Adjuvant Breast Cancer Treatment—Evolution or Revolution?

Adjuvant Breast Cancer Treatment: Evolution or Revolution?

Nancy Lin, MD, and Eric Winer, MD, Dana-Farber Cancer Institute, Boston

For years, clinicians have appreciated that breast cancer is not one disease, but a family of diseases, each with a distinct natural history and response to treatment. Yet, over the past two decades, adjuvant trials have largely enrolled patients on the basis of tumour size and lymph node status, rather than by biologic features. There were relatively few concessions to the biologic heterogeneity of breast cancer in the design of clinical trials. Admittedly, patients with hormone responsive tumours were generally given tamoxifen in addition to chemotherapy, but only a few large trials focused exclusively on questions in receptor-positive or receptor-negative cohorts.¹²

This issue of the Breast International Group (BIG) Newsletter focuses upon recent progress in adjuvant breast cancer treatment. Martine Piccart and Kathleen Pritchard review the evidence for the use of aromatase inhibitors (AI) in postmenopausal women with receptor-positive breast cancer. Maureen Trudeau discusses the role of taxanes. Brian Leyland-Jones and Soheyl Baban outline advances in genomics and proteomics. What is clear from these articles is that the care of patients with breast cancer has evolved substantially. However, if we want to achieve more dramatic advances, new and more innovative approaches to clinical trial design will be required.

(CONTINUED ON PAGE 3)
we have used this issue to focus on some of the important messages coming from the most recent San Antonio Breast Cancer Symposium and the St. Gallen International Consensus Conference, both among today’s most exciting breast cancer conferences. We are particularly pleased that Drs. Nancy Lin and Eric Winer, colleagues from the Dana-Farber Cancer Institute in Boston, have written the editorial for this issue. This underscores the importance of the transatlantic collaborations that have developed over the years. One of the inspirations for the creation of BIG back in 1996 was, in fact, the Breast Cancer Intergroup of North America (TBCI), a network of National Cancer Institute (NCI)-sponsored Clinical Trials Cooperative Groups. We are pleased that our transnational collaborations continue to grow and are confident that this is the way to move forward to effectively address the types of challenges (stemming from many of our successes!) outlined in the editorial and other articles in this issue.

Martine Piccart
Carolyn Straehle

Watch for upcoming issues on patient advocacy, the EU Clinical Trials Directive, and clinical trials for populations such as the elderly and the young.

Are there other topics you would like to see discussed in future BIG Newsletters?

Don’t hesitate to contact us (big@bordet.be) with your ideas and feedback!
The early results of BIG 1-98 are remarkably consistent with the ATAC (Arimidex, Tamoxifen, Alone or in Combination) study. Als represent an evolution from tamoxifen, a new class of drugs that also target the hormone receptor (HR) pathway. However, ongoing trials have also sparked a change in our thinking about receptor-positive breast cancer. Although extending tamoxifen beyond 5 years does not improve outcomes, the results of MA-17 have reopened the question of extended endocrine therapy; and renewed our awareness of the persistently high risk of recurrence over time faced by women with receptor-positive disease. Furthermore, exploratory analyses of some of the AI trials, most notably the ATAC trial, suggest that the benefits of specific hormonal therapies may vary according to the biologic features of the tumour.

Outcomes according to human epidermal growth factor receptor-2 (HER-2) status have not been reported from the large adjuvant AI trials; however, limited data from neoadjuvant studies suggest that HER-2 may modulate the benefit of tamoxifen.

Characteristics of the host may also be important in making these decisions, particularly with regard to the risk of toxicity. Both clinical data and the results of gene profiling studies suggest that HR-positive breast cancer is remarkably heterogeneous. Quantitative estrogen levels explain some of the variability, but the existence of co-activators and corepressors result in a far more complex landscape.

It is becoming increasingly apparent that a “one size fits all” strategy does not work for adjuvant chemotherapy. As pointed out by Dr. Trudeau, NSABP B-27 and PACS-01, as well as other more mature studies, have demonstrated a benefit from the addition of a taxane to standard chemotherapy. A key challenge at this time is to identify those women who will benefit to maximize disease outcomes while minimizing unnecessary treatment.

Several groups have recently presented analyses of chemotherapy benefit according to biomarkers—and although the studies were exploratory, the results are compelling. Berry and colleagues reported a striking difference in chemotherapy benefit according to estrogen receptor (ER) status in three sequential CALGB adjuvant chemotherapy trials. Compared to the low dose arm of CALGB 8541, women with ER-negative tumours treated on the experimental arm of CALGB 9741 achieved a 63% relative reduction in the risk of recurrence, and a 59% relative reduction in the risk of death. The benefit in women with ER-positive tumours was far less pronounced. Albain and colleagues found that low or intermediate ER score was predictive of benefit for CAF (cyclophosphamide, doxorubicin, and fluorouracil) chemotherapy in post-menopausal receptor-positive patients who also received tamoxifen. Paik and colleagues analyzed the utility of the 21-gene recurrence score assay to predict the benefit of chemotherapy in NSABP B-20. Although the analysis was based on a small number of events, chemotherapy led to a 22% absolute reduction in the risk of recurrence in patients with high scores; there was no benefit in patients with low scores. Finally, the influence of both tumour grade and ER status is also reflected in the likelihood of a pathological complete response (pCR) to preoperative chemotherapy. In six consecutive neoadjuvant studies conducted at M.D. Anderson Cancer Center, the pCR rate was consistently higher in women with ER-negative tumours.

Taken together, these data strongly indicate that chemotherapy is, on average, less effective against ER-positive breast cancers than ER-negative cancers, but there is likely a subgroup of patients with ER-positive tumours who derive substantial benefit from chemotherapy. It is uncertain if the benefits from chemotherapy in this subgroup of ER-positive tumours are similar to, less, or greater than those seen in patients with ER-negative tumours. It is also uncertain how these benefits vary across different chemotherapy regimens.

As we move forward, many challenges lie ahead. As reviewed by Drs. Leyland-Jones and Baban, both clinicians and scientists recognize the extraordinary heterogeneity across breast cancer, but devising clinically relevant classification systems remains complex. Should we define subgroups on the basis of single gene markers, genomic profile, or proteomic profile? Once defined, classification techniques must be tested and validated. For example, Piccart and colleagues recently presented results of an external validation of the Amsterdam 70-gene prognostic signature developed by Van’t Veer and colleagues. Such efforts are crucial, and it will be important to mandate collection of tissue blocks as part of ongoing studies. Neoadjuvant studies may provide a more rapid platform for both gene discovery and validation than adjuvant studies; to this end, NSABP B-40 will incorporate research biopsies before and during neoadjuvant therapy.

Despite the uncertainty regarding the “best” classification technique, we are in a position to start asking biologically based questions in clinical trials. The MINDACT study is powered to examine the utility of the Amsterdam signature in assigning patients to chemotherapy, compared to clinical-pathological criteria. It is hypothesized that fewer women in the “gene signature” arm will receive chemotherapy, but that outcomes in the two arms will be equivalent. The planned Breast Cancer Intergroup (TBCI) trial (PACCT) proposes to test the value of chemotherapy in addition to endocrine therapy in a group of women with an intermediate recurrence score on the 21-gene assay (Oncotype Dx). In both TBCI and the Breast International Group, distinct clinical trials have been developed for patients withHER-2 positive disease, recognizing the unique
clinical and biological features of this important subtype and the availability of a targeted therapy. We would argue that it is also time to consider focused trials in the following: a) women with triple negative or basal-like cancers; and b) women with high grade, ER-positive, HER-2-negative tumours. It is possible that principles that have been established in unselected patients (eg, the benefits of anthracycline-based regimens) will need to be reevaluated as we reclassify breast cancer. We may need to discard some of our dearly held assumptions. Intriguing findings from retrospective analyses, both positive and negative findings, need to be tested in prospective trials.

The revolution in breast cancer treatment is both about developing new drugs and in the way we design future studies, with the ultimate goal of rapidly improving outcomes by being wiser and more selective in the way we match specific drugs with specific patients. The limitations of the traditional approach are multiple: (1) we may prematurely discard new agents if they are effective only within a small subgroup of patients; (2) we may waste precious financial and patient resources by conducting excessively large trials with new treatments that have their greatest hope of working in a subset; (3) we may falsely conclude that a regimen should be given to all women, when in fact, only a small subgroup benefits; and (4) we may falsely conclude that progress is being made in all patients, when only small subgroups may be benefiting.

The good news is that with the molecular tools that are now available, we are in a better position than ever to home in on specific, prospectively defined subgroups of breast cancer, and to design “tailored” adjuvant trials. The revolution will only occur if we make a concerted effort to incorporate breast cancer biology in the design of future trials, launch bold trials that may challenge old assumptions, and continue to nurture close collaborations across disciplines and between institutions.

REFERENCES

Breast Cancer Adjuvant Endocrine Therapy in 2005: A Pandora’s Box or a Goldmine?

Martine J. Piccart, MD, PhD, Jules Bordet Institute, Brussels Belgium, and Kathleen Pritchard, MD, Toronto Sunnybrook Regional Cancer Centre, Toronto, Canada

How many of us—who were already practicing oncologists in the 1980s—would have predicted the current revolution that is taking place in adjuvant endocrine therapy for breast cancer? In just a few months’ time we have moved from the comfortable position of prescribing tamoxifen to almost all women with hormone receptor (HR)-positive disease to a daily struggle of assessing which patients need the incorporation of a third-generation aromatase inhibitor (AI) into their adjuvant endocrine treatment scheme. Some of us, perhaps, are still trying to resist the strong current that is pushing our familiar, cheap, and relatively safe standard endocrine treatment—five years of adjuvant tamoxifen—out of our oncology world and oppose the optimists who are ready to abandon this old friend in favour of the AIs. An intermediate group feels strongly that a sequence of 2 to 3 years of tamoxifen followed by an AI is the treatment of choice for a majority of women with HR-positive disease. The debate will continue until the mature data of the large randomized trials do or do not show a survival gain associated with the use of AIs, and provide a reliable assessment of their long-term side effects.

Given the history of our adjuvant clinical trials in breast cancer, in which disease-free survival (DFS) improvements have usually matched overall survival gains with longer follow-up, it is very likely that AIs will end up improving long-term survival of women with HR-positive breast cancer. In contrast, there is a real, although small, possibility that their prolonged use might unveil serious toxicities. While bone health is an obvious source of concern, slightly increased numbers of cardiac events and cognitive sequelae cannot be ruled out at present. These open questions make pharmacogenetic research a priority, because this work has the potential to identify individuals at higher risk for the development of some of these worrisome side effects.

There are already a number of important conclusions to draw from the results generated by the five large adjuvant trials shown in Figures 1 and 2.

- Women who have completed 5 years of tamoxifen retain a 2 to 4% annual risk of relapse in years 6 through 10 following tamoxifen discontinuation and benefit from “extended therapy” with an AI (in this case, letrozole). This means that we need to start thinking about sequential, non–cross-resistant endocrine therapies covering more than a 5-year period.

- Following the 2004 San Antonio Breast Cancer Symposium meeting, we know of two large trials providing level 1 evidence that switching women on tamoxifen for 2 to 3 years to an AI (in these cases exemestane or anastrozole) is better than continuing tamoxifen in terms of DFS. In the absence of reliable molecular markers telling us whether the tumour will remain tamoxifen-sensitive for another 2 years, most physicians will adopt the early sequencing strategy (tamoxifen for 2 years followed by AI) rather than the late one (tamoxifen for 5 years followed by AI).

Figure 1

Figure 2
• Following the 2005 St. Gallen Consensus Conference, there was a second trial, BIG 1-98 / IBCSG 18-98, supporting the results of the ATLAS trial. This study showed that starting endocrine therapy with an AI after surgery instead of tamoxifen reduces the risk of a relapse in general and of distant relapse in particular. This suggests that a survival gain may emerge with longer follow-up. This survival gain, however, has not yet been seen for ATAC, which now has a median follow-up of 68 months.

The biggest challenge to patients and physicians, therefore, is the upfront choice between an AI and a sequence of tamoxifen for 2 to 3 years, followed by an AI. For those women whose disease recurs during years 1 to 3 years of tamoxifen, when that would have been prevented by anastrozole, the upfront AI would seem preferable. Nevertheless, the question of the optimal approach will remain open until the BIG 1-98 / IBCSG 18-98 study releases its mature results in 2007. But even then, we will only get a global answer for the whole trial population.

Is this answer going to be satisfactory? In the era of molecular oncology, we have doubts that it will. We are in search of “tailored” therapies and by “tailored” we mean therapies that take into account the genetic makeup of the tumour as well as the unique characteristics of its host. Our past and recent clinical trials have not been powered to look at differential benefits in biologically relevant subsets of patients. Retrospective and suboptimal translational research studies already suggest marked heterogeneity of endocrine responsive breast cancer to tamoxifen and AIs, with improved responses to the latter in case of PgR negativity or HER-2 positivity. A multi gene array based on RT-PCR has recently been shown to accurately predict for the occurrence of distant metastases in tamoxifen-treated women with node-negative, estrogen receptor-positive disease. Similar efforts using other modern technologies are ongoing.

The strong message here is that it is no longer ethical to run large clinical trials without proper collection of blood and tumour material. This is because understanding heterogeneity in the magnitude of treatment benefit is of utmost importance to our patients and to the whole of society, which will soon be unable to afford expensive treatments for everyone for the benefit of only a few.

In the meantime, our tasks as clinicians will be to “guesstimate” whether the landscape of endocrine responsiveness of a given tumour is closer to Figure 3 or 4.

In the first instance, it is only by using the bicycle (tamoxifen) and the expensive car (AI) in sequence that the journey can be accomplished. In the second instance, the use of the car upfront is the only way to get over the mountain, while uncertainty remains as to whether the sequential use of a second expensive vehicle (fulvestrant?) might be needed. These two models are based on the realistic assumption that AIs are not miracle drugs, and, hence, the car has only a limited amount of fuel.

In conclusion, the limits of breast cancer endocrine therapy have been pushed far ahead. This is great news for our patients and a source of optimism for us all. Currently available data suggest that an AI should now be included as a part of adjuvant endocrine therapy for the vast majority of HR-positive postmenopausal women. This progress should be viewed as a goldmine rather than a Pandora’s box. But careful follow-up of women on adjuvant AIs remains a high priority. This underscores the crucial importance of close collaboration between industry and the academic worlds in the conduct of these expensive and labour-intensive trials that require decades of proper patient follow-up.
Adjuvant Breast Cancer Treatment—Evolution or Revolution?

San Antonio Breast Cancer Symposium 2004: The Taxane Studies

Maureen Trudeau, MD, Toronto Sunnybrook Regional Cancer Centre, Canada

At the San Antonio Breast Cancer Symposium (SABCS) in December 2004, two important studies involving taxanes were presented. The first was the neoadjuvant study of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-27, a study investigating the addition of docetaxel (pre- or postoperatively) to AC (adriamycin/ cyclophosphamide) standard preoperative therapy in palpable, operable breast cancers over 1 cm.1,2 The second was the Programme d’Actions Concertées dans le Cancer du Sein (PACS-01) study conducted in France and Belgium, a study comparing fluorouracil/epirubicin/cyclophosphamide (FEC) 100 for 6 cycles to FEC100 for 3 cycles followed sequentially by docetaxel for 3 cycles.3

The B-27 trial was a 3-arm study involving 2,411 women (2,403 evaluated). Of these, 801 were randomized to AC preoperatively in standard doses (60 mg/m$^2$ and 600 mg/m$^2$), 803 were randomized to AC followed by 4 cycles of docetaxel (100 mg/m$^2$) preoperatively, and the third group of 799 was randomized to AC preoperatively followed by docetaxel postoperatively. The study asked the following questions: 1) does docetaxel add to preoperative AC chemotherapy in terms of disease-free survival (DFS), overall survival (OS), pathologic complete response (pCR) rates, and rates of breast conservation? and 2) does preoperative versus postoperative treatment with docetaxel make a difference with regard to the same outcomes? The trial showed that the pCR in the breast was 13.6% with AC preoperatively (combined data from arms 1 and 3). This is very similar to the results previously obtained in the NSABP B-18 trial of AC preoperatively.4 The pCR in those women who received docetaxel preoperatively was 26.1% (Table 1).

Rates of breast conserving surgery were slightly improved with the addition of docetaxel to AC, but were not significantly different from those obtained with AC alone. Toxicities associated with the sequential addition of docetaxel were those usually attributed to docetaxel, including febrile toxicity, mucositis, and nail changes.

**OUTCOMES**

- Pathologic response rate correlated with outcome (DFS, OS) with those obtaining pCR having better prognosis than those who did not achieve pCR.
- Those patients who obtained a pCR whether with AC alone or with AC plus docetaxel had no difference in terms of outcome. This would suggest that it is important to know which patients have a complete pathologic response with their first 4 cycles of treatment in order to avoid potentially unnecessary therapy, although this involves a small number of patients.
- The number of axillary lymph nodes involved with metastatic disease at operation correlated best with outcome irrespective of pCR in the breast.

Overall survival was not significantly different among the three groups. This may be because: 1) the study was underpowered to show significant differences—the fact that 26% of patients achieved a pCR rate was unlikely to translate into survival differences in the size of population studied, and 2) patients also received concurrent tamoxifen treatment, and this may have impacted negatively on differences in the chemotherapy treatments.

In operable breast cancer, neoadjuvant therapy remains, for the most part, a treatment given on study to increase operability to allow for breast conserving surgery, whereas in locally advanced or inflammatory tumours, neoadjuvant therapy is generally the primary therapy. The B27 trial again confirmed improvement in survival for those who achieved

### TABLE 1: NSABP B-27—Results for Pathologic Complete Response (pCR)

<table>
<thead>
<tr>
<th>pCR in Breast</th>
<th>AC → Surgery</th>
<th>AC → D → Surgery</th>
<th>AC → Surgery → D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only DCIS</td>
<td>3.7%</td>
<td>7.2%</td>
<td>4.4%</td>
</tr>
<tr>
<td>No Invasive/No DCIS</td>
<td>9.1%</td>
<td>18.9%</td>
<td>9.9%</td>
</tr>
<tr>
<td>Total</td>
<td>12.8%</td>
<td>26.1%</td>
<td>14.3%</td>
</tr>
</tbody>
</table>

AC = adriamycin/cyclophosphamide; D = docetaxel; DCIS = ductal carcinoma in situ.
a complete pathologic response to treatment, AC ± docetaxel. The neoadjuvant setting remains one that is fruitful for investigating prognostic factors, response to therapy, molecular features of tumours, and potentially, targeted therapies. Functional imaging may also be incorporated in these studies to try and determine which tumours will respond to treatment and which will not, so that unnecessary treatment can be aborted or avoided.

The PACS-01 trial showed improved DFS and OS at 5 years for patients who received FEC100 followed by docetaxel rather than FEC100 alone. The patient population was pre- and postmenopausal women with a median age of about 50 years. In an intent-to-treat analysis, the 5-year differences in DFS and OS were significantly improved for the sequential therapy (Table 2).

All tumours were node positive, with about 60% involving 1 to 3 nodes in both treatment groups. There was an imbalance between estrogen receptor-positivity in both groups as well as in the number of tumours that were receptor negative (ie, more estrogen receptor positive, fewer hormone receptor negative in the sequential therapy arm). Premenopausal patients initially did not receive tamoxifen post-chemotherapy for receptor-positive disease. The trial was later modified to include tamoxifen in this group of patients. In an analysis by number of involved nodes, trends were seen for benefit for 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) → docetaxel in the 1 to 3 and ≥ 4 nodal subsets. In a subset analysis by age, comparing age under 50 to age 50 or over, there was significant benefit for sequential treatment in the older group of women but not in the younger group. In the younger group there appeared to be no difference between the two treatments. Whether this result is real, whether it reflects the lack of tamoxifen treatment in a subgroup of those patients, or whether it is secondary to a statistical anomaly, is uncertain.

There was significantly more febrile neutropenia for patients on FEC → docetaxel compared to those receiving FEC x 6 (4.6%, 1%; p < .001), but fewer cases of leukemia; less neutropenia in cycles 4 to 6 and less granulocyte colony stimulating factor per cycle (8.9%, 14.7%; p < .001); less congestive heart failure but more edema and nail disorders.

Chemotherapy-induced amenorrhea was similar (68.4% versus 72.4%). This would suggest that the taxane-containing regimen is at least as good for all women and probably less toxic. FEC → docetaxel will become one of the standards of care in treatment of node-positive breast cancer, once issues of funding and guideline development are addressed.

The taxanes, docetaxel and paclitaxel, have been shown to improve survival in sequential regimens compared to standard anthracycline regimens. The AC followed by paclitaxel regimen of the CALGB 9344 study demonstrated improvement in survival with 8 cycles versus 4 cycles of therapy. The PACS-01 study showed improvement in survival with the addition of the taxane sequentially after the anthracycline-based regimen, independent of number of cycles of treatment. FEC100 x 6 would be considered a more optimal regimen than AC x 4, although an ongoing comparison of the two is being undertaken in the NSABP. The decision as to who would benefit most from a taxane is yet to be fully understood. The EORTC 10994/BIG 1-00 trial is investigating p53 as a prognostic marker to determine if there is an improved response to taxanes in those tumours with mutant p53. There may be other molecular profiles that will predict for response to taxanes. At the present time, the knowledge as to which patients require chemotherapy, which require an anthracycline, which require a taxane, and which require both is evolving. This is an area of ongoing investigation through multiple clinical trials with biologic correlates, and hopefully we will be able to determine the best patient populations for whom the toxicity and cost of chemotherapy is warranted. At the present time, the final decision as to which treatment to use will depend on the training of the investigator, patient preference, and cost.

## REFERENCES


### TABLE 2: PACS-01—5-Year Results of Disease-Free and Overall Survival

<table>
<thead>
<tr>
<th>5 Year</th>
<th>FEC100 × 6</th>
<th>FEC100 × 3 → D × 3</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFS</td>
<td>73.2%</td>
<td>78.3%</td>
<td>.014</td>
</tr>
<tr>
<td>OS</td>
<td>90.7%</td>
<td>86.7%</td>
<td>.017</td>
</tr>
</tbody>
</table>

D = docetaxel; DFS = disease-free survival; FEC = fluorouracil/epirubicin/cyclophosphamide; OS = overall survival.
Genomics and Proteomics for Oncologic Treatment Tailoring, 2005

Brian Leyland-Jones, MD and Soheyl Baban, MS, MBA
Department of Oncology, McGill University, Montreal, Canada

Although large clinical trials have confirmed the value of systemic therapy, it is not possible to identify at the outset those patients who are likely to respond to adjuvant treatment or which type of treatment should be used. For example, adjuvant therapy significantly improves disease-free survival (DFS) and overall survival (OS) in breast cancer patients with both lymph node negative (LN−) and lymph node positive (LN+) disease. It is generally accepted that breast cancer patients with poor prognosis would gain the most benefit from adjuvant therapy (eg, those with invasion into axillary LNs). However, results of several studies show that 22 to 33% of breast cancer patients with no detectable LN involvement and classified into a good prognosis subgroup develop recurrence of disease after a 10-year follow-up. Therefore, accurate identification of breast cancer patients over and above current prognostic and predictive markers is critically important for rational treatment decision-making and improved clinical outcome in the individual patient.

Microarray-based gene expression profiling of human cancers has rapidly emerged as a new powerful screening technique. Recently, breast cancer gene expression signatures have been identified that are associated with the estrogen receptor (ER) and LN status of patients and can aid in classifying breast cancer patients into subgroups with different clinical outcomes after therapy. Moreover, gene expression signatures have been shown to predict response to particular chemotherapy regimens. The advantage of the microarray technologies is the ability to measure the ribonucleic acid expression of thousands of genes at one time, and to relate how the expression pattern of one gene correlates to the expression of other genes in or between different tumour samples.

Van’t Veer and colleagues have used DNA microanalysis on primary breast tumours of 98 young patients and applied supervised classification to identify a 70-gene-expression signature strongly predictive of a short interval to distant metastasis in LN− patients. The poor prognosis signature consisted of genes regulating cell cycle, invasion, metastasis, and angiogenesis. Van de Vijver and colleagues subsequently used this 70-gene prognosis profile to classify a series of 295 consecutive patients with primary breast carcinomas as having a gene-expression signature associated with either a poor or a good prognosis. All patients had stage I or II breast cancer and were younger than 53 years old; 151 had LN− disease, and 144 had LN+ disease. The predictive power of the prognosis profile was validated using univariable and multivariable statistical analyses. Among the 295 patients, 180 had a poor-prognosis signature and 115 had a good-prognosis signature, and the mean (±SE) overall 10-year survival rates were 54.6 ± 4.4% and 94.5 ± 2.6%, respectively. At 10 years, the probability of remaining free of distant metastases was 50.6 ± 4.5% in the group with a poor-prognosis signature and 85.2 ± 4.3% in the group with a good-prognosis signature. The estimated hazard ratio (HR) for distant metastases in the group with a poor-prognosis signature, as compared with that for the group with the good-prognosis signature, was 5.1 (95% confidence interval (CI), 2.9 to 9.0; \( p < .001 \)). This ratio remained significant when the groups were analysed according to LN status. Multivariable Cox regression analysis showed that the prognosis profile was a strong independent factor in predicting disease outcome. The resulting gene-expression profile was a more powerful predictor of the outcome of disease in young patients with breast cancer than standard systems based on clinical and histologic criteria.

Piccart and colleagues have recently presented the validation of the Amsterdam 70-gene prognostic signature in LN− untreated breast cancer at the San Antonio Breast Cancer Symposium (SABCS). This validation was performed as part of preparation for the launch of the large prospective randomised clinical trial (MINDACT) for LN− breast cancer powered to look at the utility in clinical practice of the Amsterdam 70-gene prognostic signature. This external validation was performed on frozen archival tumour material of LN− patients aged < 60 years old. HR were calculated under a proportional hazards model to compare event rates in high risk versus low risk groups. The events of interest were time to distant metastases (TDM), DFS, distant metastases (DMFS) free survival and OS. Risk groups were defined on the basis of clinical/pathological data according to the 2003 St. Gallen criteria or the Nottingham Prognostic Index (NPI), and on the basis of the 70-gene signature. Assuming no statistically significant heterogeneity in clinical HR, the validation criteria set a priori specified the following thresholds for the gene signature HR: 1) \( HR > 3.0 \) for TDM, and 2) \( HR > 2.0 \) for DFS or OS. In addition, the group classified as low risk by the gene signature was required to have a 5-year DMFS > 90%. Three hundred and one patients, followed for a median of...
10 years, were included in the present analysis. One hundred loco-regional relapses, 75 distant relapses, and 76 deaths were recorded. The cross-classification of clinical versus genetic risk groups revealed discordant results for 37% of women using the St. Gallen criteria and for 41% using the NPI. Significant heterogeneity between the Amsterdam and the external validation samples was found and is currently being investigated; however, the 70-gene prognostic signature outperformed both the NPI and the St. Gallen criteria in predicting (1) TDM (HR 1.85 [CI 1.14–3.0] versus HR 1.46 [CI 0.87–2.47] versus HR 1.2 [CI 0.59–2.43]), and (2) OS (HR 2.13 [CI 1.3–3.5] versus HR 1.46 [CI 0.87–2.45] versus HR 0.94 [CI 0.45–1.95]). In addition, women of the present series classified as low risk by the gene signature had a projected 5 year DMFS of 95%.

Multivariate analyses, central pathology review, and a comparison between the 70-gene prognostic signature and the Adjuvant! Online tool are in progress. While the overall performance of the 70-gene prognostic signature was inferior in this external validation series compared to the original Amsterdam series, the results provide level 3 evidence for the clinical value of this new genomic tool and are encouraging to mobilize forces for the conduct of MINDACT (Figure 1).

Real-time reverse transcription-polymerase chain reaction (RT-PCR) technology represents a second genomic platform that has great sensitivity and specificity, covers a wide dynamic range, and requires minute amounts of cells or tissue. While RT-PCR has significant diagnostic potential, it has to date been limited to viral diagnostics. Genomic Health Inc (GHI) in collaboration with National Surgical Adjuvant Breast and Bowel Project (NSABP) researchers has recently developed and commercialized a predictive gene signature (Oncotype DX [ODX]) that uses this technology, measuring the expression of 21 genes on archival pathology blocks. GHI/NSABP researchers selected 250 cancer related genes from published sources and public databases and developed a signature based on 16 cancer and 5 reference genes using 3 breast cancer studies to develop a Recurrence Score (RS) algorithm. This RS was subsequently prospectively tested in the NSABP B-14 study and was shown to provide accuracy and precision in predicting the likelihood of distant recurrence. Moreover, the RS performance exceeded standard measures such as age, tumour size, and tumour grade, both in prognostic power and in reproducibility; this technology has been recently approved by the US Food and Drug Administration (FDA) for clinical application.

Figure 1 Ctx = chemotherapy; EU FP VI NoE = European Framework Programme VI Network of Excellence; PRC = Protocol Review Committee; R = randomisation; Tam = tamoxifen
Since then, this technique has undergone extensive testing regarding validation and prognostic capabilities: (1) the previously described RS has been shown to predict response to chemotherapy. This work demonstrated that a higher RS is associated with a higher likelihood of pathologic complete response in patients treated with doxorubicin/paclitaxel neoadjuvant therapy in locally advanced breast cancer (LABC); (2) RS was shown to be not only prognostic for tamoxifen-treated patients, but also strongly predictive of response and benefit from tamoxifen in NSABP B-14 (p-value interaction: tam treatment × ER < .001); 3) moreover, RS predicted the magnitude of chemotherapy benefits in NSABP B-20: patients with tumours that had low RS derived minimal if any benefit from chemotherapy. Patients with tumours that had high RS derived a large absolute benefit from chemotherapy (similar results with both CMF and MF); 4) The initial B-14 prognostic data has been subsequently confirmed in a validation study of 220 evaluable cases and 570 matched controls in the Northern California Kaiser Permanente. RS was strongly prognostic of breast cancer specific mortality (BCSM) in this population with relative risk estimates and estimates of BCSM similar to those found in the B-14 population. Finally, 5) The RS results from NSABP B-14 were correlated and compared with 10-year outcome data estimated using Adjuvant! Online (AO). RS and AO predicted-BCSM correlated relatively weakly (concordance = 48%) with RS appearing to correlate more strongly with outcome than AO. Hence, each algorithm/assay clearly contains independent prognostic information; it would therefore be reasonable to combine these information sets in future prognostic and predictive algorithms.

Rapidly emerging proteomic technology is currently being applied to individualize oncologic therapy. Our understanding of proteomic networks in human tissue is somewhat limited at present; moreover, how these networks truly interact (eg regular, random, and/or scale-free) and are perturbed in the disease microenvironment will become a critical component of effective therapeutic intervention strategies and clinical trial design. In the past, a critical bottleneck for translational application of proteomics has been the paucity of validated antibodies with high specificity to the activated signalling molecules. Happily, within the past few years, a large compendium of well-characterized and carefully validated phospho-specific antibodies has become commercially available. A number of proteomic technologies that utilize affinity capture reagents that enrich for phosphorylated proteins, followed by mass spectrometry-based sequencing, are being used for phosphoproteomic discovery.

Protein microarrays can be used to profile the working state of cellular signal pathways in a manner over and above that which is possible with gene microarrays, because post-translational modifications cannot be accurately portrayed by global gene expression patterns alone. Protein microarray formats can be divided into two major classes: forward phase arrays (FPA) and reverse phase arrays (RPA) (Figures 2 and 3). In the FPA format, the analyte of interest is captured from

![Figure 2](Protein microarray formats. Protein microarrays consist of an array of protein samples, or protein baits, immobilized on a solid phase. The array can be queried with a mixture of labeled proteins containing analytes of interest. The analyte proteins are captured and can be detected using colorimetric, fluorescent, or chemiluminescent means. (Taken from Petricoin et al, Nature Reviews 1:683-695, 2002.)}
the solution phase by a capture molecule, usually an antibody, which is immobilized on a substratum and acts as a bait molecule. Using FPA, each spot contains one type of immobilized antibody or bait protein. Each array is incubated with one test sample, such as a cellular lysate or serum sample representing a specific treatment condition, and multiple analytes from that sample are measured simultaneously. In contrast, the RPA format immobilizes an individual complex test sample in each array spot, such that an array comprises hundreds of different patient samples or cellular lysates. With RPA, each array is incubated with one detection protein (i.e., antibody): a single analyte endpoint is measured and directly compared across multiple samples. Probing multiple arrays spotted with the same lysate concomitantly with different phospho-specific antibodies provides the effect of generating a multiplex read-out. The RPA platform has been employed to explore a variety of signalling pathways involved in malignant progression and tumour biology. For example, in a study of prostate tissue, pathway profiling of microdissected cells from normal stromal and prostate tumours revealed that activation of protein kinase C alpha is down-modulated in prostate cancer progression.

Sheehan and colleagues at the FDA-National Cancer Institute Clinical Proteomics program have recently used RPA technology to profile a matched cohort of primary and metastatic ovarian carcinomas. In characterizing signal pathway alterations between the two tissue microenvironments, they hoped to gain insights into the aberrant signalling that maintains shed neoplastic ovarian cells at secondary sites. Fifteen frozen tissue samples were obtained from 9 patients with a diagnosis of stage III or IV epithelial ovarian cancer. Six patients had matched primary ovarian tissue and omental metastases obtained during cytoreductive surgery. The histological diagnoses comprised papillary serous, endometrioid and mixed carcinomas, and one primary peritoneal carcinoma. Epithelial cells were microdissected from frozen tumour sections and printed on arrays. The slides were probed with 26 phospho-specific antibodies to proteins involved in mitogenesis, including growth factor receptors, signal-transducing proteins, and nuclear transcription factors in order to profile the phosphoproteomic signal pathway circuitry. Analysis of multiple different kinase substrates, detected by phosphorylation-specific antibodies, revealed a striking degree of heterogeneity in the activity of the signalling cascades within each patient. Unsupervised hierarchical clustering analysis revealed that the samples were divided into two large groups—one in which the majority of endpoints were activated, and the other in which they were not. This division was not based on primary or metastatic tissue origin or by histologic type. Interestingly, the primary peritoneal carcinoma did not display a significantly different phospho-proteomic portrait from that of primary ovarian tumours. Secondly, it was observed that comparison of cell signalling within the primary group (or indeed, the metastatic group) demonstrated considerable variation in the level of signal pathway activation, i.e., no common pattern was specific to either of the tissue microenvironments.
Finally, the most intriguing finding was that the metastatic signatures were dramatically changed compared to their matched primary counterparts, with entirely different portraits emerging. Each patient’s proteomic pattern had evolved as the tumour spread to a secondary site. The additional discovery that metastatic cell signalling is so dissimilar to the primary tumour highlights the critical need for patient-tailored therapy that is designed to specifically target disseminated metastatic cells because it is the aberrant pathways of the latter that most closely reflect disease behaviour within the patient. In this small cohort, each of these patients may have responded quite differently to conventional chemotherapy, despite being very similar in terms of disease stage. Acquired change in the tumoural proteome may well be associated with drug resistance. The primary question currently being addressed is whether metastasis to different secondary site (eg, liver or lung) shows the same degree of signalling heterogeneity, demonstrating organ- or patient-specific phosphorylation patterns.

Current studies such as TransHERA will employ direct comparisons of expression array, RT-PCR, and proteomic platforms in order to evaluate their relative contributions in individualizing therapy at this critical juncture in personalized medicine.

REFERENCES


History of the San Antonio Breast Cancer Symposium (SABCS)

Adapted from the SABCS Web site, with Rich Markow, Symposium Director

The First Annual San Antonio Breast Cancer Symposium was held November 11, 1978 during Breast Cancer Awareness Week, and was part of an intensive 3-year outreach program of public and professional education designed to significantly reduce the death rate caused by breast cancer in San Antonio and surrounding counties. It was sponsored by Cancer Therapy and Research Center (CTRC) and the American Cancer Society, Texas Division, in conjunction with The University of Texas Health Science Center at San Antonio (UTHSCSA) and the Bexar County Medical Society.

That all-day course for physicians and surgeons was organized and co-directed by Charles A. Coltman Jr., MD and William L. McGuire, MD, both Professors of Medicine at UTHSCSA. It featured invited presentations by a panel of internationally known specialists and was attended by 141 physicians and surgeons from a 5-state area.

Three years later, in 1981, the meeting was expanded to 2 days, a call for abstracts was distributed worldwide, and proffered papers for slide and poster presentations were incorporated into the program, thereby broadening its scope to both attract and draw from a larger, international
CONFERENCE SETTING
The 9th St. Gallen International Consensus Conference on Primary Therapy of Early Breast Cancer took place on January 26–29, 2005, in the OLMA Conference Center in St. Gallen. Close to 4,200 breast cancer specialists from various medical disciplines and from 83 countries worldwide participated at this important event,* which was followed by the annual meeting of the International Breast Cancer Study Group (IBCSG). As in the past, the conference was chaired by Richard D. Gelber (Boston, USA), Aron Goldhirsch (Lugano, Switzerland and Milano, Italy) and Hans-Jörg Senn (St. Gallen, Switzerland), together with Beat Thürlimann (St. Gallen, Switzerland), the new president of the Foundation Council of the IBCSG as Scientific Secretary General.

CONFERENCE AIM AND APPROACH
The aim of the St. Gallen Consensus was again to provide a periodic—now bi-annual—update of internationally useful treatment guidelines for the optimal therapy of patients with early (operable) breast cancer. These conferences are not intended to provide a “list of recipes,” but rather a set of opinions and guidelines for the treatment of patients outside of clinical trials (in most countries more than 95% of all newly diagnosed patients). The St. Gallen Consensus is not perfect, nor will it satisfy everyone or solve all therapeutic controversies. But it intends to help many patients and their physicians to discuss the available scientific evidence and expert opinions for reasonably balanced primary treatment decisions.

ST. GALLEN CONSENSUS: A PUBLIC PROFESSIONAL EVENT
The St. Gallen Consensus conferences are public professional events, open on a global scale to all interested physicians, surgeons, and researchers. After 3 days of lectures by top invited experts and scientific satellite workshops, an interdisciplinary panel of 30 breast cancer experts from around the world generates a reasonable treatment recommenda-

*Although some modifications have been made in the format, such as incorporating mini-symposia and, in 1997, the prestigious Brinker International Award for Cancer Research program of the Susan G. Komen Breast Cancer Foundation, the overall format remains very much the same. This reflects the objective of the Symposium, which is to provide state-of-the-art information on the experimental biology, etiology, prevention, diagnosis, and therapy of breast cancer and premalignant breast disease, to an international audience of academic and private physicians and researchers.
Adjuvant Breast Cancer Treatment–Evolution or Revolution?

Adjuvant Breast Cancer Treatment–Evolution or Revolution?

tion compromise, which should satisfy the needs of the next 2 to 3 years. Other consensus approaches and statements, such as the Oxford Overviews or the National Institutes of Health Consensus, have different aims and settings.

IMPORTANT DIFFERENCES FROM PAST ST. GALLEN PANELS/AREAS OF DISCUSSION

The St. Gallen Consensus Panel 2005† integrated several fundamental changes compared to previous consensus meetings:

• It moved away from only discussing “pure level-I evidence” with long-term overall survival data as the mandatory basis for treatment selection and recognized lower evidence levels to generate the “set of opinions and guidelines” for discussing available therapeutic options and expert opinions for balanced treatment decisions in daily routine.

• It also moved away from risk of relapse as the main criterion for treatment choice, but introduced endocrine responsiveness as the most important selection factor for both adjuvant chemo- (CT) and endocrine (HT) therapy treatments in node-negative and node-positive disease. It recognized that even the magnitude of the effect of adjuvant CT regimens is related to the endocrine responsiveness of the primary tumour. The panel also accepted that endocrine responsiveness is not dependent only on estrogen and progesterone receptor staining, but on a more complex interaction between known and unknown factors. It furthermore introduced the category of unclear degree of endocrine responsiveness.

Discussions also focused the following key issues:

• The division of the risk of relapse estimation in node-negative disease into two categories: “minimal” (lower) risk and “intermediate” (formerly average) risk, the latter integrating also node-positive 1–3 node cases, while patients with clear-cut human epidermal growth factor receptor-2 (HER-2)-overexpression and/or > 4 positive axillary nodes fall into the “high-risk” category. Although viewed as scientifically interesting, neither the coagulation markers (PAI-1/uPI) nor the elaborated “Oncotype” system were presently accepted as risk selection parameters (lack of standardisation, missing long-term results, and lack of availability on an international scale).

• The optimal use of aromatase inhibitors in the treatment of postmenopausal women with endocrine responsive or doubtful endocrine responsive disease where no consensus was reached. It was agreed, however, that tamoxifen is not out of the therapeutic armamentarium for adjuvant HT in postmenopausal women with hormone-sensitive breast cancer.

• The 30 panelists continued to have a fairly conservative approach regarding the use of taxanes and dose dense regimens in the adjuvant CT setting.

• The fact that no data are available to recommend adjuvant trastuzumab in HER-2-overexpressed patients.

PRELIMINARY CONCLUSIONS AND PUBLICATION OF CONSENSUS 2005

Overall, the St. Gallen Consensus Panel 2005 adopted a more practical approach compared to previous meetings, and the panel more intensively recognized the heterogeneous and complex biology of breast cancer. It tried to recommend treatment selections mainly according to expected treatment outcome on the basis of endocrine responsiveness. The availability of an electronic voting device for the whole panel with immediately projected majority votes transformed the closing consensus session into a spectacular exercise. The summary as presented in this article is only a preliminary statement: the final manuscript will be available in the Journal of Clinical Oncology (JCO); the Consensus Statement is to be expected on line in May/June and officially published in July/August 2005. Once accepted by the JCO Editorial Office, the Consensus Statement 2005 will also be available on the home pages of St. Gallen Oncology Conferences or the Center for Tumordetection + Prevention (ZeTuP) St. Gallen: <www.oncoconferences.ch> or <www.sg.zetup.ch>
BIG 1-98 Trial: First Results

Nadia Munarini, PhD, IBCSG Coordinating Center

**PURPOSE**

BIG 1-98 is the first clinical trial designed to incorporate both a head-to-head comparison of letrozole with tamoxifen during the first 5 years following breast cancer surgery, and a sequencing of both agents to determine the most effective approach to minimize the risk of recurrence and of side effects.

**SCOPE**

The BIG 1-98 study is being conducted in 27 countries and involves 8,028 post-menopausal women with early breast cancer.

The study was conducted under the umbrella of the Breast International Group (BIG), coordinated and managed by the International Breast Cancer Study Group (IBCSG), in collaboration with the Danish Breast Cancer Group, the Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC), the Yorkshire Group, and many other independent centres.

**DESIGN**

Multinational, phase III, double-blind, double-dummy, randomised trial administering adjuvant therapy (therapy used to prevent recurrence after surgery) following complete surgical removal of the tumour (resection). All patients will be monitored for the rest of their life to assess long-term efficacy, including overall survival and tolerability.

**RANDOMISATION**

BIG 1-98 compares the following randomisation arms:

- A. tamoxifen for 5 years
- B. letrozole for 5 years
- C. tamoxifen for 2 years followed by letrozole for 3 years
- D. letrozole for 2 years followed by tamoxifen for 3 years

**ACCUAL**

Randomisation to arms A and B: 1,835 patients
Randomisation to arms A, B, C, and D: 6,193 patients

**RESULTS**

The first results are based on the comparison of the initial treatment assignment to letrozole in arms B and D with assignment to tamoxifen in arms A and C, but excluding events occurring more than 30 days after therapy switch in arms C and D.

After a median follow-up of 25.8 months, we found a statistically significant difference in disease-free survival (DFS) in favour of letrozole:

- DFS hazard ratio 0.81, \( p = .003 \), absolute difference: 2.6% at 5 years.
- The absolute difference in cumulative breast cancer relapse is 3.4% at 5 years.
- Letrozole was particularly effective in preventing relapse at distant sites.

**PROTOCOL TARGETED ADVERSE EVENTS:**

- Similar in both treatment arms except for an excess of thromboembolic events and vaginal bleeding on tamoxifen.
- Endometrial biopsies were more frequent with tamoxifen.
- Bone fractures were more frequent with letrozole.
- Mild cholesterol elevation was more common with letrozole.
- Deaths without recurrence (particularly cardiovascular), although rare, were more frequent with letrozole.

These results were presented during the 9th International “Primary Therapy of Early Breast Cancer” in St. Gallen, Switzerland, on January 26, 2005.

Information on sequential therapy will require further follow-up.
STATISTICAL CONSIDERATIONS

Primary Core Analysis: comparing letrozole and tamoxifen as monotherapy (DFS-events in arms A and B + DFS-events in arms C and D occurring before the switch plus 30 days). 647 events required allowing the detection of a 20% relative risk reduction with 80% probability. Actual number of DFS events for the present analysis: 779. An intent-to-treat analysis was performed, excluding only the 18 patients who withdrew consent and had neither treatment nor follow-up.

PRIMARY ENDPOINT

DFS is defined as time from randomisation to first instance of invasive breast cancer recurrence, including contralateral invasive breast cancer or new second malignancy or death without recurrence.

SECONDARY ENDPOINTS

• Systemic DFS is defined as the time from randomisation to first instance of invasive regional or distant recurrence, second non-breast malignancy or death without recurrence.
• Overall survival (the time from randomisation to death from any cause).
• Safety and tolerability.

SAFETY

• Continuous medical surveillance of severe adverse events.
• 6-monthly review by the Independent Data Safety and Monitoring Committee (DSMC).
• Interim efficacy analyses blinded as to treatment assignment after 261 and 430 events presented to the DSMC.

TRIAL RESPONSIBILITIES

• IBCSG: study design, database, and data management, medical review, statistical analysis, coordination, and communication, ethics committee, independent data safety, and monitoring committee.
• Novartis: drug distribution, financial support.

PARTICIPATING COUNTRIES

Argentina  Denmark  Netherlands  South Africa
Australia  France  New Zealand  Spain
Belgium  Germany  Peru  Sweden
Brazil  Great Britain  Poland  Switzerland
Canada  Hungary  Portugal  Turkey
Chile  Iceland  Russia  Uruguay
Czech Republic  Italy  Slovenia

Additional information regarding IBCSG, BIG 1-98 can be found on the Web site <www.ibcsg.org>.
**BIG Studies for Older Patients**

**BIG 1-05/IBCSG 32-05: Chemotherapy Adjuvant Studies for Women at Advanced Age (CASA)**

**Phase III Trial Evaluating the Role of Adjuvant Pegylated Liposomal Doxorubicin (PLD, Caelyx®) for Women (age 66 years or older) with Endocrine Nonresponsive Breast Cancer who are NOT Suitable for Being Offered a “Standard Chemotherapy Regimen”**

*Coordinating Group: International Breast Cancer Study Group (IBCSG)*

**Patient Population:**

This trial is for older women (66 years of age or older) with histologically proven, resected breast cancer. The disease must be classified as endocrine nonresponsive and patients must not be candidates for endocrine therapy or for an adjuvant chemotherapy program that includes a “standard” anthracycline-containing chemotherapy regimen.

**Rationale:**

Efficacy data in women aged > 70 years are scarce, resulting in a lack of clear guidelines for patients in this age group. Thus, a therapeutic dilemma exists when a woman at advanced age presents with an endocrine nonresponsive early breast cancer. Relapses of breast cancer may occur earlier in patients with endocrine nonresponsive disease compared to those with hormone receptor-expressing tumours, even when axillary nodes are negative at presentation. This provides a rationale for reducing the risk of relapse even when life expectancy is less than decades.

Such a dilemma does not exist if the patient is biologically (and functionally) young, and a “standard” chemotherapy regimen may be offered with no concern.

The physician may decide not to offer a relatively frail patient any treatment, for fear of possible subjective or severe toxic effects of chemotherapy. Typically, however, these patients are treated in a rather heterogeneous way by arbitrarily reducing doses or modifying schedules of adjuvant chemotherapy regimens that were studied in younger women. This trial is therefore important because it is designed to test a reasonably tolerated cytotoxic regimen for a patient subpopulation uniformly treated within a randomized trial.

The choice of the population (endocrine nonresponsive) is advantageous because the magnitude of chemotherapy effect for this postmenopausal cohort is likely to be quite large, similar to the effect observed for premenopausal patients with similar biological tumour characteristics. Avoiding dilution with patients having endocrine responsive tumours (even those with high number of axillary lymph nodes involved) maximizes the chance to observe a benefit in the shortest time with the lowest number of patients.

**Tailored Treatment Investigations:**

Some of the investigators are likely to choose no adjuvant cytotoxic therapy as a standard for frail patients at advanced age, while others will prefer to offer some treatment for all patients with endocrine nonresponsive disease. The CASA studies are therefore aimed at investigating the role of adjuvant cytotoxic chemotherapy for postmenopausal women at advanced age with endocrine nonresponsive early breast cancer. A PLD (Caelyx®), was chosen as the experimental treatment (Figure 1).

These two complementary randomization options are tailored to the investigator’s decision and/or the patient’s preference about what would constitute an appropriate control treatment group for the individual patient, thus enabling the physician to express his or her own attitude and/or belief towards adjuvant treatments in this subpopulation. Because of the separate designs, at the time of randomization the investigator will be asked to select one of the two randomization options:

- **Option 1:** PLD versus nil, is designed for patients who, according to the treating physician and/or to the patient’s preferences, are candidates to receive no adjuvant therapy.
- **Option 2:** PLD versus low dose, metronomic CM, is designed for patients who, according to the treating physician and/or to the patient’s preferences, should receive some adjuvant treatment.
These trials require a rather large number of patients from a rather small subpopulation of breast cancer patients. Although the incidence of breast cancer in elderly women is quite high, it is estimated that only 15% will have a receptor negative (no expression of estrogen receptor and prandial glucose regulation) disease. Thus, a satisfactory accrual can only be reached with an international collaboration and participation around the world.

**Aim:**

The overall aim of the CASA study is to investigate the role of PLD as adjuvant chemotherapy for older postmenopausal women for whom chemotherapy is indicated, but standard regimens, derived from trials in younger women, are assumed to be too toxic or inconvenient. The stratified analysis combining the results of both randomization options will provide the primary evidence on the effectiveness of PLD. This analysis will assess PLD versus non-PLD-containing control groups (either nil or CM). In addition, analyses will be conducted separately for each of the two randomization options (adjusted for multiple comparisons) to assess each of the individual pair-wise contributions to the overall result.

**Patient Entry:**

Patients should be randomized within 6 weeks after surgery. Patient-related baseline quality of life assessments, as well as physician-documented baseline cognitive and physical functioning assessments, must also be obtained before randomization.

**Stratification Factors:**

Institution is the only stratification factor.

**Endpoints:**

**Primary:**
- Breast cancer free survival (events are reappearance of invasive breast cancer at any site including contralateral disease)

**Secondary:**
- Tolerability (treatment completion)
- Adverse events
- Quality of life
- Disease-free survival (includes second malignancies and deaths)
- Sites of failure
- Overall survival
- Causes of death

**Sample Size and Anticipated Study Duration:**

The trial is designed to include 1,296 patients (432 per year for 3 years with 1.76 years of additional follow-up—total study duration of 4.76 years).

---

**Option 1: CASA-Nil**

- **Primary Surgery**
- **Randomize**
  - **Stratify**
    - **Institution**
  - **PLD**
  - **No adjuvant therapy (nil)**

**Option 2: CASA-CM**

- **Primary Surgery**
- **Randomize**
  - **Stratify**
    - **Institution**
  - **PLD**
  - **Low-dose, metronomic CM**

---

*Figure 1: CM = cyclophosphamide plus methotrexate; PLD = pegylated liposomal doxorubicin.*
PROTOCOL SUMMARY AND RATIONALE

Approximately 50% of new diagnoses of early breast cancer are made in patients above the age of 65. In 1998, for example, approximately 27,415 women in Germany had their diagnosis of breast cancer at an age above 60, which represents approximately 60% of all newly diagnosed early breast cancers for that year. Because this age group has not been eligible to participate in most trials in the past, the effect of adjuvant therapy is still unclear in elderly patients.

The primary aim of the BIG 4-04/GBG 32 ICE (Ibandronate with or without Capecitabine in Elderly Patients with Early Breast Cancer/ICE—Study) trial will be to determine, in the presence of a bisphosphonate, the role of adjuvant chemotherapy with capecitabine in elderly patients. The high activity, acceptable toxicity, and oral formulation of capecitabine meet the requirements of elderly patients. In a recent analysis of the Early Breast Cancer Trialists’ Collaborative Group database, presented in St. Gallen by R. Gelber, it could be shown that the chemotherapy effect across age is highly affected by the frequency of hormone-sensitive tumours and that the post-correction chemotherapy effect is similar in all age groups. The only adjuvant phase III study available so far is a small French trial that demonstrated a significant contribution of weekly epirubicin to tamoxifen alone in 338 patients with mainly hormone-sensitive tumours. Therefore, the ICE study includes patients with both hormone-sensitive and insensitive tumours.

The efficacy of bisphosphonates has been established in the treatment and prevention of osteoporosis. Two studies have recently shown that adjuvant long-term use of clodronate can reduce the risk of recurrence in breast cancer. A third trial, which did not find a positive result, suffered from severe methodological inadequacies. The third-generation bisphosphonate ibandronate will be given in this trial to all patients to prevent osteoporosis and, potentially, a recurrence of breast cancer—these patients are at risk for both. Because the preference of elderly patients for intravenous or oral administration is not known, the mode of administration for ibandronate will be according to patient choice. Patient preference and compliance will be secondary endpoints.

As another one of the secondary endpoints, geriatric assessment with the Charlson Scale will be compared with the VES 13 Score. Both will be included together with age, serum albumin, hemoglobin level, and creatinine clearance in a multivariate analysis to assess their prognostic impact for outcome and toxicities.

TREATMENT SCHEDULES:

Chemotherapy:
All regimens are 16 weeks duration.

- PLD: Caelyx 20 mg/m² IV × 8 doses (delivered every 2 weeks).
- CM Regimen: Low-dose, metronomic CM administered for 16 weeks; cyclophosphamide 50 mg/day orally continuously for 16 weeks; methotrexate 2.5 mg/twice a day orally days 1 and 4 of every week for 16 weeks.

Radiotherapy:
Radiation therapy to the conserved breast is recommended. Radiation therapy to the chest wall following mastectomy is optional. Radiation therapy may be given either during operation or after all chemotherapy.

BIG 4-04/GBG 32 Ibandronate with or without Capecitabine in Elderly Patients with Early Breast Cancer/ICE—Study

An Intergroup Study—The German Experience

Collaborating Groups: German Breast Group (GBG) (coordinator) Westdeutsche Studiengruppe (WSG), Arbeitsgemeinschaft Gynäkologische Onkologie (AGO), Nordostdeutsche Gesellschaft für Gynäkologische Onkologie (NOGGO)

Principal Investigators: Ulrike Nitz, University of Düsseldorf (WSG), and Gunter von Minckwitz (GBG)
STUDY DESIGN

<table>
<thead>
<tr>
<th>Age ≥ 65 yrs, N+ or N− (high risk: T ≥ 2 cm or G II/III or Receptor negative)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibandronate 50 mg po daily or 6 mg iv, q4W, 2 yr*</td>
</tr>
<tr>
<td>Ibandronate 50 mg po daily or 6 mg iv, q4W, 2 yr* +</td>
</tr>
<tr>
<td>Capecitabine 2000 mg/m² days 1–14 q d22 × 6</td>
</tr>
</tbody>
</table>

Randomization

If ER and/or PR positive: Anastrozole 1 mg po daily for 5 yr (in sequence to capecitabine).
N = node, T = tumor size, G = grade.
* according to patient choice

PATIENT DEFINITION

Patients should be randomized within 3 months after axillary dissection, have a Charlson Scale score of ≤ 2, and a creatinine clearance calculated by the Cockcroft-Gold formula of above 50 ml/minute.
Radiotherapy should be given after chemotherapy if the patient is randomized to the capecitabine arm. In the ibandronate only arm, radiotherapy can start directly after randomization.

STRATIFICATION FACTORS

- participating centre
- nodal status
- age (65–69, 70–74, 75–79, 80+ years)
- receptor status

END POINTS

Primary endpoint: any local or distant relapse of breast cancer, any second malignancy, and any death irrespective of its cause.
Secondary endpoints: any death related and unrelated to breast cancer, any premature treatment discontinuation of capecitabine or ibandronate, any grade II to IV adverse event specified as “serious” or “nonserious;” every bone fracture, bone surgery, new diagnosis of osteoporosis; number of completed months of iv or po treatment with ibandronate, and frequency of changes of administration preference; evaluation according to EORTC Q 30, Charlson Scale and VES–13 points.
Tertiary endpoints: expression of prognostic factors (will be determined at a later stage): age, serum albumin level, hemoglobin, creatinine clearance, Charlson Scale, VES score.

SAMPLE SIZE AND STUDY DURATION

The trial is designed to include 1,394 patients in 3.5 years; the study duration including follow up: 8.5 years; first patient: July 2004.

REFERENCES

2. Gelber, R. Session 7: Best use of adjuvant systemic therapies II; Chemotherapy aspects S30: predicting response to systemic treatments: learning from the past to plan for the future; oral presentation during the 9th International Conference on Primary Therapy of Early Breast Cancer. 26–29 January 2005, St. Gallen, Switzerland.
BIG 0-01/EORTC 10994: Sharing Some Good News about the \textit{p53} Study

By Hervé Bonnefoi, MD, (Study Chairman), Hôpitaux Universitaires de Genève, Geneva, Switzerland

The first BIG study of the third millennium is not so big in size with an initial target accrual of 1,440 patients, but it does ask a big question: which patients will benefit from taxanes? The aim of this trial is to identify predictive factors of response to chemotherapy. Specifically, the \textit{p53} gene will be analysed as a primary endpoint, the question being whether \textit{p53} mutated tumours respond better to taxanes than \textit{p53} wild type tumours. Importantly, besides the \textit{p53} gene, other predictive factors will be analysed in substudies.

The study design is summarized in Figure 1. In brief, patients with large operable breast cancer or locally advanced/inflammatory disease are randomised to receive as a neoadjuvant treatment either a non-taxane (arm A) or a taxane regimen with docetaxel (arm B). \textit{p53} is assessed using a functional assay in yeast, which detects biologically important mutations and is more sensitive than sequencing (it is insensitive to contamination of samples with normal tissue). There are two primary endpoints. The first will make separate comparisons of the normal \textit{p53} subgroup and the \textit{p53} mutated group with respect to progression-free survival (PFS) in patients who received a chemotherapy without taxanes (treatment A) versus those who received a chemotherapy with taxanes (treatment B). The second will be a comparison of PFS between patients who received treatment A versus those who received treatment B, independently of \textit{p53} status.

The secondary endpoints are distant metastasis free survival, overall survival, and toxicity.

We would like to share some good news with you:

1. As shown in Figure 2, the achieved accrual is excellent despite the requirement for a frozen tumour sample (2 trucuts) before inclusion in this trial. This requirement was a real concern when developing the trial, but does not seem to be an obstacle in our experience. The \textit{p53} study is an intergroup trial (European Organization for the Research and Treatment of Cancer [EORTC], Anglo-Celtic [ACCOG], Swiss [SAKK] and Swedish [SBCG] groups) and the accrual per group is shown in Figure 3.

2. The quality of the samples collected and analysed centrally is very good:

   • 86% of tumours (or patients) are eligible for \textit{p53} analysis with more than 20% tumour cells in at least one trucut.
   • The \textit{p53} functional test in yeast has succeeded in 99% of the tumours.
   • The quality and quantity of ribonucleic acid analysed with the Agilent bioanalyser (Agilent Technologies Inc., Palo Alto, CA) (with a picochip) is excellent in 65% of the cases and therefore can be used for cDNA microarray analysis.
3. In addition, several translational research substudies (TGIF studies) have been performed or are ongoing using frozen tumour samples collected in this trial (Figure 4).

- In the TGIF1 study, tumour samples from 49 patients were tested on Affymetrix (Affymetrix Inc, Santa Clara, CA) U133A gene expression microarrays. Previous microarray studies on breast cancer identified multiple tumour classes, of which the most prominent, named luminal and basal, differ in expression of the estrogen receptor gene. In our study, the main finding is the identification of a group of breast tumours with increased androgen signalling and a "molecular apocrine" gene expression profile (Oncogene in press). The molecular apocrine group differs in the expression of genes involved in androgen and lipid metabolism, which may have potential therapeutic implications.

- In the TGIF2 study, our goal is to identify a specific gene profile that predicts for a pathological complete response (pCR) after neoadjuvant chemotherapy, either with anthracyclines (TGIF2.1 study) or docetaxel (TGIF2.2). We are using the X3P Affymetrix chip. Currently, we are conducting the supervised analysis of 72 samples treated with anthracyclines in arm A of the EORTC 10994 trial (TGIF2.1 study) (23 pCR versus 49 non pCR). This is by far the largest prospective trial looking for a cDNA profile predicting for a pathological response to an anthracycline-based chemotherapy. Moreover, the addition of more samples from patients recently included in the main trial will allow confirmation (or not) of our findings using a completely independent set of patients. A second trial (the TGIF2.2 study) looking for a profile predicting for a pCR after docetaxel (patients treated in arm B) will begin soon.

- In TGIF3 we will assess whether the prognostic 70 gene profile of the Amsterdam group remains a prognostic factor in the p53 study patient population and whether this can also be a predictive factor (predicting for a pCR). This study should have important implications for the MINDACT trial, in which the prognostic and the predictive values of the 70 gene profile will be tested.

- The TGIF4 study will concentrate on the molecular biology of inflammatory breast cancers, in particular, the interaction between stroma and tumour tissue. Oligonucleotide arrays that detect single nucleotide polymorphisms arrays will be used after the microdissection of tumour cells and stroma.

4. Lastly, because we have fewer events than planned, we have decided to increase the target accrual from 1,440 to 1,850 patients. The target accrual should be reached in September 2006, and an interim analysis will be performed at that time for the p53 positive subgroup only, because it will be too soon to do so for the normal p53 subgroup.

The EORTC 10994/BIG 00-01 study is supported with grants from Aventis-Sanofi, Pfizer and the Widmer Foundation. The TGIF1 and 2 studies are supported with grants from the EORTC Translational Research Fund, the Swiss National Science Foundation NCCR Molecular Oncology program, and the MEDIC Foundation.
SUPREMO Trial (BIG 2-04)  
Funded by UK Medical Research Council

Launch date 17 June 2005

The international SUPREMO trial (BIG 2-04), assessing the role of postmastectomy radiotherapy in intermediate risk breast cancer, was funded by the UK Medical Research Council in November 2004. A generous grant of £2.112 million will support the recruitment of 3,700 patients over 4 years with 5 years of follow-up.

The trial includes a biological sub-study that will enable tumour tissue to be archived for future molecular markers of radiation sensitivity. This may help to identify patients most likely to benefit from adjuvant radiotherapy. In addition, there are sub-studies of quality of life, markers of cardiac damage from radiotherapy and/or chemotherapy, and health economics. The tissue archive will be held at the University of Glasgow by Dr. John Bartlett on behalf of the SUPREMO trial management group.

The main trial and biological sub-study, TRANS-SUPREMO, will run internationally. The quality of life, cardiac, and economic sub-studies will run in the UK alone.

The trial will run under the auspices of the BIG group. Interest in participation has been expressed by the European Organization for the Research and Treatment of Cancer (EORTC), Anglo Celtic Cooperative Oncology Group (ACCOG), Irish Clinical Oncology Research Group (ICORG), Dutch Breast Cancer Trials Cooperative Group (BOOG), National Cancer Institute of Canada (NCIC) and the Japanese Breast Cancer Research Group (JBCRG). Currently 41 UK and 38 international centres in 18 countries would like to participate.

Participating countries include the UK, Holland, France, Belgium, Germany, Hungary, Ireland, Poland, Sweden, Turkey, Australia, New Zealand, Hong Kong, Singapore, Egypt, and the Sudan.

TRIAL DESIGN

ELIGIBILITY

1. pT1, pN1, M0 unilateral histologically confirmed invasive breast cancer.
2. pT2, N0-N1,M0 unilateral histologically confirmed invasive breast cancer
3. Multifocal breast cancer if largest discrete tumour at least 2cm if N0.
4. If the tumour area comprises multiple small adjacent foci of invasive carcinoma then overall maximum dimension taken must be greater than 2cm if N0
5. Fit for adjuvant chemotherapy (if indicated), adjuvant endocrine therapy (if indicated) and postoperative irradiation
6. Undergone mastectomy (with minimum of 1mm clear margin) and axillary staging procedure
6.1 If axillary node positive (1-3 positive nodes) then an axillary node clearance (minimum of 10 nodes removed) should have been performed.
6.2 Axillary node negative status can be determined on the basis of either axillary clearance or axillary node sampling or sentinel node biopsy
7. Written, informed consent

NB. T2N0 tumours are eligible with grade III histology and/or lymphovascular invasion.

EXCLUSIONS

1. any pT0, pN0-1, or pT1, pN0 or pT3 or pT4
2. patients who have undergone neoadjuvant systemic therapy
3. previous or concurrent malignancy other than non-melanomatus skin cancer and cancer in situ of the cervix
4. male sex
5. pregnancy
6. bilateral breast cancer
7. known BRCA1 and BRCA2 carriers
8. not fit for surgery, radiotherapy or adjuvant systemic therapy
9. internal mammary nodes positive on sentinel node scintigraphy
10. unable or unwilling to give informed consent

TO CHEST WALL RADIOTHERAPY OR NO CHEST WALL RADIOTHERAPY

RANDOMISATION

Systemic chemotherapy and endocrine therapy as appropriate.

PRIMARY ENDPOINT

Overall survival at 5 years.
**Secondary Endpoints**

1. disease-free survival
2. metastasis-free survival
3. cause of death (breast cancer, intercurrent disease)
4. acute and late morbidity
5. quality of life
6. cost effectiveness

**Follow-Up**

10 years.

**Organisation**

**Data Management**

Data management will be provided by the Cancer Clinical Trials Team (formerly Scottish Cancer Therapy Network) in Edinburgh under the direction of Dr. Liz Foster, Principal Cancer Trials Coordinator.

**Trial Management**

The trial will be run by a multidisciplinary and international management group including representation from Breast International Group (BIG). The Medical Research Council (MRC) steering committee for the trial will be chaired by Professor Barry Hancock, Yorkshire Cancer Research Council (YCRC) Professor of Clinical Oncology at the University of Sheffield. There will be a separate data monitoring committee including Dr. Chris Frost (University of London) and Professor Nick James (University of Birmingham).

Members of the trial management group include: Dr. Ian Kunkler (PI) (Edinburgh), Dr. Peter Canney (Glasgow), Mr. Mike Dixon (Edinburgh), Dr. John Bartlett (Glasgow), Dr. Edwin Aird (Northwood), Dr. Angela Bowman (Edinburgh), Professor John Cairns (London), Dr. Martin Denvir (Edinburgh), Professor Alan Price (Edinburgh), Mr. Richard Sainsbury (London), Professor Robin Prescott (Edinburgh), Dr. Gerry Thomas (Swansea), Dr. Theresa McDonagh (London), Dr. Liz Foster (Edinburgh), Dr. Niall Anderson (Edinburgh), Dr. Nicola Russell (Amsterdam), Ms. Venetia Franglen, and representatives of BIG and the EORTC.

**Trial Launch 17 June 2005**

The trial will be launched at the Royal College of Physicians in Edinburgh on Friday 17 June 2005. The scientific programme will have a strong educational component with invited lectures from distinguished speakers.

In the meantime, the submission for national ethical approval in the UK and for sponsorship of the trial is being prepared.

For further information about the trial contact:

Dr Ian Kunkler  
Dept of Clinical Oncology  
University of Edinburgh  
Western General Hospital  
Edinburgh, EH4 2XU  
Tel: + 44 131 537 2214  
Fax: + 44 131 537 2216  
E-mail: I.Kunkler@ed.ac.uk

Dr Peter Canney  
Beatson Oncology Centre  
Western Infirmary  
Dumbarton Road  
Glasgow, G11 6NT  
Tel: + 44 141 211 1743  
Fax: + 44 141 211 1743  
E-mail: Peter.canney@northglasgow.scot.nhs.uk

Dr Liz Foster  
Principal cancer trials coordinator  
Cancer Trials Clinical Team  
NHS National Services Scotland  
Gyle Square  
1, South Gyle Crescent  
Edinburgh, EH12 9EB  
Tel: + 44 131 275 6283  
Fax: + 44 131 275 7512  
E-mail: liz.foster@isd.csa.scot.nhs.uk
### Ongoing BIG Trials

<table>
<thead>
<tr>
<th>BIG Trial</th>
<th>Coordinating Group</th>
<th>Participating Groups</th>
<th>QuestionAsked/Primary End Point</th>
<th>Target No. Pts</th>
<th>Accrual as of February 2005</th>
<th>Pharma Partners</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-98/Young patients/EORTC 1002</td>
<td>EORTC</td>
<td>GBG, IBCSG</td>
<td>Attitude toward risk of loss of fertility related to adjuvant therapies in patients with early breast cancer aged &lt; 35?</td>
<td>385</td>
<td>91</td>
<td>NA</td>
</tr>
<tr>
<td>1-00/p53/EORTC 10994</td>
<td>EORTC</td>
<td>ACCOG, SAKK, SBCG</td>
<td>P53 status and response to anthracyclines or taxanes?</td>
<td>1,850</td>
<td>1,260</td>
<td>Grants from Sanofi-Aventis and Pfizer; EORTC is sponsor</td>
</tr>
<tr>
<td>1-01/HERA/BO 16348</td>
<td>BrEAST</td>
<td>20 Big groups, 10 Roche-affiliated groups, plus approx. 100 independent centres</td>
<td>Comparison of 1 year vs 2 years vs no Herceptin® in women with Her2 + primary breast cancer who have completed adjuvant chemotherapy?</td>
<td>4,482</td>
<td>5,077</td>
<td>Roche</td>
</tr>
<tr>
<td>1-02/IBCSG 27/Locoregional relapse</td>
<td>IBCSG</td>
<td>ABCSG, ANZ BCTG, BOOG, GBG centres, GEICAM, NSABP</td>
<td>Benefit of adjuvant chemotherapy for radically resected locoregional relapse of breast cancer?</td>
<td>977</td>
<td>19</td>
<td>NA</td>
</tr>
<tr>
<td>2-02/SOFT/ IBCSG 24-02</td>
<td>IBCSG</td>
<td>ANZ BCTG, BrEAST, CESSG, DBCG, EORTC, GOCCHI, ICR-CTSU, NCIC-CTG, NCRI BCSG, SAKK, SBCG, TBCI, WMBG, YBCRG</td>
<td>Benefit of ovarian suppression given in addition to tamoxifen or aromatase inhibitor in ER+ patients who receive CT and resume menses afterwards?</td>
<td>3,000</td>
<td>136</td>
<td>Pfizer</td>
</tr>
<tr>
<td>3-02/TEXT/ IBCSG 25-02</td>
<td>IBCSG</td>
<td>ANZ BCTG, BrEAST, ICR-CTSU, SAKK, TBCI</td>
<td>Benefit of tamoxifen vs aromatase inhibitor for ER+ patients receiving GnRH analogue?</td>
<td>1,845</td>
<td>284</td>
<td>Pfizer</td>
</tr>
<tr>
<td>4-02/PERCHE/ IBCSG 26-02</td>
<td>IBCSG</td>
<td>ANZ BCTG, BrEAST, ICR-CTSU, SAKK, SBCG, TBCI</td>
<td>Is CT necessary for low-risk premenopausal endocrine-responsive patients?</td>
<td>1,750</td>
<td>5</td>
<td>Pfizer</td>
</tr>
<tr>
<td>5-02/IBIS II</td>
<td>IBIS</td>
<td>ANZ BCTG, BOOG, DBCG, GBG, NCRI BCSG, SAKK, SBCG,</td>
<td>Effectiveness of anastrozole vs placebo in preventing breast cancer in healthy, high-risk postmenopausal women and comparison between tamoxifen and anastrozole in postmenopausal women with DCIS?</td>
<td>10,000</td>
<td>535</td>
<td>Astra Zeneca, partial support (unrestricted educational grant)</td>
</tr>
<tr>
<td>2-03/GBG 29</td>
<td>GBG</td>
<td>ABCSG, BOOG</td>
<td>What can we learn about the diagnosis, treatment, and maternal/foetal outcome of patients with breast cancer during pregnancy (prospective register study)?</td>
<td>1,500</td>
<td>34</td>
<td>NA</td>
</tr>
<tr>
<td>1-04/AZURE NCRI BCSG / U. Leeds Trials Unit</td>
<td>NCRI BCSG</td>
<td>ACCOG, GOIRC, ICORG, ICR-CTSU, VCOG, WMBG YBCRG,</td>
<td>Benefit of zoledronic acid in (neo)adjuvant setting for improving bone metastasis and overall DFS in stage II/III breast cancer patients?</td>
<td>3,500</td>
<td>1,317</td>
<td>Novartis</td>
</tr>
<tr>
<td>4-04/ICE</td>
<td>GBG</td>
<td>WSG</td>
<td>What is the role of adjuvant chemotherapy; ibandronate with or without capecitabine in elderly patients with early breast cancer?</td>
<td>1,394</td>
<td>110</td>
<td>Roche/Astra Zeneca</td>
</tr>
<tr>
<td>1-03/REACT/ICCG C20/001, GBG 27</td>
<td>ICCG/GBG</td>
<td>BOOG, CEEOG, DBCG, GECO PERU, GOCCHI, ICORG</td>
<td>Benefit of 2 years adjuvant chemotherapy with celecoxib compared with placebo in primary breast cancer patients?</td>
<td>2,590</td>
<td>1</td>
<td>Pfizer</td>
</tr>
<tr>
<td>3-05/GBG 26/TBP</td>
<td>GBG</td>
<td>BOOG</td>
<td>Benefit of capecitabine with Herceptin® (H) in patients with HER2+ metastatic breast cancer and progression after previous (H) treatment?</td>
<td>482</td>
<td>53</td>
<td>Roche</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>33,555</strong></td>
<td><strong>8,922</strong></td>
<td></td>
</tr>
</tbody>
</table>
### Updates on Other BIG Trials

#### Soon-to-Start/Planned BIG Trials

<table>
<thead>
<tr>
<th>BIG Trial</th>
<th>Coordinating Group</th>
<th>Participating / Interested Groups</th>
<th>Question Asked</th>
<th>Target No. of Patients</th>
<th>Pharma Partners</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-04/ SUPREMO</td>
<td>ACCOG / CTTT</td>
<td>ANZ BCTG, CEEOG, EORTC, GEOC PERU, HBSS, ICRG, IBCTG, NCIC CTG</td>
<td>What is the role of adjuvant chest wall irradiation in &quot;intermediate-risk&quot; operable breast cancer following mastectomy and axillary clearance?</td>
<td>3,500</td>
<td>NA</td>
</tr>
<tr>
<td>3-04/ MINDACT</td>
<td>EORTC</td>
<td>ABCSG, ABS at BASO, ACCOG, BOOG, DBCG, GBG, GEOC PERU, GOCCHI GOIRC, HBSS, IBCTG, ICRG, ICR-CTSU, NCRI BCCTG, SAKK, SBCG, SOETI, WSG, YBCRG</td>
<td>Will gene profile signature be a better prognostic tool to help in adjuvant decision-making than traditional clinical/pathological factors in node-negative breast cancer patients?</td>
<td>6,000</td>
<td></td>
</tr>
<tr>
<td>1-05 CASA / IBCSG 32-05</td>
<td>IBCSG</td>
<td>ANZ BCTG, BBOG, GEOC PERU, GOCCHI, ITMO, MOSG, SAKK, SBCG</td>
<td>Role of adjuvant Pegylated Liposomal Doxorubicin (PLD, Caelyx®) for women (age 66 years or older) with endocrine nonresponsive bc NOT suitable for &quot;standard&quot; CT?</td>
<td>1,296</td>
<td>Schering</td>
</tr>
<tr>
<td>2-05 ACTION</td>
<td>ICR-CTSU</td>
<td>ACCOG, BOOG, EORTC, NCRI BCTG, YBCRG</td>
<td>CT versus non CT for older ER negative / poor patients (aged ≥ 70)?</td>
<td>1,000</td>
<td>Under negotiation</td>
</tr>
</tbody>
</table>

#### Recently Closed BIG Trials

<table>
<thead>
<tr>
<th>BIG Trial</th>
<th>Coordinating Group</th>
<th>Participating Groups</th>
<th>Question Asked</th>
<th>No. of Patients</th>
<th>Reason for Closure</th>
<th>Pharma Partners</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-97/ MA.17</td>
<td>NCIC CTG</td>
<td>EORTC, IBCSG, TBCI</td>
<td>Benefit from letrozole (5 yr) after 5 yr of tamoxifen?</td>
<td>5,187</td>
<td>Reached target accrual; study outcome positive</td>
<td>Novartis</td>
</tr>
<tr>
<td>2-97/ CCC13/96</td>
<td>ICCG</td>
<td>ABCG, ANZ BCTG, CEEOG, DBCG, EORTC, FBSG, GEAG, GEICAM, GOIRC, GONO, IBCSG, ICORG, ITMO, NBCG, NWEG, SBOG, US Oncology, WCTN, YBCRG</td>
<td>Tamoxifen versus exemestane: superior to tamoxifen alone?</td>
<td>4,743</td>
<td>Reached target accrual; study outcome positive</td>
<td>Pharmacia</td>
</tr>
<tr>
<td>3-97/ HABITS</td>
<td>SBCG</td>
<td>EORTC (individual centres), GOCCHI, IBCTG</td>
<td>Hormone replacement therapy: safe after radically treated in situ, stage I or II breast cancer (&lt; 4 positive nodes)?</td>
<td>447</td>
<td>Following IDMC recommendations</td>
<td>NA</td>
</tr>
<tr>
<td>1-98/ IBCSG 18-98</td>
<td>IBCSG</td>
<td>DBCG, FBSG, Novartis group</td>
<td>Sequencing of tamoxifen/letrozole or letrozole/tamoxifen superior to either agent alone?</td>
<td>8,028</td>
<td>Reached target accrual; first analysis positive</td>
<td>Novartis</td>
</tr>
<tr>
<td>2-98/ TAX 315</td>
<td>BrEAST</td>
<td>ABCSG, DBCG, GEICAM GOCCHI, IBCTG, ICRG, SBCG</td>
<td>Incorporation of Taxotere® in sequence or combination with Adriamycin: benefit to patients?</td>
<td>2,887</td>
<td>Reached target accrual</td>
<td>Aventis</td>
</tr>
<tr>
<td>4-98/ EORTC 10963 / PEAT</td>
<td>EORTC</td>
<td>DCBIC, ICCC, YBCRG</td>
<td>Inhibitory effect of perioperative Faslodex® on development of metastasis, measured by DFS and OS?</td>
<td>20</td>
<td>Low accrual</td>
<td>Astra Zeneca</td>
</tr>
<tr>
<td>2-00/ EORTC 10974 / Lamanoma</td>
<td>EORTC</td>
<td>CEEOG, GOCCHI, ICCC</td>
<td>Benefit of conservative local therapy (vs mastectomy) in locally advanced breast cancer?</td>
<td>23</td>
<td>Low accrual</td>
<td>NA</td>
</tr>
</tbody>
</table>

**Total**

- **Soon-to-Start/Planned BIG Trials**
- **Recently Closed BIG Trials**

---

**ABBREVIATIONS:**

- ABCG = Argentine Breast Cancer Group
- ABCSG = Austrian Breast Cancer Study Group
- ABS at BASO = Association Breast Surgeons at British Association of Surgical Oncology
- ACCOG = Anglo Celtic Cooperative Oncology Group
- ANZ BCTG = Australian New Zealand Breast Cancer Trials Group
- BIG = Breast International Group
- BOOG = Dutch Breast Cancer Trialists Cooperative Group
- BrEAST = Breast European Adjuvant Studies Team
- CEEOG = Central and East European Oncology Group
- CTTT = Cancer Clinical Trials Team
- CT = chemotherapy
- DBCG = Danish Breast Cancer Cooperative Group
- DCIS = ductal carcinoma in situ
- DFS = disease-free survival
- EORTC = European Organization for the Research and Treatment of Cancer
- ER+ = estrogen receptor positive
- ESE = Exemestane Adjuvant Evaluation Group
- ESG = German Breast Group
- ENZ ROC = Estudios Nederlandse Onderzoek Collectief
- EGF = French Breast Study Group
- EGEAM = Grupo Español de Adyuvancia de Mamario
- GNO = Gruppo Oncologico Nord-Ovest
- HBSS = Hellenic Breast Surgical Society
- IBCSG = International Breast Cancer Study Group
- ICR-CTSU = Institute of Cancer Research, Clinical Trials and Statistics Unit
- IDMC = Independent Data Monitoring Committee
- ITMO = Italian Trials in Medical Oncology
- ITC = Italian Trials in Medical Oncology
- NA = not applicable
- NSABP = National Surgical Adjuvant Breast and Bowel Project
- NWEG = North West England Cancer Group
- OS = overall survival
- SAKK = Swiss Group for Clinical Cancer Research
- SBCG = Swedish Breast Cancer Group
- SOLTI = Grupo Español de Estudio, Tratamiento y otras Estrategias Experimentales en Tumores Sólidos
- TBCI = The Breast Cancer Intergroup of North America
- VCOG = Victorian Cooperative Oncology Group
- WCTN = Wales Cancer Trials Network
- WMBG = West Midlands Breast Group
- WSG = Westdeutsche Studien Gruppe
- YBCRG = Yorkshire Breast Cancer Research Group
News from BIG Groups

Prevention of Chemotherapy-induced Menopause by Temporary Ovarian Suppression with Triptorelin vs Control in Young Breast Cancer Patients. A Randomised Phase III Multicenter Study

Acronym: PROMISE (PRevention Of Menopause Induced by Chemotherapy. A Study in Early Breast Cancer Patients)

By Lucia Del Mastro, MD, Medical Oncology, National Cancer Research Institute, Genoa, Italy

BACKGROUND AND AIMS

Nearly 25% of women diagnosed with breast cancer are premenopausal and almost all are candidates for adjuvant chemotherapy (CT). As a consequence of such a treatment the majority of these patients develop early menopause. Commonly used CT regimens, such as CMF or CEF induce menopause in more than 60% of patients. Its occurrence rises with increasing age, ranging from 22% to 61% in women under 40 years of age and from 61% to 97% in those over 40. Premature menopause has significant consequences such as hot flashes and night sweats, psychosocial problems, atrophic vaginitis, dyspareunia, skeletal osteoporosis with consequent fractures, cardiovascular effects and loss of fertility. This latter effect is a major concern for young women, and in nearly 29% of cases it does influence treatment decision.

Standard methods to prevent CT-induced early menopause are unavailable to date. Current attempts to preserve ovarian function are mainly based on invasive procedures, such as cryopreservation and reimplantation of ovarian tissue not easily available in all centers. Hormonal methods may offer an important strategy to reduce the gonadal toxicity of CT. Chronic administration of luteinising hormone-releasing (LH-RH) analogs decreases follicle-stimulating hormone (FSH) secretion and suppresses gonadal function. In female rats and rhesus monkeys this approach has been demonstrated to be useful. In female cancer patients, data come from a small phase III negative study (1) and from 3 phase II positive studies (2-4). We previously performed an additional phase II study that enrolled 30 patients, and we achieved menopause preservation in 80% of patients by administering goserelin prior and during CT (5).

The PROMISE study is a prospective, multicentric, open label, randomized phase III study aimed to evaluate the incidence of CT-induced early menopause in young breast cancer patients treated with triptorelin (3.75 mg) (experimental arm) prior to and during adjuvant CT as compared to women receiving CT without triptorelin (control arm). In patients randomized to receive triptorelin, the first dose will be administered intra-muscularly at least one week and no more than 4 weeks before CT and then every 4 weeks for the duration of CT. The last administration of triptorelin will be given before the last cycle of CT.

PATIENT ELIGIBILITY SUMMARY

Stage I-II-III breast cancer patients with completely locally excised breast carcinoma; age ≥ 18 and ≤ 45; premenopausal status defined as the presence of active menstrual cycles or normal menses within six weeks before initiation of CT and FSH, LH and E2 in the premenopausal range. The type of adjuvant CT schedules allowed are the following: FE_60-75-90-100C; CMF; A→CMF; EC→Paclitaxel; FEC→paclitaxel; EC→docetaxel; AC; AC→Paclitaxel; E→CMF.

DATA COLLECTION

Patient data are collected by a remote data entry procedure and analyzed at Centro Trials e Sperimentazioni Cliniche Controllate of the National Cancer Research Institute – Genova (Statisticians: Paolo Bruzzi, Luca Boni).
**FOLLOW UP**

Menopausal status assessment will be done at 3, 6, 9 and 12 months after the last cycle of CT. Evaluation of long-term maintenance of ovarian function will be done 36 months after the start of CT.

**STATUS OF THE PROTOCOL**

Active from September 1, 2003  
No. of enrolled patients: 47 (status as of February 2005)  
No. of participating centers: 16

**SAMPLE SIZE**

Assuming an incidence of permanent menopause following CT of 60% (defined as the proportion of patients not menstruating within 1 year of termination of CT), for alpha=0.05 (2-sided) and beta=0.1 (90% power), 140 patients per arm will be needed in order to detect a 20% absolute reduction (from 60% to 40%) in the incidence of menopause in the experimental arm.

**TRIAL SUPPORT**

The PROMISE trial is sponsored by National Cancer Institute-Genoa. Research grants from the Associazione Italiana per la Ricerca sul Cancro were obtained in 2003 and 2004. Ipsen S.p.A, Milano, Italy supplies the drug triptorelin.

Investigators interested in more details should contact the study coordinator, Dr. Lucia Del Mastro, at Oncologia Medica A, Istituto Nazionale per la Ricerca sul Cancro, L.go R. Benzi 10, 16132 Genoa, Italy; lucia.delmastro@istge.it or the scientific secretary, Dr. Tiziana Catzeddu, at tiziana146@supereva.it; Tel: +390105600666 or Fax: +390105600850.

**REFERENCES**


---

**TRANSBIG News**

TRANSBIG¹ and MINDACT preparation activities are ongoing and will be reported on in future issues. In the meantime, please consult our website <www.breastinternationalgroup.org> for further information, or direct inquiries to <transbig@bordet.be>

---

¹TRANSBIG is a translational research network founded by BIG in 2004. It is partially funded by the European Commission, the Breast Cancer Research Foundation and the Prix Mois du Cancer du Sein. The funding organizations are not to be held responsible for any of the views expressed by TRANSBIG consortium partners or BIG/TRANSBIG staff.
Upcoming Events

First Brussels Breast Cancer 5K Walk/10K Run

In 2005, the American Women’s Club of Brussels (asbl) conceived the Brussels Breast Cancer 5K Walk/10K Run to honour our sisters, mothers, aunts, cousins, and friends who are fighting breast cancer. This event, being held in Brussels on 15 May, will be the first of its kind in Belgium. The hope is that it will grow, and attract more participants and raise more funds each year, until the fight against breast cancer is won. The AWCB’s partner institutions and recipients of the proceeds from this year’s events are the Jean-Claude Heuson Fund (e-mail: fonds.heuson@bordet.be) and the Breast International Group (BIG; www.breastinternationalgroup.org), both located at the internationally renowned Jules Bordet Institute (www.bordet.be). More information about the event and its sponsors can be found on the American Women’s Club of Brussels’ website (www.awcb.org).

The Jean-Claude Heuson Fund was created by the family and friends of Professor Jean-Claude Heuson, after his unexpected death in 1986. Professor Heuson had founded a breast cancer research laboratory in 1960 at the Jules Bordet Institute, and through the Heuson Fund, the continuation of his work could be ensured. The objective of the Heuson Fund is to support fundamental, translational, and clinical research in breast cancer. In the field of fundamental research, the Heuson Fund provides support to the J.C. Heuson Laboratory of Breast Cancer Research, which focuses its research on estrogen receptors and their genetic role in breast cancer. The Translational Research Unit (TRU) focuses on finding biological markers of prognostic and predictive value, and on the mechanisms of resistance and response to therapy. The aim is to better individualize the treatment of breast and other cancer patients. TRU works in close collaboration with the Microarray Laboratory, directed by Dr. Christos Sotiriou, and is also supported by the Heuson Fund. This laboratory (created in 2001) is a leader in the researching and identifying of DNA markers and defining the gene profile of individual tumors.

The Breast International Group was incorporated as a non-profit organization in 1999 to facilitate international collaboration in breast cancer research. It is a network of over 30 collaborative groups with main offices in Europe, Canada, Latin America, Australia/New Zealand and Japan, linked to approximately 3,000 hospitals and research centers. BIG also maintains ties and runs studies with The Breast Cancer Intergroup of North America. With BIG clinical trials accounting for the recruitment of over 60,000 patients, the association is an impressive integrating force in the breast cancer research arena. BIG contributes to the efficient conduct of difficult trials and to a decrease in the duplication of research efforts. BIG has also been able to develop a model for partnership with the pharmaceutical industry that preserves academic independence while fulfilling all regulatory requirements. For translational research, BIG recently founded TRANSBIG, which is partially funded by the European Commission. Its first study, the MINDACT trial, will compare micro-array technology to traditional methods for assessing the risk of breast cancer recurrence in lymph node negative patients, with the potential to spare up to 20% of women with lymph node negative breast cancer from chemotherapy and its side-effects. There are currently over 20 trials on the BIG roster, covering a wide spectrum of breast cancer research, including (neo) adjuvant chemotherapy and endocrine trials, novel biological treatments, and surveys. BIG/TRANSBIG is chaired by Dr. Martine Piccart.
NOTICE TO MEMBERS: BIG AND TRANSBIG MEETINGS

The next BIG/TRANSBIG meetings will take place as follows:

during ASCO, Orlando,
Sunday 15 May 2005, BIG General Assembly (for BIG members);

during ECCO 13**, Paris,
TRANSBIG meetings Saturday 29 October 2005 (for consortium members, by invitation),
BIG meeting Sunday 30 October 2005, details TBA (for BIG members).

**NB. Meeting days were reported incorrectly in the Winter 2005 BIG Newsletter; the correct days are as indicated here.

We are grateful to the following companies for their contributions to the Secretariat in the form of
unrestricted educational grants to support our communications activities other than this newsletter,
which is supported by Schering-Plough: Novartis, AstraZeneca, Johnson & Johnson, Amgen Europe,
Aventis, Eli Lilly, F. Hoffman-La Roche and Bristol-Myers Squibb.

PLEASE HELP US TO REFINE OUR MAILING PROCEDURE…

Fax this form to BIG at +32 2 541 3199. Please print clearly

I have received this by post, but would prefer to receive future newsletters via email.
Name: _________________________________________________________________________________________
Affiliated BIG group (if any): _______________________________________________________________________
E-mail address: __________________________________________________________________________________

I have received this newsletter via e-mail, but would prefer to receive future newsletters as hard copy.
Please provide:
Name: ___________________________________________________________________________________________
Institution: _____________________________________________________________________________________
Address: ________________________________________________________________________________________

If you know of colleagues that would also like to receive this newsletter, please provide:
Name __________________________________________________________
Institution _______________________________________________________
Mailing or email address __________________________________________

If you wish to be removed from our distribution list, please provide:
Name __________________________________________________________
Institution _______________________________________________________

New to Cambridge
Breast Cancer Online
www.bco.org
A FREE online resource for healthcare professionals

Have you discovered Breast Cancer Online?
BCO provides a FREE electronic source of peer-reviewed data and your gateway to breast cancer research on the internet.

An essential resource
Breast Cancer Online is dedicated to the promotion and dissemination of the latest information; from core basic knowledge to state-of-the-art research. The content of the website is invited and reviewed by an independent international editorial board of experts from a multi-disciplinary perspective. Breast Cancer Online is intended for healthcare professionals with an interest in breast cancer research, treatment and care.

Featuring
- Focus On – providing timely reviews of topical or controversial subject areas
- Expert Opinion – discussion and analysis of interesting clinical cases by leading international experts
- Case Studies – notable real examples from clinical practice
- Journals Club
- Journals Watch
- Email content alerts
- Conference reports and calendar

To benefit from what Breast Cancer Online has to offer, register for free at www.bco.org