Efficacy and Safety of Nirogacestat in Patients With Desmoid Tumor and Adenomatous Polyposis Coli (*APC*) Mutation: Phase 3 DeFi Analyses

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INTRODUCTION

- Desmoid tumors (DT) are rare soft-tissue tumors driven by Wnt/β-catenin signaling pathway alterations[1-3]
  - Most DT (80%–90%) are sporadic tumors characterized by somatic mutations in the *CTNNB1* gene that encodes for β-catenin[2,3]
  - Approximately 10%–20% of DT are associated with mutations in the adenomatous polyposis coli (*APC*) tumor suppressor gene, whose protein regulates cellular β-catenin levels[2,3]
- *APC* mutations may confer more aggressive DT behavior and poor prognosis, regardless of specific therapy including surgery and systemic therapies[3]
- Nirogacestat, a targeted gamma secretase inhibitor, is the only FDA-approved treatment for adults with progressing DT who require systemic treatment[4,5]
  - Nirogacestat blocks proteolytic activation of the Notch receptor. When dysregulated, Notch can activate pathways that contribute to tumor growth[4]
- In the phase 3 DeFi study, nirogacestat demonstrated significant and clinically meaningful improvement versus placebo in the following:
  - The primary endpoint of progression-free survival (PFS; HR, 0.29 [95% CI, 0.15–0.55]; *P*<0.001)
  - The secondary endpoint of objective response rate (ORR; 41% versus 8%; *P*<0.001) with median (min, max) time to response of 5.6 (2.6, 19.4) months[6]
- As DT can exert substantial symptom burden on patients, including pain and functional limitation, treatment goals should extend beyond clinical outcomes to include patient-reported outcomes (PROs)[7,8]
  - In the DeFi study, nirogacestat demonstrated significant and clinically meaningful improvement versus placebo in secondary endpoints of change from baseline at cycle 10 in PROs of pain, DT-specific symptom burden and their impact on patients' lives, physical functioning, role functioning, and overall quality of life (all *P*≤0.01)[6]

OBJECTIVE

- A post hoc analysis of the DeFi study was conducted to assess the effects of nirogacestat in patients with *APC* mutations

METHODS

- DeFi (NCT03785964) was a global, multicenter, double-blind, pivotal phase 3 study that evaluated the efficacy, safety, and tolerability of nirogacestat in adults (aged ≥18 years) with progressing DT
- Patients were randomized 1:1 to receive oral nirogacestat (150 mg) or placebo twice daily in continuous 28-day cycles
- Descriptive post hoc subgroup analyses (data cutoff: April 7, 2022) were conducted to assess effects of nirogacestat versus placebo in patients with somatic and/or germline *APC* mutations:
  - PFS
  - ORR
  - PROs
    - Brief Pain Inventory–Short Form (BPI-SF) average pain intensity (API) of worst pain
    - Gounder-Desmoid Tumor Research Foundation Desmoid Symptom/Impact Scale (GODDESS) consisting of the Desmoid Tumor Symptom Scale (DTSS) total symptom score and Desmoid Tumor Impact Scale (DTIS) physical functioning domain score
    - European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30) scales for physical functioning, role functioning, and global health status–quality of life
  - Volumetric magnetic resonance imaging (MRI), T2 hyperintensity, and tumor size
  - Adverse events from the time of the first dose through 30 days after the last dose

RESULTS

PATIENT POPULATION

- Of 142 patients in the DeFi intent-to-treat population (nirogacestat, n=70; placebo, n=72), 29 had identified *APC* mutations (nirogacestat, n=13; placebo, n=16)
- Baseline patient demographics and disease characteristics are shown in **Table 1**

Table 1. Baseline demographics and disease characteristics of patients with *APC* mutations

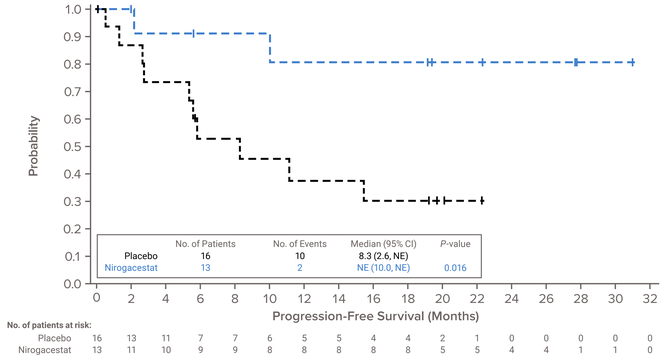
	Nirogacestat (n=13)	Placebo (n=16)
Sex, n (%) Male Female	 3 (23) 10 (77)	 7 (44) 9 (56)
Age, median (min, max), y	29.0 (18, 51)	33.5 (22, 56)
Age group, n (%) ≤30 y >30 y	 9 (69) 4 (31)	 7 (44) 9 (56)
Time since diagnosis to randomization, median (min, max), mo	27.24 (0.7, 133.4)	60.88 (5.6, 338.4)
Desmoid tumor treatment status, n (%) Refractory Treatment-naive Recurrent	 9 (69) 3 (23) 1 (8)	 13 (81) 3 (19) 0
Tumor location at randomization, n (%) Extra-abdominal Intra-abdominal	 8 (62) 5 (38)	 7 (44) 9 (56)
Family history of familial adenomatous polyposis, n (%)	10 (77)	12 (75)
Any prior therapy[a], n (%) Lines of any prior therapy, median (min, max)	10 (77) 1 (0, 14)	13 (81) 3 (0, 13)
Any somatic *APC* mutation, n (%) Any germline *APC* mutation, n (%) Any somatic and germline *APC* mutation, n (%)	11 (85) 9 (69) 7 (54)	11 (69) 12 (75) 7 (44)

[a]Systemic, radiation, surgery.

EFFICACY

- PFS was improved with nirogacestat versus placebo in patients with *APC* mutations (HR, 0.21 [95% CI, 0.05–1.00]; *P*=0.016) (**Figure 1**)
  - The probability of being progression-free at month 12 was 80.8% (95% CI, 42.3%–94.9%) with nirogacestat versus 37.5% (95% CI, 14.1%–61.2%) with placebo

Figure 1. Progression-free survival in patients with *APC* mutations



CI, confidence interval; NE, not evaluable; No, number.

- In patients with *APC* mutations, ORR was higher with nirogacestat (5/13, 38%) versus placebo (2/16, 13%)
  - There were no patients who achieved a complete response in either group
  - Median (min, max) time to response (n=5) was 8.31 (6.0, 13.8) months with nirogacestat
- All PRO assessments (pain, symptom burden, physical and role functioning, and overall quality of life) demonstrated clinically meaningful between-group improvements for nirogacestat versus placebo (**Table 2**)

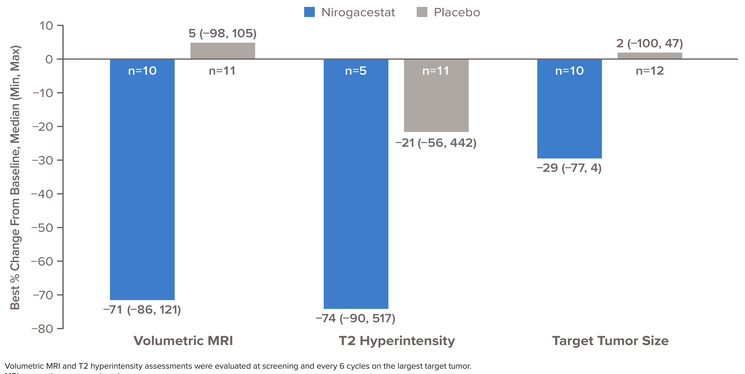
Table 2. Mean change from baseline in PROs at cycle 10 in patients with *APC* mutations

	Nirogacestat (n=13)		Placebo (n=16)			
PRO	n	Mean (SD)	n	Mean (SD)	Difference	Clinically meaningful improvement between-group difference[9-11]
BPI-SF API[a]	8	−2.4 (2.01)	5	−0.1 (0.58)	−2.3	≤−1.0
GODDESS DTSS Total Symptom Score[a]	8	−1.6 (1.17)	6	−0.4 (0.92)	−1.2	≤−1.0
GODDESS DTIS Physical Functioning[a]	8	−1.0 (1.06)	5	−0.2 (0.57)	−0.8	≤−0.5
EORTC QLQ-C30 GHS/QoL[b]	7	11.9 (29.60)	5	5.0 (13.94)	6.9	≥5–10
EORTC QLQ-C30 Physical Functioning[b]	7	11.4 (14.76)	5	4.0 (16.06)	7.4	≥5–10
EORTC QLQ-C30 Role Functioning[b]	7	26.2 (30.21)	5	−6.7 (49.44)	32.9	≥5–10

[a]A negative change from baseline value indicates improvement of symptoms. [b]A positive change from baseline value indicates improvement of symptoms.
BPI-SF API was the (up to) 7-day average of BPI Question #3 - Worst pain in last 24 hours.
BPI-SF API, Brief Pain Inventory–Short Form average pain intensity; 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; GHS, global health status; GODDESS, Gounder/Desmoid Tumor Research Foundation Desmoid Symptom/Impact Scale; PRO, patient-reported outcome; QoL, quality of life; SD, standard deviation.

- Nirogacestat-treated patients demonstrated greater reduction in median best percent change from baseline compared with patients in the placebo group in volumetric MRI, T2 hyperintensity, and target tumor size (**Figure 2**)

Figure 2. Best percent change from baseline in volumetric MRI, T2 hyperintensity, and target tumor size in patients with *APC* mutations



Volumetric MRI and T2 hyperintensity assessments were evaluated at screening and every 6 cycles on the largest target tumor.
MRI, magnetic resonance imaging.

SAFETY

- In patients with *APC* mutations, the most frequently reported treatment-emergent adverse event was diarrhea (69% with nirogacestat and 63% with placebo)
- In patients treated with nirogacestat, increased rates of skin events (rash maculopapular, 62%; dermatitis acneiform, 38%) and stomatitis (46%) were reported in patients with *APC* mutations compared with those in the overall DeFi population (32%, 22%, and 29%, respectively)[6]
- In nirogacestat-treated patients with *APC* mutations, ovarian toxicity occurred in 9 of 10 females of reproductive potential (6 resolved as reported by the investigator, 2 were lost to follow-up, 1 was ongoing and receiving nirogacestat); no patients in the placebo group had ovarian toxicity

CONCLUSIONS

- Improvements in PFS, ORR, PROs (pain, DT-specific symptom burden, role and physical functioning, and overall quality of life), and reductions in tumor size, volume, and T2 hyperintensity were observed with nirogacestat compared with placebo in patients with DT and identified *APC* mutations
  - These results were generally consistent with the overall DeFi population[6]
  - Median time to response with nirogacestat was relatively longer in patients with *APC* mutations compared with nirogacestat-treated patients in the overall DeFi population[6]
- The safety profile of nirogacestat in patients with identified *APC* mutations was generally consistent with findings for nirogacestat-treated patients in the overall DeFi population[6]
- While analyses were limited due to the small sample size, results suggest that nirogacestat can provide clinically meaningful benefits in the challenging population of patients with progressing DT and *APC* mutations

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