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DeFi: A Phase 3 Trial of Nirogacestat for Progressing Desmoid Tumors (DT)

Bernd Kasper, Ravin Ratan, Thierry Alcindor, Patrick Schöffski, Winette T. van der Graaf, Breelyn A. Wilky, Richard F. Riedel, Allison Lim, L. Mary Smith, Stephanie Moody, Steven Attia, Sant Chawla, Gina D'Amato, Noah Federman, Priscilla Merriam, Brian A. Van Tine, Bruno Vincenzi, Shivaani Kummar, Mrinal Gounder, on behalf of the DeFi Study Investigators

September 10, 2022

Declaration of Interests

- Bernd Kasper's declaration of interests:
  - Financial interests
    - Ayala (advisory board, personal), Bayer (advisory board, personal), Blueprint (advisory board, personal), Boehringer Ingelheim (advisory board, personal), GSK (advisory board, personal), PharmaMar (advisory board, personal), SpringWorks Therapeutics (advisory board, personal)
  - Nonfinancial interests
    - Ayala (coordinating PI, institutional, no financial interest), PharmaMar (coordinating PI, institutional, no financial interest), SpringWorks Therapeutics (coordinating PI, institutional, no financial interest), European Organisation for Research and Treatment of Cancer (EORTC; leadership role, Chair of the EORTC Soft Tissue and Bone Sarcoma Group [STBSG])

Gamma Secretase Inhibition in Desmoid Tumors

- Desmoid tumors (DT) are rare, locally aggressive, and invasive soft-tissue tumors that are challenging to manage due to variable presentation, unpredictable disease course, and a lack of approved therapies[1,2]
- Treatment should be individualized to optimize tumor control and improve symptom burden, including pain, physical function, and overall quality of life[3]
  - A global consensus initiative has been launched by The Desmoid Tumor Working Group aiming to harmonize management strategies[4]
- There is mechanistic rationale for the use of gamma secretase inhibitors (GSI) in DT as these tumors highly express Notch, which can be blocked by GSIs[5,6]
- Nirogacestat is an investigational, oral, selective, small-molecule GSI that has shown evidence of antitumor activity in DT in Phase 1 and 2 trials with a manageable adverse event profile[1,7,8]

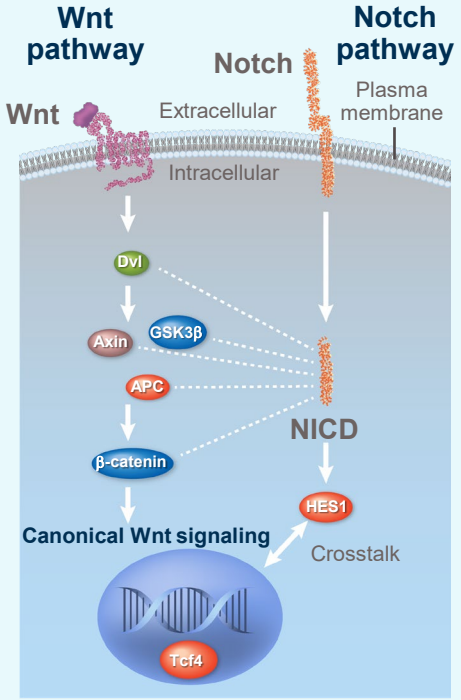


Image adapted from Andersson et al. *Development* (2011) and Bui and Kummar. *Oncotarget* (2017).

DT, desmoid tumor; GSI, gamma secretase inhibitor; NICD, Notch intracellular domain.

1. Villalobos et al. *Ann Surg Oncol.* 2018;25:768-775. **2.** Kasper et al. *Oncologist.* 2011;16:682-693. **3.** Gounder et al. *Cancer.* 2020;126:531-539. **4.** Desmoid Tumor Working Group. *Eur J Cancer.* 2020;127:96-107. **5.** Andersson et al. *Development.* 2011;138:3593-3612. **6.** Gounder et al. *Cancer.* 2015;121:3933-3937. **7.** Messersmith et al. *Clin Cancer Res.* 2015;21:60-67. **8.** Kummar et al. *J Clin Oncol.* 2017;35:1561-1569.

DeFi: Phase 3 Study of Nirogacestat vs Placebo in Adult Patients With DT

Trial Summary

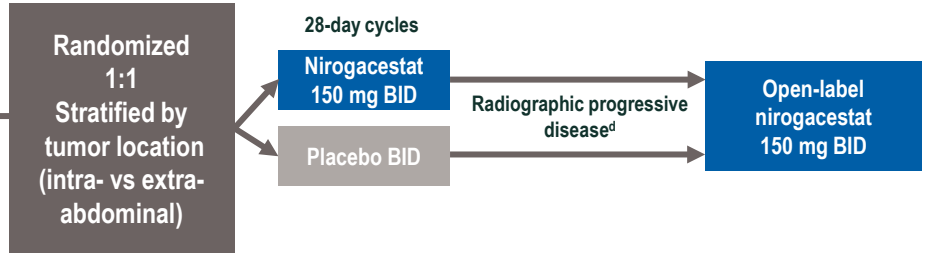
- Global, randomized, double-blind, placebo-controlled, Phase 3 trial comparing the efficacy, safety, and tolerability of nirogacestat vs placebo in adult patients with progressing DT
- 142 patients randomized across 37 sites in North America and Europe

Key Endpoints

- **Primary:** Progression-free survival[b]
- **Secondary:** Objective response rate and patient-reported outcomes, including symptom burden, physical/role function, and overall quality of life[c]

Adult Eligible Patients

- Histologically confirmed DT with progressive disease per RECIST v1.1[a]
  - Treatment-naïve with DT not amenable to surgery, or
  - Refractory or recurrent disease (after ≥1 line of therapy)



Primary Analysis Data Cutoff: April 7, 2022

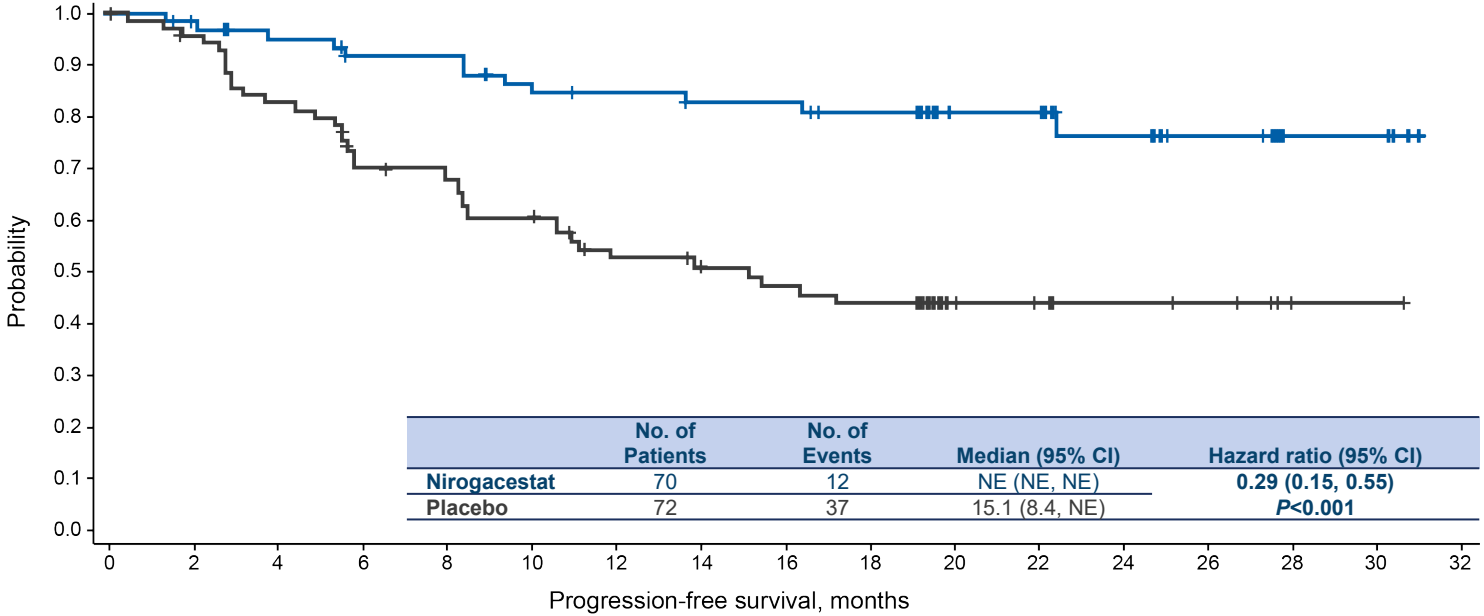
[a]Progressive disease defined by histologically confirmed DT that has progressed ≥20% within the past 12 months by RECIST v1.1. Target tumors identified at screening by the Investigator.
[b]Progression-free survival was calculated from the time of randomization until disease progression or death due to any cause. Progression was determined via blinded, independent, central review and included radiographic progression per RECIST v1.1 and clinical progression.
[c]As assessed by change from baseline for BPI-SF, GODDESS DTSS, GODDESS DTIS, and EORTC QLQ-C30 at Cycle 10.
[d]Radiographic disease progression or once the required number of events have been observed and the primary progression-free survival analysis has been completed.
BID, twice-daily dosing; BPI-SF, Brief Pain Inventory–Short Form; DT, desmoid tumor; DTIS, GODDESS DT Impact Scale; DTSS, GODDESS DT Symptom 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; RECIST, Response Evaluation Criteria in Solid Tumors.
ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03785964. Accessed August 24, 2022.

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)

[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.
API, average pain index; BPI-SF, Brief Pain Inventory–Short Form ITT; intention to treat.

Nirogacestat Significantly Reduced the Risk of Disease Progression



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

No. of Participants at Risk:

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

Median follow-up time was 19.2 months for nirogacestat and 10.9 months for placebo.
NE, not estimable.

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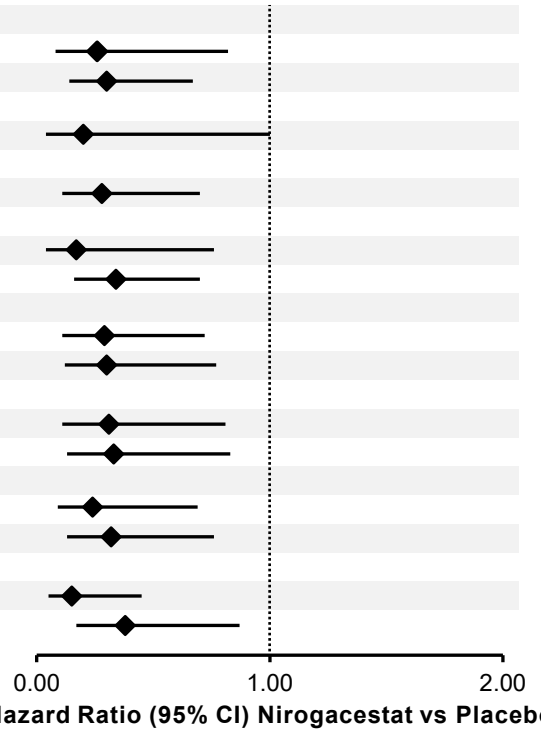
PFS Benefit With Nirogacestat Was Observed Across Prespecified Subgroups

	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



PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

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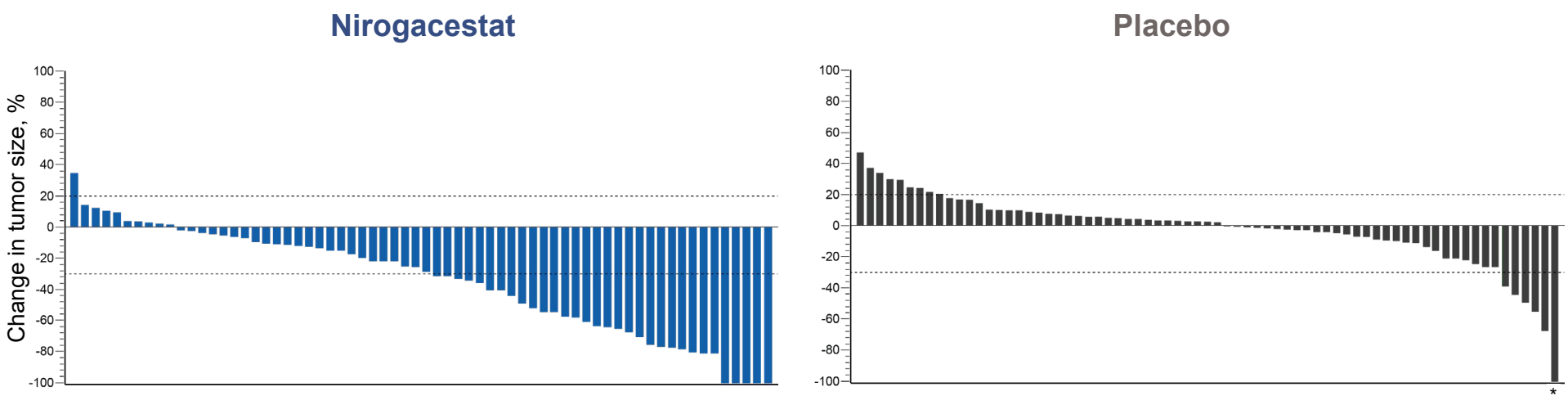
Objective Response Rate by Blinded Independent Central Review

	Nirogacestat (n=70)	Placebo (n=72)
Objective response rate (CR+PR), n (%) 95% CI Two-sided *P* value	**29 (41)** **(30.2, 54.5)** **<0.001**	**6 (8)** **(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 duration of objective response, median (95% CI), mo[a]	NE (NE, NE)	NE (8.3, NE)

[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.
CR, complete response; NE, not estimable; PR, partial response.

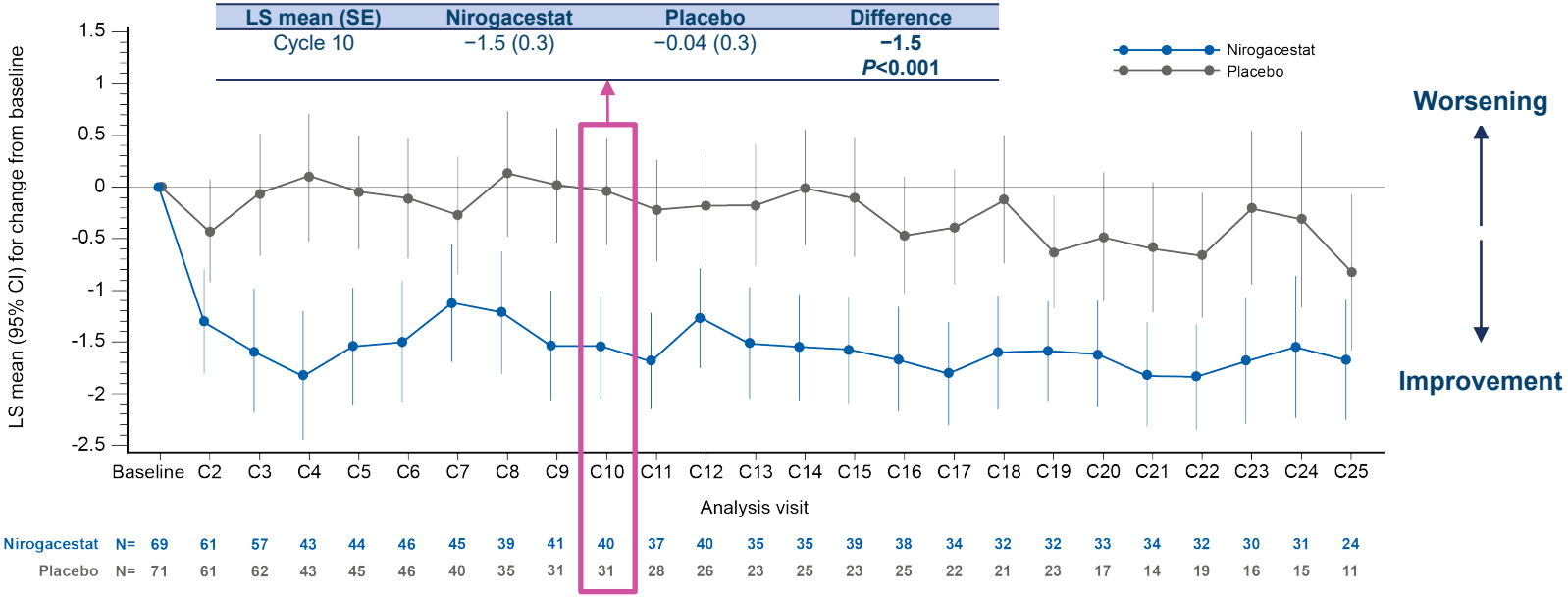
Nirogacestat Resulted in Substantial Reductions in Tumor Size



*Patient had a complete resolution of the target lesion but still had documented non-target lesion; therefore, not a complete response.
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 Significantly Reduced Pain

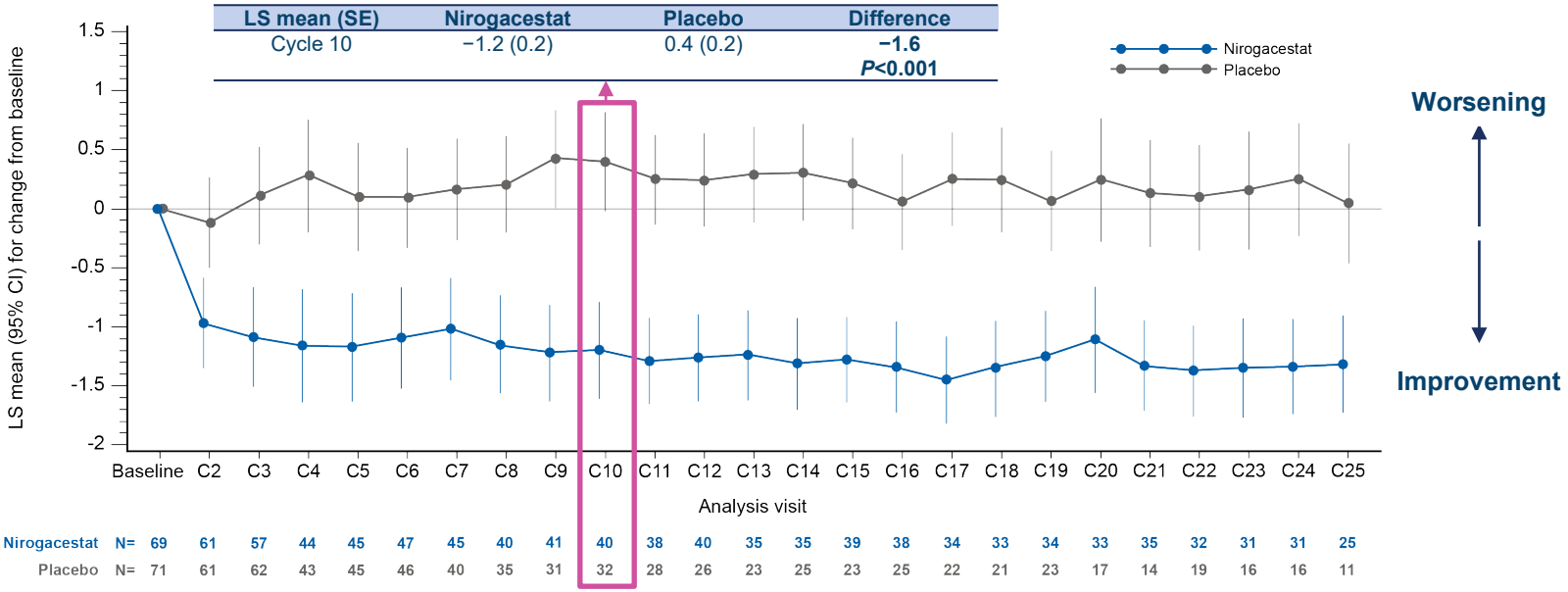
Brief Pain Inventory-Short Form – Worst Pain Intensity



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 of "worst pain in last 24 hours".
LS, least squares.

Nirogacestat Significantly Reduced DT-Specific Symptom Severity

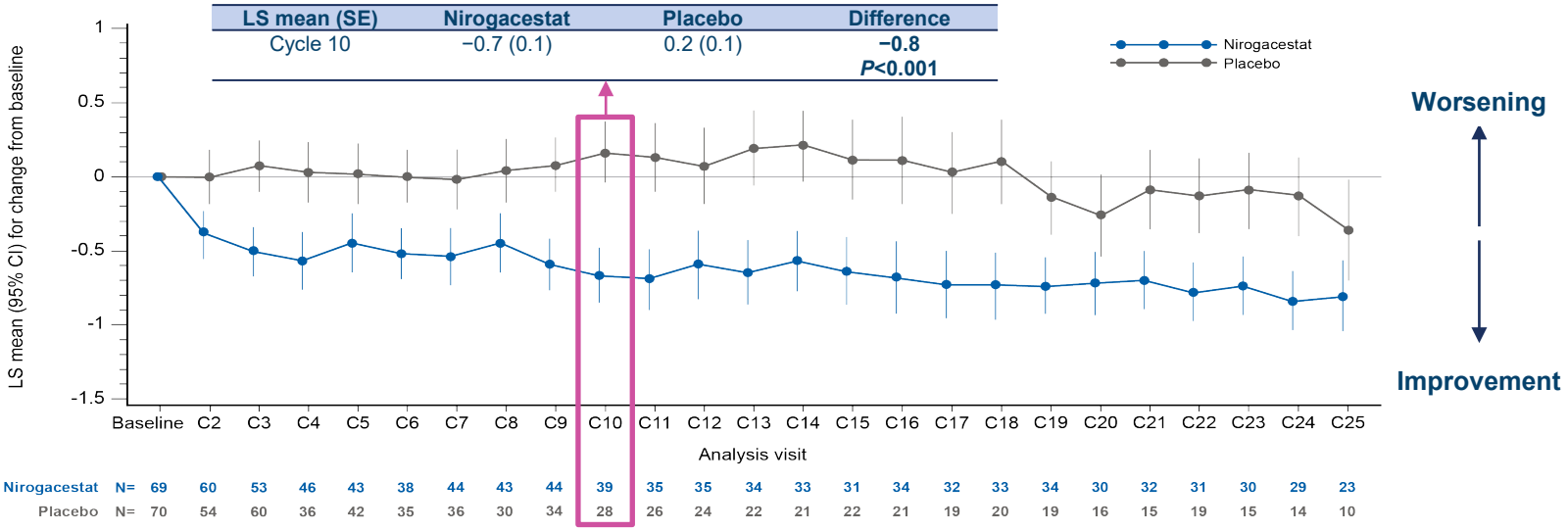
GODDESS DTSS – Total Symptom Score



Mean (SD) baseline scores: nirogacestat, 3.4 (2.34); placebo, 3.5 (2.57). Differences at Cycle 10 were statistically significant and clinically meaningful.
DTSS total symptom score includes pain, fatigue, swelling, muscle weakness, and difficulty moving.
DT, desmoid tumor; DTSS, GODDESS DT Symptom Scale; GODDESS, GOunder/Desmoid Tumor Research Foundation DEsmoid Symptom/Impact Scale; LS, least squares.

Nirogacestat Significantly Improved Physical/Role Functioning and QoL

GODDESS DTIS – Physical Functioning Impact Score



- **Nirogacestat also significantly improved EORTC QLQ-C30 physical functioning (*P*<0.001), role functioning (*P*<0.001), and global health status/QoL (*P*=0.007) at Cycle 10 compared with placebo**

Mean (SD) baseline scores: nirogacestat, 2.8 (1.14); placebo, 2.7 (1.24). Differences at Cycle 10 were statistically significant and clinically meaningful. DTIS physical functioning includes moving, reaching, vigorous activity, moderate activity, accomplishing less. DT, desmoid tumor; DTIS, GODDESS DT 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; QoL, quality of life.

Nirogacestat Safety Profile

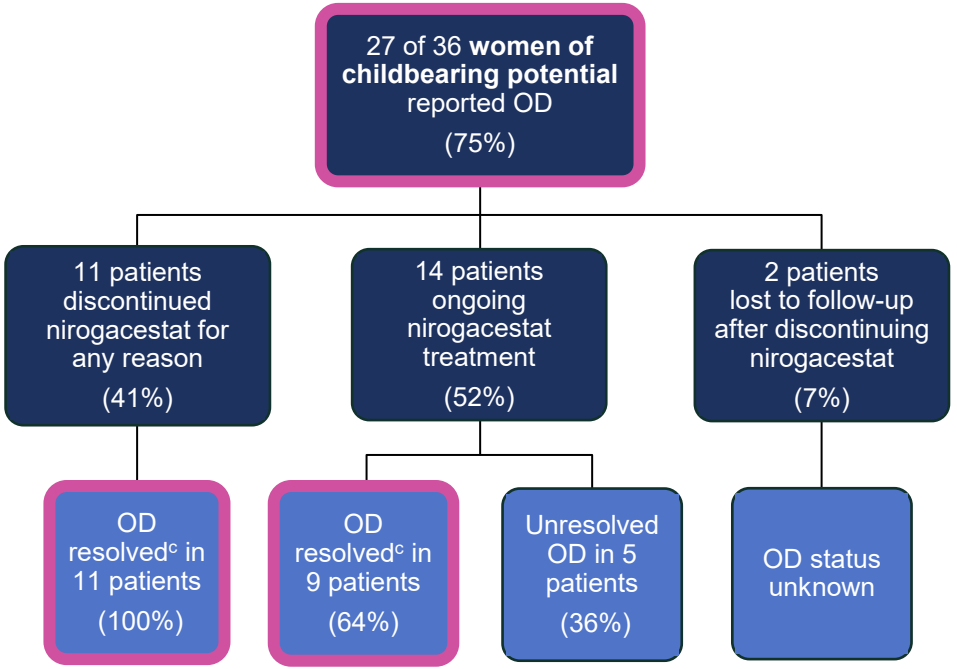
Safety population, n (%)	Nirogacestat (n=69)		Placebo (n=72)	
Duration of study drug exposure, median (range), mo	20.6 (0.3, 33.6)		11.4 (0.2, 32.5)	
Dose intensity, median (range), mg/d	288.3 (169, 300)		300.0 (239, 300)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any TEAE	69 (100)	39 (57)	69 (96)	12 (17)
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**

[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%]).
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[b]
  - Median time to first onset of OD: 8.9 weeks
  - Median duration of OD events: 21.3 weeks



[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.
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.

Summary

- **DeFi represents the largest and most rigorous randomized controlled trial conducted to date in DT**
  - DeFi is also the first Phase 3, randomized, controlled trial to demonstrate clinical benefit with a GSI in any indication
- **Nirogacestat demonstrated rapid, sustained, and statistically significant improvements in all primary and secondary efficacy endpoints**
  - 71% reduction in the risk of disease progression as compared with placebo
  - Objective response rate of 41%, including a 7% complete response rate
  - Statistically significant and clinically meaningful improvements in pain, disease-specific symptom burden, physical/role functioning, and overall quality of life ($P \leq 0.007$)
- **Nirogacestat exhibited a manageable safety profile, with 95% of all treatment-emergent adverse events being Grade 1 or 2**
- **Nirogacestat has the potential to become the standard of care for patients with DT requiring systemic treatment**

DT, desmoid tumor, GSI, gamma secretase inhibitor.

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Author Affiliations

BK: University of Heidelberg, Mannheim University Medical Center, Mannheim Cancer Center, Sarcoma Unit, Mannheim, Germany. **RR**: MD Anderson Cancer Center, Houston, TX, USA. **TA**: McGill University Health Center, Montreal, Quebec. **PS**: University Hospitals Leuven, Leuven, Belgium. **WTG**: Netherlands Cancer Institute, Amsterdam, The Netherlands. **RFR**: University of Colorado Anschutz Medical Campus, Aurora, CO, USA; Duke Cancer Institute, Durham, NC, USA. **AL, LMS**: SpringWorks Therapeutics, Stamford, CT, USA. **SM**: PharPoint Research, Durham, NC, USA. **SA**: Mayo Clinic, Jacksonville, FL, USA. **SC**: Sarcoma Oncology Center, Santa Monica, CA, USA. **GD**: University of Miami Sylvester Cancer Center, Miami, FL, USA. **NF**: David Geffen School of Medicine, University of California, Los Angeles, CA, USA; UCLA Jonsson Comprehensive Cancer Center, Los Angeles, CA, USA. **PM**: Dana-Farber Cancer Institute, Boston, MA, USA. **BAVT**: Washington University, St. Louis, St Louis, MO, USA. BV: Policlinico Universitario Campus Bio-Medico, Rome, Italy. **SK**: Division of Hematology & Medical Oncology, Oregon Health & Science University, Portland, OR, USA. **MG**: Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York City, NY, USA.

Correspondence

Dr. Kasper's Email: bernd.kasper@umm.de

For questions or to request a copy of this presentation, please contact SpringWorks Medical Information at:

Email: medinfo@springworkstx.com

Web: SpringWorks (springworkstxmedical.com)