FIGHTING BREAST CANCER AROUND THE GLOBE

The POSITIVE trial: good news for women with breast cancer who want to have a baby
COLOPHON

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NOTE FROM THE EDITORS

It is with great sadness that we learned of the passing of Professor Dr Hans-Jörg Senn, a long-standing friend and colleague of BIG. A world-renowned oncologist, he was also the founder of the St. Gallen Breast Cancer Conference and one of the founding members of the International Breast Cancer Study Group (IBCSG). Professor Senn died on 13 January 2023, and his incredible legacy will continue to inspire future generations of cancer scientists and oncologists. Our thoughts are with his family, friends, and colleagues. For an In Memoriam tribute, please see page 15.

On a positive note, we are delighted to congratulate Professor Giuseppe Viale for receiving the St. Gallen International Breast Cancer Award 2023. He has been recognised for his decades-long commitment to breast cancer research and for his significant contributions to the field, including many studies under the BIG umbrella. We thank him for his invaluable contributions to advancing the understanding and treatment of breast cancer. See also page 17.

The themed article of this BIG Research in Focus sheds light on the POSITIVE study, which examines the safety of pausing endocrine therapy for young women with breast cancer who wish to conceive. The early study results, presented at SABCS 2022, demonstrate that women who interrupt their endocrine therapy for approximately two years have a comparable risk of breast cancer recurrence to those who do not interrupt treatment. Thank you Professors Olivia Pagani, Ann Partridge, David Cameron, Richard Gelber, Monica Ruggeri and Tanja Spanic for generously having accepted to be interviewed on this topic by medical journalist Jenny Bryan. See from page 2.

The POSITIVE study would not have been possible without global collaboration. As a network, BIG holds a unique position in breast cancer research, with 58 member groups working together to develop and conduct studies such as POSITIVE. Not motivated by commercial interests, studies like these are financed through the groups’ own resources and our philanthropic communities. In honour of World Cancer Day 2023 (4 February), BIG and ETOP IBCSG Partners Foundation joined forces to launch a media awareness campaign on POSITIVE. See page 23.

The section “BIG Network” provides an overview of activities carried out by BIG Headquarters (HQ) and includes news from BIG members. At BIG’s General Assembly of 16 January 2023, ITMO (Italian Trials in Medical Oncology) was admitted as an Effective (voting) Member of BIG. A warm welcome is extended to the group! See page 14.

For Pink October 2023, BIG and its philanthropic unit, BIG against breast cancer, will build on their previous awareness and communications campaign with the theme and visual concept of “Missing”. First launched for Pink October 2022, the campaign’s primary goal is to boost BIG’s visibility, enhance brand recognition, and increase awareness about the importance of global academic breast cancer research. For an overview of activities carried out during Pink October 2022, see from page 18.

The section “Clinical Trials and Activities” gives an update on BIG trials, their status and abstracts presented at ESMO, ASCO, EBCC and SABCS, as well as an overview of recently published manuscripts. See from page 24.

It also highlights BIG members’ own research and related activities around the world. For the overview of “Other trials and activities by BIG Member Groups”, see from page 32.

Finally, you will find the tables with the “Overview of the Current Studies Run within the BIG Network”, from page 44.

We hope you enjoy the reading and look forward to our on-going collaboration with you.

Together, we achieve more

BIG HQ’s Editorial Team
Young women with breast cancer can safely pause endocrine therapy for approximately two years to try to get pregnant, according to early results from the POSITIVE trial, presented at SABCS 2022. The findings, soon to be published in a prominent journal and also highlighted in BIG’s campaign for World Cancer Day 2023 (see page 23), showed that women who paused endocrine therapy after 18-30 months had a similar risk of breast cancer recurrence to those in previous studies who did not interrupt treatment. The POSITIVE study was sponsored and conducted by the International Breast Cancer Study Group (IBCSG), a division of ETOP IBCSG Partners Foundation, and the Alliance for Clinical Trials in Oncology in North America, in partnership with BIG, and included 116 hospitals in 20 countries. It clearly demonstrated the power of international collaboration in answering key questions of great importance to patients and clinicians – as medical journalist Jenny Bryan discovered when she talked to some of those involved.

About one in five women with breast cancer is diagnosed when she is young enough to have children, and numbers are rising, including in the Middle East, Africa and Asia. But the endocrine therapy offered to most young women with hormone-receptor (HR) positive breast cancer after surgery, to reduce their risk of recurrence, prevents conception – at a time when some want to have children.

“Women have often been told that it isn’t safe to interrupt endocrine treatment to try to have a baby because their cancer is driven by hormones, and pregnancy will boost those hormones. As endocrine therapy lasts for five to 10 years, by the time many women finish treatment it is too late for them to get pregnant as their fertility reduces with age, especially if they have chemotherapy for breast cancer,” explains Olivia Pagani, POSITIVE’s international study chair, and Professor of Oncology, University of Geneva and Lugano, Switzerland.

BIG Chair, David Cameron, Professor of Oncology at Edinburgh University, UK, agrees that the clinical view — based on logic rather than evidence — has been that if treatment is stopped early, this will adversely affect survival:

“There has been a natural concern that if you stop treatment you will reduce long term survival. So clinicians have wanted their patients to continue endocrine therapy for as long as possible. Younger women with breast cancer have faced a difficult choice — interrupt treatment and risk their survival or continue treatment and risk not being able to get pregnant.”

Retrospective data showed that getting pregnant after treatment for HR-positive breast cancer did not increase the risk of recurrence. However, there was a clear need for a prospective study to find out if women could safely interrupt endocrine treatment for breast cancer to get pregnant. In 2013, the BIG-NCTN (National Clinical Trials Network) Endocrine...
Working Group, chaired at that time by the late Professor Aron Goldhirsch, proposed a prospective study which became the POSITIVE (BIG8-13) trial (*Pregnancy Outcomes and Safety of Interrupting Therapy for Women with Endocrine Responsive Breast Cancer*).\(^3\)

“In 2013, the Group was considering which important questions needed international collaboration in order to get answers, and everyone got behind the idea for POSITIVE and wanted to put the effort and resources into it. Although breast cancer in young women is not common, everyone had a few patients and understood what it would mean to them if they could interrupt their endocrine therapy to try to become pregnant without increasing their risk of recurrence,” recalls POSITIVE Trial Senior Statistician Richard Gelber, Professor in the Department of Biostatistics, Harvard University, and Dana-Farber Cancer Institute, Boston, USA.

Knowing that they were unlikely to get significant pharmaceutical support for POSITIVE was a considerable hurdle for the IBCSG, BIG, the Alliance for Clinical Trials in Oncology, and all the collaborative groups, but it did not deter them. Cameron explains that BIG saw it as a key question for women with breast cancer and was committed to moving the study forward. The fact that there was no major pharmaceutical funding – as there isn’t in about a third of trials that BIG is involved in – was not a barrier.

“POSITIVE is unusual in being carried out in both North America and the Rest of the World. BIG was able to facilitate global recruitment because it was familiar with systems in North America and it could offer a framework for IBCSG to share the idea with other collaborative groups within BIG and establish agreements. BIG also helped raise funds through *BIG against breast cancer*, BIG’s philanthropic arm,” he says.
Monica Ruggeri, Head of Program for Young Patients at IBCSG, is convinced that such a study would not have been possible without such an extensive collaboration and without all those who gave so generously to fund it, including Fonds Baillet Latour, Belgium, Pink Ribbon Switzerland and Rising Tide Foundation for Clinical Cancer Research, Switzerland.

“It shows what we can achieve when we join forces beyond frontiers to answer burning questions for patients, and that academic research is still possible. We are continuing to raise funds because we still need more than €2 million for critical longer term confirmation of the initial results of POSITIVE and additional funding to carry out important translational research to evaluate the biological factors that contribute to the findings of the study,” says Ruggeri.

POSITIVE: DESIGN AND PATIENT POPULATION

POSITIVE is a single arm prospective study to assess the risk of breast cancer relapse associated with temporary interruption of endocrine therapy. As a randomised, controlled trial design was not considered feasible and ethical, an external control cohort was established and outcomes from POSITIVE, such as breast cancer relapse, were compared with those from participants with similar characteristics who took part in the SOFT/TEXT trials to identify optimal endocrine therapy for premenopausal women with early breast cancer. These trials were also run by IBCSG, under BIG’s umbrella.

“POSITIVE is one of the most important studies I’ve been involved in, and the results can reassure young women with breast cancer who want to interrupt their endocrine therapy to have a child and empower them to make informed decisions,” says Gelber.

He explains that of the more than 5,000 women who were recruited for SOFT/TEXT, almost 2,000 would have been eligible for POSITIVE, i.e., aged 42 years or younger and completed two years of endocrine therapy. Patients from this SOFT/TEXT cohort were matched with those in POSITIVE for disease characteristics, treatment and other relevant parameters. Breast cancer recurrence and other outcome data were then compared for women in the trials who had interrupted endocrine therapy (POSITIVE) or had not interrupted treatment (SOFT/TEXT).

“The primary entry criterion for recruitment into POSITIVE was that women expressed a desire to become pregnant, and that had to be without any encouragement from their doctor,” explains Gelber. “Initially, recruitment was slow, and this may have been because women who were already on treatment were not considering pregnancy. When investigators started seeing newly diagnosed patients, more of these asked about the possibility of pregnancy and were then told about POSITIVE.”

From December 2014 to December 2019, 518 women aged 42 or younger who wanted to become pregnant enrolled in the study. Before interrupting their treatment, women were to have completed between 18 and 30 months of adjuvant endocrine therapy. If women did not become pregnant within one year of trying, investigators were advised to refer them for fertility checks and, if these showed that pregnancy was unlikely, to strongly recommend that women return to endocrine therapy as soon as possible.

In 2021, an analysis was published of the characteristics of the women who enrolled in POSITIVE to gain insights into which patients and doctors considered it acceptable to interrupt endocrine therapy to try for a pregnancy and potentially guide future practice. At enrolment, the median age of participants was 37 years, three quarters of women had no children, and about half used fertility preservation. Over 90% had stage I/II disease, two thirds were node-negative, 55% had breast conserving surgery and 62% had received neo/adjuvant chemotherapy. The most commonly prescribed form of endocrine therapy was tamoxifen
alone (42%), followed by tamoxifen with ovarian function suppression (35%). A greater proportion of North American women were less than 35 years at enrolment (43%), had a mastectomy (59%) and received tamoxifen alone (59.8%). More Asian women were childless (81%), had node negative disease (76%) and received tamoxifen and ovarian suppression (56%). More European women had received chemotherapy (70%).

Ann Partridge, lead investigator of POSITIVE in the USA and Vice Chair of Medical Oncology at Dana-Farber Cancer Institute and Professor of Medicine at Harvard Medical School, Boston, USA, points out that some variations in patient characteristics in POSITIVE probably reflected differences in culture and healthcare systems:

“Understanding these differences will help us offer women the support they need at the right time and place. For example, if women want to wait longer before they interrupt their hormone therapy or they live in a country such as the US, where they are more likely to have chemotherapy, we may need to be extra careful about getting fertility preservation in place for them,” explains Partridge. “Having this information from POSITIVE will also help in the development of future studies so we recruit the right patients to answer our research questions,” she adds.

WHAT POSITIVE HAS SHOWN

At the San Antonio Breast Cancer Symposium in December 2022, Partridge reported that the three-year rate of breast cancer recurrence in POSITIVE was 8.9%, which is similar to the 9.2% reported in the external control cohort taken from SOFT/TEXT trials of adjuvant endocrine treatment for premenopausal breast cancer.

“The POSITIVE trial showed that, in this early follow up, women who interrupted endocrine therapy to try and get pregnant were not at increased risk of breast cancer recurrence, which was very reassuring,” says Partridge. “We need to see the effect on recurrence in longer term follow up but these results are very important in helping to answer critical questions for younger women with breast cancer over the safety and feasibility of taking a break from endocrine therapy,” she adds.

Pagani agrees about the importance of the POSITIVE results for young women with breast cancer, and she stresses their importance to those who are not breast cancer specialists, including oncologists who treat a range of cancers including breast cancer, as well as to gynaecologists and family doctors.

“Breast cancer specialists were already aware of the retrospective data supporting the safety of pregnancy in women with breast cancer, and the POSITIVE results reinforce that knowledge. But doctors who do not specialise in breast cancer are less aware of the previous data and have tended to discourage women from interrupting their endocrine therapy by suggesting they could be risking their lives. It is very important to spread the word about POSITIVE, so everyone is aware of the results,” she says.

The POSITIVE data also showed that 368 of 497 women (74%) who were followed for pregnancy status had at least one pregnancy, and 317 (63.8%) had at least one live birth, with a total of 365 babies born. These rates of conception and childbirth were comparable with or higher than those typically seen in the general public and were not greatly affected by whether women had undergone chemotherapy. Rates of pregnancy complications, healthy babies and congenital malformations also appeared similar to those seen in healthy populations. Trial participants were strongly advised to resume endocrine therapy after a pregnancy attempt or success and data from the initial analysis show that, at that time, 76.3% had followed this advice.

Pagani points out that the women in POSITIVE were very motivated to become pregnant and that they had teams of obstetricians and neonatologists to help them, so it is perhaps not surprising that the pregnancy rates were so good.

“The pregnancy results from POSITIVE underline the fact that all women who want to have a baby after breast cancer treatment really do need more expert care to help them achieve this than typical healthy women who do not have breast cancer,” she says.

For women now wanting to pause their endocrine therapy for a pregnancy on the basis of the POSITIVE data, Pagani advises adhering to timings used in the trial, i.e., 18-30 months of hormone treatment before pausing, and a maximum two years off treatment.

“These timings were agreed on the basis that the minimum effective duration of tamoxifen to reduce breast cancer recurrence was known to be 18 months and, at the upper end, younger women who completed three years could probably wait another two years
to complete treatment before getting pregnant, as opposed to older premenopausal patients," she says. “The two-year time limit before returning to treatment was based on the fact that women need time to ‘wash out’ from hormone treatment, become pregnant and give birth and possibly breast feed. It also allows for the fact that, in some cultures, women may have two pregnancies in two years – something that did happen in POSITIVE,” she adds.

Pagani also advises that physicians and women should be aware that 94% of those in POSITIVE had Stage 1/2 disease.

“Women with Stage 2 have nodal involvement, so we included women with this degree of tumour spread. However, we can only say that the POSITIVE results apply to those with the stages included in the study. It is of course up to doctors and patients to discuss whether to interrupt endocrine treatment based on each situation,” Pagani points out.

Partridge agrees:

“My job is to share information with my patients and be their navigator, and I’m going to support the decisions they make. POSITIVE really advances what we know, but even among patients with Stage 3 disease some are at higher risk than others, so we want to tailor treatment to a patient’s risk and to their preferences, and work out the best compromise for them,” she says.

DILEMMAS FOR YOUNGER PATIENTS WITH BREAST CANCER

Tanja Spanic was 26 when she was diagnosed with breast cancer in 2008, and her oncologist advised that, as she was so young, there would be time for her to have children when she completed endocrine therapy even with prolonged treatment for 10 years.

“At first, I was happy with that answer but a few years later I started to worry about the effects of chemotherapy on my body and my fertility. In Slovenia where I live, fertility preservation was not available at that time and, because I was high risk, I had the full 10 years of endocrine therapy,” explains Spanic, a member of the POSITIVE Steering Committee and President of Europa Donna Slovenia and Europa Donna, European Breast Cancer Coalition.

Having taken advice from oncologists and waited six months after she completed treatment, Spanic decided to try for a baby. She conceived naturally, had a normal pregnancy and gave birth to a healthy daughter in 2020.

“I was fortunate but, in my role as patient advocate, I have met many women with less good outcomes, and this is why the results of the POSITIVE trial are so important. Even healthy women over the age of 35 can find it hard to get pregnant, so we don’t want to encourage young women with breast cancer to wait. POSITIVE brings forward the time when women receiving hormone treatment can start trying to get pregnant,” says Spanic.

Fertility is undoubtedly a major concern for young women with breast cancer. In the Helping Ourselves, Helping Others (HOHO) North American prospective cohort study, led by the Dana-Farber Cancer Institute, Boston, USA, 51% of 620 women newly diagnosed with early breast cancer were concerned about their fertility and, in 28%, these concerns significantly affected treatment decisions, including adherence to endocrine therapy. Only 10% used fertility preservation strategies (e.g., embryo, egg or ovarian tissue cryopreservation, or gonadotropin releasing hormone [GnRH] agonists during chemotherapy). In the European HOHO cohort, sponsored by the IBCSG, of 297 participants, 64% expressed concerns about fertility, and 15%
decided not to follow prescribed therapies. Twenty-seven per cent used fertility preservation strategies.

“In Slovenia, we now have a well-established pathway for fertility preservation but this is not the case in many parts of Europe and around the world. In addition, some women want to start treatment straight away and not to wait for fertility preservation, so the POSITIVE findings are particularly important for all these women,” adds Spanic.

Spanic explains that surveys among young women with breast cancer suggest that fertility is discussed at consultations but it is generally patients rather than clinicians who raise the issue – something she hopes will change, especially in the light of the POSITIVE results. “Hopefully doctors will feel more confident about talking to patients about fertility options, including interrupting hormone treatment, and women will be given all the information they need. Recurrence or progression of breast cancer is one of the biggest fears for women and, now that POSITIVE has shown there is no greater risk from pausing treatment and getting pregnant, this will be very reassuring for women and their doctors. It will also be important even if a woman’s breast cancer does progress after a pregnancy because we can tell her that she should not blame herself for deciding to interrupt her treatment,” says Spanic.

IBCSG: PROGRAM FOR YOUNG PATIENTS

In 2013, the IBCSG under the leadership of the late Professor Goldhirsch, committed to the Program for Young Patients focused on women with breast cancer under the age of 40, and the POSITIVE trial was one of the first initiatives.

“The aim of these ambitious, academic programmes is to provide healthcare professionals with information to better understand the needs of young women with breast cancer and to design studies that can find solutions to some of the difficult issues facing these patients,” explains Ruggeri.

Within the current programmes, IBCSG is sponsoring and conducting the POSITIVE trial and the European arm of the HOHO study in young women with breast cancer. In addition to young women’s fertility concerns, the HOHO study is investigating short and long-term disease and treatment issues, and psychosocial concerns at baseline and for 10 years following diagnosis.

“Our commitment to these studies is a strong statement about the importance we place on research to support young women with breast cancer, and we recognise the commitment of the hundreds of women who are taking part in POSITIVE and HOHO, as well as the thousands more who participated in SOFT TEXT – all of whom are needed to get answers that will benefit other young women in the years ahead,” says Ruggeri.

WHAT NEXT FOR POSITIVE?

POSITIVE researchers are continuing to monitor study participants to assess recurrence over time, and a long term follow up for 10 years is planned, as are multiple secondary analyses of factors related to outcomes ranging from pathology analysis (e.g., oestrogen/progesterone/HER2 receptor, Ki-67), ctDNA levels in women who became pregnant and those who did not, reasons for failing to get pregnant and for use of assisted reproductive technology (ART) and fertility preservation, and the psychological effects of stopping treatment to try for a pregnancy.

“The initial results from POSITIVE are very encouraging but grade 1/2 breast cancer can recur for at least 20 years after diagnosis, so it is essential that we have long term follow up from the study,” says Cameron.

Spanic agrees: “We would definitely like to see longer term experience of interrupting endocrine therapy, both from the POSITIVE trial and from observational real-world studies. With all the new treatments for breast cancer, we are increasingly hoping and expecting women to have a near normal life expectancy, so we need to know that interrupting hormone therapy to try for one and possibly more than one pregnancy does not affect recurrence in the long term.”

To women and their physicians asking whether women can pause endocrine treatment for reasons other than to try for pregnancy, Partridge explains that POSITIVE did not address that question. She points out that, while the SOLE trial (also conducted by IBCSG under the BIG umbrella) showed that intermittent endocrine therapy in years five to 10 of adjuvant treatment did not result in worse outcomes than continuous treatment, it did not look at intermittent therapy in the first five years of endocrine treatment.
“In general, we know that people who do not adhere well to endocrine therapy typically do worse than those who take all their medication, and it’s possible that pregnancy has a good impact on disease outcomes in breast cancer that offsets any negative impact from taking the break from endocrine therapy. But that would be difficult to study,” says Partridge.

FUTURE RESEARCH IN YOUNG WOMEN WITH BREAST CANCER

There are still many questions about breast cancer in younger women that need to be answered, and Ruggeri would like to see younger women included in many more breast cancer trials.

“Young women are definitely under-represented in major breast cancer trials, and they are in danger of over-treatment because of their age. There are still many questions to be answered if we are going to establish optimal care for young women with breast cancer,” she says.

Pagani and Cameron agree. “It’s another taboo that young women are at higher risk of relapse and need more treatment – either with 10 years of endocrine treatment just because they are young or having chemotherapy which they may not need. We need to be much more precise in the way we treat young women with breast cancer,” says Pagani.
Cameron would like studies in premenopausal women to identify patients who do not need chemotherapy because their cancer does not respond to it.

“We usually base decisions on the risk of the cancer coming back, with the lower the risk the less they have to gain from treatment. But it would be wonderful to be able to advise patients according to the biology of their cancer and whether chemotherapy can change their risk. If it won’t change their risk, they can not only avoid the acute toxicity of chemotherapy but also the ovarian damage in women who would like to conceive,” says Cameron.

In addition, he would like to get a better understanding of how long a woman is likely to remain fertile so hormone treatment can be personalised according to whether she is likely to remain fertile five, 10 or more years after her treatment. He adds that although newer drugs, such as those for HER2-positive breast cancer, do not appear to damage ovarian function, there is a need to continually investigate their effects.

“The drugs that are being used are changing, and the pivotal trials that examine their efficacy don’t address questions like these that are only important to a minority of patients. So we’re always playing ‘catch up’ in clinical research because each new agent needs to be checked out,” he says.

Partridge also calls for greater inclusion of women of childbearing age in Phase 3 trials of new agents for breast cancer:

“We need to routinely follow up menstrual and fertility outcomes in these women, and we also need to look at the late effects of treatment on their general health. They may live 40, 50 or more years after their treatment so we need to know what morbidities they may develop and how these affect them in much later life.”

As Pagani concludes: “POSITIVE was the last clinical trial of my career, and it is a good way to end my career because it gives hope. We have fought for many years to help women with breast cancer to live longer but POSITIVE is about how they live. We have enabled them to live longer but we also need to give them something to enable them to live their life better.”
REFERENCES:


Despite the continued difficulties that Covid-19 had on the global economic climate, and despite the Ukrainian conflict and global energy crisis, BIG is thankful that it can continue to rely on the loyalty of its existing partners. We are very grateful for the commitment and generosity of our partners for whom breast cancer research is essential.

To all partners, we would like to say a heartfelt “THANK YOU!” You have helped us in our efforts by involving your staff in our activities, by inviting them to raise funds, or by asking your clients and partners to support breast cancer research. All of these efforts in turn help support the work of our research groups, enabling patients to participate in our studies and results to be achieved more quickly.

Academic studies needing support
Thanks to BIG’s unique position in the field of breast cancer research, academic studies without commercial interest are developed by BIG researchers and can be financed in-part through our philanthropic community.

The precious support of foundations made the difference that allowed us to continue to ensure progress in the BIG studies POSITIVE, AURORA and EXPERT. Funding is still required for these studies, either to enrol the number of patients needed or to continue with follow-up, both essential to generate robust data and results and to answer important questions.

For six consecutive years, BIG has been blessed with the support of Fonds Baillet Latour, specifically for the POSITIVE study. This charitable trust was created to encourage, promote, and foster human excellence in Belgium, with a diligent but open approach to social development. Over the years, and through the allocation of grants, prizes and scholarships, the organisation has increased its scope of action focusing on five pillars: health, culture, education, environment, and sports. All the projects and initiatives supported in each field have a Belgian dimension.

Mr Benoit Loore, General Manager at Fonds Baillet Latour, kindly accepted to be interviewed for this BIG Research in Focus.

Why has Fonds Baillet Latour chosen to support BIG’s breast cancer research and, more specifically, the POSITIVE study?
As a philanthropic foundation, we are continuously looking for ways that improve the impact of our initiatives. We firmly believe that strong
collaborations and partnerships are key to achieve this. From this perspective, BIG, an international Belgian based not-for-profit organisation which constitutes the largest worldwide network for independent research against breast cancer, appeared to be an obvious partner for us. For instance, in order to conduct its POSITIVE study, BIG had the capacity to find a sufficient number of participants by enrolling patients in more than 20 countries including Belgium. An individual research group would probably not have been able to do so.

We are extremely happy of course to learn that the first results of the POSITIVE study are encouraging and show that young women with breast cancer who paused their endocrine treatment to try to get pregnant, were able to do so safely. It makes us proud to know that our support to the POSITIVE study will be able to make a difference to many young women.

Why is it, in your opinion, important for foundations and companies to support BIG's research?

Breast cancer is the most diagnosed cancer among women worldwide. According to the WHO, in 2020, there were 2.3 million women diagnosed with breast cancer and 685,000 deaths globally. As of the end of 2020, there were 7.8 million women alive who were diagnosed with breast cancer in the past 5 years, making it the world’s most prevalent cancer. Supporting non-commercial, independent research in this area is therefore critical for the health and wellbeing of millions of people. BIG has demonstrated that its approach based on a global network of collaborative research groups and data centres, is effective and able to deliver concrete answers and better treatments for patients with breast cancer.

What is your hope for the future of breast cancer research?

Working together accelerates our understanding of diseases and contributes to the faster development of better treatments. We hope of course that collaboration efforts will further develop and extend also towards further interdisciplinary integrated research. For example, an improved understanding of the links between cancer and nutrition might allow better prevention strategies and eventually significantly reduce the number of cases.

For more information, please visit:
www.fondsbailletlatour.com

BIG’S PHILANTHROPIC COMMUNITY

BIG’s dedicated philanthropy unit – BIG against breast cancer – conducts vital fundraising to help finance academic clinical trials and research programmes that have no commercial interest but are crucial for patients with breast cancer. These collaborative efforts have led to practice-changing achievements in the field of breast cancer care. The funds raised help BIG’s member groups (made up of breast cancer experts across the globe), their affiliated hospitals, and research staff at BIG Headquarters to finance their efforts and patients’ participation in one or more BIG studies.
January 2023

BIG’S GENERAL ASSEMBLY

On 16 January 2023, in a virtual General Assembly (GA), the following decisions were taken by BIG groups:

> BIG’s 2023 budget was approved
> Six seats on BIG’s Executive Board will be filled during the 2023 elections
> ITMO (Italian Trials in Medical Oncology) was admitted as an Effective (voting) Member of BIG
> All future GAs will take place virtually.

The January GA took place after the meeting on 20 December 2022, which exceptionally did not meet the quorum of 50% presence. As stated in BIG’s statutes, if a quorum is not met during a GA, a new meeting must be scheduled within 30 calendar days, and decisions are taken regardless of the number of participants.

The next GA, open to all BIG members but requiring the quorate presence of the official group representatives (or appointed delegates), will take place virtually from 13:00 – 15:00 CEST on Monday 26 June 2023.

New BIG member group

GRUPPO ITMO – ITALIAN TRIALS IN MEDICAL ONCOLOGY

At BIG’s General Assembly of 16 January 2023, ITMO (Italian Trials in Medical Oncology) was admitted as an Effective (voting) Member of BIG. This brings the total number of BIG member groups to 58.

Gruppo ITMO is a free, non-profit association that brings together medical oncologists and individuals with an interest in the study and treatment of neoplasms. Professor Emilio Bajetta, ITMO’s founder and president, serves as the group’s official BIG representative.

In the late 1980s, the continuous demand to conduct studies according to international standards (GCP) and multiple case studies to provide reasonable scientific evidence led to the establishment of several research groups in oncology. Gruppo ITMO, founded in September 1989, was among them.

Gruppo ITMO, based in Italy, focuses on multicentre research with the primary objective of studying new drugs and/or programmes for the medical treatment of neoplasms.

ITMO’s main purposes are to:

> **promote clinical research** by conducting multicentre studies with collaboration from medical oncologists,
> **contribute to the updating of medical members** through an educational programme,
> **operate as a coordination agency** for other clinical research groups,
> **sponsor and/or participate** in scientific and/or cultural initiatives related to medical oncology.

ITMO’s main scientific lines of interest are:

- oncology of the gastrointestinal tract
- breast cancer
- neuroendocrine tumours
- lung oncology
- prostate cancer
- renal cell carcinoma
- immunotherapy
- geriatric oncology
- studies with biopharmaceuticals

A warm welcome is extended to the group!

For further information, please visit [www.itmo.it](http://www.itmo.it)
It is with great sadness that we learned of the passing of one of BIG’s long-lasting friends and colleagues, Professor Hans-Jörg Senn, a world-renowned oncologist, founder of the St. Gallen Breast Cancer Conference and one of the founding members of the International Breast Cancer Study Group (IBCSG). Professor Senn died on 13 January 2023, and his incredible legacy will continue to inspire future generations of cancer scientists and oncologists. Our thoughts are with his family, friends, and colleagues.

Professor Senn was born in Switzerland in 1934. As a young physician, he relocated to the United States with his family to learn about the intricacies of specialising in medical oncology. Upon returning to Switzerland, he became one of the country’s first cancer specialists, with a particular focus on breast cancer.

He was Co-Chair of the Department Internal Medicine and Head of the Division Oncology-Haematology at the St. Gallen Cantonal Hospital, Switzerland. After two decades, together with a dedicated team, he opened the Tumor- and Breast Center ZeTuP in St. Gallen, where they aimed to make prevention and early detection a core part of cancer care.

One of Professor Senn’s most notable contributions to breast cancer research is the establishment of the St. Gallen International Breast Cancer Conference, in 1985. In the 1970s, together with Allan Coates, Richard Gelber and Aron Goldhirsch, he developed the concept and format of the conference, which brings together international experts in breast cancer treatment and research to share knowledge and advance the field. The conference has always been an important event for BIG members and continues to be a vital forum for discussing and disseminating the latest advances in breast cancer treatment. It is a testament to Senn’s vision and leadership that it has become one of the most respected conferences in the field of breast cancer.

Professor Senn’s work led to the development of the St. Gallen Consensus Guidelines, which are now a widely recognised standard for treatment of individuals with early breast cancer. The guidelines are updated after each St. Gallen International Breast Cancer Conference and provide clinicians with evidence-based recommendations on the most appropriate breast cancer treatment approaches, based on the individual patient’s patterns, biological and clinical breast cancer characteristics, as well as on patient preferences.

To do such developmental work, Professor Senn founded the Foundation St. Gallen Oncology Conferences (SONK). Within this context, various conferences and seminars were established, which focused not only on finding a cure but also on preventing side effects and considering long-term quality of life. In 1987, a
Conference on Supportive Care in Cancer Patients convened in St. Gallen. It was the first such international meeting ever held. The event attracted around 700 attendees, with nearly half of them being specialist nurses, mainly from the United States and Australia. Participants from 75 different countries were represented in total.

This was the beginning of the Multinational Association of Supportive Care in Cancer (MASCC), which continues to lead efforts in the practice, education, and research of supportive care in cancer. The conference also led to the creation of the Journal Supportive Care in Cancer, which was formally established at the first meeting and started publication in 1993. Professor Senn served as its Editor-in-Chief.

A compassionate and dedicated physician who always put his patients first, Professor Senn was also known for his kind and thoughtful approach to patient care. His efforts to advance the field of breast cancer care have made a significant impact on the lives of countless patients and their families.

In addition to his work in breast cancer care, he was also a teacher and mentor to many young doctors and researchers. Senn believed in the importance of education and training in the field of oncology and worked tirelessly to inspire and encourage the next generation of cancer care professionals.

Professor Senn’s contributions to the field of breast cancer care and cancer care in general have been widely recognised and celebrated. He received numerous awards and honours throughout his career, including:
- the Science Writer Award from the American Cancer Society, 1967
- the Dora Seif-Cancer Award from the University of Basel, 1969
- the San Salvatore Cancer Award for achievement in cancer treatment, Lugano, 1985
- the Swiss National Cancer Award, Bern, 1997
- the FECS-Pezcoller Award for Recognition for Contribution to Oncology by the Federation of European Cancer Societies, 2003
- the Lifetime Achievement Award, European Society for Medical Oncology (ESMO), 2011.

In 2017, the German Society of Gynaecology and Obstetrics acknowledged his remarkable achievements in the field of Women’s Health honouring him as one of “The Big Four of the Millennium”, alongside Umberto Veronesi, Craig Jordan and Harald Zur Hausen.

In 2003, Professor Senn created the St. Gallen Breast Cancer Award, which recognises exceptional individuals who have made significant contributions to breast cancer research.

Next to being one of the founders of the IBCSG, which was established in 1992 and which he led as first Foundation Council President until 1995, Professor Senn was also President of the Swiss Group for Clinical Cancer Research (SAKK) and involved in many leadership committees in cancer medicine, especially in senology.

Professor Hans-Jörg Senn was editor of Journals like the European Journal of Cancer, The Breast and the Journal of Supportive Care in Cancer. He authored or co-authored more than 600 publications, including peer-reviewed journal articles, book chapters, and other scientific works. These publications reflect Senn’s expertise in the diagnosis, treatment, and management of breast cancer, as well as his commitment to improving cancer care and outcomes for patients.

OTHER OBITUARIES:
St. Gallen International Breast Cancer Award 2023

PROFESSOR GIUSEPPE VIALE HONOURED

At this year’s St. Gallen Breast Cancer Congress (SGBCC, 15-18 March 2023), Professor Giuseppe Viale was honoured with the St. Gallen International Breast Cancer Award 2023 for devoting decades of his career to breast cancer research and for his exceptional contributions to the field.

St. Gallen Oncology Conferences (SONK) is privileged to count on Professor Viale as an active contributor and supporter of the St. Gallen International Breast Cancer Conference and Consensus Guidelines.

This year’s St. Gallen Breast Cancer Award holds a special significance as it not only recognises the remarkable achievements of Professor Viale but also pays tribute to the visionary late Professor Senn, who passed away on 13 January 2023. Senn established the Foundation St. Gallen Oncology Conferences (SONK) and paved the way for the development of the St. Gallen Consensus Guidelines – now widely recognised as the gold standard for the treatment of individuals with early breast cancer. It was Professor Senn who created this prestigious award back in 2003, to honour outstanding contributions to the field of breast cancer research and treatment.

With this recognition, Professor Viale joins a list of well-known scientists who have been honoured with the St. Gallen International Breast Cancer Award, including Professors Philip Poortmans (2021), Monica Morrow (2019), Martine Piccart-Gebhart (2017), Alan Coates (2015), Aron Goldhirsch (2013), V. Craig Jordan (2011), Richard Gelber (2009), Michael Baum (2007), Umberto Veronesi (2005), and Dr. Gianni Bonadonna (2003).

Professor Giuseppe Viale, on receiving this award:

“I am more than happy and honoured to be the recipient of the St. Gallen International Breast Cancer Award 2023 and to join past recipients who I have long admired and respected. I had the privilege of collaborating for many years with high-quality clinical research groups, such as the IBCSG and BIG, and I am convinced that this award is above all an acknowledgment of my work within these organisations.”

And he concludes: “I also consider the St. Gallen International Breast Cancer Award 2023 as a token of appreciation for the contribution pathologists have made, and will increasingly make in the context of a multidisciplinary teamwork, to the advances in clinical and translational research and in local and systemic treatments for patients with breast cancer.”

On behalf of BIG, we would like to extend our sincerest congratulations to Professor Viale for receiving this well-deserved recognition. We thank him for his unwavering drive and tireless efforts to advance the understanding and treatment of breast cancer.

Career overview
- Giuseppe Viale, MD, FRCPPath
- Chairman, Department of Pathology and Laboratory Medicine
- European Institute of Oncology IRCCS
  Milan, Italy

Professor Viale earned his MD degree at the University of Milan in 1976. He became a specialist in pathology in 1979, and professor of Pathology at the University of Milan School of Medicine in 1987. He is the Chairman of the Department of Pathology and Laboratory Medicine at the European Institute of Oncology in Milan since 1994. A member from 1987, he was elected Fellow of the Royal College of Pathologists (FRCPath) in 1997.

He is the chairman of the Central Pathology Office of the International Breast Cancer Study Group (IBCSG) and of the Pathology Board of the Michelangelo Foundation, and lead pathologist of the Breast International Group (BIG). Professor Viale is the head of the central reference laboratory for several international randomised clinical trials of targeted therapies and immunotherapies for patients with early and advanced breast cancer.
Pink October 2022 and 2023

BIG’S “MISSING” CAMPAIGN

For Pink October 2022, BIG and its philanthropic unit BIG against breast cancer developed a compelling awareness and communications campaign centred around a specific theme and visual concept: “Missing”.

Launched for Pink October 2022 and to be highlighted in a new variation for Pink October 2023, “Missing” has the objective of boosting BIG’s visibility, enhancing brand recognition, and increasing awareness about the significance of global breast cancer research.

The campaign was announced with a press conference on 22 September 2022 and ran through 31 October 2022. Throughout this period, various BIG communications activities and events targeting both lay and scientific audiences were organised while also attracting new donors and corporate partnerships.

CAMPAIGN CONCEPT AND TAGLINE

The visual concept behind “Missing” in 2022 consisted of two group photographs that capture the same life scenario, for example a dinner with friends, a meeting at work, a family reunion, and more. However, in the second picture, one person is missing from the scene. A campaign tagline was used in all communications materials, and adapted according to each photo used:

**Act before they’re / she’s / he’s gone!**

**Support breast cancer research now.**

Our goal is to inspire positive action by tapping into the emotions evoked by these pictures or testimonials. By highlighting the absence of a loved one who lost their life to breast cancer, we hope to encourage people to support breast cancer research and contribute to progress against this disease. For further information, see also: [https://bigagainstbreastcancer.org/big-missing-campaign/](https://bigagainstbreastcancer.org/big-missing-campaign/)

CAMPAIGN IMAGES:
Act before she’s gone! Support breast cancer research now.

#BIGagainstBC
#BIGMissingCampaign
22 SEPTEMBER 2022

*Press conference and official kick-off of “Missing”*

Held at BIG Headquarter offices in Brussels, the press event included presentations from breast cancer experts within the BIG network, as well as moving testimonials from individuals who had lost a loved one to breast cancer, emphasising the importance of continued research and increased awareness.

The attendees were greeted with a warm welcome from Professor David Cameron (BIG chair, Professor of Oncology at Edinburgh University, UK), via a pre-recorded video message. He introduced BIG and its mission. This was followed by insightful presentations by Professor Martine Piccart (co-founder of BIG, President of BIG against breast cancer, Professor at the Faculty of Medicine of Université Libre de Bruxelles, Belgium), and Dr Philippe Aftimos (oncologist and Clinical Trials Development Leader at the Jules Bordet Institute, Brussels, Belgium). The presentations focused on the importance of research in saving lives, and highlighted BIG’s significant contributions to academic and clinical breast cancer research, including the ground-breaking HERA, OlympiA, and AURORA studies. At the end of the press conference, the campaign images were unveiled.

29 SEPTEMBER 2022

*Exclusive round-table with Her Majesty the Queen of the Belgians*

BIG had the honour of hosting its Honorary President, Her Royal Highness the Queen of the Belgians, Professor Martine Piccart, co-founder of BIG and President of BIG against breast cancer, and David Cameron, chair of BIG, for a round-table session with over 40 influential people from the Belgian business world.

This exclusive event was initiated on the idea of Her Majesty, bringing together patients, scientists, and captains of industry to discuss the current state of breast cancer in the world and the progress made through the research conducted by the BIG network over the past 23 years.

The aim was also to further raise awareness about the importance of supporting BIG’s research in order to improve treatments and ultimately develop cures.

Attendees were divided into five groups, with each one touching on a specific topic:
1. Why is BIG unique?
2. Metastatic breast cancer
3. The future of research
4. Male breast cancer
5. The de-escalation of treatments

See also: [https://bigagainstbreastcancer.org/a-round-table-with-her-majesty/](https://bigagainstbreastcancer.org/a-round-table-with-her-majesty/)
4 OCTOBER 2022

Vernissage and art exhibition showcasing “Missing” campaign images (until 29/10)

As part of the Pink October campaign, BIG partnered with the “Art’s Big” gallery (Waterloo, Belgium) and their “Pink Touch” art exhibition. Under the auspices of the gallery, a strong supporter of BIG for several years, a vernissage was organised to showcase the “Missing” campaign images. The exhibition ran throughout October, with participating artists generously donating a percentage of their sales to BIG. The funds raised during the exhibition will be invested in BIG’s breast cancer research.

12 OCTOBER 2022

BIG’s Committee of Ambassadors’ annual Platinum Gala

BIG’s most recent annual gala dinner marked the return of the event since the end of the Covid-19 pandemic. Themed “The Four Seasons”, the exclusive evening raised funds for BIG’s breast cancer research, particularly for BIG’s academic research programmes or clinical trials with no commercial interest that ask essential questions and address important, patient-oriented, unmet medical needs: POSITIVE, AURORA and EXPERT.

About 450 attendees joined the event and participated in an auction that featured unique and exclusive prizes donated by BIG’s partners and individual benefactors. The evening resulted in almost 350,000 EUR being raised.

BIG is grateful for the support and contributions of the organising committee, the Committee of Ambassadors of BIG against breast cancer, our partners, and all participants whose efforts were instrumental in making this annual event a success. We also extend our appreciation to our corporate partners for their valuable support.
19 OCTOBER 2022

Annual EORTC-BIG webinar for scientific audience

On 19 October 2022, and as part of the global Pink October campaign, BIG and the EORTC organised for the fourth consecutive year a free one-hour webinar for a scientific audience.

The goal of the webinar was to foster collaboration and information-sharing among experts in breast cancer and geriatric oncology, with a particular emphasis on advancing research in the field. The webinar centred around the theme of “The unmet needs of older patients with breast cancer” to raise awareness about the importance of including more elderly patients in clinical trials.

The webinar provided facts and figures, focused on the importance of geriatric assessment, recommended screening tools, and highlighted examples of recent research being done in elderly patients, such as the phase 2 APPALACHES trial, carried out by the EORTC under the BIG network umbrella. This is the first study to compare palbociclib with chemotherapy in patients with high-risk ER-positive breast cancer treated with standard adjuvant endocrine therapy.

Speakers included breast cancer experts from the BIG and EORTC networks such as Dr Etienne Brain (France), Dr Hans Wildiers (Belgium), Dr Laura Biganzoli (Italy) and Tanja Spanic (Slovenia).

For further details, visit: https://www.eortc.org/event/22441/

1 – 31 OCTOBER 2022

Pink October, a month of activities

Other activities and initiatives developed by BIG and BIG against breast cancer for breast cancer awareness month and BIG’s “Missing” campaign:

- Display in Brussels’ streets of large digital boards with campaign images
- Circulation of a BIG branded tram through Brussels’ streets
- Digital campaign and social media activities
- Media partnerships
- BIG website: dedicated campaign landing page
- Mailing with a “call to donate”
Every year on 4th of February, World Cancer Day (WCD) is observed. Like the previous year, this year’s theme for WCD was “Close the Care Gap.” This global campaign, which emphasises that we are stronger when we are united, also celebrates real-world progress and allows us to demonstrate the importance of global academic breast cancer research and the impact it has on the quality of life of many of us.

To support the campaign, the communications team at BIG Headquarters partnered with the ETOP IBCSG Partners Foundation to create a media awareness campaign, showcasing the latest results of the POSITIVE study. The objective of this campaign was to raise awareness, and promote understanding of the study’s significance, specifically to show how the study addresses a question critical for many young women, thus closing a care gap.

KEY MESSAGE OF THE CAMPAIGN

The start of a new year always brings hope. The POSITIVE study lives up to its name and brings positivity and real hope to young women with hormone-sensitive early breast cancer who dream to become pregnant one day. The first study results showed that pausing anti-hormone therapy to try to get pregnant can be done without additional risk of recurrence of their disease in the short term. This academic study would not have been possible without global collaboration.

How academic research helps to close the gaps:
BIG as a network holds a distinct position in the field of breast cancer research. Our 58 member groups working together allow us to develop and conduct studies such as POSITIVE. Not motivated by commercial interests these studies are financed through the groups’ own resources and our philanthropic communities.

The precious support of foundations, companies and private donors is vital to complete POSITIVE, including many years of follow-up needed to ensure that the safety of treatment interruption endures over time. This work is of tremendous benefit to numerous young women who aspire to conceive after undergoing breast cancer treatment.

CAMPAIGN MATERIALS DEVELOPED BY BIG AND ETOP IBCSG PARTNERS FOUNDATION – SHARED WITH BIG MEMBER GROUPS:

Media alert: issued to national and international media, scientific and general public. Produced in three languages (English, French and Dutch) and also posted on the BIG website: https://bigagainstbreastcancer.org/world-cancer-day-positive-closing-the-gap/

Video testimonial: testimonial of Sabrina, Swiss breast cancer patient who participated in POSITIVE and is now mother of two. Published on BIG’s website and shared via our social media channels on Saturday 4 February, on WCD. It is available here: https://bigagainstbreastcancer.org/world-cancer-day-positive-closing-the-gap/

Four language versions of Sabrina’s testimonial video were created: the original one, in German with no subtitles; and three duplicates with English, French and Dutch subtitles.

Digital communications: calendar and posts for Facebook, Instagram, Twitter and LinkedIn.

If your group is interested in taking part in World Cancer Day 2024, please contact BIG’s communications team: communications@bigagainstbc.org.
APHINITY (BIG 4-11)

Adding pertuzumab to the standard therapy does not increase cardiac events

Trastuzumab is known to increase the incidence of cardiac events in patients with breast cancer. However, the standard of care for high-risk human epidermal growth factor receptor 2 (HER2)-positive early breast cancer patients is dual blockade with pertuzumab and trastuzumab, which significantly improves outcomes. Dr. Evandro de Azambuja and colleagues conducted an exploratory analysis of the cardiac safety of pertuzumab and trastuzumab in the phase III APHINITY trial.

After more than 6 years of median follow-up, this exploratory analysis shows that adding pertuzumab to the standard trastuzumab and chemotherapy given after breast cancer surgery did not increase the rate of cardiac events. In case of a cardiac event, the majority of patients recovered (~81%). This finding is reassuring for patients and clinicians as it provides strong evidence from a large, randomised phase III trial.

Key messages:
• Pertuzumab and trastuzumab improve clinical outcomes, compared to trastuzumab alone, in HER2-positive early breast cancer.
• After more than 6 years of median follow-up, pertuzumab and trastuzumab did not increase cardiotoxicity risk compared to trastuzumab.
• Treatment with pertuzumab and trastuzumab was associated with a low incidence of cardiac events (3.5%), mostly reversible.
• The analysis confirms that a dual blockade with pertuzumab and trastuzumab does not increase the risk of cardiac events compared with trastuzumab alone. The use of anthracycline-based chemotherapy increases the risk of a cardiac event; hence, non-anthracycline chemotherapy may be considered, particularly in patients with cardiovascular risk factors.

The “Cardiac safety of dual anti-HER2 blockade with pertuzumab plus trastuzumab in early HER2-positive breast cancer in the APHINITY trial” article by Dr. Evandro de Azambuja, et al. was published in ESMO Open.

Study information:
- Study PIs: M. Piccart, S. Loibl, J. Bines
- Lead partners: This study is conducted by BIG Headquarters, Institut Jules Bordet – Clinical Trials Support Unit (IJB/CTSU), and Frontier Science Scotland (FSS).
- 24 BIG member groups participating in the study
- Pharmaceutical partner: Roche (Sponsor)
- Accrual: A total of 4,805 patients were recruited, 2,647 of them from the BIG groups.
- ClinicalTrials.gov Identifier: NCT01358877

REFERENCE:

INTERNATIONAL MALE BREAST CANCER PROGRAMME (BIG 2-07)

Results presented at SABCS

The International Male Breast Cancer Programme was launched in 2006 by the EORTC under the BIG umbrella in collaboration with the NCTN and TBCRC to help us better understand the clinical characteristics, tumour biology, and treatment outcomes of male patients with breast cancer.

On 7 December 2022, results from an analysis by Danielle Zakon and colleagues were presented during a spotlight poster session during the San Antonio Breast Cancer Symposium (SABCS). This poster reported on the “Evaluation of the Sensitivity to Endocrine Therapy Index (SET2,3) in Early Male Breast Cancer: Results from an analysis in the EORTC 10085/TBCRC/BIG/NABCG International Male Breast Cancer Programme”.

The International Male Breast Cancer Programme consists of three parts:
1. A retrospective collection of data and samples from 1822 male patients with breast cancer treated in 23 participating centres across 9 countries
2. A prospective registry of 557 newly diagnosed cases during a period of approximately 30 months, with central collection of clinical data and tumour samples and follow up period of 10 years
3. A prospective clinical study to optimise the management of these patients

Parts 1 and 2 have already been completed thanks to the tireless efforts of several research partners, many funding organisations, and individual donors.

In the work by Dr Zakon and colleagues, they used the “SET 2,3 index” a hormone receptor (HR)-related gene expression biomarker to analyse the outcomes of 321 male patients with breast cancer. They showed that the SET 2,3 index is prognostic in this group, similar to prior findings among female patients. Of the male patients analysed, 65.7% had a high SET 2,3 index, indicating high endocrine activity and a lower risk of recurrence, while 34.3% patients had a low index, indicating low endocrine activity and a higher risk of recurrence. This might imply that among male patients with breast cancer, selected patients might benefit from additional chemotherapy in addition to endocrine therapy. However, these findings need further validation.

Since the inception of the International Male Breast Cancer Programme, collaborative research has generated much hope for this group of patients, although much work still needs to be done. Today, we have deeper knowledge of the clinical and biological characteristics of male patients with breast cancer. There is also greater awareness and support for understanding their treatment preferences. Finally, there are now more opportunities for male patients to participate in breast cancer trials, opening avenues for gaining a greater understanding of breast cancer in this rare, yet important patient group.

**Study information:**
- Study PIs: F. Cardoso, S. Giordano
- Leading group (sponsor EU): European Organisation for Research and Treatment of Cancer (EORTC); and NCTN and TBCRC (US)
- 7 BIG member groups participating in the study
- Accrual: 1822 (retrospective); 557 (prospective)
- ClinicalTrials.gov Identifier: NCT01101425

**REFERENCES:**


**NEOALTTO (BIG 1-06)**

**Results of the final analysis published**

The NeoALTTO study was set up to investigate whether combining trastuzumab with lapatinib – given either alone, together, or one after the other – could benefit patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer in the neoadjuvant (pre-surgical) setting.

In January 2023, the results of the final pre-planned 10-year survival analysis of NeoALTTO and the association between pathologic complete response (pCR) and survival outcomes were published in the *European Journal of Cancer*.

The study found that that patients with HER2-positive breast cancer showed a durable survival benefit of neoadjuvant anti-HER2 therapy, irrespective of treatment arm. Patients who achieved pCR have significantly sustainable better outcomes than patients without pCR. The result was numerically greater in women treated with the drug combination and those with hormone receptor-negative tumours. There were no new or long-term safety concerns. The clinical data and collected biomaterial represent a valuable resource for future translational research.

**Study information:**
- Study PIs: O. Pagani, B. Walley
- Lead partners: This study is conducted by SOLTI, BIG Headquarters, Institut Jules Bordet/ Clinical Trials Support Unit, and Frontier Science Scotland (FSS)
- 10 BIG member groups participating in the study
- Pharmaceutical partner: Novartis, previously GSK
- Accrual: 455 patients across 23 countries around the globe were enrolled
- ClinicalTrials.gov Identifier: NCT00553358

REFERENCE:


POSITIVE (8-13)

Manuscript soon to be published in prominent journal (expected end April 2023)∗.

Pausing endocrine treatment to try to get pregnant can be done without additional risk of recurrence in the short term.

See also themed article page 3 - 13

Study information:
- Study PI: O. Pagani
- Leading group (sponsor): International Breast Cancer Study Group
- 11 BIG member groups participating in the study
- Accrual: A total of 518 patients enrolled
- ClinicalTrials.gov Identifier: NCT02308085

∗At the time of printing, details were not yet accessible.

SOFT (BIG 2-02) - TEXT (BIG 3-02)

Long-term results of the combined SOFT-TEXT analysis published

The updated results of the combined SOFT-TEXT analysis after 13 years of follow-up, presented at the San Antonio Breast Cancer symposium 2021, were published in the Journal of Clinical Oncology.

The SOFT and TEXT clinical trials produced practice-changing results that persist over time. The combined SOFT and TEXT analysis was performed to evaluate the role of exemestane and tamoxifen in premenopausal hormone receptor (HR)-positive women with postoperative breast cancer undergoing ovarian function suppression (OFS). Given the potential late recurrence of HR-positive breast cancer and the late survival advantage of adjuvant aromatase inhibitors over tamoxifen in postmenopausal women, reporting long-term effects is crucial.

After a median follow-up of 13 years, the updated analysis reported by Dr. Olivia Pagani et al. confirmed a long-term reduction in relapses with adjuvant exemestane with OFS compared to tamoxifen with OFS. Overall survival was similar in both treatments.

The SOFT trial is sponsored by ETOP IBCSG Partners Foundation in collaboration with Cancer and Leukemia Group B, National Cancer Institute (NCI), NSABP Foundation Inc, NCIC Clinical Trials Group, North Central Cancer Treatment Group, Southwest Oncology Group and the Breast International Group.

The TEXT trial is sponsored by ETOP IBCSG Partners Foundation in collaboration with National Cancer Institute (NCI) and the Breast International Group.

Study information:
- Study PIs: G. Fleming, P. Francis
- Leading group (sponsor): International Breast Cancer Study Group
- 13 BIG member groups participating in the study
- Pharmaceutical partner: Pfizer
- Accrual: A total of 3,066 patients enrolled
- ClinicalTrials.gov Identifier: NCT00066690

TEXT (BIG 03-02)

- Study PIs: O. Pagani, B. Walley
- Leading group (sponsor): International Breast Cancer Study Group
- 8 BIG member groups participating in the study
- Pharmaceutical partner: Pfizer
- Accrual: A total of 2,672 patients enrolled
- ClinicalTrials.gov Identifier: NCT00066703

REFERENCE:

RECENTLY PUBLISHED MANUSCRIPTS ABOUT BIG TRIALS

ALTTO (BIG 2-06)
> Nader-Mart A., Debien V., Eiger D., et al. Outcomes of patients with small and node-negative HER2-positive early breast cancer treated with adjuvant chemotherapy and anti-HER2 therapy—a sub-analysis of the ALTTO study, British Journal of Cancer, November 2022, 127(10), p. 1799-1807. [https://doi.org/10.1038/s41416-022-01963-8](https://doi.org/10.1038/s41416-022-01963-8)

APHINITY (BIG 4-11)

NeoALTTO (BIG 1-06)

OlympiA (BIG 6-13)

SOFT (BIG 2-02)
BIG TRIALS AT CONFERENCES

ESMO 2022 – 9-13 SEPTEMBER

RIBOLARIS (BIG 21-02)
New BIG study presented at ESMO

The RIBOLARIS study (NCT05296746), led by SOLTI under the BIG umbrella, began in April 2022. The study aims to evaluate the safety and long-term efficacy of a chemo-free therapy in patients who have had a biological response to (neo)adjuvant ribociclib and letrozole and are continuing this therapy in the adjuvant setting. The abstract of the study was presented at ESMO Congress 2022 in Paris, France, with the title “Neoadjuvant and adjuvant RIBOciclib + endocrine therapy for clinically high-RISk ER+/HER2-negative breast cancer.”

ASCO VIRTUAL PLENARY 2022 – 18 OCTOBER

PALLAS (BIG 14-03)

Results of a preplanned subgroup analysis of PALLAS was presented at ASCO Virtual Plenary on 18 October 2022. It showed that adding adjuvant palbociclib to endocrine therapy did not improve outcomes for stage IIA luminal breast cancer. Further translational research analyses within the transPALLAS program will be conducted, and an analysis with 10 years of follow-up is also planned. PALLAS is a co-led BIG study sponsored by ABCSG and Alliance Foundation Trials.
At the 2022 European Breast Cancer Conference (EBCC) in Barcelona, Spain, a MINDACT study poster was presented on the usefulness of the 70-gene signature test.

Tailored recommendations for adjuvant chemotherapy in breast cancer patients are of great importance. Gene signatures, such as the 70-gene MammaPrint® test, have been shown to provide additional prognostic information and are used to refine risk estimations and adjuvant chemotherapy recommendations for individual patients. These signatures have also been incorporated into international guidelines. This survey assessed agreement among oncologists on risk assessment and chemotherapy recommendations, as well as the impact of adding the 70-gene signature result to clinical-pathological characteristics, and any changes over time. The survey showed that among breast cancer specialists, there is variability in the risk assessment of early-stage breast cancer patients. The 70-gene signature provided valuable information, resulting in fewer patients being assessed as high risk and fewer recommendations for chemotherapy, which increased over time. Importantly, this study also shows the impact that large clinical trials investigating the use of gene signatures have had on the international care of early-stage breast cancer patients.

Another poster related to the NeoALTTO study was also presented, entitled “Gene expression profile at week 2 of neoadjuvant therapy course predicts outcome in HER2-positive breast cancer patients: an exploratory analysis from NeoALTTO.” The aim of this research was to determine whether the assessment of a gene expression profile (GEP) following two weeks of anti-HER2 therapy (with tumour biopsy taken during the chemotherapy-free window at day 14+2) could be used to predict clinical outcomes in patients with HER2-positive breast cancer. The researchers found that biomarkers of early T-cell and monocyte-macrophage activation, as well as HER2 downregulation, could potentially identify patients likely to achieve a pCR (pathologic complete response) and have a favourable prognosis. However, new effective treatments need to be explored for cases lacking an early GEP response.

REFERENCES:


At San Antonio Breast Cancer Symposium (SABCS) 2022, the following ALTTO-related poster was presented: “Characterization and validation of biologically-driven HER2-positive breast cancer subgroups in the ALTTO and NeoALTTO clinical trials”.

It is known that tumour and microenvironment features, including the luminal phenotype as well as metabolic, immune, and stroma activation, impact prognosis and treatment response in HER2-positive breast cancer. Against this background, the present research aimed to identify subgroups that depict biological processes associated with prognosis in patients receiving adjuvant trastuzumab in the phase III ALTTO trial and to validate their biological and prognostic characteristics in the phase III neoadjuvant NeoALTTO trial.

In ALTTO, five biologically driven HER2-positive breast cancer subgroups were identified, highlighting the heterogeneity of this disease. The biological features and clinical behaviour of these subgroups were subsequently validated in the NeoALTTO population, suggesting the robustness of these findings. Immune enriched and non-HER2-enriched tumours could be considered for treatment de-escalation approaches, but additional validation in cohorts receiving standard (neo)adjuvant therapies is warranted.

The International Male Breast Cancer Programme (BIG 2-07)

On 7 December 2022, results from an analysis by Danielle Zakon and colleagues were presented during a spotlight poster session during SABCS. This poster reported on the “Evaluation of the Sensitivity to Endocrine Therapy Index (SET2,3) in Early Male Breast Cancer: Results from an analysis in the EORTC 10085/TBCRC/BIG/NABCG International Male Breast Cancer Programme”.

See also page 24.

PALLAS (BIG 14-03) and PENEOLE-B (BIG 1-13) collaboration

A collaboration between two trials under the BIG umbrella, PALLAS and Penelope-B, resulted in the development and validation of a composite biomarker (luminal A, ERBB2 and PR) predictive of palbociclib and endocrine treatment benefit in early breast cancer. The results of this collaboration were also presented during a poster discussion at SABCS: “Development and validation of a composite biomarker predictive of Palbociclib + endocrine treatment benefit in early breast cancer: PENEOLE-B and PALLAS trials.”

POSITIVE (BIG 8-13)

The first results of the POSITIVE study were presented at SABCS.

See featured article page 3-13.
The great promise of ctDNA as early response marker in early breast cancer in the neoadjuvant setting

Liquid biopsies (LB), or more specifically the analysis of tumour components floating in body fluids such as blood, have shown promising clinical utility in many solid tumours, including breast cancer. The centrepiece of many applications has been the analysis of circulating tumour DNA (ctDNA) in plasma using next-generation sequencing (NGS)-based technologies. The role of ctDNA in guiding treatment decisions by identifying actionable targets or alterations mediating resistance is well established, and a couple of ctDNA approaches have already entered clinical practice. More recently, ctDNA has been proven a powerful biomarker for detecting minimal residual disease (MRD) following curative-intent treatment or as a response marker for neoadjuvant treatment, for which accurate response assessment poses a clinical challenge.

A landmark study by Garcia-Murilla and colleagues demonstrated that the detection of ctDNA in patients with early-stage breast cancer during follow-up was associated with a higher risk of relapse. Other groups have reported that a quick decline or clearance of ctDNA levels during neoadjuvant systemic therapy is associated with excellent treatment responses and pathological complete responses (pCR). In contrast, the presence of ctDNA at the end of the treatment correlates with residual disease and thus a higher risk of relapse. Magbanua and colleagues have reported that persistence of ctDNA during neoadjuvant systemic treatment is a significant predictor of poor response and metastatic recurrence.

We tested the use of ctDNA to predict response to neoadjuvant systemic therapy in 145 patients with early breast cancer recruited to the prospective, randomised, neoadjuvant phase II ABCSG 34 trial. To this end, we profiled 93 genes in tissue from 193 patients with early breast cancer. Patient-specific assays were designed for 145 patients to track ctDNA before, during, and after neoadjuvant treatment in plasma. ctDNA presence and levels were correlated with pCR and residual cancer burden (RCB) as well as clinicopathologic characteristics of the tumour to identify potential proxies for ctDNA release.

Presence of ctDNA was significantly associated with a higher stage and a positive lymph node status. Moreover, higher ctDNA levels were significantly associated with higher proliferation rates, confirming previous reports. Interestingly, the presence of ctDNA was also associated with intratumoural TILs, whereas stromal TILs only had borderline significance.

Furthermore, we demonstrated that the detection and persistence of ctDNA in the middle of neoadjuvant therapy can negatively predict response to treatment and may identify patients with significant residual cancer burden (RCB II or III). Minimally invasive identification of RCB may aid clinical decision-making with respect to treatment escalation in non-responders, who are known to benefit from additional adjuvant therapy. At the same time, patients with pCR who might not derive benefit from breast surgery after neoadjuvant therapy can be identified by minimally-invasive means.

Taken together, our liquid biopsy study in the ABCSG 34 trial confirms the great promise of ctDNA as an early response marker in early breast cancer patients undergoing neoadjuvant treatment. Therefore, a minimally-invasive assessment of tumour response based on ctDNA may be beneficial to guide treatment decisions in future. We believe that our results together with further refinement of technologies used for ctDNA detection may greatly impact the design of future clinical trials in the neoadjuvant setting.

Contribution by Professor Marija Balic and Professor Ellen Heitzeg. Both are affiliated with the Medical University Graz, Austria, and with the ABCSG.
REFERENCES:


An interview with Michael Gnant, president of the ABCSG

For the third time already, Austria’s internationally renowned cancer researcher Professor Michael Gnant, MD, FACS, FEBS has been named as one of the worldwide “Highly Cited Researchers 2022”.

Frequently cited researchers have a great influence on the scientific community and study achievements. Thus, they make a significant contribution to new, far-reaching developments to improve therapeutic options. As a Highly Cited Researcher one ranks among the top one percent of all scientific researchers whose work can be found on the Web of Science™ (https://clarivate.com). In 2022, 6,938 scientists were listed. The publications in the Cross Field category, for which Dr Gnant received his award, are characterised by their strong influence on several scientific disciplines. In Austria, there were 25 Cross Field honourees, including only three within the field of clinical medicine.

Professor Gnant, why is research and its publication important and how do you think it affects or influences the general public?

Research determines our lives – whether we are aware of it or not. Creating knowledge plays a crucial role in all the advances to which mankind aspires. This applies to everyday life, technology, the hopefully successful fight against climate change, and, of course, in medicine. Unfortunately, especially in Austria, the public awareness of the importance of research is quite modest – as recently indicated by the Eurobarometer surveys results. This is distressing, given that, in some fields of science, Austrian researchers are among the world pioneers, as the current list of Highly Cited Researchers shows.

What value do you ascribe to interdisciplinary scientific discourse, especially in your field of research?

Contemporary science needs interdisciplinary discourse. By the way, the same pertains to medical excellence in clinical care. Especially in oncology, and particularly in breast cancer research, significant progress has been made through interdisciplinary collaboration. By shaping the knowledge and innovations of individual disciplines involved in diagnosis and treatment, common improvements have been achieved for those affected.

What does it take, on a personal level, to achieve decisive success in research? Do you set milestones for yourself?

Successful research depends on diligence, creativity, and resilience. For instance, the ABCSG-16 study – one of our greatest joint research achievements, highly recognised on a global level – lasted more than 20 years! And since innovation cannot be directly planned, it requires constant attention. Always stay up to date, read a lot and, what’s most important: keep it up and don’t lose courage! Institutionally, research advances are not only promoted through diversity, but also by reaching a crucial mass of smart people. Furthermore, do not merely allow out-of-the-box thinking, but actively encourage it!

Which fundamental or most urgent problems do you see within your field of research?

In comparison with other countries, we still have an embarrassingly low research quota in Austria with respect to public funding, especially in basic research. However, clinical research as well is neglected by the public sector as well, with a lot of it being left to industry, which is of course also strongly influenced by commercial considerations when it comes to the choice of research topics. It definitively takes a national effort to make Austria an “innovation leader” in considerably more scientific fields. While I’m delighted for the great Anton Zeilinger on his well-deserved Nobel Prize, I also see the apparent danger of settling back and resting on one’s laurels, “since everything’s fine anyway...”. This also means that we need to keep an eye on academic careers, which must be sustainable, attractive, and characterised by academic freedom.

On a final note, how does it feel to once again rank among the world’s most cited research elite?

Personally, of course, such an honour is pleasant and appreciated, and is also the reward for many years of hard work and invested spare time. However, what is way more important to me is that it represents the appreciation for and success of a large group of Austrian enthusiasts. Decades of collaboration have come to fruition and, for that, I’m deeply grateful!
BCT-ANZ
(BREAST CANCER TRIALS AUSTRALIA AND NEW ZEALAND)

> ANZ 1601/BIG 16-02 (EXPERT)

The EXPERT study aims to improve personalised use of radiation therapy in early breast cancer patients by using a genomic test to identify women who may safely avoid this treatment and the possible side effects.

This is a randomised phase III trial of adjuvant radiation therapy versus observation following breast conserving surgery and endocrine therapy, in patients with molecularly characterised luminal A early breast cancer.

BCT-ANZ leads the study in Australia and New Zealand. The BIG consortium leads the study in Italy, Spain, Switzerland, Argentina and Chile through the following study groups: GOCCHI, GAICO, GOIRC, IBCSG and SOLTI. The Taiwan Breast Cancer Consortium is leading the study in Taiwan. The international accrual target is 1,170 participants, and currently 659 patients have been recruited worldwide.

Professor Boon Chua is the BCT-ANZ Study Chair of the EXPERT study.

> BCT 1703 (DIAmOND)

The DIAmOND clinical trial is investigating if the addition of two immunotherapy drugs to trastuzumab will improve treatments and outcomes for women and men who have HER2-positive metastatic breast cancer. New immunotherapy drugs like durvalumab and tremelimumab assist the body's natural immune system to attack the cancer cells. The combination of these two drugs has been given previously to people with lung cancer, but this is the first trial that will test the combination of these two drugs in people with breast cancer. DIAmOND has recruited 68 participants with a target of 78 in total, and involves 11 institutions in Australia.

Professor Sherene Loi is the BCT-ANZ Study Chair of DIAmOND.

> BCT 1901 (CAPTURE)

The CAPTURE clinical trial aims to identify women and men with hormone-receptor positive metastatic breast cancer who may benefit from a novel combination of drugs that may improve progression-free survival and offer a new treatment option. This is a phase II randomised study that will evaluate alpelisib plus fulvestrant versus capecitabine in oestrogen receptor positive, HER2-negative advanced breast cancer patients with PIK3CA mutant circulating tumour DNA. The study is using a liquid biopsy technique which is a simple blood test, to identify women with the PIK3CA mutation. Twenty-two institutions in Australia are recruiting to this study, and 39 patients have been randomised as of this writing, with an accrual target of 140.

Professor Sarah-Jane Dawson is the BCT-ANZ Study Chair of the CAPTURE trial.

> BCT 2003 (RAPID)

RAPID EBC is pending activation and is a randomised phase III trial that will examine the effect of intravenous iron replacement on anaemia and anaemia-related symptoms in breast cancer patients receiving adjuvant or neoadjuvant chemotherapy. The trial will open in the second quarter of 2023 and aims to recruit 290 patients in 18 institutions.

The BCT-ANZ Study Chair is Associate Professor Nick Murray.

> OLIO

Young women diagnosed with breast cancer have a higher rate of recurrence and death from breast cancer, and this has been demonstrated to be relatively worse in patients with HR+ HER2- breast cancers. However the reasons for this are unexplained. In a large genomic analysis including tumours from nearly 1,300 premenopausal women under the age of 45 years, researchers have identified a new drug target that may improve their outcome.

In this pending study, researchers will evaluate a specific diagnostic and therapeutic approach for young women with genomic features of homologous recombination deficiency (HRD) in their cancers. They will evaluate the best assay for detecting these features in breast cancer as well as conduct a clinical trial evaluating two possible treatment arms based on our preliminary data.

OLIO is pending activation and the BCT-ANZ Study Chair will be Professor Sherene Loi.
GEICAM (SPANISH BREAST CANCER GROUP)

DIANER: GEICAM is leading an important study to reduce the incidence of neratinib-related diarrhoea and improve treatment tolerability

DIANER GEICAM (BIG 18-03) is an international, multicentre, open-label, randomized phase II study aiming to evaluate the incidence of neratinib discontinuations due to diarrhoea within the first 3 cycles in the extended adjuvant treatment of early-stage HER2-positive, hormone receptor-positive breast cancer patients. Patients will be treated with neratinib plus loperamide prophylaxis versus neratinib with initial dose escalation plus loperamide as needed versus neratinib plus loperamide plus colesvelam prophylaxis. See figure 1 for the study design.

We are planning to enrol 315 male or female patients with histologically confirmed stage IB through stage IIIC primary adenocarcinoma of the breast who have completed their neoadjuvant/adjuvant trastuzumab-based therapy (more than 2 weeks and less than or equal to 1 year) before receiving the first dose of neratinib. This study is an EMA post-commitment trial sponsored by GEICAM, funded by PUMA, and run under the BIG umbrella as a supporter study. There are 83 participating sites (55 in Spain and 28 in other European countries).

The enrolment started in September 2022, and it is estimated that the last patient will be enrolled in September 2024.

GEICAM’s Clinical Practice Guidelines for Neoadjuvant Treatment of Breast Cancer

GEICAM has created “Clinical Practice Guidelines for the Diagnosis and Neoadjuvant Treatment of Breast Cancer” (in Spanish), which provide a series of recommendations on some of the most controversial aspects of this clinical situation. This includes diagnosis, response assessment, optimisation of drug use based on tumoral subtype, and special situations such as pregnancy. The guidelines can be accessed on GEICAM’s website https://guia-cancerdemama-neoadjuvancia.geicam.org/ and are included in GuíaSalud, the Spanish National Catalogue of Clinical Practice Guidelines.

GEICAM latest publications

> Quality of life from the GEICAM/2014-12 (FLIPPER) trial

The FLIPPER trial was a phase II study that aimed to compare the efficacy and safety of palbociclib/fulvestrant versus placebo/fulvestrant in postmenopausal women with endocrine--sensitive...
HR+/HER2− advanced breast cancer (ABC). The trial results have already been published. Recently, GEICAM published an analysis of health-related quality of life for this population, which is available in the journal Therapeutic Advances in Medical Oncology: https://doi.org/10.1177/17588359221148921

> Patients with early-stage triple negative breast cancer are most likely to benefit from capecitabine: new analysis of the GEICAM/CIBOMA trial

A prespecified correlative analysis of the phase III GEICAM/CIBOMA clinical trial, published in Clinical Cancer Research, shows that patients with early-stage triple negative breast cancer for whom non-basal status has been identified by PAM50 are most likely to benefit from capecitabine. https://doi.org/10.1158/1078-0432.CCR-22-2191

> Type does matter. Use VIRGIN olive oil as your preferred fat to reduce your risk of breast cancer: EpiGEICAM study

A sub-analysis of the EpiGEICAM a case-control study about breast cancer and lifestyle suggests that the type of oil we consume can affect our risk of developing the disease. The results were published in the European Journal of Clinical Nutrition and showed some potential benefits from olive oil consumption, such as reducing the risk of breast cancer. But this benefit was only observed when consuming high amounts of virgin olive oil. https://doi.org/10.1038/s41430-022-01101-w

GEICAM at SABCS22: REgistEM, POSITIVE, RxPONDER studies and more

At last year’s San Antonio Breast Cancer Symposium (SABCS22), GEICAM presented three reports of the RegistEM registry of characteristics and therapeutic approach to metastatic breast cancer. In addition, oral presentations from the RxPONDER and the POSITIVE (BIG 13-08) studies, in which GEICAM participated, were presented. Poster discussions were held for the COOPERA, PENELOPE-B (BIG 13-01) and PALLAS (BIG 14-03) studies, along with ongoing trial posters of the AMEERA-6 (BIG 20-01), LIDERA TRIO045 and FLAMINGO trials. The abstracts of these presentations can be found on the SABCS website: https://www.sabcs.org/.

REFERENCE:

**JBCRG (JAPANESE BREAST CANCER RESEARCH GROUP)**

**Ongoing clinical trials and publications**

The Japanese Breast Cancer Research Group (JBCRG) is running the following clinical trials:

- **JBCRG-C07 (REIWA)**: an observational study to evaluate the impact of a gene panel test on treatment decision-making in breast cancer throughout Japan as a whole.

- **JBCRG-ABCD project**: the Advanced Breast Cancer Database (ABCD) project.

- **JBCRG-C08 (ATTRIBUTE)**: Atezolizumab in patients with TRIPLE-negative Breast cancer, multi-center observational study for Treatment safety and Efficacy.

- **JBCRG-C07-A1 (REIWA2)**: an exploratory study,
  
a) using gene expression analysis to assess the predictability of resistance to hormone therapy and chemotherapy sensitivity in luminal breast cancer patients who have a treatment history of CDK4/6 inhibition, and

b) investigating patients with luminal or triple negative breast cancer showing FGF•FGFR mutation/amplification detected using FoundationOne® comprehensive gene expression analysis.

- **JBCRG-M08 (AMBER)**: innovation of the 1st line strategy optimised as abemaciclib with endocrine therapy based on the ESR1 mutation of ctDNA for HR-positive HER2-negative advanced metastatic breast cancer patients (JBCRG-M08) – a multi-institutional phase II trial.

**Presentations at congresses**

1) ESMO Virtual Congress 2022 (9-13 September 2022): JBCRG-M07

Presentation by Dr Kenichi Watanabe: Fulvestrant with additional palbociclib in advanced or metastatic hormone receptor-positive HER2-negative breast cancer after progression to fulvestrant monotherapy: JBCRG- M07 (FUTURE trial).

2) San Antonio Breast Cancer Symposium 2022 (6-10 December 2022): JBCRG-C06

Presentation by Dr Kaho Utsunomiya: Retrospective study using database for the effectiveness of medroxyprogesterone acetate in patients with ER-positive/HER2-negative postmenopausal advanced breast cancer: An additional analysis of the JBCRG-C06 Safari study.

**Recent publications**

1) JBCRG-C05 in Breast Cancer 2022


2) JBCRG-C06 in Japanese Journal of Clinical Oncology 2022


**Participation in global trials**

JBCRG is involved in the following studies run under the BIG umbrella: ALEXANDRA/IMpassion030 (BIG 16-05), OlympiA (BIG 6-13), POSITIVE (BIG 8-13), Penelope-B (BIG 1-13) and PALLAS (BIG 14-03).

For details about the trial leadership, please refer to the overview of BIG trials on page 44-47.
LACOG (LATIN AMERICAN COOPERATIVE ONCOLOGY GROUP)

1st LACOG Annual Scientific Meeting 2022
In October 2022, the 1st LACOG Annual Scientific Meeting took place in São Paulo, Brazil, bringing together more than 150 members from different Latin American countries representing LACOG’s 10 oncology specialty groups. Discussions held during the meeting included studies in progress, new proposals, and publications. The LACOG team presented the group's new organisational structure. The meeting was a great milestone for the LACOG group, reflecting its maturity and professionalism.

Forum on Immunotherapy for Cancer Patients - CURA Meetings
On 8 October 2022, the 1st Forum on Immunotherapy for Patients was held by Instituto Projeto CURA. The theme addressed in this edition was “Clinical research as a way of accessing immunotherapy in Brazil”. The hybrid event provided valuable information about immunotherapy and was an opportunity for patients to learn more about the topic and possibilities in clinical trials.

LACOG programme to develop new Brazilian research sites in remote areas
LACOG, in collaboration with the “Instituto Vencer o Cancer, presented the “Amor à pesquisa contra o câncer” project, which aims to structure research sites in Brazil in remote areas to give patients in these regions the opportunity to enrol in cancer clinical trials. Six cancer sites are receiving support from LACOG within this project. They were presented to contract research organisations and pharmaceutical industry, describing their existing structures, patient populations, and readiness to receive clinical trials.

San Antonio Breast Cancer Symposium (SABCS) 2022
During the last SABCS, LACOG investigators presented two posters on ongoing breast cancer studies: "LACOG 0221 - BRAVE - Real-World Data on First-line Treatment of Hormone Receptor-positive, HER2-negative, Metastatic Breast Cancer in Brazil”, presented by the study PI, Dr Gustavo Werutsky, and “LACOG 0419 - NEOSAMBA - Evaluation of Sequencing of Anthracyclines and Taxanes for Locally Advanced HER2-negative Breast Cancer”, conducted in partnership with GBECAM, and presented by study PIs Dr Tomás Reinert and Dr José Bines.

Recent Publications
The article “Time interval between diagnosis to treatment of breast cancer and the impact of health insurance coverage: a sub analysis of the AMAZONA III Study (GBECAM 015)” was published in Breast Cancer Research and Treatment by Dr Daniela Rosa and Raíra Maschmann, LACOG and GBECAM investigators respectively. The analysis included data from 1,709 stage I-III breast cancer patients from AMAZONA III, a prospective, observational study comprising 22 centres in Brazil. The diagnosis-to-treatment interval was higher in women treated in the public system compared to the private system (56 vs. 34 days, p < 0.0001). By characterising the delays in care delivery, the study will help stakeholders to design better interventions and allocate resources to improve timely breast cancer treatment in Brazil.
INSTITUTO PROJETO CURA

Instituto Projeto Cura: 2022, a year of many accomplishments

The Renata Thormann Procianoy Award 2022

In June 2022, the 4th edition of the Renata Thormann Procianoy Award ceremony took place. The purpose of this award is to encourage and recognise Brazilian researchers. The winner of the 2022 edition was Dr. Verônica Torres, a physician at ICESP - Cancer Institute of the State of São Paulo. She is the principal investigator of a prospective study designed to assess the performance of the 2021 CKD-EPI equation without the racial coefficient among adults with solid tumours, for aspects related to the care of renal treatment in cancer patients.

The Neosamba Study

Instituto Projeto Cura submitted and obtained approval from PRONON, the National Support Programme for Oncological Care of the Brazilian Ministry of Health, for the Neosamba study. Thanks to this approval and with the help of 13 companies from different sectors of civil society, including financial institutions, oil companies, agribusiness, among others, it was possible to raise more than 100% of the amount needed to finance the study.

Cura meetings

Instituto Projeto Cura launched a series of events with the purpose of bringing together different public and private entities involved in the development of research in Brazil, such as representatives of regulatory bodies, investigators, physicians, CROs, industry and patients. The events aimed to expand knowledge, discuss the bottlenecks, and seek solutions to expand studies in Brazil. The three meetings took place on 29 April, 10 June and 7 October.
Movement “Research Save Lives”

In October the Instituto Projeto Cura launched this crucial campaign designed to clarify the benefits of cancer research from the perspective of cancer patients. To learn more, click here and watch a video statement by patient Iramara Fluminham.

About Us

Instituto Projeto CURA is a not-for-profit association where people have the opportunity to learn about the importance of supporting clinical research in the fight against cancer in Brazil and, in the future, throughout Latin America. In addition to developing different cultural, social, sports and educational awareness-raising activities, we promote mobilisation and fundraising actions to finance academic oncological research. Further information is available at www.projetocura.org/en.
OTHER TRIALS AND ACTIVITIES

**SOLTI BREAST CANCER RESEARCH GROUP (SPAIN)**

Hospital Clínic is the first site to launch a pioneering immunotherapy trial based on tumour infiltrating lymphocytes for triple negative breast cancer, coordinated by SOLTI.

The TILs001 trial, which is open to patients with metastatic triple-negative breast cancer, is the first study to assess the safety and efficacy of cell therapy based on tumour infiltrating lymphocytes (TILs).

The TILs001 trial, a study led by Dr. Aleix Prat and funded by the Spanish Association Against Cancer (AECC), is already underway at the Hospital Clínic in Barcelona. This trial will include eight patients with metastatic triple negative breast cancer and will also be conducted in three other Spanish sites: Hospital Vall d’Hebron in Barcelona, Clínica Universidad de Navarra, and Hospital 12 de Octubre in Madrid. The study is coordinated by SOLTI.

“We are very pleased to announce that we have opened our first academic clinical trial using tumour infiltrating lymphocytes, called TILs001, for patients with metastatic triple-negative breast cancer,” announces Dr. Prat, president of SOLTI and head of the Translational Genomics and Targeted Therapies in Solid Tumours group at IDIBAPS. “This procedure has already shown promising results in patients with metastatic melanoma and other types of tumours, and now we are beginning to test its feasibility in this more aggressive type of breast cancer,” he adds.

Metastatic triple negative breast cancer (mTNBC) is the most aggressive type of breast cancer and represents approximately 10-15% of all breast cancers. It is a little-known disease that affects about 5,000 women in Spain each year. Among those who develop mTNBC, the five-year survival rate is 12%, compared to 28% for those with other types of metastatic breast cancer. Due to the nature of mTNBC, treatment options are much more limited.

Cell-based immunotherapy using tumour infiltrating lymphocytes (TILs) is a heterogeneous mixture composed of T lymphocytes, mainly directed against tumour cells. “Lymphocytes are cells of the immune system involved in function and regulation and are responsible for destroying tumour or infected cells. TILs are found naturally in the inflammatory infiltrates of some solid tumours,” explains Dr. Manel Juan, head of the Immunology Service at Hospital Clínic and of the Immunogenetics and Immunotherapy in Immune and Autoinflammatory Response group.

The adoptive transfer of T lymphocytes or TIL therapy in solid tumours is a programme that has been launched jointly by the Medical Oncology and Immunology services of Hospital Clínic. It is a type of cell therapy conceptually similar to CAR-T, selecting T lymphocytes with antitumour activity present in the tumour. The Clinic-IDIBAPS has already developed CART therapies for the treatment of acute lymphoblastic leukaemia, with authorisation for use by the Spanish Agency of Medicines and Health Products (AEMPS), or for multiple myeloma, which is now under evaluation by the same agency.

The process consists of three parts. First, a pre-selection is performed to choose the tumours most likely to be enriched by TILs, by determining the PD1 biomarker in the tumour. Next, the T lymphocytes that have the capacity to act against cancer cells (PD1-positive TILs) are isolated and selected, of which many copies are produced in the laboratory. Finally, these lymphocytes are injected back into the patient intravenously. The final infusion product is produced by the Hospital Clínic de Barcelona under the name NUMARZU-001 and, thanks to the validation and structuring work of Dr. Núria Chic, Dr. Marta Español, Dr. Azucena González and Dr. Eulàlia Olestí, it has been demonstrated that it is possible to obtain it reproducibly from patients, a fundamental step in obtaining authorisation from the AEMPS to initiate this trial.

SOLTI will be the organisation that will manage the development of the trial, coordinating all the activities in the four participating hospitals, where, for the first time in Spain, a treatment of this type of immunotherapy for breast cancer will be administered. Dr. Tomás Pascual, SOLTI's scientific director and oncologist at Hospital Clínic, explains that the TILs001 trial “represents a new therapeutic option for patients with metastatic triple-negative breast cancer. As a cooperative group, which bases its research on networking with hospitals, leading an academic trial that responds to an unmet clinical need, with a technology as innovative as the one used by TILs001, is our reason to be and reaffirms the important work we do as cooperative groups”.

In addition to the support of the AECC, the trial has received funding from the FERO Foundation, as well as through other campaigns and anonymous donations via the Immunotherapy against cancer project of the Clinic-IDIBAPS. The latter is supported by the “la Caixa” Foundation, thanks to a strategic alliance established between these two institutions.
### Overview of the CURRENT STUDIES RUN WITHIN THE BIG NETWORK

**Open trials / research programmes**

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<td>A. Pérez-Fidalgo C. Criscitiello P. Bedard</td>
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<td><strong>AURORA (Metastatic Breast Cancer GPS)</strong></td>
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<td>P. Aftimos M. Benelli A. Guerrero Zolano</td>
<td>BIG-sponsored programme (Co)-Leading partners: BIG HQ (sponsor) / UB-CTSU / FSS Pharma partner: N/A Funding: BCRF as the main funder, Fondation Cancer (Luxembourg), Pfizer grant for non-drug research, Fondation contre le Cancer (Belgium), National Lottery (Belgium), NIF Foundation, Rhone Trust, Barrie and Dena Webb, Candriam, Fondation Futur 21, Sogerim, Think Pink Belgium (SMART Fund), Cognizant Foundation, Eurofins Foundation and many individual donors. AURORA has also been supported by the Fund Friends of BIG, managed by the King Baudouin Foundation.</td>
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<td><strong>EXPERT (BIG Radio Tuning)</strong></td>
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<td>B. Chua G. Gruber</td>
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## Follow-up or post-study activities, recently closed studies

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<td>A randomised phase III trial comparing atezolizumab (anti-PD-L1 inhibitor), given in combination with standard chemotherapy vs. chemotherapy alone as adjuvant treatment in patients with operable TNBC - NCT03498716</td>
<td>M. Ignatiadis, H. McArthur, S. Saji</td>
<td>Lead trial (Co-Leading partners: BIG HQ / UB-CTSU / IJB-CTSU / FSTRF and AFT) Pharma partner: Roche/Genentech (sponsor) Funding: Roche / Genentech</td>
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<tr>
<td>ALITTO</td>
<td>BIG 2-06</td>
<td>Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation: sequence and combination for patients with HER2/Erbb2 positive primary breast cancer - NCT00490139</td>
<td>M. Piccart, A. Moreno-Aspitia</td>
<td>Lead trial (Co-Leading partners: BIG HQ / UB-CTSU / FSTRF / Alliance (former NCCTG, sponsor for the US) Pharma partner: Novartis (global sponsor for all countries with the exception of US) Funding: GSK (past) / Novartis</td>
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<tr>
<td>AMEEA-6</td>
<td>BIG 20-01</td>
<td>Axicabtagen in patients with HR+, HER2-negative/positive breast cancer who experienced toxicities with aromatase inhibitors - NCT05128773</td>
<td>D. Cameron, E. Brain, O. Metzger</td>
<td>Co-Lead trial (Co-Leading partners: EORTC / AFT / BIG HQ Pharma partner: Sanofi (sponsor)</td>
</tr>
<tr>
<td>APHINITY</td>
<td>BIG 4-11</td>
<td>Comparison of single-versus-dual anti-HER2 therapy (Trastuzumab, pertuzumab) for patients with HER2-positive primary breast cancer - NCT01358877</td>
<td>M. Piccart, S. Loibl, J. Bines</td>
<td>Lead trial (Co-Leading partners: BIG HQ / UB-CTSU / FSTRF Pharma partner: Roche (sponsor) Funding: Roche</td>
</tr>
<tr>
<td>APPALACHES</td>
<td>BIG 18-01</td>
<td>A Phase II study of Adjuvant PALbociclib as an Alternative to CChemotherapy in Elderly patients with high-risk ER+/HER2- early breast cancer - NCT03609047</td>
<td>H. Wildiers, E. Brain, K. Punie</td>
<td>Supporter trial (Co-Leading partners: EORTC (sponsor) Pharma partner: Pfizer</td>
</tr>
<tr>
<td>BRAVO</td>
<td>BIG 5-13</td>
<td>Niraparib for patients with HER2-negative, germline BRCA mutation-positive, locally advanced or metastatic breast cancer - NCT01905592</td>
<td>N. Turner, J. Balmaña, D. Cameron, J. Erban</td>
<td>Co-Lead trial (Co-Leading partners: EORTC / BIG HQ Pharma partner: Tesaro (sponsor) Funding: Tesaro</td>
</tr>
<tr>
<td>DCIS</td>
<td>BIG 3-07</td>
<td>Radiation doses and fractionation schedules for women with DCIS - NCT00470236</td>
<td>B. Chua</td>
<td>Supporter trial (Co-Leading partner: TROG (sponsor) Pharma partner: N/A Funding: National Health &amp; Medical Research Council Project Grant, Susan G. Komen</td>
</tr>
<tr>
<td>Exceptional Responders</td>
<td>BIG 16-04</td>
<td>A global hunt for exceptional responders in the BIG network: aiming to identify breast cancer patients with a truly remarkable clinical response to anticancer treatments, and to characterise their tumours molecularly</td>
<td>A. Irrthum (coordinator)</td>
<td>BIG-sponsored programme (Co-Leading partner: BIG HQ Pharma partner: N/A Funding: Breast Cancer Research Foundation</td>
</tr>
<tr>
<td>FINESSE</td>
<td>BIG 2-13</td>
<td>Oral lucitanib for patients with FGFR1 ER+ metastatic breast cancer - NCT02053636</td>
<td>F. André, J. Cortés</td>
<td>Lead trial (Co-Leading partners: BIG HQ / UB-CTSU / FSS Pharma partner: Servier (sponsor) Funding: Servier</td>
</tr>
<tr>
<td>IBIS-II</td>
<td>BIG 5-02</td>
<td>Prevention study of anastrozole for postmenopausal women at increased risk of breast cancer; and of effects of tamoxifen vs. anastrozole in postmenopausal women with DCIS - NCT00072462</td>
<td>J. Cuzick</td>
<td>Supporter trial (Co-Leading partner: IBIS Pharma partner: AstraZeneca Sponsor: Queen Mary University of London Funding: Cancer Research UK, Queen Mary University of London</td>
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<tr>
<td>INTERNATIONAL MALE BREAST CANCER PROGRAMME</td>
<td>BIG 2-07</td>
<td>Registration and biologic characterisation programme of breast cancer in men - NCT01101425</td>
<td>F. Cardoso, S. Giordano</td>
<td>Supporter programme (Co-Leading partners: EORTC (sponsor) / NABCG NCTN / TBCRC (US) Pharma partner: N/A Funding: Breast Cancer Research Foundation</td>
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<tr>
<td>Study</td>
<td>Code</td>
<td>Title</td>
<td>Lead</td>
<td>Funding</td>
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<td><strong>LORELEI</strong></td>
<td>BIG 3-13</td>
<td>Neoadjuvant letrozole plus tisleltib versus letrozole plus placebo in postmenopausal women with ER+, HER2-negative, early-stage breast cancer - NCT02273973</td>
<td>C. Saura, E. de Azambuja</td>
<td>Co-lead trial (Co-Leading partners: ABCSG, SOLTI and BIG HQ Pharma partner: Genentech (sponsor) Funding: Genentech)</td>
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<tr>
<td><strong>MA.32 Metformin</strong></td>
<td>BIG 5-11</td>
<td>Effect of metformin on recurrence and survival in early stage breast cancer - NCT01101438</td>
<td>P. J. Goodwin</td>
<td>Supporter trial (Co-Leading partner: CCTG (sponsor) Pharma partner: Apotex Funding: NCI/NIH grants, Cancer Research UK, the Canadian Cancer Society, the Breast Cancer Research Foundation® (BCRF) and the Canadian Breast Cancer Foundation.)</td>
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<tr>
<td><strong>MINDACT</strong></td>
<td>BIG 3-04</td>
<td>Can addition of 70-gene signature to common clinical-pathological criteria safely spare patients with 0 to 3 node positive breast cancer from adjuvant chemotherapy? - NCT00433589</td>
<td>E. Rutgers, F. Cardoso, M. Piccart</td>
<td>Co-lead trial (Co-Leading partners: EORTC (sponsor) / BIG-HQ Commercial partners: Roche, Sanofi, Novartis and Agenda Funding: European Commission, Roche, Sanofi and Novartis grants, BCRF, Susan G. Komen for the Cure, Cancer Research UK, EORTC Charitable Trust, numerous national cancer societies and many other charitable grants*)</td>
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<tr>
<td><strong>NEO-ALITTO</strong></td>
<td>BIG 1-06</td>
<td>Comparison of dual HER2 inhibition (lapatinib, trastuzumab) plus chemotherapy before surgery versus single HER2-targeted therapy - NCT00553358</td>
<td>S. Di Cosimo, J. Huober</td>
<td>Co-lead trial (Co-Leading partners: EORTC (sponsor) / BIG HQ Pharma partner: Novartis (global sponsor for all countries with the exception of US, where Alliance is the sponsor) Funding: Novartis)</td>
</tr>
<tr>
<td><strong>OLYMPIA</strong></td>
<td>BIG 6-13</td>
<td>Olaparib vs. placebo for patients with BRCA-mutated, high-risk HER2-negative breast cancer, having completed local treatment and neoadjuvant chemotherapy - NCT02032823</td>
<td>A. Tutt, D. Cameron, B. Kaufman, J. Garber, C. Geyer</td>
<td>Lead trial (Co-Leading partners: NRG Oncology (sponsor in US), BIG HQ and FSTRF Pharma partner: AstraZeneca (global sponsor for all countries excluding the US) and Merck (co-developer of the drug) Funding: AstraZeneca)</td>
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<tr>
<td><strong>PALLAS</strong></td>
<td>BIG 14-03</td>
<td>PALbociclib CoLaborative Adjuvant Study: palbociclib with standard adjuvant endocrine therapy versus standard adjuvant endocrine therapy alone for HR+ / HER2-negative early breast cancer - NCT02513394</td>
<td>E. Mayer, M. Grant, A. DeMichele</td>
<td>Co-Lead trial (Co-Leading partners: ABCSG, Alliance for Clinical Trials in Oncology Foundation (sponsors for Rest of the World and the US respectively) and BIG HQ Pharma partner: Pfizer Funding: Pfizer grant)</td>
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<tr>
<td><strong>PELOPE-B</strong></td>
<td>BIG 1-13</td>
<td>Post-neoadjuvant palbociclib for patients with HR+, HER2-normal primary breast cancer with high relapse risk after neoadjuvant chemotherapy - NCT01864746</td>
<td>G. von Minckwitz</td>
<td>Supporter trial (Co-Leading partner: GBG (sponsor) Pharma partner: Pfizer Funding: Pfizer grant)</td>
</tr>
<tr>
<td><strong>POSITIVE (BIG time for Baby)</strong></td>
<td>BIG 8-13</td>
<td>Endocrine therapy interruption to enable conception for young women with ER+ breast cancer - NCT02308085</td>
<td>O. Pagani</td>
<td>Supporter trial (Co-Leading partner: IBCSG (sponsor) Pharma partner: N/A Funding: IBCSG, Fonds Baillet-Latour, national and local funding bodies, individual donors)</td>
</tr>
<tr>
<td><strong>PYTHIA</strong></td>
<td>BIG 14-04</td>
<td>Palbociclib plus fulvestrant for pretreated patients with ER+/HER2- metastatic breast cancer - NCT02536742</td>
<td>L. Malorni</td>
<td>Co-lead trial (Co-Leading partners: IBCSG (sponsor) and BIG HQ Pharma partner: Pfizer Funding: research grants and drugs from Pfizer and AstraZeneca. BIOVICA supplied support for sample handling and thymidine kinase assays.)</td>
</tr>
</tbody>
</table>

* full information available on the BIG website.

| SNAP   | BIG 2-12 | Schedules of nab-Paclitaxel: evaluation of different schedules of nab-paclitaxel for metastatic breast cancer - NCT01746225 | A. Gennari  
G. Jerusalem | Supporter trial  
(Co)-Leading partner: IBCSG (sponsor)  
Pharma partner: Celgene  
Funding: Celgene grant |
|--------|----------|-----------------------------------------------------------------------------------------------------------------|-----------------|--------------------------------------------------------|
| SOFT   | BIG 2-02 | Evaluation of ovarian suppression and of exemestane as adjuvant therapy for premenopausal women with endocrine responsive breast cancer - NCT00066690 | P. Francis  
G. Fleming | Supporter trial  
(Co)-Leading partner: IBCSG (sponsor)  
Pharma partner: Pfizer  
Funding: grants from BCRF, Cancer Research CH, Pfizer, Ipsen, Debiopharm, TerSera Therapeutics, US NCI, IBCSG and many participating collaborative academic groups, as well as various charities. Pfizer and Ipsen provided the drugs for these studies |
| SOLE   | BIG 1-07 | A phase III trial evaluating the role of continuous letrozole versus intermittent letrozole following 4 to 6 years of prior adjuvant endocrine therapy for postmenopausal women with hormone-receptor positive, node positive early stage breast cancer (SOLE - Study Of Letrozole Extension) - NCT00553410 | M. Colleoni  
P. Karlsson  
S. Aebi  
J. Chirgwin | Supporter trial  
(Co)-Leading partner: IBCSG (sponsor)  
Pharma partner: Pfizer  
Funding: grants from BCRF, Cancer Research CH, Pfizer, Ipsen, Debiopharm, TerSera Therapeutics, US NCI, IBCSG and many participating collaborative academic groups, as well as various charities. Pfizer and Ipsen provided the drugs for these studies |
| SUPREMO | BIG 2-04 | Selective Use of Postoperative Radiotherapy After Mastectomy: adjuvant chest wall irradiation for 'intermediate risk' breast cancer following mastectomy - NCT00966888 | I. Kunkler  
P. Canney | Supporter trial  
(Co)-Leading partner: SCTBG  
Sponsor: IBCSG  
Pharma partner: N/A  
Funding: UK Medical Research Council, EORTC, Cancer Australia, William and Elizabeth Davies Charitable Trust, Peter Chan Jee Yat Foundation, Yeung Ying Yin and May Yeung Foundation |
| TEXT   | BIG 3-02 | Tamoxifen and Exemestane Trial: evaluation of exemestane plus GnRH analogue for premenopausal women with endocrine responsive breast cancer - NCT00066703 | O. Pagani  
B. Walley | Supporter trial  
(Co)-Leading partner: IBCSG (sponsor)  
Pharma partner: Pfizer  
Funding: grants from BCRF, Cancer Research CH, Pfizer, Ipsen, Debiopharm, TerSera Therapeutics, US NCI, IBCSG and many participating collaborative academic groups, as well as various charities. Pfizer and Ipsen provided the drugs for these studies |
| TREAT-CTC | BIG 1-12 | TRastuzumab in HER2-negative Early breast cancer as Adjuvant Treatment for Circulating Tumor Cells (CTC) - NCT01548677 | M. Ignatiadis  
M. Piccart  
J.-Y. Pierga  
B. Rack  
C. Sotiriou | Supporter trial  
(Co)-Leading partners: EORTC BCG, SUCCESS, UNICANCER  
Sponsor: EORTC  
Pharma partner: Roche, Janssen Diagnostics  
Funding: Roche educational grant/medication, Janssen test kits |
| ULTIMATE | BIG 16-01 | Immunotherapy combined with standard endocrine therapy as neoadjuvant treatment for women with ER+/HER2-negative breast cancer - NCT02997995 | F. André  
A. Prat | Co-lead trial  
(Co)-Leading partners: French Breast Cancer Intergroup Unicancer (UCBG) (sponsor) and BIG HQ  
Pharma partner: AstraZeneca  
Funding: AstraZeneca grant |

NB: This table does not include the studies in development and all closed trials. For more information, please visit www.BIGagainstbreastcancer.org.
ABOUT BIG

THE BIG NETWORK: GLOBAL RESEARCH COLLABORATION TO CURE BREAST CANCER

For almost 25 years, BIG’s academic research groups have been working together to find better treatments and cures for breast cancer. The Breast International Group (BIG) is an international not-for-profit organisation that represents the largest global network of academic research groups dedicated to finding cures for breast cancer. Its mission is to facilitate and accelerate breast cancer research at an international level.

In 1999, BIG was founded with the aim to address fragmentation in European breast cancer research. Research groups from other parts of the world rapidly expressed interest in joining BIG and, two decades later, BIG represents about 60 like-minded research groups from around the world and reaches across approximately 70 countries on 6 continents.

Through its network of groups, BIG connects several thousand specialised hospitals, research centres and world-class breast cancer experts who collaborate to design and conduct pioneering breast cancer research. Each BIG group plays a crucial role. The combined expertise, collaborative spirit, dedication and hard work are essential to improving the lives of patients confronted with breast cancer. BIG is thus global and local.

More than 30 clinical trials are run or are under development under the BIG umbrella at any one time. BIG also works closely with the US National Cancer Institute and the North American Breast Cancer Group, to act as a strong integrating force in the field of breast cancer research. Thanks to this global collaboration, BIG enrols large numbers of patients from around the world into clinical trials quickly, which in turn leads to faster results.

BIG’s research is supported in part by its philanthropy unit, known as BIG against breast cancer. This denomination is used to interact with the general public and donors, and to raise funds for BIG’s purely academic breast cancer trials and research programmes.
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