Efficacy of Nirogacestat in Patients With Desmoid Tumors and Presence or Absence of Poor Prognostic Factors: Post Hoc Analyses of the Phase 3 DeFi Trial

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INTRODUCTION

- Desmoid tumors (DT) are rare, locally aggressive, and invasive soft-tissue tumors, often associated with debilitating symptom burden[1,2]
- Nirogacestat is an oral, targeted gamma secretase inhibitor and the only US FDA- and European Commission-approved treatment for adults with progressing DT who require systemic treatment[3-5]
- In the global, multicenter, phase 3 DeFi trial (NCT03785964), nirogacestat demonstrated statistically significant and clinically meaningful improvement versus placebo in the primary and secondary endpoints of[6]:
  - Progression-free survival (PFS; hazard ratio, 0.29 [95% CI, 0.15–0.55]; *P*<.001)
  - Objective response rate (ORR; 41% versus 8%; *P*<.001)
  - Patient-reported outcomes (PRO) in pain, DT-specific symptom burden, physical and role functioning, and overall quality of life (all *P*≤.01)
- Historically, prognosis of DT has been associated with multiple patient- and tumor-related factors[7-14]
  - Larger tumor size, younger age, presence of S45F or T41A *CTNNB1* gene mutations, and presence of pain at baseline

OBJECTIVE

- A post hoc analysis of the DeFi trial was conducted to further evaluate the efficacy of nirogacestat versus placebo in subgroups of patients with DT with or without a poor prognostic factor, with further characterization of longitudinal PRO

METHODS

- In DeFi (data cutoff April 7, 2022), patients were randomized 1:1 to nirogacestat 150 mg (N=70) or placebo (N=72), taken twice daily in 28-day cycles
- Post hoc analyses of PFS, ORR, and PRO were conducted for subgroups of patients with or without factors associated with poor prognosis:
  - Tumor size >10 cm or ≤10 cm
  - Age ≤30 years or >30 years
  - Presence of S45F or T41A *CTNNB1* mutation
    - Other *CTNNB1* mutations were not assessed due to small sample size
  - Presence or absence of pain at baseline
    - Presence of pain was determined by an average pain intensity (API) of worst pain score of >0 on the Brief Pain Inventory–Short Form (BPI-SF); absence of pain was determined by an API of worst pain score of 0
- PRO were evaluated as mean change from baseline score:
  - BPI-SF 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
  - Additional analyses with GODDESS Desmoid Tumor Impact Scale (DTIS) physical functioning domain score and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30) scales for physical functioning, role functioning, and overall quality of life were also conducted (**Supplemental Figure S1**, via the QR code)

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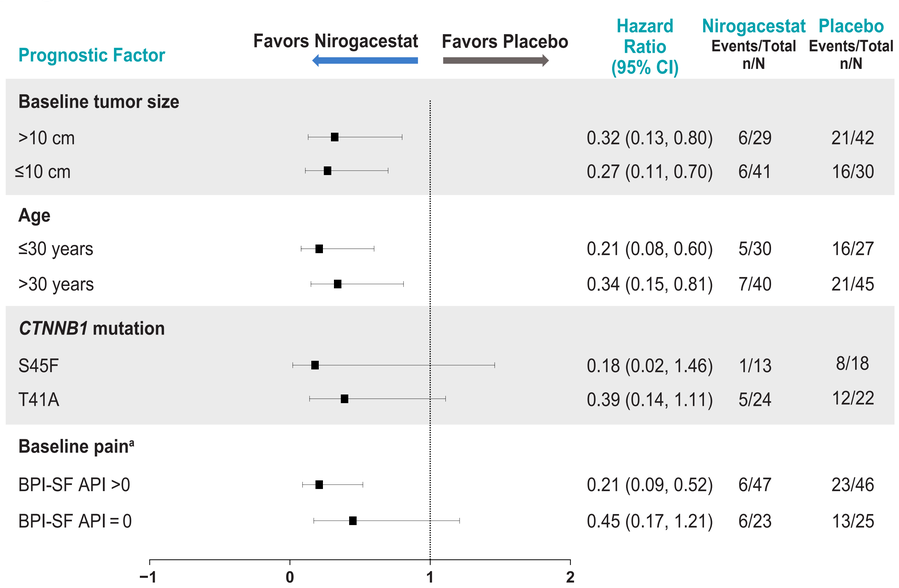
RESULTS

- Nirogacestat treatment resulted in improved PFS versus placebo in patients with or without a poor prognostic factor (**Figure 1**)

Figure 1. Progression-free survival in subgroups with or without poor prognostic factors

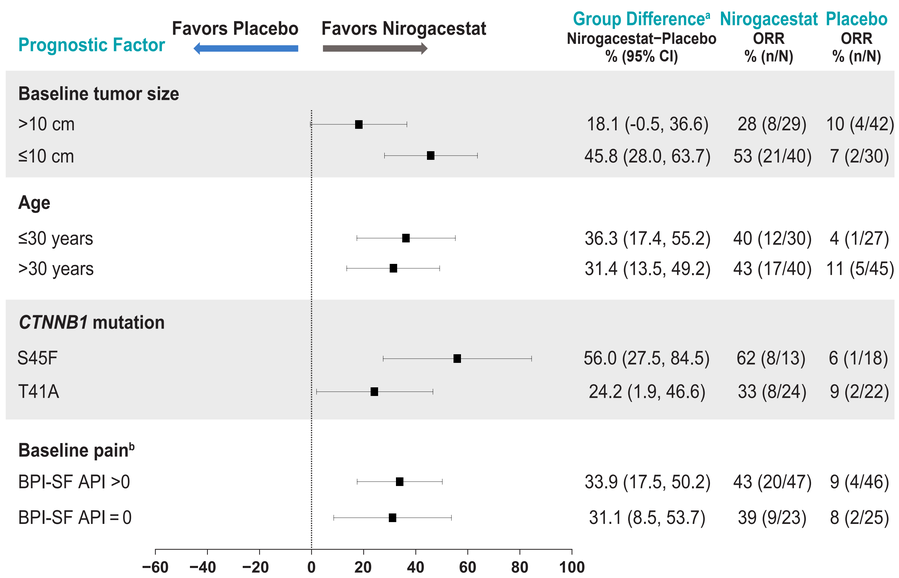


Prognostic Factor	Hazard Ratio (95% CI)	Nirogacestat Events/Total n/N	Placebo Events/Total n/N
Baseline tumor size			
>10 cm	0.32 (0.13, 0.80)	6/29	21/42
≤10 cm	0.27 (0.11, 0.70)	6/41	16/30
Age			
≤30 years	0.21 (0.08, 0.60)	5/30	16/27
>30 years	0.34 (0.15, 0.81)	7/40	21/45
***CTNNB1* mutation**			
S45F	0.18 (0.02, 1.46)	1/13	8/18
T41A	0.39 (0.14, 1.11)	5/24	12/22
Baseline pain[a]			
BPI-SF API >0	0.21 (0.09, 0.52)	6/47	23/46
BPI-SF API = 0	0.45 (0.17, 1.21)	6/23	13/25

For PFS, hazard ratio was estimated from the stratified Cox proportion hazards model using the exact method for ties, stratified by tumor location. PFS was calculated as the earliest date of death, centrally-read radiographic/qualified clinical progression, or censoring from randomization. Patients who discontinued treatment early by investigators for clinical progression but could not be verified as events were censored. Patients who did not progress or die by the date of the last valid CT/MRI assessment were censored.
[a]Pain was assessed using BPI-SF item 3 (worst pain in the past 24 hours). API was calculated using daily scores from up to a 7-day period prior to each visit; scores ranged from 0–10, with higher scores indicating worse pain.
API, average pain intensity; BPI-SF, Brief Pain Inventory–Short Form; CI, confidence interval; CT, computed tomography; MRI, magnetic resonance imaging; PFS, progression-free survival.

- Nirogacestat treatment resulted in improved ORR versus placebo in patients with or without a poor prognostic factor (**Figure 2**)

Figure 2. Objective response rate in subgroups with and without poor prognostic factors

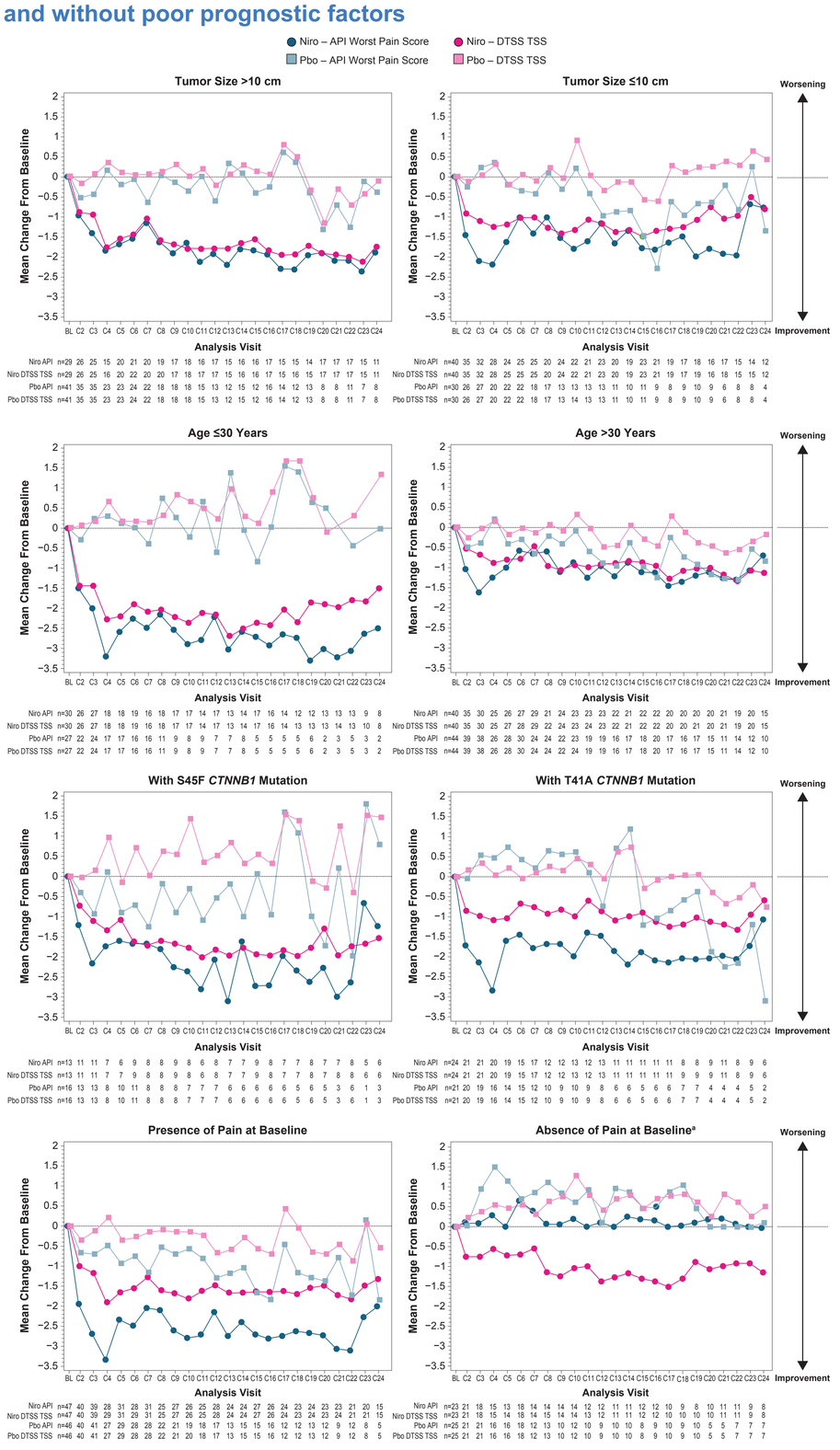


Prognostic Factor	Group Difference[a] Nirogacestat−Placebo % (95% CI)	Nirogacestat ORR % (n/N)	Placebo ORR % (n/N)
Baseline tumor size			
>10 cm	18.1 (-0.5, 36.6)	28 (8/29)	10 (4/42)
≤10 cm	45.8 (28.0, 63.7)	53 (21/40)	7 (2/30)
Age			
≤30 years	36.3 (17.4, 55.2)	40 (12/30)	4 (1/27)
>30 years	31.4 (13.5, 49.2)	43 (17/40)	11 (5/45)
***CTNNB1* mutation**			
S45F	56.0 (27.5, 84.5)	62 (8/13)	6 (1/18)
T41A	24.2 (1.9, 46.6)	33 (8/24)	9 (2/22)
Baseline pain[b]			
BPI-SF API >0	33.9 (17.5, 50.2)	43 (20/47)	9 (4/46)
BPI-SF API = 0	31.1 (8.5, 53.7)	39 (9/23)	8 (2/25)

[a]The difference between the ORR in nirogacestat and placebo; a risk difference >0 favors nirogacestat.
[b]Pain was assessed using BPI-SF item 3 (worst pain in the past 24 hours). API was calculated using daily scores from up to a 7-day period prior to each visit; scores ranged from 0–10, with higher scores indicating worse pain.
API, average pain intensity; BPI-SF, Brief Pain Inventory–Short Form; CI, confidence interval; ORR, objective response rate.

- Nirogacestat-treated patients with or without a poor prognostic factor reported greater improvement from baseline versus placebo in BPI-SF API and GODDESS DTSS total symptom score (**Figure 3**)
  - Similar results were observed in the GODDESS DTIS physical functioning domain score and EORTC QLQ-C30 scales for physical functioning, role functioning, and overall quality of life (**Figure S1**)
  - PRO improvements were observed early and sustained on treatment with nirogacestat versus placebo

Figure 3. PRO of pain and DT-specific symptom burden in subgroups with and without poor prognostic factors



[a]Patients who reported an absence of pain at baseline (BPI-SF API = 0) could not experience further improvement in pain.
Pain was assessed using BPI-SF item 3 (worst pain in the past 24 hours). API was calculated using daily scores from up to a 7-day period prior to each visit (on a scale of 0–10).
A negative change from baseline value indicates improvement. The BPI-SF and GODDESS DTSS total symptom score are each on a scale of 0–10.
API, average pain intensity; BL, baseline; BPI-SF, Brief Pain Inventory–Short Form; C, cycle; DTSS, Desmoid Tumor Symptom Scale; GODDESS, GOunder/Desmoid Tumor Research Foundation DEsmoid Symptom/Impact Scale; Niro, nirogacestat; Pbo, placebo; TSS, total symptom score.

CONCLUSION

- In DeFi, patients with DT treated with nirogacestat experienced consistent improvement versus placebo in PFS, ORR, and PRO of pain, DT-specific symptom burden, physical and role functioning, and overall quality of life regardless of the presence or absence of poor prognostic factors