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**DeFi: A Phase 3, Randomized, Double-blind Trial of Nirogacestat Versus Placebo for  
Progressing Desmoid Tumors/Aggressive Fibromatosis (DTs/AF)**

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**Background:** DTs/AF are rare, locally aggressive soft-tissue tumors that can lead to significant morbidities. Although chemotherapy and tyrosine kinase inhibitors have been used off-label, there are no approved systemic therapies for DTs/AF; surgery can be mutilating and is associated with high rates of recurrence. Nirogacestat, a novel small-molecule, gamma secretase inhibitor, demonstrated promising tolerability and clinical activity in Phase 1 and 2 trials in patients with DTs/AF.

**Methods:** DeFi is a randomized, double-blind, placebo-controlled, Phase 3 trial of nirogacestat in adults with DTs/AF (NCT03785964). DeFi enrolled 142 adults with histologically confirmed DTs/AF that progressed by  $\geq 20\%$  per RECIST v1.1 within 12 months of screening. Patients had treatment-naïve disease not amenable to surgery or had recurrent or refractory DTs/AF following  $\geq 1$  line of therapy. Patients were stratified by primary tumor location (intra- or extra-abdominal) and randomized 1:1 to receive nirogacestat 150 mg twice daily or matching placebo taken continuously in 28-day cycles. The primary endpoint was progression-free survival (PFS). Disease progression was determined via blinded, independent central review and included radiographic progression per RECIST v1.1 or clinical progression. Radiographic imaging was performed at screening and every 3 cycles. Key secondary endpoints were safety and tolerability, objective response rate per RECIST v1.1, and health-related quality of life, as measured by the Brief Pain Index short form, GOUnder/Desmoid tumor Research Foundation Desmoid Symptom/Impact Scale, and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30, respectively. Patients who experience radiographic progression or who remain on study drug when the double-blind treatment period ends may be eligible to receive nirogacestat treatment in an open-label extension phase of the study.

**Results:** Topline results are expected in June 2022.

**Conclusions:** This is the first report of a Phase 3, randomized, controlled trial of a gamma secretase inhibitor in DTs/AF.