

Efficacy of Nirogacestat in Improving Emotional Outcomes in Adults With Desmoid Tumors: Post Hoc Analysis From the DeFi Trial

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INTRODUCTION

- Desmoid tumors (DT) are rare, locally invasive, soft-tissue tumors that can result in severe pain, functional morbidity, and quality of life impairment^{1,2}
- Impaired quality of life due to DT symptoms—especially pain—is well documented to contribute toward persistent emotional distress, such as feelings of anxiety and depression³⁻⁵
- Nirogacestat is an oral, targeted gamma secretase inhibitor and the only US Food and Drug Administration-, European Commission-, and UK Medicines and Healthcare Product Regulatory Agency-approved treatment for adults with progressing DT who require systemic treatment
- In DeFi (NCT03785964), a global, randomized, placebo-controlled, multicenter, phase 3 trial evaluating the efficacy and safety of nirogacestat, treatment with nirogacestat resulted in a significant and clinically meaningful reduction in all prespecified assessments of patient-reported outcomes (PRO), including DT-related pain intensity, compared with placebo⁶
- PRO assessments have demonstrated the high emotional and psychological burden of DT, with patients experiencing fear, frustration, and hopelessness related to their condition; however, the effect of DT treatment on patients' emotional well-being has not been explored

OBJECTIVE

- To evaluate the emotional impact of DT treatment via emotion-related PRO and their correlation with pain in patients with DT assigned to nirogacestat or placebo in the DeFi trial

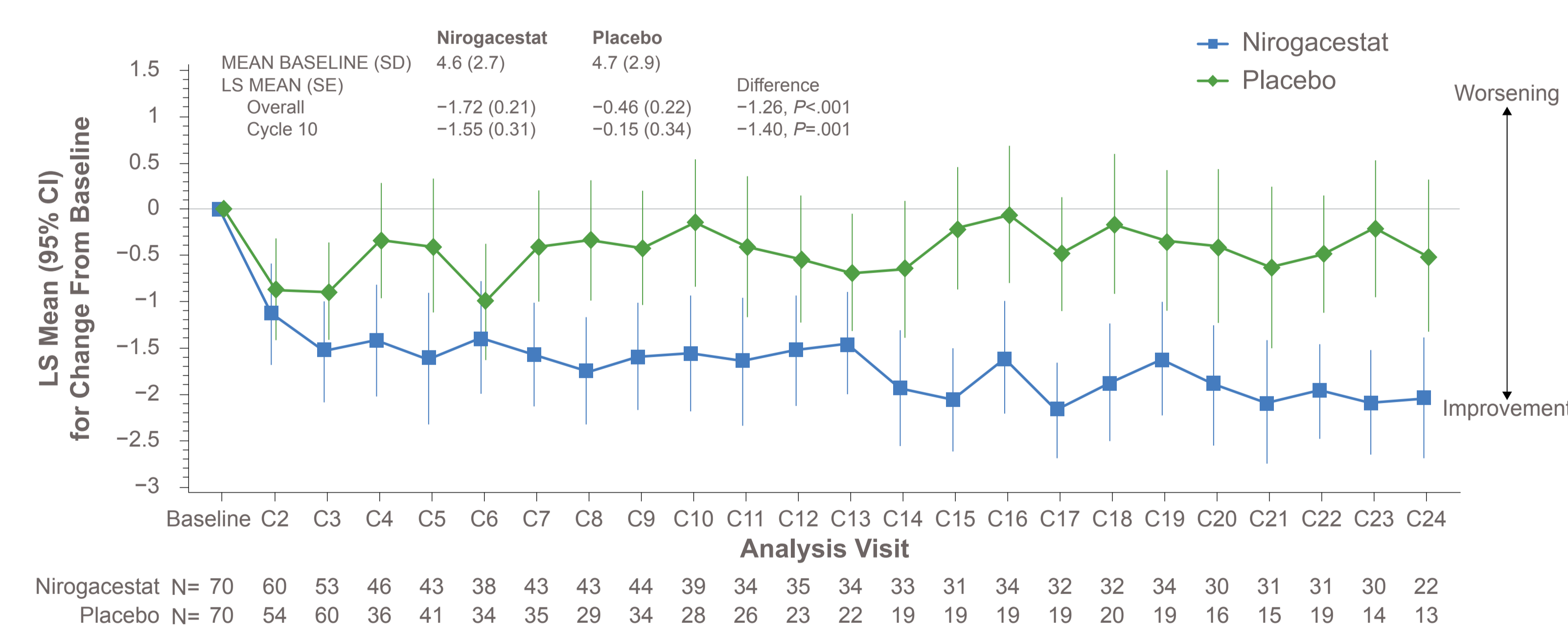
METHODS

- This post hoc analysis of the DeFi double-blind phase (final database lock 19 December 2024) evaluated emotional outcomes using emotion-related item scores from 2 PRO assessment tools:
 - Emotional Domain scores from the Gounder/Desmoid Tumor Research Foundation Desmoid Symptom/Impact Scale (GODDESS) DT Impact Scale (DTIS), scored on an 11-point numerical rating scale (0-10), with higher scores indicating more severe negative emotional impact overall⁷
 - Individual GODDESS DTIS emotion-related items were also assessed: "Fear of Future Diagnostic Tests," "Fear of Desmoid Tumor Recurrence/Growth," "Hopelessness," "Frustration," "Anger," "Anxiety," "People Avoidance Due to Appearance," and "Dissatisfaction About Appearance"
 - Emotional Functioning scores from the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), scored between 0 and 100; Emotional Functioning score was calculated as $(1 - [\text{raw score} - 1] / \text{range}) \times 100$, with higher scores denoting improvement in overall emotional well-being
 - Individual EORTC QLQ-C30 emotion-related items were also assessed: "Feel Tense," "Worry," "Feel Irritable," and "Feel Depressed"; item scores were calculated as $([\text{raw score} - 1] / \text{range}) \times 100$, with higher scores denoting a worsening negative impact
- Least squares (LS) mean change from baseline in emotional outcome scores was compared between treatment arms at Cycle 10 and overall (up to Cycle 24) using mixed model with repeated measures, per published DeFi methods demonstrating the effect of nirogacestat on PRO⁸
 - Baseline for DTIS and EORTC QLQ-C30 assessments was defined as the most recent measurement prior to the first administration of study treatment
 - Treatment and visit were used as factors, with corresponding baseline score and primary tumor location (intra-abdominal or extra-abdominal) used as covariates, and included baseline-by-visit and treatment-by-visit interactions
 - Only patients with a baseline measurement and ≥ 1 postbaseline PRO score were included in each analysis; scheduled visits with < 10 patients in the arm and unscheduled visits were not included
- Correlation between the change from baseline in DTIS Emotional Domain/EORTC QLQ-C30 Emotional Functioning scores and the change from baseline in average pain intensity (API) was assessed at Cycle 10 for patients assigned to nirogacestat
 - API was calculated using the Brief Pain Inventory–Short Form (BPI-SF) item 3 (worst pain in the past 24 hours; 0–10 scale)
 - Baseline BPI-SF API was defined as the weekly average of the baseline period (study days –7 through –1); if there were < 4 days of assessments during this period, the weekly average of the screening visit assessments was used, provided there were ≥ 4 days of assessments during that period
- All PRO measures were completed by patients at screening, baseline (ie, Cycle 1), and then in 28-day cycles thereafter, using home electronic PRO devices

RESULTS

- The analysis set comprised 70 patients assigned to nirogacestat and 71 patients assigned to placebo
- At baseline, all patients reported a moderately high DT symptom–related emotional impact
 - Mean (SD) baseline scores for patients assigned to nirogacestat and placebo were 4.6 (2.7) and 4.7 (2.9) for DTIS Emotional Domain, respectively; and 63.6 (22.3) and 66.0 (24.7) for EORTC QLQ-C30 Emotional Functioning, respectively
- Differences between nirogacestat and placebo in LS mean change from baseline for DTIS Emotional Domain scores favored nirogacestat at Cycle 10 (-1.4 ; $P=.001$) and overall up to Cycle 24 (-1.26 ; $P<.001$; **Figure 1**)

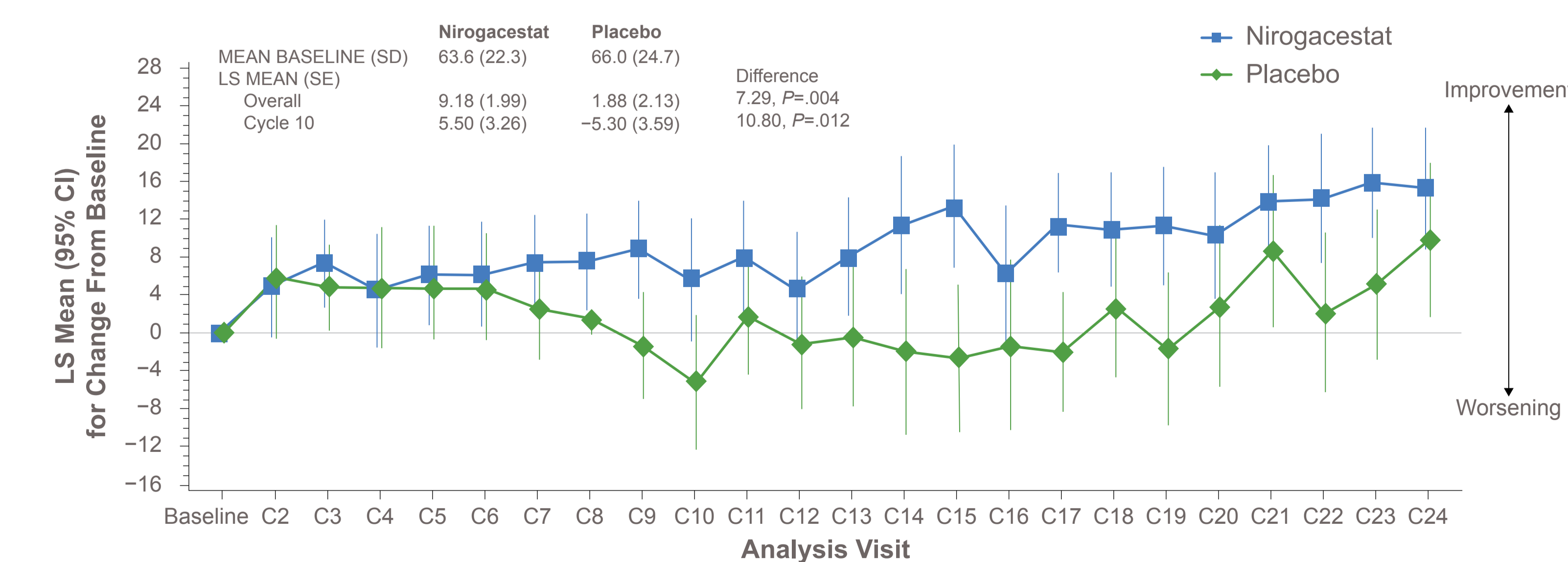
Figure 1. Change From Baseline in DTIS Emotion Domain Score by Visit



A positive change from baseline indicates worsening impact; a negative change from baseline indicates an improvement. A negative LS mean difference (between nirogacestat and placebo) favors nirogacestat over placebo. DTIS, Desmoid Tumor Impact Scale; LS, least squares.

- LS mean differences favored nirogacestat for EORTC QLQ-C30 Emotional Functioning scores at Cycle 10 (10.80; $P<.05$) and overall up to Cycle 24 (7.29; $P<.01$; **Figure 2**)

Figure 2. Change From Baseline in EORTC QLQ-C30 Emotional Functioning by Visit

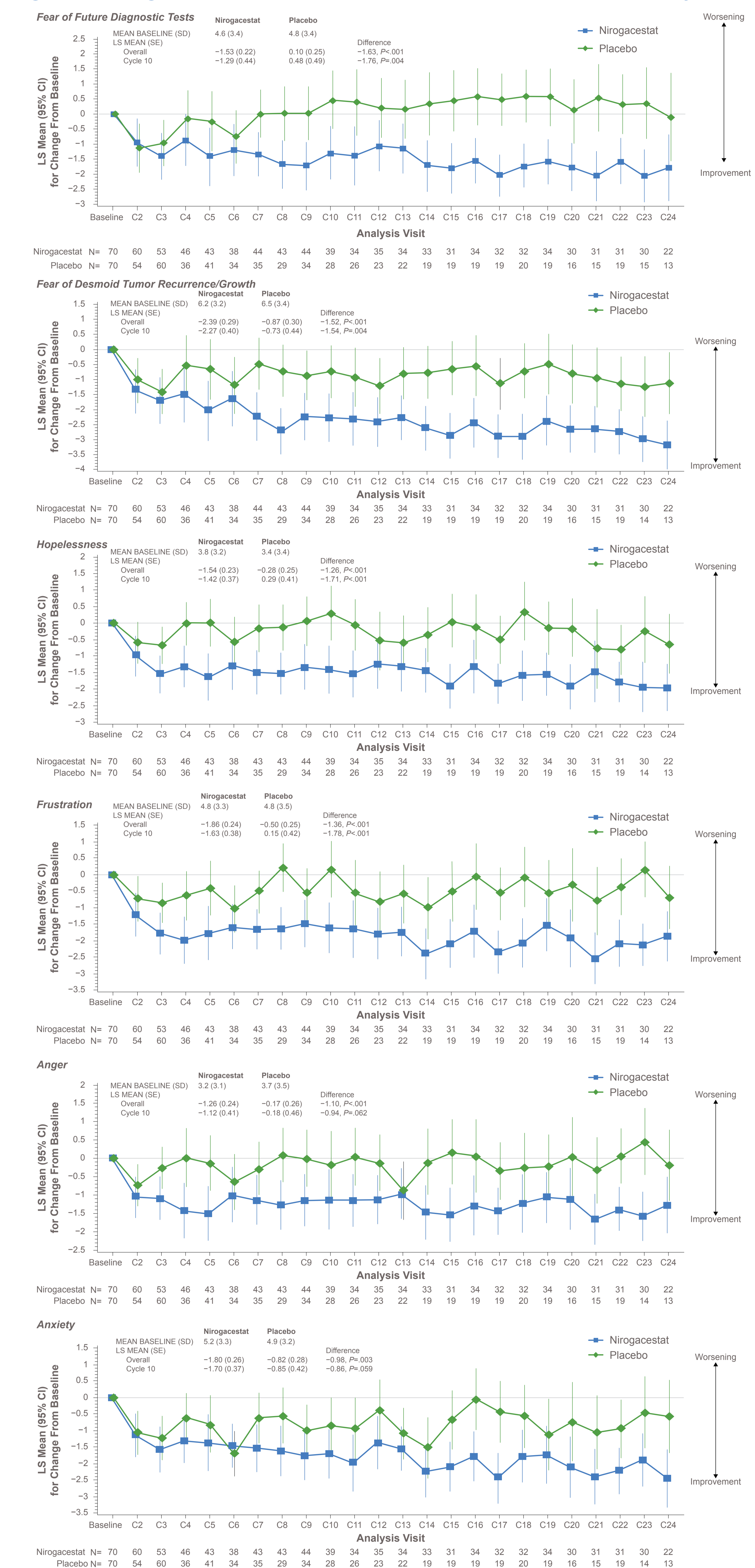


A positive change from baseline indicates worsening impact; a negative change from baseline indicates an improvement. A positive LS mean difference (between nirogacestat and placebo) favors nirogacestat over placebo. EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; LS, least squares.

RESULTS (CONT.)

- For patients with pain at baseline (API > 0) treated with nirogacestat ($n=24$), API reduction did not correlate with emotional improvement in DTIS Emotion Domain or EORTC QLQ-C30 Emotional Functioning scores at Cycle 10
- Compared to placebo, nirogacestat had a positive impact on individual emotion-related item scores in DTIS and EORTC QLQ-C30 based on LS mean change from baseline; placebo showed worsening from baseline or no impact
 - Improvement with nirogacestat versus placebo was seen in the individual DTIS Emotion Domain items "Fear of Future Diagnostic Tests," "Fear of Desmoid Tumor Recurrence/Growth," "Hopelessness," "Frustration," "Anger," and "Anxiety" (**Figure 3**)
 - Improvement with nirogacestat was also seen with the individual DTIS items "People Avoidance Due to Appearance" and "Dissatisfaction About Appearance," as well as the EORTC QLQ-C30 items "Feel Tense," "Worry," "Feel Irritable," and "Feel Depressed" (data not shown)

Figure 3. Change From Baseline in DTIS Emotion Individual Item Scores by Visit



A positive change from baseline indicates worsening impact; a negative change from baseline indicates an improvement. A negative LS mean difference (between nirogacestat and placebo) favors nirogacestat over placebo. DTIS, Desmoid Tumor Impact Scale; LS, least squares.

CONCLUSIONS

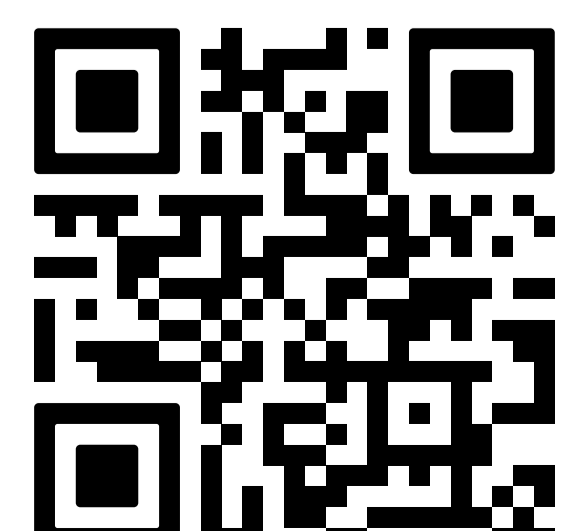
- Baseline emotion scores indicate that patients in the DeFi trial with progressing DT experienced a significant level of DT symptom–related emotional burden, suggesting the need for proactive assessment and management
- Treatment of DT with nirogacestat led to improvement in patient-reported emotional burden that emerged early and was sustained over time
- Patient-reported improvement in pain intensity did not correlate with changes in emotional health, suggesting potential multifactorial drivers of emotional burden in patients with progressing DT

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