Desmoid tumors (DTs) are rare and understudied fibroblastic monoclonal lesions that are frequently recurrent and often locally invasive. Although commonly managed by surgery, these surgeries can be frequent and mutilating. Moreover, desmoid tumor patients often experience chronic pain, organ dysfunction, decrease in quality of life, and even death. The lack of animal model, immortalized cell lines, and other biological material available are a barrier to entry in the field. Sorafenib has emerged as a promising and novel therapeutic strategy based on compassionate use. These preliminary data led to an ongoing prospective phase III clinical trial. Concurrently, we conducted a comprehensive analysis of sorafenib efficacy in a large panel of desmoid cell strains to probe for response mechanism. Within all desmoid cells tested, we found a distinctive group of responders and non-responders. When we clustered the non-responder group, surprisingly, we observed that all cells were S45F mutants. Several studies have shown that the mutation S45F correlates with a higher risk of DT recurrence and to a lack of response to meloxicam, suggesting the more aggressive behavior of desmoid tumors so mutated. Autophagy is a well-established mechanism of cell stress response that is often activated in response to anti-cancer regimens. Thus we assessed basal autophagy in the responders and non-responders. When autophagy was inhibited genetically or pharmacologically in the S45F mutant cell strains, sensitivity to sorafenib was restored. These results suggest that profiling β-catenin status could guide clinical trial management of desmoid patients considering sorafenib treatment.