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Impact of nirogacestat on pain, a key symptom in patients with desmoid tumors (DT): Results from the phase 3 DeFi study

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Background: Pain reduction is a key treatment goal in desmoid tumor (DT, aggressive fibromatosis): 60% of patients with DT experience chronic pain. In the global, phase 3, randomized, controlled DeFi study, nirogacestat (n=70) significantly improved progression-free survival compared with placebo (n=72) in patients with progressing DT (HR: 0.29 [95% CI, 0.15–0.55]; *P*<0.001). Also as previously reported, nirogacestat significantly reduced pain severity by 1.51 points (on a 0–10 scale) compared with placebo at cycle 10 (28-day cycles; *P*<0.001) per the prespecified secondary endpoint of "worst pain" from the Brief Pain Inventory Short Form (BPI-SF). Additional assessment tools, which included pain measurements, were reported by patients in DeFi to further characterize treatment impact on this key symptom.

Methods: In DeFi, patients completed 3 prespecified assessment tools that included pain measurements through end of treatment: BPI-SF (worst pain), GOunder/Desmoid Tumor Research Foundation DEsmoid Symptom Scale (GODDESS-DTSS pain scale: worst pain, dull pain, shooting pain), and European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (QLQ-C30 pain scale: pain, pain interference with daily activities). Change from baseline in pain scores was compared between treatment arms; analyses included mixed models for repeated measures to compare change from baseline and stratified Cochran-Mantel-Haenszel to compare proportions of patients with clinically meaningful pain reduction (defined using prespecified thresholds) at cycle 10. Cycle 10 was prespecified as the post-treatment time point for between-arm comparisons to allow adequate time for a treatment effect to be observed.

Results: Treatment with nirogacestat resulted in statistically significant early and sustained improvements in pain compared with placebo. At cycle 10, statistically significant and clinically meaningful pain reduction was observed with nirogacestat compared with placebo across all 3 pain assessment tools (all *P*<0.001; **Table 1**). Significantly greater proportions of patients achieved a clinically meaningful pain reduction from baseline at cycle 10 with nirogacestat than placebo according to the BPI-SF "worst pain" score (*P*=0.001) and the GODDESS-DTSS pain score (*P*<0.001; **Table 2**).

Conclusions: In the phase 3 DeFi study, patients with progressing desmoid tumors who received nirogacestat achieved a rapid, sustained, and consistent reduction in different aspects of pain (eg, worst pain, dull pain, shooting pain, pain interference with daily activities) compared with those who received placebo. Significantly greater proportions of patients achieved clinically meaningful reduction in pain with nirogacestat compared with placebo. The benefit of nirogacestat versus placebo in reducing pain was consistent across multiple patient-completed assessment tools, which included pain measurements. As pain is the most commonly reported symptom by patients with desmoid tumors, pain reduction should be a key clinical study endpoint and treatment goal.

Table 1. Changes in Patient-Reported Pain from Baseline at Cycle 10

	Nirogacestat	Placebo	Difference between arms	Meaningful improvement between arms	*P* value
Measure	**LS Mean (SE)**	**LS Mean (SE)**			
BPI-SF "worst pain" score	−1.553 (0.2645)	−0.045 (0.2732)	−1.508	≥1.0 decrease	<0.001
GODDESS-DTSS pain score	−1.778 (0.2746)	0.341 (0.2801)	−2.118	≥1.2 decrease	<0.001
EORTC QLQ-C30 pain subscale	−22.363 (3.3851)	6.998 (3.6512)	−29.361	≥5–10 decrease	<0.001

LS, least squares; SE, standard error.

Table 2. Proportions of Patients with Clinically Meaningful Pain Reduction from Baseline at Cycle 10

		Responder*		Odds ratio (95% CI)	*P* value
	Response threshold†	Nirogacestat (n=70)	Placebo (n=72)		
Measure					
BPI-SF "worst pain" score	2.0 points	68.2%	26.3%	6.08 (1.95–18.98)	0.001
GODDESS-DTSS pain score	1.9 points	58.7%	18.9%	6.24 (2.16–17.99)	<0.001

Note: analysis is based on a multiple imputation model and the denominator is the intention-to-treat population.

*For the BPI-SF "worst pain" responder analysis, the value of 2 points was used as the threshold to determine clinically meaningful improvement. Threshold values of 30% or greater change, or 2-point or greater change in numerical rating of BPI-SF scores, have been proposed in the literature to detect clinically important improvements in cancer-related breakthrough pain and chronic pain states.

†Within-patient clinically meaningful response threshold.

CI, confidence interval.

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