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Impact of nirogacestat on patient-reported outcomes in adults with desmoid tumor with a best overall response of stable disease: post hoc analysis from the DeFi study

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Background: Nirogacestat is a targeted gamma secretase inhibitor and the only systemic treatment for desmoid tumors (DT) that is FDA-approved for adults with progressing DT. DeFi was a global, multicenter, double-blind phase 3 study (NCT03785964) to determine the efficacy, safety, and tolerability of nirogacestat in adults with progressing DT. Nirogacestat demonstrated statistically significant and clinically meaningful improvement vs placebo in progression-free survival (PFS), objective response rate (ORR), and patient-reported outcomes (PROs). As not all patients achieve a complete or partial response during systemic therapy, it is important to understand if patients who achieve stable disease (SD) with nirogacestat treatment may still experience a benefit in PROs.

Methods: Patients were randomized to receive nirogacestat (150 mg) or placebo taken twice-daily in continuous 28-day cycles. Primary endpoint was PFS; key secondary endpoints were ORR by RECIST v1.1 and change from baseline at cycle 10 in PROs: Brief Pain Inventory - Short Form (BPI-SF), Gounder/Desmoid Tumor Research Foundation Desmoid Symptom/Impact Scale (GODDESS), and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30). Post hoc analyses of PROs were conducted in patients with a best overall response (BOR) of SD (07Apr2022 datacut).

Results: ORR was significantly greater with nirogacestat (29/70 [41%]) than placebo (6/72 [8%]; $P<0.001$). A total of 35/70 (50%) nirogacestat-group patients had a BOR of SD by RECIST vs 55/72 (76%) placebo-group patients. Nirogacestat-treated patients with a BOR of SD had significantly greater improvement from baseline at cycle 10 than placebo in all PROs evaluated ($P<0.05$, all): BPI-SF worst pain (LS mean change from baseline: -1.48 vs 0.13, respectively), GODDESS total symptom score (-1.13 vs 0.68) and physical functioning (-0.53 vs 0.16), and EORTC QLQ-C30 physical functioning (7.93 vs -5.32), role functioning (5.05 vs -13.29), and overall quality of life (QoL; 4.05 vs -9.02). Improvements in PROs were observed early and sustained throughout the study.

Conclusions: In this post hoc analysis of DeFi, patients that achieved a BOR of SD by RECIST v1.1 had significantly greater improvement with nirogacestat than placebo in pain and DT-specific symptom burden, physical and role functioning, and overall QoL. These results suggest that nirogacestat can provide clinically meaningful benefits to patients with DT, including those with SD as best response.