A Phase II trial of PF-03084014 in adults with Desmoid tumors/Aggressive Fibromatosis

Background: Desmoids are locally invasive, slow growing rare soft tissue tumors. Desmoids are characterized by stabilization and abnormal nuclear localization of β-catenin. 85-90% of desmoid have mutations in the *CTNNB1*. They can be associated with familial genetic syndromes, such as familial adenomatous polyposis, or be sporadic. PF-030844014 (PF) is an oral reversible γ-secretase inhibitor (GSI). Gamma-secretase cleaves intracellular Notch resulting in Notch signaling. We conducted a phase II study of PF in patients (pts) with progressive, symptomatic desmoid tumors that had progressed following at least one line of therapy. Objectives were to determine the response rate; assess symptom measures. Methods: PF was administered orally at 150mg BID; for 21 day cycles. Archival samples were sequenced for germline and somatic mutations in *APC* and *CTNNB1* genes. Dynamic contrast-enhanced MRI (DCE-MRI) was obtained at baseline and with every restaging. Results: The study is fully accrued. 13/17 pts (76.4%) remain on study; 4 pts stopped treatment by choice/co-morbid conditions. No pt had progressive disease at this time. Median follow-up time is 10 months (range 2-14months), 6 pts remain on study ≥1year. Grade 3 toxicities observed include hypophosphatemia (3 pts, 17.6%) and diarrhea (1 pt, 5.8%). Dose reduction to 100mg BID daily occurred in 2 pts. 16 pts (94%) experienced stable disease to date with 1 PR(5.8%). In 15/17 pts (88.2%), a somatic or germ line mutation was identified. Kinetic analysis from DCE-MRI is still in progress. Conclusions: PF is active at the selected dose, with a manageable side effect profile.