buparlisib (PI3K inhibitor); F: fulvestrant; mBC: metastatic breast cancer; S: selumetinib (MEK inhibitor); SoC: standard of care; V: vehicle.
Sources: (1) Sokol et al., 2019; (2) Zheng et al., 2020.

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

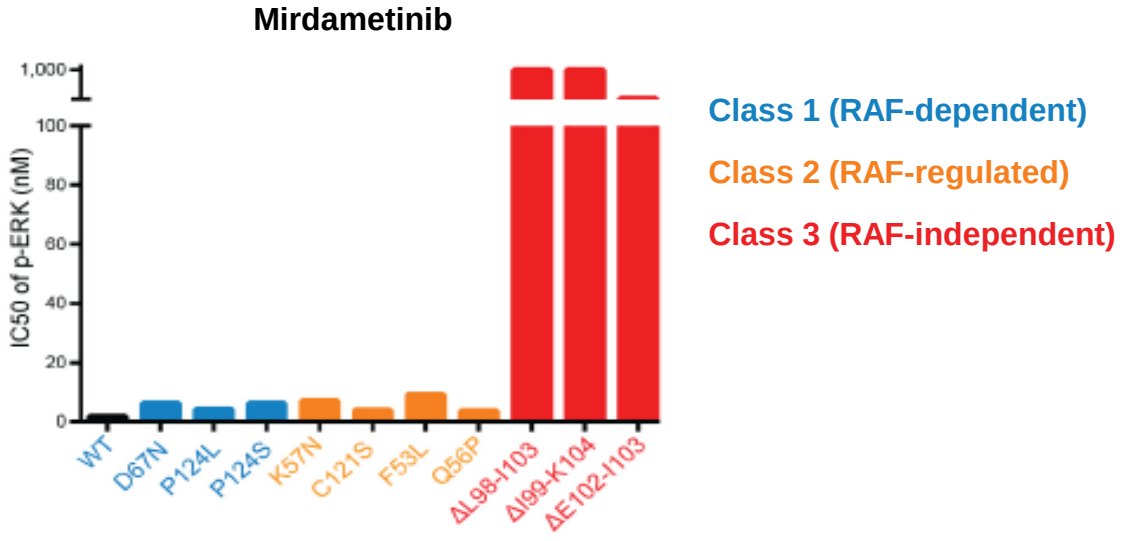
- Mirdametinib shows potent preclinical activity against Class 1 and Class 2 mutations in *MEK1* and *MEK2*[1]
- *MEK1* and *MEK2* have been validated as oncogenic targets with mutations present in ~2% of solid tumors[2]
- Clinical case reports with allosteric MEK inhibitors also support utility of mirdametinib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

## MEK 1/2 Mutants Occur Across Tumor Types[2]




**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*[1]




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

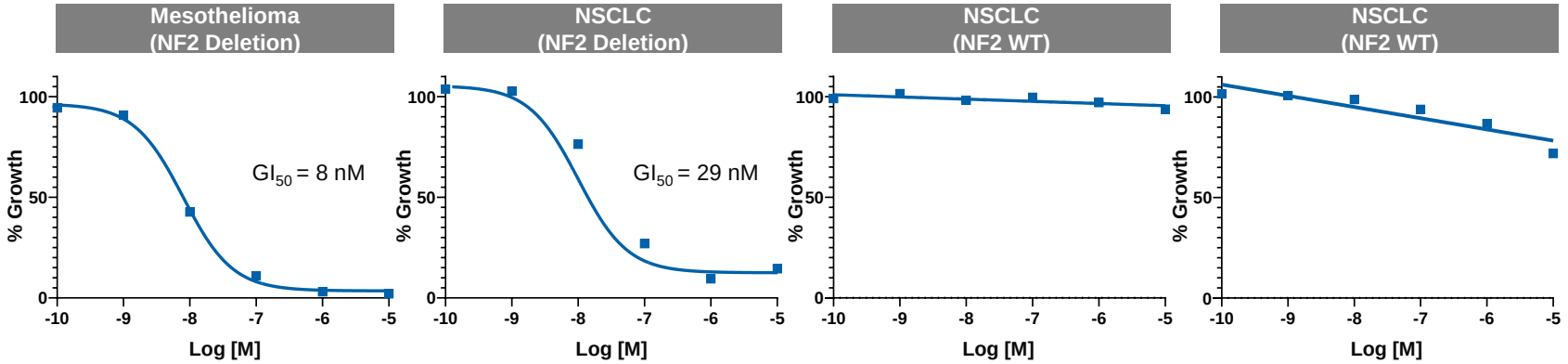


Sources: (1) Gao et al., 2018; (2) Hanrahan et al., 2020.

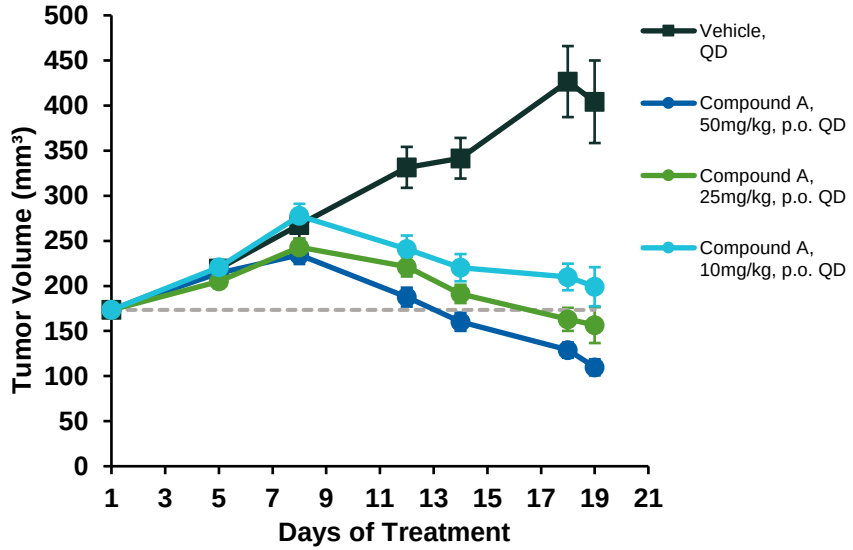
SpringWorks THERAPEUTICS

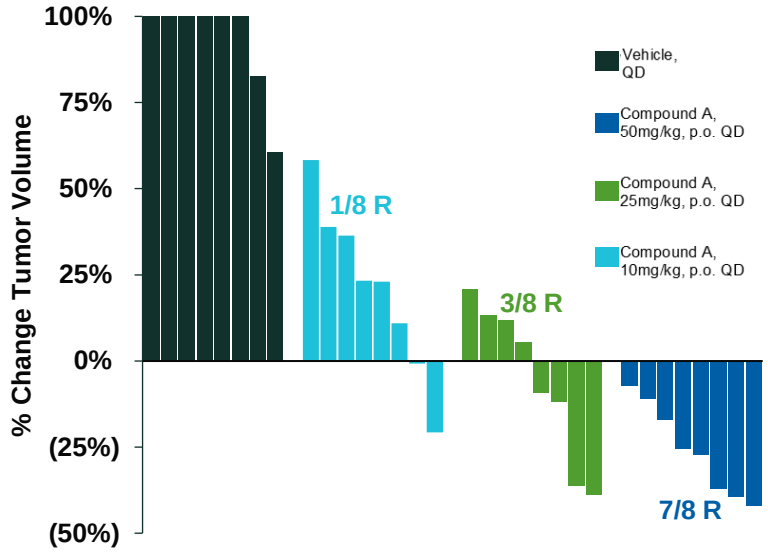
# TEAD Inhibitor: Program in Lead Optimization With Selectivity, Potency and In Vivo Tumor Growth Inhibition Demonstrated in Hippo-Driven Models

**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.

# EGFR Inhibitor Portfolio: Developing Several Novel Targeting Approaches to Address De Novo Oncogenic Drivers and Resistance Mechanisms

**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

# Well-Capitalized to Execute on Important Value-Driving Milestones

**$380.7M**

**Cash, Cash Equivalents & Marketable Securities[1]**

**No Debt**

**NASDAQ: SWTX**

**49.4M**

**Common Shares Outstanding[2]**

(1) As of March 31, 2022.
(2) Basic common shares outstanding as of April 29, 2022.



SpringWorks THERAPEUTICS

# 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 potential for nirogacestat to become the 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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