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Further analysis of BIG 1-98 shows overall survival benefit of letrozole compared with tamoxifen

San Antonio, Texas, December 10, 2009 — At the CTRC-AACR San Antonio Breast Cancer Symposium, results from the BIG 1-98 trial comparing five years of letrozole (Femara) with five years of tamoxifen were analyzed using an established methodology called inverse probability of censoring weighted (IPCW) analysis. The IPCW analysis was conducted by the International Breast Cancer Study Group (IBCSG) to clarify the clinical benefit of letrozole compared with tamoxifen in the BIG 1-98 trial reported at SABCS in 2008. At that time, the intent-to-treat (ITT) and censored analyses were presented but identified as potentially biased due to the “selective crossover” of about 25% of patients in the tamoxifen treatment group who accepted the opportunity to take the more effective treatment, letrozole, after disease-free survival results were first presented in 2005.

The term “selective crossover” identifies a special case of non-adherence to a randomized treatment following the report of positive trial results. Specifically, control group patients are offered and accept the opportunity to cross over to change to the experimental treatment. This terminology is distinct from a protocol-defined treatment switch, or ad hoc non-adherence to randomized assignment, and emphasizes the potential for selection bias in the decision of whether or not to cross over. Selective crossover disturbs the randomized comparison in updated analyses performed subsequent to first results. As first results are often based on positive findings of disease-free survival, selective crossover particularly impacts the overall survival outcome. Selective crossover is common to many trials in which an early result ethically mandates change to better therapy, as in BIG 1-98 as well as the adjuvant trastuzumab trials.

With selective crossover and further follow up, the treatment received by patients on the control arm (in this trial tamoxifen) becomes a mix of the control and experimental treatments. And with the potential for selection bias, the benefits of randomization erode and the trial becomes a hybrid of a randomized trial and observational study. For a randomized clinical trial, the intent to treat analysis is the “gold standard” analytic approach designed to control bias. As the selective crossover transforms the randomized trial toward an observational study, we need to shift our analysis approach to use established modeling methods to address issues of bias due to treatment selection, in this case using IPCW.

The IPCW analysis estimates the clinical benefit of letrozole that might have been observed had there been no selective crossover in the trial. Results showed that five years of letrozole after surgery significantly improved both disease-free survival by 15% (HR 0.85; 95% CI 0.76, 0.96; $P < 0.05$) and overall survival by 17% (HR 0.83; 95% CI 0.71, 0.97; $P < 0.05$).

“Selective crossover creates a statistical challenge when analyzing clinical trial results. Statistical methods such as IPCW can provide physicians with a more accurate estimate of the clinical benefit of a particular therapy,” said Meredith Regan, Sc.D., Assistant Professor, Department of Medicine, Harvard Medical School and co-author of the BIG 1-98 study IPCW analysis. “By adjusting for the crossover bias in the BIG 1-98 study, we have clarified the magnitude of benefit of letrozole compared with tamoxifen on both overall survival and disease-



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free survival, offering physicians critical information when making treatment decisions for patients.”

The BIG 1-98 Clinical Trial

In 2005, IBCSG presented data from the BIG 1-98 trial demonstrating the superiority of letrozole over tamoxifen in improving disease-free survival and reducing the risk of recurrence in postmenopausal women with hormone-receptor positive early breast cancer. At that time, the tamoxifen-only treatment arm was unblinded, which opened the opportunity for trial patients to selectively cross over to the superior treatment. This resulted in approximately 25% of patients in the tamoxifen arm switching to letrozole.

Selective crossover may occur when early results indicate a significant benefit with one of the study treatments. While selective crossover is often in the best interest of patients, it complicates later trial analyses with further patient follow up because the randomized, blinded trial design is compromised, making accurate assessments of outcomes that require longer-term follow up, such as overall survival, difficult.

In 2008, two analyses were presented. The ITT analysis, which made no adjustment for the crossover of 25% of patients in the tamoxifen arm, suggested an overall survival benefit for letrozole versus tamoxifen, (13% reduced risk of death, $P=0.08$). The censored analysis, which included patient data only up to time of crossover, showed an overall survival benefit for patients receiving letrozole versus tamoxifen (19%; HR 0.81; 95% CI: 0.68, 0.96). At that time, IBCSG concluded potential biases existed with both the ITT and censored analyses, thus leading to the need for additional analysis with a statistical method such as the IPCW.

“Allowing patients to cross between arms of a clinical trial when one treatment demonstrates statistical superiority over another is ethical and appropriate, and can lead to better outcomes for those patients,” said Prof. Alan S. Coates, Scientific Committee Co-Chairman of the International Breast Cancer Study Group. “However, the standard intent to treat analysis is weakened by selective crossover. We need to utilize trusted statistical methods, like the IPCW, in order to achieve the best estimate of the relative benefit of experimental treatments to best inform clinical decision making.”

BIG 1-98 Background

BIG 1-98 was designed to explore both a head-to-head comparison of an aromatase inhibitor versus tamoxifen monotherapy, as well as sequencing of an aromatase inhibitor and tamoxifen therapy in the first five years following breast cancer surgery, in order to determine the most effective manner in which to reduce hormone-receptor positive early breast cancer recurrence. This Phase III, randomized, double-blind, controlled clinical trial enrolled postmenopausal women with early breast cancer, in 27 countries.

Patients were randomly assigned one of four treatment regimens: (1) five years of tamoxifen only; (2) five years of letrozole only; (3) two years of tamoxifen followed by three years of letrozole; (4) two years of letrozole followed by three years of tamoxifen. In 1998 the first cohort began enrolling patients to receive either letrozole or tamoxifen alone. Combined, the monotherapy arms of the trial included 4,922 patients randomly assigned either letrozole or tamoxifen treatment.



The primary endpoint of the study was disease-free survival, defined as the time from randomization to the first of one of the following events: recurrence at local, regional, or distant sites; a new invasive cancer in the contralateral breast; any second, non-breast primary cancer; or death without a prior cancer event. Other endpoints included time to breast cancer recurrence, time to distant breast cancer recurrence and overall survival.

Contact persons:

Dr. Meredith M. Regan, IBCSG Group Statistician, IBCSG Statistical Center, Dana-Farber Cancer Institute, Boston, MA. Phone: 617-632-2471 email: mregan@jimmy.harvard.edu.

Prof. Richard D. Gelber, IBCSG Director of Statistical and Data Management Centers, IBCSG Statistical Center, Dana-Farber Cancer Institute, Boston, MA. Phone: 617-632-3603 email: gelber@jimmy.harvard.edu.

Prof. Alan S. Coates, IBCSG Scientific Committee Co-Chair, Sydney, Australia. Phone: +61 406 933931 email: alan.coates@ibcsg.org.

Anita Hiltbrunner, IBCSG Director, Effingerstrasse 40, 3008 Bern, Switzerland. Phone: +41 31 389 91 79, email: anita.hiltbrunner@ibcsg.org.