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"ARST1921: A Safety Pharmacokinetic and Efficacy Study of a γ-Secretase Inhibitor, Nirogacestat (PF-03084014), in Children with Adolescents with Progressive, Unresectable Desmoid Tumors."

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Abstract:
Most desmoid tumors have a mutation in the CTNNB1 gene (which encodes β-catenin) and less commonly in the APC gene (regulator of β-catenin), implicating the WNT signaling pathway in this disease. Nirogacestat (PF-03084014, SpringWorks Therapeutics, Inc.) is an oral potent, selective, reversible inhibitor of γ-secretase. γ-secretase is an enzyme that plays a role in the release of Notch intracellular domain (NICD), which then translocates into the nucleus and activates transcription of target genes that inhibit differentiation, promote survival, and accelerate proliferation. One of the post-translation roles of NICD is thought to be its interaction with components of WNT signaling, specifically β-catenin. In early phase adult clinical trials of nirogacestat, the drug was well-tolerated and durable disease stabilization and tumor responses were observed in desmoid tumors. Based on these promising results, the Children's Oncology Group is conducting a single-arm, open-label study (clinicaltrials.gov NCT04195399) of nirogacestat in children and adolescents with progressive, unresectable existing or recurrent desmoid tumor. Nirogacestat will be administered orally twice daily on a continuous dosing schedule of 28-day cycles at a dose of 90 mg/m^2 (maximum per dose 150 mg). The aims of the study are to describe the toxicities, characterize the pharmacokinetics and estimate the progression-free survival (PFS) and objective response rate (ORR) in this patient population receiving nirogacestat. We will also compare various tumor imaging response assessments, explore biomarkers for response and outcome in archival tumor tissue and blood as well as explore relationships between patient reported outcomes and PFS and ORR.