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**Abstract #16**

**Further analysis of BIG 1-98 data supports survival advantage for Novartis drug Femara<sup>®</sup> over tamoxifen in breast cancer patients**

- *Analysis performed by IBCSG reported significant 17% reduction in risk of death for Femara versus tamoxifen in postmenopausal breast cancer patients after surgery*
- *Latest statistical analysis of the BIG 1-98 trial adjusts for potential bias resulting from the selective crossover of patients from tamoxifen to Femara*
- *Selective crossover is common in cancer clinical trials in which early positive results ethically mandate that medically appropriate patients be offered the better therapy*

**Basel, December 10, 2009** — A supportive analysis of the monotherapy arms in the Breast International Group (BIG) 1-98 study reported a significant survival benefit for Femara<sup>®</sup> (letrozole) versus tamoxifen following surgery for postmenopausal women with hormone receptor-positive early breast cancer. These results from an Inverse Probability of Censoring Weighted (IPCW) analysis were presented today at the 32<sup>nd</sup> Annual CTCR-AACR San Antonio Breast Cancer Symposium (SABCS).

The IPCW analysis was conducted by the International Breast Cancer Study Group (IBCSG) to clarify the clinical benefit of Femara relative to tamoxifen in the BIG 1-98 study reported at SABCS in 2008. These 2008 results from the intent-to-treat (ITT) and censored analyses were potentially impacted by the selective crossover that occurred when some patients receiving tamoxifen crossed over to Femara, the more effective treatment, after disease-free survival results were first presented in 2005.

The IPCW analysis presented today provides an estimate of clinical benefit of Femara that might have been observed had there been no selective crossover in the trial. Results showed that five years of Femara after surgery significantly improved 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, ScD, 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-free survival, offering physicians critical information when making treatment decisions for patients.”

### **The story of the BIG 1-98 study**

In 2005, IBCSG presented data from the BIG 1-98 trial demonstrating the superiority of Femara over tamoxifen in improving disease-free survival and reducing the risk of recurrence in postmenopausal women with hormone receptor-positive early breast cancer.<sup>1</sup> 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 Femara.

Selective crossover is common in trials when early results indicate a significant benefit with one of the study treatments. While selective crossover may be in the best interest of patients, it often complicates later trial analyses with additional patient follow-up because the randomized blinded trial design is compromised, making accurate assessments of 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 Femara versus tamoxifen although not statistically significant (13% reduced risk of death,  $P=0.08$ ).<sup>2,3</sup> The censored analysis, which included patient data only up to time of crossover, showed an overall survival benefit for patients receiving Femara versus tamoxifen (19%; HR 0.81; 95% CI 0.69, 0.94).<sup>2,3</sup> At that time, IBCSG concluded that the ITT analysis was likely biased in favor of tamoxifen and the censored analysis was potentially biased in favor of Femara.<sup>3</sup> This led to the need for additional analysis with a statistical method like the IPCW. The IPCW analysis showed that five years of Femara 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;  $P<0.05$ ). These results were statistically significant.

“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 study background**

BIG 1-98 is the only clinical trial designed to explore both the head-to-head comparison of an aromatase inhibitor versus tamoxifen monotherapy, as well as the 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 Femara only; (3) two years of tamoxifen followed by three years of Femara; (4) two years of Femara followed by three years of tamoxifen. In 1998 the first cohort began enrolling patients to receive either Femara or tamoxifen alone. Combined, the monotherapy arms of the trial included 4,922 patients randomly assigned either Femara 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.

In the initial adjuvant setting, Femara is the only aromatase inhibitor to have demonstrated a significant reduction in distant metastases versus tamoxifen (median follow-up 26 months). These results were subsequently confirmed by analyses conducted at a median 51 months and 76 months. In the IPCW analysis presented at SABCS, Femara demonstrated improvement in reducing the risk of distant metastases by 19% compared with tamoxifen (HR 0.81; 95% CI 0.69, 0.96, P<0.05). The early reduction of distant metastases is of particular importance since they are the most common type of early recurrence and are associated with the worst prognosis. Nearly four out of five patients are at risk of dying within five years when distant metastases are the first recurrence.

Adverse events for Femara and tamoxifen were found to be consistent with the known safety profiles of both drugs. Patients will continue to be monitored to track disease status, safety and overall survival. The long-term BIG 1-98 findings add to the large body of clinical evidence regarding the established safety profile of Femara.

### **About Femara**

Femara is a leading once-daily oral aromatase inhibitor available in more than 100 countries, including the US, major European countries and Japan. It is approved for a number of indications:

- Adjuvant treatment of postmenopausal women with hormone receptor-positive early breast cancer
- Extended adjuvant treatment of hormone-dependent early breast cancer in postmenopausal women who have had prior standard adjuvant tamoxifen therapy for five years\*\*
- First-line treatment in postmenopausal women with hormone-dependent advanced breast cancer
- Advanced breast cancer in women with natural or artificially induced postmenopausal status after relapse or disease progression who have been treated with antiestrogens
- Pre-operative therapy in postmenopausal women with localized hormone receptor-positive breast cancer which allows subsequent breast-conserving surgery in patients not originally considered suitable for this type of surgery

\* Femara is also approved as neo-adjuvant (pre-operative) therapy in Japan, and in some countries for patients with metastatic disease.

\*\* Not all indications are approved in every country.

### **Important Safety Information**

Femara should not be taken by women who have previously had any unusual or allergic reactions to letrozole or any of its ingredients. Femara should not be taken by women who are pregnant or breastfeeding. Only women who are of postmenopausal endocrine status should take Femara. Patients with severe liver impairment should be monitored closely. The use of Femara in patients with significantly impaired kidney function warrants careful consideration.

The most frequent adverse reactions of Femara are hot flushes, nausea, fatigue and arthralgia. Other common side effects are anorexia, appetite increase, peripheral oedema, headache, dizziness, malaise, vomiting, dyspepsia, constipation, diarrhea, alopecia, increased sweating, rash, myalgia, bone pain, osteoporosis, bone fractures, weight increase, hypercholesterolemia and depression. Other rare, but potentially serious adverse events include leukopenia, cataract, cerebrovascular accident or infarction, thrombophlebitis, pulmonary embolism, arterial thrombosis, general oedema, ischemic cardiovascular disease, angioedema, anaphylactic reaction, hepatitis, toxic epidermal necrolysis and erythema multiforme.

**This press release is not intended for United Kingdom media.**

## **Disclaimer**

The foregoing release contains forward-looking statements that can be identified by terminology such as “risk,” “potential,” “potentially,” “can,” “may,” “likely,” “will,” “long-term,” or similar expressions, or by express or implied discussions regarding potential new indications or labeling for Femara or regarding potential future revenues from Femara. You should not place undue reliance on these statements. Such forward-looking statements reflect the current views of management regarding future events, and involve known and unknown risks, uncertainties and other factors that may cause actual results with Femara to be materially different from any future results, performance or achievements expressed or implied by such statements. There can be no guarantee that Femara will be submitted or approved for any additional indications or labeling in any market. Nor can there be any guarantee that Femara will achieve any particular levels of revenue in the future. In particular, management’s expectations regarding Femara could be affected by, among other things, the company’s ability to obtain or maintain patent or other proprietary intellectual property protection; competition in general; unexpected regulatory actions or delays or government regulation generally; unexpected clinical trial results, including unexpected new clinical data and unexpected additional analysis of existing clinical data; government, industry and general public pricing pressures; the impact that the foregoing factors could have on the values attributed to the Novartis Group’s assets and liabilities as recorded in the Group’s consolidated balance sheet, and other risks and factors referred to in Novartis AG’s current Form 20-F on file with the US Securities and Exchange Commission. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those anticipated, believed, estimated or expected. Novartis is providing the information in this press release as of this date and does not undertake any obligation to update any forward-looking statements contained in this press release as a result of new information, future events or otherwise.

## **About Novartis**

Novartis provides healthcare solutions that address the evolving needs of patients and societies. Focused solely on healthcare, Novartis offers a diversified portfolio to best meet these needs: innovative medicines, cost-saving generic pharmaceuticals, preventive vaccines, diagnostic tools and consumer health products. Novartis is the only company with leading positions in these areas. In 2008, the Group’s continuing operations achieved net sales of USD 41.5 billion and net income of USD 8.2 billion. Approximately USD 7.2 billion was invested in R&D activities throughout the Group. Headquartered in Basel, Switzerland, Novartis Group companies employ approximately 99,000 full-time-equivalent associates and operate in more than 140 countries around the world. For more information, please visit <http://www.novartis.com>.

## **References**

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