Supplementary Appendix

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This appendix has been provided by the authors to give readers additional information about the work.

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Supplementary Materials

Nirogacestat, a γ-Secretase Inhibitor for Desmoid Tumors

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Table of Contents

Supplementary Appendix

Methods

Literature review of representativeness of study population

To evaluate the overall representativeness of the study population in DeFi, the literature was reviewed to identify key clinical characteristics and epidemiology of this rare patient population. Online medical literature databases (PubMed) were queried with search terms for desmoid tumor or aggressive fibromatosis and the respective epidemiology or clinical characteristics. Key findings are summarized in Table S2.

Trial design, data collection, analysis, and manuscript preparation

This trial was conducted in accordance with the protocol and ethical principles derived from the Declaration of Helsinki, Council for International Organizations of Medical Sciences International Ethics Guidelines, International Council for Harmonization and Good Clinical Practice guidelines, and applicable laws and regulations.

The DeFi trial was designed by Allison Lim, L. Mary Smith, Stephanie Moody, Victor Villalobos, Shivaani Kummar, Bernd Kasper, and the study sponsor, SpringWorks Therapeutics, Inc. All authors not affiliated with SpringWorks Therapeutics were involved in gathering the data. Stephanie Moody and the study sponsor analyzed the data. All authors vouch for the data and analysis, and agree to be accountable for all aspects of the work. All authors contributed to the writing of the paper and made the decision to publish.

Many of the authors were also principal investigators for the DeFi trial clinical sites, and they and/or their institution are party to a clinical trial agreement with the sponsor, which contains standard confidentiality provisions, including ensuring that the site-specific results of the trial are not released until the sponsor-coordinated multicenter publication or a period of time has elapsed after the multicenter trial has concluded, whichever occurs earliest. In addition, the authors for this publication signed standard publication agreements with the sponsor, containing

customary confidentiality provisions concerning the nondisclosure and limited use of the full trial results solely for the purpose of developing this and other related publications in coordination with the sponsor.

Prespecified subgroup analyses

A prespecified subgroup analysis was planned for progression-free survival and objective response rate. Prespecified subgroups presented in this manuscript are:

- Sex
- Stratification factor in randomization
- Familial history of FAP
- Presence of somatic *APC* mutation
- Presence of somatic *CTNNB1* mutation
- Tumor focality
- Prior surgery
- Prior chemotherapy
- Prior tyrosine kinase inhibitor treatment
- DT treatment status

Clinical and laboratory assessments

Clinical laboratory tests were performed at screening; days 1, 8, 15, and 22 of Cycle 1; day 28 of Cycle 2; day 1 of Cycle 4; day 1 of Cycle 7 and every 3 cycles thereafter; end of treatment; and follow-up visit (if applicable). In response to early observations of ovarian dysfunction, reproductive hormone assessments in all participants (male and female) were added to the protocol with an amendment.

Secondary PROs

General and disease-specific PRO questionnaires were selected as secondary efficacy endpoints to evaluate the effect of nirogacestat on symptom burden, functioning, and health-

related quality of life. Participants completed PRO questionnaires at baseline and the start of every treatment cycle. Scores for BPI-SF and GODDESS Desmoid Tumor Symptom Scale are calculated as the average of the 7 days preceding the Cycle assessment timepoint. Components of the key secondary PRO endpoints are described below and in Figure S1.

The BPI-SF assessment is a measurement questionnaire used to assess clinical pain. Patients rate pain severity and the degree to which pain interferes with feeling and function. The short form of the assessment used in this trial consists of 9 questions assessed on an 11-point numeric rating scale from the last 24 hours. Higher scores indicate worse pain and interference.[1] Clinically meaningful improvement thresholds for BPI-SF average pain and severity score are ≥1-point decreases, corresponding to 30% to 35% decreases from baseline.[1]

The GODDESS questionnaire was developed by the Memorial Sloan Kettering Cancer Center and Desmoid Tumor Research Foundation to measure disease-specific symptoms and impact of desmoid tumors.[2] The GODDESS Desmoid Tumor Symptom Scale consists of 11 items assessing the severity of key signs and symptoms of desmoid tumors, including pain, fatigue, swelling, muscle weakness, difficulty moving, and tumor location-specific signs and symptoms. Items are assessed on an 11-point numeric rating scale from 0 (none) to 10 (as bad as you can imagine) from the last 24 hours. The GODDESS questionnaire was available in 10 languages (English, Spanish, German [Germany, Belgium], Dutch [Netherlands, Belgium], French [France, Belgium, Canadian], Italian).

The GODDESS Desmoid Tumor Impact Scale assesses 17 items relating to the impact of symptoms on functioning and daily living. The impact scale items are evaluated either with an 11-point numeric rating scale to assess severity or a 5-point Likert scale ranging from “none of the time” to “all of the time” to measure frequency of impact over the past 7 days.

Clinically meaningful improvement thresholds for the validated GODDESS Desmoid Tumor Symptom and Impact Scales are ≥1.0-point and ≥0.5-point decreases, respectively.[12]

The EORTC QLQ-C30 version 3.0 is a 30-item questionnaire composed of multi-item and single-item measures designed to assess functioning and symptoms in cancer patients. Five functional scales (physical, role, cognitive, emotional, social) and 3 symptom scales (fatigue, pain, nausea/vomiting) are assessed on a scale from 1 (not at all) to 4 (very much). Higher scores indicate worse symptom/functional burden. A global health status/quality of life scale is assessed on a scale from 1 (very poor) to 7 (excellent). Higher scores indicate better quality of life. Clinically meaningful improvement thresholds for EORTC QLQ-C30 are ≥5-points increases.[3,4]

Table S1. Representativeness of Study Participants

Category	Example
Disease, problem, or condition under investigation	Desmoid tumors, or aggressive fibromatosis
Special considerations related to	
Sex and gender	Desmoid tumors occurs in both male and female patients, with a female to male ratio of ~2-3:1[5-10]
Age	Desmoid tumors most commonly occurs in individuals between the ages of 15 to 60 years[7-10]
Race or ethnic group	In a review of the literature, no significant association between racial or ethnic background and desmoid tumors was identified
Geography	In a review of the literature, no clear association between geography and desmoid tumors was identified
Overall representativeness of this trial	The participants enrolled in DeFi demonstrated the expected ratio of women to men (65% female). The age range reported at baseline in this trial was consistent with the expected age range (range, 18-76 years).

Table S2. Confirmed Tumor Response: Intent-to-Treat Population

	Nirogacestat n=70	**Placebo n=72**
Objective response rate, n (%) [95% CI]	29 (41) [30.2, 54.5]	6 (8) [3.1, 17.3]
P value	<0.001	
Time to response, months, median (range)	5.6 (2.6, 19.4)	11.1 (2.8, 16.4)
Kaplan-Meier estimate of duration of response, months, median (95% CI)[a]	NE (NE, NE)	NE (8.3, NE)
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)
Disease control rate, n (%)	64 (91)	61 (85)

CR, complete response; NE, not estimable; PR, partial response. [a]Duration of objective response was defined as duration in months from the time CR or PR (whichever came first) was met until the date of progression or death.

Table S3. Serious Adverse Events in Safety Population

Category[a]	Nirogacestat n=69	Placebo n=72
Any serious TEAE, n (%)	14 (20)	8 (11)
Premature menopause[b]	3 (4)	0
Tumor hemorrhage	1 (1)	1 (1)
Abdominal abscess	1 (1)	0
Abdominal infection	1 (1)	0
Appendicitis	1 (1)	0
Groin abscess	1 (1)	0
Infected cyst	1 (1)	0
Ovarian failure[b]	1 (1)	0
Abdominal pain	1 (1)	0
Small intestinal obstruction	1 (1)	0
Stomatitis	1 (1)	0
Spindle cell sarcoma	1 (1)	0
Tumor pain	1 (1)	1 (1)
Atrial fibrillation	1 (1)	0
Cholecystitis	1 (1)	0
Hematuria	1 (1)	0
Rash, maculopapular	1 (1)	0
Sepsis	0	3 (4)
Drug-induced liver injury	0	1 (1)
COVID-19	0	2 (3)
Infection	0	1 (1)
Diarrhea	0	1 (1)
Duodenal perforation	0	1 (1)
Gastrointestinal fistula	0	1 (1)
Pulmonary embolism	0	1 (1)
Treatment-related serious TEAEs, n (%)	9 (13)	0
Premature menopause[b]	3 (4)	0
Ovarian failure[b]	1 (1)	0
Groin abscess	1 (1)	0
Infected cyst	1 (1)	0
Atrial fibrillation	1 (1)	0
Stomatitis	1 (1)	0
Cholecystitis	1 (1)	0
Rash, maculopapular	1 (1)	0

COVID-19, coronavirus disease 2019; TEAE, treatment-emergent adverse event. [a]All data are presented as n (%). [b]These events were reported as serious because of medical importance. However, after a protocol amendment, subsequent events of ovarian dysfunction were designated by the investigator as TEAEs of special interest.

Figure S1. Prespecified secondary patient-reported outcome questionnaires for (A) Brief Pain Inventory Short Form,[1] (B) GODDESS DTSS/DTIS,[2] and (C) EORTC QLQ-C30.[3,4,11] DTIS, Desmoid Tumor Impact Scale; DTSS, Desmoid Tumor 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.

A

Brief Pain Inventory Short Form – Average Pain Intensity

AVERAGE PAIN										
Worst pain in last 24 hours										
0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

B

GODDESS

DTSS

PAIN	EXTRA-ABDOMINAL	INTRA-ABDOMINAL	OTHER
Pain	Swelling	Abdominal pain	Fatigue
Dull pain	Muscle weakness	Nausea	
Shooting pain	Difficulty moving	Fullness	

DTIS

SLEEP	PHYSICAL	EMOTIONAL	OTHER
Falling asleep	Moving	Fear of tests	Avoidance because of appearance
Comfortable in bed	Reaching (frequency)	Fear of growth/recurrence	Reaching (difficulty)
Staying asleep	Vigorous activity	Hopelessness	Dissatisfied with appearance
	Moderate activity	Anger	
	Accomplished less	Anxiety	
		Frustration	

C

EORTC QLQ-C30 (version 3)

PHYSICAL FUNCTIONING	ROLE FUNCTIONING	GLOBAL HEALTH STATUS/ QUALITY OF LIFE
Strenuous activities	Work and daily activities	Overall health
Long walk	Hobbies and leisure activies	Overall quality of life
Short walk		
Stay in bed		
Help with daily activities		

Figure S2. Participant disposition. [a]Participants who took at least 1 dose of treatment were included in the safety population. [b]Adverse events leading to discontinuation of nirogacestat were diarrhea (n=4), premature menopause (n=3), alanine aminotransferase increase (n=3), aspartate aminotransferase increase (n=2), vomiting (n=1), ovarian failure (n=1), decreased appetite (n=1), hypophosphatemia (n=1), fatigue (n=1), Sjogren's syndrome (n=1), mental impairment (n=1), maculopapular rash (n=1), and hot flush (n=1). In 3 participants, >1 adverse event was associated with premature discontinuation. [c]Adverse events leading to discontinuation of placebo were drug-induced liver injury (n=1). [d]Number of events reflects total resulting in the discontinuation of study treatment not in the analysis of progression-free survival. [e]At the time of analysis.

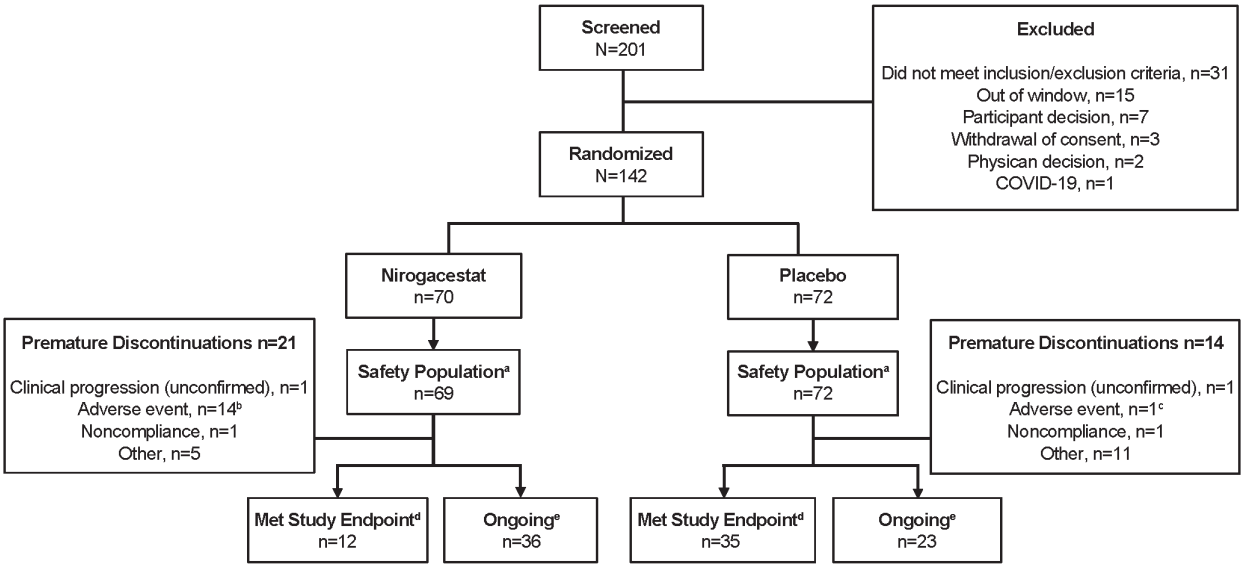
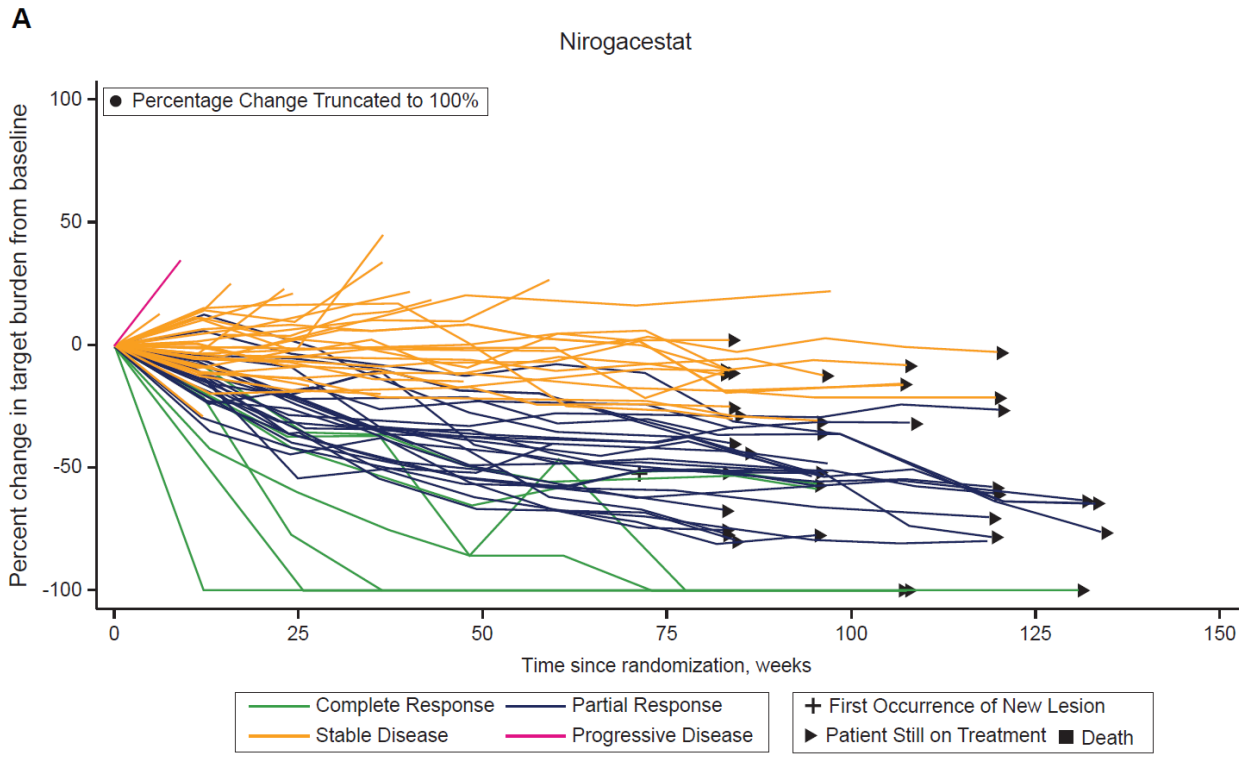
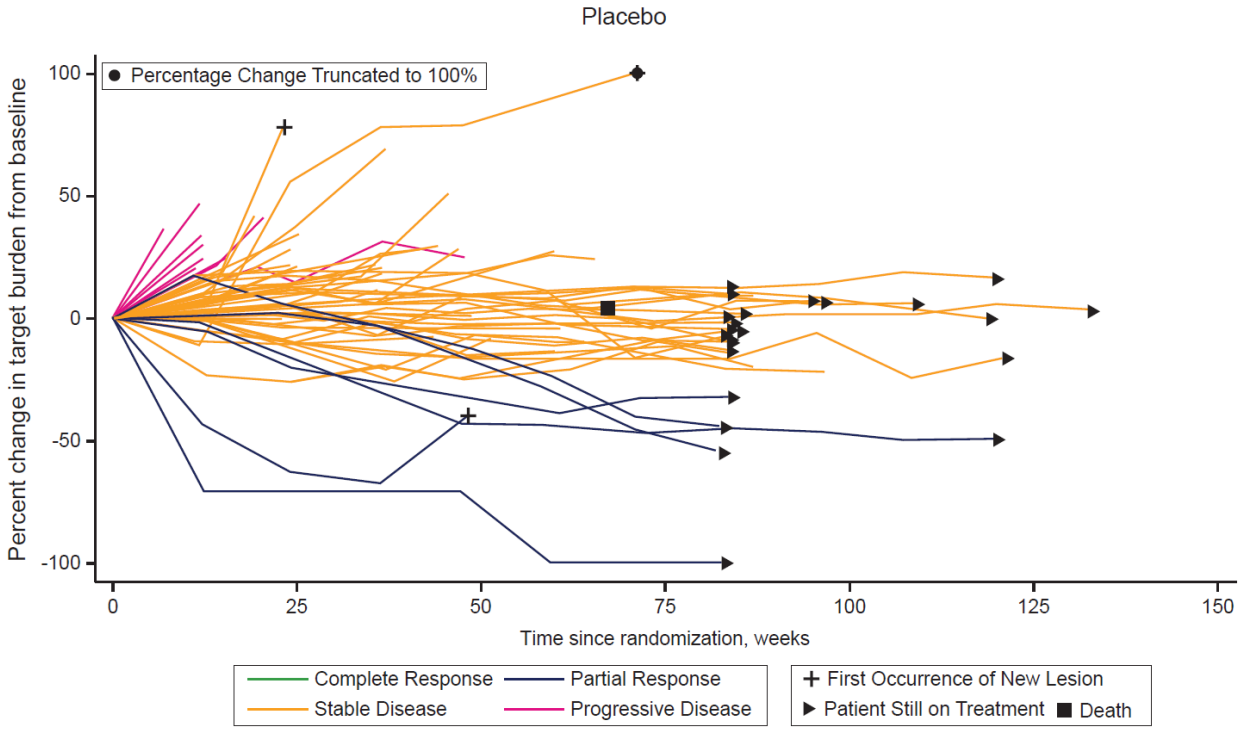


Figure S3. **Spider plot of change in target lesions from baseline in tumor-evaluable participants in the** (A) **nirogacestat and** (B) **placebo arms.** Color coded by complete response + partial response, stable disease, and progressive disease.



B


Placebo
Percentage Change Truncated to 100%
Percent change in target burden from baseline
100
50
0
-50
-100
0
25
50
75
100
125
150
Time since randomization, weeks
Complete Response
Partial Response
Stable Disease
Progressive Disease
First Occurrence of New Lesion
Patient Still on Treatment
Death

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