Corporate Presentation

February 2024

SpringWorks® THERAPEUTICS

Forward-Looking Statements

Note: Unless otherwise indicated, the information presented herein is as of February 2024 and made publicly available on February 27, 2024.

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 and commercialization plans, our preclinical and clinical results, the market potential of OGSIVEO for adult patients with desmoid tumors, expectations regarding timing and results of the European Medicine Agency’s (EMA) review of the Marketing Authorisation Application (MAA) for nirogacestat, including its ongoing validation of our submission package, and the adequacy of the data contained in the MAA to serve as the basis for marketing approval for the treatment of desmoid tumors in the European Union, the potential for the results of the Phase 2b ReNeu clinical trial to support an NDA submission for mirdametinib in 1H 2024, our plans to report additional data from the Phase 2b ReNeu clinical trial at an upcoming medical conference and submit for publication data from such clinical trial in a peer-reviewed medical journal in 2024, 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, expectations regarding the timing and initial data from the Phase 2 trial evaluating nirogacestat in patients with recurrent ovarian granulosa cell tumors, our plans to initiate a Phase 1 trial of SW-682 in Hippo mutant solid tumors in the first half of 2024, our plans to report additional clinical data of nirogacestat in combination with BCMA-directed therapies and initiate additional planned Phase 1 collaborator studies, our expectations regarding the potential for the Phase 1b dose expansion phase of brimarafenib, our plans to present additional data for brimarafenib monotherapy in MAPK-mutant solid tumors in 2H 2024, our plans to support MapKure’s initiation of a Phase 1b trial of brimarafenib with panitumumab in CRC and pancreatic cancer patients in 1Q 2024, expectations 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 of our commercialization efforts with respect to OGSIVEO, (ii) our limited experience as a commercial company, (iii) our ability to obtain or maintain adequate coverage and reimbursement for OGSIVEO, (iv) the success and timing of our product development activities, including the initiation and completion of our clinical trials, (v) our expectations regarding the potential clinical benefit of OGSIVEO for adult patients with desmoid tumors, (vi) the potential for OGSIVEO to become the new standard of care for adult patients with desmoid tumors who require systemic treatment, (vii) estimates regarding the number of adult patients who are diagnosed with desmoid tumors annually per year in the U.S. and the potential market for OGSIVEO, (viii) 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, (ix) the success and timing of our collaboration partners’ ongoing and planned clinical trials, (x) 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), European Medicines Agency (EMA), and other regulatory authorities, investigational review boards at clinical trial sites and publication review bodies, (xi) whether FDA, EMA, or other regulatory authorities will require additional information or further studies, or may fail or refuse to approve or may delay approval of our product candidates, including nirogacestat and mirdametinib, (xii) our ability to obtain regulatory approval of any of our product candidates or maintain regulatory approvals granted for our products, (xiii) our plans to research, discover and develop additional product candidates, (xiv) our ability to enter into collaborations for the development of new product candidates and our ability to realize the benefits expected from such collaborations, (xv) our ability to maintain adequate patent protection and successfully enforce patent claims against third parties, (xvi) the adequacy of our cash position to fund our operations through any time period indicated herein, (xvii) our ability to establish manufacturing capabilities, and our and our collaboration partners’ abilities to manufacture our product candidates and scale production, and (xviii) our ability to meet any specific milestones set forth herein.

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 a Commercial-Stage Targeted Oncology Company Delivering New Advances for Patients

First and only FDA-approved therapy for desmoid tumors with launch of OGSIVEO™

Potential best-in-class data in NF1-PN expected to support NDA submission for possible second approval by 2025

Diversified pipeline of emerging programs under study in additional underserved patient populations

Strong financial position and durable IP protection for lead assets

SpringWorks THERAPEUTICS

Differentiated Lead Programs With Practice-Changing Potential in Rare Tumor Types and Broad Indication Expansion Opportunities

Nirogacestat

- OGSIVEO (nirogacestat) launch ongoing as the first and only FDA-approved therapy for desmoid tumors(1) with $5.4M in net revenue for the first partial quarter of sales (Q4 2023)
- Novel and differentiated product profile and broad label underpins potential to become the standard of care
- Robust launch to date with strong early demand from sarcoma COEs, integrated health systems, and large community practices
- Submitted Marketing Authorisation Application for desmoid tumors in Europe in February 2024
- Advancing expansion opportunities as monotherapy in OvGCT and BCMA combination therapy in multiple myeloma
- Durable patent portfolio of 16 Orange Book-listed patents, with latest expiry in 2043; received Orphan Drug exclusivity from FDA

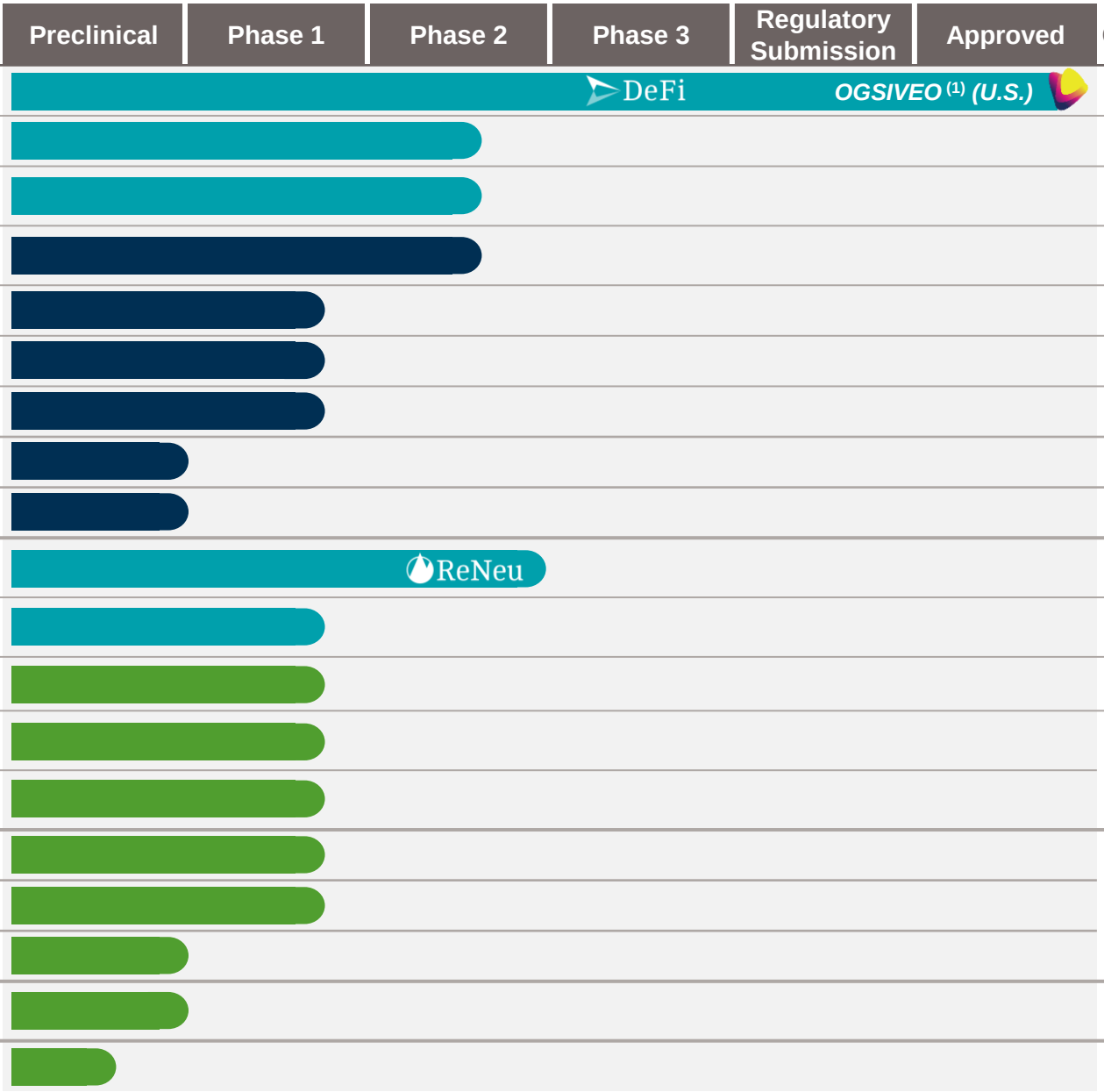
Mirdametinib

- Topline data from pivotal Phase 2b ReNeu trial showed best-in-class product potential for both pediatric and adult patients with NF1-PN
- Deep and durable responses confirmed by BICR and manageable safety profile were received favorably in physician survey when compared to existing treatment options(2)
- NDA submission on track for 1H 2024 and positions us for potential second product approval by 2025
- Monotherapy and combination studies ongoing in additional indications, including RAS/RAF-mutated solid tumors
- Fast Track and Rare Pediatric Disease Designations from FDA; Orphan Drug Designation from FDA and European Commission
- Durable patent portfolio of 10 patents that may be Orange Book-listable and latest expiry in 2043

Note: COE: Center of Excellence; OvGCT: Ovarian granulosa cell tumors; NF1-PN: Neurofibromatosis type 1-associated plexiform neurofibroma.
(1) OGSIVEO was approved for the treatment of adult patients with progressing desmoid tumors who require systemic treatment on November 27, 2023.
(2) SpringWorks primary market research, December 2023 (N=100 HCPs, each treating an average of >20 NF1-PN patients). Respondents answered questions based on review of blinded profiles derived from FDA labeling (selumetinib) and ReNeu topline data (mirdametinib).

Diversified Targeted Oncology Pipeline Spanning Solid Tumors and Hematological Cancers

Compound	Indication	Development Approach	Collaborator(s)
Nirogacestat Gamma Secretase Inhibitor	Desmoid Tumors*	Monotherapy (adult)	
		Monotherapy (pediatric)	
	Ovarian Granulosa Cell Tumors	Monotherapy	
	Multiple Myeloma *(BCMA Combinations)*	+ Belantamab mafodotin (belamaf) (ADC)	
		+ Teclistamab (Bispecific)	
		+ Elranatamab (Bispecific)	
		+ Linvoseltamab (Bispecific)	
		+ SEA-BCMA (mAb)	
		+ ABBV-383 (Bispecific)	
Mirdametinib MEK Inhibitor	NF1-Associated Plexiform Neurofibromas†	Monotherapy	
	Pediatric Low-Grade Gliomas	Monotherapy	
	NRAS Mutant Solid Tumors	+ Lifirafenib (Pan-RAF inhibitor)	
	ER+ Metastatic Breast Cancer	+ Fulvestrant (SERD)	
	MEK 1/2 Mutant Solid Tumors	Monotherapy	
Brimarafenib RAF Fusion & Dimer Inhibitor	MAPK Mutant Solid Tumors	Monotherapy	
	MAPK Mutant Solid Tumors	+ Mirdametinib	
	MAPK Mutant Solid Tumors	+ Panitumumab	
SW-682 TEAD Inhibitor	Hippo Mutant Tumors	Monotherapy and combo	
EGFR Program	EGFR Mutant Tumors	Monotherapy and combo	



* Received Orphan Drug Designation. † Received Orphan Drug, Fast Track, and Rare Pediatric Disease Designations. (1) Indicated for adult patients with progressing desmoid tumors who require systemic treatment. (2) Being developed by MapKure, LLC, jointly owned by SpringWorks and BeiGene.

Rare Oncology | BCMA Combos | Biomarker-Defined Solid Tumors

SpringWorks THERAPEUTICS

Building Our Opportunity Set With Value-Driving Execution Across Our Pipeline in 2024

	Anticipated 2024 Milestones
Nirogacestat *(Gamma Secretase Inhibitor)*	❑ Continue establishing OGSIVEO as standard of care for adult desmoid tumor patients ✓ Submit MAA to EMA in 1H 2024 ❑ Report initial data for Phase 2 study of nirogacestat in OvGCT in 2H 2024 ❑ Support additional data disclosures by partners for ongoing BCMA collaborations and advance development of nirogacestat combination across lines of multiple myeloma treatment
Mirdametinib *(MEK Inhibitor)*	❑ Submit NDA to FDA for children and adults with NF1-PN in 1H 2024 ❑ Present ReNeu trial data at a major medical congress in 1H 2024 ❑ Publish ReNeu trial data in peer-reviewed academic journal in 2024
Brimarafenib(1) *(RAF Fusion and Dimer Inhibitor)*	❑ Present additional data for brimarafenib monotherapy in MAPK-mutant solid tumors in 2H 2024 ❑ Initiate Phase 1b trial of brimarafenib with panitumumab in CRC and pancreatic cancer patients in 1Q 2024
Portfolio Expansion	❑ Initiate Phase 1 trial of SW-682 (TEAD inhibitor) in Hippo-mutant solid tumors in 1H 2024 ❑ Advance early-stage assets and discovery work, while seeking to expand portfolio through investment in internal programs and opportunistic business development

(1) Being developed by MapKure, a joint venture owned by SpringWorks and BeiGene. Listed milestones to be achieved through MapKure.
Note: MAA: Marketing Authorisation Application; EMA: European Medicines Agency; OvGCT: ovarian granulosa cell tumors; CRC: colorectal cancer.

OGSIVEO (nirogacestat)

Desmoid Tumors

SpringWorks® THERAPEUTICS

The First and Only FDA-Approved Therapy for Adult Patients With Desmoid Tumors Is Now Available

OGSIVEO is a gamma secretase inhibitor indicated for adult patients with progressing desmoid tumors who require systemic treatment

SpringWorks THERAPEUTICS

The Wait Is Over for Desmoid Tumor Patients

Aggressive, invasive, and highly debilitating soft tissue tumors

Can cause severe and chronic pain, loss of physical function, disfigurement, and anxiety

Complications can lead to nerve compression, intestinal obstruction, and internal bleeding

High rates of surgical recurrence and suboptimal outcomes with off-label systemic therapies left a critical unmet need

No FDA-approved therapies specifically for desmoid tumors prior to approval of OGSIVEO

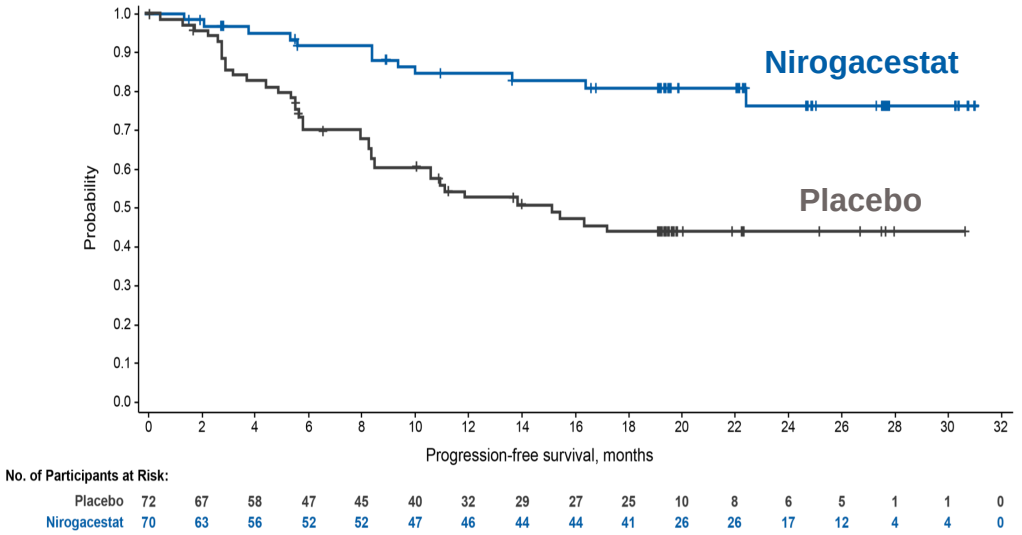
My desmoid tumor **wrapped around my nerves, veins and artery** behind my knee. I've had **ten surgeries total**, six to remove the tumor and four related to complications, and it **keeps growing back.**

- DeAnn, desmoid tumor patient

Strong Label Positions OGSIVEO to Become the Standard of Care for Desmoid Tumors

Efficacy Summary from USPI

	OGSIVEO (n=70)	Placebo (n=72)
Progression-Free Survival		
Number (%) of patients with event	12 (17)	37 (51)
Radiographic progression[a]	11 (16)	30 (42)
Clinical progression[a]	1 (1)	6 (8)
Death	0	1 (1)
Median (months) (95% CI)[b]	NR (NR, NR)	15.1 (8.4, NR)
Hazard ratio (95% CI)	0.29 (0.15, 0.55)	
p-value[c]	<0.001	
Objective Response Rate[a]		
ORR, n (%)	29 (41)	6 (8)
95% CI[d]	(29.8, 53.8)	(3.1, 17.3)
CR	5 (7)	0
PR	24 (34)	6 (8)
p-value[e]	<0.001	



"Progression-free survival results were supported by change from baseline in patient-reported worst pain favoring the OGSIVEO arm."

- OGSIVEO USPI

Safety Summary from USPI

Warnings and Precautions

- Diarrhea, ovarian toxicity, hepatotoxicity, non-melanoma skin cancers, electrolyte abnormalities, embryo-fetal toxicity

Most Common Adverse Reactions[f]

- Diarrhea, ovarian toxicity, rash, nausea, fatigue, stomatitis, headache, abdominal pain, cough, alopecia, upper respiratory tract infection, dyspnea

No Boxed Warnings, REMS Program, or Contraindications

Full prescribing information is available at www.OGSIVEO.com.; USPI: U.S. Prescribing Information; CI: confidence interval; ORR: objective response rate; CR: complete response; PR: partial response; NR: not reached.

a) Assessed by blinded independent central review.
b) Obtained using Kaplan-Meier Methodology.
c) p-value was from a one-sided stratified log-rank test with placebo as reference.
d) Obtained using exact method based on binomial distribution.
e) p-value was from a two-sided Cochran-Mantel-Haenszel test.
f) Reported in over 15% of patients.

SpringWorks THERAPEUTICS

OGSIVEO Can Address the Needs of Patients at All Stages of Their Desmoid Tumor Treatment

U.S. Patient Population

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

Incidence of 3 – 5 per million per year with over 90% of patients receiving active intervention over the course of their disease

>70% of patients prefer medication over surgery

>75% of physicians believe OGSIVEO offers clinical benefits not offered by other treatments

~5,500-7,000
patients actively managed annually

Includes patients under continuous management since first diagnosis and those with tumor recurrence

>70% of physicians are aware of OGSIVEO

~90% of physicians expect to use OGSIVEO within the first year of approval

30,000+
total diagnosed prevalent patients

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

>80% of physicians expect to recontact patients who are not under treatment / surveillance

We expect OGSIVEO will be the standard of care for adult desmoid tumor patients

Sources: SWTX Primary Market Research; Van Broekhoven et al., Annals of Surgical Oncology, 2015; Reitamo et al., American Journal of Clinical Pathology, 1982; Anneberg et al., Cancer Epidemiology, 2022.

Launch Priorities for OGSIVEO

ADOPT

Position OGSIVEO as first or next systemic treatment and standard of care

SUPPORT

Provide comprehensive patient support to help maximize patient access and adherence

LEAD

Reinforce commitment to desmoid tumor community and improve patient outcomes

EXPAND

Educate physicians and patients to broaden the role of systemic therapy

Encouraging Early Signals for OGSIVEO Through First Partial Quarter of Launch Support Standard of Care Potential for Desmoid Tumors

$5.4M in OGSIVEO net product revenue for the first ~4 weeks following approval

Drug in channel and available within 5 business days of approval, with first patient receiving OGISVEO the following day

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) updated to recommend nirogacestat as an NCCN Category 1, Preferred treatment option for desmoid tumors within 2 weeks of approval

Confirmed reimbursement from payers representing over 98% of commercial and Medicare lives with broad coverage to label(1) and growing number of published policies aligned to label

Field team driving strong awareness of and engagement with OGSIVEO, with over 85% of SARC / NCCN centers and significant number of other academic and community accounts reached

Promising breadth of prescribing across all customer types and positive indicators revealing depth of utilization

Desmoid tumor-specific ICD-10 codes continue to provide real-time view on patients and where they are being treated

(1) Based on actual reimbursement of OGSIVEO to date ahead of final published coverage criteria.

NCCN: National Comprehensive Cancer Network® (NCCN®). Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Soft Tissue Sarcoma V.3.2023. © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. Accessed January 5, 2024. To view the most recent and complete version of the guideline, go online to NCCN.org.

SpringWorks THERAPEUTICS

Strong Engagement With Our Comprehensive Patient Support and Access Program

SpringWorks CareConnections™

Coverage and Access Support

Resources to facilitate reimbursement and timely and appropriate access to OGSIVEO

Financial Assistance

Financial support for eligible patients, including co-pay program and Patient Assistance Program

Personalized Support

Dedicated nurse advocates to support patients throughout their treatment journey

Mirdametinib

NF1-PN

SpringWorks® THERAPEUTICS

A Substantial Unmet Need Remains for a More Effective Treatment Option for Adult and Pediatric NF1-PN Patients

Disfiguring and highly morbid growth along nerves, often causing chronic, disabling pain

Significant impact on patient and caregiver quality of life with emotional and psychological burden

Surgery is difficult due to infiltrative growth along nerves and is viewed as an inadequate long-term solution

Challenging dosing / administration, tolerability, and label restrictions limit utility of currently approved MEK inhibitors

No approved options for adult NF1-PN patients

I was diagnosed with NF1 as a baby. I've had **18 surgeries. 24 hospital stays** and have been **on a ventilator since 2013**. I was told that my life expectancy would be short, but even so, I went to college, I have a good job, and **I continue to fight NF.**

- Antwan, NF1-PN patient

Positive Topline Results From Pivotal Phase 2b ReNeu Trial Demonstrate Mirdametinib's Potential Differentiation and Transformative Benefit for NF1-PN Patients

Potential best-in-class profile for both pediatric and adult NF1-PN patients

Deep and durable responses confirmed by BICR and statistically significant improvements in pain and physical functioning

Manageable safety profile with low rates of Grade 3+ toxicities and dose interruptions supports potential for extended treatment durations

Pediatric formulation and convenient administration with no fasting requirement to enhance compliance

~100,000

Individuals with an NF1 diagnosis in the U.S.(1)

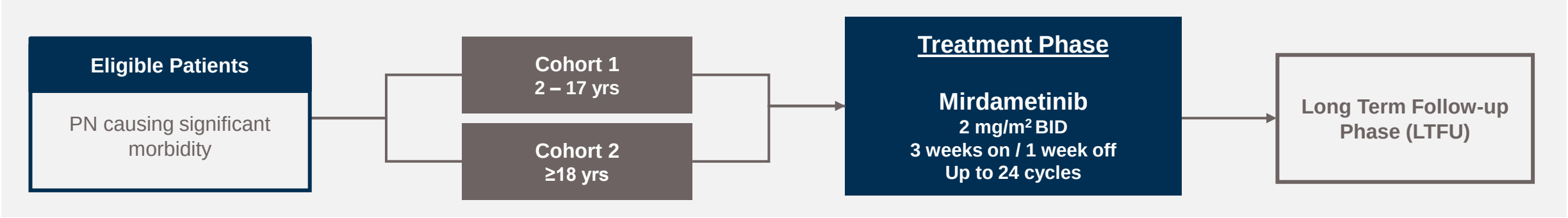
~40,000

Patients living with NF1-PN in the U.S.(2,3)

Note: BICR: Blinded Independent Central Review.
Sources: (1) Lammert et al., Arch Dermat, 2005. U.S. Census Data; (2) Fisher et al., Neuro-Oncology, 2022. (3) SpringWorks market research.

Phase 2b ReNeu Trial Summary

Trial Design	▪ Phase 2b open-label; n = 114 patients in 2 cohorts (pediatric and adults) across 37 U.S. sites ▪ 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 ▪ Pediatric formulation (dispersible tablet) introduced in 2H 2020
Primary Endpoint	▪ Confirmed objective response rate (≥20% reduction in tumor volume per REiNS criteria) determined by BICR by end of treatment phase
Secondary / Exploratory Endpoints	▪ Safety and tolerability, duration of response, QoL and physical functioning assessments (including measures of pain)



Note: REiNS: Response Evaluation in Neurofibromatosis and Schwannomatosis; BICR: blinded independent central review; BID: twice daily; QoL: quality of life.

Baseline Patient Demographics and Disease Characteristics

Pediatric Participants (n=56)

Characteristic	n (%)
Patients enrolled	56
Median age at enrollment [range] - years	10.0 [2 – 17]
Sex	
Male	26 (46)
Female	30 (54)
Location of target neurofibroma	
Head and Neck	28 (50)
Lower / Upper Extremities	8 (14)
Paraspinal	4 (7)
Other	16 (29)
Type of neurofibroma-related complication	
Pain	39 (70)
Disfigurement or Major Deformity	28 (50)
Motor Dysfunction or Weakness	15 (27)
Airway Dysfunction	7 (13)
Other	12 (21)
Target PN progressing at study entry	35 (63)

Adult Participants (n=58)

Characteristic	n (%)
Patients enrolled	58
Median age at enrollment [range] - years	34.5 [18 – 69]
Sex	
Male	21 (36)
Female	37 (64)
Location of target neurofibroma	
Head and Neck	28 (48)
Lower / Upper Extremities	17 (29)
Paraspinal	5 (9)
Other	8 (14)
Type of neurofibroma-related complication	
Pain	52 (90)
Disfigurement or Major Deformity	30 (52)
Motor Dysfunction or Weakness	23 (40)
Airway Dysfunction	3 (5)
Other	10 (17)
Target PN progressing at study entry	31 (53)

Data presented is topline data as of September 20, 2023 data cutoff.
Note: PN: plexiform neurofibroma.

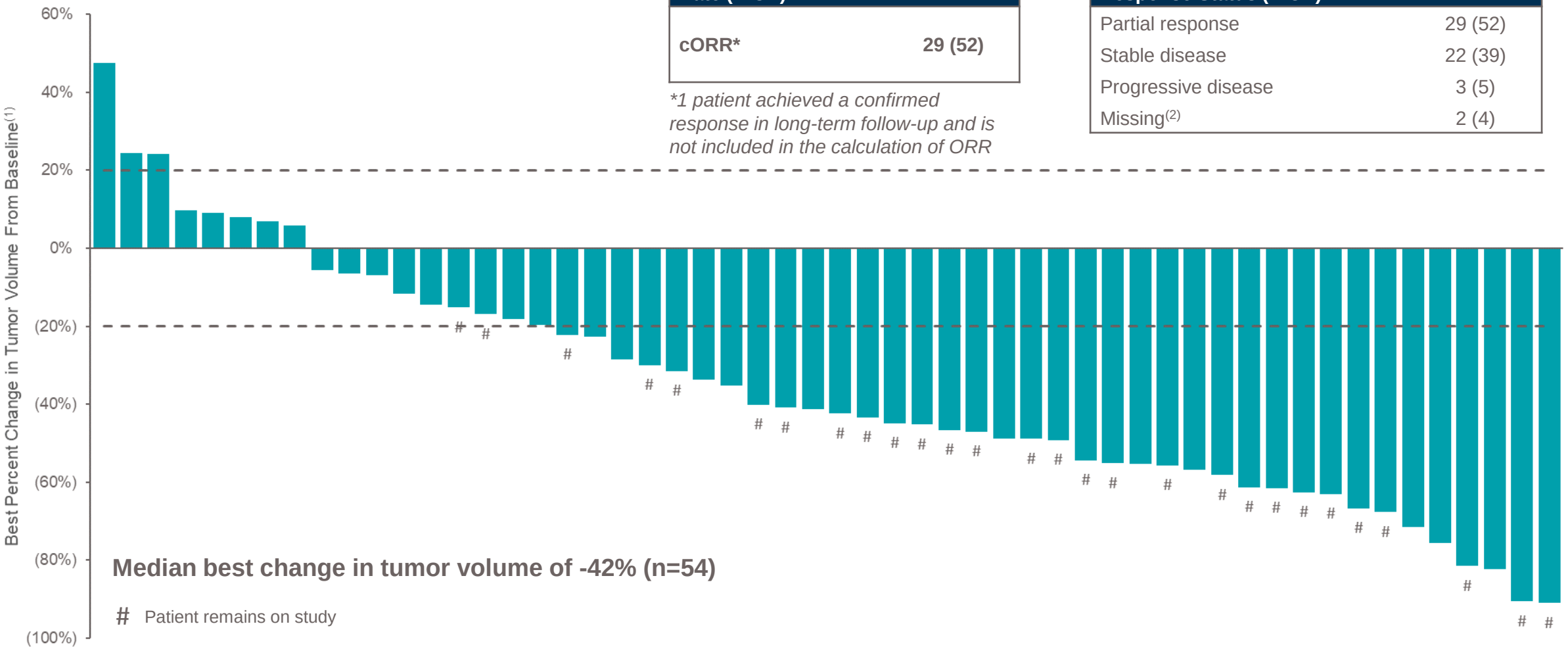
Best Tumor Response

Pediatric Cohort

Confirmed Response Rate (BICR)	n (%)
cORR*	29 (52)

*1 patient achieved a confirmed response in long-term follow-up and is not included in the calculation of ORR

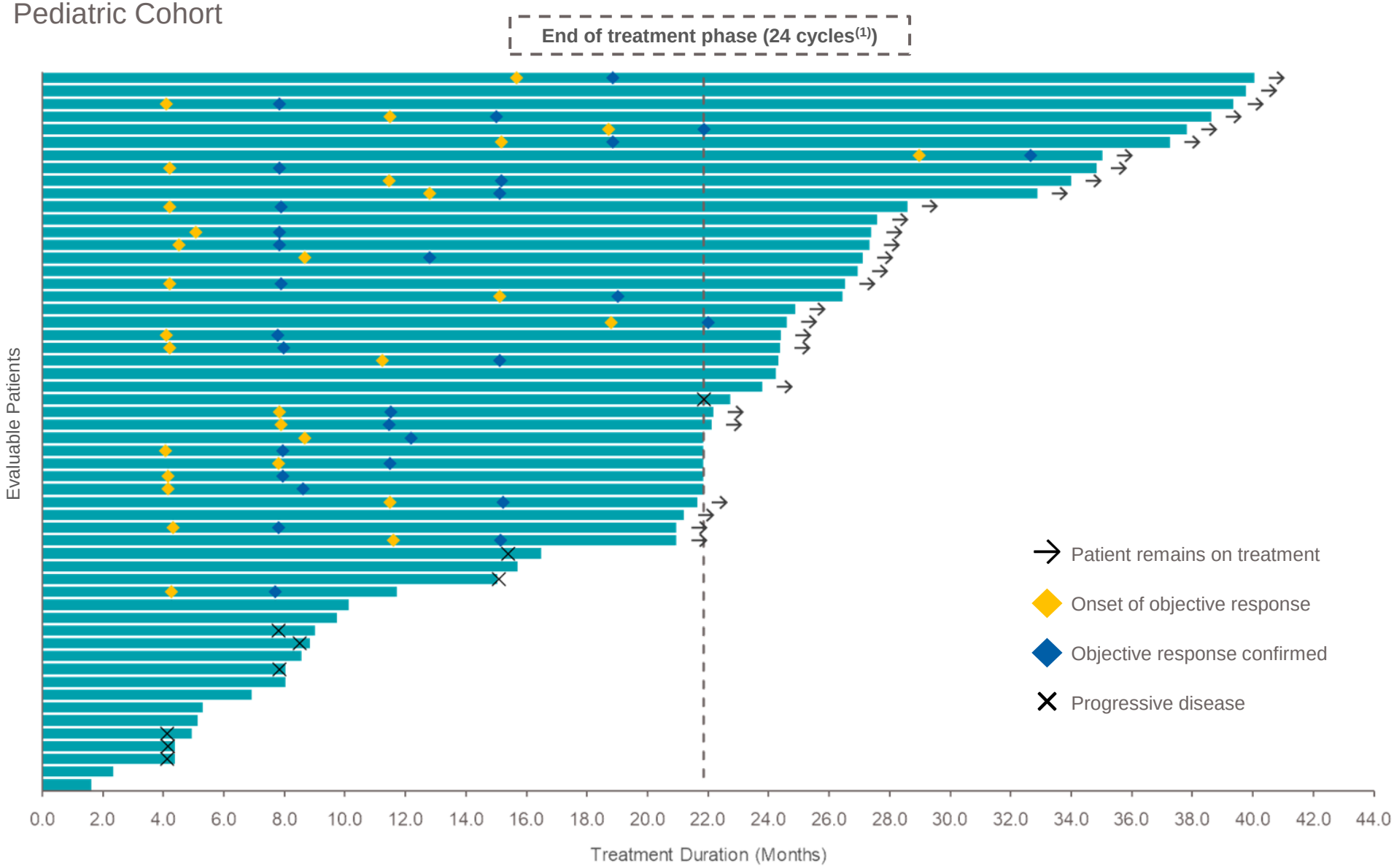
Best Overall Confirmed Response Status (BICR)	n (%)
Partial response	29 (52)
Stable disease	22 (39)
Progressive disease	3 (5)
Missing[2]	2 (4)



Data presented is topline data as of September 20, 2023 data cutoff.
Note: BICR: blinded independent central review; cORR: confirmed objective response rate.
(1) Shows best change in tumor volume achieved at any point, including unconfirmed partial responses.
(2) Participants that discontinued study prior to any on-treatment MRI assessment.

Treatment Duration and Response

Pediatric Cohort



- Median duration of treatment was 22.0 months
- Median time to first response was 7.9 months
  - 45% of patients had their onset of confirmed response by Cycle 5 assessment (4.2 months)
- Median duration of response was not reached
- 28 patients remained on treatment as of data cutoff
- 85% of patients that completed the treatment phase chose to continue receiving treatment in the long-term follow-up portion of the study

Data presented is topline data as of September 20, 2023 data cutoff.

(1) 4-week cycles of 3 weeks on, 1 week off. Treatment phase ends 3 weeks into final cycle.

Patient-Reported Outcomes

Pediatric Cohort

Scale	p-Value for Change from Baseline[1]
Target Tumor Pain – Numeric Rating Scale (NRS-11)[2] (n=17)	0.003
Pain Interference Index (PII)[3]	
Self-Report (n=22)	0.017
Parent Proxy (n=20)	0.025
Pediatric Quality of Life Inventory (PedsQL)[4] – Total Score	
Self-Report (n=38)	0.096
Parent Proxy (n=43)	0.005
Pediatric Quality of Life Inventory (PedsQL)[4] – Physical Functioning	
Self-Report (n=38)	0.033
Parent Proxy (n=43)	0.037

Data presented is topline data as of September 20, 2023 data cutoff (updated).

(1) Change from baseline at Cycle 13, the pre-specified assessment for patient-reported outcome analysis per the ReNeu statistical analysis plan. Least squared means estimates using a mixed model for repeated measures (MMRM).

(2) The NRS-11 assesses target tumor pain on a scale from 0 – “no pain” to 10 – “worst pain you can imagine.” NRS-11 assessments were performed for six consecutive days prior to a visit as well as on the visit day, except for the ET visit, which is done on the visit day only. The mean of these seven assessments is taken as the visit score. Baseline is defined as the most recent NRS-11 score taken on or before treatment start date.

(3) The PII assesses the degree to which pain has impacted the participants’ daily activities on a scale from 0 – “not at all” to 6 – “completely.” PII assessments were performed on the six consecutive days prior to a visit as well as on the visit day, except for the ET visit, which is done on the visit day only. The mean of these seven assessments is taken as the visit score. Baseline is defined as the most recent PII score taken on or before treatment start date.

(4) PedsQL assess quality of life on a Likert scale from 0 to 4. These items are then reverse scored and linearly transformed to a 0-100 scale as follows: 0=100, 1=75, 2=50, 3=25, 4=0, with higher scores indicating a higher quality of life. Baseline is defined as the most recent PedsQL score taken on or before treatment start date.

Safety Summary

Pediatric Cohort

(n=56)	TEAEs ≥ 20% Subjects		TRAEs	
Preferred Term	**All Grades – n (%)**	**≥ Grade 3 – n (%)**	**All Grades – n (%)**	**≥ Grade 3 – n (%)**
Any TEAE	**56 (100)**	**22 (39)**	**53 (95)**	**14 (25)**
Rash[1]	36 (64)	2 (4)	33 (59)	2 (4)
Diarrhea	31 (55)	3 (5)	21 (38)	1 (2)
Dermatitis acneiform	24 (43)	1 (2)	24 (43)	1 (2)
Vomiting	22 (39)	0 (0)	8 (14)	0 (0)
Headache	19 (34)	1 (2)	6 (11)	0 (0)
Paronychia	18 (32)	0 (0)	17 (30)	0 (0)
Nausea	15 (27)	0 (0)	12 (21)	0 (0)
Abdominal pain	15 (27)	2 (4)	8 (14)	2 (4)
Ejection fraction decreased	15 (27)	1 (2)	11 (20)	1 (2)
COVID-19	14 (25)	0 (0)	0 (0)	0 (0)
Upper respiratory tract infection	13 (23)	0 (0)	1 (2)	0 (0)
Blood creatine phosphokinase increased	12 (21)	4 (7)	11 (20)	4 (7)
Cough	12 (21)	0 (0)	0 (0)	0 (0)

(n=56)	n (%)
TEAE leading to dose interruption[2]	17 (30)
TEAE leading to dose reduction	7 (13)
TEAE leading to discontinuation	5 (9)

(1) Composite adverse event including dermatitis acneiform, rash, rash maculo-papular, rash erythematous, acne, seborrheic dermatitis, exfoliative rash, papule, rash papular, dermatitis, rash macular, rash pruritic.
(2) Dose interruptions due to treatment-related adverse events occurred in 8 patients (14%).
Note: TEAE: treatment-emergent adverse event; TRAE: treatment-related adverse event. Data presented is topline data as of September 20, 2023 data cutoff.

ReNeu SpringWorks THERAPEUTICS

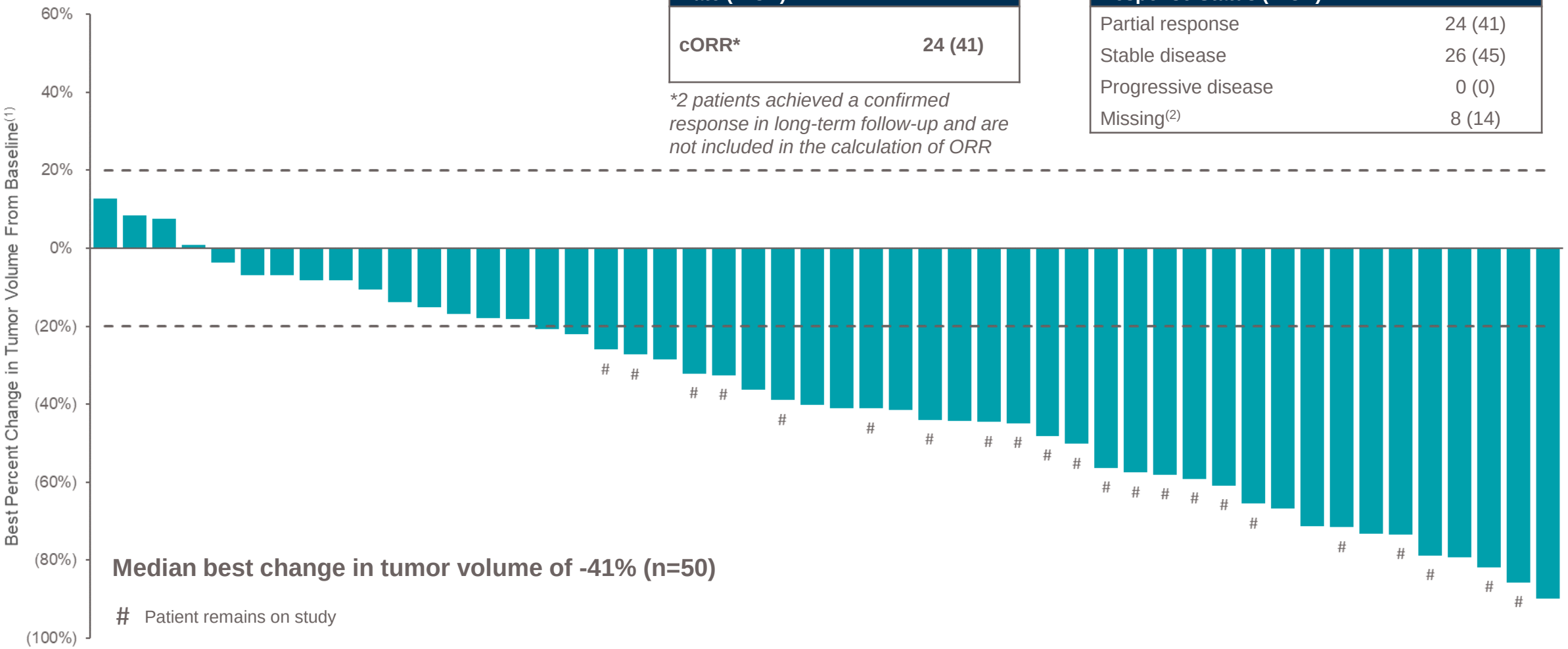
Best Tumor Response

Adult Cohort

Confirmed Response Rate (BICR)	n (%)
cORR*	24 (41)

**2 patients achieved a confirmed response in long-term follow-up and are not included in the calculation of ORR*

Best Overall Confirmed Response Status (BICR)	n (%)
Partial response	24 (41)
Stable disease	26 (45)
Progressive disease	0 (0)
Missing[2]	8 (14)

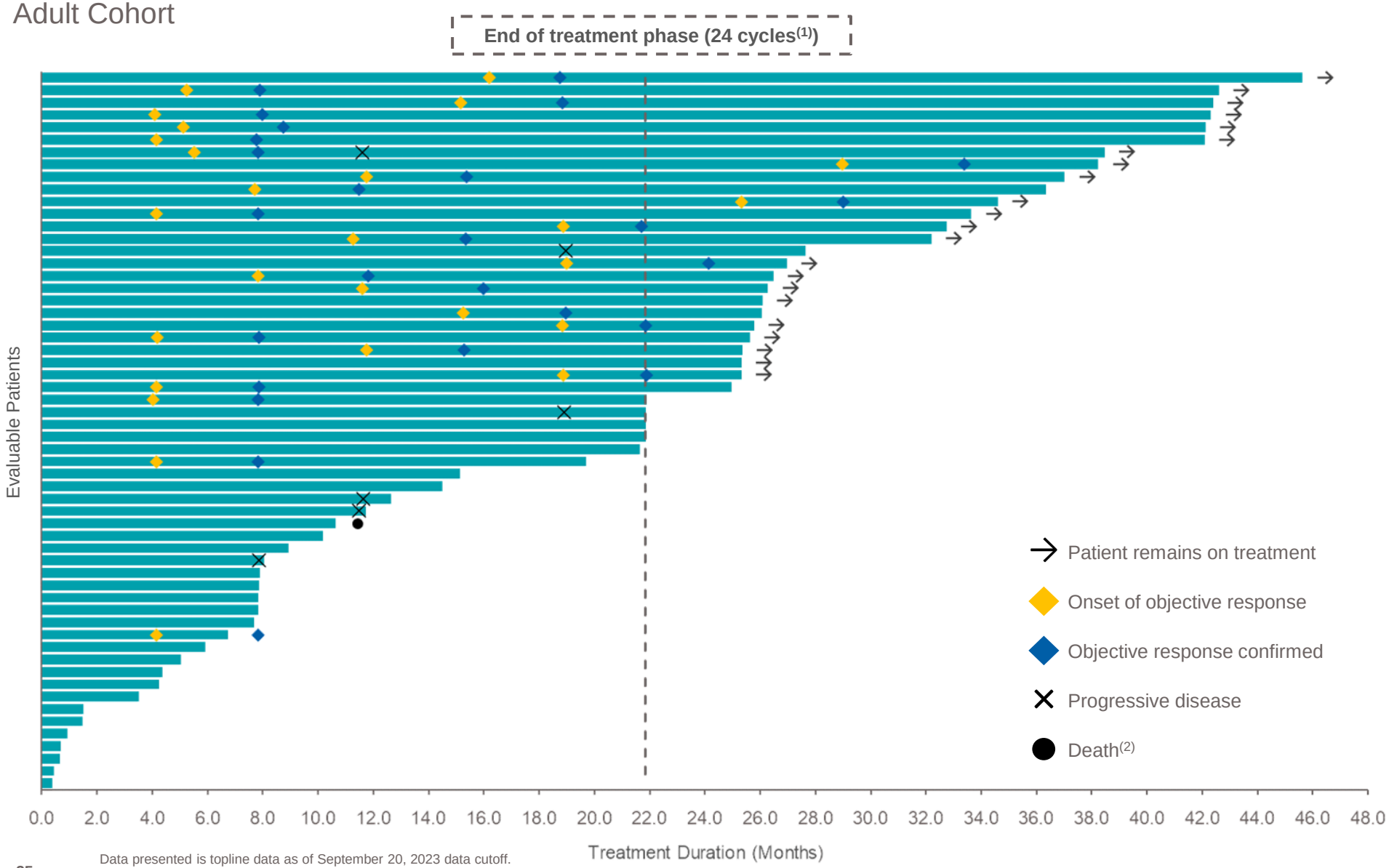


Data presented is topline data as of September 20, 2023 data cutoff.
Note: BICR: blinded independent central review; cORR: confirmed objective response rate.
(1) Shows best change in tumor volume achieved at any point, including unconfirmed partial responses.
(2) Participants that discontinued study prior to any on-treatment MRI assessment.

ReNeu SpringWorks THERAPEUTICS

Treatment Duration and Response

Adult Cohort



- Median duration of treatment was 21.8 months
- Median time to first response was 7.8 months
  - 46% of patients had their onset of confirmed response by Cycle 5 assessment (4.2 months)
- Median duration of response was not reached
- 22 patients remained on treatment as of data cutoff
- 84% of patients that completed the treatment phase chose to continue receiving treatment in the long-term follow-up portion of the study

Data presented is topline data as of September 20, 2023 data cutoff.

(1) 4-week cycles of 3 weeks on, 1 week off. Treatment phase ends 3 weeks into final cycle.

(2) One patient death due to COVID-19 occurred within 30 days of discontinuing study treatment and was deemed not related to mirdametinib.

Patient-Reported Outcomes

Adult Cohort

Scale	p-Value for Change from Baseline[1]
Target Tumor Pain – Numeric Rating Scale (NRS-11)[2] (n=21)	<0.001
Pain Interference Index (PII)[3] (n=22)	<0.001
Pediatric Quality of Life Inventory (PedsQL)[4] – Total Score (n=34)	0.018
Pediatric Quality of Life Inventory (PedsQL)[4] – Physical Functioning (n=34)	0.012

.

Data presented is topline data as of September 20, 2023 data cutoff (updated).

(1) Change from baseline at Cycle 13, the pre-specified assessment for patient-reported outcome analysis per the ReNeu statistical analysis plan. Least squared means estimates using a mixed model for repeated measures (MMRM).

(2) The NRS-11 assesses target tumor pain on a scale from 0 – “no pain” to 10 – “worst pain you can imagine.” NRS-11 assessments were performed for six consecutive days prior to a visit as well as on the visit day, except for the ET visit, which is done on the visit day only. The mean of these seven assessments is taken as the visit score. Baseline is defined as the most recent NRS-11 score taken on or before treatment start date.

(3) The PII assesses the degree to which pain has impacted the participants’ daily activities on a scale from 0 – “not at all” to 6 – “completely.” PII assessments were performed on the six consecutive days prior to a visit as well as on the visit day, except for the ET visit, which is done on the visit day only. The mean of these seven assessments is taken as the visit score. Baseline is defined as the most recent PII score taken on or before treatment start date.

(4) PedsQL assess quality of life on a Likert scale from 0 to 4. These items are then reverse scored and linearly transformed to a 0-100 scale as follows: 0=100, 1=75, 2=50, 3=25, 4=0, with higher scores indicating a higher quality of life. Baseline is defined as the most recent PedsQL score taken on or before treatment start date.

Safety Summary

Adult Cohort

(n=58)	TEAEs ≥ 20% Subjects		TRAEs	
Preferred Term	**All Grades – n (%)**	**≥ Grade 3 – n (%)**	**All Grades – n (%)**	**≥ Grade 3 – n (%)**
Any TEAE	**58 (100)**	**21 (36)**	**57 (98)**	**9 (16)**
Rash[1]	54 (93)	6 (10)	54 (93)	6 (10)
Dermatitis acneiform	45 (78)	5 (9)	45 (78)	5 (9)
Diarrhea	34 (59)	0 (0)	28 (48)	0 (0)
Nausea	30 (52)	0 (0)	21 (36)	0 (0)
Vomiting	22 (38)	0 (0)	16 (28)	0 (0)
Fatigue	17 (29)	1 (2)	12 (21)	1 (2)
COVID-19	13 (22)	3 (5)	0 (0)	0 (0)
SARS-COV-2 test positive	12 (21)	2 (3)	0 (0)	0 (0)

(n=58)	n (%)
TEAE leading to dose interruption[2]	18 (31)
TEAE leading to dose reduction	10 (17)
TEAE leading to discontinuation	13 (22)

(1) Composite adverse event including dermatitis acneiform, rash, rash maculo-papular, rash erythematous, acne, seborrheic dermatitis, exfoliative rash, papule, rash papular, dermatitis, rash macular, rash pruritic.
(2) Dose interruptions due to treatment-related adverse events occurred in 5 patients (9%).
Note: TEAE: treatment-emergent adverse event; TRAE: treatment-related adverse event. Data presented is topline data as of September 20, 2023 data cutoff.

Physicians View Mirdametinib's Profile as Clinically Compelling and Differentiated

Mirdametinib Can Address Unmet Needs in NF1-PN

92% agreed there is an unmet need for pediatric NF1-PN patients

98% agreed there is an unmet need for adult NF1-PN patients

100% believed mirdametinib's clinical profile will address key unmet needs in most or some adult NF1-PN patients

Mirdametinib's Differentiation vs. Existing Treatments

96% found mirdametinib's overall clinical profile to be more compelling than selumetinib's for pediatric NF1-PN patients

89% found mirdametinib's clinical profile to be more compelling than selumetinib's on efficacy

81% found mirdametinib's clinical profile to be more compelling than selumetinib's on safety

Source: SpringWorks primary market research, December 2023 (N=100 HCPs, each treating an average of >20 NF1-PN patients). Respondents answered questions based on review of blinded profiles derived from FDA labeling (selumetinib) and ReNeu topline data (mirdametinib). No head-to-head studies have been conducted between mirdametinib and selumetinib.

Regulatory Status and Next Steps Toward Potential Mirdametinib Approval

Regulatory Status

NDA submission to FDA expected in 1H 2024

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

Rare Pediatric Disease Designation granted by FDA in July 2023, which provides eligibility for priority review voucher upon FDA approval

Upcoming Data and Publications

Expect to present detailed study results from pediatric and adult cohorts of the ReNeu trial at a medical conference in 1H 2024

Preparation of manuscript for peer-reviewed journal publication is underway, with anticipated submission in 2024

Note: EMA: European Medicines Agency.

Emerging Portfolio

SpringWorks® THERAPEUTICS

Broad Emerging Pipeline Continues to Advance and Offers Substantial Upside Potential

Nirogacestat	Ovarian Granulosa Cell Tumors	Phase 2 ongoing
	Multiple Myeloma	+ BCMA-directed agents: Phase 1 and Phase 2 studies ongoing
Mirdametinib	Pediatric Low-Grade Gliomas	Phase 1/2 ongoing
	MAPK Mutant Solid Tumors	+ Lifirafenib: Phase 1/2 ongoing
	ER+ Metastatic Breast Cancer	+ Fulvestrant: Phase 1b/2a ongoing
	MEK1/2 Mutant Solid Tumors	Phase 1b/2 ongoing
Brimarafenib[1]	MAPK Mutant Solid Tumors	Phase 1 ongoing
	MAPK Mutant Solid Tumors	+ Mirdametinib: Phase 1/2a ongoing
	MAPK Mutant Solid Tumors	+ Panitumumab: Phase 1b planned
Additional Programs	Hippo Mutant Solid Tumors	SW-682: Phase 1 study planned
	EGFR Mutant Tumors	Discovery

(1) Being developed by MapKure, a joint venture owned by SpringWorks and BeiGene.

Rare Oncology | BCMA Combos | Biomarker-Defined Solid Tumors

Nirogacestat in Ovarian Granulosa Cell Tumors (OvGCT) Represents a Meaningful New Expansion Opportunity

Disease Overview

Background and Rationale

- OvGCT accounts for ~5-7% of all ovarian cancers[1,2]
- >97% of OvGCT are driven by activating mutations in FOXL2, which have been shown to be sensitive to Notch inhibition[3,4]

Meaningful Addressable Population

- Median diagnosis age of 50 years
- Estimated U.S. incidence: ~1,000-1,500 per year; significant prevalent population: ~10,000-15,000[5,6]

No Approved Treatments

- Early-stage disease managed with surgery; however, ~45% of patients experience post-surgical recurrence[7]
- 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)
- Trial initiated in September 2022; announced full enrollment in May 2023

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

Initial clinical data from the Phase 2 trial in OvGCT is expected in 2H 2024

Sources: (1) Dridi et al., International Journal of Surgical Oncology, 2018; (2) Ayhan et al., Eur J Gynaecol Oncol, 1994; (3) Li et al., Journal of Ovarian Research, 2018; (4) Irusta et al., Biol Reprod, 2013; (5) SEER; (6) Torre L. et al., CA Cancer J Clin, 2018; (7) Klar et al., Journal of Surgical Oncology, 2023.

Nirogacestat in OvGCT Could Address Need for Targeted Therapy in Underserved Indication

OvGCT Are Potentially Susceptible to GSIs

- >97% of OvGCT are driven by C124W mutation in FOXL2, which 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

NCCN Guidelines Highlight Substantial Unmet Need

- 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

Preliminary Market Research Survey to Assess Practice Demographics, Treatment Practices, and Physician Feedback

- Key insights related to unmet need 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: 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. SpringWorks market research.

Nirogacestat in Multiple Myeloma: A Potential Combination With BCMA-Directed Therapies

Rationale and Development Strategy

- Gamma secretase directly cleaves membrane BCMA, a clinically validated multiple myeloma target across modalities (ADC, CAR T, mAb, bispecific)
  - Inhibition of gamma secretase increases expression of BCMA on multiple myeloma cells, allowing enhanced binding of BCMA-directed therapies and anti-BCMA activity to induce multiple myeloma cell death
- 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 multiple myeloma

~80,000 MM patients receiving 1L and 2L therapy annually in the U.S.(1)

~10,000 r/r MM patients receiving 3L+ therapy annually in the U.S.(1)

Combination use being investigated with BCMA-targeted therapy modalities

Potential for use alongside SoC MM therapies across lines of treatment

Preclinically validated across all key modalities:

Antibody-drug conjugates

Bispecific antibodies

CAR-T cell therapies

Monoclonal antibodies

Industry Collaborators

abbvie

GSK

janssen PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Pfizer

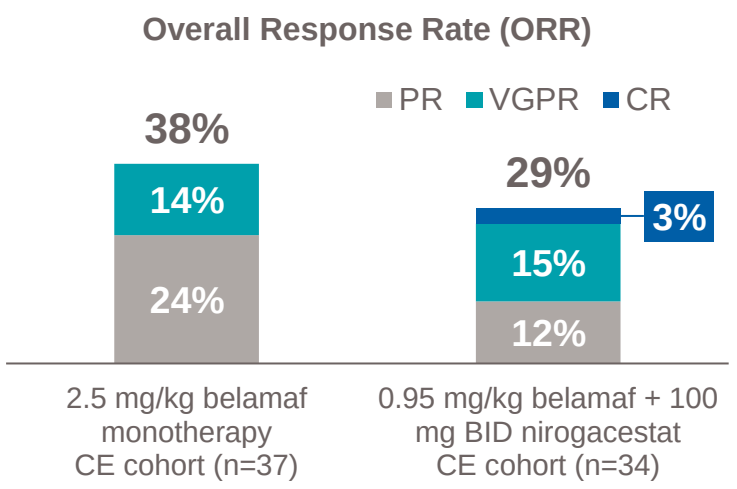
REGENERON

Seagen®

Source: (1) Kanas et al 2020.
Note: MM: multiple myeloma; r/r: relapsed / refractory.

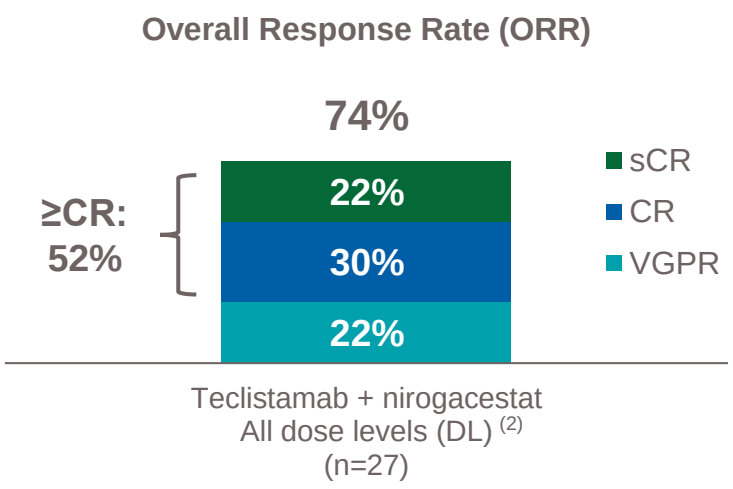
Nirogacestat in Multiple Myeloma: Emerging Clinical Data Supports Validation of BCMA Combination Development Approach Across Modalities

Nirogacestat + Belamaf Ph 1/2



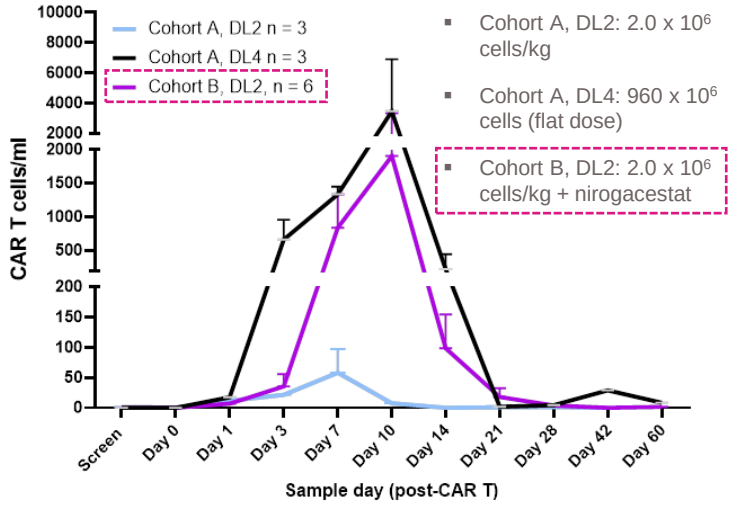
- Comparable efficacy with substantial reduction in Grade 3 ocular adverse events observed
- Posterior probability ORR(1) of 36% for nirogacestat + belamaf combo vs. 33% for belamaf alone
- Additional trials with SoC agents and investigator-sponsored studies ongoing
- Expanded non-exclusive collaboration announced in September 2022 enables potential development into earlier treatment lines

Nirogacestat + Teclistamab Ph 1b



- High and deep response rates observed with teclistamab + nirogacestat in patients with relapsed/refractory multiple myeloma
- Safety profile optimized with delayed administration of lower-dose nirogacestat
- Initial profile established for nirogacestat + BCMA bispecific combination

Nirogacestat + BCMA CAR-T Ph 1/2



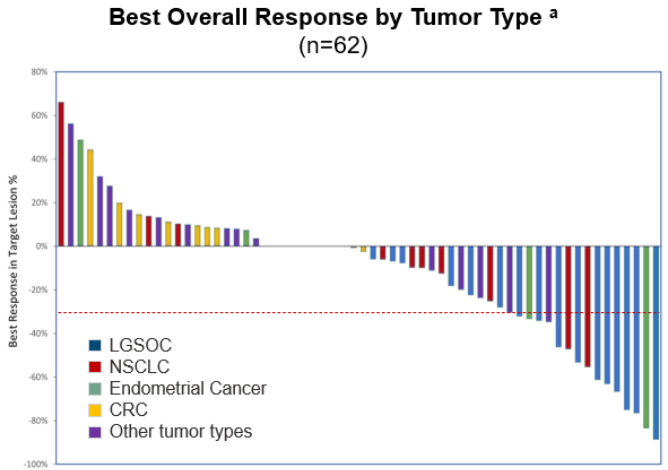
- Similar level of expansion and persistence observed with nirogacestat + low-dose allogeneic BCMA CAR-T cells vs. monotherapy CAR-T cells
- Improved cell expansion correlated with increased clinical activity

(1) Incorporating prior ORR for low-dose belamaf + nirogacestat from DREAMM-5 sub-study 3 DE cohort (observed ORR 60% [6/10]) and for monotherapy from DREAMM-2 2.5mg/kg monotherapy cohort (observed ORR 31% [30/.97] per prespecified analysis plan.
(2) Dose level 1: teclistamab SC 0.72 mg/kg QW + concurrent nirogacestat PO 100 mg BID (n=8); dose level 2: teclistamab SC 0.72 mg/kg QW + delayed nirogacestat PO 100 mg QD (n=7); dose level 3: teclistamab SC 1.5 mg/kg QW + delayed nirogacestat PO 100 mg QD (n=13).
Note: PR: partial response; VGPR: very good partial response; CR: complete response; sCR: stringent complete response; CE: cohort expansion; DE: dose exploration; BID: twice daily; SoC: standard of care.
Source: Lonial et al., EHA, 2023. Offner et al., EHA, 2023. Precision BioSciences investor materials (ASH 2021 presentation on December 11, 2021; Allogeneic CAR-T Update presentation on June 8, 2022; 3Q 2022 Earnings Release as of November 8, 2022); preliminary data from Precision-sponsored trial (NCT04171843).

Mirdametinib Expansion Opportunities in Biomarker-Defined Solid Tumors and Rare Oncology

Mirdametinib + Lifirafenib in MAPK Mutant Solid Tumors

- Lifirafenib is a pan-RAF inhibitor under study as combination therapy with mirdametinib through collaboration with BeiGene
- Combination led to sustained inhibition of MAPK pathway signaling and significant tumor regression in preclinical models
- Clinical data for Phase 1b dose-escalation presented at AACR 2023, with dose-expansion portion of the study initiated in September 2023 following first patient dose
  - Favorable safety profile, with few dose-limiting toxicities and discontinuations
  - Antitumor activity seen in LGSOC, NSCLC (especially with NRAS and BRAF mutations), and endometrial cancer
  - Continue dose-expansion in NRAS-mutated solid tumors



Additional Expansion Opportunities

Pediatric Low-Grade Glioma (Monotherapy)(1)

ER+ Metastatic Breast Cancer (Combination Therapy)(2)

MEK1/2 Mutant Solid Tumors (Monotherapy)(3)

Source: Solomon et al., AACR 2023.
Note: LGSOC: low-grade serous ovarian cancer; NSCLC: non-small cell lung cancer.
(1) Through a partnership with St. Jude Children's Research Hospital.
(2) In combination with fulvestrant, through a partnership with Memorial Sloan Kettering Cancer Center.
(3) Through a partnership with Memorial Sloan Kettering Cancer Center.

Brimarafenib in Biomarker-Defined Solid Tumors: Under Investigation as Monotherapy and in Combination Studies

- Brimarafenib is a RAF fusion and dimer inhibitor under development by MapKure, a joint venture owned by SpringWorks and BeiGene
- Preclinical research of brimarafenib has demonstrated activity against a broad spectrum of BRAF class I/II/III mutations and fusions
- Clinical data for Phase 1 monotherapy trial presented at AACR 2023, with encouraging antitumor activity and efficacy across mutations and tumor types; combination trial with mirdametinib initiated 1Q23

Key Highlights from Initial Phase 1b Monotherapy Clinical Data

Safety

- Manageable safety profile, with AE findings consistent with those of other MAPK inhibitors
- 40 mg was determined to be maximum tolerated dose

Efficacy

- Encouraging antitumor activity was observed in the heavily pretreated heterogeneous patients
  - ORR (confirmed): 6/33, 18%; CBR: 14/33, 42%; DCR: 26/33 (79%)
- Efficacy in patients with tumors harboring BRAF V600E progressed on prior BRAF/MEK inhibitors, BRAF Class II mutations, BRAF fusions, and NRAS mutations

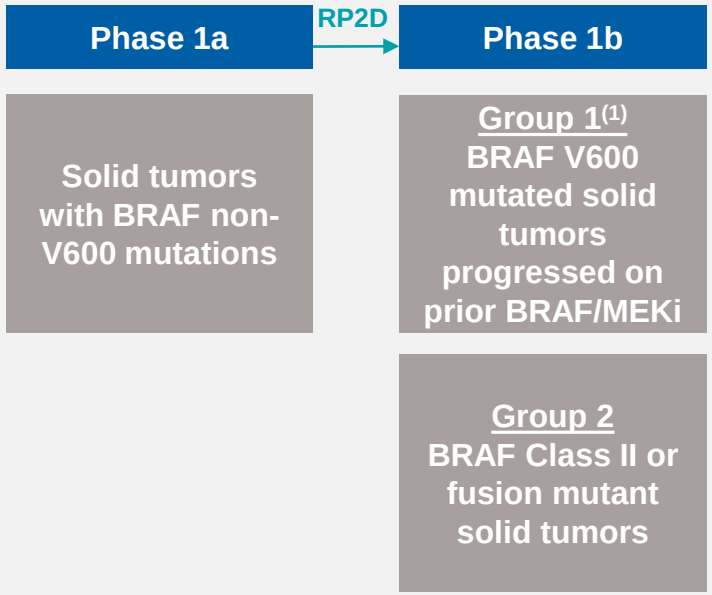
Next Steps

- Data support ongoing investigation of brimarafenib in defined cohorts
- Evaluation of brimarafenib in combination with MEK inhibitor, mirdametinib, in MAPK-altered advanced solid tumors has been initiated (NCT05580770)
- Phase 1b combination study of brimarafenib with EGFR-targeting monoclonal antibody, panitumumab, for CRC and pancreatic cancer patients with known MAPK pathway mutations to initiate 1Q24

Source: Schram et al., AACR 2023.
Note: AE: adverse event; ORR: overall response rate; CBR: clinical benefit rate; DCR: disease control rate; CRC: colorectal cancer.

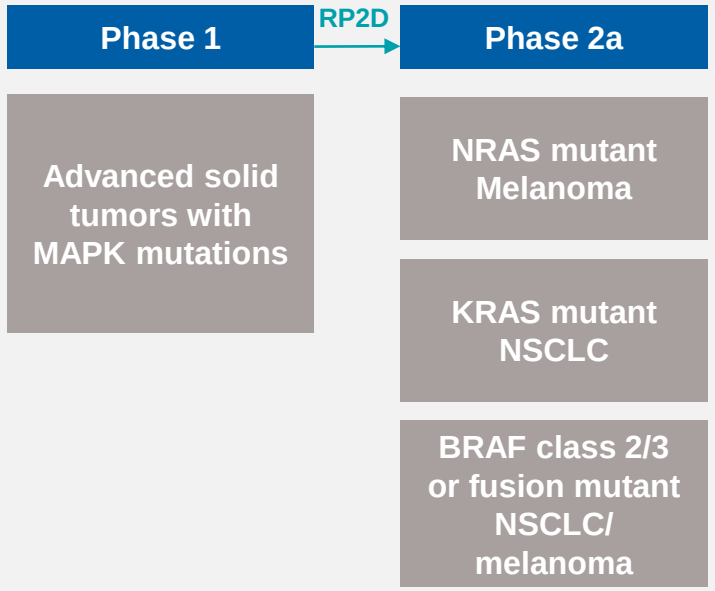
Brimarafenib in Biomarker-Defined Solid Tumors: Clinical Trial Summary

Monotherapy Development



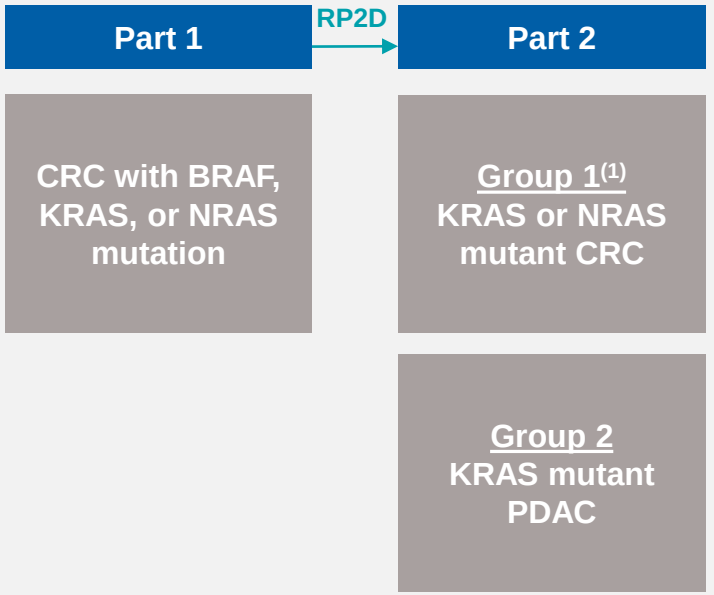
Advanced into Phase 1b in 3Q22

Combination Trial With Mirdametinib



Dosed first patient in Phase 1 in 1Q23

Combination Trial With Panitumumab

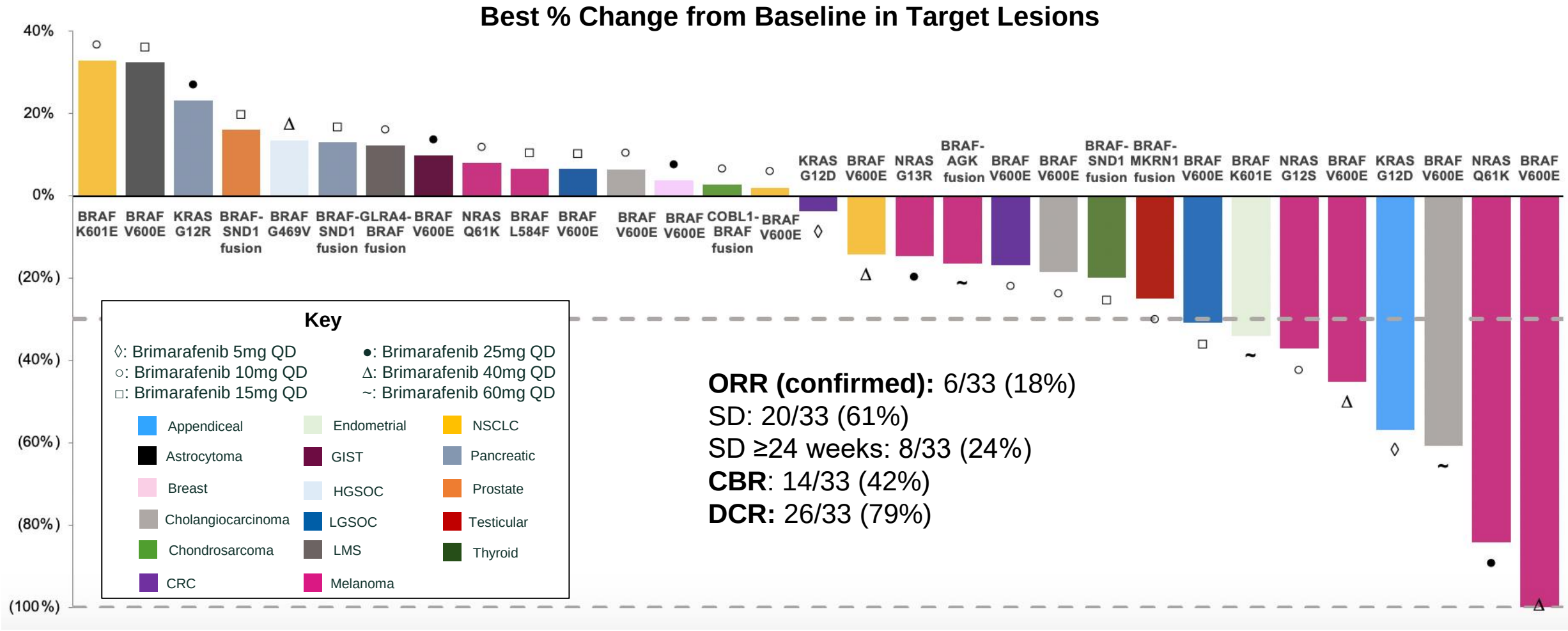


Trial to be initiated Q1 2024

Note: RP2D: Recommended phase 2 dose; NSCLC: non-small cell lung cancer; CRC: colorectal cancer; PDAC: pancreatic ductal adenocarcinoma
(1) Solid tumors other than CRC

SpringWorks THERAPEUTICS

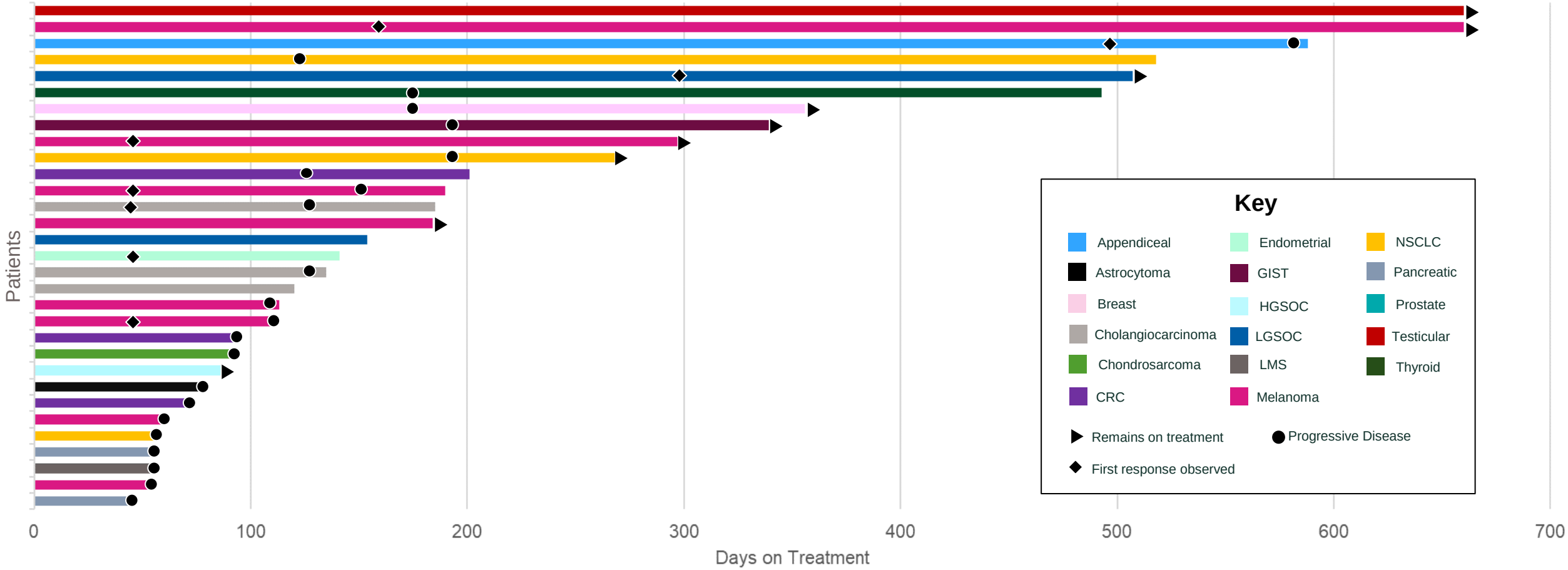
Brimarafenib Monotherapy: Anti-Tumor Activity Presented at AACR 2023



Overall data profile of brimarafenib as monotherapy supports ongoing investigation in defined cohorts

Source: Schram et al., AACR 2023.
Note: Data are preliminary, investigator assessed, and have not been centrally reviewed. Data as of September 1, 2022.
Note: Follow up scans on two patients indicated new lesions with progressive disease (PD) recorded as their best objective response. These follow-up scans did not measure target lesion and therefore are not included in the waterfall plot.
Note: CRC: colorectal cancer; GIST: gastrointestinal stromal tumor; HGSOC: high grade serous ovarian cancer; LMS: leiomyosarcoma; LGSOC: low-grade serous ovarian cancer; NSCLC: non-small cell lung cancer.

Brimarafenib Monotherapy: Time on Treatment Presented at AACR 2023



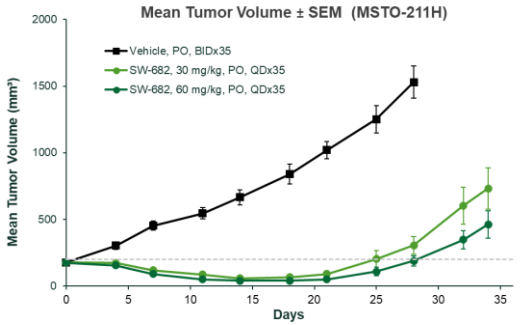
- As of data cut (September 1, 2022), median time on treatment: 154 days (range: 54 – 660 days)
- 9 patients remain on treatment

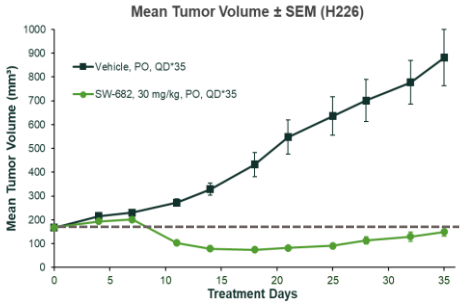
Source: Schram et al., AACR 2023.
Note: Data are preliminary, investigator assessed, and have not been centrally reviewed. Data as of September 1, 2022.

Additional Programs Broaden Portfolio With Monotherapy and Combination Opportunities

SW-682

- SW-682 is an investigational novel, potent, and selective antagonist of TEAD dependent transcription, with activity against all TEAD isoforms
- Potent and selective inhibition of proliferation of Hippo-mutant tumor cell lines
- Demonstrates robust anti-tumor activity in Hippo altered xenograft models in vivo
- IND cleared by FDA in 1Q24
- Phase 1 trial in Hippo-mutant solid tumors expected to begin in 1H24





EGFR Inhibitor Portfolio

- Collaboration with Dana-Farber Cancer Institute and Stanford developing a portfolio of next-generation EGFR inhibitors
- Lead optimization focuses on CNS penetrant, C797S active inhibitors to address osimertinib resistance
- Additional strategies being advanced to address de novo EGFR driver and resistance mutations through first-in-class targeting approaches

Dana-Farber Cancer Institute

Stanford Medicine

Research is being conducted in collaboration with Nathanael Gray, PhD (Stanford) and Pasi Jänne, MD, PhD (Dana-Farber)

Source: Chen et al., AACR 2023.
Note: CNS: central nervous system.

SpringWorks THERAPEUTICS

The SpringWorks Opportunity

Well-Capitalized to Fully Fund the Commercialization of Our Two Lead Assets and Advancement of Emerging Portfolio

$662.6M

Cash, Cash Equivalents & Marketable Securities(1)

No Debt

NASDAQ: SWTX

73.8M

Common Shares Outstanding(2)

(1) As of December 31, 2023.
(2) Basic common shares outstanding as of February 21, 2024.

SpringWorks THERAPEUTICS

Foundation and Clear Drivers in Place for Long-Term Success

First product launch underway with near-term approval path for second asset, each serving a distinct patient population

Advancing deep pipeline of late- and early-stage oncology programs with several near-term catalysts

Robust intellectual property portfolio with Orange Book listable patents providing durable protection into 2043 for both lead assets

Experienced leadership team with track record of successful execution through drug discovery, approval, and commercialization

Capital efficient operating model and strong balance sheet with $662.6M in cash(1) expected to fully fund commercialization of two lead assets and further pipeline development

(1) Represents cash, cash equivalents and marketable securities balance as of December 31, 2023.

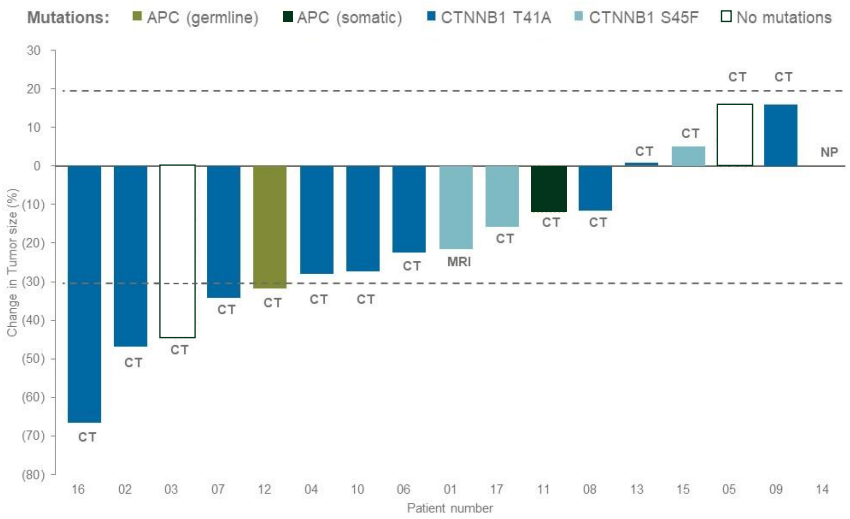
Appendix: Nirogacestat Clinical Trials

Desmoid Tumors

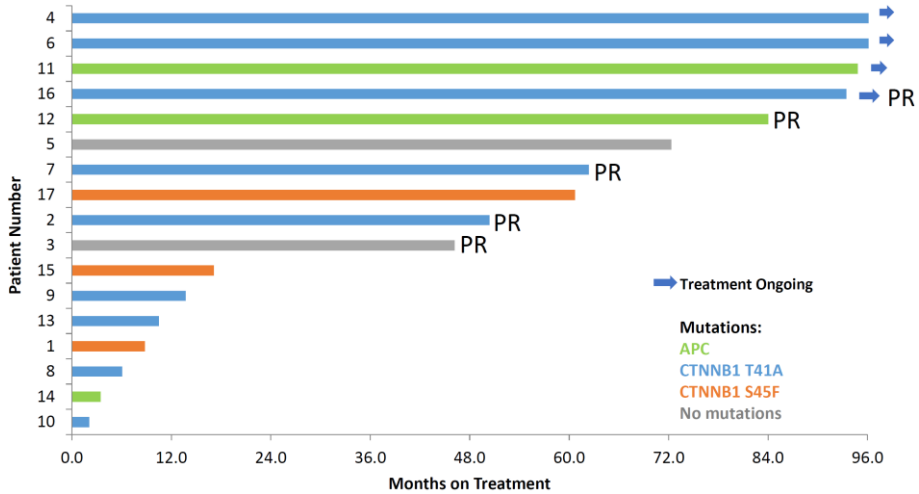
SpringWorks® THERAPEUTICS

Encouraging Phase 2 Data With Extended Duration of Treatment Set the Stage for Phase 3 DeFi Trial

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.

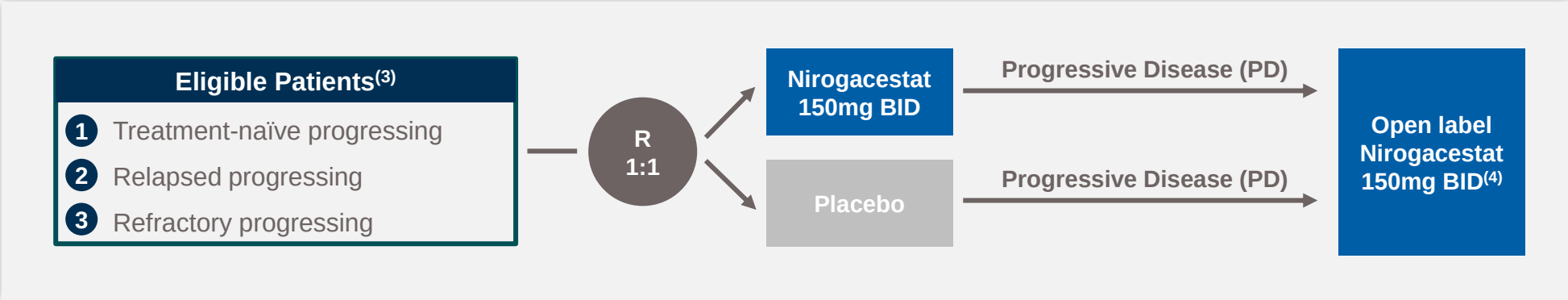
Phase 3 DeFi Trial Was Designed to Robustly Demonstrate Clinical Benefit of Nirogacestat

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.

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)
Chemotherapy	24 (34)	27 (38)
Tyrosine kinase inhibitor	23 (33)	24 (33)
Sorafenib	17 (24)	18 (25)
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)

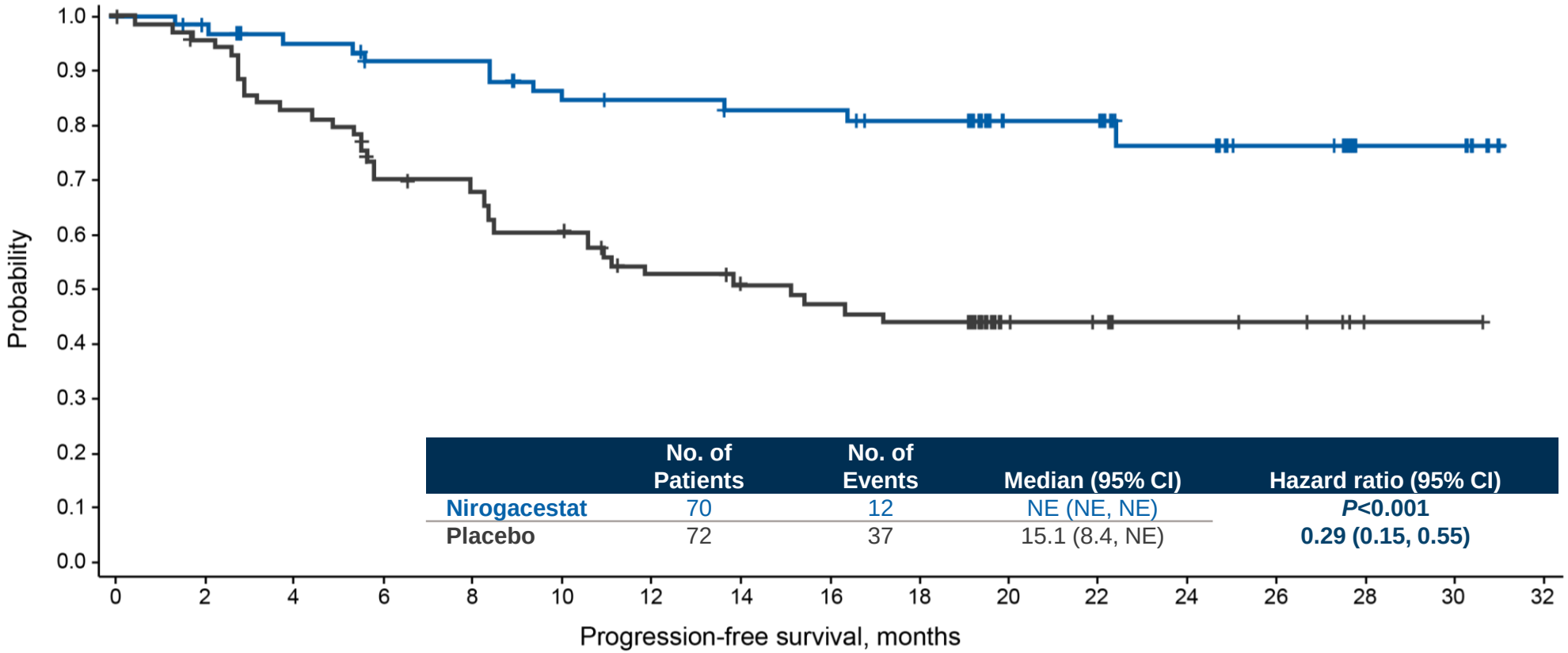
Source: Kasper et al., *ESMO,* 2022; Gounder et al., *NEJM,* 2023. Data as of the time of primary analysis (04/07/22).
a) Evaluable samples not available for all patients. Samples were analyzed for 51 and 53 patients in the nirogacestat and placebo arms, respectively.
b) Defined as a score of >4 calculated 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 Demonstrated Highly Significant and Clinically Meaningful Impact on Primary and All Key Secondary Endpoints

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.

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)**

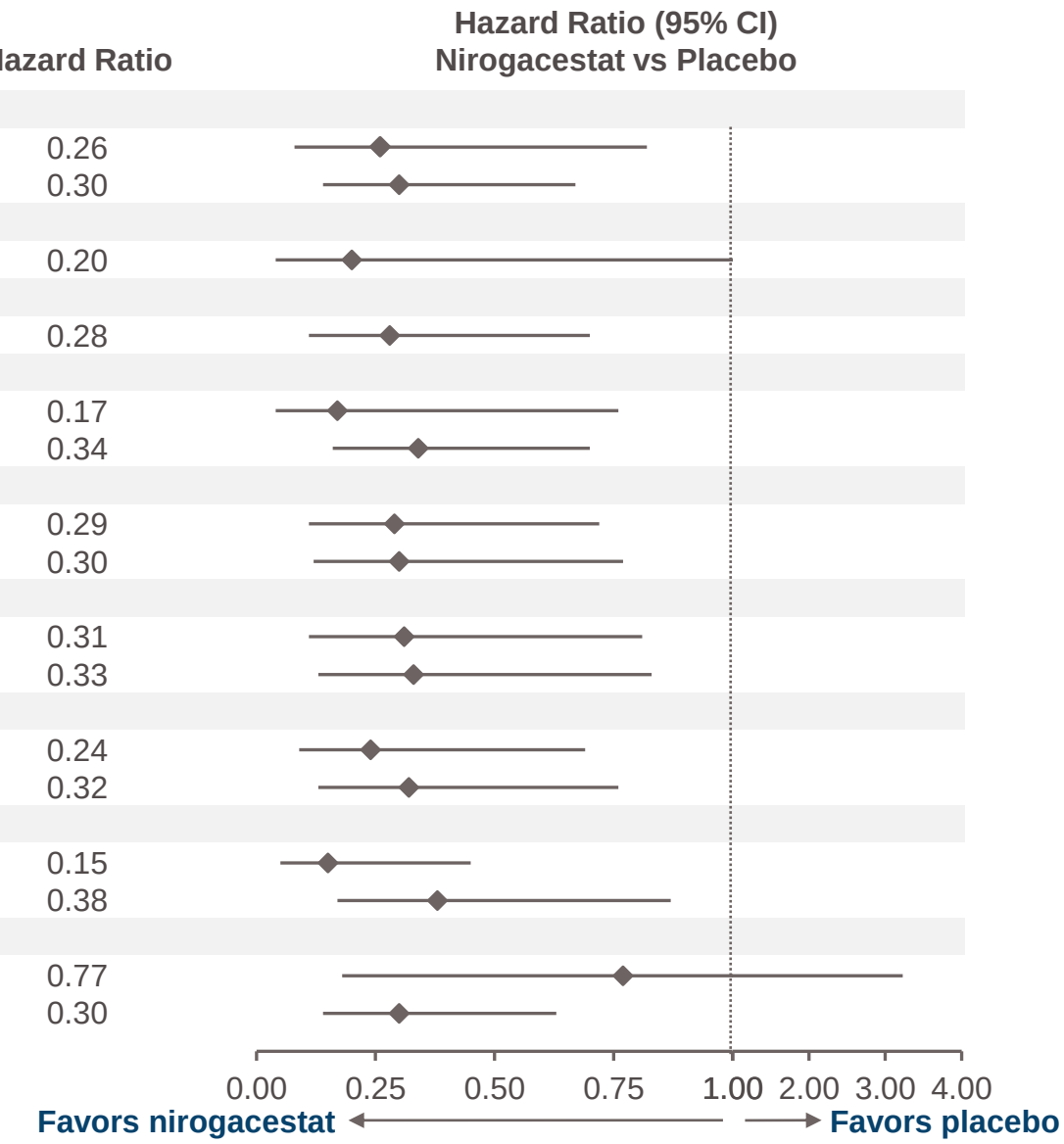
No. of Participants at Risk:

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

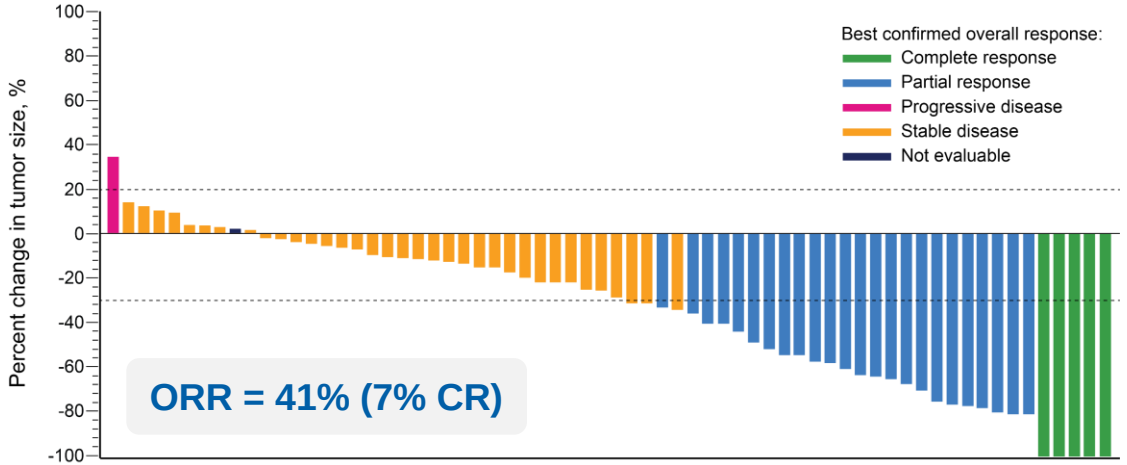
	Nirogacestat	Placebo	Hazard Ratio
	no. of events / no. of patients		
Sex			
Male	4 / 25	11 / 25	0.26
Female	8 / 45	26 / 47	0.30
***APC* mutation**			
Yes	2 / 11	8 / 13	0.20
***CTNNB1* mutation**			
Yes	6 / 43	21 / 42	0.28
Target tumor location			
Intra-abdominal	2 / 17	11 / 18	0.17
Extra-abdominal	10 / 53	26 / 54	0.34
Focality			
Single	6 / 43	19 / 41	0.29
Multifocal	6 / 27	18 / 31	0.30
Prior surgery			
Yes	5 / 31	23 / 44	0.31
No	7 / 39	14 / 28	0.33
Prior chemotherapy			
Yes	5 / 24	17 / 27	0.24
No	7 / 46	20 / 45	0.32
Prior TKI treatment			
Yes	4 / 23	16 / 24	0.15
No	8 / 47	21 / 48	0.38
Treatment status			
No previous treatment	3 / 18	5 / 14	0.77
Refractory or recurrent disease after previous treatment	9 / 52	32 / 58	0.30



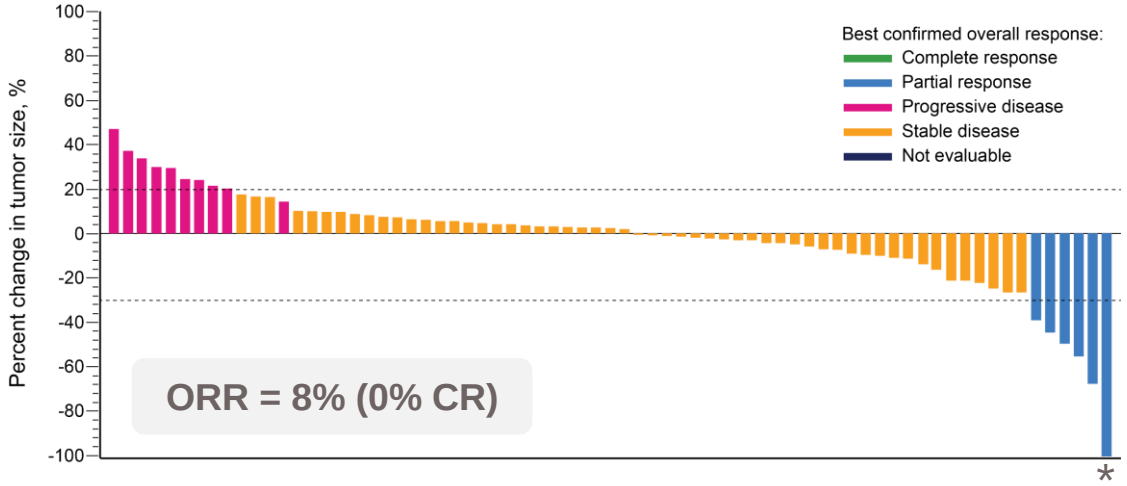
Source: Kasper et al., *ESMO,* 2022; Gounder et al., *NEJM,* 2023. Data as of the time of primary analysis (04/07/22).
Note: PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

Nirogacestat Treatment Resulted in Substantial Reductions in Tumor Size

Nirogacestat (n=70)



Placebo (n=72)

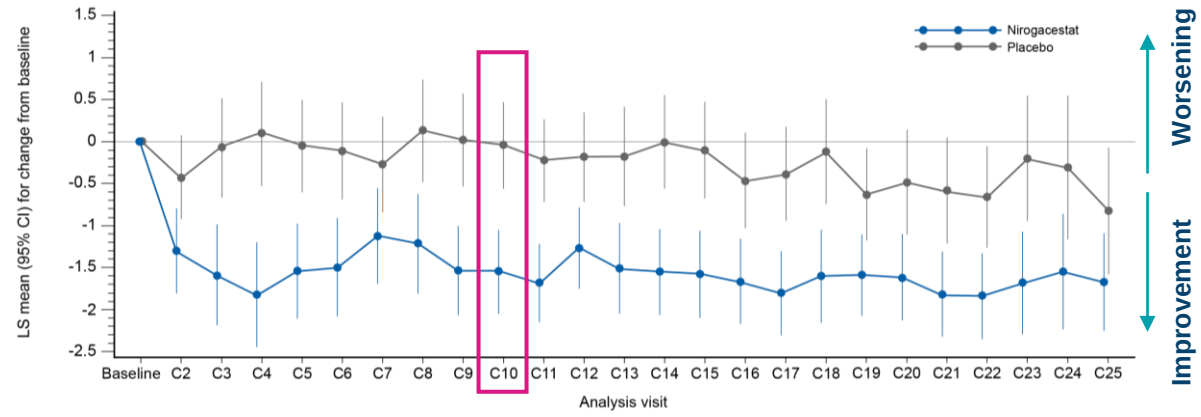


Median time to objective response of 5.6 months for nirogacestat vs. 11.1 months for placebo

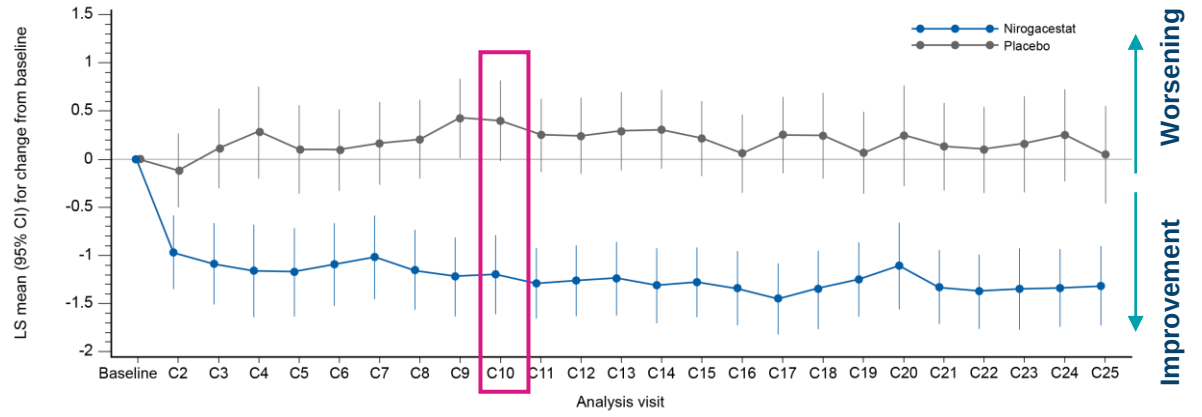
Source: Kasper et al., ESMO, 2022. Data as of the time of primary analysis (04/07/22). Gounder at al., CTOS, 2022.
* Patient had a complete resolution of the target lesion but still had documented non-target lesion; therefore, not a complete response.
Note: Best percent change values are averaged between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

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

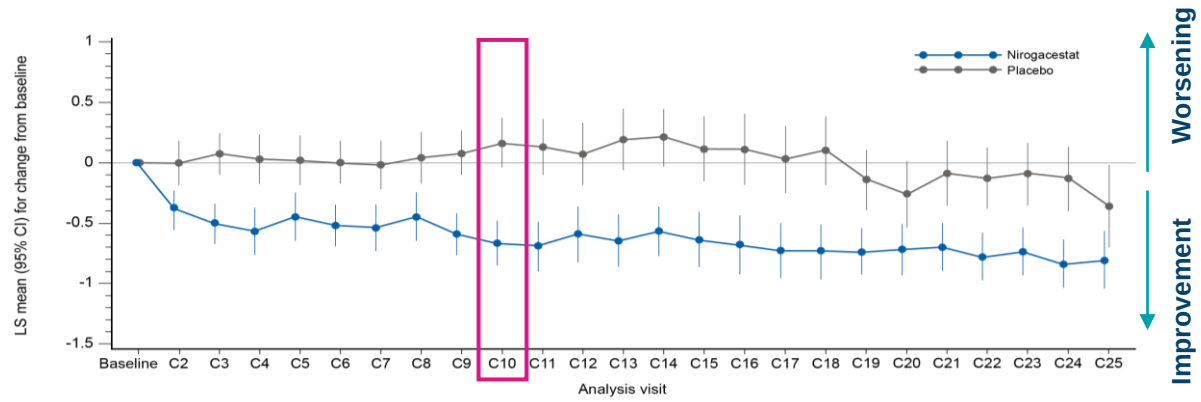
Brief Pain Inventory-Short Form – Average Pain Intensity



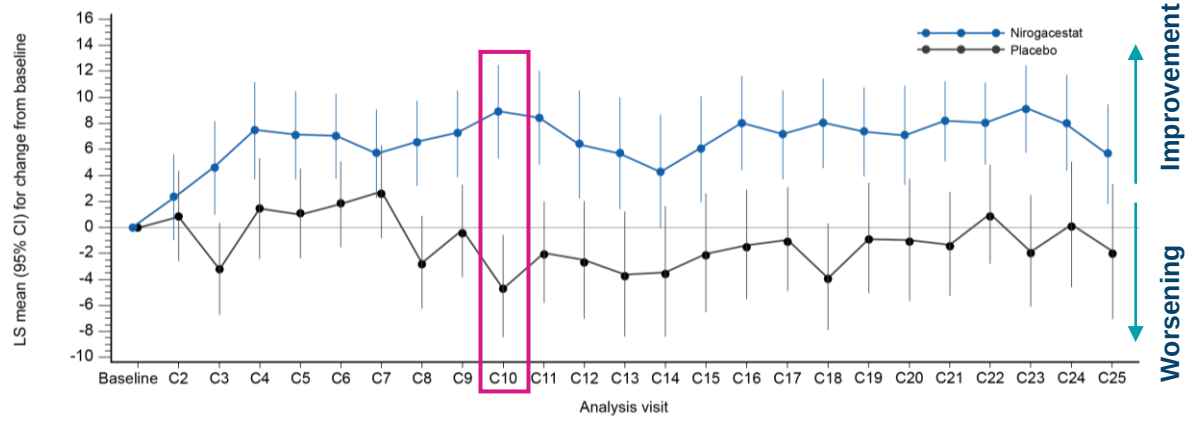
DT-Specific Symptom Severity (GODDESS DTSS)



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

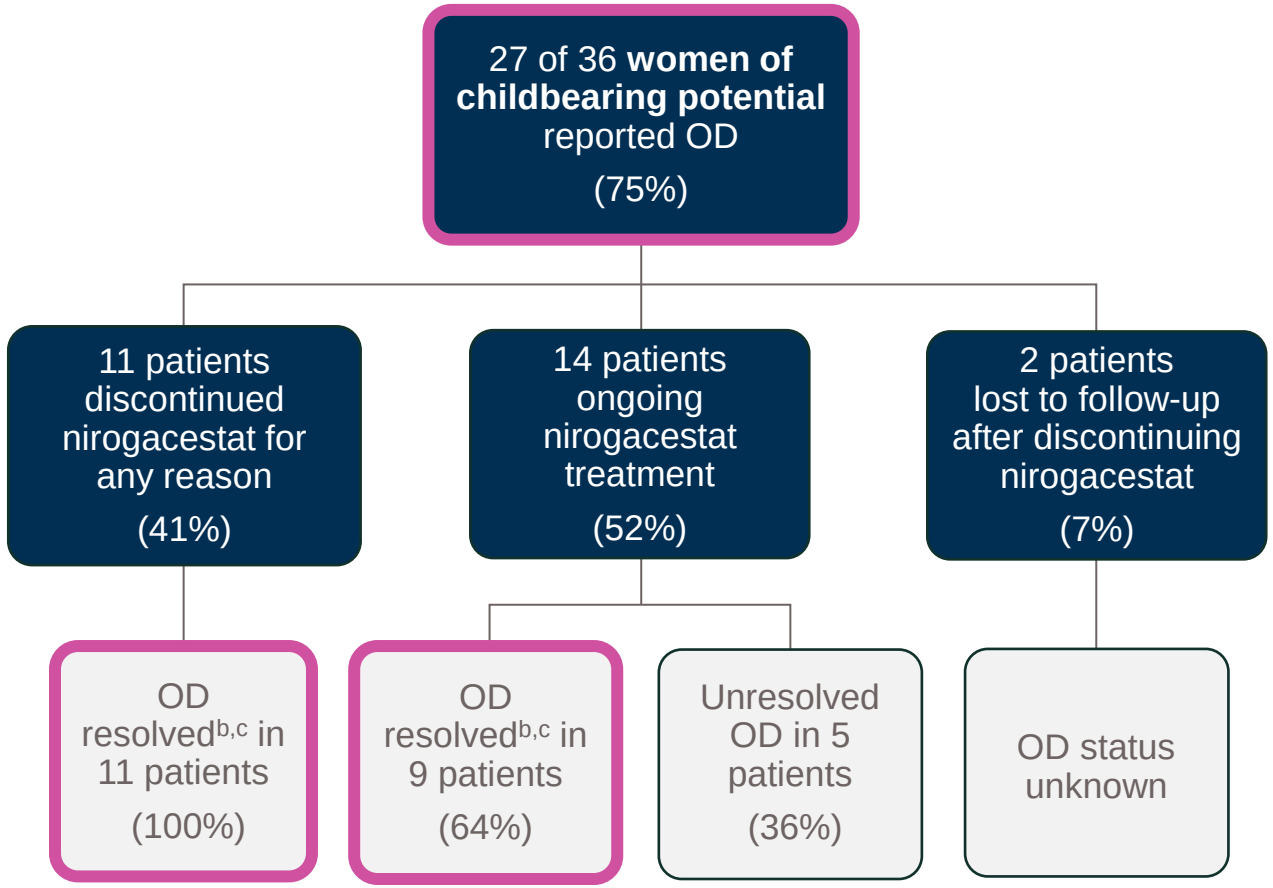
Safety population, n (%)	Nirogacestat (n=69)		Placebo (n=72)	
Duration of study drug exposure, median (range), months	20.6 (0.3, 33.6)		11.4 (0.2, 32.5)	
Dose intensity, median (range), mg/d	288.3 (169, 300)		300.0 (239, 300)	
	Any Grade	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Any TEAE	69 (100)	39 (57)	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
- No changes in male hormonal levels or TEAEs pertaining to male reproductive potential were reported



Source: Kasper et al., *ESMO,* 2022. Data as of the time of primary analysis (04/07/22). Gounder et al., *CTOS*, 2022. Gounder et al., *NEJM,* 2023.
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; TEAE, treatment-emergent adverse event.
Note: Ovarian dysfunction is a composite term functionally equivalent to ovarian toxicity, which is the term used to describe the adverse event in the U.S. prescribing information for OGSIVEO.
1) Thurston et al., *Obstet Gynecol Clin North Am.* 2011;38:489-501; 2) Mauri et al., *Front Endocrinol (Lausanne).* 2020;11:572388.

THANK YOU