Clinical trial design supports original accelerated approval of sunitinib for GIST

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Patients benefitted from an important design element in the pivotal phase III clinical trial that led to Food and Drug Administration and worldwide regulatory approval of sunitinib for the treatment of gastrointestinal stromal tumors resistant to the only other available therapy, according to a study in *Clinical Cancer Research,* a journal of the American Association for Cancer Research.

"The importance of these results cannot be understated," said George D. Demetri, M.D., senior vice president for experimental therapeutics at the Dana-Farber Cancer Institute and director of the Ludwig Center at the Dana-Farber/Harvard Cancer Center in Boston, Mass. "The study worked as we had hoped, and it showed that it is possible to do a definitive placebo-controlled trial while protecting the safety of patients."

The double-blind, placebo-controlled, randomized phase III trial was designed as a crossover trial, meaning that patients initially randomized to receive placebo were offered the opportunity to cross over to sunitinib treatment upon disease progression or following unblinding of the trial, whichever came first. The trial was unblinded after an interim analysis that demonstrated the clinical benefit of sunitinib, as assessed by time to tumor progression.

"The crossover design of the trial meant that our final analysis using conventional statistical methods indicated no 'statistically significant' effect of sunitinib on overall survival, because the long-term survival

interpretation was shifted by the activity of the drug in patients who received sunitinib after crossover. However, we expected this and also assessed overall survival using a statistical method to model what might have happened in the absence of crossover," said Demetri. "We found that sunitinib conferred a clear statistical benefit on overall survival. This really is key; it shows that we can design clinical trials that indicate a drug works and offer that active therapy to patients from the placebo arm of the trial — this protects the interests of patients and yet allows the study to provide rigorous proof of the safety and efficacy of the study drug, in this case sunitinib."

Of the 243 patients enrolled in the study, 118 received placebo. Of these, 103 crossed over to receive sunitinib. Conventional statistical methods analyzing the long-term survival data suggested that sunitinib had no statistical effect on overall survival — median survival was 72.7 weeks for those patients in the sunitinib arm and 64.9 weeks for those initially in the placebo arm (the vast majority of whom crossed over to receive sunitinib). Analysis using a method that modeled the absence of crossover (rank-preserving structural failure time) estimated that treatment with sunitinib conferred substantial overall survival benefit — the modeled median survival for placebo would have been 39 weeks.

The majority of gastrointestinal stromal tumors (GIST) are caused by mutations in the KIT proto-oncogene. These mutations result in the KIT protein constantly transmitting activating signals that drive the growth of the tumor. First-line treatment for GIST is the targeted therapy imatinib (Gleevec), a small-molecule inhibitor of KIT.

Sunitinib (Sutent) is another small-molecule inhibitor of KIT. The FDA approved it in 2006 for the treatment of patients with imatinib-resistant or -intolerant GIST, after interim analysis of the phase III trial demonstrated statistically significant increases in time to tumor progression. In that analysis, median time to tumor progression was 27

weeks for patients in the sunitinib arm of the trial and six weeks for those in the placebo arm.

"Approval of sunitinib for this indication was extremely rapid," Demetri noted. "The first GIST patient received sunitinib in 2002, and the interim results led to its approval in 2006. Our final analyses show that this rapid development was appropriate; it did not cut any corners. Faster, more reliable clinical trials are needed to enhance the drug development process, and I think that we have shown that these goals really are possible to achieve by designing studies around the best science and choosing diseases that are deeply understood at a molecular level, such as GIST."

Provided by American Association for Cancer Research