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Efficacy of Nirogacestat in Patients with Desmoid Tumors and Poor Prognostic Factors: Patient-Reported Outcomes, Progression-Free Survival, and Objective Response Rate in the Phase 3 DeFi Trial

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Disclosures

- Dr. Bruno Vincenzi reports the following:
  - Consulting fees from Eisai, Eli Lilly, Bayer, Deciphera, PharmaMar, Blueprint, Pfizer, GSK, Accord, Abbott
  - Consulting/Advisory role for Eisai, Eli Lilly, Novartis, PharmaMar, Abbott, GSK, Deciphera
  - Honoraria from Novartis, PharmaMar, Abbott, GSK, Accord, Deciphera
  - Testimony for Abbott, GSK, Accord
  - Research funds received by employing institution from Eli Lilly, Novartis, PharmaMar
- The DeFi trial was sponsored by SpringWorks Therapeutics, Inc

Nirogacestat and the Phase 3 DeFi Trial

- **Nirogacestat**: oral, targeted gamma secretase inhibitor[1]
  - Only FDA-approved therapy for adults with progressing DT who require systemic treatment[2]
- **DeFi (NCT03785964)**: global, randomized, multicenter, placebo-controlled, phase 3 trial for nirogacestat[3]
  - Adults with progressing DT (≥20% by RECIST v1.1) were randomized to nirogacestat 150 mg (n=70) or placebo (n=72), twice daily in 28-day cycles until progression or unacceptable toxicities
- **In DeFi, nirogacestat demonstrated statistically significant and clinically meaningful** improvement versus placebo in the primary and key secondary endpoints of[3,a]**:**
  - Progression-free survival (HR: 0.29, 95% CI: 0.15–0.55; P<.001)
  - Objective response rate (41% nirogacestat vs 8% placebo; P<.001)
  - PROs (at cycle 10): pain, DT-specific symptom burden, physical and role functioning, and overall QoL (P≤.01)

[a]Datacut: 07Apr2022.

1. OGSIVEO® (nirogacestat) [package insert]. Stamford, CT: SpringWorks Therapeutics, Inc: 2023. 2. SpringWorks Therapeutics, Inc. SpringWorks Therapeutics Announces FDA Approval of OGSIVEO (nirogacestat) as the First and Only Treatment for Adults with Desmoid Tumors. November 27, 2023. https://ir.springworkstx.com/news-releases/news-release-details/springworks-therapeutics-announces-fda-approval-ogsiveotm. Accessed Sept 27, 2024. 3. Gounder MM, et al. *N Engl J Med*. 2023;388(10):898-912.

CI, confidence interval; DT, desmoid tumor; FDA, food and drug administration; HR, hazard ratio; PROs, patient-reported outcomes; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; QoL, quality of life.

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Poor Prognosis in Patients with Desmoid Tumors

Objective: Assess the effect of nirogacestat in subgroups of patients with DT who have risk factors associated with poor prognosis

Post-hoc analyses of PFS, ORR, and PROs were performed in the following subgroups of patients:

Larger Tumor Size (>10 cm)

Larger size of primary tumors (>10 cm) has been associated with lower rates of 5-year recurrence-free survival and poorer local control[1,2]

Presence of S45F or T41A *CTNNB1* Mutation

Of patients with *CTNNB1* gene mutations, T41A and S45F mutations are the most common[3]

S45F mutation may be associated with poorer outcomes compared with T41A mutation[3-5]

Younger Age (≤30 years)

Some evidence has suggested younger patients (eg, ≤30 years) could potentially have a higher risk of DT recurrence and worse local control than older patients[1,2,6,7]

Presence of Pain at Baseline[a]

Patients reporting pain at baseline have been shown to have higher disease progression rates and lower event-free survival compared with those without pain[8,9]

[a]Determined by an average pain intensity score of >0 on the BPI-SF.

1. Crago AM, et al. *Ann Surg*. 2013;258(2):347-53. 2. Bishop AJ, et al. *Cancer*. 2020;126(14):3265-73. 3. Timbergen MJM, et al. *Ann Surg*. 2021;273(6):1094-1101. 4. Colombo C, et al. *Cancer*. 2013;119(20):3696-3702. 5. Lazar AJF, et al. *Am J Pathol*. 2008;173(5):1518-27. 6. Lev D, et al. *J Clin Oncol*. 2007;25(13):1785-91. 7. Sørensen A, et al. *Acta Orthop Scand*. 2002;73(2):213-19. 8. Cuomo P, et al. *BMC Cancer*. 2021;21(1):437. 9. Penel N, et al. *Int J Cancer*. 2023;153(2):407-16.

BPI-SF, Brief Pain Inventory–Short Form; DT, desmoid tumor; ORR, objective response rate; PFS, progression-free survival; PROs, patient-reported outcomes.

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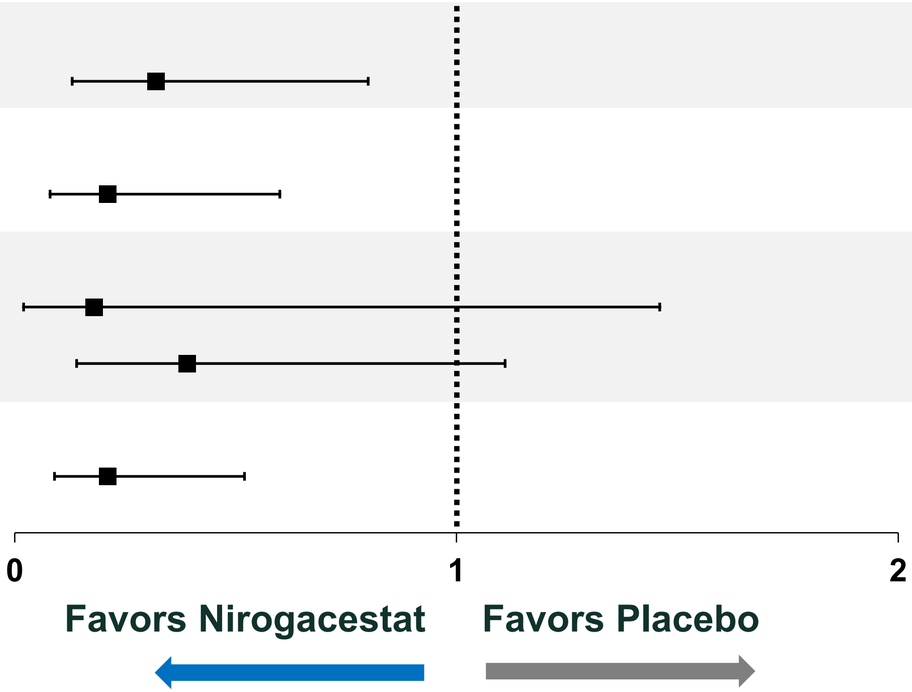
Patients with Poor Prognostic Factors Experienced Improved PFS with Nirogacestat Treatment



Poor 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
Age			
≤30 years	0.21 (0.08, 0.60)	5/30	16/27
***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

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, progression, or censoring from randomization. Patients who were discontinued 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 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.

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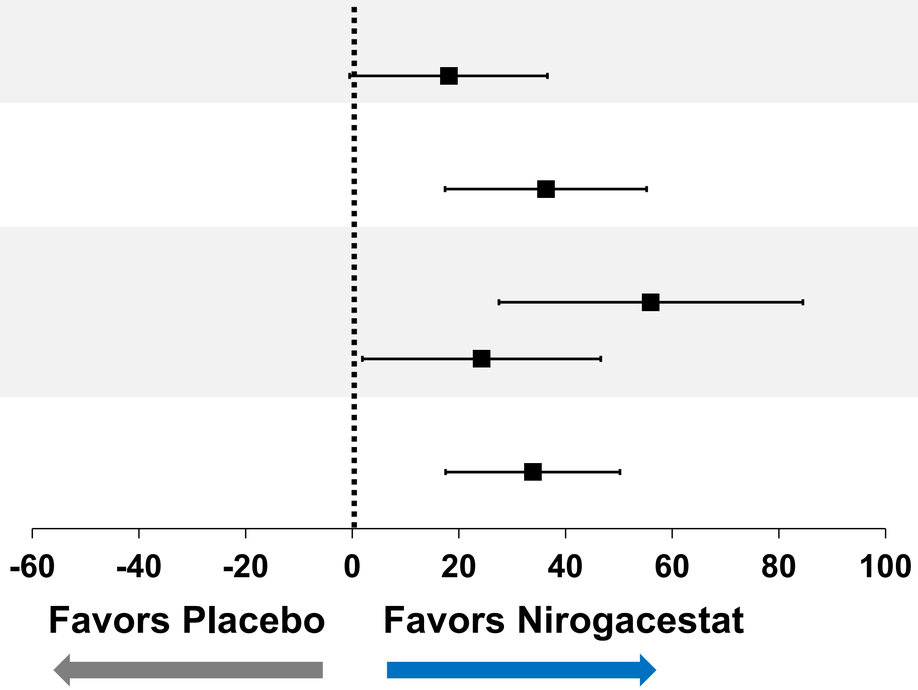
Patients with Poor Prognostic Factors Experienced Improved ORR with Nirogacestat Treatment



Poor 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)
Age ≤30 years	36.3 (17.4, 55.2)	40 (12/30)	4 (1/27)
***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)

[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 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.

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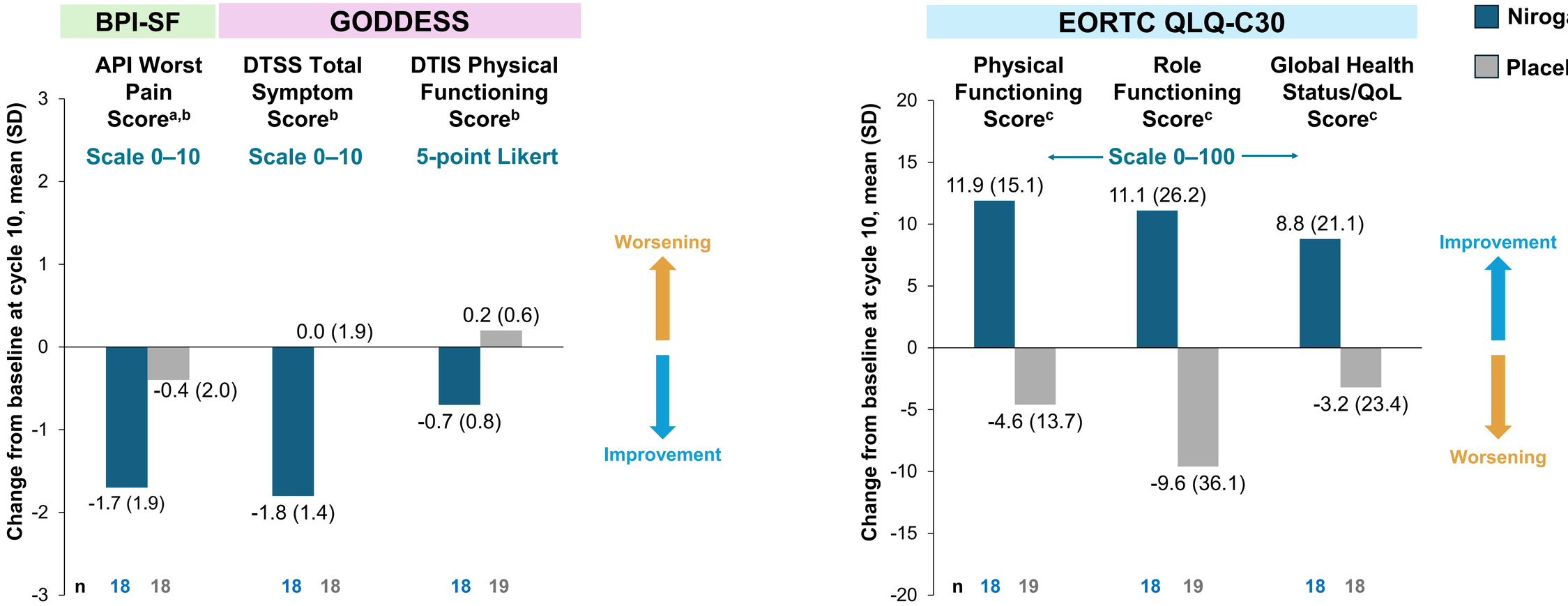
Patients with Large Tumor Size (>10 cm) Reported Less Pain and Improved Functioning with Nirogacestat Treatment



[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 (on a scale of 0–10).
[b]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; the GODDESS DTIS physical functioning score is based on a 5-point Likert scale.
[c]A positive change from baseline value indicates improvement. The EORTC QLQ-C30 is scored on a scale of 0–100.
API, average pain intensity; BPI-SF, Brief Pain Inventory–Short Form; 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; QoL, quality of life; SD, standard deviation.

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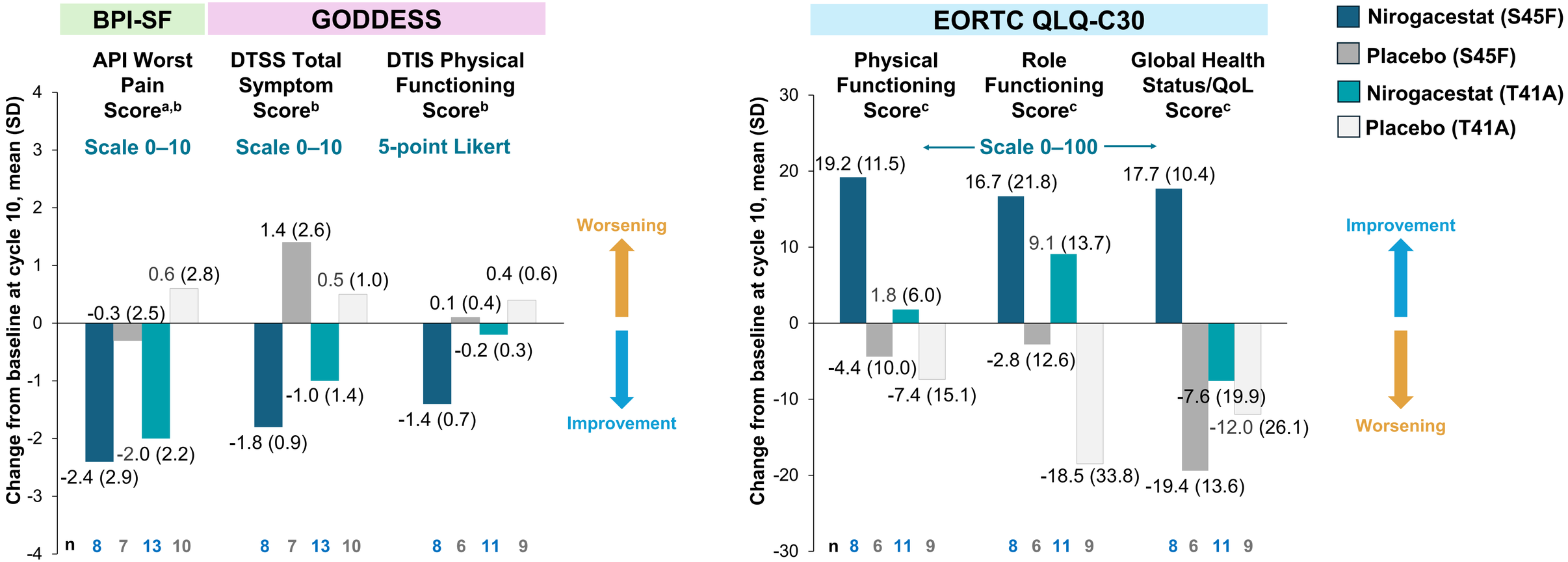
Patients with *CTNNB1* Mutations Reported Less Pain and Improved Functioning with Nirogacestat Treatment



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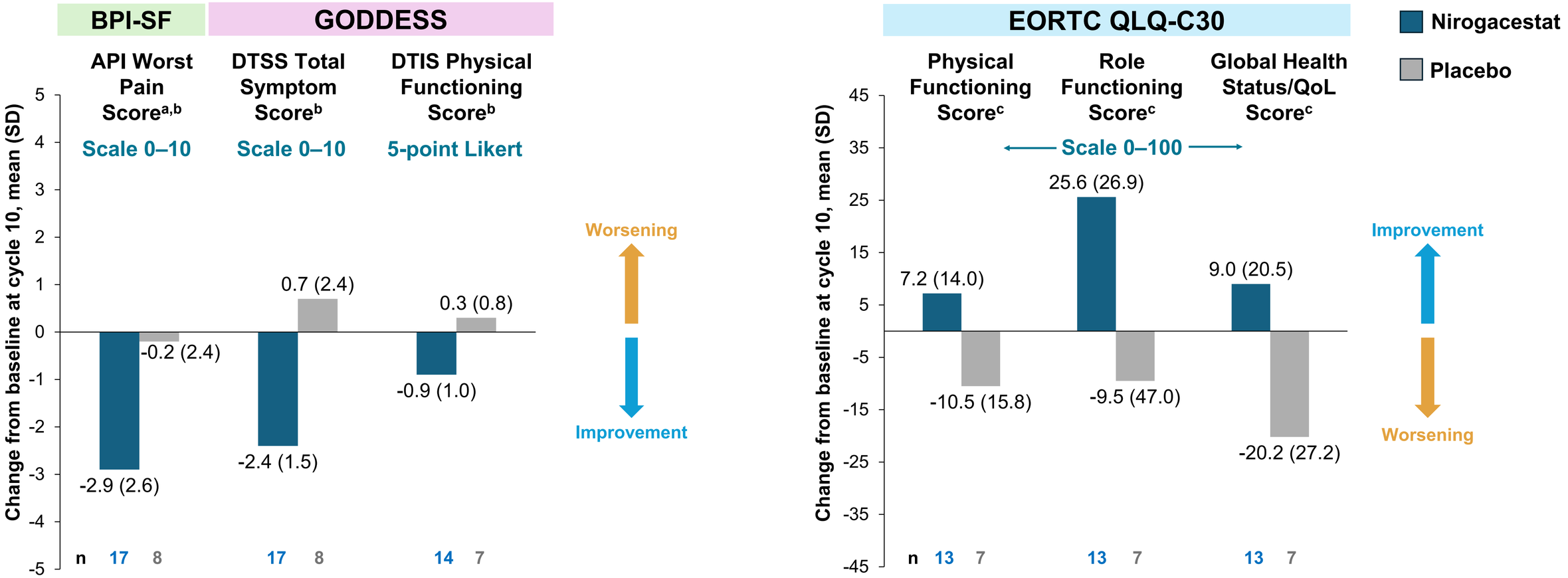
Patients of Younger Age (≤30 years) Reported Less Pain and Improved Functioning with Nirogacestat Treatment



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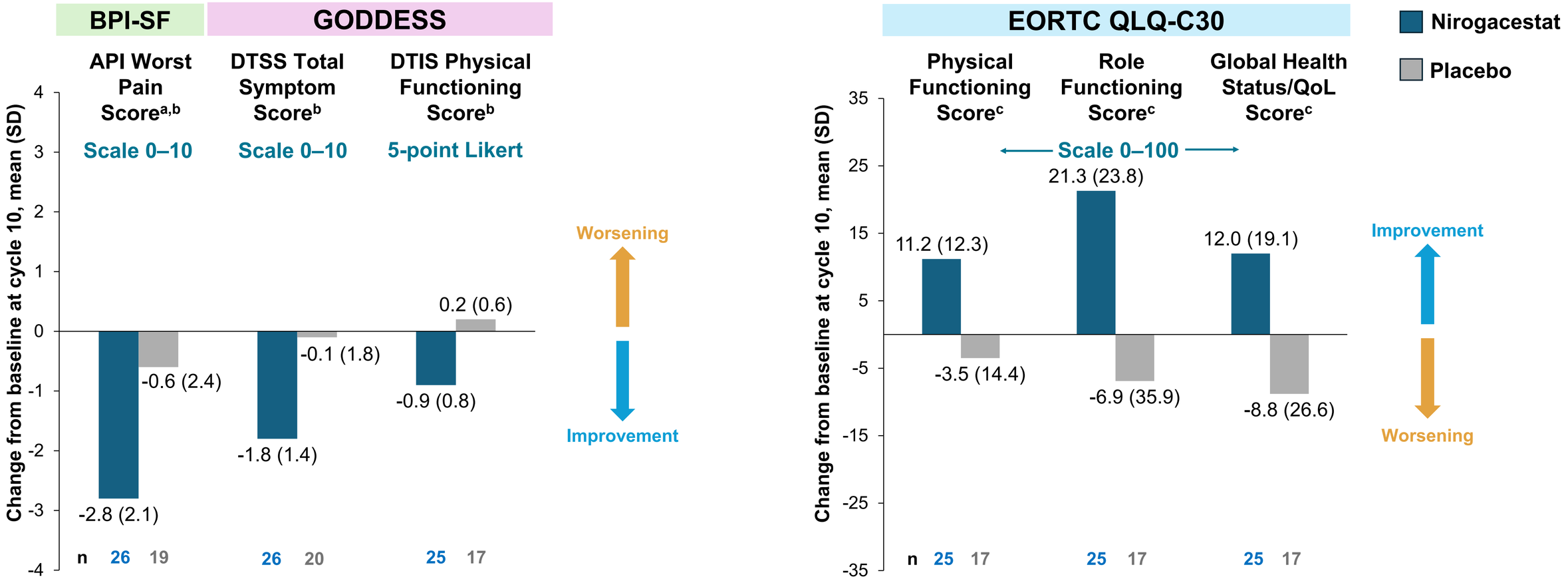
Patients with Pain at Baseline (BPI-SF API >0) Reported Less Pain and Improved Functioning with Nirogacestat Treatment



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Conclusions

- In DeFi, patients treated with nirogacestat experienced consistent improvement vs placebo in PFS, ORR, and PROs of pain, DT-specific symptom burden, physical and role functioning, and overall QoL in patients with factors associated with poor prognosis in DT

- The results of this descriptive analysis suggest that patients with poor prognostic factors for DT benefit from nirogacestat

DT, desmoid tumor; ORR, objective response rate; PFS, progression-free survival; PROs, patient-reported outcomes; QoL, quality of life.

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Sarcoma Patient Advocacy Global Network (SPAGN)

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