DANA-FARBER
CANCER INSTITUTE

CENTER FOR SARCOMA AND BONE ONCOLOGY

GASTROINTESTINAL STROMAL TUMOR (GIST)

RESEARCH DESCRIPTION

For more than a decade, researchers at Dana-Farber have led groundbreaking, world-renowned studies that continue to make a tangible difference in the lives of people with GIST – the most common form of sarcoma, with an estimated 3,300 to 6,000 new cases expected in the United States in 2013. Our investigators have provided a solid foundation for several targeted therapies, notably including all three drugs – imatinib, sunitinib, and regorafenib – currently FDA-approved for metastatic and inoperable GIST.

Of the three drugs, regorafenib received approval most recently in February 2013. A large-scale international trial led by investigators at Dana-Farber formed the basis of FDA approval. Results from this study showed a significant increase in survival for patients whose disease had developed resistance to first-line therapies. Thus, regorafenib bridges an important gap created by resistance to treatment with imatinib and sunitinib. However, as with most drugs, patient response can vary; George Demetri, MD, director of the Center for Sarcoma and Bone Oncology, and Suzanne George, MD, the center's clinical director, and their colleagues now seek to explain – and ultimately reduce – this variability.

As the first investigators to have studied regorafenib for the treatment of GIST, Drs. Demetri and George treat some of the patients who have been on the drug for the longest duration. Thus, they have a unique opportunity to evaluate the genetic profiles of these patients' tumors. Matching this information to clinical outcomes offers a deeper understanding of the biology underlying the length and degree of treatment response.

Importantly, the study team is also leading critical studies focused on the mechanisms of resistance to regorafenib. The clinical data amassed by Drs. Demetri and George serves as the basis for laboratory research that will help to optimize how regorafenib is used in GIST. For example, leading pathologist Jonathan Fletcher, MD, and his team collaborate with Dr. Demetri to use clinical data as the foundation of basic science research. These investigations aim to make treatment as effective as possible by revealing the intricacies of the interaction between resistance-conferring mutations and existing drugs. Additionally, researchers are exploring the benefits of introducing new therapeutic agents to treatment protocols. The results could potentially point to novel ways of using drug combinations to combat a broader range of resistance mechanisms.

With guidance and support from Drs. Demetri and Fletcher, César Serrano, MD, is part of this ambitious effort to create a roadmap that defines new therapeutic strategies to overcome resistance. Dr. Serrano is profiling the resistant mutations in patients who have received imatinib, which is the most common first-line treatment for GIST. This therapy inhibits signaling initiated by the protein KIT, which influences cell survival, proliferation, and differentiation. When KIT is over-expressed, however, it produces cancer-driving signals that fuel the majority of GIST.

Previous research has demonstrated that drivers of resistance in GIST are secondary mutations in KIT, meaning that cancer cells evolved to harbor these mutations as a response to treatment. There are two different mutations that occur, and Dr. Serrano's data indicates that each confers different sensitivity to sunitinib and regorafenib. Results from the study of sunitinib showed that while the first mutation sensitizes the cancer cells to the drug, the second results in strong resistance to it. Preliminary results from Dr. Serrano's investigation of regorafenib show that the second mutation appears to have the opposite response, and is effective against GIST that are sunitinib-resistant.

These findings make the two drugs complementary, but their similarity precludes using them in a traditional combination therapy due to anticipated toxicity. Therefore, the study team has devised an innovative treatment regimen cycling sunitinib and regorafenib for patients with GIST who have developed resistance to other therapies. Dr. Serrano is currently working on modeling this novel approach using cells cultivated from tumor biopsies to create robust preclinical evidence, which is needed to merit translating the findings into clinical trials. In recognition of this high quality research, the Connective Tissue Oncology Society invited Dr. Serrano to present his findings at the society's annual meeting in October 2013, and named him as one of only two recipients of the society's prestigious Young Investigator Award.