Annual Report 2013

“We will find a cure for breast cancer through global research and collaboration”
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About BIG

The Breast International Group (BIG) is a non-profit organisation for academic breast cancer research groups from around the world, with its headquarters in Brussels, Belgium.

BIG facilitates and accelerates international breast cancer research by stimulating cooperation between its members and other academic networks, and collaborating with, but working independently from, the pharmaceutical industry.

Truly international reach
BIG is a truly international body focused exclusively on conducting and coordinating breast cancer research, primarily through clinical trials and innovative research programmes. To test new treatments with enough patients to be confident about the results, clinical research should not be limited to one institution, or even to one country.

Real research
BIG designs and conducts its own research through its member groups and their extended network of hospitals and investigators – BIG does not simply redistribute funding to other third parties. BIG trials that are conducted in collaboration with the pharmaceutical industry are done so in a manner designed to maintain independence and eliminate bias, keeping patients’ interests at the heart. About 30 clinical trials and several research programmes are ongoing or are under development under the BIG umbrella at any given time. BIG also works closely with the US National Cancer Institute and the North American Breast Cancer Group, so that together they act as a strong integrating force in the breast cancer research arena.

Research principles
BIG facilitates academic research but also works closely with the pharmaceutical industry in a way that is “win-win” for all. BIG trials respect specific principles of research conduct to ensure that data collected are handled and analysed independently, generating highly credible results. Moreover, patients are followed long after treatment ends, with the aim to detect long-term side effects. BIG studies are also governed by committees and policies designed to reduce bias and protect the patient. Finally, the processes surrounding access by scientists to precious tumour and other tissues donated by patients for future research are subject to strict rules to ensure that only the best research ideas are supported.

Faster results
BIG has the ability to achieve faster results and greater patient benefits by enrolling larger numbers of patients into clinical trials more quickly, and doing so in many countries around the world.

“Finding a cure for breast cancer is one of the biggest challenges faced by researchers from around the world.

Significant progress has been made to improve both the chances of survival and the quality of life of women affected by the disease. However, breast cancer remains the second most common cancer in the world and is still responsible for too many deaths annually.

By bringing together the top breast cancer experts from around the world to conduct innovative research, BIG has the global reach and expertise required to find a cure. We need to support such critical research to give hope to women affected by this devastating disease, and their families.”

Her Majesty the Queen of the Belgians
BIG’s Honorary President
This past year has been one of change. After almost fifteen years of conducting large, international adjuvant trials of chemo-, hormone- and biological therapies for early breast cancer, in 2013 the Breast International Group (BIG) directed its efforts largely towards research in metastatic breast cancer, as well as rarer forms of the disease, such as those driven by BRCA1/2 gene mutations.

While research has made great strides in recent decades to improve and extend the life of patients with early breast cancer, research initiatives focusing on patients with metastatic disease have not been equally successful.

In this context BIG built AURORA, an innovative international programme. AURORA will use molecular screening to improve our understanding of metastatic breast cancer and its response or lack of response to available drug therapies. In total 1300 women and men from over 60 hospitals in 15 European countries are expected to take part in the programme. Over time, BIG hopes to expand the programme well beyond Europe to involve even more patients.

2013 has also been a year of sowing many seeds of time and effort to prepare the ground for the launch of new trials. Among others, these include ANABELA in the metastatic setting; OlympiA, Neo-OlympiA and BRAVO, designed to understand how to best treat patients with BRCA mutations; POSITIVE, a purely academic trial to help young women affected by breast cancer safely plan and accomplish a pregnancy; and NeoPHOEBE and LORELEI, both aiming to test new, promising drugs given before surgery. We expect that these exciting developments will lead to a rich harvest of knowledge about breast cancer, and that this knowledge in turn will give patients better treatments and hope in the future.

None of BIG’s achievements in 2013 – and in the past – would have been possible without the dedication and hard work of its 49 collaborative member groups, which represent an impressive network of more than 8000 breast cancer experts worldwide.

We, as a network, have the global reach and expertise required to conduct innovative research to best serve the needs of patients. We have the opportunity to make a real difference in patients’ lives, both today and in the future. And it is our obligation to seize it.

We hope you enjoy the reading.

Prof Martine Piccart-Gebhart
BIG Chair

Prof Aron Goldhirsch
BIG Vice-Chair
Research and collaboration are the essence of BIG. Research cannot be successful without collaboration, and BIG is all about collaboration!

For almost fifteen years BIG has been conducting international clinical trials and research programmes, enrolling thousands of patients all over the world. In particular, BIG is known for its large adjuvant trials of chemo-, hormone- and biological therapies for early breast cancer. These studies have involved as many as 946 hospitals from over 25 BIG collaborative groups covering 44 countries at a time. Many of these studies have been practice-changing, including the trials that helped put aromatase inhibitors on the map or that led to major breakthroughs for HER2-positive breast cancer.

In 2013 BIG decided to direct its efforts towards research in advanced or metastatic breast cancer, as well as rarer forms of the disease, such as those driven by BRCA1/2 gene mutations. With little or inconclusive data available about optimal treatment options, it is difficult for physicians to choose the best treatment path for individual patients.

Moreover, despite the fact that the overall breast cancer death rate has dropped steadily over the last decade and significant improvements in survival have been made, metastatic breast cancer represents the leading cause of cancer-related death among women. At the same time, there is an unprecedented opportunity to make more rapid progress, as ever more powerful technologies become available to analyse the molecular make-up of cancer cells. The more profoundly we are able to understand the mechanisms driving cancer development, the greater our chances are of identifying how to stop the disease.

The BIG Members – a worldwide network of 49 academic research groups and thousands of investigators – have played a crucial role in making these ambitious plans come true: none of BIG’s successes in 2013 or in the past would have been possible without their collaborative spirit, dedication and hard work.

Finally, a special acknowledgement goes to all the many patients who take part in BIG trials. Their contribution is essential to moving research forward… and to improving the lives of everyone confronted with breast cancer.
Metastatic Breast Cancer

While research has made great strides in recent decades to improve and significantly extend the lives of patients with early breast cancer, research initiatives focusing on patients with metastatic disease have not been equally successful. In this context, the BIG network shifted its focus substantially in 2013, building its flagship programme AURORA and developing several associated clinical trials.

AURORA aims to...

build a longitudinal map of the clonal evolution of breast cancer by interrogating the primary tumour as well as the metastases, and to accelerate new molecularly-targeted drug development across Europe.

AURORA will be the largest international programme with a lot of translational research totally devoted to metastatic breast cancer.”

Prof Martine Piccart
AURORA Principal Investigator and BIG Chair

2013 was BIG’s year to build AURORA, an innovative international programme set up to significantly improve the lives of patients with metastatic breast cancer. In total 1300 women and men from over 60 hospitals in 15 European countries (from 11 BIG member groups) are expected to take part in the programme, being launched in early 2014. Over time, BIG hopes to expand the programme well beyond Europe to involve even more patients.

Today’s technology enables us to characterise cancer on the genetic level in great detail. This heralds tremendous promise with regard to understanding the genetic changes (aberrations) within tumours over time, and their genetic heterogeneity. For breast cancer in particular, many recent studies – using a type of genetic analysis referred as next generation sequencing – have uncovered a large number of genetic aberrations in tumours that occur at a low frequency. In some cases, experimental drugs being developed could be used as targeted treatment against these aberrations, and potentially lead to extending patients’ lives significantly.

There is increasing evidence to demonstrate that when breast cancer spreads (1 breast cancer patient out of 3 develops metastases), it acquires genetic aberrations that differ from those that were present when the disease first appeared. In addition, different resistance mechanisms to treatments may emerge over time. Obtaining biopsies from metastatic breast tumours and comparing them to biopsies taken at the time the breast cancer first occurred will help uncover mechanisms of treatment resistance – but also why some patients respond exceptionally well to treatment.
Recently many individual hospitals, private laboratories and even national governments have established molecular screening initiatives that aim to provide physicians and patients with a report of all the genetic aberrations found in a patient’s tumour. While these initiatives may be well intentioned, they have major limitations because they generate results that might lose their potential and impact if not interpreted in a properly structured clinical setting involving multiple cancer specialists and geneticists. Moreover, the use of modern technologies is likely to result in breast cancer being classified into ever smaller genetic sub-types. This means that clinical trials aiming to test new treatments for these sub-types cannot be run by individual hospitals or even on national levels; instead, they will require well-organized, international collaboration to be able to enrol enough patients to generate meaningful study results, something that BIG is well positioned to do.

In practice, AURORA consists of collecting biopsy samples from both primary and metastatic tumours. Initially they will be subjected to molecular profiling with a panel of more than 400 cancer-related genes. Plasma and blood samples will also be collected, and any samples not analysed immediately will be stored in an independent bio-repository to enable future research. An innovative bioinformatics platform has been developed to support the collection of AURORA data. These data are being collected in a way that will allow sharing and collaborating in the context of other initiatives started by researchers in North America. Governed by a Steering Committee of renowned metastatic breast cancer and molecular experts as well as patient advocates, critical work for AURORA will be carried out by its Molecular Advisory Board, involving cancer geneticists, pathologists, bioinformaticians and oncologists.

**How will AURORA benefit patients?**

AURORA will enable us to understand both why breast cancer metastasises and why some patients respond poorly to standard treatment, while others respond very well. Whenever possible, patients participating in AURORA will be offered to participate in a clinical trial testing new and promising drugs that target the specific genetic characteristics of their tumours. The ultimate hope is that AURORA will benefit patients by leading us to both better treatments and to finding cures for the women and men affected by this disease.

AURORA is being conducted with the Breast European Adjuvant Study Team and Frontier Science Scotland. It is made possible in part by generous grants from the Breast Cancer Research Foundation®, the Fondation Cancer (Luxembourg), the National Lottery (Belgium), NIF Trust, and individual donors.

**AURORA pilot study**

Prior to the official launch of AURORA, BIG set up a molecular screening pilot study in collaboration with four European hospitals. This pilot study, involving 30 patients, aims to test all steps of AURORA, from patient recruitment to collection, handling, and analysis of samples (blood or metastatic lesions). The pilot study will also contribute to evaluating the efficiency and user-friendliness of AURORA’s innovative IT platform with regard to the screening of patients for participation in future molecularly defined clinical trials in metastatic breast cancer. The final results of the pilot study, which was supported by a grant from the Breast Cancer Research Foundation®, are expected in the second half of 2014.

Several trials for metastatic breast cancer and for which AURORA patients may be eligible are under development within the BIG network, including, among others, ANABELA.

**ANABELA**

Co-led by the European Organisation for Research and Treatment of Cancer and BIG Headquarters in collaboration with the pharmaceutical partner (and sponsor) PUMA Biotechnology, ANABELA will involve 35 patients from about 50 different hospitals and cancer centres from about 10 BIG member groups. In some breast cancers cases scientists have identified mutations of the gene ERBB2 that leads to the formation of the protein HER2. This protein enables cancer cells to grow and proliferate more rapidly. ERBB2 mutated type of breast cancer is quite rare (estimated to affect approximately 2% of the breast cancer population), meaning that only a tremendous international effort such as that made possible by BIG will lead to success in treating this type of disease.

ANABELA will evaluate the action of a new drug called neratinib that inhibits, among others, the action of HER2 and thus holds the promise to inhibit the growth of cancer cells with either overexpression of the protein or mutation of the gene. The study will improve our understanding of the ERBB2 mutated type of breast cancer. It will also determine the safety and tolerability of neratinib for these patients. Ultimately, it will tell us whether the survival and quality of life of women with ERBB2 mutated breast cancer can be significantly improved with this drug.
BRCA Gene Mutations and Breast Cancer

Inherited abnormalities in the BRCA1 (BReast CAncer gene 1) and BRCA2 (BReast CAncer gene 2) genes are responsible for an increased risk of developing breast cancer and ovarian cancer in women. Also men with these mutations show an increased risk of breast cancer and, possibly, of prostate cancer. BRCA1 and BRCA2 gene mutations are rare, but if present, they can lead to the development of an aggressive form of breast cancer. Physicians, however, cannot yet make treatment decisions based on these genes because data regarding the impact of BRCA1 and 2 mutational status on breast cancer treatment are currently inconclusive.

To try to fill this gap, the BIG network undertook multiple initiatives to determine how to best treat breast cancer patients with BRCA mutations.

OlympiA

BIG Headquarters dedicated considerable time and effort in 2013 coordinating the global set-up of OlympiA - a multicentre study being run by BIG Headquarters and Frontier Science & Technology Research Foundation in association with NRG Oncology and AstraZeneca. The study aims to recruit 1320 patients from approximately 300 different hospitals in 23 countries from 22 BIG member groups.

This study will assess the efficacy and safety of olaparib versus placebo as adjuvant treatment in patients with BRCA1/2 mutations and high risk HER2-negative primary breast cancer who have completed definitive local treatment and neoadjuvant or adjuvant chemotherapy. Approximately 5% of breast cancers are associated with a mutation in the BRCA1 and/or BRCA2 gene.

Patients will receive a post-operative oral dose of olaparib or matching placebo twice daily for 12 months. The primary end point of the study is invasive disease-free survival, and the secondary end points include overall survival and quality of life indicators. A strong translational research programme has been planned for the samples to be collected during the study.

What is OlympiA?

A randomised, double-blind, parallel group, placebo-controlled multi-centre phase III study to assess the efficacy and safety of olaparib versus placebo as adjuvant treatment in BRCA mutated high risk HER2-negative breast cancer patients who have completed definitive local treatment and neoadjuvant or adjuvant chemotherapy.
In 2013, the German Breast Group, SOLTI, and BIG Headquarters, in association with AstraZeneca, also started developing the Neo-Olympia study. This companion to OlympiA is a multicentre neoadjuvant study that aims to recruit 300 patients from approximately 100 different hospitals from about 10 BIG member groups.

Newly diagnosed patients with “triple negative” breast cancer and germline (hereditary) BRCA1/2 mutation, suitable to start chemotherapy, will be eligible to participate. Triple negative breast cancer is a specific type of breast cancer characterised by the absence of three commonly used markers for clinical decision making, namely the two hormone receptors ER and PgR, and the oncoprotein HER2.

To be eligible for the Neo-Olympia trial, patients must have completed 4 cycles of pre-randomisation neoadjuvant chemotherapy with anthracycline plus carboplatin, showing no clinical or radiological evidence of disease progression on treatment. Patients will be randomised to receive either double-blinded olaparib plus weekly paclitaxel or double-blinded placebo plus weekly paclitaxel, or open-label monotherapy olaparib for 12 weeks, followed by surgery, followed by the same treatment except paclitaxel. The primary end point is pathological complete response (pCR) defined as the absence of any residual invasive cancer in the resected breast specimen and all sampled ipsilateral lymph nodes.

As with OlympiA, a strong translational research programme has been planned for the samples to be collected during the study.

Neo-Olympia

What is Neo-Olympia?

A phase III, randomised, three-arm, parallel group, multi-centre study to compare the pathological complete response rate and safety and tolerability of olaparib (monotherapy and in combination with paclitaxel) versus weekly paclitaxel in the neoadjuvant treatment of triple negative breast cancer patients with germline BRCA1/2 mutations following initial neoadjuvant chemotherapy with carboplatin and anthracycline.

BRAVO

Conducted by the European Organisation for Research and Treatment of Cancer, BIG Headquarters and the pharmaceutical partner Tesaro, BRAVO is an international multicentre study involving 306 patients with metastatic breast cancer from several hospitals in Europe, Canada and the USA. Eleven BIG member groups are participating in the study. BRAVO aims to test the efficacy of a new drug called niraparib.

Niraparib belongs to a category of drugs known as PARP inhibitors. These drugs have the potential to selectively kill cancer cells by affecting one DNA repair mechanism. Some patients with breast cancer are carriers of inherited harmful BRCA gene mutations, which compromise this DNA repair mechanism. Such patients might respond well to treatment with the experimental drug niraparib.

Patients who test positive for the BRCA mutations and meet all other criteria to participate in study will be randomised to treatment as follows: 2 out of 3 will receive niraparib, while 1 out of 3 will receive a chemotherapy drug that is already approved for metastatic breast cancer. Both the patients and their treating physicians will know which drug each patient receives.

The purpose of this study is to compare the efficacy and safety of treatment with niraparib in patients with germline (hereditary) BRCA mutation-positive breast cancer patients with niraparib versus physician’s choice in previously-treated, HER2 negative, germline BRCA mutation-positive breast cancer patients.

What is BRAVO?

A phase III, randomised, open label, multicenter, controlled trial of niraparib versus physician’s choice in previously-treated, HER2 negative, germline BRCA mutation-positive breast cancer patients.
Purely Academic Trials

POSITIVE

Young women represent a significant sub-population among the patients affected by breast cancer. About 15% of patients with breast cancer are diagnosed during their reproductive years. Fearing that a future pregnancy could increase the risk of recurrence of the disease, an increasing number of those women see breast cancer as a major obstacle to their desire to conceive. Furthermore, for some young women the postponement of pregnancy after the completion of their 5 to 10 years of anti-cancer treatment may considerably compromise their chances of becoming pregnant.

The majority of young women with early breast cancer have oestrogen receptor positive (ER+) disease. They are treated with standard endocrine treatment, and it has been observed that their long-term survival is good. According to our current understanding of the disease and to a recent study, evidence suggests that pregnancy after breast cancer treatment does not have a negative impact on the risk of recurrence.

POSITIVE is a purely academic study that represents a unique opportunity to allow young women with breast cancer to safely plan and accomplish pregnancy without waiting many years after completing their adjuvant treatment. For the scientific community this study is also an opportunity to improve our understanding of the correlation between pregnancy and the risk of breast cancer recurrence. This study investigates both the pregnancy outcomes and the safety of temporarily interrupting endocrine therapy for young women with ER+ breast cancer who desire pregnancy.

The International Breast Cancer Study Group took the lead of this ambitious international project within the framework of the BIG and North American Breast Cancer Groups collaboration. Thirty-six breast cancer centres from around the world have shown interest in participating in this clinical trial, which will enrol 516 patients in total. POSITIVE is expected to launch during the 1st quarter of 2014, and the study will last 3 to 5 years. Participants will be followed for at least 10 years after their enrolment.

What is POSITIVE?

A phase II trial investigating endocrine therapy interruption to enable conception for young women with ER+ breast cancer; breast cancer recurrence and offspring outcomes will be the primary trial endpoints. The trial will also allow for the testing of biologic correlates of pregnancy and disease outcome. It will provide prospective information to be used by patients and their physicians to safely plan and pursue a pregnancy after breast cancer.

“POSITIVE has been launched with great excitement, because we as doctors are often approached by patients about the safety of having a baby after breast cancer treatments.”

Dr Olivia Pagani
POSITIVE Principal Investigator

International Programme of Breast Cancer in Men

Because of the rarity of male breast cancer, which accounts for less than 1% of all breast cancers diagnosed worldwide, men affected by breast cancer find little support in their fight against the disease. They are frequently excluded from breast cancer trials and, in deciding which treatments to offer, their doctors usually extrapolate evidence from the studies assessing therapies among women with breast cancer.

In 2006 BIG and its North American counterpart, the North American Breast Cancer Group decided to join efforts to better understand this rare disease and raise awareness and interest among the scientific community. The result was the very first international academic research programme to study male breast cancer.

The International Programme of Breast Cancer in Men is being led by the European Organisation for Research and Treatment of Cancer with the help of the American Translational Breast Cancer Research Consortium. This is a purely academic programme funded by several grants, including significant support from the Breast Cancer Research Foundation®. To date 17 countries and 118 hospitals have joined.

The programme’s objective is to gather and analyse critical medical information about the biology and evolution of male breast cancer, in order to help cancer physicians learn more about this rare disease and to guide them towards better treatments and support for their patients in the future.

The first stage of the programme consists in analysing a significant number of tumour blocks from male breast cancer cases diagnosed from 1990 to 2010 in the various participating hospitals worldwide. By the end of 2013 physicians had compiled the largest ever collection of male breast cancer samples with a total of 1822 patients enrolled. By 2016 the first data extracted from the collected tumour samples will be available and shared in a collaborative way between Europe and North America.

In 2013 physicians started building the second stage of the programme, an international registry of male patients affected by breast cancer. The purpose of the registry is to gather data on risk factors, demographics, and treatments, as well as to collect biological material and quality of life assessments in a prospective way.

In a third phase, one or more clinical trials dedicated to male breast cancer patients will be set up and hopefully lead to the better support and treatment of men affected by this rare disease.

“Men often suffer additional stress when they learn from their doctor that little is known about the disease and that they will be treated like their female counterparts until we are able to better understand the disease and find a therapy tailored specifically to them.”

Dr Fatima Cardoso
Co-Principal Investigator, International Programme of Breast Cancer in Men
What is SUPREMO?  
A phase III randomised trial to assess the role of adjuvant chest wall irradiation in women with intermediate risk breast cancer after mastectomy. The primary endpoint is overall survival and patients are followed up for ten years.

Supremo

Conducted by the Common Services Agency, NHS Lothian and the University of Edinburgh, and supported by the UK Medical Research Council (MRC EME, a national organisation funded by UK taxpayers), European Organisation for Treatment of Cancer, Trans-Tasman Radiation Oncology Group and BIG, the SUPREMO trial was closed to recruitment on 30 April 2013. It recruited a total of 1688 patients from 19 countries in 183 hospitals. In particular, SUPREMO was the first BIG trial that involved significant participation from hospitals in China. This trial is an excellent example of international cooperative effort that proves that language and distance are not unsurmountable barriers!

Launched in 2006, SUPREMO’s purpose is to test the risks and benefits of radiotherapy given to patients diagnosed with early breast cancer and who are at intermediate risk of the cancer returning, after having had their breast removed by surgery (mastectomy).

In patients at high risk of recurrence (for example when four or more lymph nodes are involved by cancer underneath the armpit or when the tumour is large) postoperative radiotherapy is a standard of treatment. Currently, though, there is no evidence that the same treatment is needed for patients at intermediate risk (less than four lymph nodes under the armpit involved or none involved but with other features of the cancer which increase the risk of it coming back) – with SUPREMO, scientists hope finally to get some clarity.

Radiotherapy can cure some cancers and can reduce the risk of cancer coming back in the same place after surgery. When it is given along with anti-cancer drug treatment (chemotherapy or hormonal therapy), it may also improve long-term survival. However, it can also cause side effects.

To this end, a sub-study running alongside the main trial SUPREMO specifically evaluates the quality of life of patients undergoing radiotherapy after mastectomy.

Quality of life studies are important to BIG and – whenever possible – BIG trials include the evaluation of this aspect.

What is DCIS?

Conducted by the Trans-Tasman Radiation Oncology Group under the BIG umbrella, DCIS is an active randomised trial that aims to individualise radiotherapy after breast conserving surgery for women with higher risk ductal carcinoma in situ (DCIS) by tailoring radiation dose escalation to the tumour bed and fractionation schedules to their individual risks of recurrence, principally invasive recurrence. The study aims to optimise patient outcomes and to contribute to the cost-effective use of radiotherapy.

Importantly, the study will identify factors that result in progression of DCIS to invasive breast cancer in order to develop effective treatment strategies tailored to individual recurrence risk. Biological specimens that are being collected from study participants will be a valuable resource for subsequent studies.

This international study with a sample size of 1600 patients and involving 123 centres was activated in Australia and New Zealand in 2007, and internationally under the BIG umbrella in 2009. It now involves the NCIC Clinical Trials Group, European Organisation for Research and Treatment of Cancer, International Breast Cancer Study Group, All Ireland Cooperative Oncology Research Group and the Scottish Cancer Trials Breast Group.

When the study reaches its overall target of 1600 patients in 2014, it will have accomplished this two years ahead of schedule. The quality of life sub-study has completed accrual of a target sample size of 1020 patients.

With a clear focus on quality, the study team has been able to continue central pathology reviews and electronic radiotherapy quality audits. At an operational level, the trial centre team has streamlined – and where appropriate – automated study management processes to optimise resource utilisation and cost control measures. Communication and collaboration between the study teams at the trial centre in Australia, BIG Headquarters, the headquarters of the contributing groups and their participating sites remain strong and have proved to be a major asset in the study management.

The study is funded by the National Health and Medical Research Council in Australia, NCIC Clinical Trials Group, European Organisation for Research and Treatment of Cancer, Dutch Cancer Society, UK Breast Cancer Campaign, Oncosuisse, All Ireland Cooperative Oncology Research Group and Susan G. Komen®.
Other Trials and Initiatives

NeoPHOEBE

Co-led by three partners – the German Breast Group (GBG), SOLTI and BIG Headquarters – NeoPHOEBE is a multicentre study that will involve 220 patients from approximately 54 different hospitals and cancer centres from 7 BIG member groups. NeoPHOEBE aims to test the efficacy of a new drug called buparlisib (BKM120).

Human Epidermal Growth Factor Receptor 2 (HER2) is an oncoprotein, overexpressed in 15-20% of breast cancer cases that has been associated with an aggressive clinical course of the disease. Trastuzumab is a molecularly targeted agent blocking HER2 that substantially improves the clinical outcome of patients with HER2-positive breast cancer. For primary breast cancer, administering trastuzumab with chemotherapy pre-operatively (neoadjuvant treatment) is an effective therapeutic strategy. However, sometimes a tumour may become resistant to trastuzumab-based therapy, even in patients with early stage disease.

Scientists found out that a biological mechanism called the PI3K signalling pathway, which consists of a group of molecules working together to control cell functions like division or death, can help cancer cells “resist” trastuzumab-based therapy. The identification of this biological mechanism has led to the development of investigational drugs targeting different molecular components of that pathway.

The hypothesis studied by NeoPHOEBE is that blocking PIK3CA, PIK3CB and PIK3CD through Buparlisib will potentiate the antitumour activity of standard preoperative anti-HER2 treatment within patients with and without PIK3CA mutations in their tumours.

The hypothesis studied by NeoPHOEBE is that blocking PIK3CA, PIK3CB and PIK3CD through Buparlisib will potentiate the antitumour activity of standard preoperative anti-HER2 treatment within patients with and without PIK3CA mutations in their tumours.

LORELEI

Co-led by three partners – the Austrian Breast & Colorectal Cancer Study Group (ABCSG), SOLTI and BIG Headquarters – LORELEI is a multicentre study involving 330 patients from approximately 54 different hospitals and cancer centres in about 20 countries from 6 BIG member groups. LORELEI aims to test the efficacy of a new drug developed by Genentech called GDC-0032.

Endocrine therapy has proven to be efficient against tumour activity in the setting of hormone receptor positive (HR+) breast cancers. However, sometimes the tumour may become resistant to endocrine therapy, even in patients affected by the early stage of the disease. Scientists have discovered that a biological mechanism called the PI3K signalling pathway, which consists of a group of molecules working together to control cell functions like division or death, confers endocrine resistance to the cancer cell, thus helping the tumour to “resist” endocrine therapy. Different molecular aberrations or gene mutations can activate the PI3K pathway mechanism, with mutations of the gene PIK3CA being the most common ones. In order to inhibit the PI3K pathway, GDC-0032 aims to block the protein corresponding to the PIK3CA gene. The hypothesis studied by LORELEI is that inhibiting the PIK3CA gene with GDC-0032 will increase the efficacy of another drug called letrozole (standard therapy given before surgery), which thereby will result in greater clinical benefit to patients affected by HR+ early breast cancer.
Neo-ALTTO

Neoadjuvant therapy is treatment given to shrink or eliminate a tumour before surgery. In some patients with breast cancer, neoadjuvant therapy effectively eliminates the tumour, and no invasive cancer is detectable in breast tissue and lymph nodes removed during surgery. These patients are said to have had a pathologic complete response.

Neo-ALTTO, a collaboration between SOLTI, the Breast European Adjuvant Study Team, BIG Headquarters and GlaxoSmithKline, was BIG’s first neo-adjuvant trial. A randomised, phase III clinical trial, it was designed to evaluate whether a combination of two HER2-targeted therapies, trastuzumab and lapatinib, given with standard paclitaxel chemotherapy before surgery is better than just one of the HER2-targeted therapies given with the same chemotherapy. The study’s first results, presented at the 2010 San Antonio Breast Cancer Symposium (SABCS), showed that patients receiving the combination therapy achieved a higher rate of pathological complete response.

At the 2013 SABCS, updated results were presented. These showed that patients with HER2-positive breast cancer who achieved a pathologic complete response had significantly better rates of event-free and overall survival compared with patients who did not.

The definitive conclusions, however, about the effectiveness of dual treatment with trastuzumab and lapatinib for early stage HER2-positive breast cancer will not be known until the results of Neo-ALTTO’s “sister” trial, ALTO, which is testing the effectiveness of dual treatment with lapatinib and/or trastuzumab after surgery, are reported in 2014.

APHINITY

In August 2013 the APHINITY trial successfully finished patient recruitment. A total of 4805 women were enrolled in less than two years in 563 participating centres from 24 BIG groups in 42 countries. Important changes were made to the trial protocol in late 2012 to restrict recruitment to patients with node-positive breast cancer and to increase sample size by 1000 patients. Contrary to all expectations, these modifications did not decrease the recruitment pace, and the study reached its new accrual target three months ahead of plan.

This successful and extremely rapid recruitment reflects the dedication and ability of the BIG network and its partners to accelerate breast cancer research – and bring results to patients and the wider community.

The study aims to demonstrate that treatment with dual HER2 blockade (with the combination of pertuzumab and trastuzumab) is superior to single HER2 blockade in the adjuvant setting of HER2-positive breast cancer.

APHINITY’s first results are expected to be reported in 2016.

This trial is led by BIG Headquarters, the Breast European Adjuvant Study Team and Frontier Science - responsible for data management and statistical analysis, respectively - and in partnership with Roche.

What is Neo-ALTTO?

A randomised, phase III trial of neoadjuvant lapatinib and/or trastuzumab treatment optimisation. In the Neo-ALTTO trial, patients with HER2-positive breast cancer were randomly assigned to preoperative therapy with paclitaxel and lapatinib, paclitaxel and trastuzumab, or paclitaxel plus both anti-HER2 drugs. The overall goal of the trial was to determine whether pathologic complete response rate achieved with lapatinib plus trastuzumab translated into better overall survival or event-free survival.

What is APHINITY?

A randomised multicenter, double-blind, placebo-controlled comparison of chemotherapy plus trastuzumab plus placebo versus chemotherapy plus trastuzumab plus pertuzumab as adjuvant therapy in patients with operable HER2-positive primary breast cancer.

Prof José Baselga

Neo-ALTTO Principal Investigator and BIG Executive Board Member
A BIG effort to improve translational research sample collection

Adequate tissue handling is of utmost importance for progress to be made in breast cancer research. Among the numerous studies coordinated by BIG, translational research has been prioritised, with obligatory tissue collection to enable future clinical and basic research.

Recent experience has highlighted, however, that the adoption of good laboratory practices on tissue handling still varies enormously between different laboratories.

In a need to re-emphasise the importance of appropriate tissue handling, and to do so with an international perspective, BIG decided to develop clear and user-friendly educational material (a movie, a poster and a flyer in six languages) to provide guidance for good laboratory practices for handling tissues.

The main aim of this project is to achieve a long-term, durable, and optimal implementation of tissue handling procedures, since optimising the use of tissue material from international trials for translational research can accelerate the progress in breast cancer research. This project was realised in collaboration with the Jules Bordet Institute and its pathology laboratory in particular, thanks to funding obtained from the University of Michigan and the Breast Cancer Research Foundation.

IMPAKT 2013 & pre-IMPAKT training course

The IMPAKT Breast Cancer Conference – established by BIG and the European Society of Medical Oncology with other leading European cancer organisations – is Europe’s niche conference for translational research in breast cancer.

Focused on facilitating and advancing a personalised approach to breast cancer management, the 2013 edition gathered some 550 breast cancer specialists from 51 countries around the world. They had the opportunity to hear opinion leaders debating how to turn the latest scientific discoveries and new technologies into clinical practice, into real value for breast cancer patients! The conference, a main theme of which was breast cancer heterogeneity, was chaired by Professors Andrew Tutt (The Institute of Cancer Research and King’s College London) and Peter Dubsky (Medical University of Vienna).

The conference was preceded by a training course specifically designed for oncologists in their early career that aimed to provide them with the tools and basic notions to understand translational research.

“IMPAKT is definitely unique: it brings together innovative thinkers and takes a more fundamental approach than other breast cancer conferences, to figure out how to best develop and better individualise new strategies against breast cancer.”

Professors Andrew Tutt and Peter Dubsky
IMPAKT 2013 Co-Chairs
Collaboration

BIG was founded as a non-profit network of collaborative groups in 1999 to address fragmentation in European breast cancer research, and today gathers 49 like-minded research groups from around the world. Adhering to the same principles of research conduct, BIG members strive to achieve balanced partnerships between academia and the pharmaceutical industry in order to best serve the needs of patients.
Hospitals represented by BIG member groups: >3000

Investigators represented by BIG member groups: >8000
BIG Principles of Research Conduct

1. BIG research serves to advance knowledge about breast cancer in order to improve treatments and outcomes for patients.

2. All BIG trials retain independence from the pharmaceutical and biotechnology industry, even if they are sponsored wholly or in part by industry.

3. Independence means that a BIG member group or affiliated trials unit controls the database, and that industry partners may access the full trial data only after its release by the Steering Committee for the trial, and the Independent Data Monitoring Committee. In addition, all statistical analyses and study reports related to BIG trials are executed or supervised by a statistician, who may be a member of the BIG group or trials unit responsible for the trial, but who is independent of any other funding partners involved in the study.

4. Each trial has a Steering Committee that is representative of the groups and centres participating in the trial.

5. The Steering Committee of large trials, registration trials and those using treatments with potential safety concerns is advised by an Independent Data Monitoring Committee, the members of which may neither participate in the trial, nor represent the industry sponsor(s).

6. Trial monitoring may be conducted in part or exclusively by industry partners, but must involve supervision by the BIG group or trials unit coordinating the trial.

7. The trial Steering Committee is responsible for publications & presentations, which follow accepted scientific practice, academic standards, the study protocol, and any specific guidelines established by the Steering Committee for the trial.

8. All BIG trials follow Good Clinical Practice guidelines and any applicable regulatory standards.

9. BIG research embeds biological specimen collection for future research. Access to and use of biological samples collected in the context of research conducted under BIG is governed by policies approved by the trial Steering Committee and any applicable laws.

10. In consideration of the importance of long-term efficacy and safety evaluations, BIG strongly endorses the long-term follow-up of patients participating in randomised clinical trials.
The 2010-2014 BIG Executive Board consists of:

**Martine Piccart-Gebhart, MD, PhD, Chair**
Institut Jules Bordet, Brussels, Belgium
Université Libre de Bruxelles, Brussels, Belgium

**Aron Goldhirsch, MD, PhD (h.c.), Vice-Chair**
European Institute of Oncology, Milan, Italy
Regional Hospital, Lugano, Switzerland

**Michael Grant, MD, Treasurer**
Department of Surgery and Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria
Austrian Breast and Colorectal Cancer Study Group, Vienna, Austria

**José Baselga, MD, PhD**
Memorial Sloan-Kettering Cancer Center, New York, NY, USA
Vall d’Hebron Institute of Oncology, Barcelona, Spain

**David Cameron, MD**
The University of Edinburgh, Scotland, UK
NHS Lothian, Scotland, UK

**Angelo Di Leo, MD, PhD**
Hospital of Prato, Istituto Toscano Tumori, Prato, Italy

**Mitchell Dowsett, PhD**
Royal Marsden Hospital, London, UK
Institute of Cancer Research, London, UK

**Richard D. Gelber, PhD**
Harvard Medical School, Boston, MA, USA
Dana-Farber Cancer Institute, Boston, MA, USA

**Gunter von Minckwitz, MD, PhD**
German Breast Group (GBG) Research Institute, Neu-Isenburg, Germany
Thank you to all BIG Members!
Think BIG Campaign

The Think BIG campaign was established in 2012 to enable BIG supporters to join in a movement that would approach breast cancer as a problem to be solved in our lifetime, uniting the power of global collaboration and cutting-edge science.

For the past two years, the Think BIG campaign has been raising funds that will enable BIG scientists to address the burning questions that mean so much to women and men everywhere affected by breast cancer:

- What do differences at the genetic level of a breast cancer tumour mean for choosing the most effective treatment?
- How can we identify the patients who would do just as well with less toxic treatments, allowing them a much better quality of life during and after breast cancer?
- How do we serve young women who still want to become pregnant after a breast cancer diagnosis?
- Why does cancer spread from the breast to other parts of the body and how can we prevent these highly lethal metastases?
- What is different about male breast cancer, and how can we best treat male patients?

Our goal is to let our scientists Think BIG. We need to enable them to identify the burning questions and come together to solve them, independently of any commercial interests. The campaign is patient focused, and dedicated to finding the resources required to conduct research that benefits patients.

The pillars of our campaign include the following three areas:

BIG against breast cancer roundtable at the Royal Palace, Brussels, Belgium, February 2013
**Academic research**

The “burning questions” we mentioned above are addressed by our Academic research programme, which enables scientists to obtain the resources required and to enrol sufficient numbers of patients to test their hypotheses.

There are many areas of research that hold great promise for patients, but are not particularly attractive to the pharmaceutical industry and their shareholders. It is possible that many patients could be cured or otherwise benefit from a “lighter” exposure to traditional cancer treatments, for example by reducing the dosage or duration of drugs or radiation. The impact could be the same positive results, with fewer detrimental side effects and potentially lower treatment costs.

A primary aim of purely academic trials is to improve patients’ quality of life during treatment, without reducing their chances for cure or for significant extension of life. Not commercially motivated, these studies hold tremendous potential for patients and promise long-term gains to society, in all regions of the world.

**Operational needs**

Think BIG also looks to secure funding for the operational costs of BIG Headquarters. Clinical trials do not run themselves, and BIG plays an important role in facilitating and managing global projects to ensure both timely and highly credible scientific results.

Think BIG aims to ensure that BIG Headquarters has the resources required to support its existence as long as there is need for an international breast cancer research network. We are seeking dedicated supporters who will guarantee the continuation of our core operations, thereby allowing us to allocate 100% of any additional funding raised to BIG research projects.

**Education**

Think BIG aims to enable early-career scientists or clinicians to gain hands-on experience with the world’s leading breast cancer experts and contribute directly to groundbreaking scientific discoveries. For the explosion of knowledge and developments arising out of today’s research to continue to bear fruit tomorrow, it is essential to empower future leaders by providing systematic educational and research opportunities.

Doing so will ensure that we manage to bridge the gap between the growing prevalence of breast cancer and the number of trained specialists, as well as help address the imbalance between developed and emerging regions. BIG sees enormous potential for developing regions to begin or expand their participation in international trials – or to develop highly relevant regional research – and to share in the growing body of breast cancer knowledge. BIG will launch the first of such outreach projects in the next year.

**Let’s Think BIG**

Think BIG supporters share these goals and are making possible the pioneering breast cancer research done by BIG scientists all over the world. You can help by:

- Organising an event to raise awareness and funds for BIG
- Introducing BIG to your personal or professional network
- Donating your time and professional skills to support BIG
- Making a tax-deductible donation

**Will you Think BIG?**
## Financials

### Balance Sheet

<table>
<thead>
<tr>
<th>Assets</th>
<th>2013</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fixed assets</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intangible fixed assets</td>
<td>25,875</td>
<td>1,845</td>
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<tr>
<td>Tangible fixed assets</td>
<td>34,357</td>
<td>31,638</td>
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<tr>
<td>Financial fixed assets</td>
<td>500</td>
<td>999,402</td>
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<tr>
<td><strong>Current assets</strong></td>
<td>17,455,083</td>
<td>14,019,072</td>
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<tr>
<td>Receivables up to one year</td>
<td>5,325,090</td>
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<tr>
<td>Current investments</td>
<td>7,999,609</td>
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<tr>
<td>Cash at bank</td>
<td>4,037,015</td>
<td>1,221,506</td>
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<tr>
<td>Deferred charges and accrued income</td>
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<td>56,010</td>
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<tr>
<td><strong>Total Assets</strong></td>
<td>17,515,920</td>
<td>15,051,957</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Liabilities</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Equity</strong></td>
<td>5,245,686</td>
<td>5,319,296</td>
</tr>
<tr>
<td>Unrestricted net assets</td>
<td>5,245,686</td>
<td>5,319,296</td>
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<tr>
<td><strong>Debts</strong></td>
<td>12,270,234</td>
<td>9,732,661</td>
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<tr>
<td>Amounts payable after more than one year</td>
<td>1,326</td>
<td>6,777</td>
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<td>Amounts payable within one year</td>
<td>11,702,091</td>
<td>9,156,098</td>
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<tr>
<td>Current portion of amounts payable after more than one year falling due within one year</td>
<td>4,959</td>
<td>5,253</td>
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<tr>
<td>Trade debts</td>
<td>11,528,236</td>
<td>8,994,670</td>
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<tr>
<td>Tax, remuneration and social security</td>
<td>168,896</td>
<td>156,175</td>
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<tr>
<td>Deferred charges and accrued income</td>
<td>566,817</td>
<td>569,786</td>
</tr>
<tr>
<td><strong>Total Liabilities</strong></td>
<td>17,515,920</td>
<td>15,051,957</td>
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</tbody>
</table>

### Income & Expenses Statement

<table>
<thead>
<tr>
<th></th>
<th>2013</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operating income &amp; expenses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turnover (research)</td>
<td>13,476,223</td>
<td>13,559,247</td>
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<tr>
<td>Other goods &amp; services</td>
<td>-11,961,505</td>
<td>-12,692,299</td>
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<tr>
<td>Operating margin</td>
<td>1,514,718</td>
<td>866,948</td>
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<td>Remuneration, social security &amp; pension costs</td>
<td>-1,653,334</td>
<td>-1,454,208</td>
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<td>Operating result</td>
<td>-138,616</td>
<td>-587,261</td>
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<tr>
<td>Financial result</td>
<td>118,571</td>
<td>100,270</td>
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<tr>
<td>Extraordinary income (+)</td>
<td>1,822</td>
<td>2,855,800</td>
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<tr>
<td>Extraordinary expenses (-)</td>
<td>-55,386</td>
<td>-301,898</td>
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<tr>
<td><strong>Result for the financial year</strong></td>
<td>-73,610</td>
<td>2,066,911</td>
</tr>
</tbody>
</table>
Acknowledgements

BIG is extremely grateful to all those – foundations, institutions and individuals – who, through supporting its activities and projects, made it possible to get a step closer to finding a cure for breast cancer:

- Breast Cancer Research Foundation®
- European Commission
- Fondation Cancer (Luxembourg)
- National Lottery (Belgium)
- NIF Trust
- Susan G. Komen®
- Mr and Mrs Barrie Webb

BIG would also like to thank the King Baudouin Foundation for their collaboration and advice in BIG’s development activities.