

# BIG

RESEARCH  
IN FOCUS

April 2022 - issue n°16

## FIGHTING BREAST CANCER AROUND THE GLOBE

*The OlympiA trial - new hope for  
women and men with BRCA mutations*

## COLOPHON

### BIG Executive Board

Carlos Barrios, MD  
Philippe Bedard, MD  
Judith Bliss, MSc  
Etienne Brain, MD, PhD  
David Cameron, BIG Chair, MD  
Eva Carrasco, MD  
Boon Chua, MD, PhD  
Barbro Linderholm, MD, PhD  
Sherene Loi, MD, PhD  
Seamus O'Reilly, MD, PhD  
Evangelia Razis, MD, PhD  
Shigehira Saji, MD, PhD  
Ander Urruticoechea, MD, PhD  
Ines Vaz-Luis, MD, PhD

### Managing editors

Lina Lonneville  
Gia Questiaux  
Oriana Spagnolo  
Carolyn Strahle  
Valerie Van der Veecken

### Design

www.kalman.be  
Photos © Shutterstock

### Print

VCP Graphics BV

BIG Research in Focus is published by the Breast International Group (BIG)-aisbl.

The opinions or conclusions stated or implied in the articles herein are those of the authors and do not necessarily reflect those of the publisher.

BIG Headquarters' contact address:

Breast International Group (BIG)-aisbl Rue de Bretagne / Bretnestraat 20 1200 Brussels, Belgium

Tel: +32 2 486 16 00

VAT: BE 0468 176 240

E-mail: info@BIGagainstbc.org

www.BIGagainstbreastcancer.org



# CONTENTS

1	NOTE FROM THE EDITOR
3	RESEARCH: THE OLYMPIA TRIAL - NEW HOPE FOR WOMEN AND MEN WITH BRCA MUTATIONS
10	BIG NETWORK
14	CLINICAL TRIALS AND ACTIVITIES
32	OVERVIEW OF BIG STUDIES
36	BIG MEMBER GROUPS



# HOW TO FEEL HOPEFUL ABOUT 2022?

As we write, the world is facing another unprecedented trauma. Concerns about the Russian-Ukrainian conflict, causing a humanitarian crisis with economic and countless other consequences impacting the lives of millions of people, are now overshadowing COVID-19. Let us **hope** that all parties can work towards dialogue and a diplomatic solution, avoiding further escalation and tragedy. *See also page 10.*

The start of 2022 had brought us **optimism**, with reason to believe that the acute phase of the pandemic was nearing its end. Despite more than two years of COVID-19, and despite its adverse effects, many clinicians have reported **positive outcomes** (i.e., video and telephone consultations, digitalisation initiatives, virtual conferences, use of social media for science communication, etc.). We adapted to this new normal, showing resilience and persistence, and embraced new opportunities.

The themed article of this edition of BIG Research in Focus highlights the **OlympiA trial**. The **highly encouraging results** published last year were greeted with great interest and enthusiasm across the breast cancer community. For the first time, research showed that patients who carry a mutation in the *BRCA1/2* genes and have developed a high-risk, HER2-negative, early breast cancer, benefited from adjuvant treatment with the PARP inhibitor olaparib after completing local treatment and neoadjuvant or adjuvant chemotherapy. Medical journalist Jenny Bryan discusses the background to OlympiA and the implications for breast cancer care with some of those closest to this important trial. The BIG Headquarters communications team would like to thank **Professor Andrew Tutt, Professor Judy Garber, Professor David Cameron, Dr Tanja Spanic and Ms Sue Friedman**, who kindly accepted to be interviewed by Jenny. *For the full article, see as of page 3.*

The BIG network makes it possible to rapidly enrol a large number of patients into complex international clinical trials, to share best practices, expertise, and data. We have seen new and strengthened collaborations across borders, with **two new research groups** joining BIG in 2021: the **European Breast Cancer Research Association of Surgical Trialists (EUBREAST) Network**, with the German association EUBREAST e.V. and its Italian counterpart EUBREAST ETS.

We extend our warm welcome to two new official BIG representatives: **Dr Soumen Das, for the Breast Intergroup of Eastern India (BIEI), and Professor Purvish M. Parikh, ad interim for the Indian Co-**

**Operative Oncology Network (ICON ARO)**. We are happy to see that the work of their predecessors, the late Dr Ashis Mukhopadhyay (BIEI) and Dr Gouri Bhattacharyya (ICON ARO), is being continued, inspiring future generations of cancer scientists and oncologists. *See as of page 10.*

The section **“BIG Network”** highlights the project **“Understanding a multi-disciplinary team (MDT) perspective about omission of surgery for early-stage breast cancer”**. For her involvement in the project, **Dr Carmela Caballero, MD, Medical Advisor at BIG Headquarters**, was honoured in November 2021 with the “ESSO 40 Dragon’s Den: Best Clinical Trial Proposal” award from the **European Society of Surgical Oncology (ESSO)**. She says: “I am very grateful to ESSO for recognising this project which will be conducted with the members of the ESSO-EYSAC Research Academy and, hopefully, with colleagues and patient partners from the BIG network. This survey is the first step in developing a framework for MDTs within and beyond Europe, for safely omitting surgery for selected patients with early-stage breast cancer. The framework will also take into account patients’ perspectives.” *See as of page 11.*

The section **“Clinical Trials and Activities”** gives an update on BIG trials, their status and abstracts presented at Virtual SABCS 2021. *See as of page 14.*

The section **“Other trials and activities by BIG Member Groups”** highlights BIG member’s research and related activities around the world. *See as of page 22.*

Finally, you will find the tables with the **“Overview of the current clinical studies run within the BIG network”** as of page 32.

**BIG against breast cancer**, BIG’s dedicated philanthropy unit within BIG HQ, conducts vital fundraising to support BIG’s clinical trials and research programmes that have no commercial interest but are crucial for breast cancer patients. The funds raised – through the generosity of foundations, companies, ambassadors, and other individuals – contribute to the work of BIG member groups and their affiliated hospitals and help support patient participation in a study. *See as of page 12.*

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

*Together, we achieve more*

BIG’s Editorial Team



**OlympiA** *The OlympiA trial: practice-changing results*  
Olaparib in Adjuvant  
 BRCA breast cancer

# NEW HOPE FOR WOMEN AND MEN WITH BRCA MUTATIONS



Highly encouraging results from the OlympiA trial published last year were greeted with great interest and enthusiasm across the breast cancer community.<sup>1</sup> For the first time, research showed that patients who carried a mutation in the *BRCA1/2* genes and developed a high-risk, HER2-negative, early breast cancer benefited from adjuvant treatment with the PARP inhibitor, olaparib, after completing local treatment and neoadjuvant or adjuvant chemotherapy. Medical journalist Jenny Bryan discusses the background to OlympiA and the implications for breast cancer care with some of those closest to this important global collaborative trial coordinated by BIG, in partnership with Frontier Science & Technology Research Foundation, NRG Oncology, the US National Cancer Institute, AstraZeneca and MSD. The trial is sponsored by NRG Oncology in the US and by AstraZeneca outside the US.

## OLYMPIA: PRACTICE-CHANGING RESULTS FOR PATIENTS WITH GERMLINE *BRCA1/2* MUTATIONS AND HIGH-RISK EARLY BREAST CANCER

In 2014, when investigators started looking for patients with high-risk early breast cancer and germline *BRCA1* or *BRCA2* mutations to take part in the OlympiA trial, they were optimistic that adjuvant treatment with the poly(ADP-ribose) polymerase (PARP), olaparib, would be beneficial but they could not have predicted how rapidly and clearly they would achieve their desired endpoints.

OlympiA Steering Committee Chair, Andrew Tutt, Professor of Oncology at The Institute of Cancer Research, London, and King's College London, UK, explains that a small, proof-of-concept study had shown that olaparib worked in patients with advanced *BRCA1/BRCA2* mutated, human epidermal growth factor receptor (HER)-negative breast cancer.<sup>2</sup> However, when OlympiA started, the drug was awaiting approval in the metastatic setting and the registration studies to support that approval had not been published.<sup>3,4</sup>

*“We moved fast and early to address a clear need to reduce the risk of life-threatening recurrence in the five per cent of people with breast cancer who have *BRCA1* or *BRCA2* mutations. We understood the biology of the disease and we had a targeted treatment that we hoped would be as effective in the curative setting as it had been in metastatic disease,” he recalls.*

In a planned interim analysis in February 2021, the independent data monitoring committee for OlympiA concluded that, after a median of just 2.5 years follow up, the trial had crossed the superiority boundary for its primary endpoint and a full analysis should be carried out.

OlympiA was designed so that a reduction in life-threatening recurrence over 30% would be clinically significant. The full analysis showed that olaparib reduced the risk of invasive breast cancer recurrences, second cancers or death by 42%.<sup>1</sup> At three years, invasive disease-free survival (IDFS) was 85.9% in patients treated with olaparib compared to 77.1% of those in the placebo group,  $p < 0.001$ .

“We were delighted that there was such a clear difference with the addition of olaparib in OlympiA. The results exceeded my expectations. It’s a lot to ask patients to have yet more treatment after they’ve already had surgery, chemotherapy and sometimes radiation, but the results showed that olaparib was effective without a lot of additional toxicity,” points out **OlympiA Principal Investigator Judy Garber, Chief of the Division of Cancer Genetics and Prevention at Dana-Farber Cancer Institute, Boston, USA.**

OlympiA also showed that olaparib reduced the risk of distant recurrences away from the breast and deaths by 43%. Distant disease-free survival (DDFS) at three years was 87.5% with olaparib compared to 80.4% with placebo,  $p < 0.001$ .

As one of the original team whose laboratory research suggested that BRCA1 or BRCA2 dysfunction could be exploited by targeting DNA repair pathways in cancer cells with PARP inhibitors, Tutt is particularly gratified by the OlympiA data:

“Not only was the reduction in life-threatening recurrence greater than anticipated, it occurred earlier than we expected by one to two years. It was also very pleasing that treatment did not just reduce more innocuous recurrences such as those occurring locally in the breast, but we were also substantially reducing metastases which are what generally kill patients,” he says.

Initial overall survival (OS) data showed that there were numerically fewer deaths in the olaparib than the control group, and results of a second interim analysis reported in March 2022 confirmed that the difference was statistically significant and clinically meaningful. There was a 32% reduction in risk of death with olaparib relative to placebo ( $p = 0.009$ ), with an OS rate at four years of 89.8% for patients treated with olaparib versus 86.4% for those on placebo.

“OlympiA shows that for women with inherited BRCA mutations, olaparib can not only reduce the risk of their cancer coming back, but can also improve their overall survival,” adds Tutt. “It’s an exciting demonstration of the benefits of targeting the specific biology of disease for women with this type of early-stage breast cancer, and raises the prospect that more patients will now be cured of their disease.”

## WHAT GREAT COLLABORATION HAS ACHIEVED

Coordinating the OlympiA trial was a huge challenge, not least because BRCA1/2 mutated breast cancer is uncommon; 420 centres in 23 countries were needed to find, recruit and treat the 1,836 patients who ultimately took part in the global study programme. BIG was the primary coordinator between the global non-US collaborative groups, the US sponsor, NRG, and the non-US sponsor, AstraZeneca, which also funded the trial.

*“OlympiA needed an organisation with the networks and coordinating experience of BIG to bring together all the researchers required to identify a pool of patients with BRCA1/2 mutations that was large enough to find the numbers needed for the study,” says BIG Chair David Cameron, Professor of Oncology at Edinburgh University, UK.*

He explains that OlympiA was more complicated than many studies because, for logistical reasons, two databases were needed – US and the rest of the world – with results then brought together for independent analysis.

“By carrying out a study as large and well powered as OlympiA, we felt we could get better data and avoid the duplication likely to happen if the research was done in multiple smaller studies,” adds Cameron.

He has now taken over, as one of the OlympiA Principal Investigators, the role previously carried out by the renowned and exceptional Israeli oncologist, Bella Kaufman, who sadly passed away in May 2021. Bella was the founder and leader of the Israeli Consortium for Hereditary Breast Cancer and Head of the Breast Cancer Unit at Chaim Sheba Medical Centre at Tel Hashomer in Israel, which is affiliated with the University of Tel Aviv.

“Bella was not only a Principal Investigator in OlympiA, she played a key role as a physician in driving research in genetic breast cancer and contributed to other important studies of PARP inhibitors. She was passionate in trying to improve treatment for her patients and it’s particularly sad that she lost her life before publication of OlympiA, as she had put so much into it,” says Cameron.

## ENSURING PATIENTS HAD A VOICE IN OLYMPIA

Before OlympiA investigators asked thousands of patients to take part in the trial, it was essential that those involved in its design fully understood the likely needs and concerns of participants. For this reason, BIG invited patient advocates onto the Steering Committee of OlympiA, as it does routinely with other studies.

**Tanja Spanic, President of Europa Donna Slovenia and a member of the OlympiA Steering Committee,** stresses the importance of involving the patient community from the start.

“Patients are the core of any trial, so their practical insights are essential to the design of the study, not just after it has started. For example, we can advise on the frequency of hospital visits and ask how much can be done by phone calls and telemedicine, we can advise on the lay language used in information for patients, and we can help look after the quality of life of those taking part in a study - not just the effects of the treatment itself but also in relation to the protocol,” she explains.

Patient groups, such as **Europa Donna** in Europe and **Facing Our Risk of Cancer Empowered (FORCE)** in the USA, give patients a voice in clinical research and draw attention to the kind of studies that patients feel are needed.

“The fact that studies like OlympiA are being designed for patients with inherited mutations is huge for the cancer community as it’s getting into personalised aspects of treatment,” says **OlympiA Steering Committee member, Sue Friedman, Executive Director of FORCE**, which advocates for people with hereditary cancer in the USA. “It’s also important because people with hereditary mutations are often at risk of multiple cancers, and inherited cancers tend to occur at a younger age and are more aggressive than cancers that are not inherited.”

“OlympiA speaks to the feasibility of carrying out studies on inherited cancers and suggests what may be possible for better treatment for patients and their families with mutations as they currently carry a disproportionate burden of cancer,” she adds.



Patient organisations were also important in spreading the word about OlympiA to patients who might be eligible for the study and for offering support.

“We gave people information about OlympiA and answered their questions. I think it also helped recruitment that people could see there were patient representatives on the OlympiA Steering Committee who had advised about the design and what was important to patients,” says Spanic.

## OVERCOMING BRCA1/2 TESTING CHALLENGES

With only one in 20 patients with breast cancers likely to be carrying *BRCA1/2* mutations, testing patients for eligibility to OlympiA was a significant challenge.

“When OlympiA was being planned, *BRCA1/2* testing was quite commonly available in the prevention setting for those who wanted to know if they were at risk of getting breast cancer due to *BRCA* mutations. However, it typically took months to get results which was too long for OlympiA as decisions about treatment options depended on test results,” Tutt explains.

Fortunately, OlympiA was able to offer centralised *BRCA1/2* testing for patients recruited to the study by investigators who did not have access to local, rapid testing, and approximately 15,000 patients were screened in this way.

Since the introduction of PARP inhibitors in the treatment of metastatic and locally advanced *BRCA*-mutated, HER2-negative breast cancer in recent years, and for some ovarian, prostate and pancreatic cancers, *BRCA1/2* testing has become more widely available in high-income countries with results generally provided within a few weeks.

“It is becoming much easier to test patients upfront when they are diagnosed with breast cancer, but it requires that oncologists plan ahead for patients who have high-risk disease and could benefit from targeted therapies,” says Garber.

“As most high-risk patients will need surgery and chemotherapy, and possibly radiotherapy, there is certainly time to get *BRCA* test results back before patients are ready for their PARP inhibitor. There is also potential for streamlining testing processes now that we know that results have implications for treatment,” she adds.

Friedman points out that patients who have already completed treatment for breast cancer, and are seen as survivors, may also benefit from *BRCA* testing.

“Testing may not have been available when they were diagnosed and they may fall outside current testing guidelines but it’s important that they know about testing because they may be at high risk of another breast cancer or ovarian cancer,” she says.

Spanic reports that, in Europe, a growing proportion of insurers in EU countries are paying for *BRCA* testing when results will determine choice of treatment but, outside the EU, testing is still not available in some countries due to lack of facilities or cost. She and Friedman stress the importance of genetic counselling alongside testing.

“It’s very important that patients are fully informed about *BRCA* testing and what it means both for them and their family members. In most EU countries there are genetic teams who provide counselling and written information, and it is important for patients to have time to talk and ask questions,” says Spanic.

Friedman agrees the value of genetic counselling before and after *BRCA* testing:

“Genetic counsellors are highly trained in the science of testing and the meaning of results, not just the psychological aspects. At FORCE, we strongly recommend that people see a counsellor to discuss genetic testing and, if there is a shortage of counsellors in their area, to investigate seeing someone through telemedicine,” she says.

## WHY PARP INHIBITION?

PARP is an enzyme involved in the repair of breaks in single strands of DNA. In 2005, reports from two large research groups described how dysfunctional *BRCA1* or *BRCA2* activity, arising from mutations in *BRCA1/2* genes, sensitised tumour cells to the effects of PARP inhibitors.<sup>2,3</sup> These agents trap PARP on DNA at single strand breaks, resulting in double strand breaks. Normal cells in people with *BRCA1/2* mutations have mechanisms for repairing double strand breaks. But these are missing in tumour cells, leading to chromosomal instability and cell death.

Tutt stresses that one of the reasons OlympiA was successful was the important work of a large group of laboratory scientists, led by Alan Ashworth in London and Thomas Helleday in Sheffield, who established the potential of PARP inhibitors to interfere with DNA damage repair mechanisms in cancer cells.

“It’s been an incredible privilege to have been part of the original research that demonstrated the

effects of *BRCA* genes, the lab studies with PARP inhibitors and then the clinical trials including OlympiA. But we must also give credit to everyone who was involved in the research over many years which has brought us to the exciting place we are today,” says Tutt.

Following the landmark laboratory research, extensive clinical trials have demonstrated the effects of PARP inhibition in the treatment of ovarian, prostate and pancreatic cancers in patients with *BRCA1/2* mutations.

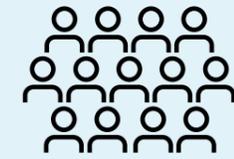
In 2010, positive results were reported from a proof-of-concept study of the PARP inhibitor, olaparib, in 54 women with germline *BRCA1/2* mutations and recurrent advanced breast cancer who had been treated with a median three previous chemotherapy regimens.<sup>4</sup> This study set the scene for OlympiA and its findings were subsequently confirmed by two Phase 3 trials of the PARP inhibitors, olaparib and talazoparib, in patients with advanced breast cancer and germline *BRCA1/2* mutations which showed improved progression-free survival compared to standard therapy.<sup>5,6</sup>

## IMPLICATIONS FOR FUTURE PRACTICE

After OlympiA data were presented at the 2021 Annual Meeting of the American Society of Clinical Oncology (ASCO), ASCO guidance for the management of hereditary breast cancer was updated to include a recommendation for use of olaparib in patients with early stage, high-risk breast cancer with *BRCA1/2* mutations.<sup>7</sup> The National Comprehensive Cancer Network also added olaparib for a similar indication to its breast cancer guidelines and the St Gallen International Consensus Guidelines for Treatment of Early Breast Cancer 2021 endorsed the use of olaparib for patients meeting OlympiA inclusion criteria.

*“It’s very heartening to watch the guidelines change in response to the evidence from OlympiA. It’s also important for advocacy groups in helping patients understand the importance of clinical trials and their impact on future treatment, as well as the value of participating in research,” says Friedman.*

# OlympiA



**1,836**  
patients

**21**

BIG member groups

**23**

countries

**OVER 600**

hospitals and cancer centres

## Breast cancer

**2.3 million**

diagnosed in 2020 worldwide\*  
\* World Health Organization. Estimated number of cases in 2020, worldwide, both sexes, all ages.

**91%**

diagnosed at an early stage in the US

**5%**

BRCA mutations found<sup>9</sup>

In the USA, olaparib underwent priority review by the Food and Drug Administration and, in March 2022, received regulatory approval for the adjuvant treatment of patients with *BRCA*-mutated HER2-negative high-risk early breast cancer who have already been treated with chemotherapy either before or after surgery. Other regulatory authorities are performing similar reviews.

“Following regulatory approval, olaparib should be offered to all women who would have met criteria for enrolment in OlympiA. The trial results also open the door to evaluating the drug in women with lower risk of recurrence than in OlympiA and for considering the possibility that PARP inhibition might ultimately substitute for more toxic therapies as part of the treatment for patients with less risky *BRCA*-associated breast cancers,” says Garber.

“We’re not suggesting that olaparib should be given to everyone just because it worked in OlympiA. We will need trials to investigate these possibilities. Treatment will be expensive and will have to be agreed by insurers and payors, but we shouldn’t lose sight of just how exciting the OlympiA results are. We will need to find ways to enable everyone internationally who could benefit to receive it appropriately,” she adds.

Cameron would also like to see studies that investigate the duration of olaparib treatment in patients meeting OlympiA criteria.

“Although it looks as though olaparib doesn’t cause toxicity, it would be nice to understand whether the one year of therapy we had in OlympiA is the right duration. If we can get the same effect with less treatment or more effect with longer treatment that might be good for some patients. We need to refine treatment to work out who does or doesn’t need treatment and how long they should have it,” he explains.

Tutt would like to know whether PARP inhibition could have a role in prevention of breast cancer in people with *BRCA1/2* mutations:

“This would be a very different situation from treating patients who already have breast cancer and there would need to be careful consideration of drug toxicity in people who are otherwise healthy. How much drug would they need to take and for how long?” he asks.

He also underlines the potential for therapies targeting DNA damage repair mechanisms in other forms of inherited breast cancer that do not involve *BRCA1/2* mutations:

“There is a lot of interest in *PALB2* which is another quite frequently mutated familial breast cancer gene which functions in the same biological processes as *BRCA1/2*, and there is already evidence from studies in incurable disease that PARP inhibitors are active,” he says.

However, recruiting sufficient patients to a study in high-risk early breast cancer would be an even greater challenge than for OlympiA – given the lower frequency of *PALB2* mutations. Could the OlympiA data be used to inform use of PARP inhibitors in patients with this and other genetic mutations?

*“We are living in very exciting times for inherited breast cancer but there are still a lot of unanswered questions. OlympiA has made a really important contribution to discussions about where we go next and has been an outstanding example of what can happen when researchers come together to answer really important questions for patients,” he concludes.*



## REFERENCES

1. Tutt ANJ, Garber JE, Kaufman C et al. Adjuvant Olaparib for Patients with *BRCA1*- or *BRCA2*-Mutated Breast Cancer. *N Engl J Med*. 2021 Jun 24;384(25):2394-2405. doi: 10.1056/NEJMoa2105215. Epub 2021 Jun 3.
2. Tutt A, Robson M, Garber JE et al. Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with *BRCA1* or *BRCA2* mutations and advanced breast cancer: a proof-of-concept trial. *Lancet* 2010 Jul 24;376(9737):235-44.
3. Farmer H, McCabe N, Lord CJ et al. Targeting the DNA repair defect in *BRCA* mutant cells as a therapeutic strategy. *Nature* 2005 Apr 14;434(7035):917-21.
4. Robson M, Im SA, Senkus E, et al. Olaparib for metastatic breast cancer in patients with a *germline BRCA* mutation. *N Engl J Med* 2017; 377: 523-33.
5. Litton JK, Rugo HS, Ettl J, et al. Talazoparib in patients with advanced breast cancer and a *germline BRCA* mutation. *N Engl J Med* 2018; 379: 753-63.
6. ASCO. Management of Hereditary Breast Cancer. August 2021. <https://www.asco.org/practice-patients/guidelines/breast-cancer#143725>
7. National Comprehensive Cancer Network. Breast Cancer. December 2021. [https://www.nccn.org/professionals/physician\\_gls/pdf/breast.pdf](https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf)
8. Burstein HJ, Curigliano G, Thürlimann B et al. Customizing local and systemic therapies for women with early breast cancer: the St. Gallen International Consensus Guidelines for treatment of early breast cancer 2021. *Ann Oncol*. 2021 Oct;32(10):1216-1235.
9. Mitri Z, et al. The HER2 Receptor in Breast Cancer: Pathophysiology, Clinical Use, and New Advances in Therapy. *Chemother Res Pract*. 2012;743193

## MEET THE EXPERTS



**David Cameron, MD**  
Chair of BIG  
Professor of Oncology at  
Edinburgh University  
Edinburgh, UK



**Tanja Spanic, MD, PhD**  
Breast Cancer Patient  
Advocate and President of  
Europa Donna Slovenia  
Ljubljana, Slovenia



**Sue Friedman, MD**  
Executive Director and  
founder of FORCE (Facing  
Our Risk of Cancer  
Empowered)  
Tampa, Florida, USA



**Andrew Tutt, MD, PhD**  
Professor of Oncology  
Head of the Division of Breast  
Cancer Research and Director  
of the Breast Cancer Now  
Toby Robins Research Centre  
at the Institute of Cancer  
Research and Guy’s Hospital  
King’s College  
London, UK



**Judy Garber, MD, PhD**  
Professor of Medicine at  
Harvard Medical School  
Chief of the Division  
of Cancer Genetics and  
Prevention at the Dana-Farber  
Cancer Institute  
Boston, USA

The **Breast International Group** is a global organisation, but with roots and headquarters firmly established in Europe. With the Russian / Ukrainian conflict at our doorstep, we wish to express our strong condemnation of war, and the senseless death, misery and destruction that it causes. This holds true regardless of where military conflict occurs in the world, and our hearts and thoughts go to all of its victims, wherever they may be. Moreover, as an

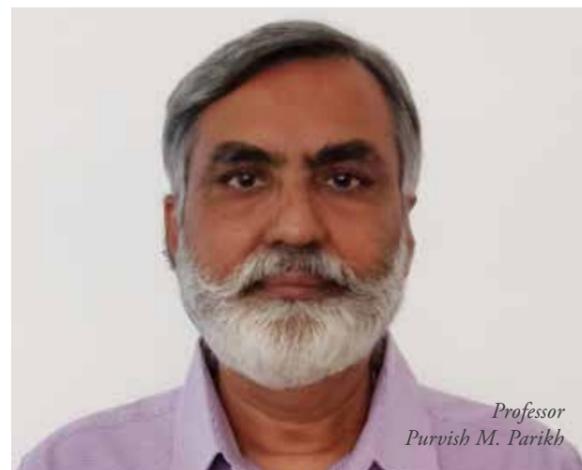
organisation dedicated to cancer research, we are sensitive to the suffering experienced by all the people touched by this disease and who, as a result of this brutal war in Europe, can no longer access treatment for their cancer, further putting their lives at risk. It is with tremendous sadness that we write this in 2022, at a time when history has shown us so many times that wars do not resolve disagreements, but only deepen hatreds and intensify human suffering.

## Two new official BIG representatives

### INDIAN BIG MEMBER GROUPS BIEI AND ICON ARO

The first half of 2021 brought us great sadness with the passing of two eminent Indian oncologists and longstanding friends and colleagues from BIG: **Dr Ashis Mukhopadhyay** († January 26, 2021), founding member of the **Breast Intergroup of Eastern India (BIEI)**, and **Dr Gouri Bhattacharyya** († May 1, 2021), founding member of the **Indian Co-Operative Oncology Network (ICON ARO)**. They had been involved in the BIG network for many years and their friendship, advice, expertise, and passion for breast cancer research is truly missed by their colleagues and patients. They were examples for many of us, and their legacies will live on forever.

**Dr Soma Mukhopadhyay**, Dr Ashis Mukhopadhyay's wife, is a researcher and scientist at the Netaji Subhas Chandra Bose Cancer Hospital in Kolkata and is now managing the affairs of her late husband's oncology centre.



Professor  
Purvish M. Parikh



Dr Soumen Das

**Dr Soumen Das has been nominated new BIEI official representative within BIG.** He is Chief Consultant, Breast Bowel & HIPEC Services, Department of Surgical Oncology at the Netaji Subhas Chandra Bose Cancer Hospital.

**Professor Purvish M. Parikh now serves as ICON ARO's official BIG representative.** He is a medical oncologist and Chief Mentor at the Mumbai Oncocare Centre. Professor Parikh has taken on this official representative role for an interim period, until the group nominates the person that will continue Dr Gouri S. Bhattacharyya's leadership.

We wish Dr Soumen Das and Professor Purvish M. Parikh a warm welcome to the BIG network! We're happy to see that the work of their predecessors is continued, inspiring future generations of cancer scientists and oncologists.

## Project "Understanding a multi-disciplinary team (MDT) perspective about omission of surgery for early-stage breast cancer"

### DR CARMELA CABALLERO HONOURED WITH ESSO AWARD



Carmela Caballero, MD, Medical Advisor at BIG's headquarters in Brussels (Belgium), received an award from the **European Society of Surgical Oncology (ESSO)** for her involvement in the project **"Understanding a multi-disciplinary team (MDT) perspective**

**about omission of surgery for early-stage breast cancer"**, which she presented at the Dragon's Den Session of the 40th Congress of the European Society of Surgical Oncology (*ESSO40: Enhancing the Future of Cancer Surgery, 8-10 November 2021, Lisbon, Portugal*).

Dr Caballero is a surgeon from the Philippines and, as medical advisor at BIG, oversees the activities for the AURORA, APHINITY and EXPERT studies, as well as the BIG Patient Partnership Initiative and the BIG Asia Collaboration. She's a Steering Committee member of the ESSO Young Surgeon's Alumni Club (ESSO-EYSAC) and the ESSO Educational Training Committee for Breast Cancer Surgery. Dr Caballero is also serving as a research mentor for Science Integrated Direction for High School Investigators (SIDHI) Mentorship Programme.

Dr Caballero, on winning this award: *"I am very grateful to ESSO for recognising this project which will be conducted with the members of the ESSO-EYSAC Research Academy and, hopefully, with colleagues and patient partners from the BIG network. This survey is the first step in developing a framework for MDTs within and beyond Europe, for safely omitting surgery for selected patients with early-stage breast cancer. The framework will also take into account patients' perspectives."*

ESSO-EYSAC aims to enable young surgeons to perform an active role in shaping the future of surgical oncology training in Europe and to empower them to be leaders of high-quality cancer surgery research. The ESSO Dragon's Den Programme started in 2019 and is held in conjunction with the society's annual congress. Here, study proposals or trials in progress

from young surgeons can be submitted to be evaluated and critiqued by a panel of experts of MDT specialists and patient advocates. The winning proposal gets the chance to be shared, or potentially conducted, within the ESSO network.

**Key aspects of the project: "Understanding a multi-disciplinary team perspective about omission of surgery for early-stage breast cancer"**

Dr Caballero's project aims to gather the perspectives of the MDT about important considerations prior to omitting breast cancer surgery among selected patients. Currently, no clear and validated guidelines have been developed to address this issue. The key to achieving the best outcomes for a de-escalation strategy is careful selection from the MDT as well as understanding patient preferences.

Hence, it will be important to understand the knowledge and attitudes of different members of the MDT on the issue of omitting surgery as well as:

- > To identify the variation of MDT insights across participating regions, countries, and hospitals.
- > To assess the willingness of MDT members to include patients in "de-escalation" trials for breast cancer surgery
- > To identify potential barriers for effective and safe implementation of this strategy in daily practice

The proposal is to conduct an electronic survey among MDTs across the ESSO-EYSAC network (and other partner networks) with the following target participants: surgeons, oncologists, radiologists, pathologists, radio-oncologists, nurses / patient managers and patient advocates.

Following the combined analysis of the MDT perspective and the patient perspective, Dr Caballero hopes to develop a wholistic framework for a safe omission of surgery for selected breast cancer patients. More news to follow soon.

# TOGETHER WE ARE



## BIG against breast cancer

THE BREAST INTERNATIONAL GROUP'S RESEARCH IS SUPPORTED, IN PART, BY **BIG AGAINST BREAST CANCER**, BIG'S PHILANTHROPIC ARM.

Dedicated entirely to raising vital funds, **BIG against breast cancer** helps finance purely academic breast cancer clinical trials and research programmes under the BIG umbrella that have no particular interest for commercial partners but are crucial for patients. These collaborative efforts have led to practice-changing achievements in the field of breast cancer care for over more than 20 years.

From unique art exhibitions and breathtaking gala dinners to adventurous family rallies, as well as corporate partnerships and foundation grants, **BIG against breast cancer** collects funds in many ways. These funds

contribute to supporting BIG's member groups, their affiliated hospitals, and BIG scientific staff to enable patient participation in three of the network's academic studies.

One study for which **BIG against breast cancer** has been raising funds is the **AURORA** academic research programme (also known as **BIG Metastatic Breast Cancer GPS**). In October 2021, the *"Pink is the New Black Gala Dinner"* was entirely dedicated to this. More than 250 people dressed in their very finest, attended the dinner and dance party, with all the benefits going to support the research programme. Thanks to the dedication of the organising committee, our partners, the support of our sponsors and the generosity of the participants, the funds raised support the equivalent of **20 patients participating in the AURORA programme for one year.**



Besides this, vital funds were also collected for the **POSITIVE** study (also known as **BIG Time for Baby**), and the **EXPERT** study (or **BIG Radio Tuning**) through a variety of fundraising activities.

**A SPECIAL MENTION MUST GO TO THE MANY PERSONAL FUNDRAISING INITIATIVES LAUNCHED BY INDIVIDUALS VIA OUR MOVEFORBIG.ORG PLATFORM.**

Just since October 2021, five new initiatives have been launched to collect funds for BIG's research. These initiatives all stem from inspiring people, such as Heidi Wouters who will be taking on the Ironman World Championship in Hawaii or a group of determined runners who will be running the 7-day "Marathon des Sables", a footrace in the Moroccan Sahara desert, all to support **BIG against breast cancer!** Their inspiring stories are worth a look, and support.

**In a few months these incredible initiatives have already raised over 4,000 euros!**

**Visit [MoveforBIG.org](https://MoveforBIG.org) now and discover what motivates our community.**

The determination and commitment of the BIG network, and the enthusiasm and creativity of the **BIG against breast cancer** community show us that all our actions matter, whether they are small or BIG, taking place in the Moroccan Sahara or even Hawaii. **By collecting our efforts and working together we can achieve so much more!**



Spread the word: act BIG from a distance! Whether you live in Japan, Israel, Sweden or anywhere else in the world, create a fun and original fundraiser together with colleagues, friends and family! From a 10,000-step challenge with your neighbourhood to hosting a comedy night with friends.

**The sky isn't the limit, think and act BIG!**

#1

# BIG TRIAL UPDATES

## TWO NEW STUDIES LAUNCHED:

### 1. AMEERA-6 (BIG 20-01)

The AMEERA-6 trial opened early 2022 with a first site activated in Chile in January and a first patient randomised on 17 March 2022.

This is a two-arm study that aims to evaluate the efficacy and tolerability of amcenestrant in comparison with tamoxifen, in patients with hormone receptor-positive (HR+), HER2-negative or HER2-positive breast cancer who were unable to continue their adjuvant aromatase inhibitor therapy due to side effects (treatment-related toxicity).

The study will last approximately 10 years (5 years of treatment and 5 years of follow-up).

**18 BIG member groups are participating in this trial, which will involve 3,738 patients from 650 sites in about 29 countries.**

AMEERA-6 is coordinated by the **Breast International Group (BIG Headquarters)**, in collaboration with the **European Organisation for Research and Treatment of Cancer (EORTC)** and **Alliance Foundation Trials (AFT)**.

**Sanofi** is the pharmaceutical partner and sponsor of the study, providing funding and study drugs.

**AMEERA-6:** Study of amcenestrant (SAR439859) vs. tamoxifen for patients with hormone receptor-positive (HR+) early breast cancer who have discontinued adjuvant aromatase inhibitor therapy due to treatment-related toxicity

### 2. DECRESCENDO (BIG 19-02)

#### Update by IJB-CTSU



The **Institut Jules Bordet (IJB)**, and specifically its **Clinical Trial Support Unit (IJB-CTSU)**, has been a partner of **BIG** for many years and, among the numerous studies initiated in recent years, is the **DECRESCENDO** trial (BIG 19-02). This is a multicentre, open-label, dual-

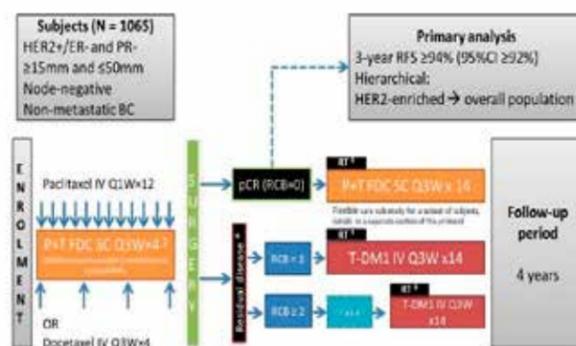
phase single arm phase II de-escalation trial evaluating neo-adjuvant treatment in patients with HER2-positive, hormone receptor-negative early breast cancer who achieved pathological complete response. It aims to demonstrate that, in some patients, it should be possible to reduce chemotherapy by increasing targeted therapies.

**The study is being run in 12 countries** (France, Belgium, Ireland, Italy, Israel, Republic of Korea, Australia, New Zealand, Argentina, Canada, Sweden and Switzerland) **and will include more than 1,000 patients.** The Institut Jules Bordet is the sponsor of this study, co-led with **BIG**. **12 BIG member groups are taking part in the study.**

The treatment used to block HER2 is pertuzumab combined with trastuzumab (called **PHESGO**) and is supplied by **Roche**. In addition to this treatment, paclitaxel or docetaxel is administered, with the choice of chemotherapy agent being left up to the investigator. During surgery, a sample of the remaining tumour cells is collected and analysed to determine the effectiveness of the neo-adjuvant treatment and guide the choice of the upcoming treatment administered to the patient. Patients who respond well to treatment continue the HER2 blockade without chemotherapy and can also participate in a sub-study called **Flexible Care**. Those who do not respond well receive an alternative drug called trastuzumab-emtansine (T-DM1), before which chemotherapy may be required. At the end of the treatment phase, a follow-up phase including regular medical visits is initiated to monitor the health of the patients.

*Figure 3: DECRESCENDO main-study design (credit: IJB)*

*Flexible Care sub-study: this sub-study aims to evaluate*



the administration of pertuzumab and trastuzumab outside the hospital by a healthcare professional in the adjuvant phase of the study. This sub-study is being conducted in selected sites in some of the countries that participate in the main study (France, Belgium, Ireland, Italy and Israel).

As of 21 March 2022, 23 sites had been opened and 4 patients included in the study.

DECRESCENDO is made possible by a research grant and drugs provided by Roche.

**DECRESCENDO:** De-Escalation of adjuvant ChemotheRapy in HER2-positive, ESrogen reCEptor-negative, Node-negative early breast cancer patients who achieved pathological complete response after neoadjuvant chemotherapy and Dual HER2 bIockade.

### ALPHABET (BIG 18-04)

#### alphabet

As of 22 March 2022, 46 sites were active in Spain and 6 patients had been randomised in the ALPHABET trial, which was officially launched in July 2021.

The aim of ALPHABET is to test the efficacy and safety of alpelisib, given in combination with trastuzumab, and to compare this treatment with chemotherapy and trastuzumab, as a new strategy to overcome treatment resistance in patients with advanced HER2-positive breast cancer that is also positive for a PIK3CA mutation.

This new study will enrol **about 300 patients in approximately 110 hospitals from 6 European countries.**

ALPHABET is an international study run and sponsored by **GEICAM (the Spanish Breast Cancer Group)** in collaboration with **IBCSG (the International Breast Cancer Study Group)** and the **Breast International Group (BIG)**.

**5 BIG member groups are participating in the study, in addition to GEICAM.**

ALPHABET is made possible by a research grant and provision of the study drug (alpelisib) by Novartis.

**ALPHABET:** A randomised phase III trial of trastuzumab + ALpelisib +/- fulvestrant versus trastuzumab + chemotherapy in patients with PIK3CA mutated previously treated HER2+ Advanced BrEasT cancer

<sup>1</sup>Genomic and transcriptomic analyses of breast cancer primaries and matched metastases in AURORA, the Breast International Group (BIG) molecular screening initiative. Afimos P, Oliveira M, Irrthum A et al. *Cancer Discov.* 2021 Nov;11(11):2796-2811. doi: 10.1158/2159-8290.CD-20-1647. Epub 2021 Jun 28.

### AURORA (BIG 14-01):

#### Extension of the programme to specific subtypes of metastatic breast cancer



With the generous support of the **Breast Cancer Research Foundation**<sup>®</sup>, an extension of the study starting in 2022 will focus on specific subtypes of metastatic breast cancer, namely triple-negative, invasive lobular and patients with late relapses (at least 10 years after their primary breast cancer diagnosis).

This extension will run across a selected number of centres and countries. **About 260 patients** are foreseen to be included in 4 years.

Recruitment of the first 1,000 patients in the programme concluded in August 2020 and the initial results, based on the first 381 enrolled patients, were published in *Cancer Discovery*<sup>1</sup> in 2021. **As of February 2022, over 1,150 patients had been included in AURORA**

**10 BIG member groups** and 1 independent site are participating in the study.

AURORA is sponsored by the **Breast International Group (BIG)** and coordinated by BIG Headquarters in collaboration with the **Institut Jules Bordet's Clinical Trials Support Unit (IJB-CTSU)** and **Frontier Science Scotland (FSS)**.

The study is made possible in part by generous grants from the Breast Cancer Research Foundation<sup>®</sup> (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.

## EXPERT (BIG 16-02): ALSO OPEN IN THE REST OF THE WORLD THROUGH BIG GROUPS

### Update by BCT-ANZ

We are delighted that the **EXPERT** clinical trial is now open in Australia, New Zealand, Taiwan, Spain, Switzerland, Argentina, Chile and, soon, Italy.

The primary aim of the trial is to see whether a genomic test of breast cancer tissue can be used to identify women who can safely avoid radiation therapy after breast cancer surgery.

The **EXPERT** trial (public name: BIG radio tuning) is studying whether some patients with low-risk early breast cancer could be spared radiotherapy after breast conserving surgery. A genomic test on breast cancer tumours is being used to determine the risk of the cancer coming back. In patients at low risk of recurrence, the combination of standard radiotherapy and hormone treatment is being compared with hormone treatment alone.

The results of **EXPERT**, which **will run in 8 countries around the globe and enrol a total of 1,170 patients**, could influence how 2 in 5 women with breast cancer are treated. If the study proves that certain patients do not need radiation therapy, many women affected by this disease may be spared its potential side effects, and healthcare systems could also make significant savings.

This study is coordinated by the **Breast Cancer Trials – Australia & New Zealand (BCT-ANZ)** in collaboration with the **Breast International Group (BIG) Headquarters**. It is funded by BCT-ANZ (sponsor) and the National Health and Medical Research Council of Australia, Loterie Nationale (Belgium), plus funds raised by the BIG Headquarters' philanthropy team.

**5 BIG member groups are participating in the study, in addition to BCT-ANZ.**

**EXPERT: EX**amining **PE**rsonalised **R**adiation Therapy for Low-risk Early Breast Cancer

## PYTHIA (BIG 14-04): FIRST RESULTS PUBLISHED IN EUROPEAN JOURNAL OF CANCER

### Update by IBCSG

The **International Breast Cancer Study Group (IBCSG)** and **BIG** co-led the phase II **PYTHIA** (palbociclib in molecularly characterised ER-positive/HER2-negative metastatic breast cancer) trial, which published its first results in the *European Journal of Cancer*<sup>1</sup>. The first investigations focused on circulating thymidine kinase activity (TKa) as a potential prognostic and monitoring marker for patients treated with palbociclib+fulvestrant. High baseline TKa and incomplete suppression of TKa during treatment may identify patients with poor prognosis and primary resistance to palbociclib+fulvestrant. TKa may represent a novel biomarker to select patients for alternative treatment modalities and warrant further investigation in prospective comparative trials.

**PYTHIA** is a “downstream” trial of **BIG's AURORA** research programme, an international initiative collecting and characterising biological samples, both primary and metastatic tissue, from patients with advanced breast cancer. Detailed molecular information (including somatic mutations, copy number variation, gene expression profiling and circulating biomarkers) are being analysed from **AURORA** for patients enrolled in **PYTHIA**. Results are expected to be presented at a scientific meeting later in 2022.

**PYTHIA** is made possible by research grants and drugs provided by Pfizer (palbociclib) and AstraZeneca (fulvestrant). **BIOVICA** supplied support for sample handling and thymidine kinase assays.

**3 BIG member groups are participating in the study, in addition to IBCSG (sponsor).**



## Recently published manuscripts about BIG trials

**APHINITY (BIG 4-11):** Gelber RD, Wang WV, Cole BF et al. Six-year absolute invasive disease-free survival benefit of adding adjuvant pertuzumab to trastuzumab and chemotherapy for patients with early HER2-positive breast cancer: A Subpopulation Treatment Effect Pattern Plot (STEPP) analysis of the APHINITY (BIG 4-11) trial. *Eu J Can* 166:219-228, 2022 <https://pubmed.ncbi.nlm.nih.gov/35313167/>

**BRAVO (BIG 5-13) :** Turner NC, Balmaña J, Poncet C et al. Niraparib for Advanced Breast Cancer with Germline BRCA1 and BRCA2 Mutations: the EORTC 1307-BCG/BIG5-13/ TESARO PR-30-50-10-C BRAVO Study. *Clin Cancer Res*. 2021 Oct 15;27(20):5482-5491. doi: 10.1158/1078-0432.CCR-21-0310. Epub 2021 Jul 22. <https://aacrjournals.org/clincancerres/article/27/20/5482/671723/Niraparib-for-Advanced-Breast-Cancer-with-Germline>

**MINDACT (BIG 3-04):** Lopes Cardozo JMN, Drukker CA, Rutgers EJT et al. Outcome of Patients With an Ultralow-Risk 70-Gene Signature in the MINDACT Trial. *J Clin Oncol*. DOI: 10.1200/JCO.21.02019. Published online January 21, 2022 <https://ascopubs.org/doi/10.1200/JCO.21.02019>

**PALLAS (BIG 14-03):** Gnant M, Dueck AC, Frantal S et al. Adjuvant Palbociclib for Early Breast Cancer: The PALLAS Trial Results (ABCSG-42/AFT-05/BIG-14-03). *J Clin Oncol*. 2022 Jan 20;40(3):282-293. doi: 10.1200/JCO.21.02554. Epub 2021 Dec 7. <https://pubmed.ncbi.nlm.nih.gov/34874182/>

**PYTHIA (BIG 14-04):** Malorni L, Tyekucheva S, Hilbers FS et al. Serum thymidine kinase activity in patients with hormone receptor-positive and HER2-negative metastatic breast cancer treated with palbociclib and fulvestrant. <https://www.sciencedirect.com/science/article/abs/pii/S0959804922000028?dgcid=coauthor>

<sup>1</sup> Luca Malorni, Svitlana Tyekucheva, Florentine S. Hilbers, et al. Serum thymidine kinase activity in patients with hormone receptor-positive and HER2-negative metastatic breast cancer treated with palbociclib and fulvestrant. *European Journal of Cancer*, Volume 164, March 2022, Pages 39-51.

# 2

# BIG TRIALS AT CONFERENCES

## SAN ANTONIO BREAST CANCER SYMPOSIUM 2021

(virtual SABCS 2021, from 7 to 10 December 2021)



Due to the global pandemic, the 2021 annual San Antonio Breast Cancer Symposium took place as a hybrid model, including both onsite and virtual meetings.

The symposium aims to provide the most up-to-date information on the experimental biology, aetiology, prevention, diagnosis, and therapy of breast cancer and premalignant breast disease.

Several oral presentations and posters related to BIG trials and research collaborations were presented over the course of these four days; here is a peek at some of them.



## MA.32 (BIG 5-11)

### Metformin not effective against early-stage breast cancer

The first results of the MA.32 trial show that the widely used and inexpensive Type 2 diabetes drug metformin, once hoped to hold enormous promise in treating breast cancer, does not prevent or stop the spread of the most common forms of the disease.

These findings were presented at the 2021 San Antonio Breast Cancer Symposium by trial investigator Dr Pamela Goodwin, medical oncologist at Sinai Health and a clinician-scientist at the Lunenfeld-Tanenbaum Research Institute in Toronto.

The landmark trial, run by the **Canadian Cancer Trials Group (CCTG)** under the umbrella of the **Breast International Group (BIG)**, is the largest of its kind to date, tracking **more than 3,600 breast cancer patients from across Canada, the U.S., Switzerland and the U.K.**

“The CCTG MA.32 trial illustrates the importance of international academic group collaboration to test new treatment approaches with a goal to advance clinical care,” says CCTG Senior Investigator Dr Wendy Parulekar.

While metformin was found not to be effective in treating the most common forms of breast cancer, Dr Goodwin said the trial found a potentially important result for individuals with HER2-positive breast cancer. For this subtype, researchers found there was evidence that use of metformin for five years might lead to a reduction in deaths.

A potential next step will be to prospectively test the impact of metformin in patients with HER2-positive breast cancer in a randomised clinical trial.

### 3 BIG member groups are participating in the study, in addition to CCTG.

The study is funded by NCI/NIH grants, Cancer Research UK, the Canadian Cancer Society, the Breast Cancer Research Foundation® (BCRF) and the Canadian Breast Cancer Foundation.

**MA.32:** A Phase III Randomized Trial of Metformin vs Placebo in Early-Stage Breast Cancer

## OLYMPIA (BIG 6-13)

### Quality of Life results

Results of the quality of life (QoL) analysis from the phase III OlympiA trial were presented at SABCS 2021. This analysis showed that, overall, olaparib as additional adjuvant therapy was well tolerated, and one year of treatment did not meaningfully affect recovery after standard of care (neo)adjuvant therapy.

Furthermore, increased treatment-emergent symptoms with olaparib were small and resolved after treatment. QoL scores (e.g., physical and emotional functions), as well as global health, were similar and slowly improved during the 24 months after (neo)adjuvant treatment in all patients.

The main results from OlympiA were presented by the study co-Principal Investigator Andrew Tutt at the 2021 American Society of Clinical Oncology (ASCO) Annual Meeting and were simultaneously published in the *New England Journal of Medicine*. <https://www.nejm.org/doi/full/10.1056/NEJMoa2105215>

The first findings showed a statistically significant and clinically meaningful improvement in invasive disease-free survival (iDFS) with olaparib versus placebo in the adjuvant treatment of patients with germline BRCA-mutated (gBRCAm) high-risk human epidermal growth factor receptor 2 (HER2)-negative early breast cancer.

A total of **1,836 patients have been enrolled in the study.**

OlympiA is a global collaborative trial coordinated by the Breast International Group (BIG) worldwide, in partnership with NRG Oncology, the US National Cancer Institute (NCI), Frontier Science & Technology Research Foundation (FSTRF), AstraZeneca and MSD. The trial is sponsored by NRG Oncology in the US and by AstraZeneca outside the US.

**21 BIG member groups are participating in the study.**

## PALLAS (BIG 14-03)

### No benefit with palbociclib in early

# PALLAS

A COLLABORATIVE STUDY BY  
AFT, ABCSG & BIG

### breast cancer

Professor Michael Gnant, co-Principal Investigator of the study, presented the data from the final analysis of the global PALLAS study. Findings show that, in the adjuvant setting, the addition of palbociclib to endocrine therapy did not provide any benefit in terms of improving invasive disease-free survival. These results were simultaneously published in the *Journal of Clinical Oncology*<sup>3</sup>. <https://ascopubs.org/doi/abs/10.1200/JCO.21.02554>

Despite the unexpected negative results, PALLAS is a great example of worldwide collaboration between academia and industry to run a huge pivotal clinical trial and advance breast cancer research. It will enable us to know more about the effects of palbociclib in the treatment of patients with hormone receptor-positive (HR+), HER2-negative early breast cancer.

Thousands of physicians, researchers, nurses, administrators and other health care and research professionals in 21 countries around the globe have been working together to make this happen.

Moreover, the **5,796 patients enrolled in PALLAS** will be followed for at least 10 years, and both clinical data and collected biomaterial build a huge treasure trove for future translational research.

The first results from the expansive transPALLAS programme are expected in 2022.

This study is conducted and sponsored by the Alliance Foundation Trials, LLC (AFT), and Austrian Breast & Colorectal Cancer Study Group (ABCSG), in collaboration with the Breast International Group (BIG). Funding and drug were provided by Pfizer.

<sup>3</sup> Adjuvant Palbociclib for Early Breast Cancer: The PALLAS Trial Results (ABCSG-42/AFT-05/BIG-14-03). Gnant M, Dueck AC, Frantal S et al. DOI: 10.1200/JCO.21.02554 *Journal of Clinical Oncology* 40, no. 3 (January 20, 2022) 282-293. Published online December 07, 2021

**23 BIG member groups are participating in the study, in addition to ABCSG.**

**PALLAS:** PALbociclib CoLLaborative Adjuvant Study: A randomised phase III trial of palbociclib with standard adjuvant endocrine therapy versus standard adjuvant endocrine therapy alone for hormone receptor positive (HR+) / human epidermal growth factor receptor 2 (HER2)-negative early breast cancer

### **SOFT & TEXT (BIG 2-02 / BIG 3-02): UPDATED LONG TERM RESULTS (12-13 YEARS FOLLOW-UP)**

#### **Update by IBCSG**

Updated results of the SOFT and TEXT phase III randomised clinical trials led by the **International Breast Cancer Study Group (IBCSG)** under the BIG umbrella were presented by **Dr Meredith Regan, ScD**, at the 2021 San Antonio Breast Cancer Symposium<sup>1</sup>. The trials are evaluating adjuvant endocrine therapy in more than 5,700 premenopausal women with early-stage hormone receptor positive (HR+) breast cancer. The presentation focused on overall survival and late treatment effects. Findings were based on 12- and 13-year median follow-up of patients in the two trials.

For premenopausal women with HR+ breast cancer enrolled in SOFT, adjuvant ovarian function suppression, combined with tamoxifen or the aromatase inhibitor (AI) exemestane, provided persistent reduction in the risk of recurrence and death compared to tamoxifen alone. The benefits were most clinically-substantial for those patients who had received chemotherapy prior to enrolment in SOFT and were at higher clinical risk, in the order of 10% reduction in death at 12 years after enrolment. The study also continues to support the use of tamoxifen alone as adjuvant therapy for selected premenopausal patients with low-risk clinical-pathologic features.

The combined analysis of TEXT and SOFT demonstrate the reduction in distant recurrence – with the use of exemestane plus ovarian suppression

vs. tamoxifen plus ovarian suppression – is consistent with that for postmenopausal women, and of greater magnitude for those at higher risk of recurrence. The extended follow-up showed a later-emergent reduction in death with the use of exemestane over tamoxifen with ovarian suppression of 3.3% for those with HER2-negative disease who received chemotherapy.

Long-term follow-up of these young women is quite important because of a continued risk of having a recurrence of their breast cancer even after 10 years. The IBCSG plans five more years of follow-up with these women. A final update of results is planned for 2026 and will have minimum follow-up of 15 years and a median follow-up of approximately 18 years.

In total SOFT and TEXT enrolled **5,738 women with hormone-sensitive early breast cancer.**

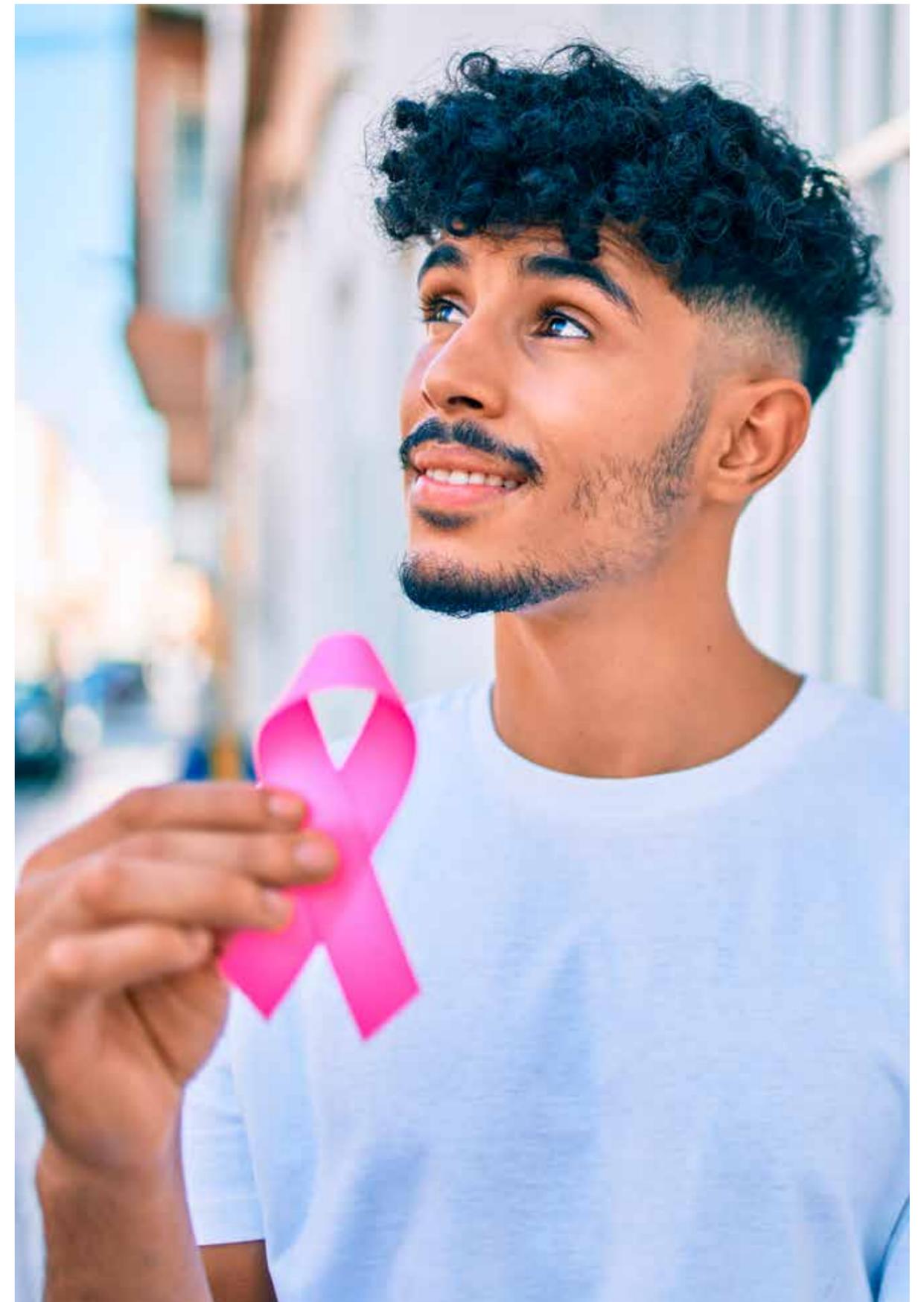
**13 BIG member groups are participating in the SOFT study and 8 in the TEXT study.**

The long-term follow-up of these studies is made possible thanks to grants from Breast Cancer Research Foundation, 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.

**SOFT:** Suppression of Ovarian Function with either tamoxifen or exemestane compared with tamoxifen alone in treating premenopausal women with hormone-responsive breast cancer

**TEXT:** Triptorelin with either EXemestane or Tamoxifen in treating premenopausal women with hormone-responsive breast cancer (TEXT).

<sup>1</sup>. Regan MM, Walley BA, Fleming GF, et al. SOFT and TEXT Investigators. Randomized comparison of adjuvant aromatase inhibitor exemestane+ovarian function suppression (OFS) vs tamoxifen OFS vs tamoxifen in premenopausal women with hormone receptor-positive (HR+) early breast cancer (BC): update of the TEXT and SOFT trials. *SABCS 2021 [hybrid]* (abstr GS2-05). [IBCSG 24-02, 25-02]. <https://www.ibcsg.org/en/all-news-and-events/402-sabcs-2021-text-sofi-updates>.



#3

# OTHER TRIALS AND ACTIVITIES BY BIG MEMBER GROUPS

## ABCSG

### The Positive Impact of Disclosing “Negative” Research Results

For the **Austrian Breast and Colorectal Cancer Study Group (ABCSG)**, the year 2021 showed how successful and thriving – and at times challenging – clinical research can be. From practice-changing study results to the positive impact and opportunities of disclosing negative trial outcome, **Professor Michael Gnant, President of the ABCSG**, provides insight into some ABCSG clinical research areas of the past year, and what we can learn from these findings.

### INTERVIEW FROM JANUARY 2022

**The ABCSG-16 / S.A.L.S.A. study results published in the New England Journal of Medicine in July 2021 were surely among the most significant achievements for the ABCSG research team in the past year, since they set a practice-changing standard in the treatment of postmenopausal patients with hormone receptor-positive breast cancer. If you, as the study initiator, look at it in retrospect, which parameters make a study successful?**

**Professor Gnant:** For ABCSG-16, “resilience” is probably the most characteristic feature. The first ideas were discussed in the year 1999 (!), recruitment eventually started in 2004 – and then it took more than two decades to get to the final results! This shows that academic research often needs stamina and unwavering confidence – I am not sure that our academic systems always provide optimal circumstances in this respect, particularly for young researchers. However, ABCSG-16 eventually provides evidence for another important de-escalation of standard (adjuvant endocrine) therapy: 7 years treatment duration is enough for the vast majority of our patients – avoiding unnecessary and side-effect rich overtreatment is important!

**At SABCS 2021, you presented the data from the final analysis of the global PALLAS study. In the adjuvant setting, the addition of palbociclib to endocrine therapy did not provide any benefit in terms of improving invasive disease-free survival. Are you disappointed with the results, or is the study considered a success despite the negative outcome?**

For sure, we had hoped for another adjuvant breakthrough for patients with luminal breast cancer when we started this huge enterprise. However, it is science, not religion (as one of my academic teachers once said) – we do learn at least as much from “negative” trial results as we do from outrightly “positive” trials. Apparently, not every aspect of progress we achieve in the advanced breast cancer setting can easily be transferred to the adjuvant setting, and the biological target might matter as well as dosing and scheduling issues. In any case, developing, leading, and successfully conducting a global trial with the help of many wonderful people in the BIG network, and in transparent partnership with industry, but under full academic control, has been and remains a great experience. And the journey has just begun – we expect the first exciting results from the huge transPALLAS programme already in 2022 – this trial is going to provide research opportunities for many years to come!

**What do you expect from the results of the PALLAS Translational Research Programme (“transPALLAS”) and the first call for project proposals within the BIG Network?**

Key to the successful conduct of transPALLAS will be that innovative research ideas are brought forward by bright minds within the network. The stage is set – with mandatory tissue banking, serial serum sample collection, and long-term follow-up, all the elements are in place for young investigators to interrogate this huge treasure trove of information. An interdisciplinary and collaborative spirit will guide us through this exciting next chapter of the trial.



Professor Michael Gnant, President of ABCSG

**Do we need to adopt a more flexible mindset in which sharing well-conducted research is valued, regardless of whether the initial research hypothesis was confirmed/verified? Or not?**

Clearly, there is a negative publication bias in the system of high-ranking medical journals, which is regrettable. In “Star Wars”, Master Yoda says: “Failure, the greatest teacher is” – and this is absolutely true! Some of the greatest advances in medicine were not planned but detected by an ingenious moment, based on systematic and laborious collection of data. Even in the molecular age of clinical research, with all its wonderful opportunities provided by global databases, the increasing options of *in silico* research (experimental techniques performed

by computers), artificial intelligence, and machine learning, this will remain the basic process: collaborative data collection, resilience and endurance in the process, and providing opportunities and facilitating inspiration, particularly for young researchers.

## BCT-ANZ (BREAST CANCER TRIALS AUSTRALIA AND NEW ZEALAND)

**EXPERT (BIG 16-02): also open in the Rest of the World through BIG groups.**

See study update page 16

**BCT 1902 (Neo-N)** is a randomised phase II trial evaluating the efficacy of a nivolumab monotherapy lead in “window” or commencement of nivolumab concurrently with paclitaxel and carboplatin as neoadjuvant therapy in early-stage triple negative breast cancers. BCT-ANZ is collaborating with IBCSG (International Breast Cancer Study Group) to see this study recruit 108 patients throughout Australia, New Zealand and Italy. We anticipate recruitment to finish in the first half of 2022 with results expected to be presented in 2023.

**BCT 1702 (CHARIOT)** is a phase II study evaluating efficacy and safety of ipilimumab and nivolumab with neoadjuvant weekly paclitaxel after anthracycline-based chemotherapy in high-risk primary triple negative breast cancer, followed by definitive surgery and one year total duration of nivolumab. CHARIOT completed recruitment in 2020 and BCT-ANZ expects to present pCR primary endpoint data in 2022. ●



## GEICAM (SPANISH BREAST CANCER GROUP)

**Publication of FLIPPER study in the European Journal of Cancer**

Interesting results of the **FLIPPER** study (NCT02690480) were published in the European Journal of Cancer. See: [https://www.ejccancer.com/article/S0959-8049\(21\)01221-1/pdf](https://www.ejccancer.com/article/S0959-8049(21)01221-1/pdf)

The FLIPPER study is an international, multicentre, double blind, placebo-controlled, randomised phase II study comparing the efficacy and safety of palbociclib/fulvestrant versus placebo/fulvestrant as first-line therapy in postmenopausal women with HR-positive, HER2-negative, endocrine-sensitive advanced breast cancer.

The progression-free survival at 12 months showed superiority of the combination therapy over fulvestrant, with a manageable safety profile.

These results support the palbociclib plus fulvestrant combination for first-line therapy for patients with truly endocrine-sensitive advanced breast cancer.

**RegistEM, the Spanish registry of advanced breast cancer, presented at SABCS**

RegistEM is the first Spanish registry of patients with advanced breast cancer (ABC). This project has prospectively collected data from more than 1,900 patients in Spain. Two analyses of this database were presented at SABCS 2021, describing the following characteristics in this population:

**Breast cancer brain metastases:**

- > 12% of this population has brain metastasis (BM)
- > Patients with de novo metastatic breast cancer develop BM later than patients with ABC who have recurred from early breast cancer (BC)
- > Considering all patients, irrespective of BC subtype, overall survival from BM diagnosis is longer in patients with BM at ABC diagnosis (compared to BM after ABC diagnosis)
- > Triple negative BC is associated with a shorter time to develop BM and a worse outcome than other BC subtypes, as reported in the literature

**Features of patients with HER2+ metastatic breast cancer:**

- > In this cohort of HER2+ patients, 50% of cases had de novo disease
- > De novo ABC was associated with better OS compared to recurrent early BC. Younger age was also associated with better OS
- > HR status and menopausal status at ABC diagnosis were not prognostic factors for OS

**Pathology and breast cancer: GEICAM-FSEAP collaboration agreement**

The connection between pathologists and oncologists is gaining prominence as knowledge of molecular changes in cancer advances. This allows us to achieve more accurate diagnoses and more personalised and effective treatments.

For this reason, GEICAM signed in 2021 a collaboration agreement with the Spanish association of pathologists **FSEAP (Fundación Sociedad Española de Anatomía Patológica)**, with the aims of encouraging a better understanding of issues related to pathology and breast cancer, working together in research activities, promoting precision medicine strategies, training professionals in a multidisciplinary way, and providing information to patients on the different phases of the healthcare process.

**Hereditary breast cancer: GEICAM-AMOH collaboration agreement**

In 2021, GEICAM also signed a collaboration agreement with **AMOH, a Spanish association of hereditary breast and ovarian cancer patients**. This collaboration will allow both entities to raise awareness on hereditary breast cancer, its research and early detection, as well as to start new clinical trials and projects on these subjects.

**PEARL study: new important data reported in 2021**

Resistance to endocrine therapy is one of the main current challenges of breast cancer management. The delay of chemotherapy to avoid its related adverse events is always desirable to maintain a patient's

quality of life (QoL). In this context, GEICAM developed the **PEARL** study. This is a multicentre, phase III randomised study to evaluate the efficacy of the combination of palbociclib plus endocrine therapy (ET) over chemotherapy (capecitabine) in patients with aromatase inhibitor (AI)-resistant metastatic breast cancer (MBC).

The primary results of the study were published in the Annals of Oncology in 2020 (<https://doi.org/10.1016/j.annonc.2020.12.013>). It was reported that palbociclib plus ET did not improve progression-free survival over capecitabine; the combination, however, was better tolerated. In 2021, the overall survival results were presented at ESMO showing no differences between the two study arms.

With these efficacy similarities, the QoL comparison appeared to be relevant. These results were published in the European Journal of Cancer in 2021 (<https://doi.org/10.1016/j.ejca.2021.07.004>). They showed that patients receiving palbociclib plus ET experienced a significant delay in deterioration of their global health status/QoL and in several functional and symptom scales compared with capecitabine, providing additional evidence that palbociclib plus ET is better tolerated.

This is valuable information that should be taken into consideration when treating postmenopausal patients with MBC who previously progressed on an AI, and when deciding between these two therapeutic strategies. ●



## IBCSG

The **International Breast Cancer Study Group (IBCSG)** provided the following study updates:

**PYTHIA (BIG 14-04): First results published in *European Journal of Cancer***

*See page 16*

**SOFT & TEXT (BIG 2-02 / BIG 3-02): updated long term results (12-13 years follow-up)**

*See page 20*

## IJB CTSU

The **Institut Jules Bordet Clinical Trials Support Unit (IJB CTSU)** provided a study update on the **DECRESCENDO** trial.

*See page 14*

## JBCRG

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, mUlticenter 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

## PRESENTATIONS AT CONGRESSES

**ESMO Virtual Congress 2021 (16-21 September 2021): JBCRG-16Follow**

Presentation by Dr Tomomi Fujisawa: Long-term follow-up of neoadjuvant dual anti-HER2 therapy with trastuzumab and lapatinib plus paclitaxel, with or without endocrine therapy for HER2-positive primary breast cancer: Neo-LaTH (JBCRG-16) study

**ESMO Virtual Congress 2021 (16-21 September 2021): JBCRG-22TR**

Presentation by Dr Tomomi Nishimura: Genomic profile and response prediction of eribulin mesylate based neoadjuvant chemotherapy in triple negative breast cancer patients (JBCRG-22TR)

**ESMO Virtual Congress 2021 (16-21 September 2021): JBCRG-22TR**

Presentation by Dr Takayuki Ueno: Immune microenvironment, homologous recombination deficiency and therapeutic response to neoadjuvant chemotherapy in triple negative breast cancer: JBCRG22 TR

**ESMO Virtual Congress 2021 (16-21 September 2021): JBCRG-22TR**

Presentation by Dr Kosuke Kawaguchi: Longitudinal alteration of cytokine profile in the peripheral blood and clinical response for neoadjuvant chemotherapy in triple-negative breast cancer patients (Translational Research of the JBCRG-22 Trial)

## RECENT PUBLICATIONS

**JBCRG-16 (Neo-LaTH) Follow in Cancers 2021**

Five-year analysis of neoadjuvant dual HER2 blockade therapy with trastuzumab and lapatinib plus paclitaxel with or without endocrine therapy for HER2-positive primary breast cancer (Neo-LaTH study): a randomized, multicenter, open-label phase II trial.

Eriko Tokunaga, et al.

<https://doi.org/10.3390/cancers13164008>

**JBCRG-17 in Breast Cancer Research and Treatment 2021**

A phase II study of sequential treatment with anthracycline and taxane followed by eribulin in patients with HER2-negative, locally advanced breast cancer.

Ippei Fukada, et al.

<https://doi.org/10.1007/s10549-021-06396-0>

**JBCRG-19 in International Journal of Clinical Oncology 2021**

Clinical usefulness of eribulin as first- or second-line chemotherapy for recurrent HER2-negative breast cancer: a randomized phase II study.

Kenjiro Aogi, et al.

<https://doi.org/10.1007/s10147-021-01920-0>

**JBCRG-22 (Neo-Entrance) in Breast Cancer Research and Treatment 2021**

Eribulin-based neoadjuvant chemotherapy for triple-negative breast cancer patients stratified by homologous recombination deficiency status: a multicenter randomized phase II clinical trial.

Norikazu Masuda, et al.

<https://link.springer.com/article/10.1007/s10549-021-06184-w>

**JBCRG-S01 in Breast Cancer 2021**

Meta-analysis of nanoparticle albumin-bound paclitaxel used as neoadjuvant chemotherapy for operable breast cancer based on individual patient data.

Manabu Futamura, et al.

<https://doi.org/10.1007/s12282-021-01238-9>

## PARTICIPATION IN GLOBAL TRIALS

JBCRG is involved in the following studies run under the BIG umbrella: **AMEERA-6, ALEXANDRA/IMpassio030, OlympiA, POSITIVE, PenelopeB and PALLAS**. For details about the trial leadership, *please refer to the Trials Table on page 32-35.* ●

**SOLTI has launched HARMONIA, an international phase III study to identify the best therapeutic option for selected patients with aggressive HR+/HER2-advanced breast cancer**

- > **HARMONIA is the first prospective phase III trial to enrol selected patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2-) advanced breast cancer (ABC) identified using an RNA-based subtype classification**
- > **The trial seeks to identify the best therapeutic option between ribociclib and palbociclib, two commercially available CDK4/6 inhibitors for patients with HR+/HER2- ABC and a HER2-enriched (HER2-E) subtype, a tumour biology which confers particularly poor prognosis and is associated with endocrine resistance**
- > **SOLTI will collaborate with Alliance Foundation Trials and Novartis Pharma AG to conduct the trial across 80 hospitals in Spain, Portugal, and the United States**

SOLTI has launched **HARMONIA**, the first phase III clinical trial that will compare treatment options for patients with difficult-to-treat hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2-) advanced breast cancer (ABC). There is an unmet patient need to understand the optimal treatment approach for patients with HER2-enriched (HER2-E) disease, a subtype associated with a very poor prognosis and endocrine-resistance, compared to luminal disease.

HARMONIA is the first phase III trial to select patients based on their tumour's RNA-based molecular subtype. It will be one of the most important clinical and translational prospective research efforts ever conducted to help understand specific subgroups of patients with advanced HR+/HER2- ABC. HARMONIA will provide a better understanding of the biological heterogeneity of these tumours as well as insights into changes that can occur over time under specific therapies. The study will be conducted in Spain, Portugal and the United States, with the participation of 80 hospitals, and with the aim to include more than 500 patients. HARMONIA will be led by SOLTI in collaboration

with the US-based Alliance Foundation Trials organisation and Novartis Pharma AG.

The primary objective of the study is to test the value of two CDK4/6 inhibitors in patients with the HER2-E subtype. This particular subtype represents 10-20% of HR+/HER2- ABC patients and is associated with poor response and survival if treated with endocrine therapy (ET) only. In this group of patients, ribociclib, a CDK4/6 inhibitor, has demonstrated pronounced efficacy in a large retrospective analysis of 3 phase III clinical trials. Now, HARMONIA will test the hypothesis prospectively that ribociclib may improve the course of HR+/HER2- disease by changing the tumour biology, enabling a better response to endocrine therapy compared to palbociclib, another approved CDK4/6 inhibitor. This may further substantiate differences seen with CDK4/6 inhibitors in demonstrating overall survival benefit.

Additionally, the study will offer therapy with a chemotherapy-based regimen to patients with the basal-like subtype, a subgroup representing 3-5% of patients with HR+/HER2- ABC. Patients with this tumour biology, which behaves more like a triple-negative breast cancer, typically face a very poor prognosis when treated with endocrine-based therapies.

In the last 5 years, SOLTI has focused on studying breast cancer at the RNA level to demonstrate the prognostic and predictive value of the 4 molecular subtypes and has run small prospective studies pre-selecting patients based on their RNA-based profile. HARMONIA will need to screen approximately 2,500 patients to reach its target accrual of over 500 included with HR+/HER2- ABC. This represents about 70% of all patients with ABC and marks a tremendous advancement. As stated by Aleix Prat, SOLTI's President, Head of the Medical Oncology Department at Hospital Clínic of Barcelona, Head of the Translational Genomics Group and Targeted Therapies in Solid Tumors at IDIBAPS and Professor of Medicine at the University of Barcelona: "HARMONIA is the consequence of many years of research in the field of RNA-based profiling and metastatic breast cancer. We are very proud to conduct this huge clinical and translational effort to improve the diagnosis and treatment of patients who suffer from this devastating disease".

**Aleix Prat, MD PhD**, SOLTI President and Head of the Medical Oncology Department and Translational Genomics & Targeted Therapeutics Group at the Hospital Clínic of Barcelona (Barcelona, ESP), along with **Lisa A. Carey, MD ScM**, co-Chair of the Breast Cancer Committee at the ALLIANCE and Deputy Director of Clinical Science at Lineberger Comprehensive Cancer Center (Chapel Hill, NC, US), will provide leadership for HARMONIA. **Daniel Stover, MD**, Assistant Professor of Medicine at Ohio State University College of Medicine and Medical Oncologist at the Stefanie Spielman Comprehensive Breast Center (Columbus, OH, US) and **Tomás Pascual, MD**, Medical Oncologist and Chief Scientific Officer at SOLTI, will also co-lead the project and serve as study chairs.

It is anticipated that HARMONIA will recruit the first patient in March 2022 and that the trial will last for 5 years.

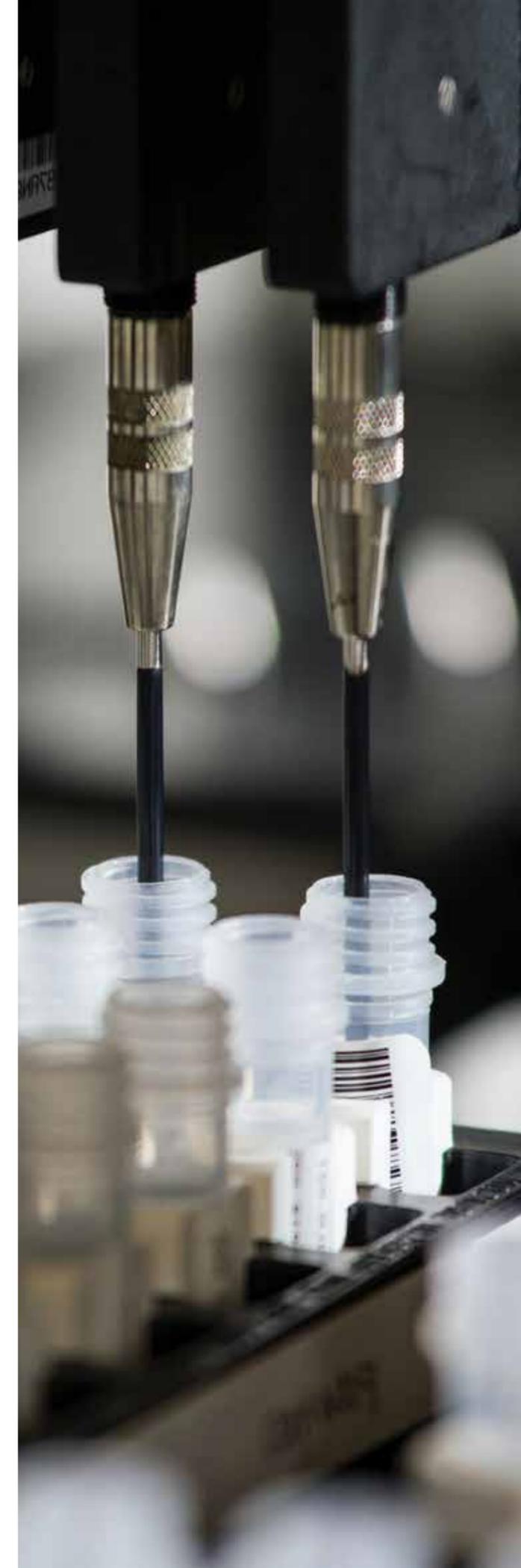
▶ For a video explaining the HARMONIA trial, please click on: <https://www.youtube.com/watch?v=DJxmQS8T7RU>

#### About SOLTI

SOLTI is a leading cooperative group in the field of clinical cancer research. With its academic and translational core, the group is committed to designing and executing clinical trials based on the molecular biology of tumours. Its focus is on breast cancer, but it also explores other kinds of tumours. The main goal of SOLTI is to promote through disruptive means the development of innovative research that will improve the well-being and future outcomes of cancer patients. Since its creation in 1995, SOLTI's purpose has been to bring about a paradigm shift in clinical and translational cancer research from within academia. With 77 clinical trials under their belt and more than 40 ongoing investigations, SOLTI counts on the work of more than 400 researchers from a network comprising more than 100 hospitals in Spain and Portugal, all coordinated by the team of 50 workers from the head office. SOLTI is a member of the Spanish Society of Medical Oncology (SEOM).

**To find out more about SOLTI:**  
 visit [www.gruposolti.org](http://www.gruposolti.org) /  
 Twitter: @\_SOLTI / LinkedIn / Youtube

**For further information:**  
 Laura Sierra García  
 Press & Media Relations Officer  
[laura.sierra@gruposolti.org](mailto:laura.sierra@gruposolti.org)





## OUR MISSION

BIG's mission is to facilitate and accelerate breast cancer research at the international level.

## OUR VISION

Together we will find a cure for breast cancer through global research and collaboration.

## GLOBAL AND LOCAL

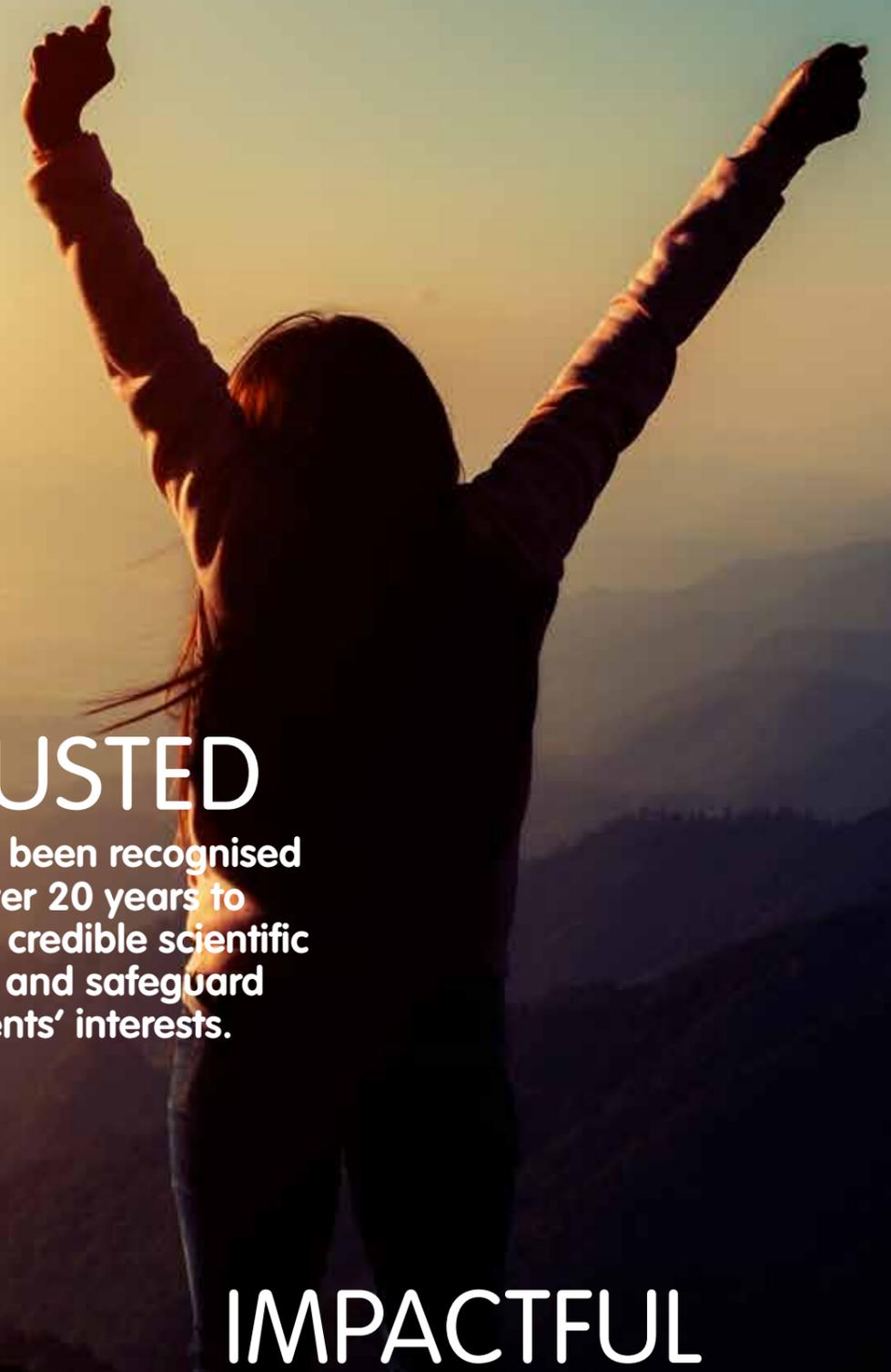
BIG is the largest global network of breast cancer research groups and their affiliated experts. Their work benefits patients locally.

## TRUSTED

We have been recognised for over 20 years to generate credible scientific results and safeguard patients' interests.

## IMPACTFUL

Our research changes practice in the treatment of women and men with breast cancer. We have a real impact on patients' lives.



# CURRENT STUDIES RUN WITHIN THE BIG NETWORK

## Open trials / research programmes

Study name	BIG number	Short description	Principal Investigator(s)	Trial model & partners
<b>ALEXANDRA / IMpassion 030</b>	BIG 16-05	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	M. Ignatiadis H. McArthur S. Saji	Lead trial (Co)-Leading partners: BIG HQ / IJB-CTSU (IJB-CTSU) / FSTRF and AFT Pharma partner: Roche/Genentech (sponsor) Funding: Roche / Genentech
<b>ALPHABET</b>	BIG 18-04	A randomised phase III trial of trastuzumab + ALpelisib +/- fulvestrant vs. trastuzumab + chemotherapy in patients with PIK3CA mutated previously treated HER2+ Advanced BrEasT cancer	A. Pérez-Fidalgo C. Criscitiello P. Bedard	Co-lead trial (Co)-Leading partners: GEICAM (sponsor) / IBCSG and BIG HQ Pharma partner: Novartis Funding: Novartis
<b>AMEERA-6</b>	BIG 20-01	Amcenestrant in patients with HR+, HER2-negative/positive breast cancer who experienced toxicities with aromatase inhibitors - NCT05128773	D. Cameron E. Brain O. Metzger	Co-lead trial (Co)-Leading partners: EORTC / AFT / BIG HQ Pharma partner: Sanofi (sponsor) Funding: Sanofi
<b>APPALACHES</b>	BIG 18-01	A Phase II study of Adjuvant PALbociclib as an Alternative to CHemotherapy in Elderly patients with high-risk ER+/HER2-early breast cancer - NCT03609047	H. Wildiers E. Brain K. Punie	Supporter trial Coordinating group: EORTC (sponsor) Pharma partner: Pfizer
<b>AURORA (Metastatic Breast Cancer GPS)</b>	BIG 14-01	The AURORA programme: aiming to understand the molecular aberrations in metastatic breast cancer - NCT02102165	P. Aftimos M. Benelli A. Guerrero Zotano	BIG-sponsored programme (Co)-Leading partners: BIG HQ (sponsor) / IJB-CTSU / FSS Pharma partner: N/A Funding: Breast Cancer Research Foundation® (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.
<b>Breast Cancer in Pregnancy</b>	BIG 2-03	Prospective registry of women treated for breast cancer while pregnant - NCT00196833	S. Loibl G. von Minckwitz	Supporter trial (Co)-Leading partner: GBG (sponsor) Pharma partner: N/A Funding: GBG, Deutsches Konsortium für Translationale Krebsforschung

<b>DECRESCENDO</b>	BIG 19-02	De-escalation of adjuvant chemotherapy in HER2-positive, HR-negative breast cancer - NCT04675827	M. Piccart G. Zoppoli	Co-lead trial (Co)-Leading partners: IJB-CTSU (sponsor) and BIG HQ Pharma partner: Roche Funding: Roche (grant)
<b>EXPERT (BIG Radio Tuning)</b>	BIG 16-02	A randomised phase III trial of adjuvant radiation therapy vs observation after breast conserving surgery for patients with molecularly characterised low-risk luminal A early breast cancer - NCT02889874	B. Chua G. Gruber	Co-lead trial (Co)-Leading partners: BCT-ANZ (sponsor) and BIG HQ Pharma partner: N/A Funding: BCT-ANZ, the National Health and Medical Research Council of Australia, and BIG HQ fundraising initiatives
<b>POLAR</b>	BIG 18-02	Palbociclib for HR+ isolated local or regional recurrence of breast cancer - NCT03820830	E. Munzone S. Aebi	Supporter trial Coordinating group: IBCSG (sponsor) Pharma partner: Pfizer

## Follow-up or post-study activities, recently closed studies

Study name	BIG number	Short description	Principal Investigator(s)	Trial model & partners
<b>ALTO</b>	BIG 2-06	Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation: sequence and combination for patients with HER2/ ErbB2 positive primary breast cancer - NCT00490139	M. Piccart A. Moreno-Aspitia	Lead trial (Co)-Leading partners: BIG HQ / IJB-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
<b>APHINITY</b>	BIG 4-11	Comparison of single-versus-dual anti-HER2 therapy (trastuzumab, pertuzumab) for patients with HER2-positive primary breast cancer - NCT01358877	M. Piccart S. Loibl J. Bines	Lead trial (Co)-Leading partners: BIG HQ / IJB-CTSU / FSTRF Pharma partner: Roche (sponsor) Funding: Roche
<b>BRAVO</b>	BIG 5-13	Niraparib for patients with HER2-negative, germline BRCA mutation-positive, locally advanced or metastatic breast cancer - NCT01905592	N. Turner J. Balmaña D. Cameron J. Erban	Co-lead trial (Co)-Leading partners: EORTC / BIG HQ Pharma partner: Tesaro (sponsor) Funding: Tesaro
<b>DCIS</b>	BIG 3-07	Radiation doses and fractionation schedules for women with DCIS - NCT00470236	B. Chua	Supporter trial (Co)-Leading partner: TROG (sponsor) Pharma partner: N/A Funding: National Health & Medical Research Council Project Grant, Susan G. Komen
<b>Exceptional Responders</b>	BIG 16-04	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	A. Irrthum (coordinator)	BIG-sponsored programme (Co)-Leading partner: BIG HQ Pharma partner: N/A Funding: Breast Cancer Research Foundation
<b>FINESSE</b>	BIG 2-13	Oral lucitanib for patients with FGFR1 ER+ metastatic breast cancer - NCT02053636	F. André J. Cortés	Lead trial (Co)-Leading partners: BIG HQ / IJB-CTSU / FSS Pharma partner: Servier (sponsor) Funding: Servier

<b>IBIS-II</b>	BIG 5-02	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	J. Cuzick	Supporter trial (Co)-Leading partner: IBIS Pharma partner: AstraZeneca Sponsor: Queen Mary University of London Funding: Cancer Research UK, Queen Mary University of London
<b>INTERNATIONAL MALE BREAST CANCER PROGRAMME</b>	BIG 2-07	Registration and biologic characterisation programme of breast cancer in men - NCT01101425	F. Cardoso S. Giordano	Supporter programme (Co)-Leading partners: EORTC (sponsor) / NABCG (US) Pharma partner: N/A Funding: Breast Cancer Research Foundation
<b>LORELEI</b>	BIG 3-13	Neoadjuvant letrozole plus taselisib versus letrozole plus placebo in postmenopausal women with ER+, HER2-negative, early-stage breast cancer - NCT02273973	C. Saura E. de Azambuja	Co-lead trial (Co)-Leading partners: ABCSG, SOLTI and BIG HQ Pharma partner: Genentech (sponsor) Funding: Genentech
<b>MA.32 Metformin</b>	BIG 5-11	Effect of metformin on recurrence and survival in early stage breast cancer - NCT01101438	P. J. Goodwin	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.
<b>MINDACT</b>	BIG 3-04	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	E. Rutgers F. Cardoso M. Piccart	Co-lead trial (Co)-Leading partners: EORTC (sponsor) / BIG HQ Commercial partners: Roche, Sanofi, Novartis and Agendia 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*
<b>NEO-ALTO</b>	BIG 1-06	Comparison of dual HER2 inhibition (lapatinib, trastuzumab) plus chemotherapy before surgery versus single HER2-targeted therapy - NCT00553358	S. Di Cosimo J. Huober	Co-lead trial (Co)-Leading partners: IJB-CTSU / FSS / SOLTI / BIG HQ Pharma partner: Novartis (global sponsor for all countries with the exception of US, where Alliance is the sponsor) Funding: GSK (past) / Novartis
<b>OLYMPIA</b>	BIG 6-13	Olaparib vs. placebo for patients with BRCA-mutated, high-risk HER2-negative breast cancer, having completed local treatment and (neo)adjuvant chemotherapy - NCT02032823	A. Tutt D. Cameron B. Kaufman J. Garber C. Geyer	Lead trial (Co)-Leading partners: NRG Oncology (sponsor in US), BIG HQ and FSTRF Pharma partner: AstraZeneca (sponsor in Rest of the World) Funding: AstraZeneca
<b>PALLAS</b>	BIG 14-03	PALbociclib Collaborative Adjuvant Study: palbociclib with standard adjuvant endocrine therapy versus standard adjuvant endocrine therapy alone for HR+ / HER2-negative early breast cancer - NCT02513394	E. Mayer M. Gnant A. DeMichele	Co-Lead trial (Co)-Leading partners: ABCSG (RoW), AFT (US) (sponsors) and BIG HQ Pharma partner: Pfizer Funding: Pfizer grant
<b>PENELOPE-B</b>	BIG 1-13	Post-neoadjuvant palbociclib for patients with HR+, HER2-normal primary breast cancer with high relapse risk after neoadjuvant chemotherapy - NCT01864746	G. von Minckwitz	Supporter trial (Co)-Leading partner: GBG (sponsor) Pharma partner: Pfizer Funding: Pfizer grant
<b>POSITIVE (BIG time for Baby)</b>	BIG 8-13	Endocrine therapy interruption to enable conception for young women with ER+ breast cancer - NCT02308085	O. Pagani	Supporter trial (Co)-Leading partner: IBCSG (sponsor) Pharma partner: N/A Funding: IBCSG, Fonds Baillet-Latour, national and local funding bodies, individual donors

<b>PYTHIA</b>	BIG 14-04	Palbociclib plus fulvestrant for pretreated patients with ER+/HER2- metastatic breast cancer - NCT02536742	L. Malorni	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.
<b>SNAP</b>	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
<b>SOFT</b>	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.
<b>SOLE</b>	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 Coordinating group: IBCSG Sponsor: IBCSG Pharma partner: Novartis Funding: Novartis
<b>SUPREMO</b>	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: UK Medical Research Council 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.
<b>TEXT</b>	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.
<b>TREAT-CTC</b>	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
<b>ULTIMATE</b>	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](http://www.BIGagainstbreastcancer.org).

\* full information available on the BIG website.

**Legend:** AFT: Alliance Foundation Trials, LLC; BCRF: Breast Cancer Research Foundation; FSS: Frontier Science Scotland, LTD; FSTRF: Frontier Science and Technology Research Foundation, Inc;  
**N/A:** not applicable; NCCTG: North Central Cancer Treatment Group; NCI: US National Cancer Institute; SCTBG: Scottish Cancer Trials Breast Group; TBCC: Translational Breast Cancer Research Consortium

# ABOUT BIG

## THE BIG NETWORK: GLOBAL RESEARCH COLLABORATION TO CURE BREAST CANCER

*For over 20 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 over 55 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 enrolls 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.



### AFRICA

**BGICS** Breast Gynaecological International Cancer Society

### ASIA

**BDPCC** Breast Disease Professional Committee of CMEA

**BIEI** Breast Intergroup of Eastern India  
**CTRG** Cancer Therapeutics Research Group

**HKBOG** Hong Kong Breast Oncology Group

**ICON ARO** Indian Co-operative Oncology Network

**IOSG** Indian Oncology Study Group

**JBCRG** Japan Breast Cancer Research Group

**KCSG** Korean Cancer Study Group  
**SKMCH & RC** Shaikat Khanum Memorial Cancer Hospital & Research Centre

**TCOG** Taiwan Cooperative Oncology Group

**TSCO** Thai Society of Clinical Oncology

### AUSTRALASIA

**BCT-ANZ** Breast Cancer Trials Australia and New Zealand

**TROG** Trans-Tasman Radiation Oncology Group

### EUROPE

**ABCSG** Austrian Breast & Colorectal Cancer Study Group

**AGO-B** Arbeitsgemeinschaft Gynäkologische Onkologie Breast Study Group

**BOOG** Borstkanker Onderzoek Groep

**CEEOG** Central and East European Oncology Group

**CT-IRE** Cancer Trials Ireland

**DBC** Danish Breast Cancer Cooperative Group

**EORTC BCG** European Organisation for Research and Treatment of Cancer Breast Cancer Group

**FBCG** Finnish Breast Cancer Group

**GBG** German Breast Group

**GCSG** Georgian Cancer Study Group

**GEICAM** Spanish Breast Cancer Group  
**GOIRC** Gruppo Oncologico Italiano di Ricerca Clinica

**HSBS** Hellenic Society of Breast Surgeons

**HeCOG** Hellenic Cooperative Oncology Group

**HORG** Hellenic Oncology Research Group

**IBCG** Icelandic Breast Cancer Group

**IBCSG** International Breast Cancer Study Group

**IBIS** International Breast Cancer Intervention Studies

**ICCG** International Collaborative Cancer Group

**ICR-CTS** Institute of Cancer Research - Clinical Trials & Statistics Unit

**IJB-CTS** Institut Jules Bordet Clinical Trials Support Unit

**ITMO** Italian Trials in Medical Oncology

**MICHELANGELO** Fondazione Michelangelo

**NBCG** Norwegian Breast Cancer Group

**NCRI-BCSG** National Cancer Research Institute - Breast Cancer Clinical Studies Group

**SABO** Swedish Association of Breast Oncologists

**SAKK** Swiss Group for Clinical Cancer Research

**SLO** Société Luxembourgeoise d'Oncologie

**SOLTI** Breast Cancer Research Group  
**SUCCESS** Study Group

**SweBCG** Swedish Breast Cancer Group

**UCBG** Unicancer Breast Group  
**WSG** Westdeutsche Studiengruppe

### LATIN AMERICA

**GAICO** Grupo Argentino de Investigación Clínica en Oncología

**GECO PERU** Grupo de Estudios Clínicos Oncológicos Peruano

**GOCCHI** Chilean Cooperative Group for Oncologic Research

**GOCUR** Grupo Oncológico Cooperativo Uruguayo

**LACOG** Latin American Cooperative Oncology Group

### MIDDLE EAST

**IBG** Israeli Breast Group

**ICRC** Iranian Cancer Research Center  
**SBCG** Sheba Breast Collaborative Group

### NORTH AMERICA

**CCTG** Canadian Cancer Trials Group



A graphic featuring a blue heart with the text "SUPPORT BIG" inside, surrounded by radiating lines. Below the heart is a blue outline of a hand holding the heart.

# TODAY'S RESEARCH FOR TOMORROW'S CURES

**IBAN BE08 0689 0916 0213**  
(communication: BIG RESEARCH)

**OR DONATE ONLINE:**  
[www.BIGagainstbreastcancer.org/donate](http://www.BIGagainstbreastcancer.org/donate)



**BIG**  
Breast International Group

**BIG**  
RESEARCH  
IN FOCUS

The magazine that's keeps you up to date with trending topics in the world of breast cancer and BIG member groups' academic research.

A FREE bi-annual digital or print copy?

**SIMPLY SCAN THE QR CODE WITH  
YOUR SMARTPHONE OR TYPE  
IN THE LINK [HTTPS://RESEARCH.](https://research.bigagainstbreastcancer.org/library/big-newsletter)**

**BIGAGAINSTBREASTCANCER.ORG/LIBRARY/  
BIG-NEWSLETTER TO BE DIRECTED TO THE  
SIGN-UP FORM.**



**SUBSCRIBE  
NOW**

for your FREE copy  
of 'BIG Research  
in Focus'



[www.BIGnews.BIGagainstbreastcancer.org](http://www.BIGnews.BIGagainstbreastcancer.org)