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Efficacy of nirogacestat in patients with poor prognostic factors for desmoid tumors: Analyses from the randomized phase 3 DeFi study

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Background: Poor prognosis of patients with desmoid tumors (DT) is potentially dependent on multiple factors, including tumor location, size, patient's age, mutational status, and presence of pain. Nirogacestat, a targeted gamma secretase inhibitor, is the only treatment that is FDA-approved for adults with progressing DT. In the phase 3 DeFi study, nirogacestat demonstrated significant and clinically meaningful improvement vs placebo in the primary and key secondary endpoints of progression-free survival (PFS: HR, 0.29 [95% CI: 0.15-0.55]; $P<0.001$), objective response rate (ORR: 41% vs 8%; $P<0.001$), and patient-reported outcomes (pain, DT-specific symptom burden, physical and role functioning, and overall quality of life; $P\leq0.01$, all). The objective of this analysis was to determine the effect of nirogacestat in patient subgroups associated with poor prognosis (larger tumor size, younger age, *CTNNB1* mutation, and presence of pain).

Methods: DeFi (NCT03785964) was a global, multicenter, double-blind study to determine the efficacy, safety, and tolerability of nirogacestat in adults with progressing DT. 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 and ORR were conducted in individuals stratified by patient- and tumor-related poor prognostic factors.

Results: PFS and ORR improvement favored nirogacestat vs placebo regardless of the patient subgroup: larger baseline tumor size (>10 cm), younger age (≤30 y), *CTNNB1* mutation (S45F, T41A), and presence of pain at baseline (Brief Pain Inventory Worst Pain Score >0). Across subgroups, PFS hazard ratio ranged from 0.18 to 0.39, with values <1 favoring nirogacestat over placebo. ORR risk difference (nirogacestat – placebo) ranged from 18.1% to 56.0%, with values >0 favoring nirogacestat.

Conclusions: Nirogacestat demonstrated consistent improvement in PFS and ORR vs placebo in patients with DT and characteristics associated with poor prognosis.