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

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INTRODUCTION

- Desmoid tumors (DT) are rare, invasive, soft-tissue tumors that are challenging to manage given variable presentation, unpredictable disease course, and lack of approved therapies[1,2]
- Treatment strategies should be individualized to optimize tumor control and improve symptom burden, including pain; physical function; and quality of life[3]
- Nirogacestat is an investigational, oral, selective, small-molecule gamma secretase inhibitor (GSI) that has shown evidence of antitumor activity in DT in Phase 1 and 2 trials and has a manageable adverse event profile[1,4,5]

OBJECTIVE

- To assess the efficacy and safety of nirogacestat treatment in a randomized, double-blind, placebo-controlled, Phase 3 trial of adult participants with progressing DT

METHODS

STUDY DESIGN

- DeFi is an ongoing, global, randomized, Phase 3 trial (ClinicalTrials.gov NCT03785964) investigating the efficacy, safety, and tolerability of nirogacestat in participants with progressing DT. The current analysis reports on the double-blind, placebo-controlled phase of the study
- Eligible participants had histological confirmation that DT had progressed ≥20% in the past 12 months by RECIST v1.1. Participants could have had the following:
  - DT that was treatment-naïve and not amenable to surgery, or
  - DT that was refractory or recurrent after ≥1 line of therapy
- Participants were randomized 1:1, stratified by tumor location (intra- vs extra-abdominal), and received either 150 mg of nirogacestat or placebo twice daily in 28-day cycles
- Eligible participants could be enrolled into open-label extension after radiographic disease progression or once the required number of events had been observed and primary progression-free survival (PFS) analysis was completed

KEY ENDPOINTS

- The primary endpoint was PFS, determined radiographically using RECIST v1.1 or clinically by independent, blinded, central radiologic or clinical review
- Secondary endpoints included objective response rate and participant-reported outcomes to determine change (at Cycle 10) from baseline in pain, symptom burden, physical/role function, and overall quality of life based on the following:
  - Brief Pain Inventory–Short Form
  - GOunder/Desmoid Tumor Research Foundation Desmoid Symptom/Impact scales (GODDESS)
  - European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30)

RESULTS

PARTICIPANT DISPOSITION AND BASELINE CHARACTERISTICS

- 142 participants (nirogacestat, n=70; placebo, n=72) were randomized across 37 sites in North America and Europe from May 2019 to August 2020 (Table 1)

Table 1. Participant Demographics and Characteristics, ITT Population

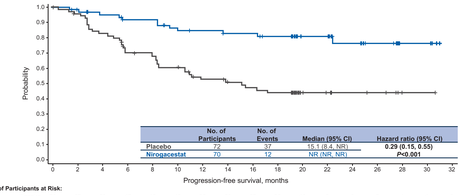
CHARACTERISTIC	NIROGACESTAT (n=70)	PLACEBO (n=72)
Age, median (min, max), y	33.5 (18, 73)	34.5 (18, 76)
Sex, n (%)		
Male	25 (36)	25 (35)
Female	45 (64)	47 (65)
Somatic mutations in analyzed participants, n (%)[a]		
APC	11 (16)	11 (15)
CTNNB1	43 (61)	42 (58)
Tumor location, n (%)		
Intra-abdominal	17 (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 (min, max)	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)
Participants with uncontrolled pain per BPI-SF API >4, n (%)[b]	27 (39)	31 (43)

API, average pain index; BPI-SF, Brief Pain Inventory–Short Form; ITT, intention to treat; WOCBP, women of childbearing potential. [a]Evaluable samples not available for all participants. Samples were analyzed for 51 and 53 participants 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 last 24 hours" over the 7-day period before the baseline visit.

EFFICACY OUTCOMES

- Nirogacestat demonstrated statistically significant improvement in PFS compared to placebo, with a 71% reduction in the risk of disease progression (hazard ratio, 0.29 [95% CI, 0.15, 0.55; *P*<0.001]; Figure 1)
  - Median follow-up time was 19.2 months for nirogacestat and 10.9 months for placebo
  - Kaplan-Meier–estimated median PFS was not reached in the nirogacestat arm due to the low number of events and was 15.1 months (95% CI, 8.4, not estimable) in the placebo arm
    - > Based on a subgroup analysis, PFS benefit with nirogacestat treatment was also observed across prespecified subgroups of sex, *APC* and *CTNNB1* mutations, target tumor location, tumor focality, prior surgery, prior chemotherapy, and prior TKI therapy
  - The DeFi study was not powered to assess differences between subgroups

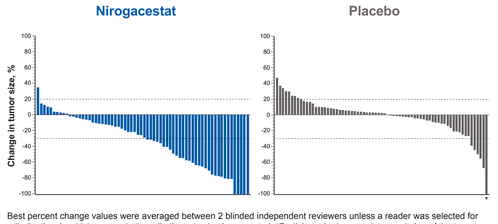
Figure 1. Nirogacestat Significantly Improved Progression-Free Survival.



NR, not reached.

- Objective response rate was 41% (n=29) for nirogacestat and 8% (n=6) for placebo (*P*<0.001)
  - Complete responses were observed in 7% of participants treated with nirogacestat; no complete responses were observed for those treated with placebo
  - Median (range) time to response was 5.6 (2.6, 19.4) months for nirogacestat and 11.1 (2.8, 16.4) months for placebo
- Nirogacestat substantially reduced tumor size (Figure 2)

Figure 2. Nirogacestat Resulted in Substantial Reductions in Tumor Size.

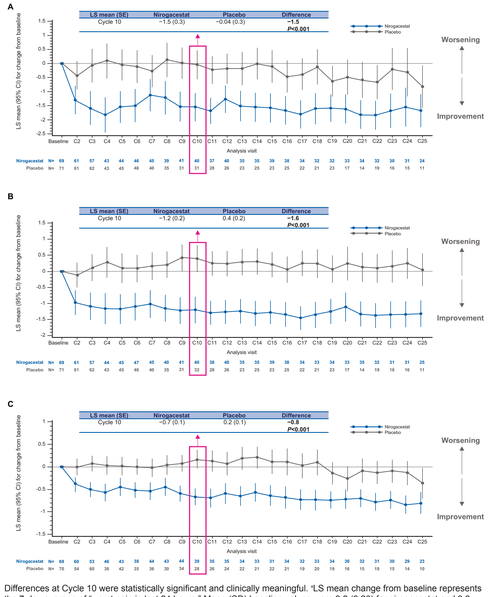


Best percent change values were averaged between 2 blinded independent reviewers unless a reader was selected for adjudication, in which case only the adjudicated value is presented. [a]Participant had a complete resolution of the target lesion but still had a documented non-target lesion; therefore, this participant did not have a complete response.

PARTICIPANT-REPORTED OUTCOMES

- At Cycle 10, compared with placebo, nirogacestat demonstrated statistically significant and clinically meaningful changes in pain, disease-specific symptom burden, and physical functioning (Figure 3)
  - Improvements in most PROs occurred early and were sustained throughout the trial

Figure 3. Nirogacestat Demonstrated Sustained Improvement Across (A) Brief Pain Inventory–Short Form – Worst Pain Intensity,[a] (B) GODDESS DTSS – Total Symptom Score,[b] and (C) GODDESS DTIS – Physical Functioning Domain.[c]



Differences at Cycle 10 were statistically significant and clinically meaningful. [a]LS mean change from baseline represents the 7-day average of "worst pain in last 24 hours." Mean (SD) baseline values were 3.2 (3.26) for nirogacestat and 3.3 (3.31) for placebo. [b]DTSS total symptom score includes pain, fatigue, swelling, muscle weakness, and difficulty moving. Mean (SD) baseline values were 3.4 (2.34) for nirogacestat and 3.5 (2.57) for placebo. [c]DTIS physical functioning includes moving, reaching, vigorous activity, moderate activity, and accomplishing less. Mean (SD) baseline values were 2.8 (1.14) for nirogacestat and 2.7 (1.24) for placebo. DT, desmoid tumor; DTIS, GODDESS DT Impact Scale; DTSS, GODDESS DT Symptom Scale; GODDESS, GOunder/Desmoid Tumor Research Foundation DEsmoid Symptom/Impact Scale; LS, least squares; SD, standard deviation.

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

SAFETY OUTCOMES

- Adverse events for the safety population (nirogacestat, n=69; placebo, n=72) are shown in Table 2

Table 2. Adverse Events

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)	
TEAEs	**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 participants 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]	

TEAE, treatment-emergent adverse event. [a]Death due to sepsis. [b]TEAEs leading to discontinuations in >1 participant include gastrointestinal disorders (n=4 [6%]), ovarian dysfunction (n=3 [4%]), alanine aminotransferase increase (n=3 [4%]), aspartate aminotransferase increase (n=2 [3%]), and metabolism/nutritional disorders (n=2 [3%]).

- 95% of TEAEs were Grade 1 or 2; the first onset of TEAEs in most patients occurred during Cycle 1
- Ovarian dysfunction was reported in 75% (27 of 36) of women of childbearing potential who received nirogacestat and in 0 who received placebo
  - These events resolved in 20 participants (74.1%), 9 while ongoing treatment (64%) and 11 while off treatment for any reason
  - 5 participants are unresolved with ongoing treatment (36%), and 2 participants were lost to follow-up
- No changes in male hormonal levels or TEAEs pertaining to male reproductive potential were observed

CONCLUSIONS

- To date, DeFi is the largest and most rigorous randomized controlled trial in DT and the first Phase 3 trial to demonstrate clinical benefit with a GSI for any condition
- Nirogacestat treatment resulted in rapid, sustained, and statistically significant improvements for progression-free survival, objective response, pain, disease-specific symptom burden, physical/role functioning, and overall quality of life, while exhibiting a manageable safety profile
- Nirogacestat has the potential to become standard systemic treatment for patients with DT

DISCLOSURES: ***Bernd Kasper*** *has financial interests and has served on the advisory board for Ayala, Bayer, Blueprint, Boehringer Ingelheim, GSK, ParmaMar, and SpringWorks Therapeutics.*

ACKNOWLEDGEMENTS: *This study was sponsored by SpringWorks Therapeutics, Inc. Writing and editorial support for this poster was provided under the direction of the authors by MedThink SciCom and funded by SpringWorks Therapeutics, Inc. This poster was previously presented at ESMO 2022; September 9-13, 2022; Paris, France.*

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