EUROPA DONNA—The European Breast Cancer Coalition

Deirdre O’Connell, Vice President EUROPA DONNA—The European Breast Cancer Coalition, Chair Europa Donna Ireland, The Irish Breast Cancer Campaign

EUROPA DONNA—The European Breast Cancer Coalition was founded in 1994 and works to raise public awareness of breast cancer and to mobilize the support of European women in pressing for improved breast cancer education, appropriate screening, optimal treatment and care, as well as increased resources for breast cancer research. Membership is open to all European countries (as defined by the World Health Organization) and currently stands at 37. Membership of the National Fora comprises patients, female health professionals, breast cancer-related organisations and institutions, and others wishing to identify with the fight against breast cancer.

As a result of a concept presented at the EUSOMA Congress in Paris in 1993 by Professor Umberto Veronesi, EUROPA DONNA was established as an educational programme of the European School of Oncology in Milan with the support of Dr. Alberto Costa. The first EUROPA DONNA Pan-European conference was held in Milan in 1994 under the guidance of founding President Gloria Freilich and a board of women representing various European countries. The organisation, now fully independent, is well established as Europe’s breast cancer advocacy organisation and recognized as such by the institutions of the European Union (EU).

(continued on page 3)
In recent issues of the BIG Newsletter, we have highlighted several types of positive collaborations that have developed between academic research groups around the world and between industry and academia. What we hope to have conveyed is that a spirit of openness and collaboration is vital to all our research endeavours.

While the collaborative process is inevitably fraught with challenges, including occasional setbacks that send us back to the drawing board to reevaluate our positions and to come up with new and creative solutions, the benefits are many. This was recently highlighted by the presentations of the trastuzumab trials (to be featured in an upcoming newsletter) at ASCO 2005. As echoed by Deirdre O’Connell, Vice-President of EUROPA DONNA—The European Breast Cancer Coalition, “collaboration is not easy and poses challenges for all of us, but we all have the same aim, which is the development of ever more effective treatments for women with breast cancer.”

Our lead article in this issue therefore focuses on the critical role played by patient advocates in the research process. In the European context, EUROPA DONNA provides such leadership, by acting as the link between patients, the scientific community, and political decision makers.

Similar broad collaborations are also in their early stages with regard to fundraising initiatives that involve BIG. The articles on the first Brussels Breast Cancer Walk Run and the Jean-Claude Heuson Fund highlight this, another new frontier in our efforts to generate awareness about breast cancer, the essential role of research, and the need to secure adequate funding to ensure that such progress continues.

We are certain that we are only at the beginning of realizing the potential of our collaborative partnerships and look forward to the many fruits these will bear.

Martine Piccart
Carolyn Straehle

Watch for upcoming issues on targeted therapy trials (trastuzumab), the EU Clinical Trials Directive, and 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 Ten Goals of EUROPA DONNA are as follows:

- To promote the dissemination and exchange of factual, up-to-date information on breast cancer throughout Europe
- To promote breast awareness
- To emphasize the need for appropriate screening and early detection
- To campaign for the provision of optimum treatment
- To ensure provision of quality supportive care throughout and after treatment
- To advocate appropriate training for health professionals
- To acknowledge good practice and promote its development
- To demand regular quality assessment of medical equipment
- To ensure that all women understand fully any proposed treatment options, including entry into clinical trials and their right to a second opinion
- To promote the advancement of breast cancer research

From its foundation EUROPA DONNA has maintained a close connection with scientists and clinicians in the field, initially through its relationship with EUSOMA and subsequently with EORTC, when all three groups worked together to create the European Breast Cancer Conferences, the first being held in Florence in 1998. This historic initiative involved an advocacy group as an equal partner in a scientific conference for the first time and the partnership has developed and strengthened over subsequent years and subsequent conferences, with EUROPA DONNA acting as co-chair.

This connection means that EUROPA DONNA has always been very conscious of the need to inform and educate women and decision makers at national and European levels as to the optimum conditions for the diagnosis and treatment of breast cancer, which is illustrated by the Ten Goals. Breast cancer mortality rates still vary immensely, not only between countries, but also between regions within countries and even between hospitals in the same region. The essential role played by standards and guidelines is very clear to us. EUROPA DONNA is also very conscious of the essential role played by research in improving treatments for women with breast cancer and works to inform women in this area. EUROPA DONNA has established an annual Advocacy Course (now funded by the European Commission) where delegates from member countries are briefed on current directions in breast cancer research and treatment by leading European physicians and researchers, and also receive communications training. EUROPA DONNA Pan-European Conferences also provide an opportunity to inform and educate our members, as does attendance at the European Breast Cancer Conferences. The result is that we are building a corps of informed advocates, mostly breast cancer survivors, who will campaign, along with professionals, for the best possible breast cancer services for European women, including access to research.

The strong connection with the scientific community also means that EUROPA DONNA is committed to communicating the views and needs of women to scientists and clinicians, and the European Breast Cancer Conferences provide a useful forum for such communication, as does our representation on a number of scientific and medical committees. Our involvement in BIG has led us to participate in committees of trials such as BIG 1-01/HERA and BIG 3-97/HABITS, and we have been following closely the development of translational research. Aware as we are of the importance of translational research, we are very pleased to sit on the Steering Committee, the Ethical Legal Committee, and the Spreading of Excellence Committee of TRANSBIG. TRANSBIG is in its early stages, but it is to be hoped that it will provide a model for the inclusion of patient advocate groups in the research process in Europe. It is an exciting development for patient advocates to be involved in a trial such as the BIG 1-01/HERA trial and to see results such as those announced at the American Society of Clinical Oncology annual meeting this past May. Every improvement in mortality and every improvement in quality of life is of vital importance to us.

Developments in biomedical research have improved prospects for treatment tailoring in the clinic, but also raise issues of concern to us. The use of biological materials, informed consent, patient confidentiality, and the consequences for patients and their families resulting from germline genetic testing are among the ethical issues that come with the new developments. EUROPA DONNA has facilitated discussion on these issues, both among its members and by communicating its concerns to the scientific community. As always, awareness of each other’s points of view is the key to mutual collaboration.

It seems to me that an advocacy group such as EUROPA DONNA can play a useful role in bringing stakeholders together. At the European level and in some of our member states we have brought the research community together with politicians to inform the politicians of best standards in breast cancer services and of the need for support for research. Since we began lobbying at the European level we have stressed the need for greatly increased funding of independent research. The Breast Cancer Resolution presented to the European Parliament in June 2003 by Karin Jöns, MEP and President of Europa Donna Forum Germany, included the following section, paragraph 6, which

“For the allocation of EUR 400 million for cancer research in the sixth framework programme of research and calls on the Commission and the Member States to:

a. ensure more effective coordination between national and European research,

b. ensure that evidence-based medicine also constitutes the basis for breast cancer treatment in Europe,
c. incorporate the positive findings of fundamental research into treatment as soon as possible and further strengthen clinical research, in particular the clinical trials coordinated by the European Organisation for Research and Treatment of Cancer (EORTC) and conducted in cancer centres and clinics across the EU,
d. provide more funding than in the past for breast cancer research in order to:
   • step up the search for the causes of the disease and for forms of therapy,
   • improve prediction of the effect of treatment and certainty of outcomes,
   • further investigate the relationship between breast cancer and potential risk factors such as tobacco, diet, hormones and life-style (body weight, physical activity),
   • increase research into in-patient and out-patient treatment protocols, with a view to reducing the unnecessary burden on patients of clinical and medical treatment services, and
   • develop a method for the standardised risk assessment of women potentially in danger of developing a hereditary breast disease.

The European Parliamentary Group on Breast Cancer (EPGBC), for which EUROPA DONNA provides the secretariat, brings experts in to advise it on various relevant aspects of breast cancer care and treatment.

At the European level EUROPA DONNA has become involved in the wider patient advocacy movement. We are founder members of the European Patients’ Forum, whose organisations have a mutual interest in research. We very much welcome the foundation of the European Cancer Patient Coalition (ECPC) as a significant addition to the voice of the cancer patient in Europe. EUROPA DONNA is also a member of the EU Health Policy Forum set up by the European Commission’s Health and Consumer Protection Directorate-General (DG SANCO), which provides another forum for our informed input and where we support professional groups calling for more research funds.

There is no doubt that there is a need for much greater public awareness of research and of clinical trials. Public knowledge of clinical trials is low and probably inaccurate.

EUROPA DONNA has published a booklet *Clinical Trials and Breast Cancer*, designed to give women diagnosed with breast cancer the information they need. The booklet is intended to be a public education piece for well women, so that they know something about trials before they must make a decision concerning participation. However, the occasion of a cancer diagnosis is a very difficult and challenging time for patients and the more informed the population at large is about clinical trials the more likely newly diagnosed patients are to agree to participate. Both patient groups and the research community need to collaborate to develop a better informed public. Including patient groups in the administration and conduct of research should result in more patient friendly procedures, and EUROPA DONNA is committed to involvement in this area. We are also, of course, very aware of the effects on independent research of the EU Directive on Clinical Trials (Directive 2001/20/EC) and continue to inform ourselves on this.

What is the future for collaboration in the field of breast cancer between patient groups and the scientific community? Collaboration has been established at the European level, largely as a result of the relationship begun at the foundation of EUROPA DONNA and continued through the European Breast Cancer Conferences. In our member countries there is much room for improvement. In some countries the role of the patient advocate on the Ethical Committees and other administrative committees of clinical trials is reasonably well established and accepted. In other countries this is not the case. EUROPA DONNA would like to see this situation change because we are convinced that patient advocates can play a very positive role on these bodies. We believe that training is vital for all members of these committees, including patient advocates. There is also the question of funding research areas that women themselves may feel are neglected, examples being psychosocial research and survivor studies.

Collaboration is not easy and poses challenges for all of us, but we all have the same aim, which is the development of ever more effective treatments for women with breast cancer. For its part, EUROPA DONNA will be working towards achieving the maximum benefit for present and future breast cancer patients by facilitating translational research resulting in better treatment outcomes, while ensuring that patient concerns are met satisfactorily.
First Brussels Breast Cancer Walk/Run Attracts Hundreds to Tervuren Park

“What a beautiful event,” enthused one runner, echoing the feelings of most of the 670 runners and walkers and 102 volunteers at the first annual Brussels Breast Cancer 5K Walk/10K Run in Tervuren Park on Sunday, May 15.

Pomi Kershaw, The American Women’s Club of Brussels, asbl/vzw, chairperson for the event, said that while the organizers hoped to raise a good sum of cash for cancer research at the Jules Bordet Institute, another goal of the event was to increase awareness of breast cancer, encourage women to go for cancer screening exams, and spread the word about cancer support organisations available to Brussels residents.

“We estimate that for every participant or volunteer, there are at least five other people in that person’s life who were aware of our walk/run and gave some extra thought to breast cancer today,” said another organizer. “Roughly 4,000 more people thinking about breast cancer—that’s a good start! That we also raised close to 15,000 euros for breast cancer research in Belgium gives us all the energy and enthusiasm we’ll need to start planning next year’s event.”

Many of the runners training for the Brussels 20K found the 10K to be a good warm-up. One runner complimented “the wonderful volunteers who yelled words of support and pointed which way to go along the route.” A walker said, “the venue could not have been more perfect…the walk was spectacular.” Most participants were motivated by more than a desire for a good morning’s exercise, however. As Canadian runner Kim Freeland put it, “I have paid tribute to some dear friends and family members who have lost their battles with cancer. You gave me an opportunity to fight on their behalf.”

The American Women’s Club of Brussels, asbl/vzw, wishes to thank all the sponsors who took a chance on this first-year event. Many sponsors showed their support not only with money, but with whole-hearted participation on the day.

Thanks also go to WE CARE, the English-speaking cancer support group that provided pamphlets and books about cancer. Many people stopped to pick up literature and learn about the event’s beneficiaries, the Jean-Claude Heuson Fund, Breast International Group, and Kom op Tegen Kanker.

The American Women’s Club of Brussels, asbl/vzw, was founded in 1949 by 36 American women residents in Belgium. Since then, the Club has grown to a membership that has exceeded 600 in recent years. The AWCB is also one of the few American women’s clubs overseas to own its own Clubhouse, complete with library, English language videos, and tea room. The Club’s primary objectives have remained the same throughout the years: to organise a center for philanthropic, social, and cultural activities for its members, to engage in welfare and cultural activities that will contribute to closer Belgo-American understanding, and to foster fellowship for the American women resident in Brussels and environs. For more information, consult <www.awcb.org>
Professor Jean-Claude Heuson founded a breast cancer research laboratory in 1960 at the Jules Bordet Institute in Brussels, Belgium. When he died unexpectedly in 1986, his family and friends donated funds to the breast cancer unit to ensure that his work would continue. Thus was born the Jean-Claude Heuson Fund to promote research in breast cancer.

The objective of the Heuson Fund is to support fundamental research, translational research, 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 patients with breast and other cancers. TRU works in close collaboration with the Microarray Laboratory directed by Dr. Sotiriou and also supported by the Heuson Fund. This laboratory—created in 2001—is a leader in the research and identification of DNA markers and defining the gene profile of individual tumours.

The financial backing that the Fund provides for breast cancer research comes from donations made by individuals and private institutions alike. Other sources of funding include charity events that take place throughout the year, such as concerts, exhibitions, Christmas markets, show jumping, golf, raffles, and sales of CDs, etc. The Fund has also published two books on breast cancer that are available free of charge to patients and their families: La voix de la sérénité en réponse à celle des inquiétudes/De kracht van de berusting tegen het knagen van de onrust and Ce que vous aimeriez savoir sur le cancer du sein/Wat wilde je weten over borstkanker? These are currently only available in French and Dutch. Further information can be obtained by contacting the Fund directly.

Donations can be made to the following account: 001-2704927-61 of the Fonds Jean-Claude Heuson Recherche en Cancérologie Mammarie (donations of 30 Euro or more are tax deductible. A receipt for tax purposes is sent to the person making the donation).

Contact Information:
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The Jean-Claude Heuson Fund at the Jules Bordet Institute in Brussels
News about BIG Studies

BIG 3-98/EORTC 10002 Intergroup Study: SURVEY

A Survey of the Breast International Group to Assess the Attitude of Patients Aged Less than 35 Years with Early Breast Cancer towards the Potential Risk of Loss of Fertility Because of Adjuvant Treatment

ELIGIBILITY

The eligibility criteria are simple and include being female age \( \leq 35 \) at the time of diagnosis, still premenopausal and relapse-free at the time of registration, and having a histologically confirmed early breast cancer. The questionnaire is administered once after registration.

QUESTIONNAIRE

The questionnaire includes nine questions pertaining to the situation of the patient (children before and/or after diagnosis, wish for (additional) children, presence of regular menses), plus three questions concerning attitudes towards the risk of sterility linked to adjuvant chemotherapy. The questionnaire is available in English. Translations of the questionnaire are available in Afrikaans, Arabic, Croatian, Dutch, French, German, Hungarian, Italian, Portuguese, Serbian, Turkish, Spanish, Slovenian, and Polish.

CURRENT STATUS OF THE STUDY

So far 12 EORTC Breast Cancer Group institutions from Serbia, Peru, Portugal, Turkey, The Netherlands, Belgium, Lebanon, and Slovenia, and 2 IBCSG centres (in South Africa and Switzerland) have registered 156 patients (target sample size 385).

The study is easy and simple...Please don't wait! Simply contact the EORTC Data Centre (or IBCSG coordinating centre or GBG coordinating centre) to get all necessary information and documents.

!!!!!!! WE NEED YOUR PARTICIPATION TO COMPLETE ACCRUAL QUICKLY !!!!!!!

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

Phase III Trial Evaluating the Role of Adjuvant Pegylated Liposomal Doxorubicin (PLD, Caelyx®, Doxil®) 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)

The CASA trial is in its final stages of protocol and case report form development, and the IBCSG expects to send out these documents to interested centres and groups for Ethical Committee review and approval in the summer of 2005. Interested groups should contact the IBCSG Coordinating Center in Bern, Switzerland, to receive the protocol (contact trial coordinator Melanie Strausak by E-mail: ibcsg32-05_CASA@ibcsg.org; phone: +41 31 389 93 91; fax: +41 31 389 93 92).

The CASA 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.

A complete report of the CASA trial was presented in the Spring 2005 BIG Newsletter, so here we have provided a short update. The two randomisation options of the CASA trial (Figure 1) enable physicians and patients to choose which control group (nil or low dose cyclophosphamide and methotrexate [CM]) is appropriate for a given patient, while the experimental treatment, pegylated liposomal

**Option 1: CASA-Nil**
- Primary Surgery
- Stratify:
  - Institution

**Option 2: CASA-CM**
- Primary Surgery
- Stratify:
  - Institution

**Figure 1:** Timing of randomisation: Due to the hypothesized benefit of early initiation of chemotherapy for patients with endocrine nonresponsive breast cancer, randomisation and commencement of chemotherapy (if assigned) should begin as soon as possible following surgery, but no later than 16 weeks.

Chemotherapy regimens are 16 weeks in duration. PLD is given as 20 mg/m² iv x 8 doses (delivered every 2 weeks). Low-dose, metronomic CM is given as 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.

CM = cyclophosphamide plus methotrexate; PLD = pegylated liposomal doxorubicin.
doxorubicin (PLD) is part of both options. At the time of each patient’s randomisation, the investigator must select one of the two options:

Option 1, CASA-nil, 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, CASA-CM, 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.

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 progesterone receptor) disease. Thus, accruing the required 1,296 patients can only be reached with international collaboration and participation from around the world.

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 primary endpoint is breast cancer free interval (events are reappearance of invasive breast cancer at any site including contralateral disease).

BIG 3-05/GBG 26: Treatment Beyond Progression—Study

A Multicenter Randomized Phase III Study to Compare Capecitabine Alone or in Combination with Trastuzumab in Patients with HER2-Positive Metastatic Breast Cancer and Progression after Previous Treatment with Trastuzumab

An Intergroup Trial coordinated by the German Breast Group (GBG) under the umbrella of BIG in cooperation with the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO), Germany; Central European Cooperative Oncology Group (CECOG), Austria; Borstkanker Onderzoeksgroep Nederland (BOOG), the Netherlands; Clinical Trials Research Unit (CTRU), United Kingdom and Dr. D. Stanculeanu, Principal Investigator, Romania

By Gunter von Minckwitz, MD, and Patricia Segura-Eicke, PhD (GBG)

INTRODUCTION AND RATIONALE

All patients with HER2-overexpressing metastatic breast cancer who receive combination therapy with trastuzumab and chemotherapy will eventually progress. It is unknown whether progression warrants discontinuation of trastuzumab or whether continued treatment with the antibody in combination with further chemotherapy is beneficial.

Conventional strategies in tumour progression during therapy prefer treatment discontinuation. While this might be true for classic cytotoxic agents, novel biological agents with minimal toxicity and distinct noncytotoxic effects could ask for continuation of the treatment. Furthermore, preclinical data indicate that trastuzumab is effective against tumour cells as long as it is present, whereas trastuzumab withdrawal results in rapid tumour regrowth.1

It could be hypothesized that despite continued growth and resistance to chemotherapy, tumour cells may retain sensitivity to the activity of trastuzumab. The synergistic and additive effects of combinations of trastuzumab with different chemotherapeutic agents may be at least in part due to different interactions between the mechanisms of action of trastuzumab and the combination agent. Due to these interactions, substituting one chemotherapeutic agent with another at disease progression may produce greater clinical benefit than could be expected if trastuzumab is withdrawn and replaced with chemotherapy alone.2

Trastuzumab and capecitabine are both effective in breast cancer, and have different modes of action and toxicity profiles; therefore, combining these agents is of interest in the treatment of HER2-overexpressing breast cancer. An antagonistic interaction has, however, been reported between trastuzumab and 5-fluorouracil (5-FU) in an in vitro anti-proliferative assay.3 Kaori Fujimoto-Ouchi and colleagues investigated the efficacy of trastuzumab in combination with capecitabine or its intermediate metabolite, 5-FU, in HER2-overexpressing human breast cancer xenograft models. They showed that in vivo anti-tumour activity (tumour growth inhibition and tumour growth delay) of the combination was at least additive in human breast cancer models KPL-4 and BT474. This was despite the fact that in vitro treatment with trastuzumab and 5’-dFUr/5-FU together showed antagonistic antiproliferative activity in these models. The reason for the discrepancy between these in vivo and in vitro results is not clear.4

Combination of capecitabine and trastuzumab in humans has been tested in a pilot study with the results promising effica-
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cy and a beneficial side-effects profile. In 17 patients the response rate was 53% with a median duration of response of 7 (4–7) months and a median time to progression of 3 (0–8) months.4,5

The randomised, phase III Treatment Beyond Progression (TBP) study is designed to assess the clinical value of continued trastuzumab administration after progression on a trastuzumab/chemotherapy combination treatment. The study will also evaluate the therapeutic efficacy of capecitabine for this selected group of patients with advanced metastatic breast cancer.

STUDY DESIGN

Patients with HER2 positive metastatic breast cancer and progression after previous treatment with trastuzumab are being randomized to either

Randomization

Capecitabine 2,500 mg/m² BSA (X) until progression*

or

Capecitabine 2,500 mg/m² BSA +
Trastuzumab continuation 6 mg/kg BSA q3w (XH) until progression*

*or unacceptable toxicity, patient’s request or withdrawal from study.

PATIENT DEFINITIONS

Age ≥ 18 years

Disease progression during or after previous chemotherapy and trastuzumab treatment as follows (trastuzumab has to be given previously for at least 12 weeks; treatment-free interval of trastuzumab for a maximum of 6 weeks):

• Taxanes + trastuzumab given as adjuvant therapy
• Taxanes + trastuzumab given as first line therapy for palliation
• Trastuzumab given as first line therapy for palliation alone or in combination with chemotherapeutic agents other than capecitabine or taxanes

No more than 1 chemotherapy for palliation (max. Adriamycin dose ≤ 400 mg/m²; Epirubicin ≤ 600 mg/m²)

STRATIFICATION FACTORS

• Participating center
• The type of previous therapy of trastuzumab and chemotherapy:
  • Taxanes and trastuzumab given as adjuvant therapy
  • Taxanes and trastuzumab given as first line therapy for palliation
  • Any other chemotherapeutic agent given as adjuvant therapy and trastuzumab given as first line therapy alone or in combination with further chemotherapy with exception of taxanes and trastuzumab

OBJECTIVES

PRIMARY OBJECTIVE

To compare the time to disease progression in patients with HER2-positive metastatic breast cancer and progression after previous treatment with trastuzumab randomised to capecitabine alone or in combination with trastuzumab.

SECONDARY OBJECTIVES

• To compare the objective response rate between the two arms
• To compare the duration of response
• To compare the clinical benefit defined as complete response, partial response, or stable disease > 24 weeks between the two arms
• To evaluate the safety of the capecitabine + trastuzumab combination
• To compare overall survival between the two arms

TERTIARY OBJECTIVE

To determine the HER2 status in tissue collected directly before study entry in comparison to initial HER2 status and in correlation to study treatment effect.
**SAMPLE SIZE AND STUDY DURATION**

241 patients per arm

Enrolment start: June 2003
Enrolment stop: June 2007
Final analysis: June 2008

**STATUS OF THE STUDY**

**ENROLMENT**

First patient: 03 September 2003. Current status: (June 2005) 77 patients, 62 in Germany, 10 in Austria, 5 in Holland. The Protocol was already approved by the Clinical Trials Advisory and Awards Committee (CTAAC) in UK. Romania is preparing submissions. In order to extend the recruitment period as above indicated, a nonsubstantial amendment is in preparation.

**SERIOUS ADVERSE EVENTS**

The following serious adverse events have been registered: severe diarrhoea and vomiting (1, drug related), diarrhoea and vomiting (1, not drug related), diarrhoea (5, drug related), kidney dysfunction (not related), hand foot syndrome (drug related), febrile neutropenia (drug related), suspected myocardial infarction (1, drug related), curettage/adnexectomy both sides (not drug related), asthenia grade III (not related), pharyngitis/Herpes simplex/fever (drug related), cancer pain CTC II (not related), disaesthesia (drug related).

BIG groups interested in participating in this trial should notify the BIG Secretariat as soon as possible by e-mail <livia.meirsman@bordet.be>. For further details about the study protocol and enrolment of patients, please contact Dr. Patricia Segura-Eicke of the German Breast Group: <segura@germanbreastgroup.de>.

Documents to download (study synopsis, confidentiality agreement, registration form) are available at the home page of the GBG <www.germanbreastgroup.de>

**REFERENCES**


BIG 1-98/IBCSG 18-98 Substudies

Nadia Munarini, PhD, IBCSG Coordinating Center

Three BIG 1-98 substudies protocols are open for randomisation. Some important questions related to these substudies are discussed below. Please contact the BIG 1-98 team at the IBCSG Coordinating Center <ibcsg.big198@ibcsg.org> should you need any further details or if you would like to participate.

BIG 1-98 COGNITIVE FUNCTION SUBSTUDY

Why is it important to study cognitive function in BIG 1-98?

It is important because observations of cognitive function impairment are common after treatment for breast cancer, and we do not yet understand the nature of these problems (recent review by Phillips KA and Bernhard J, J Natl Cancer Inst 2003;95:190–7). BIG 1-98 provides an excellent base to compare the cognitive effects of tamoxifen and letrozole.

How is cognitive function measured in this trial?

We have chosen a computerized assessment, the CogState tool, and selected a number of tests for this trial, for example, verbal memory. The tasks for the subjects are based on card games, a common activity for most of us.

Computerised testing: couldn’t it be intimidating for the patients, especially the older ones?

No, experience with the CogState assessment shows that the patients become familiar with this tool very quickly. Playing cards is fun for many of us, even though the cards are not “real” but on the screen. This is the great advantage of this tool as compared to the conventional neuropsychologic testing.

What should the clinician do when a patient or her relatives complain about reduced cognitive function?

Patients’ complaints about cognitive dysfunction should prompt a professional evaluation. Sometimes the problems may be due to anxiety and depression, which can be treated.

Principal Investigators:

Dr. Karin Ribi is a psychologist from Berne, Switzerland and joined the IBSGC Quality of Life Office last summer. She is the trial coordinator for the BIG 1-98 Cognitive Function Substudy.

Professor Kelly-Anne Phillips is a medical oncologist from the Peter MacCallum Cancer Centre in Melbourne, Australia. Her major areas of research interest are the long-term side effects of breast cancer treatments and breast and ovarian cancer genetics.

PD Jürg Bernhard is a psychologist from Berne, Switzerland. He has been involved in the quality of life studies of the IBCSG for many years. Besides research he works as a psycho-oncologist at the University Hospital of Berne.

BIG 1-98 BONE SUBSTUDY: INVESTIGATING BONE DENSITY AND BONE LOSS WITHOUT BASELINE INFORMATION

What are the objectives of this substudy?

This substudy has four primary objectives:

1. BMD1: To compare the effects on BMD in the L2-L4 (postero-anterior, PA) region of the spine and hip.
2. BMD1: In two cohorts, to compare the incidence of radiologic gross changes and fractures identified from spine radiographs (T4-L4).
3. BMD2: To use longitudinal BMD measurements to estimate a linear rate of bone loss based on mixed effect models.
4. Bone markers: To identify serum markers for bone loss to determine how these correlate with osteoporosis, microfractures, clinical fractures, and breast cancer-related bone events.

Patients are divided into three cohorts:

This substudy will categorize patients into three cohorts based on their baseline visit:

• Cohort 1: Baseline is the end of year 2 from randomisation
• Cohort 2: Baseline is the end of year 3 from randomisation
• Cohort 3: Baseline is the end of year 4 or 5 from randomisation
### What are the Inclusion Criteria?

1. Patients on the BIG 1-98 trial without known, symptomatic bone disease.
2. Patients have not yet completed 5 years of trial treatment and have not had a breast cancer recurrence or a second primary cancer.
3. Written informed consent must be obtained and must be signed and dated by both the patient and the investigator. The informed consent form must be kept in the patient’s records at the participating site and be available for monitoring, auditing, and Health Authority inspection.
4. Patients need to be enrolled in the bone substudy at the time of the *annual* (at 24, 36, 48, or 60 months after randomization) follow-up visit.

### What are the Exclusion Criteria?

1. Uncontrolled thyroid and parathyroid disease, Cushing’s disease, or other pituitary diseases.
2. Any known bone disease (including osteomalacia, osteogenesis imperfecta).
3. Malabsorption syndrome or a clinically relevant vitamin D deficiency.
4. Use of raloxifene at any time.
5. Patients for whom the bone density determination is impossible.
6. Prior registration to BIG 1-98 BMD substudy.
7. Previous treatments: some previous treatment may lead to exclusion. Please contact the Coordinating Center for further details.

### Principal Investigator:

PD Dr. Stefan Aebi is the chair of the Bone Substudy. He is a physician at the Medical Oncology Clinic, University Hospital Inselspital in Berne, Switzerland.

### BIG 1-98 Fingernail Pilot Substudy: Investigating Chemical Properties of Fingernails to Determine the Efficacy of Nail Structure for Evaluating Bone Fragility

### What is the Fingernail Study?

The fingernail study concerns the development of the Bone Quality Test (BQT), which may detect the onset of osteoporosis and likely bone fragility by measuring the disulphide bond content of the fingernail using Raman spectroscopy. This can possibly be used as an analogue for bone quality because both nail keratin and bone collagen require sulphation and disulphide bond formation for structural integrity.

### Why is IBCSG Interested?

Women on breast cancer drugs have higher risks of osteoporosis. Being able to monitor the changing bone structure during chemo-preventative treatment would be a significant step forward in the maintenance of women’s health; therefore, a study to verify the ability of the BQT to monitor drug-induced changes is of considerable interest.

### Who is Involved with the Fingernail Study?

Dr Mark Towler (University of Limerick) has developed the BQT in conjunction with Crescent Diagnostics Ltd (London, UK).

### What is the Advantage of the BQT?

The Raman spectroscopy based diagnostic test is less expensive, simpler to use, and more accurate than all forms of noninvasive osteoporosis detection available today. This Point of Care test has the potential to create a new gold standard for osteoporosis and bone fragility testing.

### What is the Problem with Conventional Bone Fragility Tests (ie, DEXA Scanning and Ultrasound Analysis)?

These tests only identify 60% of sufferers and are generally restricted to postmenopausal women. In the USA it is estimated that osteoporosis fracture care costs $14 billion annually. 20% of women over 50 suffer from osteoporosis, and 6.26 million hip fractures are projected annually by 2050, up from 1.66 million in 1990.

### Principal Investigator:

Dr Mark Towler C. Eng C.Sci is a Research Scholar based at the University of Limerick (Republic of Ireland). His expertise is in the development of biomedical materials for skeletal applications. He has published 30 peer reviewed papers, attracted over 3 million Euro of research funding, and currently supervises a research group of five scientists.

Additional information regarding IBCSG, BIG 1-98 or BIG 1-98 substudies can be found on the Web site <www.ibcsg.org>.
### Ongoing BIG Trials

<table>
<thead>
<tr>
<th>BIG Trial</th>
<th>Coordinating Group</th>
<th>Participating Groups</th>
<th>Question Asked/Primary End Point</th>
<th>Target No. Pts</th>
<th>Accrual as of July 2005</th>
<th>Pharma Partners</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-98/Youth patients/ EORTC 10002</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>156</td>
<td>NA</td>
</tr>
<tr>
<td>1-00/p53 EORTC 10994</td>
<td>EORTC</td>
<td>ACCOG, SAKK, SBCG</td>
<td>P5 status and response to anthracyclines or taxanes?</td>
<td>1,850</td>
<td>1,409</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>5,102</td>
<td>Roche</td>
</tr>
<tr>
<td>1-02/ IBCSG 27-02/ 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>26</td>
<td>NA</td>
</tr>
<tr>
<td>2-02/ SOFT/ IBCSG 24-02</td>
<td>IBCSG</td>
<td>ANZ BCTG, BrEAST, CEROG, 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>243</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>432</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>10</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>893</td>
<td>AstraZeneca, 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>45</td>
<td>NA</td>
</tr>
<tr>
<td>1-04/AZURE NCRI BCSG / U. Leeds Trials Unit</td>
<td>NCRI BCSG</td>
<td>ACCOG, GOIRC, 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>2,131</td>
<td>Novartis</td>
</tr>
<tr>
<td>4-04/ICE GBG</td>
<td>GBG</td>
<td>WSG</td>
<td>What is the role of adjuvant chemotherapy; ibandronate with or without capcitabine in elderly patients with early breast cancer?</td>
<td>1,394</td>
<td>278</td>
<td>Roche/AstraZeneca</td>
</tr>
<tr>
<td>1-03/ REACT/ ICCG C20001, GBG 27</td>
<td>ICCG/GBG</td>
<td>BOOG, CEEOG, DBCG, GEOPO PERU, GOCCHI, ICR-ORG</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 / TBG</td>
<td>GBG</td>
<td>BOOG</td>
<td>Benefit of capcitabine with Herceptin® (H) in patients with HER2+ metastatic breast cancer and progression after previous (H) treatment?</td>
<td>482</td>
<td>77</td>
<td>Roche</td>
</tr>
<tr>
<td>2-04/ SUPREMO ACCOG / CCTT</td>
<td>ACCOG / CCTT</td>
<td>ANZ BCTG, CEEOG, EORTC, GEOPO PERU, HBSS, ICR-ORG, JBCRG, NCIC CTG</td>
<td>What is the role of adjuvant chest wall irradiation in “intermediate-risk” operable breast cancer following mastectomy and axillary clearance?</td>
<td>3,500</td>
<td>0</td>
<td>NA</td>
</tr>
</tbody>
</table>

**Total** | | | | 37,055 | 10,803 | |
### 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>3-04/ MINDACT</td>
<td>EORTC</td>
<td>ABCSG, ABS at BASO, ACCOG, BOOG, DBCG, GBG, GECO PERU, GOCCHI GOIRC, HBSS, IBCSG, ICR-CTSU, NCRI BCSG, SAKK, SBCG, SOITI, 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, GBOG, GECO 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 “standard” 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>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>8,296</strong></td>
<td></td>
</tr>
</tbody>
</table>

### Recently Closed BIG Trials

<table>
<thead>
<tr>
<th>BIG Trial</th>
<th>Coordinating Group</th>
<th>Participating / Interested 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/ C13/96</td>
<td>ICCG</td>
<td>ABCG, ANZ BCTG, CEEOG, DBCG, EORTC, FBKG, GEAG, GECAM, GOIBC, GONO, IBCSG, ICG, ITMO, NBCG, NWEG, SBCG, US Oncology, WCTN, YBCRG</td>
<td>Tamoxifen + 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, IBCSG</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, FBKG, 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, GECAM GOCCHI, IBCSG, ICORG, 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>DCBC, ICG, 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, ICGG</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>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>21,335</strong></td>
<td></td>
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</tr>
</tbody>
</table>

**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
- CCTT = Cancer Clinical Trials Team (formerly Scottish Cancer Therapy Network)
- 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
- FBKG = French Breast Study Group
- GBG = German Breast Group
- GECAM = Grupo Español de Investigación en Cáncer de Mama
- GnRH = gonadotropin-releasing hormone
- GOIRC = Italian Oncology Group for Clinical Research
- GONO = Gruppo Oncologico Nord-Ovest
- HBSS = Hellenic Breast Surgical Society
- IBCSG = International Breast Cancer Study Group
- IBCS = International Breast Cancer Intervention Study Group
- IDMC = Independent Data Monitoring Committee
- ICR-CTSU = Institute of Cancer Research, Clinical Trials and Statistics Unit
- ITMO = Italian Trials in Medical Oncology
- MA.17 = Medical Advisory Committee 17
- NA = not applicable
- NBRC = Norwegian Breast Cancer Group
- NCIC CTG = National Cancer Institute of Canada
- NCRI BCOSG = National Cancer Research Institute Breast Clinical Studies Group
- NSABP = National Surgical Adjuvant Breast and Bowel Project
- NWEG = North West England Cancer Group
- OS = overall survival
- SAKK = Swiss Group for Clinical Cancer Research
- SOITI = Swedish Breast Cancer Group
- WCTN = Wales Cancer Trials Network
- WMBG = West Midlands Breast Group
- WSG = Westdeutsche Studien Gruppe
- YBCRG = Yorkshire Breast Cancer Research Group
MINDACT: The First Trial to Evaluate the Clinical Value of a Genomic Tool

Sherene Loi, Nuria Decker, Jacques Bines, Tuc Nguyen van, Martine Piccart, Patrick Therasse, Fatima Cardoso, Carolyn Straehle on behalf of the TRANSBIG consortium

In view of the spread of screening mammography, a growing proportion of women are being diagnosed with smaller tumours and no axillary node involvement. Although these women can enjoy long-term survival, 20 to 30% will relapse and die from their disease. Distant metastases account for the majority of these deaths and have been the impetus for proposing in addition to optimal loco-regional treatment (surgery and radiotherapy), adjuvant systemic therapy to all fit women considered to be at moderate or high risk of relapse.

There is, however, much controversy related to the optimal definition of a low/minimal versus a moderate/high risk of relapse for these women with node negative breast cancer. Therefore, many oncologists rely on the guidelines issued by experts following consensus conferences, such as the 2000 National Institutes of Health (NIH) meeting and the 2005 St. Gallen conference. Given the close to 100% death rate from metastatic breast cancer, these guidelines are produced with the goal of avoiding under-treatment of affected women, and they assign only 15 to 20% of them to a “low/minimal risk” subset for which no adjuvant treatment at all or only adjuvant endocrine treatment will be considered. As a result, many women with early breast cancer in the western world are probably over-treated, a phenomenon that not only decreases the quality of life of these women but also increases the economic burden of this frequent disease on society.

The last 10 years have witnessed several attempts to more clearly define groups of women with extremely good prognosis who can be spared adjuvant systemic therapy, or at least adjuvant chemotherapy. Some of the most interesting and provocative data in this field include the breast cancer “70-gene poor prognosis signature” identified by the Netherlands Cancer Institute (NKI) group through DNA-microarray technology. This signature seems to better predict the clinical outcome in young women (less than 55 years old) with stage I or II breast cancer, when compared to the currently used clinical-pathological criteria. The plan is to transfer this new and powerful prognostic tool into the context of a large, prospective clinical trial. This clinical trial, to be coordinated and sponsored by a BIG member group, the European Organization for Research and Treatment of Cancer (EORTC), and to be run under the BIG/TRANSBIG umbrella with major input from other BIG members in order to decrease accrual time, is already in an advanced stage of preparation.

MINDACT, the first project being launched under TRANSBIG, is a large, molecular-based adjuvant trial for node negative early breast cancer patients (Figure 1). It will use microarray technology to classify early stage breast cancer patients into high and low risk of distant relapse and to compare this assessment to the one currently used in clinical practice that takes into consideration traditional clinical-pathological factors. MINDACT will prospectively validate the 70-gene poor prognosis signature providing the level-1 evidence of its efficacy that is needed before its wide clinical application. Using this new tool, MINDACT aims to better define patient prognosis and, therefore, to better select patients who need adjuvant chemotherapy. By doing so it is expected that 10 to 20% of women who would normally receive adjuvant chemotherapy based on their clinical-pathological factors will be spared the inconvenience and morbidity of this therapy without having any negative impact on their survival.

Recent gene expression studies have confirmed that breast cancer is molecularly heterogeneous, which can help to explain why certain cancers behave quite differently than predicted using traditional methods of prognostic assessment. Accumulating evidence also suggests that subsets of patients derive a much larger benefit from certain treatments, such as adjuvant chemotherapy, while others have a much lower benefit, even though their breast cancers may be histologically indistinguishable. Treatment tailoring for the individual

\[1\] TRANSBIG is a translational research network founded by BIG in 2004. It is partially funded by the European Commission, the Breast Cancer Research Foundation, the Jacqueline Seroussi Memorial 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.
patient has therefore become the major challenge for oncologists today. In case this new tool—the 70-gene poor prognosis signature—is validated through MINDACT, a critical change in practice will occur in breast cancer management and an important step will be taken towards a better individualisation of treatment. This could also lead to a reduction of 10 to 20% in chemotherapy prescription for the highest incidence cancer in women, significantly decreasing the financial burden of this disease on health care systems.

MINDACT is expected to begin recruitment in the last quarter of 2005 and requires 6,000 women who will participate through hospitals mainly from Europe, Latin America, and probably Canada and Australasia. To take advantage of a clinical trial with such power, further randomisation arms will be optional for women, including a chemotherapy randomisation, comparing an anthracycline to a non-anthracycline-containing arm, and an endocrine randomisation.

Once patients have given their consent to participate in the trial, their tumour material will be sent to The Netherlands, where the microarray (genomic) analysis will be carried out. The analysis of the genomic and the clinical-pathological factors of the patient and the tumour will determine into which of three groups the patient falls: High/High (both the genomic data and the clinical-pathological factors indicate a high risk of the tumour recurring); Low/Low (both tools indicate low risk), or Discordant. The Discordant group splits into patients who have clinical high risk and genomic low risk (approximately 80% of discordant cases) or clinical low risk and genomic high risk (approximately 20% of discordant cases). The Discordant group will be randomised between using clinical-pathological risk assessment or the genomic risk assessment to determine whether to treat with chemotherapy or not.

For those patients receiving chemotherapy, a second optional randomisation will distinguish between two different types of treatment, anthracyline- versus taxane-based. A third optional randomisation for all patients with hormone receptor positive disease will be made between 7 years of an aromatase inhibitor (AI) and an early sequential treatment of tamoxifen followed by an AI.

As an added value, MINDACT will lead to the creation of an important biological material bank because frozen and paraffin embedded tumour samples together with serum samples will be collected from each of the 6,000 randomised patients. This represents an invaluable resource for future studies that can lead to new discoveries and/or the valida-
tion of other biological markers/signatures detected in the meantime.

TRANSBIG conducted an independent quality assessment of the clinical data at the five centres involved in providing clinical data and samples for the MINDACT validation phase, the initial results of which were presented at the 2004 San Antonio Breast Cancer Symposium (SABCS). This quality control, carried out by two independent auditors, was performed to ensure that the retrospective data provided, which was often up to 20 years old, was sufficiently accurate to allow us to be confident in our conclusions. All the clinical data were reviewed according to a predefined plan and causes of death were collected. The pathological data were independently reviewed and methods of oestrogen receptors binding and grade definition confirmed. Once all the data were corrected, the auditors entered them into a separate database, which was then locked for the final analysis.

Since the initial analysis, a central pathological review has also been performed. Specifically, one expert evaluated the most important traditional clinical factors for consistency, and the standardization of these factors adds strength to the results of our validation. Independent statisticians in Brussels were then able to analyse the data with confidence, the results of which meant the signature could compete against the best currently available prognostic tools. The reanalysis of the results revealed that the performance of the 70-gene signature was in fact stronger than we had reported at the SABCS 2004. The successful completion of this work allows us to move forward with the clinical study MINDACT with conviction. The manuscript relating to the complete validation study is currently being prepared, with an abstract reporting on the final results submitted to the 2005 SABCS.

REFERENCES

Conference Calendar 2005–2006

Nottingham Breast Cancer 9th International Conference September 13–16, 2005 Nottingham, UK http://uicc.org

Lynn Sage Breast Cancer Conference October 6–9, 2005 Chicago, Illinois, USA http://www.cancer.northwestern.edu/education/lynn sage/cfm


7th EUROPA DONNA Pan-European Conference November 5–6, 2005 Rome, Italy http://www.europadonna.org


San Antonio Breast Cancer Symposium December 8–11, 2005 San Antonio, Texas, USA http://www.sabcs.org


Breast Diseases: Detection, Intervention and Therapy March 13–16, 2006 Key Largo, Florida, USA http://www.thebreastcourse.com

Society of Surgical Oncology March 13–26, 2006 San Diego, California, USA http://www.surg onc.org

American Society of Breast Surgeons April 5–9, 2006 Baltimore, Maryland, USA http://www.breastsurgeons.org


American Association for Cancer Research April 1–5, 2006 Washington, DC, USA http://www.aacr.org

American Society of Clinical Oncology June 2–6, 2006 Atlanta, Georgia, USA http://www.asco.org


European Society for Medical Oncology September 29–October 3, 2006 Istanbul, Turkey http://www.esmo.org
NOTICE TO MEMBERS: BIG and TRANSBIG Meetings

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

• During ECCO 13, Paris
  • TRANSBIG meetings Saturday 29 October 2005 (for consortium members, by invitation)
  • BIG meeting Sunday 30 October 2005, 9:00–14:30* (for BIG members)
  • *Please note earlier than usual starting time!
• During EBCC-5, Nice
  • TRANSBIG meetings Monday 20 March 2006 (for consortium members, by invitation, details TBA)
  • BIG meeting Tuesday 21 March 2006 (for BIG members, details TBA)

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: AstraZeneca, Bayer, Eli Lilly, F. Hoffmann-La Roche and OSI Pharmaceuticals.

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