Alliance A091105: A Phase III, Double Blind, Randomized, Placebo-Controlled Trial of Sorafenib in Desmoid Tumors or Aggressive Fibromatosis (DT/DF)

Desmoid tumor (DT/DF) is a sarcoma of fibroblastic origin that afflicts children, adolescents and adults and has a median age of onset of 30 years. Desmoid tumors can occur in any anatomic location and threaten vital organs and limbs which often results in significant morbidity from organ failure, mutilating surgeries (and amputations), loss of limb function, pain and death. There is no clear-cut standard of care for the treatment of DT/DF. Surgery is associated with high rates of recurrences (~40%). In advanced disease, systemic therapies range from anti-estrogens to cytotoxic chemotherapies with variable response rates however no systemic therapies have been demonstrated to improve survival or quality of life in this orphan disease. DT/DF over express c-KIT and PDGFR and a Phase II study of imatinib showed a disappointing partial response (PR) rate of 6%. Extrapolating this, investigators treated an index patient: a 37-year-old woman who presented with a large unresectable, intra-thoracic desmoids tumor with sorafenib. Sorafenib is a multi-target kinase inhibitor of BRAF, PDGFR and VEGFR. Sorafenib has a current FDA orphan indication for renal, liver and thyroid cancers. At presentation the patient's desmoid tumor shifted her mediastinum and presented a high risk for cardiopulmonary collapse and sudden death (Figure 1). The patient was oxygen dependent and unable to ambulate more than 30 feet. Following administrationp of sorafenib, this young woman became independent of oxygen within 4 weeks, began to ambulate and within 3 months returned to work. She remains on sorafenib almost 4 years later.

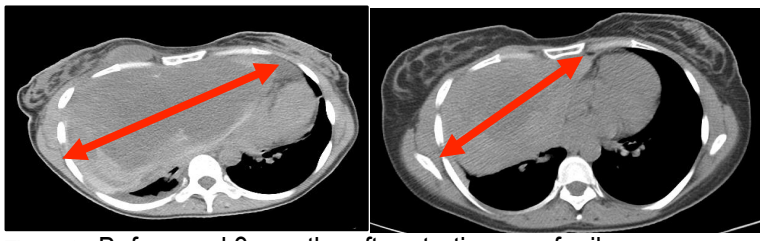

Figure 1. Before and 3 months after starting sorafenib

This partial response and dramatic clinical benefit prompted investigators to evaluate the single institution experience of sorafenib in 26 additional patients. They reported a 25% **partial response (< 30% by size, durable for >4 yrs)** and **improvement of symptoms** in 70% of patients. In addition, patients who had stable disease but reported subjective improvement in symptoms demonstrated **decrease in the MRI T2 signal intensity**.

Due to these results, the Alliance for Clinical Trials in Oncology, an NCI-sponsored network group, has activated **A091105: A Phase III, Double Blind, Randomized, Placebo-Controlled Trial of Sorafenib in Desmoid Tumors or Aggressive Fibromatosis (DT/DF).** The central hypothesis of this clinical investigation is that sorafenib will lead to improved progression free survival, objective responses and improvement in symptoms and function. This is a national phase III randomized double-blind placebo-controlled trial of sorafenib in DT patients. There is a 2 to 1 randomization (sorafenib to placebo), and patients on placebo will cross over at progression. The study will enroll 75 patients to detect a PFS difference of 9 months between the sorafenib arm (15 months) and placebo arm (6 months) which represents a hazard ratio of 0.4. The sample size will have 90% power at a 1-sided significance level of 0.025 to detect this difference. Should the study meet this primary endpoint, it will be the first phase III trial to identify an active agent in this orphan disease.

Many questions remain unanswered regarding the use of sorafenib in DT. These include: **1)** mechanism of action of sorafenib in DT, **2)** the lack of a predictive biomarker of response, **3)** the significance of decrease in MRI T2 signal and whether this represents a better imaging modality to assess drug efficacy and **4)** to

quantitate the magnitude of benefit in quality of life with sorafenib and if so, to develop a validated tool to compare effectiveness of this and future drugs. To answer biological questions, investigators will conduct genome-wide characterization (gene, methylation, microRNA and protein) of pre- and on-treatment tumor biopsies to validate targets recently identified as potential biomarkers of response. Once independently validated the goal is to develop a companion diagnostic test to select appropriate patients for this drug therapy. To improve upon current imaging modalities (i.e., RECIST) in this disease, efforts are underway to investigate MRI signal characteristics to quantitate and standardize changes in T2 signal as an accurate tool to measure efficacy of future drugs in this disease. Lastly, study investigators are developing and validating new quality of life and patient reported outcome tools in this disease to capture clinical benefit that is not adequately reflected in tumor dimensional changes. By adhering to the highest regulatory standards (randomized, blinded, placebo), this new QOL/PRO tool sets the stage for an innovative endpoint to measure drug efficacy in this rare disease. This phase III study attempts to answer important questions in a prospective and statistically robust manner.

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