# Corporate Presentation

March 2023

SpringWorks® THERAPEUTICS

# Forward-Looking Statements

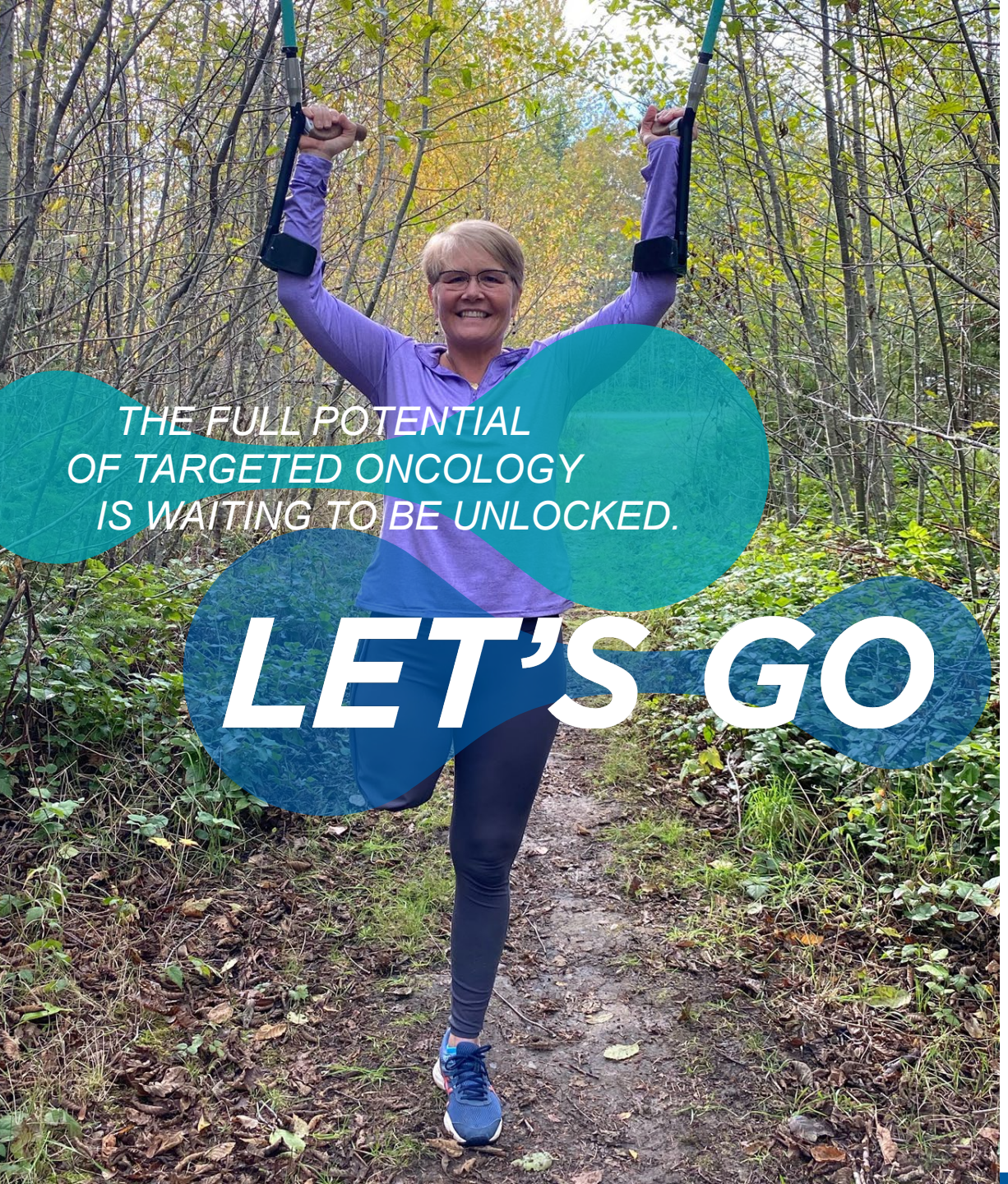
Note: Unless otherwise indicated, the information presented herein is as of March 2023 and made publicly available on March 2, 2023.

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, the potential for nirogacestat to become an important new treatment for adult patients with desmoid tumors, the potential for Marketing Authorization Application for nirogacestat, expectations regarding the timing and results of the FDA’s review of the NDA for nirogacestat, including the FDA's PDUFA target action date for the NDA, and the adequacy of the data contained in the NDA to serve as the basis for an approval of nirogacestat for the treatment of adults with desmoid tumors, the potential for the results of the Phase 2b ReNeu clinical trial to support an NDA submission for mirdametinib, the potential for mirdametinib to become an important new treatment for patients with NF1-PN, our plans for seeking regulatory approval for and making mirdametinib available for NF1-PN patients, if approved, our plans to report data from the Phase 1b/2 trial evaluating mirdametinib with lifirafenib at an upcoming medical conference, our plans to report additional data from the Phase 1 study evaluating BGB-3245 at an upcoming medical conference, our plans to report additional preclinical data of SW-682 at an upcoming medical conference, our plans to file an Investigational New Drug Application for SW-682 in 2023, our plans to report additional clinical data of nirogacestat in combination with BCMA-directed therapies and initiate additional planned Phase 1 collaborator studies, fexpectations about whether our patents for our lead assets will adequately protect SpringWorks against competition, 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 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 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 and our ability to realize the benefits expected from such collaborations, (ix) our ability to maintain adequate patent protection and successfully enforce patent claims against third parties, (x) the adequacy of our cash position to fund our operations through any time period indicated herein, (xi) our ability to establish manufacturing capabilities, and our and our collaboration partners’ abilities to manufacture our product candidates and scale production, (xii) our ability to meet any specific milestones set forth herein, and (xiii) uncertainties and assumptions regarding the impact of the COVID-19 pandemic on SpringWorks’ business, operations, clinical trials, supply chain, strategy, goals and anticipated timelines.

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

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

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




# SpringWorks Therapeutics Is Transitioning into a Commercial-Stage Targeted Oncology Company in 2023

- **Multiple late-stage programs** with the opportunity for two approvals by 2025, starting with nirogacestat for desmoid tumors this year
- **Diversified pipeline** of preclinical and clinical programs focused on solid tumors and hematological malignancies
- **Durable IP portfolio** with U.S. patent protection extending beyond 2040
- **Experienced leadership team** with end-to-end expertise spanning drug development and commercialization
- **Robust balance sheet** with ~$600M in cash and disciplined capital allocation approach(1)

(1) Cash balance as of December 31, 2022.

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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 |
| | Ovarian Granulosa Cell Tumors | Monotherapy | |
| | Multiple Myeloma *(BCMA Combinations)* | + *Blenrep* - belantamab mafodotin (belamaf) (ADC) | GSK |
| | | + Teclistamab (Bispecific) | Janssen |
| | | + Elranatamab (Bispecific) | Pfizer |
| | | + SEA-BCMA (mAb) | Seagen |
| | | + ABBV-383 (Bispecific) | abbvie |
| | | + Linvoseltamab (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 | |
| **BGB-3245** RAF Fusion & Dimer Inhibitor | MAPK Mutant Solid Tumors | Monotherapy | Mapkure(1) |
| | MAPK Mutant Solid Tumors | + Mirdametinib | |
| **SW-682** TEAD Inhibitor | Hippo Mutant Tumors | Monotherapy and combo | |
| **EGFR Program** | EGFR Mutant Tumors | Monotherapy and combo | |

Preclinical | Phase 1 | Phase 2 | Phase 3 | Regulatory Submission



* 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

# Robust Cadence of Milestones Expected in 2023

| Late-Stage Rare Oncology Portfolio | |
|---|---|
| **Nirogacestat**<br>*(Gamma Secretase Inhibitor)* | ✓ NDA submission in desmoid tumors accepted by FDA in 1Q23 with Priority Review (PDUFA date: August 27, 2023)<br>❑ Secure FDA approval and launch first FDA-approved therapy for desmoid tumor patients<br>❑ Publish Phase 3 DeFi trial data in a peer-reviewed journal and present additional analyses at upcoming medical meetings<br>❑ Continue enrollment of Phase 2 trial in ovarian granulosa cell tumor patients |
| **Mirdametinib**<br>*(MEK Inhibitor)* | ❑ Present topline data from the pediatric and adult cohorts in the Phase 2b ReNeu trial |
| **Emerging Portfolio** | |
| **Nirogacestat + BCMA Therapies** | ❑ Expand emerging data set with additional clinical data in combination with BCMA-directed therapies<br>❑ Support initiation of additional planned collaboration studies |
| **MAPK Portfolio** | ✓ Dose first patient in BGB-3245 + mirdametinib combination study in MAPK-mutant solid tumors (1Q23)<br>❑ Report additional clinical data from BeiGene collaboration programs |
| **Preclinical Programs** | ❑ Present additional preclinical data and file IND for SW-682 |

# Late-Stage Portfolio

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# Nirogacestat

Desmoid Tumors

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

- Nirogacestat is an investigational novel oral, small-molecule, selective gamma secretase inhibitor
- NDA for nirogacestat in desmoid tumors accepted by the FDA with Priority Review and being evaluated under the FDA's RTOR program
- Fast Track and Breakthrough Therapy Designations received from FDA and Orphan Drug Designation granted from both FDA and European Commission(1)
- Phase 3 DeFi trial in adult patients with progressing desmoid tumors achieved statistical significance on primary and all key secondary endpoints
- Unlocking additional monotherapy expansion opportunities, including development in ovarian granulosa cell tumors
- Potential to become cornerstone of BCMA combination therapy in multiple myeloma with several current collaborations representing major modalities

| | |
|---|---|
| **Nirogacestat in Desmoid Tumors NDA PDUFA Date:** | **Aug 27, 2023** |
| **Indications Under Development:** | **3** |
| **U.S. Patent Protection:** | **2042** |



(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.

# Desmoid Tumors Are Highly Morbid Soft Tissue Tumors with No Approved Therapies, Resulting in a High Unmet Need

## Disease Overview and Unmet Need

- Desmoid tumors (DT) can arise throughout the body and lead to significant, life-altering morbidities
  - Disease can be multifocal and patients oftentimes present with substantial pain, significant physical limitations, and diminished quality-of-life
- Severe negative outcomes from DT can include lesion ulceration, organ dysfunction, amputation, long-lasting pain, disfigurement; DTs are potentially life-threatening in the event vital organs are impacted[1]
- Clinical need is not met by available treatment options
  - No currently approved therapies; off-label systemic treatments include chemotherapy, radiation and TKIs, which are often poorly tolerated with inconsistent efficacy
  - Tumor recurrence can be up to 77% following surgery[2,3]

*"…the **pain it causes has changed my life**. It pushes on my ureters and kidneys and had wrapped itself around some of my muscles. The **shooting pains sometimes leave me unable to physically move at times, much less take care of my young children**."*

**– Amy, desmoid tumor patient**

*"My desmoid tumor wrapped around my nerves, veins and artery behind me knee. I've had **ten surgeries total, six to remove the tumor and four related to complications,** and **it keeps growing back**."*

**– DeAnn, desmoid tumor patient**

Sources: (1) Penel et al., European Journal of Cancer, 2017; (2) Tsagozis et al., Annals of Medicine & Surgery, 2017; (3) Easter et al., Annals of Surgical Oncology, 1989.

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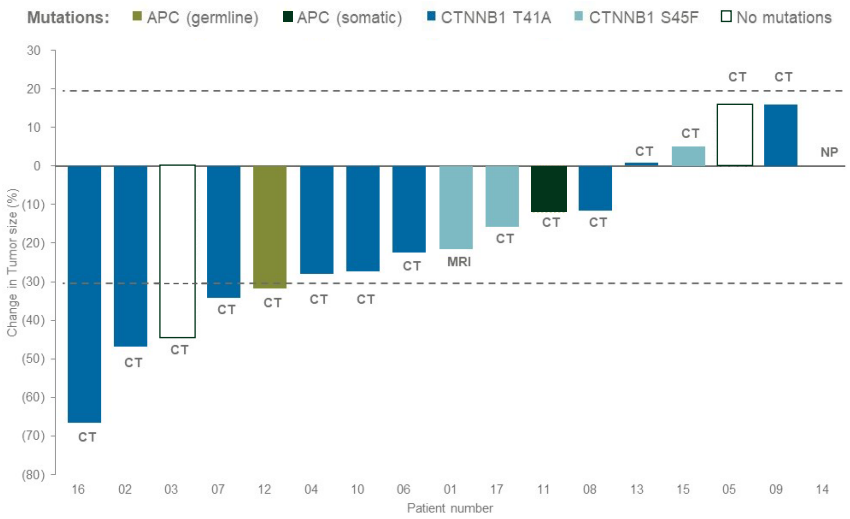
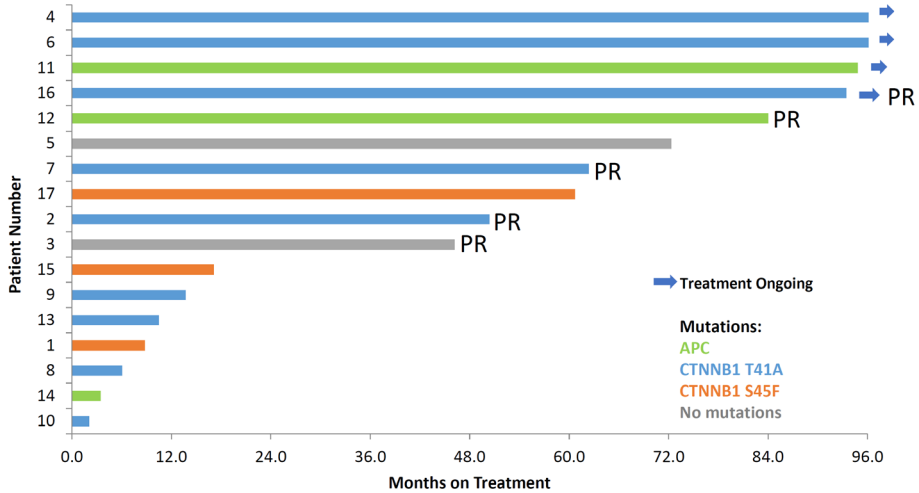
# Encouraging Phase 2 Data in Progressing Desmoid Tumors Were Published in 2017; Long-Term Safety and Efficacy Follow-Up Data from Phase 2 Trial Presented at ASCO 2022

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

## Clinical Responses by RECIST v1.1




## Long-Term Progression Free Survival




- **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

- **Among 17 treated patients, median time on treatment 4.4 years (range: 0.17 – 7.99 years)**
  - 4 patients remain on study after >7 years; no PD maintained with follow-up
  - Nirogacestat was generally well tolerated
    - > Most commonly (>50%) reported treatment-related AEs included diarrhea, fatigue, nausea, AST increase, lymphocyte decrease, hypophosphatemia, and rash (maculopapular)



Source: Kummar et al., 2017. O'Sullivan; Coyne et al., ASCO, 2022.

(1) 71% had received chemotherapy, 65% NSAIDs, and 59% TKIs; 4/5 partial responses had previously failed imatinib or sorafenib.

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

**EXPANDED ACCESS PROGRAM**

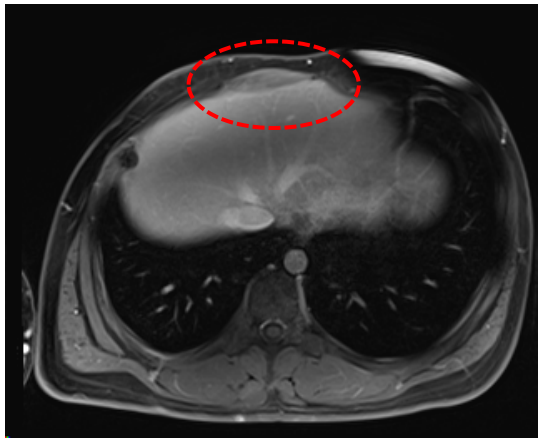
- Clinical benefit shown in four pediatric and young adult desmoid tumor patients who received nirogacestat (1 CR, 2 PR, and 1 SD)

| | 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 |

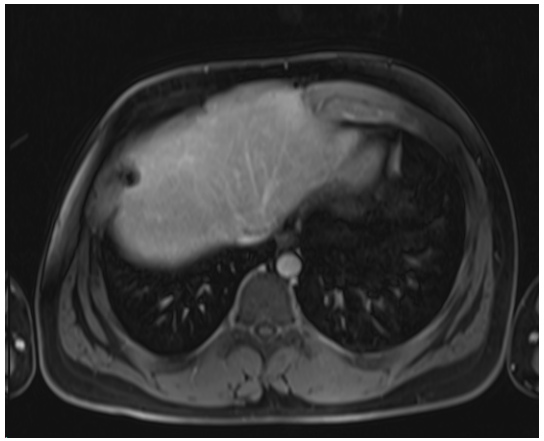
- Nirogacestat was well tolerated; no grade 3 or 4 AEs
  - 90 mg/m$^2$ per dose BID (max. 150 mg per dose BID)

## 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**

**Single-arm Phase 2 trial in collaboration with Children's Oncology Group met its accrual goal in 4Q22**



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

# Phase 3 DeFi Trial Was Designed to Robustly Demonstrate Clinical Benefit of Nirogacestat

DeFi

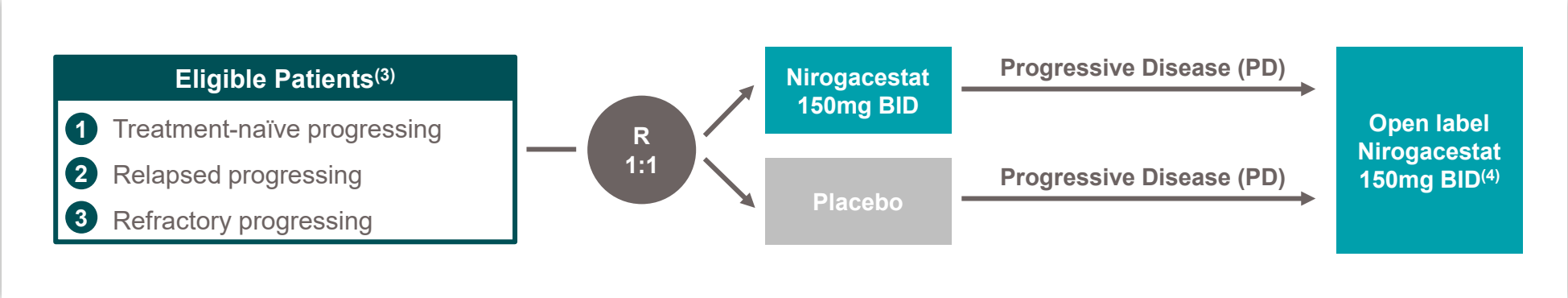
PHASE 1 | PHASE 2 | **PHASE 3**

## 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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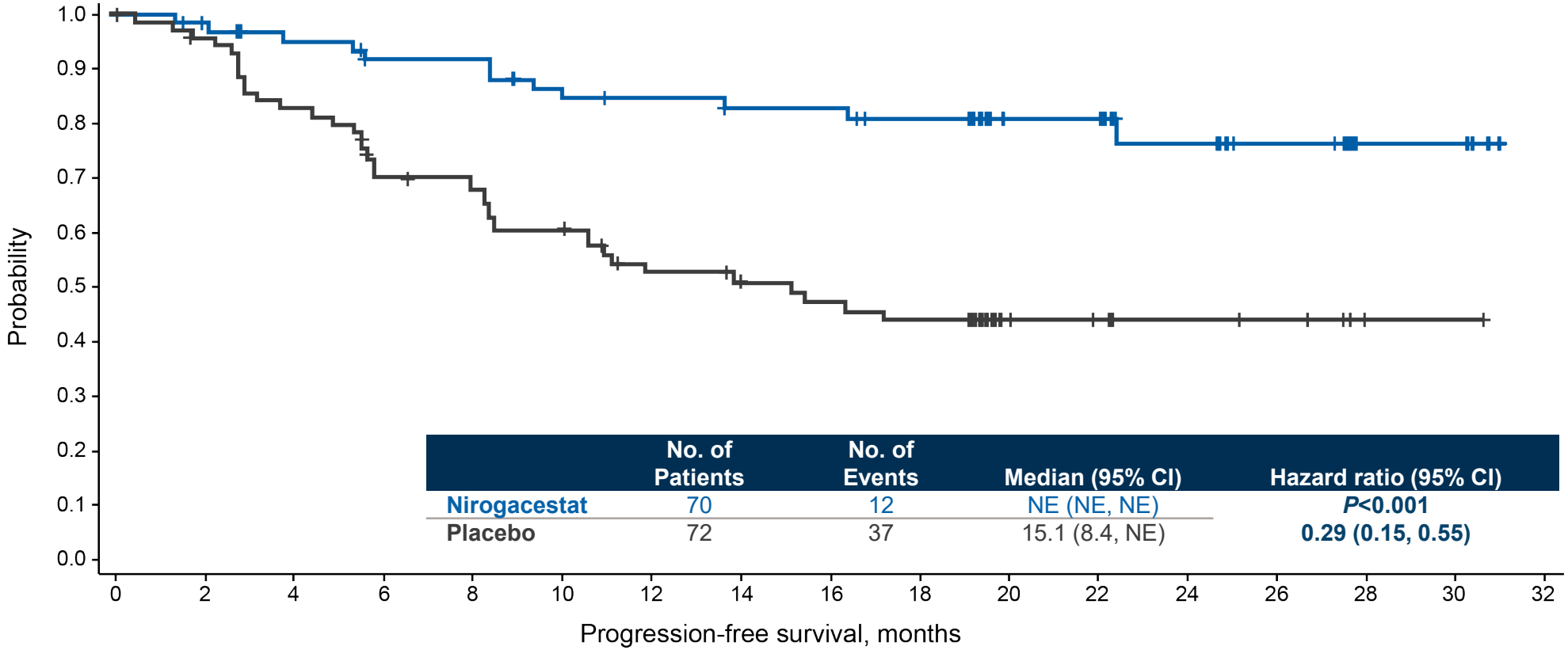
# Baseline Demographics and Characteristics

| Demographics/Characteristics, ITT Population | Nirogacestat (n=70) | Placebo (n=72) |
|---|---|---|
| Age, median (range), y | 33.5 (18, 73) | 34.5 (18, 76) |
| Sex, n (%) | | |
| Male | 25 (36) | 25 (35) |
| Female | 45 (64) | 47 (65) |
| Somatic mutations in analyzed patients, n (%)[a] | | |
| *APC* | 11 (22) | 11 (21) |
| *CTNNB1* | 43 (84) | 42 (79) |
| Tumor location, n (%) | | |
| Intra-abdominal | 17 (24) | 18 (25) |
| Extra-abdominal | 53 (76) | 54 (75) |
| Focal category, n (%) | | |
| Single | 43 (61) | 41 (57) |
| Multifocal | 27 (39) | 31 (43) |
| Desmoid tumor treatment status, n (%) | | |
| Treatment naïve | 18 (26) | 14 (19) |
| Refractory/Recurrent | 52 (74) | 58 (81) |
| Number of lines of any prior therapy, median (range) | 2 (0, 14) | 2 (0, 19) |
| Prior therapies, n (%) | | |
| Prior systemic therapy | 43 (61) | 44 (61) |
| Prior radiation therapy | 16 (23) | 16 (22) |
| Prior surgery | 31 (44) | 44 (61) |
| Patients with uncontrolled pain per BPI-SF API >4, n (%)[b] | 27 (39) | 31 (43) |

Source: Kasper et al., *ESMO,* 2022. Data as of the time of primary analysis (04/07/22).
a) Evaluable samples not available for all patients. Samples were analyzed for 51 and 53 patients in the nirogacestat and placebo arms, respectively.
b) Defined as a score of >4 calculated as the average of the daily BPI–SF Item 3 “Worst Pain in Past 24 hours” over the 7-day period before the baseline visit.
Note: API, average pain index; BPI-SF, Brief Pain Inventory–Short Form ITT; intention to treat.

# Nirogacestat Significantly Reduced Risk of Disease Progression




| | No. of Patients | No. of Events | Median (95% CI) | Hazard ratio (95% CI) |
|---|---|---|---|---|
| **Nirogacestat** | 70 | 12 | NE (NE, NE) | ***P*<0.001** |
| **Placebo** | 72 | 37 | 15.1 (8.4, NE) | **0.29 (0.15, 0.55)** |

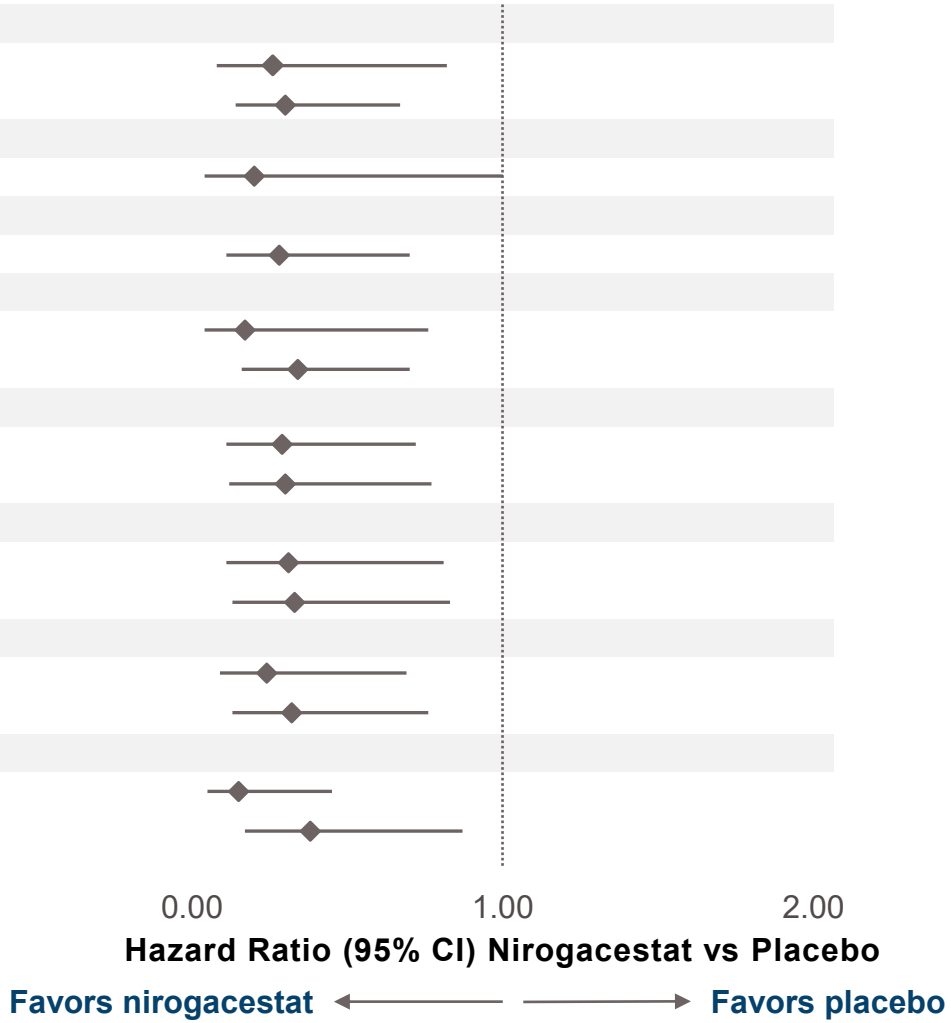
**No. of Participants at Risk:**

| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Placebo** | **72** | **67** | **58** | **47** | **45** | **40** | **32** | **29** | **27** | **25** | **10** | **8** | **6** | **5** | **1** | **1** | **0** |
| **Nirogacestat** | **70** | **63** | **56** | **52** | **52** | **47** | **46** | **44** | **44** | **41** | **26** | **26** | **17** | **12** | **4** | **4** | **0** |

Source: Kasper et al., *ESMO*, 2022. Data as of the time of primary analysis (04/07/22).
Note: Median follow-up time was 19.2 months for nirogacestat and 10.9 months for placebo.
Note: NE: not estimable.

# PFS Benefit With Nirogacestat Was Observed Across Prespecified Subgroups

| | Hazard Ratio | Nirogacestat Censored/Events | Placebo Censored/Events |
|---|---|---|---|
| **Sex** | | | |
| Male | 0.26 | 21 / 4 | 14 / 11 |
| Female | 0.30 | 37 / 8 | 21 / 26 |
| ***APC* mutation** | | | |
| Yes | 0.20 | 9 / 2 | 3 / 8 |
| ***CTNNB1* mutation** | | | |
| Yes | 0.28 | 37 / 6 | 21 / 21 |
| **Target tumor location** | | | |
| Intra-abdominal | 0.17 | 15 / 2 | 7 / 11 |
| Extra-abdominal | 0.34 | 43 / 10 | 28 / 26 |
| **Focality** | | | |
| Single | 0.29 | 37 / 6 | 22 / 19 |
| Multifocal | 0.30 | 21 / 6 | 13 / 18 |
| **Prior surgery** | | | |
| Yes | 0.31 | 26 / 5 | 21 / 23 |
| No | 0.33 | 32 / 7 | 14 / 14 |
| **Prior chemotherapy** | | | |
| Yes | 0.24 | 19 / 5 | 10 / 17 |
| No | 0.32 | 39 / 7 | 25 / 20 |
| **Prior TKI treatment** | | | |
| Yes | 0.15 | 19 / 4 | 8 / 16 |
| No | 0.38 | 39 / 8 | 27 / 21 |






Source: Kasper et al., *ESMO*, 2022. Data as of the time of primary analysis (04/07/22).
Note: PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

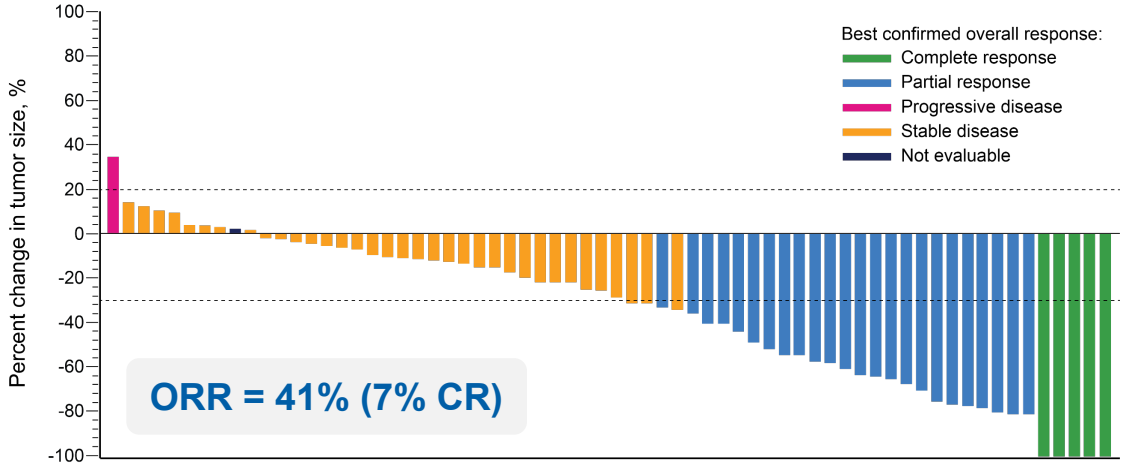
# Objective Response Rate by Blinded Independent Central Review

| | Nirogacestat (n=70) | Placebo (n=72) |
|---|---|---|
| **Objective response rate (CR+PR), n (%)**<br>95% CI<br>Two-sided *P* value | **29 (41)**<br>**(30.2, 54.5)**<br>**<0.001** | **6 (8)**<br>**(3.1, 17.3)** |
| Best overall response, n (%) | | |
| Complete response | 5 (7) | 0 |
| Partial response | 24 (34) | 6 (8) |
| Stable disease | 35 (50) | 55 (76) |
| Progressive disease | 1 (1) | 10 (14) |
| Not evaluable | 4 (6) | 1 (1) |
| Time to objective response, median (range), mo | 5.6 (2.6, 19.4) | 11.1 (2.8, 16.4) |
| Kaplan-Meier estimate of median duration of objective response (95% CI), mo[a] | NE (NE, NE) | NE (8.3, NE) |

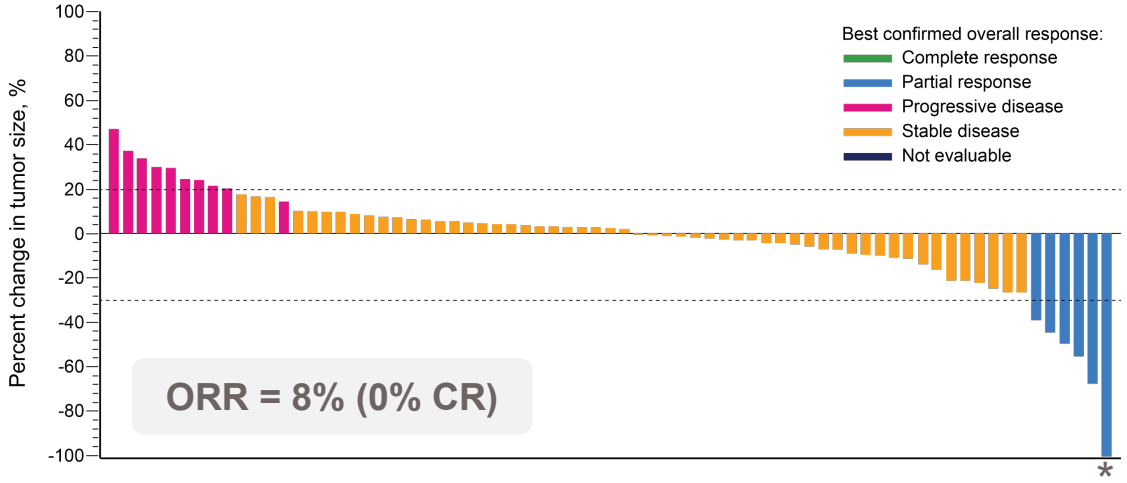
Source: Kasper et al., *ESMO,* 2022. Data as of the time of primary analysis (04/07/22).
a) Duration of objective response was defined as duration in months from the time CR or PR (which ever came first) was met until the date of progression, death, or censoring.
Note: CR, complete response; NE, not estimable; PR, partial response.

# Nirogacestat Treatment Resulted in Substantial Reductions in Tumor Size

## Nirogacestat (n=70)




## Placebo (n=72)




Source: Kasper et al., ESMO, 2022. Data as of the time of primary analysis (04/07/22). Gounder at al., CTOS, 2022.
* Patient had a complete resolution of the target lesion but still had documented non-target lesion; therefore, not a complete response.
Note: Best percent change values are averaged between 2 blinded independent reviewers unless a reader was selected for adjudication, in which case only the adjudicated value is presented.

# Nirogacestat Demonstrated Highly Significant and Clinically Meaningful Impact on Primary and All Key Secondary Endpoints

DeFi

| Clinical Outcome Measures | | P-Value |
|---|---|---|
| **Primary Endpoint** | Progression-free survival | <0.001 |
| **Secondary Endpoints** | Objective Response Rate | <0.001 |
| | Brief Pain Inventory-Short Form – Average Pain Intensity | <0.001 |
| | GODDESS Desmoid Tumor Symptom Scale – Total Symptom Score | <0.001 |
| | GODDESS Desmoid Tumor Impact Scale – Physical Functioning Impact Score | <0.001 |
| | EORTC QLQ-C30 Physical Functioning | <0.001 |
| | EORTC QLQ-C30 Role Functioning | <0.001 |
| | Global Health Status / Quality of Life | 0.007 |

Source: Kasper et al., ESMO, 2022. Data as of the time of primary analysis (04/07/22). Gounder at al., CTOS, 2022.
Note: Differences at Cycle 10 were statistically significant and clinically meaningful. DTSS total symptom score includes pain, fatigue, swelling, muscle weakness, and difficulty moving.
Note: GODDESS: GOunder/Desmoid Tumor Research Foundation DEsmoid Symptom/Impact Scale; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; PRO: patient-reported outcome.



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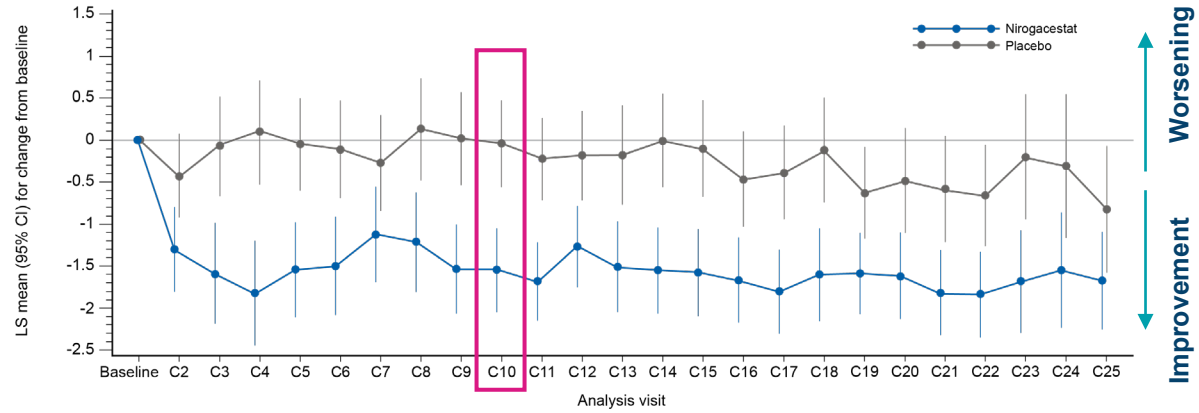
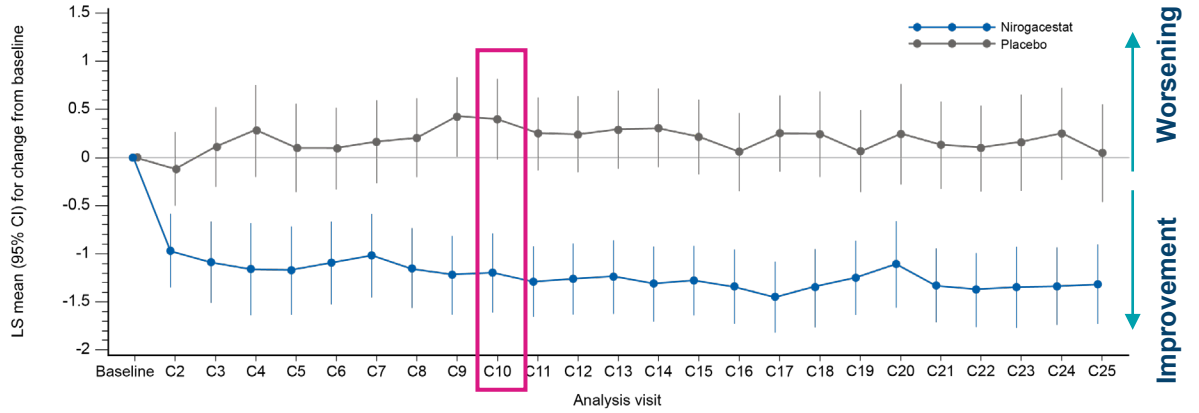
# Rapid, Early and Sustained Improvements Across Quality-of-Life Measures

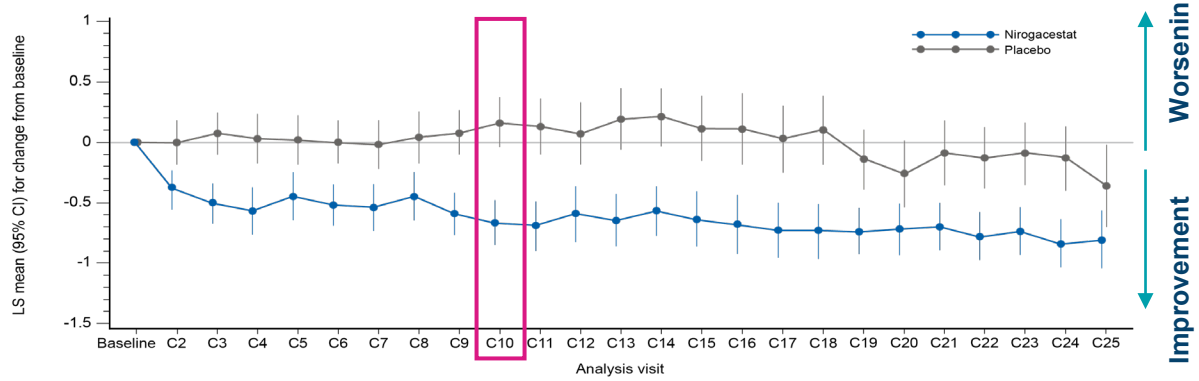
## Brief Pain Inventory-Short Form – Average Pain Intensity



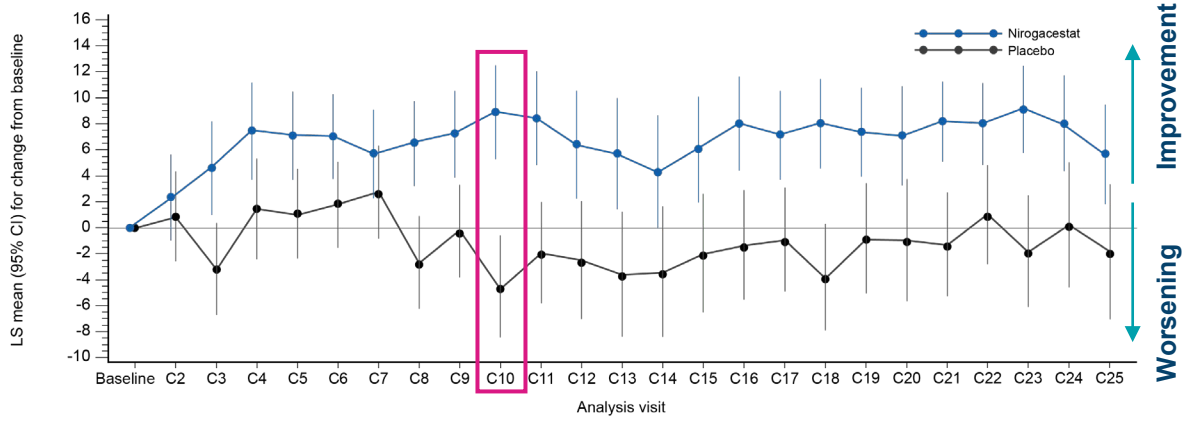

## DT-Specific Symptom Severity (GODDESS DTSS)




## Physical Functioning Impact Score (GODDESS DTIS)




## Physical Functioning (EORTC QLQ-C30)




Source: Kasper et al., ESMO, 2022. Data as of the time of primary analysis (04/07/22).
Note: DTIS: Desmoid Tumor Impact Scale; DTSS: Desmoid Tumor Symptom Score; Symptom/Impact Scale; EORTC QLQ C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; GODDESS: GOunder /Desmoid Tumor Research Foundation DEsmoid Symptom/Impact Scale; LS: least squares.
Mean (SD) baseline scores: nirogacestat, 3.2 (3.26); placebo, 3.3 (3.31). Differences at Cycle 10 were statistically significant and clinically meaningful. LS mean change from baseline represents the 7-day average.

# Nirogacestat Safety Profile

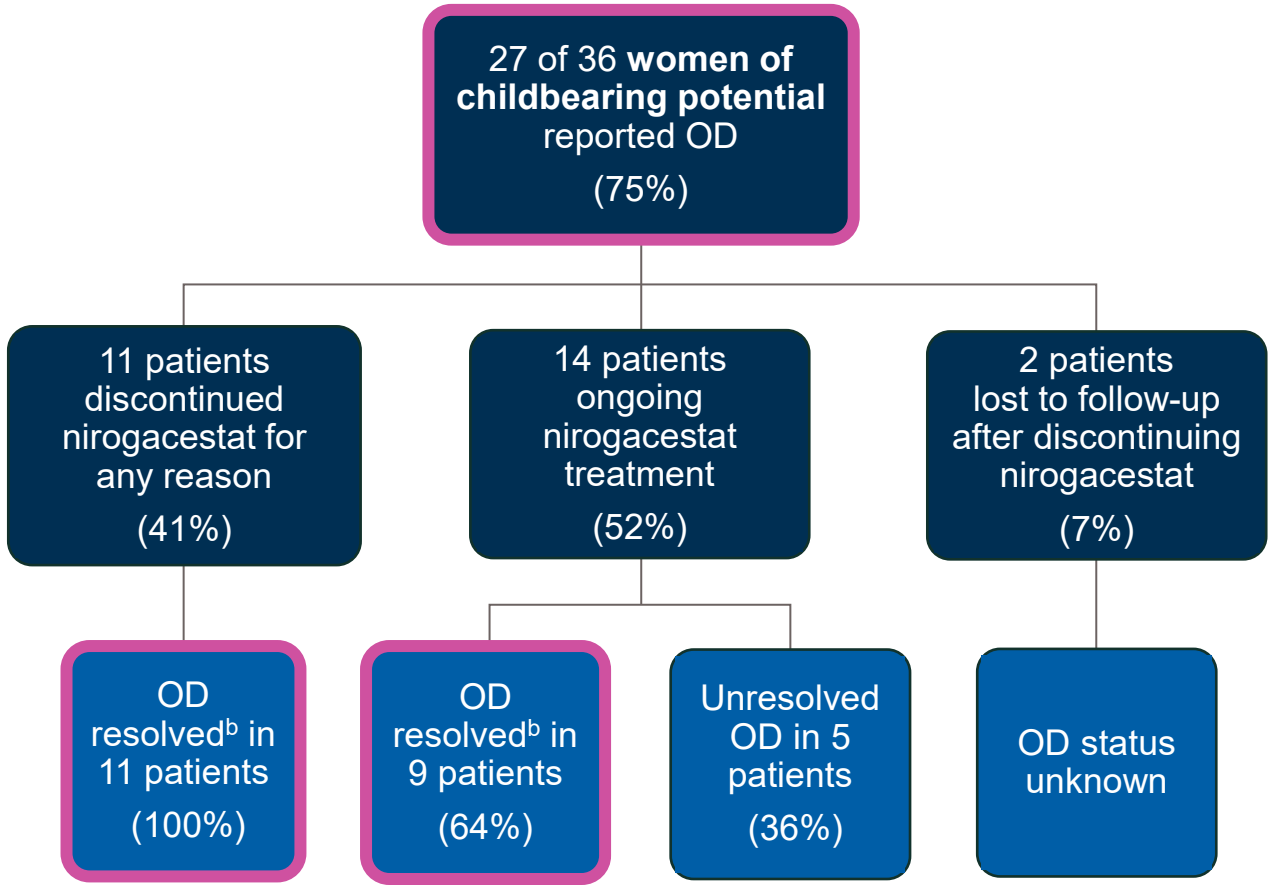
| Safety population, n (%) | Nirogacestat (n=69) | | Placebo (n=72) | |
|---|---|---|---|---|
| Duration of study drug exposure, median (range), months | 20.6 (0.3, 33.6) | | 11.4 (0.2, 32.5) | |
| Dose intensity, median (range), mg/d | 288.3 (169, 300) | | 300.0 (239, 300) | |
| | Any Grade | Grade ≥3 | Any Grade | Grade ≥3 |
| Any TEAE | 69 (100) | 39 (57) | 69 (96) | 12 (16) |
| TEAEs of any grade reported in ≥25% of patients in either arm | | | | |
| Diarrhea | 58 (84) | 11 (16) | 25 (35) | 1 (1) |
| Nausea | 37 (54) | 1 (1) | 28 (39) | 0 |
| Fatigue | 35 (51) | 2 (3) | 26 (36) | 0 |
| Hypophosphatemia | 29 (42) | 2 (3) | 5 (7) | 0 |
| Rash, maculopapular | 22 (32) | 4 (6) | 4 (6) | 0 |
| Headache | 20 (29) | 0 | 11 (15) | 0 |
| Stomatitis | 20 (29) | 3 (4) | 3 (4) | 0 |
| TEAEs leading to death | 0 | | 1 (1)[a] | |
| Dose reductions due to TEAEs | 29 (42) | | 0 | |
| Discontinuations due to TEAEs | 14 (20)[b] | | 1 (1)[b] | |

**95% of TEAEs were Grade 1 or 2; the first onset of TEAEs in most patients occurred during Cycle 1**

Source: Kasper et al., *ESMO*, 2022. Data as of the time of primary analysis (04/07/22).
a) Death due to sepsis.
b) TEAEs leading to discontinuations in ≥1 patient include gastrointestinal disorders (n=5 [4%]), ovarian dysfunction (n=4 [3%]), alanine aminotransferase increase (n=3 [2%]), aspartate aminotransferase increase (n=2 [1%]), and metabolism/nutritional disorders (n=2 [1%]).
Note: TEAE, treatment-emergent adverse event.

# Frequency and Resolution of Ovarian Dysfunction Observed With Nirogacestat

- OD is a composite adverse event associated with changes in female reproductive hormone levels and clinical manifestations[1,2]
- Protocol-mandated serum hormone collection at baseline and cycles 1, 2, 4, and every 3 thereafter
- Among women of childbearing potential, OD[a] was observed in 75% receiving nirogacestat and 0% receiving placebo
  - Median time to first onset of OD: 8.9 weeks
  - Median duration of OD events: 21.3 weeks




Source: Kasper et al., *ESMO,* 2022. Data as of the time of primary analysis (04/07/22).
a) OD among women of childbearing potential was defined by investigators who reported the MedDRA Preferred Terms of amenorrhea, premature menopause, menopause, and ovarian failure.
b) As of July 20, 2022.
c) Resolution of OD events was defined by the investigator.
Note: OD, ovarian dysfunction.
1) Thurston et al., *Obstet Gynecol Clin North Am.* 2011;38:489-501; 2) Mauri et al., *Front Endocrinol (Lausanne).* 2020;11:572388.

# Based on the DeFi Trial, We Expect That Nirogacestat's Novel and Differentiated Profile Will Transform the Standard-of-Care for Desmoid Tumor Patients

DeFi

| | |
|---|---|
| **Progression-Free Survival** | Significant PFS improvement versus placebo, with 71% reduction in risk of disease progression (hazard ratio: 0.29, p<0.001) |
| **Tumor Shrinkage** | 41% ORR, with 7% CR rate and rapid time to response (5.6 months) |
| **Quality of Life** | Significant improvements in pain, physical functioning, DT-specific symptoms and overall quality-of-life |
| **Safety** | 95% of adverse events reported were Grade 1 or 2 (most common: diarrhea, nausea, fatigue); 74% of all ovarian dysfunction events resolved(1) |
| **Durability** | 20.6 months of median time on treatment (ToT) at the time of primary analysis, with majority of nirogacestat patients ongoing, building on 4+ year median ToT in Phase 1 and 2(2) |

Sources: Kasper et al., ESMO, 2022.
Note: CR: complete response; DT: desmoid tumor; ORR: objective response rate
Note: Summary is based on the Phase 3 DeFi trial. Unless otherwise indicated results are as of the primary data cutoff date of April 7, 2022.
(1) Resolution of ovarian disfunction (OD) events was defined by the investigator. Data as of July 20, 2022. 75% of women of childbearing potential who received nirogacestat reported OD. 100% resolution in patients who discontinued treatment; 64% resolution in those remaining on nirogacestat.
(2) Sources: Messersmith et al., Clin Cancer Res., 2015; O'Sullivan Coyne et al., ASCO, 2022.



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# Significant Opportunity to Benefit Patients with Desmoid Tumors

## U.S. Patient Population

**~1,000-1,650**
new patients diagnosed annually

- Incidence of 3 – 5 per million per year[1-3]

**~5,500-7,000**
receive active treatment annually

- ~20 – 25% of total prevalent patients are under active treatment[3,4]

**30,000+**
diagnosed prevalent patients

- Meaningful proportion of the diagnosed prevalent population could be addressed with a new treatment option

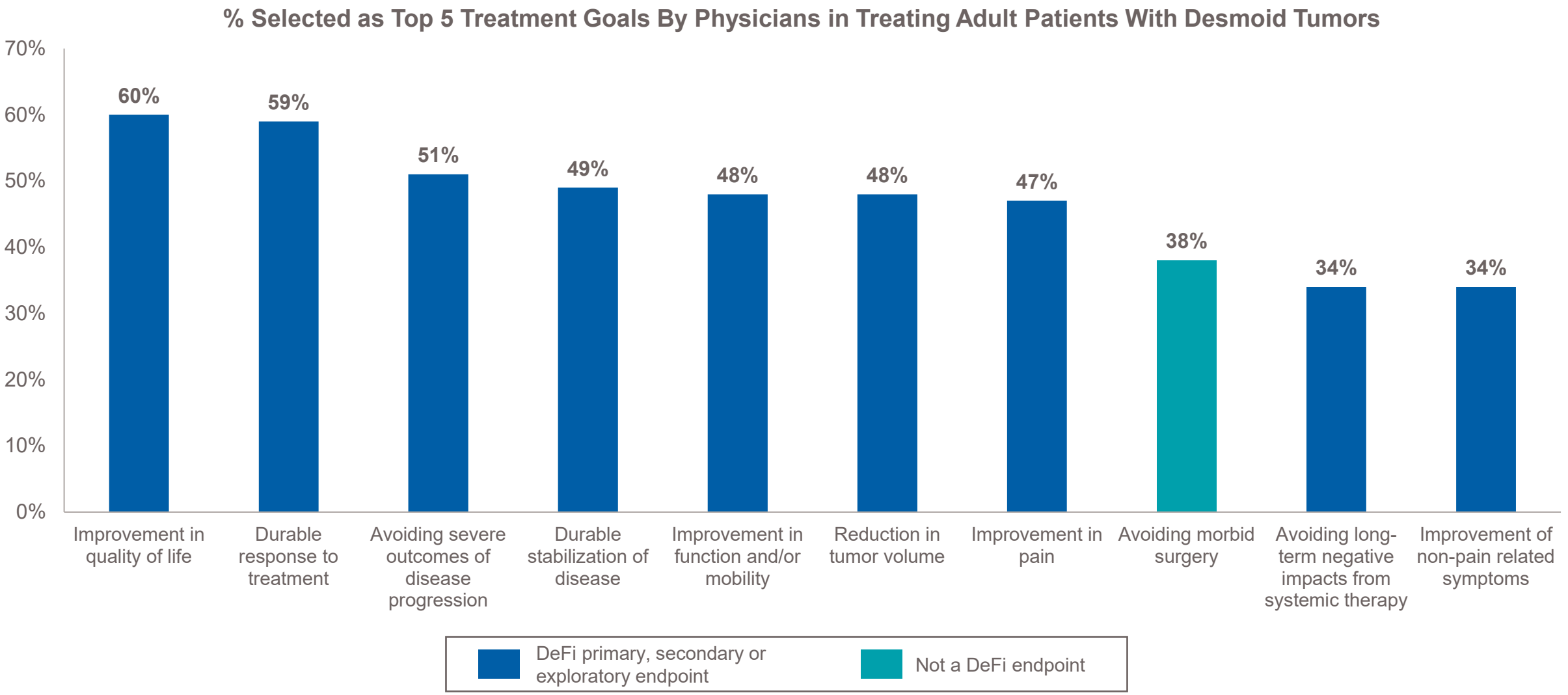
## Key Treatment Dynamics

- Propensity to treat is high – over 90% of patients receive active intervention over the course of their disease
- Continued erosion of surgery with shift away from "cut-first" mentality due to high post-surgical recurrence rates up to 77%[5,6]
- Off-label systemic therapies are often poorly tolerated with inconsistent efficacy
- Utilization of currently available therapies is fragmented due to treatment limitations
- Increased awareness leading to more "inactive" patients seeking treatment



Sources: (1) Van Broekhoven et al., Annals of Surgical Oncology, 2015; (2) Reitamo et al., American Journal of Clinical Pathology, 1982; (3) Anneberg et al., Cancer Epidemiology, 2022; (4) EMR data and KOL Qualitative interviews; (5) Skubitz et al., Mayo Clin Proc, 2017; (6) Easter DW, Halasz NA, Annals of Surgical Oncology, 1989.

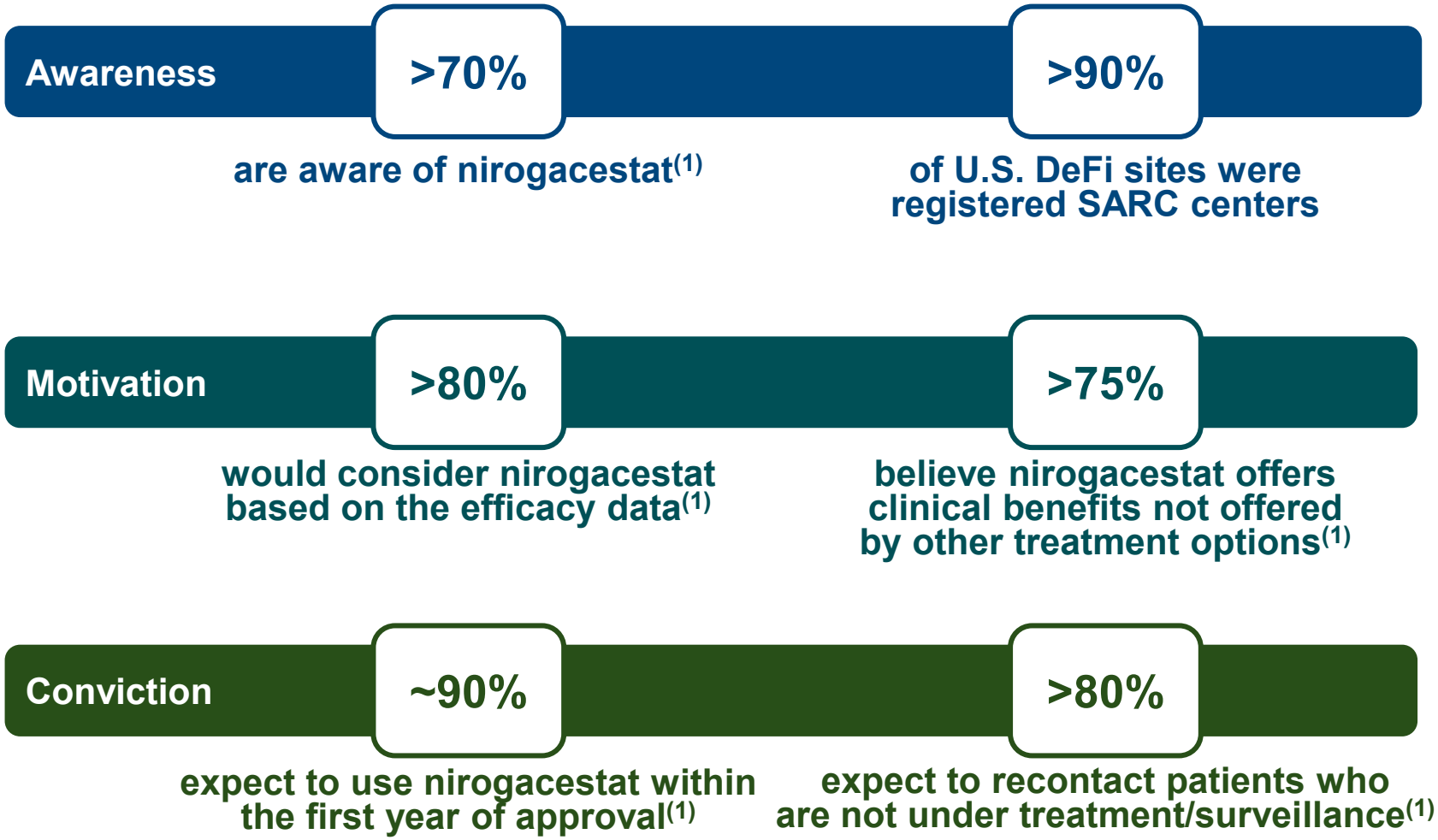
# DeFi Endpoints are Well Aligned to the Most Important Desmoid Tumor Treatment Goals






Source: SWTX Primary Market Research, 2Q22 (n=100 oncologists).

# Physician Feedback Supports Nirogacestat's Opportunity to Become the Standard of Care Systemic Therapy for Desmoid Tumors Following Approval




- ✓ Strong feedback from physicians and patient advocacy organizations
- ✓ High physician willingness to switch patients receiving TKIs or chemo
- ✓ Many physicians believe nirogacestat's risk/benefit profile is superior to surgery



Source: (1) SWTX Primary Market Research, 2022 (n=200 oncologists).

# Nirogacestat Is Well Positioned to Meaningfully Impact the Desmoid Tumor Community

| | |
|---|---|
| **Differentiated Data** | Potentially **practice-changing profile** based on antitumor activity, improvements in QoL outcomes, and manageable tolerability that has been suitable for extended treatment durations |
| **Patient Demand** | **Significant addressable patient population** with substantial unmet need due to high recurrence rates and no approved systemic treatment options |
| **Physician Awareness and Motivation** | **Awareness of nirogacestat is high** and large proportion of physicians surveyed indicate that they **expect to rapidly adopt** nirogacestat if approved |
| **Regulatory Path** | **NDA accepted in 1Q23 with Priority Review** (PDUFA date August 27, 2023); potential to be **first FDA-approved therapy** in desmoid tumors |
| **Commercial Execution** | **Launch activities rapidly advancing** to ensure successful preparation of market, organization and brand |



Note: NDA: New Drug Application; QoL: quality of life.

# Mirdametinib

NF1-PN

SpringWorks THERAPEUTICS

# 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
- Topline data from Phase 2b ReNeu trial in NF1-PN is expected in 2H 2023; NF1 is one of the largest genetic tumor predisposition syndromes with ~100k patients in the U.S. 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

| | |
|---|---|
| **Topline Data from ReNeu Trial Expected:** | **2H 2023** |
| **Clinical Trials Ongoing or On Track for 2023 Initiation:** | **6** |
| **U.S. Patent Protection:** | **2041** |



Note: NF1-PN: Neurofibromatosis type 1-associated plexiform neurofibroma; DDI: drug-drug interaction.

# A Substantial Unmet Need Remains for a Best-in-Class Therapy for NF1-PN Patients

**Kendall**
**NF1 Patient**

## Disease Overview and Unmet Need

- NF1-associated plexiform neurofibromas (NF1-PN) patients present with significant morbidities
- NF1-PN grow along nerves and can lead to extreme pain and disfigurement

**MEANINGFUL ADDRESSABLE POPULATION**

- ~100,000 patients living with NF1 in the US[1]
- NF1 pts have a ~30-50% lifetime risk of developing NF1-PN[2]

**TREATMENT PARADIGM**

- Surgical resection is difficult due to the infiltrative tumor growth pattern along nerves and is rarely performed[3,4]
- MEK inhibitors are a validated treatment option, but currently approved agent has uptake and compliance barriers
  - Limitations include challenging dosing requirements, administration, label restrictions and AEs[4,5]
  - 50%+ of patients discontinued treatment within 1 year[6]



Sources: (1) Lammert et al., Arch Dermat, 2005. U.S. Census Data; (2) Fisher et al., Neuro-Oncology, 2022; (3) Korf, American Journal of Medical Genetics, 1999; (4) SpringWorks Market Research, 2022; (5) Koselugo prescribing information; (6) Yang et al., SNO, 2022.

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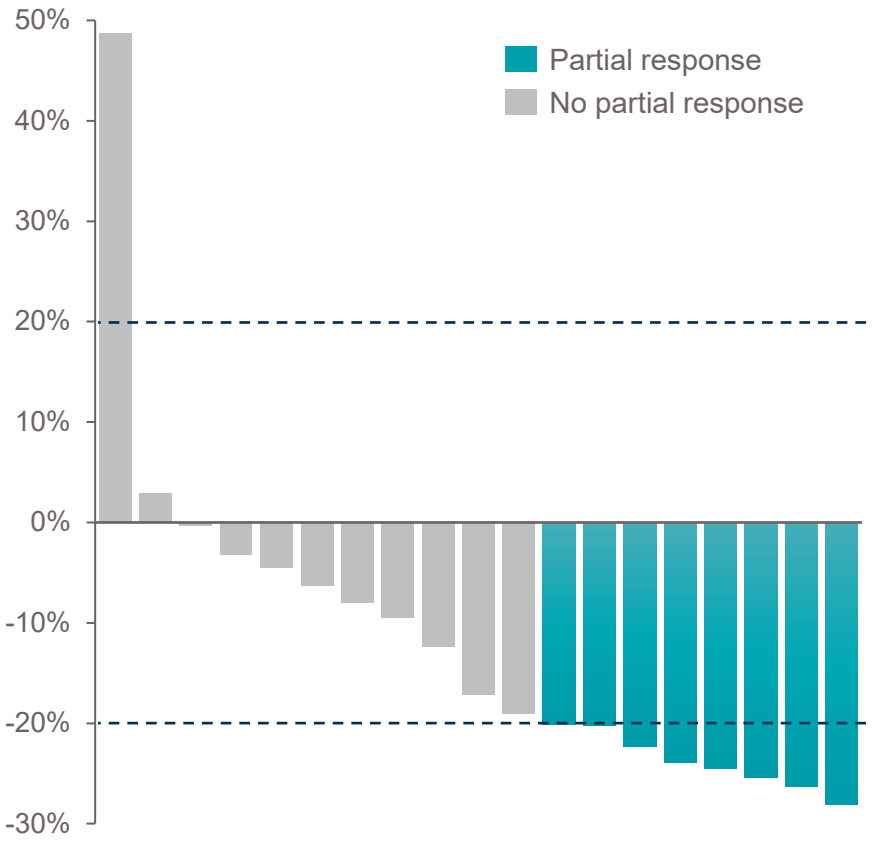
# ReNeu Trial Builds Upon Encouraging Phase 2 Results, Which Demonstrated Initial Clinical Activity, QoL Improvement for NF1-PN Patients and a Differentiated Safety Profile vs. Other MEK Inhibitors

NEUROFIBROMATOSIS CONSORTIUM

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.



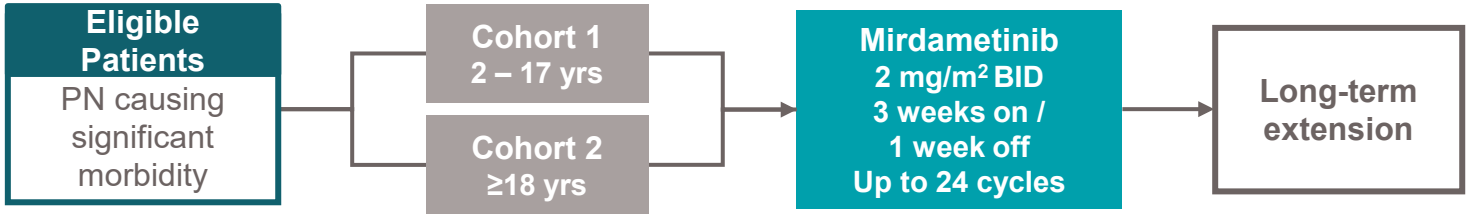
SpringWorks THERAPEUTICS

# Mirdametinib for NF1-PN: ReNeu Trial On Track for Topline Readout in 2H 2023

ReNeu

## Phase 2b ReNeu Trial Summary

| | |
|---|---|
| **TRIAL DESIGN** | ▪ Phase 2b open-label; n = 114 patients in 2 cohorts (pediatric and adults) across ~50 U.S. sites<br>▪ 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<br>▪ Pediatric formulation (dispersible tablet) introduced in 2H 2020 |
| **PRIMARY ENDPOINT** | ▪ Objective response rate (≥20% reduction in tumor volume) determined by BICR |
| **SECONDARY & EXPLORATORY ENDPOINTS** | ▪ Safety and tolerability, duration of response, QoL and physical functioning assessments |




## Opportunities for Differentiation

- With the ReNeu trial, mirdametinib has the opportunity to address the substantial unmet needs that remain for NF1-PN patients:
  - ✓ Therapeutic option for broader age spectrum
  - ✓ Enhanced efficacy
  - ✓ Improved safety and tolerability
  - ✓ More convenient therapy to drive compliance (lack of food effect, limited drug-drug interactions)
  - ✓ Differentiated product formulation for pediatric population



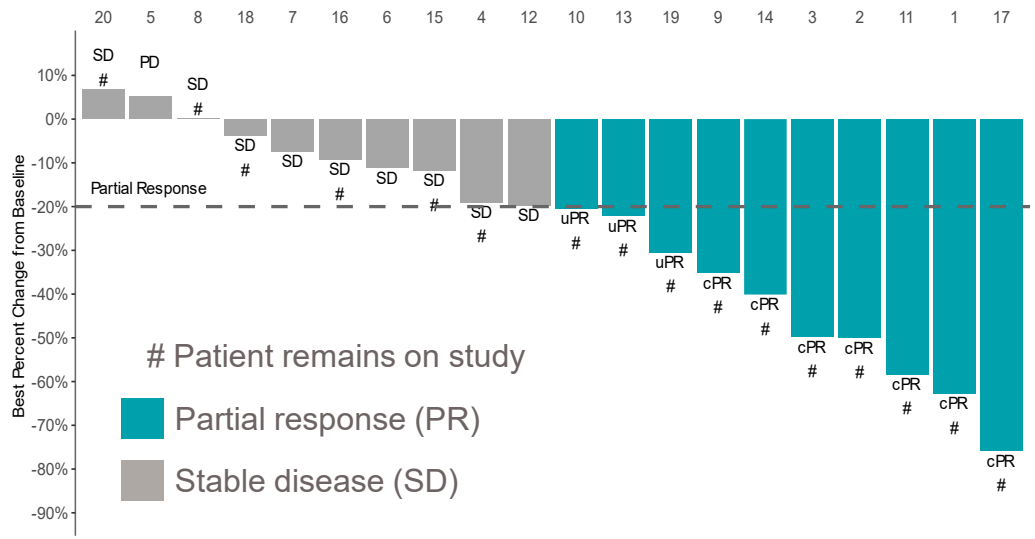
Note: BICR: blinded independent central review; BID: twice daily; QoL: quality of life.

SpringWorks THERAPEUTICS

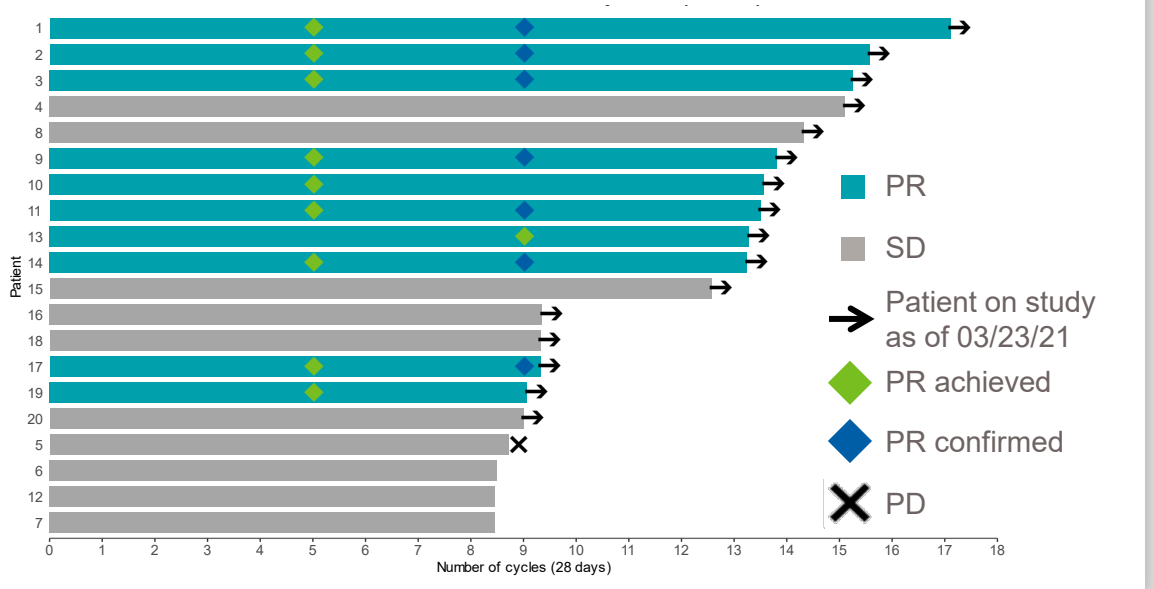
# Interim Data Update From ReNeu Trial Adult Stratum Presented at CTF in June 2021

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.

# Mirdametinib for NF1-PN: ReNeu Trial On Track for Topline Readout in 2H 2023

ReNeu

- ✓ Achieved full enrollment (2H 2021)
- ✓ FDA Type C Meeting: Received agreement on proposed statistical analysis plan and guidance on NDA submission expectations (4Q 2022)
- Planned disclosure of topline data (2H 2023)
- Anticipated NDA submission (1H 2024)

# Nirogacestat

Ovarian Granulosa Cell Tumors

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# Ovarian Granulosa Cell Tumors (OvGCT) Represent a Meaningful New Expansion Opportunity for Nirogacestat Monotherapy

## Disease Overview

- OvGCT accounts for ~5% of all ovarian cancers[1]
- >97% of OvGCT are driven by activating mutations in FOXL2, which have been shown to be sensitive to Notch inhibition[2,3]

**MEANINGFUL ADDRESSABLE POPULATION**

- Median diagnosis age of 50 years
- Estimated U.S. incidence: 1,500-2,000 per year Significant prevalent population: ~10,000-15,000[4,5]

**NO APPROVED TREATMENTS**

- Early-stage disease managed with surgery; however, ~40% of patients experience post-surgical recurrence[1]
- No currently approved therapies; limited effective treatment options in recurrent setting

## Phase 2 Trial Summary

**TRIAL DESIGN**

- Single-arm open label study, enrolling ~40 patients with recurrent OvGCT with ≥ one line of prior systemic therapy
- Dose: Nirogacestat 150mg BID
- PI: Panagiotis Konstantinopoulos, MD, PhD (Dana-Farber Cancer Institute)
- IND cleared in December 2021

**PRIMARY ENDPOINT**

- Objective response rate by RECIST 1.1 (response assessed every 2 months)

**SECONDARY ENDPOINTS**

- Progression-free survival, overall survival, duration of response, safety and tolerability, and quality of life assessments

**First patient dosed in Phase 2 trial in September 2022**



Sources: (1) Dridi et al., Int J Surg Oncol, 2018; (2) Li et al., Journal of Ovarian Research, 2018; (3) Irusta et al., Biol Reprod, 2013; (4) SEER; (5) Torre L. et al., CA Cancer J Clin, 2018.

# Gamma Secretase Inhibitors Could Address Need for Targeted Therapy Options in OvGCT

## OvGCT are potentially susceptible to gamma secretase inhibition due to mutations in *FOXL2*

**>97% of OvGCT are driven by C124W mutation in *FOXL2***, a transcription factor required for development and function of granulosa cells

**Mutant *FOXL2* alters multiple signaling pathways** and gene expression of granulosa cells related to proliferation and apoptosis

**Notch** signaling has been shown to **block apoptosis and increase proliferation** of OvGCT cells

**Preclinically, GSIs have been able to address the fundamental driver mutation in this tumor type**

## Threshold for inclusion in NCCN guidelines likely to be low given precedents and limited therapeutic options

- Modest activity in clinical studies has been observed for single agents and combination regimens to date
- Single arm trials with published data have been sufficient to support inclusion of regimens in NCCN Guidelines
- Select benchmark data from completed OvGCT trials:

| | Single agent bevacizumab | Single agent paclitaxel vs. Paclitaxel + bevacizumab | |
|---|---|---|---|
| **Study** | Ph 2 single arm study N = 36 | Ph 2 ALIENOR/ENGOT-ov7 randomized trial (n = 60) | |
| | | Paclitaxel N = 32 | Bev + paclitaxel N = 28 |
| **ORR** | 17% | 23% | 44% |
| **mPFS** | 9.3 mo | 14.9 mo | 14.7 mo |



Note: GSI: gamma secretase inhibitor; NCCN: National Comprehensive Cancer Network; OvGCT: ovarian granulosa cell tumor; ORR: objective response rate; PFS: progression-free survival.
Sources: Li et al., *Journal of Ovarian Research*, 2018; Irusta et al., *Biol Reprod*, 2013; Ray-Coquard et al., *JAMA Oncol*, 2020; Brown et al., *Cancer*, 2014.

# Emerging Insights From OvGCT Physician Market Research

- Preliminary market research survey conducted to assess practice demographics and current treatment practices and to gather feedback on physician need for new treatments for OvGCT
  - Responses were collected from 31 physicians, including OB-GYNs, gynecologic oncologists, gynecologic surgeons and medical oncologists, with practices covering the academic and community settings
  - On average, each of these physicians currently treats ~5 OvGCT patients, with ~15 patients treated per physician in the last 5 years
- Key insights relating to unmet need and current limitations of existing treatments noted by physicians include:
  - Need for options in the post-surgical recurrent setting, placing emphasis on long-term control after first recurrence and reducing recurrence rate
  - Need for late-line options that do not involve surgery
  - Improvements in screening with better diagnosis, predictive testing for stage and risk of recurrence as well as non-invasive screening options

*"There are no good options for patients after relapsed disease. Surgical and radiation options are quite poor. Systemic therapy is very much needed."*

***– Gynecological Medical Oncologist***

*"An oral option for treatment allows for greater access to care. Many patients will review an oral treatment favorably as compared to an IV."*

***– Gynecologic Surgeon***



Note: OvGCT: ovarian granulosa cell tumor.
Source: SpringWorks market research.

# Emerging Portfolio

SpringWorks® THERAPEUTICS

# Broad Emerging Pipeline Continues to Advance and Offers Substantial Upside Potential

## Multiple Myeloma – Nirogacestat + BCMA-Directed Therapy Combinations

| | |
|---|---|
| + Belantamab mafodotin (ADC) | Phase 2 ongoing |
| + Teclistamab (Bispecific) | Phase 1 ongoing |
| + Elranatamab (Bispecific) | Phase 1b/2 ongoing |
| + SEA-BCMA (mAb) | Phase 1 planned |
| + ABBV-383 (Bispecific) | Phase 1b planned |
| + Linvoseltamab (Bispecific) | Phase 1b planned |

## MAPK-Mutant Solid Tumors

| | |
|---|---|
| Pediatric Low-Grade Gliomas | **Mirdametinib**: Phase 1/2 ongoing |
| MAPK Mutant Solid Tumors | **Mirda + Lifirafenib:** Ph 1/2 ongoing |
| ER+ Metastatic Breast Cancer | **Mirda + Fulvestrant:** Ph 1b/2a ongoing |
| MEK 1/2 Mutant Solid Tumors | **Mirdametinib:** Phase 1b/2a ongoing |
| MAPK Mutant Solid Tumors | **BGB-3245:** Phase 1 ongoing |
| MAPK Mutant Solid Tumors | **Mirda + BGB-3245:** Ph 1/2a ongoing |

## Preclinical Programs

| | |
|---|---|
| Hippo Mutant Tumors | **SW-682:** IND-enabling |
| EGFR Mutant Tumors | Discovery |

## 2023 Milestones

- Highlight additional clinical data and support initiation of trials across modalities

- ✓ Dosed first patient in mirdametinib + BGB-3245 study (1Q23)
- Present data from BGB-3245 and mirdametinib + lifirafenib at a medical conference (1H23)

- File IND for SW-682



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# Nirogacestat

BCMA Combination Therapy Development in Multiple Myeloma

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# 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 with 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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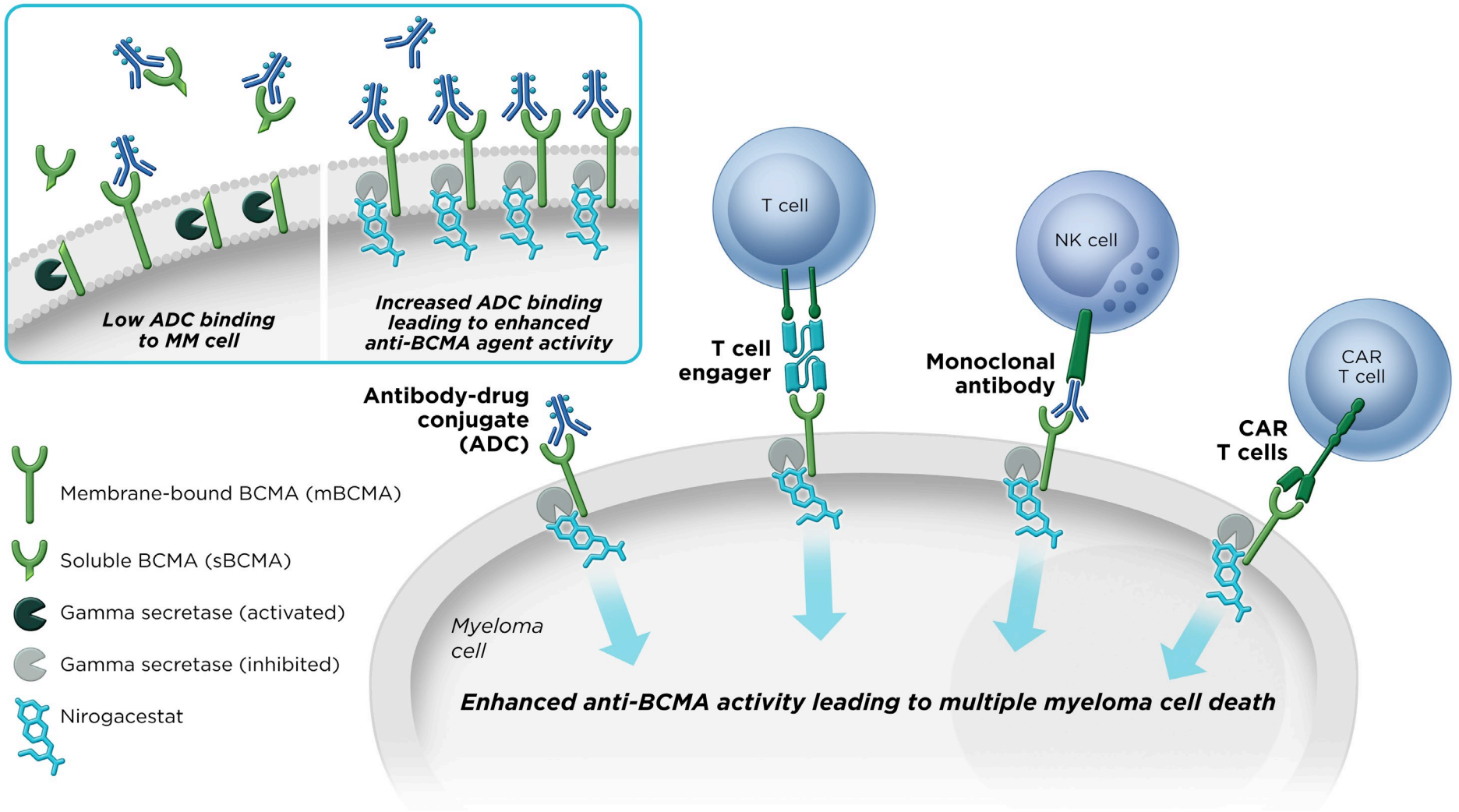
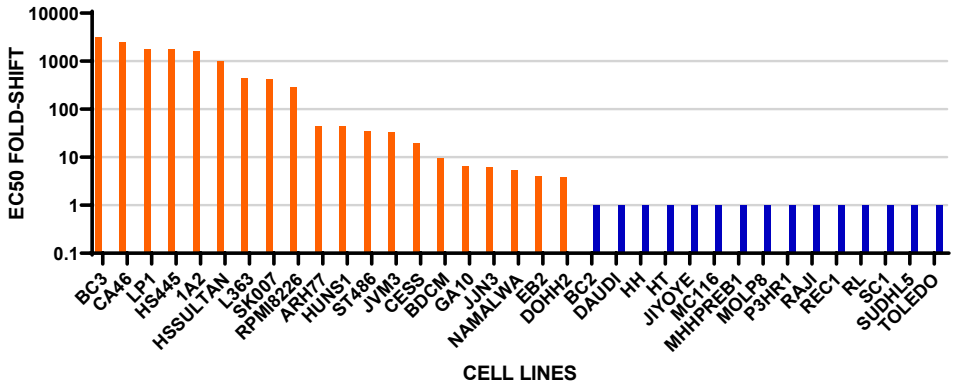
# SpringWorks is Leading the Mechanistic Understanding and Clinical Development of GSI + BCMA in Multiple Myeloma



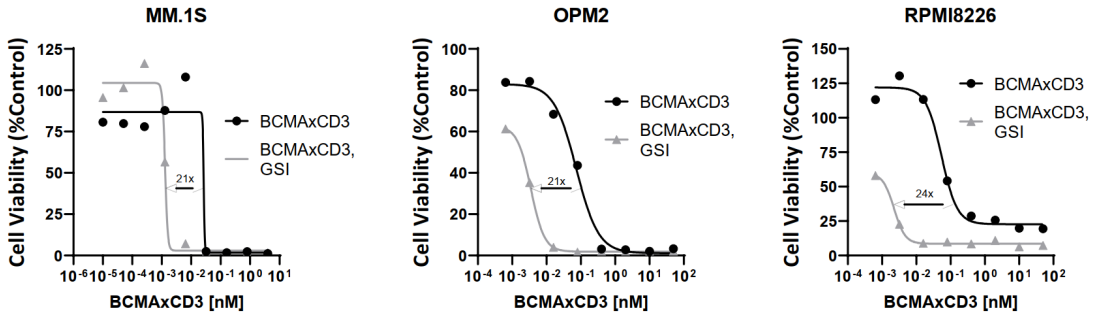

Note: GSI: gamma secretase inhibitor.

# Nirogacestat Has Been Validated Preclinically in Combination with BCMA Therapies Across All Key Modalities

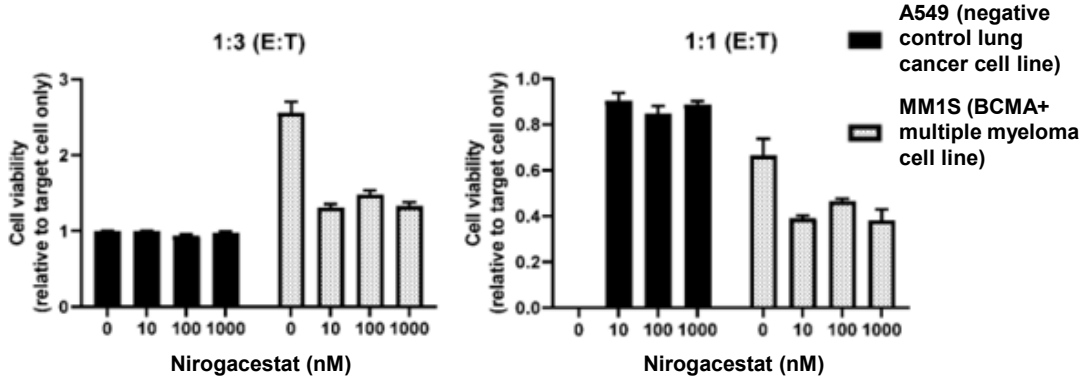
## BCMA ADC[1]



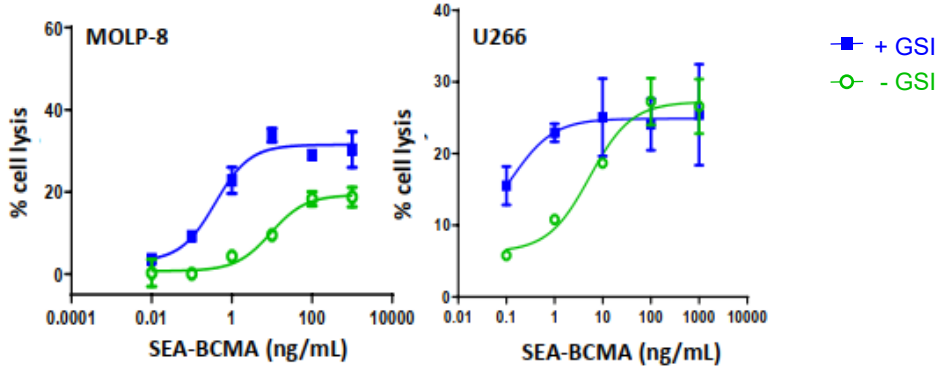

## BCMA-CD3 Bispecific[2]




## BCMA CAR-T[3]




## BCMA mAb[4]






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, July 2021; (4) Yu et al., *EHA*, 2021.

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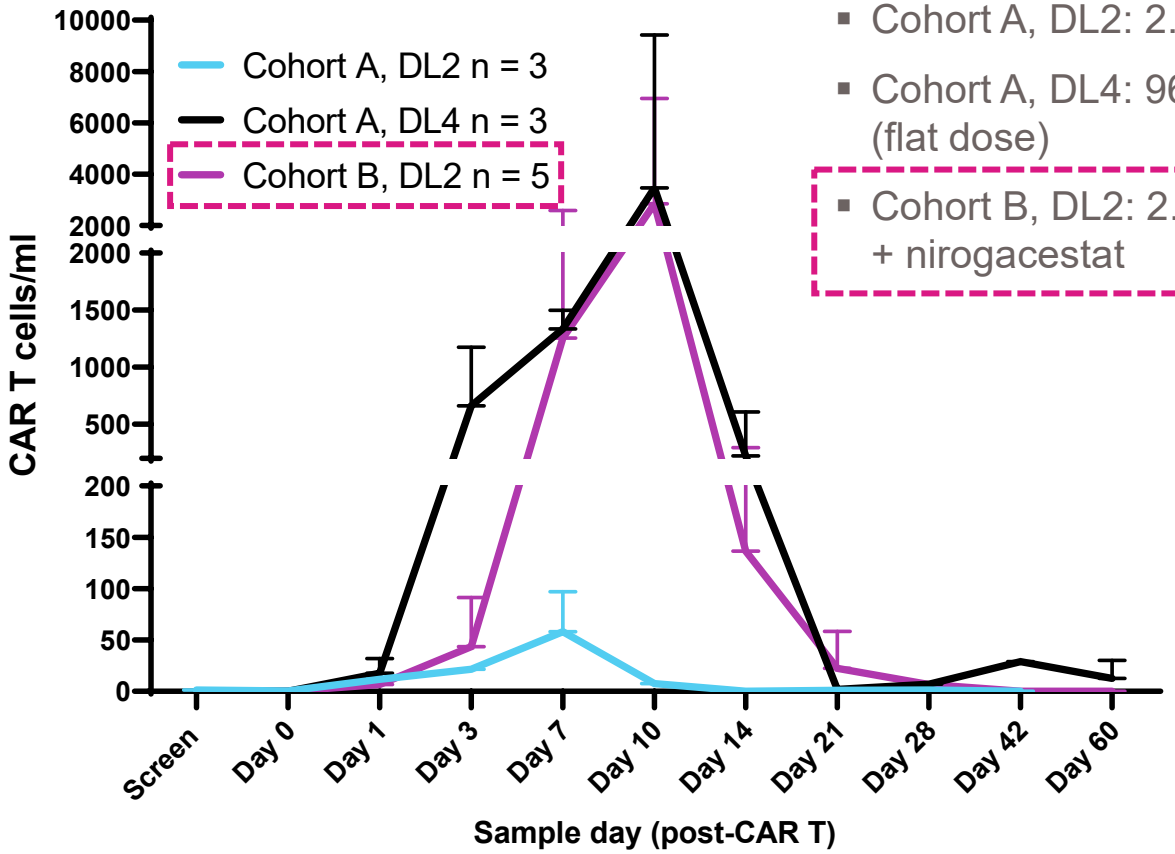
# Preliminary Clinical Data Demonstrate That Nirogacestat Treatment Can Lead to Profound Expansion of BCMA CAR-T Cells in Multiple Myeloma Patients

- 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
- 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




- 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

**Combination resulted in improved cell expansion, which correlated with increased clinical activity when compared to dose-matched PBCAR269A monotherapy treatment**


Note: DL: dose level.
Source: Precision BioSciences investor materials (ASH 2021 presentation on December 11, 2021; 3Q 2022 Earnings Release as of November 8, 2022); preliminary data from ongoing Precision-sponsored trial (NCT04171843).

# Initial Low-Dose Belamaf + 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:**
Low-dose (0.95mg/kg) belamaf Q3W + nirogacestat

**Additional Cohorts:**
Belamaf + nirogacestat

**Phase 2**
**Randomized Cohort Expansion**

2.5 mg/kg belamaf Q3W *(monotherapy arm)*

VS.

Low-dose (0.95mg/kg) belamaf Q3W + nirogacestat

*Potential for other cohorts to be expanded based on efficacy*

**Additional Planned Sub-studies with SoC Agents**

Belamaf + nirogacestat + pomalidomide + dexamethasone

Belamaf + nirogacestat + lenalidomide + dexamethasone

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



Note: SoC = standard of care.

# Interim Data from DREAMM-5 Study Evaluating Nirogacestat in Combination with Low-dose Belamaf vs. Belamaf Monotherapy Presented at ASCO 2022

| Patient Characteristics | | | |
|---|---|---|---|
| | **2.5 mg/kg Belamaf<br>CE (N = 14)** | **0.95 mg/kg Belamaf + 100 mg BID Nirogacestat<br>CE (N = 14)** | **0.95 mg/kg Belamaf + 100 mg BID Nirogacestat<br>DE (N = 10)** |
| High-risk cytogenetics | 6 (43) | 7 (50) | 8 (80) |
| Extramedullary Disease | | | |
| Yes | 1 (7) | 4 (29) | 2 (20) |
| No | 13 (93) | 10 (71) | 8 (80) |
| Autologous stem cell transplant | | | |
| Yes | 9 (64) | 10 (71) | 9 (90) |
| No | 5 (36) | 4 (29) | 1 (10) |
| Prior lines of therapy, median (min – max) | 4.5 (3 – 7) | 4.5 (3 – 10) | 4.5 (3 – 10) |



Note: CE: Cohort Expansion; DE: Dose Exploration; BID: twice daily.
Source: Lonial et al., *ASCO*, 2022.

# No Significant Difference Noted in Grade ≥ 3 Non-Ocular AEs Between Combination and Belamaf Monotherapy at Interim Analysis

| Drug-Related Grade ≥3 Adverse Events by System Organ Class and Preferred Term | | | |
|---|---|---|---|
| | 2.5 mg/kg Belamaf<br><br>CE (N = 14) | 0.95 mg/kg Belamaf +<br>100 mg BID Nirogacestat<br>CE (N = 14) | 0.95 mg/kg Belamaf +<br>100 mg BID Nirogacestat<br>DE (N = 10) |
| **Blood and Lymphatic** | **2 (14)** | **4 (29)** | **3 (30)** |
| Thrombocytopenia | 2 (14) | 3 (21) | 2 (20) |
| Febrile neutropenia | 1 (7) | 1 (7) | 1 (10) |
| **Gastrointestinal** | **1 (7)** | **3 (21)** | **1 (10)** |
| Diarrhea | 1 (7) | 2 (14) | 1 (10) |
| Upper abdominal pain | - | 1 (7) | - |
| **Investigations** | **3 (21)** | **2 (14)** | **-** |
| Blood magnesium decrease | - | - | - |
| AST increase | 1 (7) | - | - |
| Platelet count decrease | 2 (14) | 1 (7) | - |
| Blood urea increase | - | 1 (7) | - |
| **General and administration site conditions** | **-** | **-** | **-** |
| **Metabolism and nutrition** | **-** | **1 (7)** | **1 (10)** |
| Hypophosphatemia | - | 1 (7) | 1 (10) |
| **Injury and procedural complications** | **1 (7)** | **-** | **2 (20)** |
| Infusion Related Reaction | 1 (7) | - | 2 (20) |
| **Renal and urinary** | **-** | **1 (7)** | **-** |
| Proteinuria | - | 1 (7) | - |
| **Respiratory, thoracic and mediastinal** | **1 (7)** | **-** | **-** |
| Pulmonary embolism | 1 (7) | - | - |
| **Musculoskeletal and connective tissue** | **-** | **-** | **-** |



Note: Five patient deaths were also reported on study, all unrelated to study treatment.
Source: Lonial et al., *ASCO*, 2022.

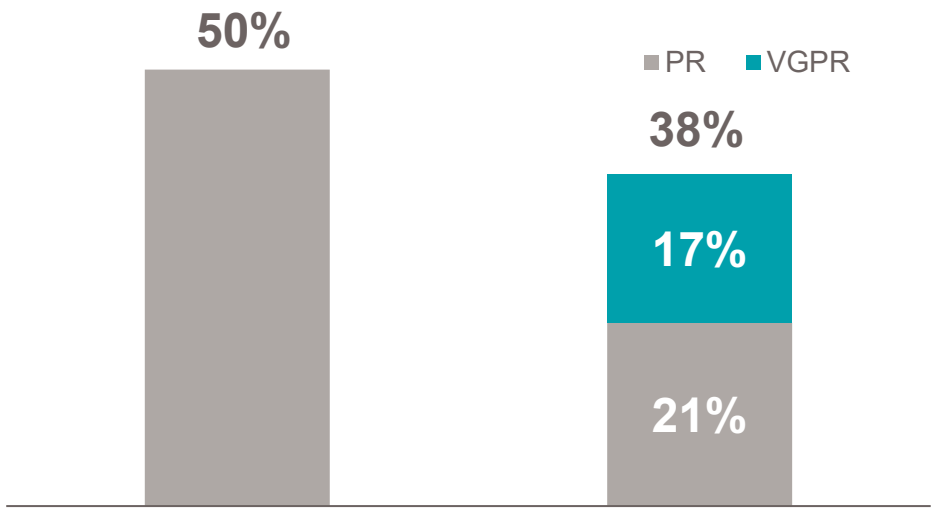
# Reduction in Ocular Adverse Events Observed with Combination Versus Belamaf Monotherapy at Interim Analysis

| | 2.5 mg/kg Belamaf<br><br>CE (N = 14) | 0.95 mg/kg Belamaf + 100 mg BID Nirogacestat<br>CE (N = 14) | 0.95 mg/kg Belamaf + 100 mg BID Nirogacestat<br>DE (N = 10) |
|---|---|---|---|
| **Grading Methodology** | **KVA** | **KVA** | **CTCAEv5** |
| Number of Subjects with Any Ocular Event | 12 (86%) | 7 (50%) | 6 (60%) |
| Grade 1 | 0 | 4 (29%) | 2 (20%) |
| Grade 2 | 5 (36%) | 2 (14%) | 2 (20%) |
| Grade 3 | 7 (50%) | 1 (7%) | 2 (20%) |
| Grade 4 | 0 | 0 | 0 |
| Median (range) number of treatment cycles | 2.0 (1-5) | 4.0 (1-9) | 8.5 (1-29) |
| Median (range) follow-up duration (weeks) | 12.0 (3–22) | 12.0 (3–24) | 34.5 (5–88) |

Note: CE: Cohort Expansion; DE: Dose Exploration; BID: twice daily; CTCAE: common terminology criteria for adverse events; KVA: keratopathy and visual acuity.
Note: Belamaf + niro combination DE cohort N=10 was fully enrolled prior to the opening of the CE cohort. CE cohorts (total N=28) were concurrently randomized.
(1) 5 of the 6 patients who experienced an ocular event of any grade by the CTCAE5 scale had a KVA event of any grade.
Source: Lonial et al., *ASCO*, 2022.

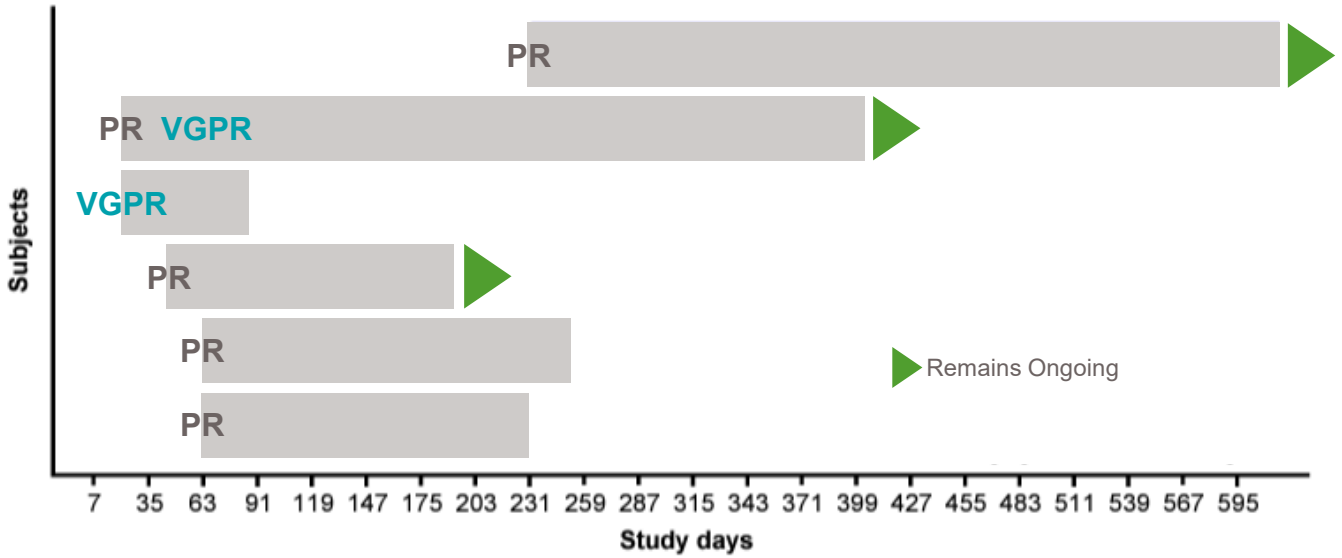
# Emerging Efficacy Profile of Low-dose Belamaf in Combination with Nirogacestat

## Objective Response Rate (ORR)




- Comparable efficacy with nirogacestat + low-dose belamaf vs. monotherapy belamaf

## Onset and Duration of Response In Responders (6/10) from the DE Cohort




- More mature data on profile of response to be presented at future congress, including data on complete CE cohorts (n=70)

**Nirogacestat and low-dose belamaf combination may provide an attractive benefit-risk profile compared to belamaf monotherapy at approved dose given a reduced incidence of Grade 3 ocular toxicity while maintaining comparable efficacy**



Note: PR: partial response; VGPR: very good partial response; BID: twice daily; CE: cohort expansion, DE: dose exploration; Q3W: once every 3 weeks.
Source: Lonial et al., *ASCO*, 2022.

# Initial Data from Belamaf and Nirogacestat Combination Sets the Stage for Further Development Across MM Lines of Therapy

## GSK-Sponsored Development of Belamaf and Nirogacestat Continues to Advance

GSK

### Phase 1/2 DREAMM-5 Platform Trial

- Sub-study 3: Belamaf + nirogacestat in RRMM
- Sub-study 6: Belamaf + nirogacestat + lenalidomide + dexamethasone in RRMM
- Sub-study 7: Belamaf + nirogacestat + pomalidomide + dexamethasone in RRMM

## Non-exclusive collaboration with GSK expanded to enable potential development into earlier lines of therapy

- In September 2022, expanded original non-exclusive collaboration to include potential for development and commercialization of *Blenrep* and nirogacestat in earlier lines of treatment, including newly diagnosed MM patients
- SpringWorks received a $75M equity investment from GSK and is eligible for up to $550M in development and commercial milestones
- SpringWorks will continue to retain full commercial rights to nirogacestat and will supply nirogacestat for future *Blenrep* development and make nirogacestat commercially available in markets where approved

## Investigator-Sponsored Studies Supported by GSK and SpringWorks

Hellenic Society of Haematology

### Planned Phase 1/2 Trial

- Belamaf + nirogacestat + lenalidomide + dexamethasone in transplant-ineligible newly diagnosed MM

Memorial Sloan Kettering Cancer Center

### Planned Phase 1b Trial

- Belamaf + nirogacestat (with nirogacestat-only run-in dosing) in RRMM



Note: RRMM: relapsed/refractory multiple myeloma.

# Mirdametinib

Additional Expansion Opportunities

SpringWorks THERAPEUTICS

# Mirdametinib: Phase 1/2 Trial in Pediatric Low-Grade Glioma Provides Additional Expansion Opportunity

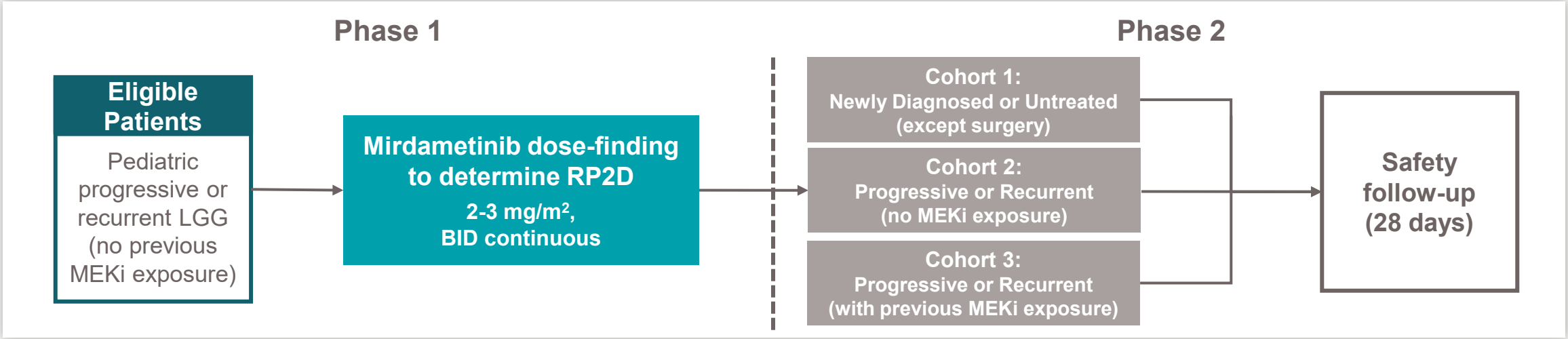
**PHASE 1/2**

## 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 (2-3 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 presented at ISPNO in June 2022**



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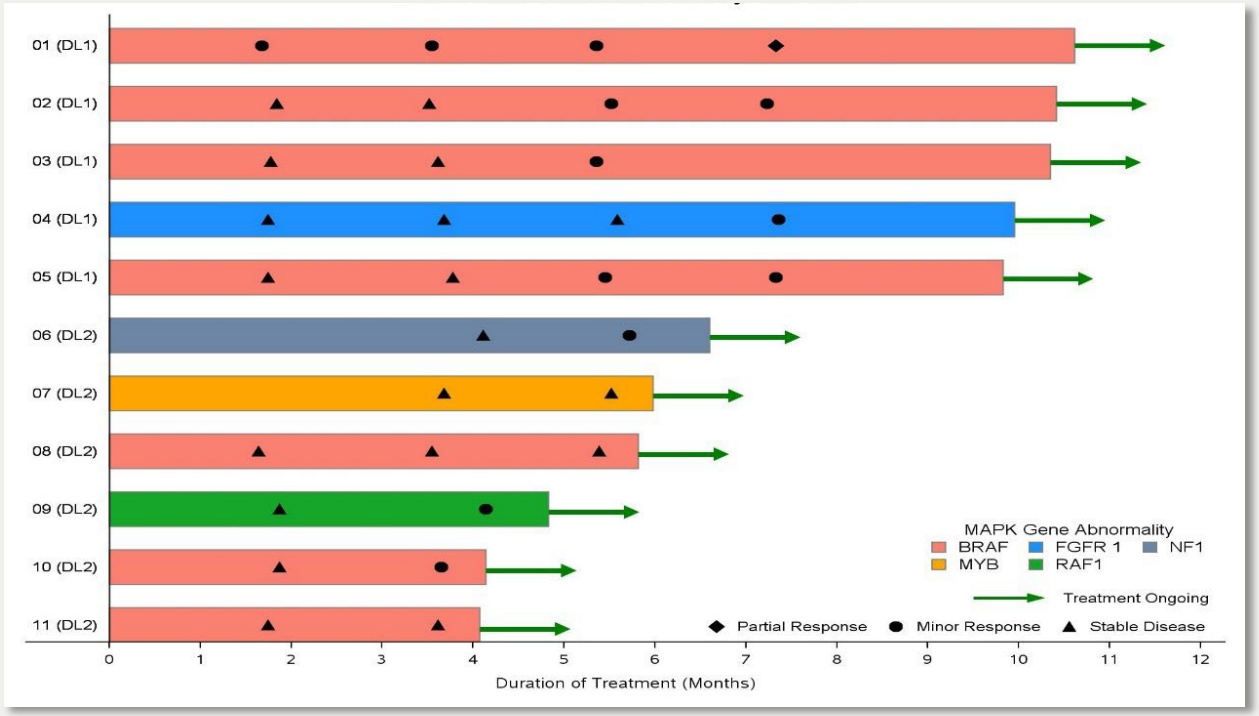
# Mirdametinib: Emerging Data Presented at ISPNO in June 2022 Show Promising Clinical Activity

**PHASE 1** | PHASE 2

- Data from first 11 patients treated across two initial dose levels during Phase 1 dose escalation, with all 11 patients treated remaining on study as of 05/01/22
  - 1 patient with partial response (decrease of 50-75%)
  - 7 patients with minor response (decrease of 25-50%)
  - 3 patients with stable disease (stable tumor size or decrease up to 25%)
- No DLTs observed
- Most common Grade 1/2 treatment-related AEs observed were elevated CPK, AST, acneiform rash and decreased neutrophil count
  - 2 treatment-related Grade 3 AEs reported: elevated CPK and decreased neutrophil count




**Once RP2D is determined, additional 10 patients will be enrolled into each expansion cohort**



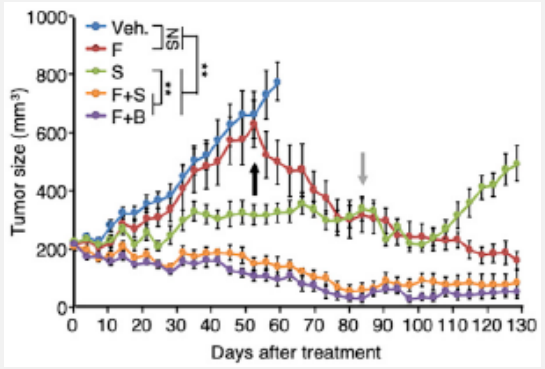
Source: Vinitsky et al., *ISPNO* 2022.
Note: AE: adverse event; DLT: dose-limiting toxicity; ISPNO: International Symposium on Pediatric Neuro-Oncology; RP2D: recommended Phase 2 dose.

# Mirdametinib: Phase 1 Trials Ongoing in ER+ Breast Cancer and MEK1/2 Mutant Solid Tumors

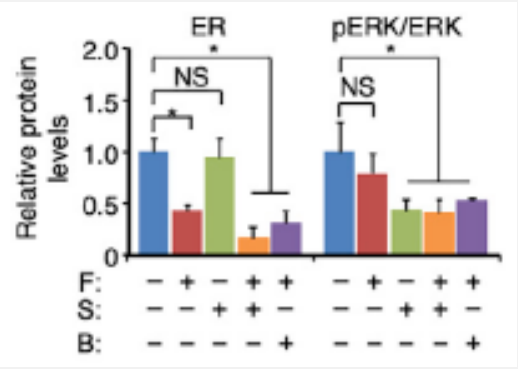
## ER+ Breast Cancer Resistance

- 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]



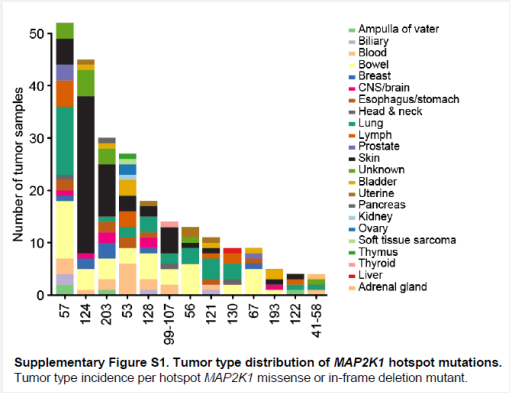

### MEKi + Fulvestrant Modulates ER and MAPK Signaling[2]




## MEK1/2 Mutant Solid Tumors

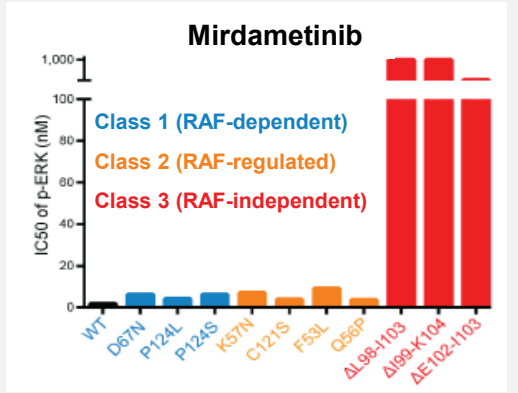
- Mirdametinib shows potent preclinical activity against Class 1 and Class 2 mutations in MEK1 and MEK2[3]
- MEK1 and MEK2 have been validated as oncogenic targets with mutations present in ~2% of solid tumors[4]
- Clinical case reports with allosteric MEK inhibitors also support utility of mirdametinib in tumors driven by MEK mutation

### MEK 1/2 Mutants Occur Across Tumor Types[4]




**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*[3]






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; (3) Gao et al., 2018; (4) Hanrahan et al., 2020.

SpringWorks THERAPEUTICS

# Building on Mirdametinib's Potential Best-In-Class Profile, We Developed Our MAPK Targeted Portfolio with Complementary Combination Opportunities in Collaboration with BeiGene

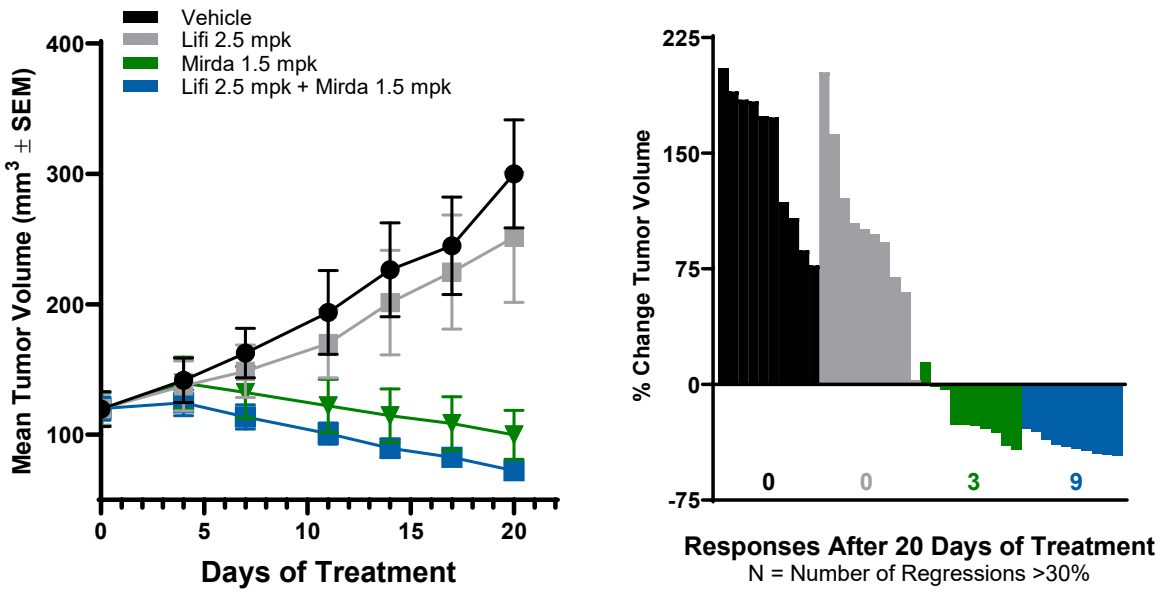
## Key Accomplishments from BeiGene Collaborations:

- Demonstrated **activity and tolerability of vertical MAPK pathway inhibition** in RAS and RAF mutant solid tumors with mirdametinib + lifirafenib combination
- Commenced first-in-human study of BGB-3245 and demonstrated **tolerability and monotherapy clinical activity** in tumor types of interest
- Defined priority tumor types and mutations for **next stage of clinical development** across MAPK portfolio
- Completed additional **equity investment in MapKure** joint venture to enable expanded focus and development

# Mirdametinib + Lifirafenib: Combination Synergy Demonstrated Across RAS Mutant Preclinical Models Informed Phase 1 Study Design

| 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)**




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



Sources: Desai et al., *J Clin Oncol*, 2020; Tang et al., *Mol Cancer Ther*, 2015; Yuan et al., *Molecular Oncology*, 2020; Yuan et al., *AACR*, 2020.

SpringWorks THERAPEUTICS

# Mirdametinib + Lifirafenib: Diverse Group of Solid Tumor Patients with MAPK Activating Mutations Enrolled in Dose Escalation Cohort

As of 11/05/21

| Baseline Characteristics | Overall, n (%) |
|---|---|
| **Patients treated** | 35 (100) |
| Still on Treatment | 13 (37.1) |
| **Sex** | |
| Male | 9 (25.7) |
| Female | 26 (74.3) |
| **Age** | |
| Mean | 58.3 |
| Median (Range) | 60 (22-78) |
| **Cancer stage at entry** | |
| III | 5 (14.3) |
| IV | 30 (85.7) |

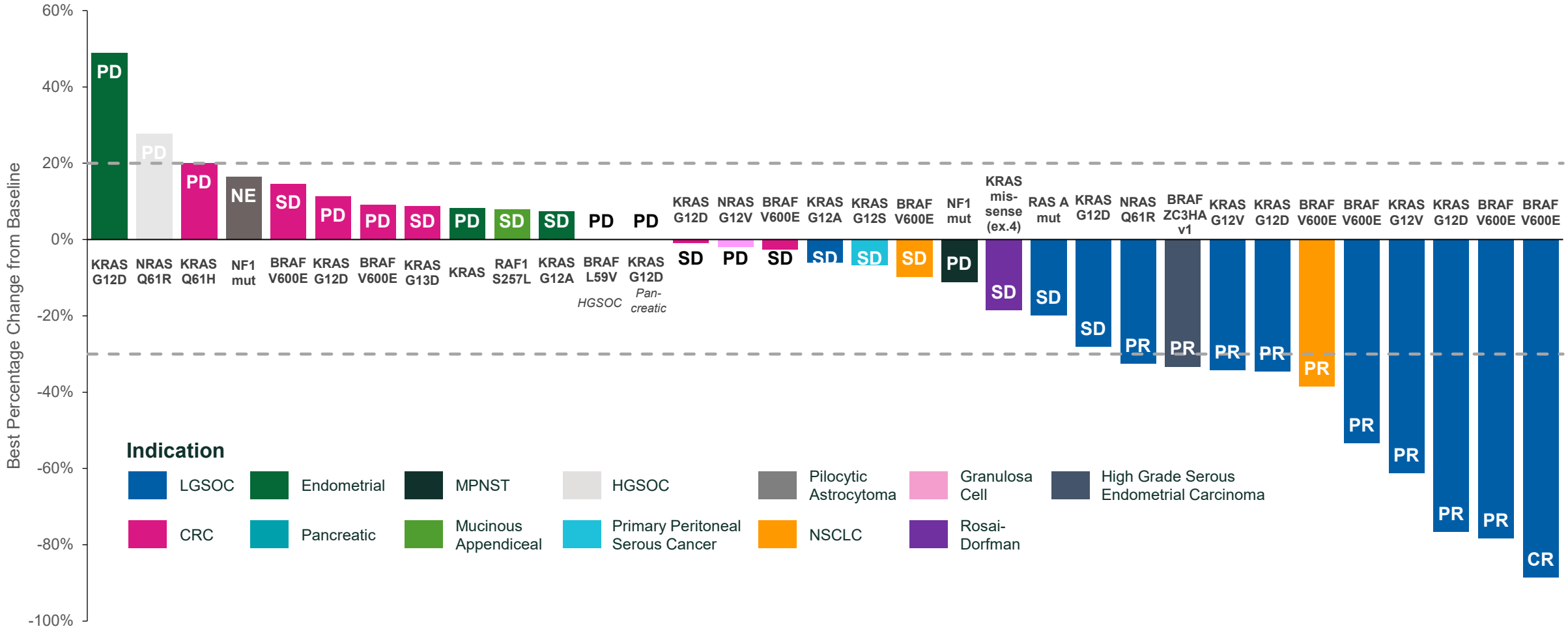
| Baseline Characteristics | Overall, n (%) |
|---|---|
| **Prior systemic cancer regimens** | |
| Median (Range) | 3 (1-9) |
| **ECOG status at entry** | |
| 0 | 24 (68.6) |
| 1 | 11 (31.4) |
| **Location of Tumor** | |
| Gynecological | 21 (60.0) |
| Gastrointestinal | 9 (25.7) |
| Lung | 2 (5.7) |
| Other | 3 (8.6) |
| **Mutation Status** | |
| RAS | 22 (62.9) |
| RAF | 11 (31.4) |
| NF1 | 2 (5.7) |



Note: Data are preliminary, investigator assessed, and have not been centrally reviewed; response data as of 11/05/21.

# Mirdametinib + Lifirafenib: Clinical Efficacy Observed During Dose Escalation

As of 11/05/21




**10 objective responses observed in 33 evaluable patients**

CR: complete response; CRC: colorectal cancer; HGSOC: high-grade serous ovarian carcinoma; LGSOC: low-grade serous ovarian carcinoma; MPNST: malignant peripheral nerve sheath tumor; PD: progressive disease; PR: partial response; SD: stable disease.

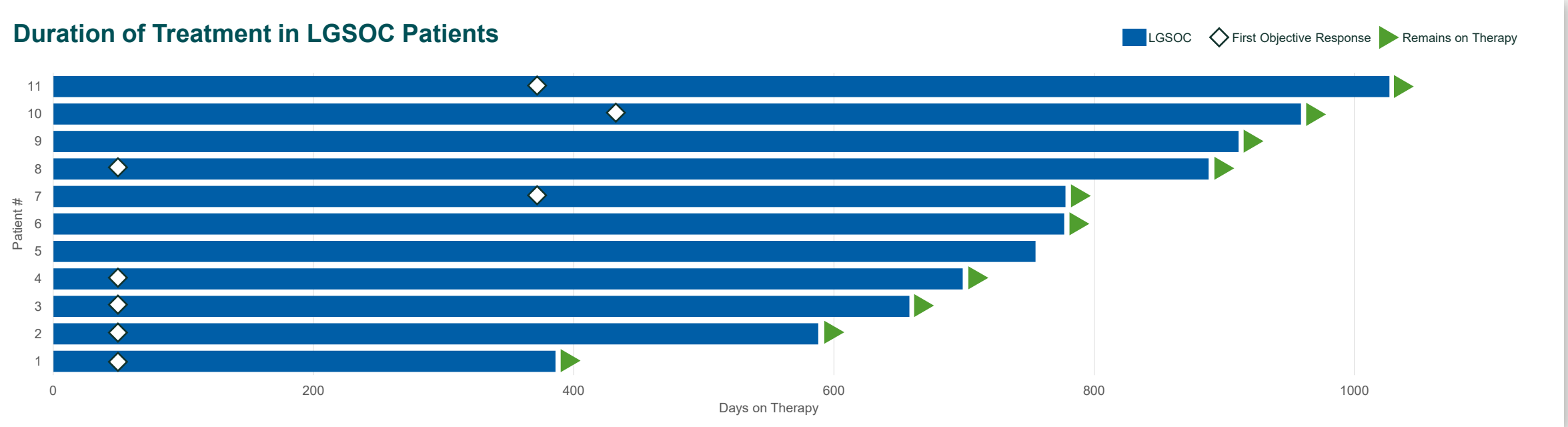
Note: Data are preliminary, investigator assessed, and have not been centrally reviewed; response data as of 11/05/21.



SpringWorks THERAPEUTICS

# Mirdametinib + Lifirafenib: LGSOC Patients Demonstrate Potential for Long Term Responses and Tolerability

Enrollment data as of 05/11/22




- 100% Disease Control Rate (DCR) with median time on therapy of ~26 months with 10 of 11 patients remaining on therapy (13-34 months) as of May 2022
- 73% ORR in LGSOC (1 CR + 7 PRs (out of 11), 3 durable SDs ≥72 weeks) with deepening or stable responses over time
- Responses seen irrespective of underlying RAS/RAF mutation (2 KRAS G12V, 2 KRAS G12D, 1 NRAS Q61R, and 3 BRAF V600E)

**Combination clinical activity and tolerability demonstrated by durable antitumor activity (median time on therapy ~26 months in LGSOC)**



Note: CR: complete response; LGSOC: low grade serous ovarian carcinoma; ORR: overall response; PR: partial response; SD: stable disease.
Note: Data are preliminary, investigator assessed, and have not been centrally reviewed; enrollment data as of 05/11/22. Assumes 30 days in one month.

# Mirdametinib + Lifirafenib: Evidence of Acceptable Safety and Tolerability Profile with Multiple Patients Exposed for >2 Years

| Grade ≥3 TEAE – All Cause | |
|---|---|
| **MedDRA PT** | **Grade ≥3 / n (%)** |
| **Overall** | **15 (42.9)** |
| Thrombocytopenia + platelet count decrease | 4 (11.4) |
| Intestinal obstruction | 4 (11.4) |
| ALT increased | 3 (8.6) |
| Hypertension | 2 (5.7) |
| Abdominal pain | 1 (2.9) |
| Anemia | 1 (2.9) |
| AST increased | 1 (2.9) |
| Febrile neutropenia | 1 (2.9) |
| Hypertriglyceridemia | 1 (2.9) |
| Other[1] | 1 (2.9) each |

| Grade ≥3 TEAE – Related | |
|---|---|
| **MedDRA PT** | **Grade ≥3 / n (%)** |
| **Overall** | **8 (22.9)** |
| Thrombocytopenia + platelet count decrease | 4 (11.4) |
| ALT increased | 2 (5.7) |
| Hypertension | 2 (5.7) |
| Abdominal pain | 1 (2.9) |
| Anemia | 1 (2.9) |
| AST increased | 1 (2.9) |
| Febrile neutropenia | 1 (2.9) |
| Hypertriglyceridemia | 1 (2.9) |

**All-cause adverse event profile aligns with relapsed/refractory cancer patients generally; related TEAEs have been manageable with few treatment discontinuation due to adverse events**



Note: MedDRA PT: Medical Dictionary for Regulatory Activities Preferred Term; TEAE: treatment-emergent adverse event.
(1) One patient each with abnormal LFTs; gamma-GT increased; rash maculopapular; urticaria; biliary infection; urinary tract infection; respiratory tract infection; neoplasm progression; metastasis to spine; acute myocardial infarction; and biliary obstruction.
Data cutoff date of 11/05/21.

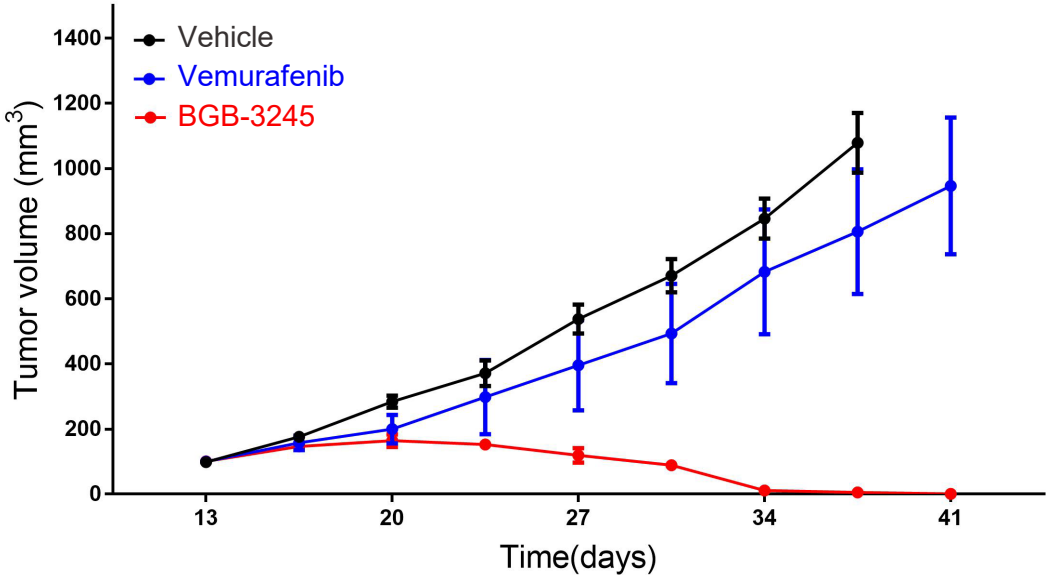
# BGB-3245

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

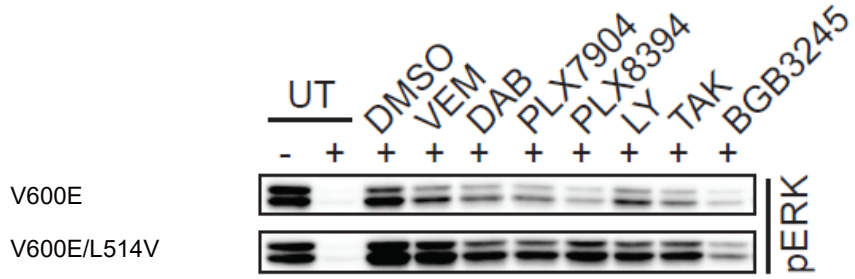
***BRAF* Fusion PDX: *In Vivo* Tumor Growth Inhibition[1]**




- 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



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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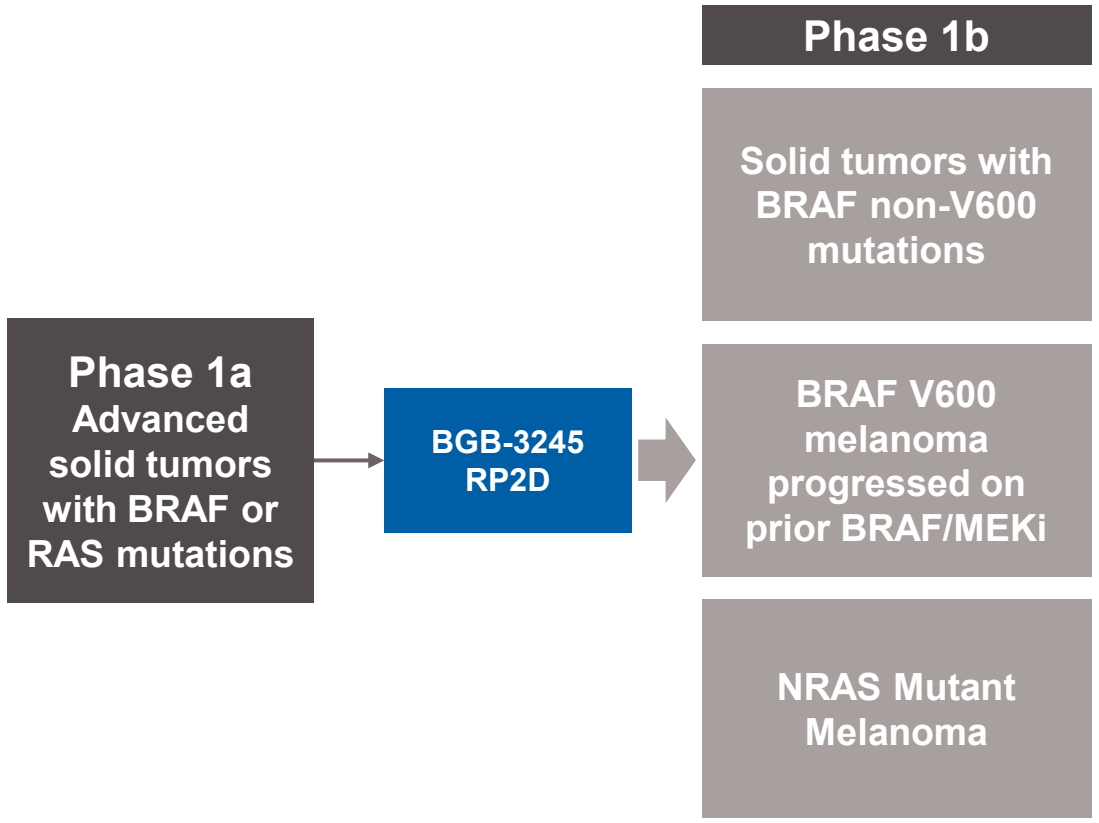
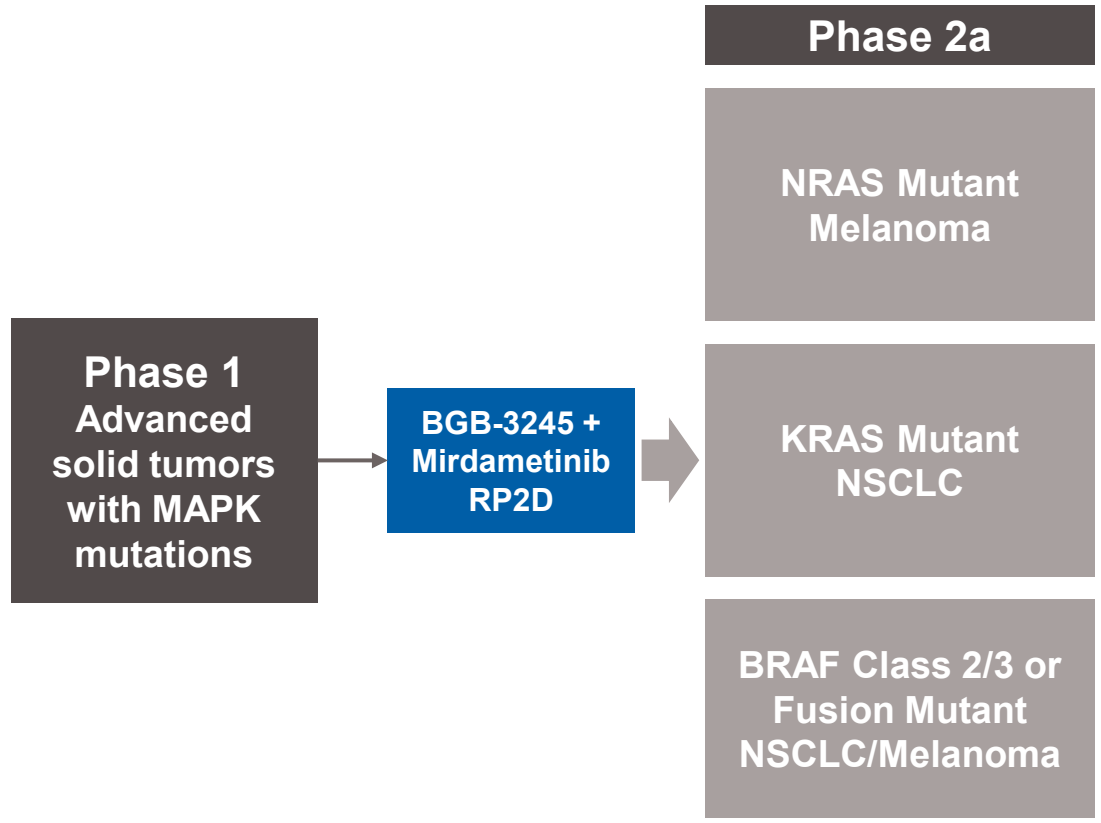
# BGB-3245: Ongoing Trials

## Ongoing Monotherapy Development




## Ongoing Combination Trial with Mirdametinib




**Advanced monotherapy trial into Phase 1b in 3Q22; combination trial dosed first patient in 1Q23**



Note: RP2D: recommended Phase 2 dose.

# BGB-3245: Monotherapy Patient Characteristics in Dose Escalation

As of 02/26/22

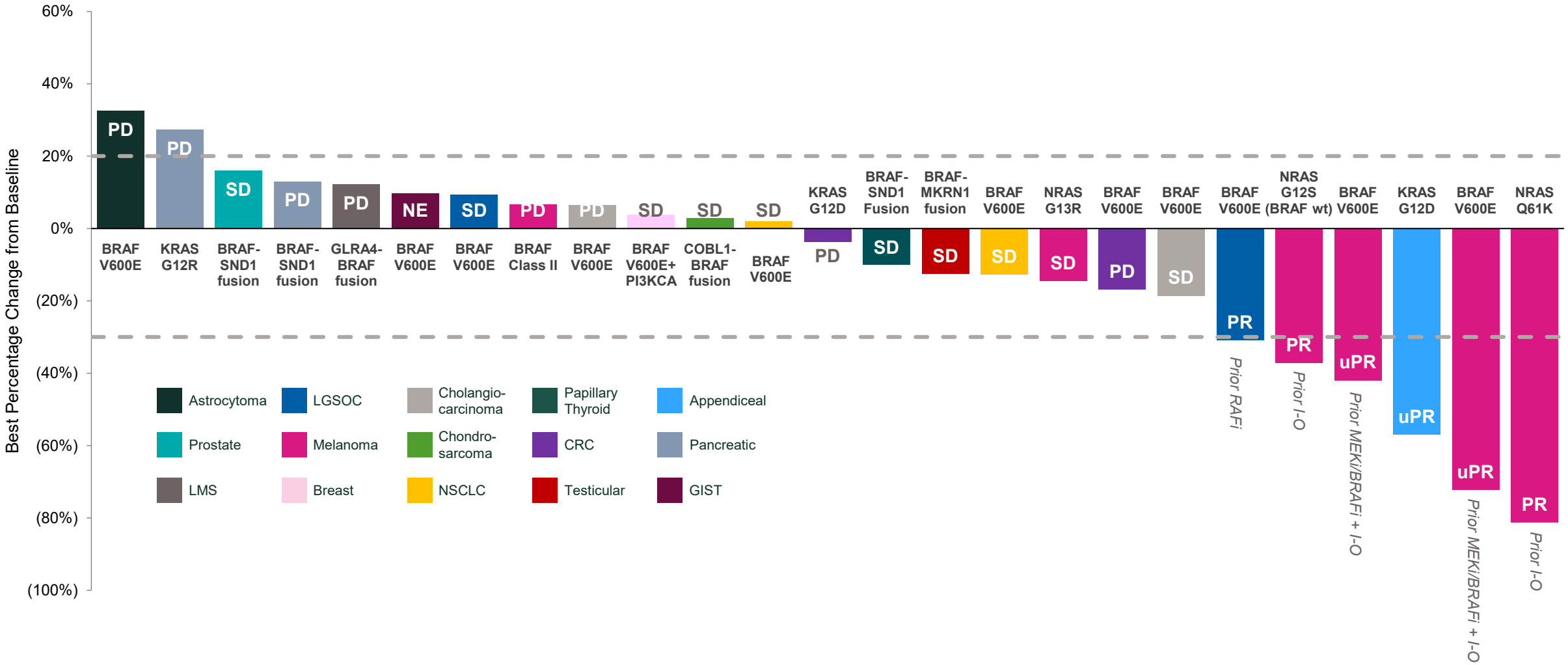
| Baseline Characteristics | Overall, n (%) |
|---|---|
| **Patients treated** | 38 (100) |
| Still on Treatment | 14 (36.8) |
| **Sex** | |
| Male | 22 (57.9) |
| Female | 16 (42.1) |
| **Age** | |
| Mean | 58.6 |
| Median (Range) | 57 (31-83) |
| **Cancer stage at entry** | |
| III/other | 5 (13.2) |
| IV | 33 (86.8) |
| **Prior systemic cancer regimens** | |
| Median (Range) | 5 (0-10) |

| Baseline Characteristics | Overall, n (%) |
|---|---|
| **ECOG status at entry** | |
| 0 | 24 (63.2) |
| 1 | 13 (34.2) |
| Undocumented | 1 (2.6) |
| **Classification of Tumor** | |
| Gastrointestinal | 13 (34.2) |
| Skin | 9 (23.7) |
| Female genitourinary | 4 (10.5) |
| Lung | 4 (10.5) |
| Thyroid | 3 (7.9) |
| Male genitourinary | 2 (5.3) |
| Brain | 1 (2.6) |
| Breast | 1 (2.6) |
| Other | 1 (2.6) |
| **Mutation Status** | |
| RAS | 11 (28.9) |
| RAF | 27 (71.1) |

**Diverse group of solid tumor patients with RAS/RAF mutations enrolled**

# BGB-3245: Early Clinical Efficacy Observed in Dose Escalation

As of 02/26/22




Note: CRC: colorectal cancer; GIST: gastrointestinal stromal tumor; IO: immuno-oncology; LMS: leiomyosarcoma; LGSOC: low-grade serous ovarian cancer; NSCLC: non-small cell lung cancer; PD: progressive disease; PR: partial response; SD: stable disease; TL: target lesion; uPR: unconfirmed partial response; wt: wildtype.
Note: Data are preliminary, investigator assessed, and have not been centrally reviewed. Response data as of 02/26/22.



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# BGB-3245: Emerging Safety Profile Manageable and Consistent with MAPK Pathway Inhibitors

As of 01/10/22

| Grade ≥3 TEAE – All Cause | |
|---|---|
| MedDRA PT | Grade ≥3 / n (%) |
| **Overall** | **14 (41.2)** |
| Rash maculopapular | 2 (5.9) |
| Dyspnea | 2 (5.9) |
| ALT increased | 3 (8.8) |
| AST increased | 2 (5.9) |
| Abdominal pain | 2 (5.9) |
| Pyrexia | 1 (2.9) |

| Grade ≥3 TEAE – Related | |
|---|---|
| MedDRA PT | Grade ≥3 / n (%) |
| **Overall** | **4 (11.8)** |
| Rash maculopapular | 2 (5.9) |



Note: TEAE: treatment-emergent adverse event.
Note: Data are preliminary, investigator assessed, and have not been centrally reviewed. Safety data as of 01/10/22.

# Preclinical Pipeline

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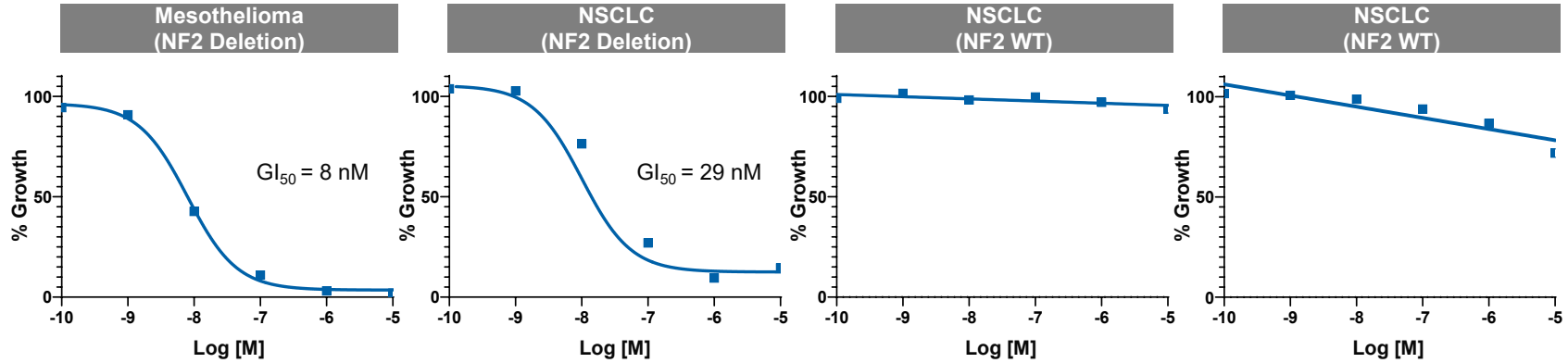
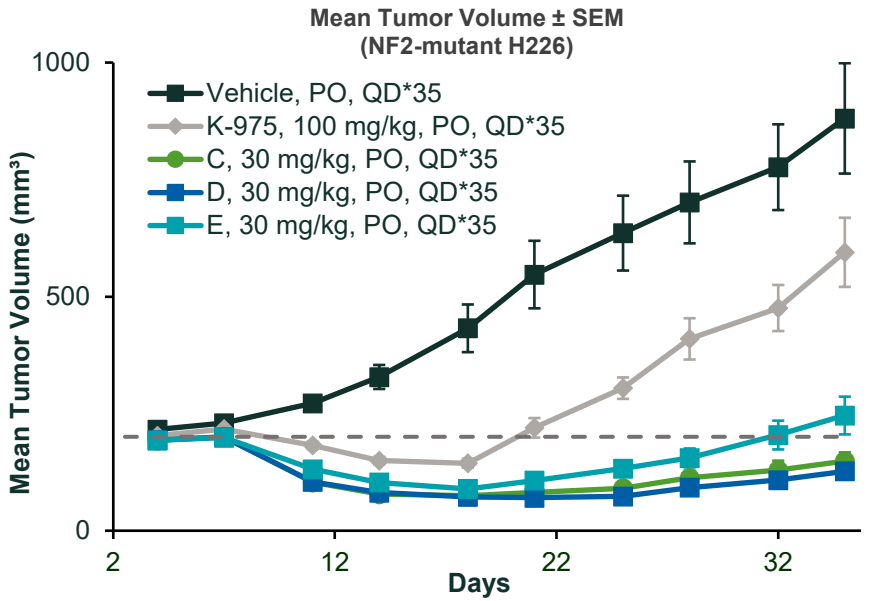
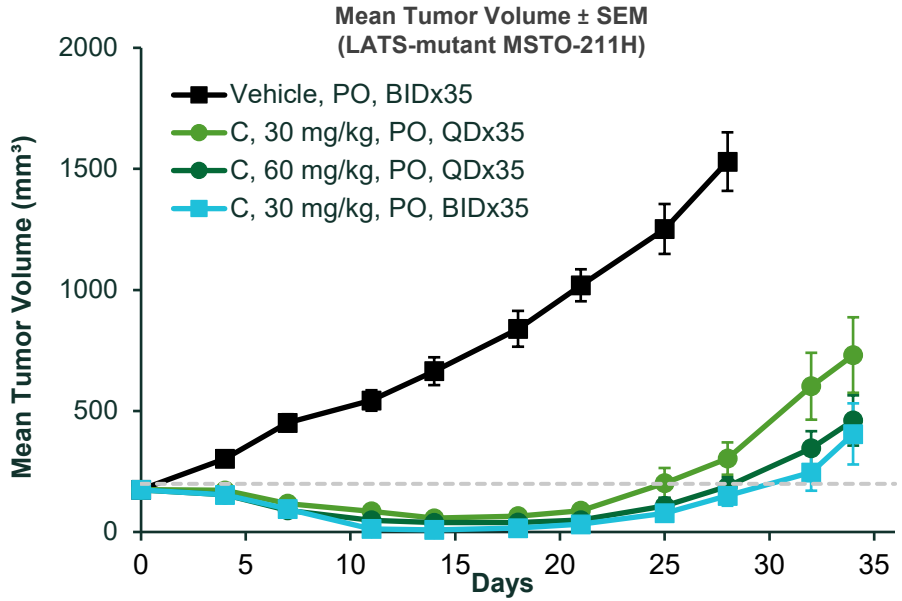
# TEAD Inhibitor: Selectivity, Potency and In Vivo Tumor Growth Inhibition Demonstrated in Hippo-Driven Models

**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 Hippo altered xenografts




**Development candidate (SW-682) nominated 4Q 2022, IND-enabling studies underway**



Note: GI50 = drug concentration producing 50% maximal growth inhibition; P.O. = by mouth; QD = once a day; BID = twice a day.

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


- 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 is being conducted in collaboration with Dr. Nathanael Gray (Stanford) and Drs. Pasi Janne, Michael Eck, and Jarrod Marto (Dana-Farber)

# The SpringWorks Opportunity

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

**$597.0M**

**Cash, Cash Equivalents & Marketable Securities(1)**

**No Debt**

**NASDAQ: SWTX**

**62.5M**

**Common Shares Outstanding(2)**

(1) As of December 31, 2022.
(2) Basic common shares outstanding as of February 22, 2023.

# Building Blocks for Substantial Value Creation in 2023 and Beyond

- Highly clinically and statistically significant data support practice-changing, first-in-class commercial opportunity for nirogacestat in desmoid tumors
- Mirdametinib topline readout in NF1-PN provides opportunity to support competitive product profile across full age spectrum
- Substantial upside opportunity across wholly-owned and partnered programs, potentially yielding value-creating and thesis-validating data
- Robust IP portfolio providing durable protection and preserving long-term value of lead assets
- Capital efficient operating model with strong financial position that supports activities into 2026

# Thank you

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