



Abstract #76 – EMBARGOED UNTIL DECEMBER 12, 2009, 5:30 PM CST

Centrally-reviewed tumor markers and St Gallen risk factors improve treatment selection for postmenopausal women with hormone receptor-positive breast cancer: results from BIG 1-98

San Antonio, Texas, December 12, 2009 — At the CTRC-AACR San Antonio Breast Cancer Symposium, results of the BIG 1-98 trial were presented according to the centrally-reviewed tumor markers ER, PgR, HER2, and Ki-67 labelling index alone and in combination with the St. Gallen risk factors to investigate their value for treatment selection. Patients enrolled in BIG 1-98 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. This analysis was limited to the subset of 5,177 (84%) patients with centrally-reviewed markers of the 6,182 randomized among all four treatment groups.

At the CTRC-AACR San Antonio Breast Cancer Symposium in 2008, the overall results comparing the three letrozole-containing regimens showed that, on average, the differences among the three regimens were modest, making the choice among treatment regimens difficult. In this analysis of the same database, the International Breast Cancer Study Group (IBCSG) first examined individual tumor markers to identify which patients may respond better to a particular treatment regimen, using Subpopulation Treatment Effect Pattern Plots (STEPP). Each of the four tumor markers showed a trend favoring letrozole monotherapy at the “higher risk” end of its spectrum, but none of the individual markers were statistically significant predictive factors to guide treatment selection. By combining several risk factors for each patient, the IBCSG developed a composite *prognostic* profile to see if such a profile might also serve to *predict* treatment differences.

The composite risk profile was calculated using a multivariable Cox model for disease-free survival. The composite risk used the St. Gallen risk factors which include ER, PgR, HER2, Ki-67, number of involved metastatic lymph nodes, tumor grade, tumor size, and presence of peritumoral vascular invasion (PVI). The key contributors to high risk were: higher number of positive lymph nodes, lower ER%, higher Ki-67, higher grade, larger tumor size, HER2+, presence of PVI, and lower PgR%. A composite risk profile score was calculated and assessed for usefulness in selecting among the BIG 1-98 treatments.

A STEPP plot of DFS according to composite risk shows, as expected, that all treatment regimens have lower DFS among patients at higher risk. The magnitude of the treatment differences with respect to 5-year DFS percent are observed as the risk increases from lowest to highest value. While 5-year DFS is similar for all four treatment regimens at the lowest level of risk, inferior results for tamoxifen alone are seen earlier in the risk spectrum, and separation among letrozole-containing treatments is apparent particularly at the highest risk levels. The composite risk seems to give predictive information in three distinct zones—low, intermediate, and high risk—each comprising about one-third of the patients in BIG 1-98.

The primary conclusions are:

- The particular composite risk profile used in this study was developed within the BIG 1-98 population and may not apply precisely to others



IBCSG

MEDIA RELEASE
International Breast Cancer Study Group



- However, assessing risk by combining multiple factors appears better than any single factor
- In the BIG 1-98 trial, a composite *prognostic* profile incorporating clinico-pathological data and biological markers was better able to *predict* the relative treatment benefit:
 - Patients at highest risk did best when treated with 5 years letrozole
 - Any of the three letrozole-containing regimens appeared acceptable for those at intermediate risk
 - Lowest risk patients did similarly well with letrozole monotherapy, sequential treatments, or tamoxifen alone

The BIG 1-98 Clinical Trial

The BIG 1-98 trial was first presented in 2005, 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. In 2008 the results of the sequencing treatments, compared with letrozole alone, were presented.

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.

The primary endpoint of the study is 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:

Prof. Giuseppe Viale, Director, Division of Pathology, European Institute of Oncology, Milan, Italy. Phone: +39-0257489419, email: giuseppe.viale@ieo.it

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.