

10TH ANNIVERSARY OF

BIG

RESEARCH
IN FOCUS

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FIGHTING BREAST CANCER AROUND THE GLOBE

BIG Patient Partnership Initiative (BIG-PPI)

*Putting the patient's voice at
the heart of BIG's research*



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NOTE FROM THE EDITORS

As BIG celebrates its 25th anniversary in 2024, we reflect on a quarter-century of dedicated breast cancer research, while considering current and future developments, initiatives, and the necessary funding to further advance research. In our next edition of BIG Research in Focus (BIG RiF21, November 2024), we will further delve into this.

This year also holds special significance as it marks the 10th anniversary of our bi-annual publication, a milestone made possible by the invaluable contributions of each and every one of you. Thank you!

In this edition, the featured article of the “**BIG Research**” section shines a spotlight on the **BIG Patient Partnership Initiative (BIG-PPI)**. Established in 2019, the BIG-PPI aims to integrate patient perspectives into all stages of our breast cancer research. Medical journalist Jenny Bryan talked to some of the people involved in the initiative and provides us with insights from BIG-PPI members and patient representatives from Australia & New Zealand, Canada and Europe. Ana Casas, Leslie Gilham, Mairead MacKenzie, and Judy Needham kindly agreed to share their experiences and the importance of patient involvement. We extend our gratitude to all members of the BIG-PPI for their ongoing commitment. Additionally, we also wish to thank BIG Executive Board members Professors Judith Bliss and Boon Chua for their contribution to this in-depth article and for their equally valuable insights from BIG's perspective. *See from page 2.*

The “**BIG Network**” section presents updates on legal matters, projects, and recent activities, including an article on changes in Belgian legislation affecting BIG member groups, the BIG SCOPE project co-funded by the European Commission, the BIG ASIA collaboration and GBCC 2024 (25-27 April, Grand Walkerhill Seoul, Korea), as well as an update on recent activities carried out by BIG HQ and **BIG against breast cancer**, BIG's dedicated philanthropic unit. *See from page 10.*

The “**BIG Clinical Trials and Activities**” section provides an overview of BIG trials presented at SABCS 2023, as well as recently published manuscripts related to BIG trials. It also showcases research and related activities by BIG member groups around the world. *See from page 16.*

Finally, you will find the tables with the “**Overview of the Current Studies Run within the BIG Network**”, *from page 32.*

We hope you enjoy reading this 20th edition of BIG Research in Focus, marking its 10th anniversary. Our inaugural edition in September 2014 featured a themed article on “**The clinical potential of liquid biopsy**”, with contributions from Drs. Ben Ho Park (Sidney Kimmel Comprehensive Cancer Center, USA), Sarah-Jane Dawson (Peter MacCallum Cancer Centre, Australia), Michail Ignatiadis (Institut Jules Bordet, Belgium), and Françoise Rothé (Breast Cancer Translational Laboratory of the Institut Jules Bordet, Belgium). *See: <https://bigagainstbreastcancer.org/wp-content/uploads/2022/12/big-research-in-focus-clinical-potential-of-liquid-biopsy.pdf>*

Stay tuned for our next edition as we will further explore key topics of the past decades and look toward the future.

Thank you for your continued support and collaboration.

Together, we can change the face of breast cancer.

BIG's editorial team



Putting the patient's voice at the heart of BIG's research

BIG PATIENT PARTNERSHIP INITIATIVE (BIG-PPI)



Established in 2019, the BIG Patient Partnership Initiative (BIG-PPI) aims to strengthen BIG's interactions with patients in defining scientific priorities for the network's breast cancer research, and to integrate patient perspectives into all stages of the design and development of its clinical trials. Medical journalist, Jenny Bryan, talks to some of the people involved in the initiative about why it is so important in advancing breast cancer care and meeting patients' needs.

Involving patient representatives in guiding and informing breast cancer research has the potential to optimise trial design, support funding, boost patient accrual and retention, and help achieve the most meaningful outcomes. It therefore comes as no surprise that BIG has always had a strong patient focus in its research programme and has worked with patient advocates through Europa Donna since the early 2000s. With the BIG-PPI, it is taking collaboration with those with lived experience of breast cancer to a global level.

"By bringing together this diverse team of patient partners from around the world, BIG has led the way in terms of equity, diversity and inclusivity in their patient engagement model," says Judy Needham, Chair of the Patient Representative Committee within the Canadian Cancer Trials Group (CCTG), and a member of the BIG-PPI.



She feels that it is very important that BIG is integrating the patient perspective into all aspects of the clinical trial lifecycle from identifying priorities in strategic planning to designing, developing and executing clinical trials.

"I believe that, by including the patient voice in the design of clinical trials, we can both increase patient accrual and enhance the patient experience of trial participation," she says.

Leslie Gilham, Chair of the Consumer Advisory Panel (CAP) of Breast Cancer Trials (BCT), Melbourne, Australia, and another patient partner in the BIG-PPI, agrees:



"When people with lived experience of breast cancer have a seat at the table they can voice the concerns of other patients and ensure that what's being asked of patients in a trial isn't too onerous and will hopefully improve outcomes and benefit future breast cancer patients. It also gives researchers a better perspective of who they are trying to help, especially if they are doing translational research and don't usually come in contact with patients," Gilham points out.

Boon Chua, Consultant Radiation Oncologist and Director of Cancer and Haematology Services at the Prince of Wales Hospital, Sydney, Australia, and a member of BIG's Executive Board and the BIG-PPI, also welcomes greater patient involvement in breast cancer research.

"The lived experience of our patient partners brings a new perspective to the focus of BIG's research, and their commitment to working with health professionals and researchers has quickly made them an indispensable part of our research team," says Chua. "We are integrating their involvement across the research trajectory, from evaluating concepts, through development of protocols and patient materials, to reporting of data," she adds.

Chua encourages patient input about the relevance of different aspects of trial design:

“Patients may question the relevance of parts of validated quality of life questionnaires that we frequently use in our studies, and what we think is important may not be important to them. We need to reflect these perspectives in our research, while at the same time ensuring that we meet the needs of the broader breast cancer population,” she says.



FRESH INSIGHTS ON SIDE EFFECTS



Side effects of treatment are another area where patient insights can influence trial protocols, points out Ana Casas, Breast Cancer Consultant and Tutorial Professor at University Hospital Virgen del Rocio, Sevilla, Spain, who has herself been treated for breast cancer and is also a patient partner of the BIG-PPI. She explains that, as a patient, she sees things differently from when she worked only as an oncologist. Previously, she would have ignored some types of adverse events, such as the effects of aromatase inhibitors on bone density, because they did not seem important compared to the benefits of treatment.

“These effects are becoming more and more important as patients with breast cancer live longer and have more time to experience the consequences of their treatment, such as osteoporosis. Now, I and other oncologists are more aware of the importance of regular bone density scans and treatments such as anti-resorptive therapies, calcium, and physical exercise to prevent osteoporosis,” says Casas.

Judith Bliss, Director of the Institute of Cancer Research Clinical Trials and Statistics Unit, London, UK, and



a member of BIG’s Executive Board and the BIG-PPI, explains that, in cancer trials, there may be little choice about the disease-related outcomes that are used, but there is a choice of safety outcomes that can be included.

“We’re rapidly learning that the lists of side effects we think are important can be different from those that are important to patients and affect their daily lives. As a result, we are focusing more on the holistic effects of treatment on patient quality of life, and regulators are moving towards more patient-reported outcomes,” Bliss says.

REPRESENTING ALL PATIENTS?

Ensuring that BIG’s patient partners represent the broadest possible breast cancer population can be a challenge, as Mairead MacKenzie, a member of Independent Cancer Patients’ Voice (ICPV) in the UK, and a BIG-PPI member points out:

“Being at the table at the start of research is an important step forward but we also need to reflect the diversity of people with breast cancer. In our advocacy communities we need a diverse range of social, cultural and economic groups so we are supporting and promoting the needs and views of all these people, but this can be difficult to achieve. Some people want to move on after their treatment and not get involved, others are prepared to get involved in advocacy, just not in research,” MacKenzie explains.

In addition, while most of BIG’s patient partners had networks and connections that enabled them to get involved, illness, time, travel and cost issues may prevent other patients from establishing such networks.



EDUCATION IS KEY

Education and training is a major priority in the BIG-PPI so that all patient partners have opportunities to learn about trial methodology, balancing risks and benefits of treatment, and other research-related issues.

“We are asking some people to step outside their comfort zone and to work outside their first language, so we recognise the importance of working together



to develop a programme of continuing education and support while, at the same time, not making assumptions about what people can and can't do," explains Bliss.

She recalls a valuable BIG-PPI meeting when researchers and patient partners discussed plans for a trial of reducing duration of treatment in some patients with breast cancer, with the aim of reducing the frequency of adverse events without compromising treatment efficacy.

"At that meeting, our patient partners helped to find what we call 'the non-inferiority threshold' – the upper limit of possible loss of efficacy in terms of disease recurrence that would be acceptable to patients undergoing reduced treatment in order to reduce the risk of adverse events," Bliss explains.

She stresses the importance of recognising that people have different perceptions of acceptable risk and benefit at different stages of their lives and that these may be different from those expected by their healthcare professionals.

"These sorts of discussions with BIG's patient partners are perhaps making the professional network think more broadly about these issues than they may have done in the past, and helping them recognise the diversity of views amongst the patient population," she says.

"At the same time, it's essential that we empower patients involved in such discussions through education and training to understand issues like weighing up risk and benefit not only for themselves but also for other groups of patients," she adds.

Chua would like to see patient partners becoming more actively involved in research if they are interested and have relevant skills and training.

"They could be involved in qualitative research, such as quality of life studies, and become the face of the research project, presenting data at congresses. This will take time but I see no reason why it shouldn't happen," she says.



Recent meeting between BIG's Executive Board and several patient advocates from our Patient Partnership Initiative.

HOW THE BIG-PPI WORKS

The BIG-PPI currently comprises the following 12 members, from various regions worldwide, including Australia & New Zealand, Canada, and several European countries such as Belgium, France, Germany, Slovenia, Spain, and the UK:

- Lynda Belhadi
- Concepcion Biurrun
- Ana Casas
- Siobhan Gaynor
- Leslie Gilham
- Mairead MacKenzie
- Lydie Meheus
- Rachida Nait
- Judy Needham
- Eva Schumacher-Wulf
- Tanja Spanic
- Hilary Stobart

They regularly attend a range of research meetings and can access extensive educational materials.

MEETINGS

BIG Patient Partners participate in key meetings where BIG's research plans are discussed including:

- > An annual strategic 'retreat' with the BIG Executive Board and HQ staff to discuss research priorities and hold strategic discussions for the further development of BIG's research.
- > Biannual scientific meetings at which representatives of BIG's member groups discuss early trial concepts in development, scientific topics related to breast cancer, and updates about trials being conducted within BIG.
- > Input meetings for comprehensive, in-depth discussions about approved study proposals to maximise the impact of the patient partners' perspective at a very early stage of study development.

- > Preparatory meetings for the BIG-NCTN Annual Meeting, a collaborative meeting held annually by BIG and the US National Clinical Trials Network (NCTN) to discuss the most pressing issues in breast cancer and how to collaborate to address them. Workshops for patient partners are held prior to the BIG-NCTN Annual Meetings to prepare for the topics that will be discussed.
- > Training sessions on a range of research related topics, offered virtually and also saved on the BIG-PPI web portal, as well as debriefing calls after events such as the Executive Board retreat and BIG scientific meetings.

TRAINING MODULES

In response to needs identified by BIG-PPI members, a series of training modules are being offered to provide background information to facilitate in-depth discussion between BIG's clinical research experts and the Patient Partners. Recent modules have focused on:

- > Using biomarkers in clinical trials:
 - Precision medicine and biomarkers in breast cancer and clinical trials;
 - Master protocols in personalised medicine.
- > Scientific and operational considerations for trial development under the BIG umbrella.

BIG-PPI PLATFORM

A password-protected online platform/web portal through which BIG-PPI members can easily access training modules, pre-reading materials for training or new trial concepts, BIG publications and research news and other relevant documents.

LEARNING FROM EXPERIENCE

At BCT in **Australia and New Zealand**, a (CAP) member is assigned to discuss a trial concept as soon as it receives a favourable response from the Scientific Committee – even before a protocol is written.

“We’re involved from concept to end of trials, in every aspect of the organisation, including fundraising and doing media interviews, and that helps to lose the ‘white coat’ aspect of research,” says Gilham.

She explains that CAP members are seen as well-informed research partners, and their views taken seriously. When CAP members raised concerns about fertility issues related to one international breast cancer trial, it led to adaptations to the consent form for patients recruited in Australia and New Zealand. In a separate Australian trial, blood sample collection for ctDNA analysis was decentralised on advocate advice so that patients did not need to travel long distances, and this has assisted in improving accrual.

CAP members have also drawn attention to language used in consent forms. For example, patients are likely to assume a biopsy is painful, even within the context of liquid biopsy, so ‘blood draw’ is now used to describe the procedure.

“We also point out where financial issues may be a barrier to trial participation, such as if people have to travel for appointments. Telehealth has made that much easier, as some appointments can be done online,” adds Gilham.

In **Canada**, Needham highlights the role of the Patient Representatives Committee of CCTG, in ensuring that patient-centred endpoints, such as patient quality of life, are included in trials.

“When patient-centred endpoints are included, patients can see the benefits to themselves as well as to science and, in one trial, I remember that accrual more than doubled as soon as the endpoints that mattered to patients were added,” says Needham.

In another trial, patient representatives identified that the number of CT scans was onerous to patients and retention of patients in the trial improved when the frequency of scans was reduced.

Equitable access to clinical trials is also a concern to patient advocates, especially in countries as large as Canada and Australia, as some patients are not treated at the bigger hospitals that participate in studies. Narrow inclusion criteria is another issue that advocates feel needs to be addressed, so that trial results are as representative as possible of the population in which a new treatment will be used.

Gilham also raises concerns about the failure of some new drugs to be marketed in some countries despite positive results in clinical trials.

“Many patients participate in trials not because they think they might benefit, but because they are helping future generations. But if a drug that shows benefits is not marketed in their country, it feels like we are asking them to participate under a false pretext,” says Gilham.

She accepts that this probably means advocating at government level but feels that BIG-PPI members would be well placed to make a strong case for change.

In **Spain**, which has one of the highest clinical trial recruitment records worldwide and the Breast Cancer Federation represents more than 20,000 people with the disease, Casas sees the BIG-PPI as a seed for disseminating knowledge to patients about breast cancer research and its importance for success in curing the disease.

“We have gone from saying nothing about breast cancer in Spain to having patient organisations in every province and widespread discussion about it amongst patients. We now need to see how we can use the BIG-PPI within this network to tell people about breast cancer trials and why they should participate,” says Casas.

In the **UK**, the ICPV was founded in 2009 as an independent patient advocate group. Since then, its members have been involved in the development of over 100 trials, with ICPV members on many trial management and steering groups.

MacKenzie explains that the ICPV is now so well integrated in breast cancer research in the UK that members are routinely asked to contribute to trial development and at conferences. For example, at the recent UK Interdisciplinary Breast Cancer Symposium, there was a patient speaking or acting as co-chair at most sessions.

“It’s taken a while to get to this position, but we can provide input to clinical trials at multiple levels, from making the title understandable to advising on the look and wording of all patient-facing materials,” she says. “Often it’s the small things in trial design that make a big difference to patients, such as taking bloods at routine visits instead of requiring extra appointments,” she adds.

Like other members of the BIG-PPI, MacKenzie stresses the importance of quality of life measures in breast cancer studies, given that the majority of people who get the disease do not now die from it.

“Including quality of life is becoming the norm, and it would be nice to think that’s partly because of patient involvement in trial design. Whatever the reason, it’s something that all researchers should plan to include when they’re starting to think about a new breast cancer trial,” MacKenzie concludes.

WHEN SHOULD PATIENTS GET INVOLVED IN RESEARCH PLANNING?

Patient representation in the design of cancer studies has come a long way since the early days when [having one or two patients in the room was considered enough to show that the patient voice was included](#).¹ As Needham explains, the patient often did not know where and when to speak and the facilitator did not want to make the patient feel uncomfortable by calling on them to comment in a primarily scientific environment.

“Identifying the appropriate touch points in the clinical trial lifecycle which need patient input, and developing the training and tools to facilitate that input – both for the patient and the investigator – has addressed this situation and led to the meaningful patient engagement that we see today,” says Needham.

In 2021, she and her colleagues at CCTG reported [how meaningful patient centricity and engagement had been implemented within the Group, and the benefits that resulted](#).² The initiative focused on the three-phase progression from ‘Inform’ to ‘Involve’ to ‘Collaborate’ set out on the International Association for Public Participation (IAP2) scale. During Phase 1, patient representatives were recruited and assigned to a wide range of CCTG committees including each of the 11 disease site committees, the Clinical Trials Committee

and the Data Safety Monitoring Committee. During Phase 2, the Patient Representative role was elevated through a series of steps including education and training, and development of support tools. In Phase 3, processes were developed and implemented so that patient representatives could participate at all stages of the clinical trial lifecycle, notably:

- Review of ideas and scoring of proposals to ensure patient input in trial design;
- Assessment of feasibility of trial design and patient related endpoints;
- Development of protocols and plain-language consent forms and other patient-facing materials;
- Review of protocols for issues that might impede patient accrual or retention;
- Ensuring materials were appropriate for widespread use and/or adapted to address cultural, economic and other factors;
- Involvement in monitoring accrual and retention to help identify and address encumbrances;
- Communicating results to patient audiences around scientific presentations and publications.

An analysis conducted in 2019/2020 concluded that greater involvement of patient representatives had contributed to CCTG experiencing the highest trial activity and accrual in six years, and a 50% increase in research funding compared to the previous four years. It was agreed that these results were evidence of a productive model that also eliminated duplication of effort regarding best practices in patient engagement.

FUTURE OPPORTUNITIES

The BIG-PPI is already benefiting from the wealth of experience brought by the 12 patient partners who are currently involved but what progress would participants like to see in the future? Moving forward, Needham would like to see the BIG-PPI identifying and collecting research questions that are important to patients so they can be fed into BIG’s overall research strategy.

“The BIG-PPI is still a new initiative, and there has been great work to develop patient input at many of the important touchpoints in the clinical trial lifecycle. I would like to see us continuing to review the lifecycle, identifying the important touchpoints, and evaluating

how we include the patient perspective at each stage,” she says. “In addition, collecting and identifying research questions that are important to patients could be one input into BIG’s overall strategic planning,” she adds.

A priority research question that MacKenzie would like to see getting more attention is metastatic breast cancer:

“A lot of progress has been made in reducing the intensity of radiotherapy and developing more targeted breast cancer treatments but we continue to hear people with metastatic breast cancer asking, ‘What about us?’”

As well as metastatic breast cancer trials, Casas would like more research in elderly patients with breast cancer and into novel ways for earlier diagnosis of breast cancer recurrence.

“We know the likely prognosis for different types of breast cancer, but recurrence is still the menace continually hanging over us, and this is what kills patients. We should not have to wait until a scan shows metastatic disease. We need new tools for earlier detection of recurrence, and we need to make more use of the tests, such as liquid biopsy, that we already have,” says Casas.

With her long background in breast cancer research, Gilham would also like to see BIG-PPI members participating in research decisions at the earliest possible stage – when trial concepts are first proposed. She hopes that trial documents can be put on the BIG-PPI portal so that all members have an opportunity to provide input as, for example, younger members may offer different insights from older members. She suggests that some members may prefer to be involved in non-research aspects of trial development, such as writing or adapting consent forms or getting involved in media programmes:

“The key to the future success of BIG-PPI will be to ensure that members stay engaged with the initiative in whatever role and at whatever level in which they feel comfortable and most able to collaborate and contribute,” she says.

Chua points out that it is early days for the BIG-PPI but looks forward to further developments.

“BIG is certainly trying to ensure that our patient partners can access meetings, education and training and share views and information wherever they live. This is especially challenging in some countries but once we have shown the benefits of the BIG-PPI, we hope to extend more broadly to other BIG member groups,” Chua says.

Bliss is already noticing the impact of the initiative within BIG:

“The BIG-PPI has undoubtedly raised the bar on research discussions at a range of BIG Executive Board meetings. We now find ourselves asking: ‘Well, what would our patient partners say and what would matter to them?’” Bliss concludes.

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*Compliance and Transparency***LEGAL STATUS BIG MEMBERS**

As follow-up to the discussions held during BIG's General Assembly on 15 December 2023 and the evolving legal landscape, BIG has initiated a review of the legal status of its Member Groups. This proactive measure aims to ensure compliance with Belgian legislation, which is the "home" of BIG as a legal entity.

In 2019 changes were introduced to the Belgian Companies and Associations Code, which required a number of changes to BIG's Articles of Incorporation, which were amended beginning in 2020. A key requirement was to be explicit about the fact that BIG Member Groups should be legal entities, set up as non-profit organizations. If for any reason this is not the case for a Group, it must be able to demonstrate that any profit resulting from work under the BIG umbrella must be reinvested in breast cancer research.

Over the years, BIG has seen shifts in legal requirements for member groups, particularly concerning their status as legal entities. Historically, when BIG was founded in 1999, Belgian law did not mandate member groups

to be legal entities, and many early members of BIG were de facto associations. Over time, most of those did become legal entities, meaning that they can be considered "Effective" (full voting) members of BIG. Any groups that are not legal entities, however, will now need to transition from Effective and Adherent Membership status. The main difference between the two is that Adherent Members do not have voting rights, although they may continue to participate in discussions and contribute their opinions.

BIG's Member Groups have been requested to provide updated information on their legal status, facilitating a seamless transition if necessary. This reflects BIG's commitment to transparency, inclusivity, and adherence to legal standards while advancing its mission of global breast cancer research and treatment.

HIGHLIGHTS FROM THE BIG-SCOPE PROJECT

As part of the EU4Health Programme 2021-2027*, in 2023, BIG was awarded an operating grant providing co-funding of up to about 1 million euros. As the curtains draw on the EU4H-2023-OG BIG-SCOPE¹ project, spanning from February to December 2023, we reflect on its successful outcomes, which have significantly supported BIG's mission of fighting breast cancer research around the world. BIG-SCOPE served as a catalyst for many of BIG Headquarters' activities that support the network's research, such as promoting expert collaboration through its regular meetings, more closely involving patients in study development, engaging in public outreach through awareness campaigns, and raising funds for fully academic trials.

Impact on collaboration

The project clearly facilitated expert collaboration by providing support for Executive Board (EB), General Assembly and Scientific Meetings. These moments open doors to explore existing research areas and identify opportunities for enhancement and exploration of new domains. In 2023, a focus on treatment optimisation demonstrated BIG's commitment to refining patient care and included diverse topics such as adjuvant chemotherapy for young women, de-escalation therapy for triple-negative breast cancer (TNBC), and the role of TILs as a biomarker for a particular type of TNBC triple-negative breast cancer. Another concept was presented for an MRI screening study to detect brain metastasis in patients with HER2-positive breast cancer, addressing a critical breast cancer complication with limited treatment options and a poor prognosis.

Patient Partnership Initiative (PPI) empowerment

BIG-SCOPE supported the creation and launch of a dedicated PPI online platform, which optimised communication channels among BIG's patient partners, BIG HQ, and the EB, facilitating the exchange of information. Similarly, specialised training sessions were held, both in breast cancer biology and treatment and scientific and operational considerations in setting-up BIG trials. Through this work, BIG aimed to further empower its patient partners and strengthen their involvement in the various meetings

¹ *BIG-SCOPE - Strengthening expert collaboration, patient partnerships, and public outreach to increase awareness about why academic breast cancer research improves treatments and leads to cures.*

during which BIG studies are developed. This approach ensures patient perspectives become integral to BIG's research, from the early strategic discussions to the actual conduct of a trial, benefiting the broader community.

Communication and philanthropy

The project also played a significant role in BIG's communications and philanthropy efforts. By disseminating valuable content through the annual webinar co-hosted with the EORTC, producing various publications and conducting a successful media campaign, BIG made a substantial contribution towards achieving the EU objective of capacity-building and raising breast cancer awareness. Additionally, the EU's support for our Pink October campaign ("I Miss You") directly impacted our ability to generate a substantial increase over the previous year with respect to awareness in the press and opportunities for funding. Moreover, BIG's enhanced online presence, showcasing these activities, actively engaged a broad audience and greatly contributed to public outreach and health literacy.

Continued journey

The journey doesn't end here; BIG aims to build on the important BIG-SCOPE outcomes, with a strong focus on standardising patient involvement and pursuing opportunities to communicate widely about this work, for example at international breast cancer conferences. BIG will also continue to seek ways to diversify its funding sources, securing grants, forming corporate partnerships, and other new avenues for support of its patient-centric breast cancer research.

Promising update: Securing a new operating grant for 2024 (BIG-SPARK)

Since the start of the year, BIG has worked assiduously to prepare and submit an application for an EU4H-2024-OG operating grant, similar to the EU4H-2023-OG BIG-SCOPE grant. As this edition of BIG RiF goes to print, we are pleased to share that we have been invited to proceed to grant agreement preparation for the operating grant BIG-SPARK, spanning from February to December 2024. More details will follow shortly.

*EU4Health, with a budget of €5.3 billion, is the fourth and largest of the EU health programmes since their launch in 2003.

BIG-ASIA AND GBCC 2024 (25-27 APRIL)

In the ongoing effort to combat breast cancer, BIG-ASIA, an initiative within the Breast International Group (BIG), exemplifies the potential of collaborative research as a testament to what can be achieved when research communities across borders unite with a shared vision.

Established in 2016, BIG-ASIA is the result of a strategic alliance within BIG, bringing together expert research groups from China, Hong Kong, Japan, Singapore, Korea, Taiwan, Thailand, together with BIG Headquarters. The objective is to execute clinical trials for patients in Asia, designed by experts in Asia, fostering a new era of collaboration amongst the region's researchers within BIG's global network. Targeted group discussions with BIG-ASIA members and BIG Headquarters have been crucial to BIG-ASIA approach. These forums have been important in assessing research priorities and tackling challenges endemic to East and South-East Asia. Another key aspect of BIG-ASIA's mission is the mentorship of its young investigators, empowering them to assume leadership roles within BIG's network.

The significance of BIG-ASIA's contributions and the vision for future collaborations are being highlighted at the **Global Breast Cancer Conference 2024** (GBCC 2024, 25-27 April, Grand Walkerhill Seoul, Korea), organised by the Korean Breast Cancer Study Group. This conference is an ideal platform to enhance BIG's visibility

in the region and encourage researchers in Asia to engage with the BIG network.

Furthermore, the GBCC session entitled "Exploring the Significance of BIG in Asia and Opportunities for Collaboration" will give the floor to the following speakers: Sung-Bae Kim, Head of the Breast Cancer Center at ASAN Medical Center, Seoul, South Korea; Janice Tsang, medical oncologist at the University of Hong Kong; Carmela Caballero, Medical Advisor at BIG Headquarters in Brussels, Belgium; and David Cameron, Professor at The University of Edinburgh and Chair of BIG. They will bring their insights to a dialogue about the profound impact of BIG in the Asian context, highlighting the collaborative experiences within BIG, and exploring the innovative BIG Patient Partnership Initiative (BIG-PPI, *see also themed article pages 2-9*) that underscores the importance of integrating patient perspectives in clinical trial development.

The GBCC 2024 is an excellent opportunity to celebrate the strides taken in global breast cancer research and to forge new pathways for cooperation and discovery for all stakeholders within the BIG community. It encapsulates the spirit of BIG-ASIA's journey and the collaboration that BIG advocates, setting the scene for continued progress in breast cancer research across Asia and beyond.





BIG HQ COMMUNICATIONS AND PHILANTHROPY EFFORTS

At BIG HQ (*Headquarters in Brussels, Belgium*), our Communications and Philanthropy Teams tirelessly work to convey BIG's core messages to the public, raise awareness about breast cancer research and BIG studies, and expand the community of **BIG against breast cancer** supporters and ambassadors.

We develop new communication tools, use various channels to convey our message, organise fundraising events, awareness and media campaigns, host webinars, and promote the MoveforBIG platform, among others. We also focus on sharing updates on BIG studies, on highlighting conferences where BIG studies are presented, and on supporting new initiatives like the BIG-PPI (Patient Partnership Initiative, *see also themed article pages 2-9*), or any other relevant and/or newsworthy project.

MoveforBIG

One notable tool developed by our Digital Communications Team is the MoveforBIG online fundraising platform. This platform provides a simple way to raise funds while allowing for personalised communication with donors and the sharing of in-depth information, stories and images. Donations made via MoveforBIG in Belgium are tax-deductible, making it an attractive option for supporters.

They move for BIG

On 1 January 2024, elite ultra-runner **Hilde Dosogne** embarked on a monumental challenge of running a marathon every day of the year, in an attempt to break the world record. At the same time, she's raising awareness and collecting funds for BIG's research. Her efforts have garnered significant media attention for BIG. Hilde has also set up her own MoveforBIG fundraiser and has already raised an impressive €13,000 to support BIG's academic studies such as AURORA, POSITIVE, and EXPERT.

[Ultra-loopster Hilde Dosogne gaat voor wereldrecord! Marathon Woman loopt in 2024 elke dag een marathon en zamelt geld in voor BIG's borstkankeronderzoek. Steun haar! | BIG against breast cancer \(koalect.com\)](#)



Recently, **Valerie Van der Veecken**, a communications manager at BIG HQ, initiated a MoveforBIG fundraiser, providing her donors and followers with regular updates on her latest ultratrail in Tanzania and on the upcoming annual "20 km of Brussels" race, all while passionately advocating for the importance of BIG's research. She encourages her audience to share BIG's story and messages within their personal networks, and invites them to join her and the "BIG 20 km Brussels Team" - over 300 enthusiastic participants running or walking for BIG. To date, she has raised just over €2,000.

[Ultra X Tanzania: Updates, pictures, race & travel report | BIG against breast cancer \(koalect.com\)](#)





Each year, the annual "20 km of Brussels" race draws numerous participants (40,000 in 2023). For the past few years, BIG has been a consistent presence with a dedicated stand and team. This year, on Sunday 26 May, we will welcome and host a team of approximately 350 runners and walkers proudly wearing BIG's colours. Participants will be encouraged to create their personal or team MoveforBIG fundraiser. Our Philanthropy and Digital Teams will offer support, send regular emails with race preparation tips and updates, how to engage with personal networks, and importantly, information

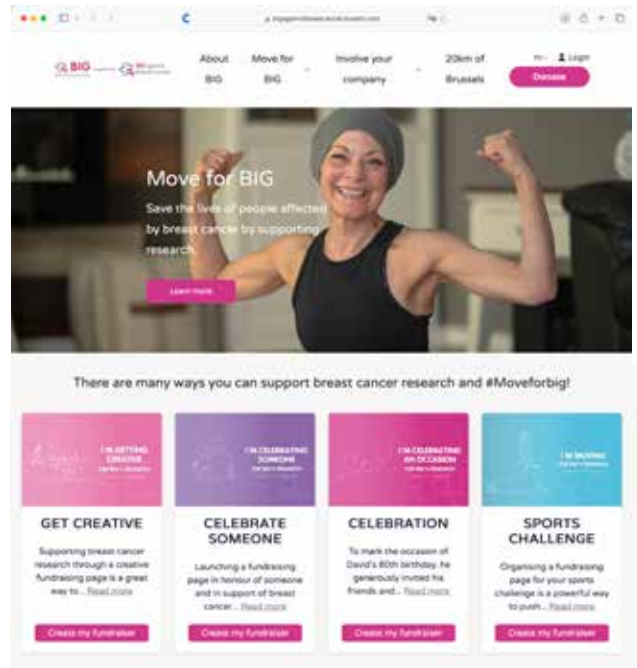
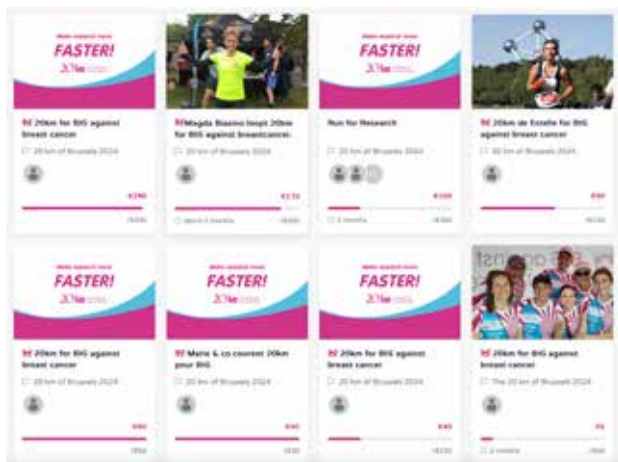
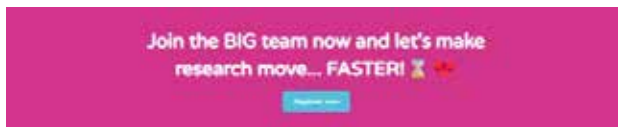
about BIG's breast cancer research. In 2023, we collected €7,810 via our MoveforBIG platform. [20 km of Brussels 2024 | BIG against breast cancer \(koalect.com\)](https://bigagainstbreastcancer.koalect.com)

Every occasion, one cause: MoveforBIG

Aside from sports challenges, there are many other occasions perfect for setting up a MoveforBIG fundraiser. Whether it's a birthday celebration, an anniversary milestone, or a special commemoration, such as honouring a loved one's memory or marking a significant achievement, MoveforBIG offers a meaningful way to contribute to breast cancer research while also celebrating life's important moments.

Through these efforts, we aim to further engage with a community that believes in research, finding new treatments, and ultimately curing breast cancer. We rely on their support, voices, and determination to continue our mission.

<https://bigagainstbreastcancer.koalect.com/en-GB>



1

BIG TRIAL UPDATES AND CONFERENCES

SABCS 2023
5-9 DECEMBER



ALEXANDRA/IMpassion030 (BIG 16-05)

The first results of the ALEXANDRA/IMpassion030 trial were presented at the San Antonio Breast Cancer Symposium (SABCS) in December 2023 by Professor Michail Ignatiadis (EORTC-Breast). This is a phase III open-label trial investigating the efficacy and safety of adjuvant atezolizumab with chemotherapy versus chemotherapy alone in patients with stage II and III operable triple-negative breast cancer. An interim analysis was conducted at 62% of invasive disease-free survival (iDFS) in the intention-to-treat (ITT) population with a median follow-up of approximately 25 months.

The analysis, along with the secondary endpoints analysis, showed that adding atezolizumab to the adjuvant chemotherapy for early-stage triple-negative breast cancer is unlikely to improve efficacy. However, this result provided evidence on the optimal use of immunotherapy in patients with triple-negative breast cancer.

APHINITY (BIG 4-11)

During SABCS 2023, Dr. Elisa Agostinetta (Institut Jules Bordet, Brussels, Belgium) shared some new findings from the APHINITY trial. This trial compares chemotherapy plus trastuzumab plus either a placebo or pertuzumab, as adjuvant (post-surgery) therapy for patients with HER2-positive breast cancer. The exploratory results showed that all patients who received pertuzumab/trastuzumab experienced similar benefits in terms of risk of breast cancer relapse (invasive disease-free survival or IDFS), regardless of the status of oestrogen receptor (ER) and HER2 expression, suggesting that adding pertuzumab to trastuzumab treatment

and chemotherapy might provide consistent benefits across different subgroups of the patients.

Moreover, the analysis also revealed that patients with a lower HER2 fluorescence in situ hybridisation (FISH) ratio and ER-positive tumours had the most significant reduction in the risk of experiencing an IDFS event when treated with pertuzumab/trastuzumab. On the other hand, those with a higher HER2 FISH ratio and ER-negative tumours experienced the smallest benefit from adding pertuzumab. These findings suggest that breast tumours that are more dependent on HER2 signalling ("HER2-addicted") might derive greater benefit from a single HER2-blockade (trastuzumab alone), while tumours that are less sensitive to HER2 ("less HER2-sensitive") might benefit relatively more from the addition of a second HER2-blocker like pertuzumab.

Further research is needed to confirm and fully understand these findings.



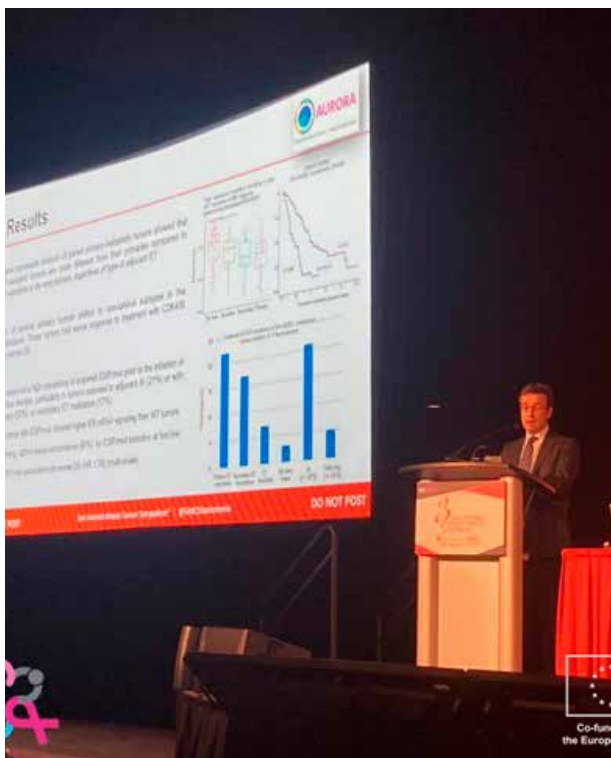
Dr. Elisa Agostinetta presenting the APHINITY trial findings

AURORA (BIG 14-01)

New updates from the AURORA-EU programme were presented at SABCS 2023 by Dr. Angel Guerrero-Zotano. AURORA-EU is providing valuable insights into metastatic breast cancer. The programme's gene expression analysis compared primary and metastatic tumours and showed that tumours resistant to endocrine treatment (ET) differ more from their primary tumours than ET-sensitive or newly developed tumours do, regardless of the type of adjuvant ET used.

9% of luminal primary tumours shifted to non-luminal subtypes in the metastatic stage. These tumours showed poorer responses to treatment with CDK4/6 inhibitor and had worse overall survival rates.

Additionally, there was a high prevalence of acquired mutations of the ESR1 gene before first-line treatment, particularly in tumours previously exposed to adjuvant aromatase inhibitors (21%) or showing primary (22%) or secondary ET resistance (17%).



New results from the AURORA-EU programme were presented by Dr. Angel Guerrero-Zotano.

NEO-ALTTO (BIG 1-06)

A poster was presented by Dr. Aranzazu Fernandez-Martinez at SABCS 2023 on the prognostic value of residual disease (RD) biology and gene expression changes during the neoadjuvant treatment in HER2+ early-breast cancer (EBC) in the NeoALTTO study. By stratifying patients based on these residual disease biomarkers, it might be possible to offer more targeted and effective treatment to improve outcomes for people with HER2-positive early breast cancer.

PALLAS (BIG 14-03)

The PALbociclib CoLLaborative Adjuvant Study (PALLAS) is a randomised phase III trial evaluating the effectiveness of palbociclib when combined with standard adjuvant endocrine therapy compared to endocrine therapy alone in patients with HR positive HER2 negative early breast cancer. At SABCS 2023, Dr. Daniel Stover presented a protocol-defined biomarker analysis of genomic subtype derived from RNA sequencing in the PALLAS trial.

While certain classifications like the PAM50 subtype did not strongly correlate with survival outcomes or treatment response, other biomarkers such as the ROR-S and ROR-P classes provided valuable prognostic information regarding the risk of cancer recurrence.

These findings contribute to our understanding of breast cancer biology and may help guide treatment decisions in the future.

Conclusions:

- Protocol-defined biomarker analysis of research PAM50 cohort:
 - Most tumors in PALLAS PAM50 cohort LumA subtype (>70%)
 - Heterogeneity in outcome and palbociclib benefit by PAM50 subtype
 - No significant association between PAM50 subtype and DFS or treatment interaction
- Secondary correlative analyses of RNAseq biomarkers
 - Significant prognostic association: ROR-S (score, class), ROR-P (class)
- Limitations:
 - Bold design to gather tissue on all patients still resulted in limited RNAseq cohort
 - Rigorous ongoing data analyses for manuscript
- TransPALLAS: A significant resource for the field
 - 1st trial of its size to mandate tissue collection of clinical specimens
 - Successful RNA sequencing of large # FFPE samples – multiple ongoing analyses
 - "Tip of the iceberg":



Dr. Daniel Stover presented a protocol-defined biomarker analysis of genomic subtype derived from RNA sequencing in the PALLAS trial.

POSITIVE (BIG 8-13)

The academic POSITIVE study shared new results at SABCS 2023. Dr. Hatem A. Azim Jr. presented a secondary analysis, expanding on the primary POSITIVE study results. The analysis involved 497 participants, with an impressive 74% achieving pregnancy after temporarily pausing endocrine therapy.

Among them, 179 chose embryo or oocyte cryopreservation, while 215 explored various Assisted Reproductive Technology methods. Remarkably, younger participants and cryopreserved embryo transfer demonstrated higher pregnancy rates without observable short-term impacts on breast cancer outcomes. Additionally, ovarian stimulation for cryopreservation, which precedes cryopreserved embryo transfer, was not associated with worse disease outcomes.

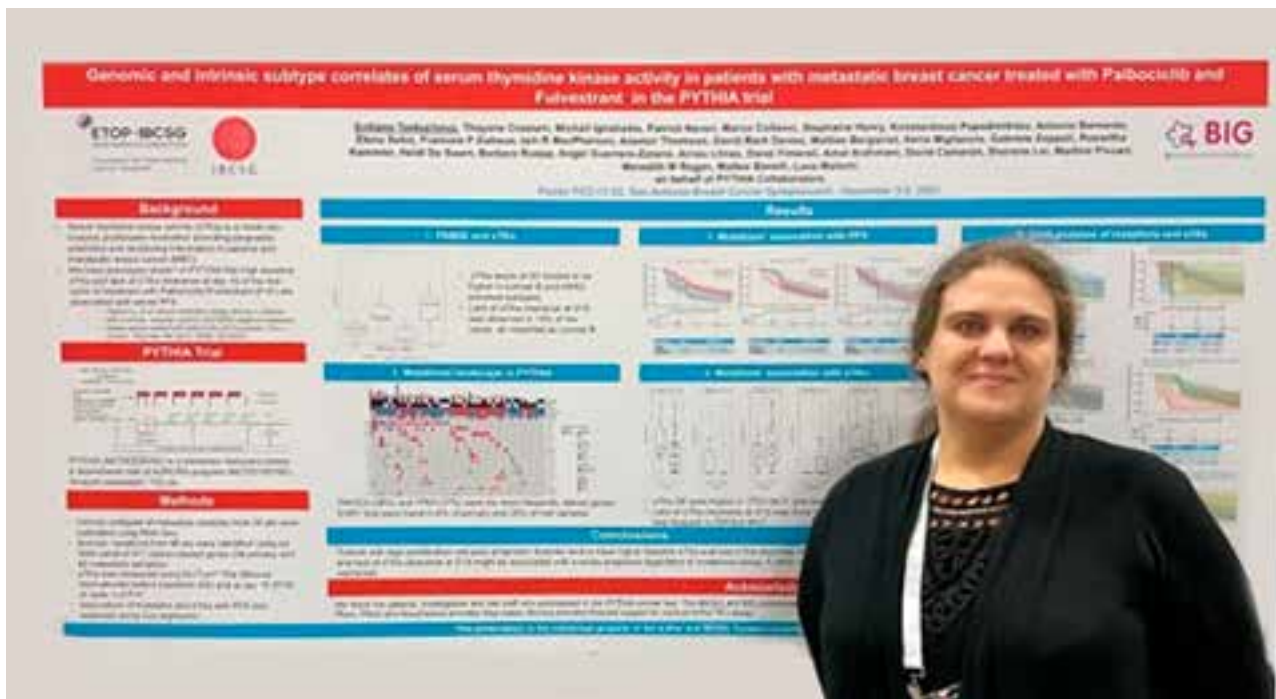
Further analysis revealed that in most patients who had amenorrhea at the start of the trial, menses resumed within six months of discontinuing endocrine therapy. Importantly, the type of adjuvant endocrine therapy the patient had received did not impact the time it took to achieve pregnancy.

While acknowledging the study's limitation of a short follow-up time, these findings provide hope and crucial insights for individuals navigating the complex intersection of breast cancer treatment and the pursuit of parenthood.

PYTHIA (BIG 14-04)

The poster "Genomic and Intrinsic Subtype Correlates of Serum Thymidine Kinase Activity in Patients with Metastatic Breast Cancer Treated with Palbociclib and Fulvestrant in the PYTHIA Trial", presented at SABCS 2023 by Dr. Svitlana Tyekucheva, sheds light on serum thymidine kinase activity (sTKa) in patients with metastatic breast cancer undergoing treatment with palbociclib and fulvestrant. The study focused on tumours with high proliferation rates and poor prognostic indicators. It was found that these tumours exhibited higher levels of baseline sTKa and showed less sTKa response during treatment. Specifically, patients with elevated tumour sTKa levels at the beginning of treatment (D0) and those with lack of sTKa clearance at D15 might have a worse prognosis, regardless of their TP53 gene status. These findings underscore the significance of sTKa as a potential prognostic indicator in patients with metastatic breast cancer receiving palbociclib and fulvestrant treatment.

Another poster from the PYTHIA study, by Dr. Matteo Benelli, was also featured at SABCS: "RBSig gene-expression signature in patients with endocrine-resistant metastatic breast cancer treated with palbociclib and fulvestrant in the PYTHIA trial". PYTHIA is a downstream trial of the AURORA programme.



Dr. Svitlana Tyekucheva presented a poster on the PYTHIA study

RECENTLY PUBLISHED MANUSCRIPTS ABOUT BIG TRIALS



ALTO (BIG 2-06)

Martins-Branco D, Kassapian M, Debieu V, et al. The impact of erythropoiesis-stimulating agents administration concomitantly with adjuvant anti-HER2 treatments on the outcomes of patients with early breast cancer: a sub-analysis of the ALTO study. *Breast Cancer Research and Treatment*. 2024;203(3). doi:[10.1007/s10549-023-07159-9](https://doi.org/10.1007/s10549-023-07159-9)

APHINITY (BIG 4-11)

Krop IE, Mitterpergher L, Paulson JN, et al. Prediction of Benefit From Adjuvant Pertuzumab by 80-Gene Signature in the APHINITY (BIG 4-11) Trial. *JCO Precision Oncology*. 2024;(8):e2200667. doi:[10.1200/PO.22.00667](https://doi.org/10.1200/PO.22.00667)

NeoALTTO (BIG 1-06)

Rediti M, Fernandez-Martinez A, Venet D, et al. Immunological and clinicopathological features predict HER2-positive breast cancer prognosis in the neoadjuvant NeoALTTO and CALGB 40601 randomized trials. *Nature Communications*. 2023;14(1):7053. doi:[10.1038/s41467-023-42635-2](https://doi.org/10.1038/s41467-023-42635-2)

Fernandez-Martinez A, Rediti M, Tang G, et al. Tumor Intrinsic Subtypes and Gene Expression Signatures in Early-Stage ERBB2/HER2-Positive Breast Cancer: A Pooled Analysis of CALGB 40601, NeoALTTO, and NSABP B-41 Trials. *JAMA Oncology*. Published online March 28, 2024. doi:[10.1001/jamaoncol.2023.7304](https://doi.org/10.1001/jamaoncol.2023.7304)

OlympiA (BIG 6-13)

Ganz PA, Bandos H, Španić T, et al. Patient-Reported Outcomes in OlympiA: A Phase III, Randomized, Placebo-Controlled Trial of Adjuvant Olaparib in gBRCA1/2 Mutations and High-Risk Human Epidermal Growth Factor Receptor 2–Negative Early Breast Cancer. *Journal of Clinical Oncology*. Published online February 2024;JCO.23.01214. doi:[10.1200/JCO.23.01214](https://doi.org/10.1200/JCO.23.01214)

PALLAS (BIG 14-03)

Pfeiler G, Hlauschek D, Mayer EL, et al. Impact of BMI in Patients With Early Hormone Receptor-Positive Breast Cancer Receiving Endocrine Therapy With or Without Palbociclib in the PALLAS Trial. *Journal of Clinical Oncology*. 2023;41(33):5118-5130. doi:[10.1200/JCO.23.00126](https://doi.org/10.1200/JCO.23.00126)

2

OTHER TRIALS AND ACTIVITIES BY BIG MEMBER GROUPS

ABCSG

AUSTRIAN BREAST AND COLORECTAL CANCER STUDY GROUP

ABCSG 63 / ERIKA (Elacestrant and Ribociclib in Ki67-tested endocrine responsive breast cancer) trial to start study recruitment in Q2 2024

ABCSG 63 is an innovative, investigator-initiated trial in its final set-up phase, to be conducted in two countries under the academic sponsorship of ABCSG, and at approximately 18 trial sites with the recruitment target of 120 patients.

It is designed as an open label, two-arm, two-step, randomised, phase II study in endocrine-responsive HER-2 negative early breast cancer patients. The present study plans to evaluate the therapeutic potential and the safety of a combination of the orally available SERD elacestrant and the CDK4/6 inhibitor ribociclib. The primary study endpoint is defined as the proportion of the PEPI score of 0 at the time of surgery. “Compared to neoadjuvant chemo/immunotherapy, preoperative systemic endocrine treatment is still not standardised and needs scientific optimisation both in terms of finding the most effective treatment as well as in selecting the appropriate patients”, said ABCSG president Michael Gnant, Professor of Surgery at the Medical University of Vienna. ABCSG’s vice president Christian Singer, Head of the Center for Breast Health at the Medical University of Vienna added: “With a modern SERD and an effective CDK 4/6 inhibitor, we are confident that this treatment can be defined as a potential new standard of neoadjuvant care for patients with hormone-responsive disease.”

Tamoxifen and AIs (in combination with GnRH agonists in premenopausal women) represent the current standard of care in HR-positive early breast cancer but are not clearly defined as a standard treatment in the neoadjuvant setting, except for frail and very old patients. Combining endocrine therapies with CDK4/6 inhibitors is standard of care in the metastatic setting for hormone-receptor positive disease, but again not well defined in the neoadjuvant setting.

In the upcoming ERIKA trial, patients will be randomised 1:1 to receive either 1 cycle of elacestrant and ribociclib or AI (plus GnRH agonist in pre-/perimenopausal women and men) and ribociclib (step 1) after which endocrine-responsive tumours will be identified via a local Ki-67 assessment. Endocrine-responsive patients will continue study treatment for further 5 cycles in each arm (step 2), whereas patients who do not demonstrate an endocrine response will not be randomised and leave the study (and potentially move on to another clinical trial). Furthermore, an extensive collection of tumour tissue and blood samples is an integral part of the study protocol in order to facilitate translational research projects.

Given the exciting study design, ABCSG and the study’s collaborative partners are eager to initiate this new research project in 2024, once again leaving a strong academic footprint in the current clinical trial landscape for the benefit of breast cancer patients.

Contribution by:

Prof. Michael Gnant, MD, FACS, FEBS

ABCSG President, Professor of Surgery at the Medical University of Vienna

Prof. Christian F. Singer, MD, MPH

ABCSG Vice President, Head of the Center for Breast Health at the Medical University of Vienna ●



*Professors Christian Singer and Michael Gnant
Photograph © Oliver Bolch*

CT-IRE CANCER TRIALS IRELAND

The SHAMROCK Study is a Phase 2 open-label, single-arm, adaptive multicentre trial for patients with early-stage or locally advanced HER2-positive breast cancer. The trial, funded by a generous grant from Breast Cancer Ireland and led by Chief Investigator Professor Bryan Hennessy, aims to investigate the effectiveness of neoadjuvant treatment with trastuzumab deruxtecan (T-DXd) for these patients.



The study is sponsored by Cancer Trials Ireland and AstraZeneca, and Daiichi-Sankyo, the co-developers of T-DXd, are supplying the drug for this study. The SHAMROCK study opened to recruitment at Beaumont Hospital in October, and is now open in Cork University Hospital, and University Hospital Limerick. It will soon open at St. James's Hospital, and thereafter in St. Vincent's University Hospital, making a total of five sites in Ireland. Four patients with HER2-positive stage 2-3 breast cancer have already been accrued to the study, with a total recruitment target of 80.

The primary study objective is to evaluate the efficacy of T-DXd in the neo-adjuvant treatment of HER2-positive breast cancer using pathological complete response (pCR) as the primary endpoint. In addition to safety assessments, measures of the efficacy of the study treatment will include event-free survival (EFS) and overall survival (OS) of patients treated with only T-DXd and trastuzumab. Several translational sub-studies will study the molecular evolution of tumours during treatment and aim to develop a biomarker panel that optimises the prediction of the pCR. One of the study's secondary objectives is to determine the sensitivity and specificity for predicting pCR of RDI and imaging, and tomosynthesis biopsy, alone and in combination. Patients participating in the study will be followed up at six-monthly intervals for up to three years from registration.

The SHAMROCK study is also integrated into the National Green Cancer Clinical Trials Initiative. Through connections made possible by BIG, Cancer Trials Ireland has gained access to a tool developed by the Liverpool Clinical Trials Centre for calculating the total carbon emissions associated with a clinical trial.

The tool was originally launched to calculate the volume of carbon emissions produced by trials that have already been completed, but Cancer Trials Ireland is participating in an Institute of Cancer Research study predicting the carbon footprint of a new trial such as SHAMROCK.

The team will calculate the potential total carbon emissions the study will generate by identifying the carbon touchpoints and inputting related data into the tool. Knowing this figure helps identify areas of the trial with high carbon outputs and drives shaping the trial to be more carbon efficient.

This innovative, investigator-initiated trial has the potential to improve outcomes for patients with early-stage or locally advanced HER2-positive breast cancer using neoadjuvant treatment with T-DXd. In addition, it is also changing how we measure and, ideally, seek to reduce the environmental impact of clinical trials in breast cancer and more broadly.

The SHAMROCK study is made possible by the funding from Breast Cancer Ireland, the support from AstraZeneca and Daiichi-Sankyo, and the leadership of Professor Bryan Hennessy and his team. ●



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Co-National Director in Medical
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Physicians of Ireland
Clinical Lead for Cancer Trials Ireland
Member of BIG's Executive Board*



EORTC BCG

EUROPEAN ORGANISATION FOR RESEARCH AND TREATMENT OF CANCER – BREAST CANCER GROUP

The EORTC Breast Cancer Group (BCG) is a group of the most important academic hospitals in Europe aiming to develop new standards of care for breast cancer patients through innovation. Our research focus is the evaluation of innovative treatments and multidisciplinary approaches to increase survival and improve the quality of life of all breast cancer patients.

Past and upcoming events

- **20-22 March 2024: EBCC-14** (Milan, Italy). More information is available on the EBCC website: [Home - EBCC 14 \(eortc.org\)](https://www.eortc.org/EBCC-14)
 - > 21 March 2024, 8.00-9.00 AM: Young investigator session on “Clinical and Translational Breast Cancer Research: Navigating Challenges and Unlocking Potential for Young Investigators”.
- **12 April 2024: EORTC BCG Spring group meeting (virtual)**
- **15-21 June 2024: 24th Workshop on Methods in Clinical Cancer Research (MCCR)**, Sint Michielgestel, The Netherlands. Applications for this workshop were open from December 2023 to February 2024. More information is available on the [EBCC website](https://www.eortc.org/EBCC-website/).
- **10-11 October 2024: EORTC BCG Fall group meeting** (Paris, France)

Recent publications

- Alaeikhanehshir S, Ajayi T, Duijnhoven FH, et al. Locoregional Breast Cancer Recurrence in the European Organisation for Research and Treatment of Cancer 10041/BIG 03-04 MINDACT Trial: Analysis of Risk Factors Including the 70-Gene Signature. *J Clin Oncol*, 2024, Jan 19;JCO2202690. doi: [10.1200/JCO.22.02690](https://doi.org/10.1200/JCO.22.02690). Online ahead of print.
- Schröder CP, van Leeuwen-Stok E, Cardoso F, et al. Quality of life (QoL) in male breast cancer (BC): prospective study of the EORTC10085/TBCRC029/BIG2-07/NABCG International Male BC Program. *The Oncologist*, Volume 28, Issue 10, October 2023, Pages e877-e883. Doi: [10.1093/oncolo/oyad152](https://doi.org/10.1093/oncolo/oyad152)
- Lopes Cardozo J, Veira S, Ait Hassou L, et al. Agreement on risk assessment and chemotherapy recommendations among breast cancer specialists: a survey within the MINDACT cohort. *Breast*. 2023 Oct;71:143-149. doi: [10.1016/j.breast.2023.05.005](https://doi.org/10.1016/j.breast.2023.05.005)

- Pasquier D, Bidaut L, Oprea-Lager DE, et al. Designing clinical trials based on modern imaging and metastasis-directed treatments in patients with oligometastatic breast cancer: a consensus recommendation from the EORTC Imaging and Breast Cancer Groups. *Lancet Oncol*. 2023 Aug; 24; 8: E331-E343. doi: [10.1016/S1470-2045\(23\)00286-3](https://doi.org/10.1016/S1470-2045(23)00286-3)
- Kaidar-Person O, Giasafaki P, Boersma L, et al. EORTC Radiation Oncology and Breast Cancer Groups. Mapping the location of local and regional recurrences according to breast cancer surgery and radiation therapy: Results from EORTC 22922/10925. *Radiother Oncol*. 2023 Aug;185:109698. doi: [10.1016/j.radonc.2023.109698](https://doi.org/10.1016/j.radonc.2023.109698). Epub 2023 May 23
- Musoro JZ, Coens C, Sprangers MAG, et al. EORTC Melanoma, Breast, Head and Neck, Genito-urinary, Gynecological, Gastro-intestinal, Brain, Lung and Quality of Life Groups. Minimally important differences for interpreting EORTC QLQ-C30 change scores over time: A synthesis across 21 clinical trials involving nine different cancer types. *Eur J Cancer*. 2023 Jul;188:171-182. doi: [10.1016/j.ejca.2023.04.027](https://doi.org/10.1016/j.ejca.2023.04.027).
- Bartels S, Donker M, Poncet C, et al. Radiotherapy or Surgery of the Axilla after a Positive Sentinel Node in Breast Cancer: 10 year Results of the Randomised Controlled EORTC 10981-22023 AMAROS Trial. *J Clin Oncol*. 2023 Apr 20;41 (12):2159-2165. doi: [10.1200/JCO.22.01565](https://doi.org/10.1200/JCO.22.01565). Epub 2022 Nov 16.

EORTC BCG has contributed to several recent meta-analyses through data sharing of clinical data:

- Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Anthracycline-containing and taxane-containing chemotherapy for early-stage operable breast cancer: a patient-level meta-analysis of 100,000 women from 86 randomised trials. *Lancet*. 2023 Apr 15;401(10384):1277-1292. doi: [10.1016/S0140-6736\(23\)00285-4](https://doi.org/10.1016/S0140-6736(23)00285-4)
- Squifflet P, Saad ED, Loibl S, et al. CTNeoBC Project. Re-Evaluation of Pathologic Complete Response as a Surrogate for Event-Free and Overall Survival in Human Epidermal Growth Factor Receptor 2-Positive, Early Breast Cancer Treated With Neoadjuvant Therapy Including Anti-Human Epidermal Growth Factor Receptor 2 Therapy. *J Clin Oncol*. 2023 Jun 1;41(16):2988-2997. doi: [10.1200/JCO.22.02363](https://doi.org/10.1200/JCO.22.02363). Epub 2023 Mar 28.

- van Mackelenbergh MT, Loibl S, Untch M, et al. CTNeoBC Project Pathologic Complete Response and Individual Patient Prognosis After Neoadjuvant Chemotherapy Plus Anti-Human Epidermal Growth Factor Receptor 2 Therapy of Human Epidermal Growth Factor Receptor 2-Positive Early Breast Cancer. *J Clin Oncol*. 2023 Jun 1;41(16):2998-3008. doi: [10.1200/JCO.22.02241](https://doi.org/10.1200/JCO.22.02241). Epub 2023 Apr 19.

Main studies in development

Several clinical trials are in advanced stage of development within the group, covering the large spectrum of breast cancer subtypes including triple negative breast cancer (TNBC) and ER+/HER2- breast cancer. The portfolio consists of early drug development trials, treatment optimisation trials, and studies focusing on quality of life (QoL) research questions. In addition, the group is still investigating clinical trials in the growing population of elderly patients with breast cancer.

Active studies, recruiting

EORTC-2129-BCG TREAT ctDNA (BIG22-01): Elacestrant for ctDNA-positive ER+/HER2- BC:

Study coordinator: Michail Ignatiadis

Study co-coordinators: Emmanouil Saloustros and Wolfgang Janni

This phase III study aims to evaluate whether elacestrant can delay occurrence of distant metastasis or death when compared to current adjuvant endocrine therapy in patients with ER+/HER2- breast cancer and with late ctDNA-relapse, treated with adjuvant endocrine therapy. Patients will be randomised after a positive ctDNA test during the screening period and after confirmation by imaging of the absence of distant metastasis or locoregional recurrence.

This trial will be conducted in collaboration with different groups, including from within the BIG network (as a BIG supporter model trial). The first sites have been activated, and the study is open to recruitment since December 2023.

RP-1828 (IMMUcan)

IMMUcan is a downstream project of the SPECTA platform. The goal is to generate broad molecular (WES and RNAseq) and cellular profiling data (multiplex IF and IMC) of the tumour and its microenvironment from cancer patients integrated

with clinical data, to understand how the immune system and tumours interact, and the impact of current therapeutic interventions. A molecular report with all clinically targetable molecular alterations will be returned to clinicians. Three cohorts of adult patients with breast cancer treated with standard of care have been opened for recruitment:

- **Cohort 1:** patients with confirmed locally advanced or metastatic triple negative breast cancer (mTNBC), naïve of treatment (in metastatic settings), to be treated in 1st line with focus on immune checkpoint inhibitor/immune checkpoint inhibitor - chemotherapy.
- **Cohort 2:** patients with confirmed diagnostic of localised TNBC (stage I to III), to be treated with neo-adjuvant chemotherapy, enrolled prior to neo-adjuvant chemotherapy.
- **Cohort 3:** patients with confirmed diagnostic of localised HER2+ (stage I to III) breast cancer, to be treated with neo-adjuvant chemotherapy, enrolled prior to neo-adjuvant chemotherapy.

Recruitment started in May 2019. As of 20 December 2023, 1,146 patients have been enrolled in IMMUCan, including 599 patients with breast cancer. Collaboration with the Institute Jules Bordet's Synergy trial is currently ongoing with the analysis of materials from 84 mTNBC patients. End of recruitment is expected for August 2024.

EORTC-1811 (E²-RADIatE)

The EORTC-ESTRO radiotherapy registry/platform was launched on 25 June 2019. This multi-cohort platform aims to collect real-world data of cancer patients treated with radiotherapy. This platform includes currently two cohorts:

• **RP-1822 OligoCare cohort**

This observational cohort evaluates radical radiotherapy for patients with oligometastatic lung, breast, prostate or colorectal cancer. As of 24 January 2024, 2,493 patients were enrolled in 61 sites in 11 countries, including 359 (14%) patients with oligometastases from their breast cancer.

• **RP-2011 ReCare cohort**

The objective of this cohort is to evaluate patients treated with high-dose re-irradiation. The first site was authorised on 15 June 2023. As of 24 January 2024, 11 sites (out of a selected total of 26) have been authorised for recruitment, and 16 patients with breast cancer have been enrolled. ●

GEICAM SPANISH BREAST CANCER GROUP

GEICAM'S PRESENCE AT SABCS 2023

Male Breast Cancer and BRCA

GEICAM presented data at SABCS 2023 regarding the characteristics of a cohort comprising 773 patients included in the first Spanish Male Breast Cancer registry, sponsored by GEICAM. This retrospective, observational study incorporates data from male breast cancer patients diagnosed between 2000 and 2019. The analysis focuses on the first cohort of unselected patients within the study who had their BRCA1/2 gen mutational status assessed. Out of the patients available in the database, 186 underwent BRCA1/2 germline genetic testing, constituting 24% of the cohort. Within this subset, 19% of patients exhibited a known pathogenic mutation in BRCA1 or 2 (BRCA1/2mut). Interestingly, this percentage appears to surpass that observed in women with breast cancer. Patients BRCA1/2mut demonstrated certain features associated with a worse prognosis, including a higher prevalence of de novo metastatic disease. While no statistically significant differences were observed in outcomes between early-stage and advanced disease, numerical variations in progression-free survival suggest a potentially more aggressive nature of BRCA1/2mut disease.

All these findings support the recommendation of conducting genetic analysis for this population, particularly those with a higher hereditary risk profile.

More information: <https://clinicaltrials.gov/study/NCT03800355>

Highlights from other GEICAM studies presented at SABCS:

> GEICAM/2013-02 (PEARL):

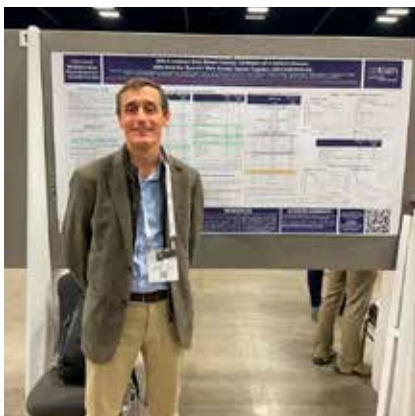
The identification of biomarkers indicating a favourable response to palbociclib plus endocrine therapy resulted from this analysis of the PEARL trial, a collaborative study between CECOG and GEICAM. (Agrawal N. et al. SABCS 2023)

> GEICAM/2014-03 (REGISTEM):

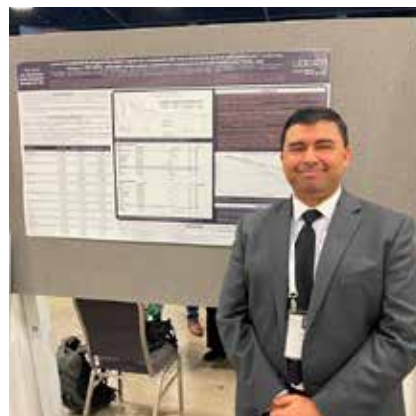
A new analysis of the Spanish metastatic breast cancer registry highlighted a higher prevalence of BRCA mutations in young patients. This finding underscores the importance of genetic testing for this population, with the possibility to offer them potential targeted therapies. (López-Tarruella S. et al. SABCS 2023)

> GEICAM/2017-07 (EMBARCAM):

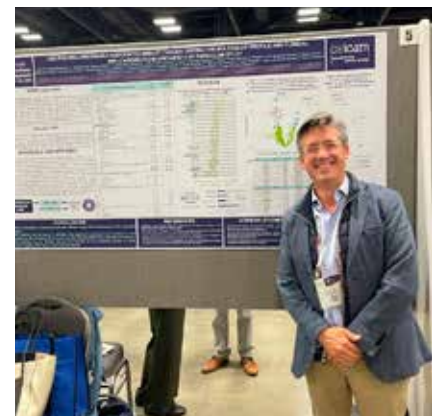
The EMBARCAM study suggests that pregnancy-related breast cancer might be considered a distinct clinical and molecular entity. Characteristics such as the basal-like subtype and a more aggressive phenotype, featuring higher genomic instability, were observed in this analysis of the EMBARCAM study. (De la Haba J. et al. SABCS 2023)



Dr. Ander Urruticoechea



Dr. Yash Agrawal



Dr. Juan de la Haba

Figure 1. Study Design

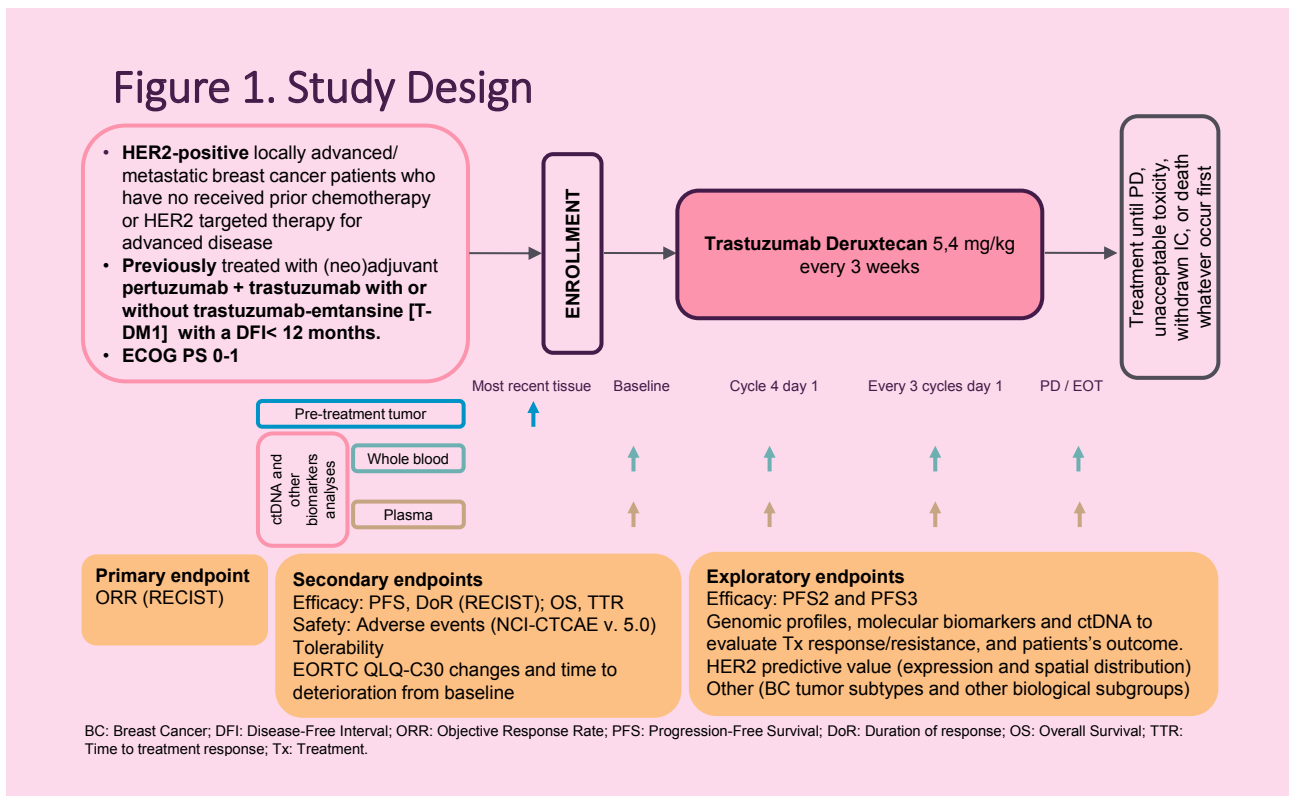


Figure 1 - TRANSCENDER Study Design

TRANSCENDER: trastuzumab deruxtecan in early relapse breast cancer patients previously treated with trastuzumab and pertuzumab and or T-DM1 in early stage.

In the context of early or locally advanced HER2-positive breast cancer, neo/adjuvant therapy has become well established. Most patients experience excellent outcomes when treated with trastuzumab and pertuzumab as neoadjuvant therapy. For those with residual invasive disease, post-neoadjuvant trastuzumab and chemotherapy, T-DM1, is considered the gold standard and also achieves good results.

Despite the favourable outcomes observed, a significant proportion of patients face disease recurrence. There is limited data regarding the optimal strategy for patients experiencing relapse within one year after completing adjuvant anti-HER2 treatment, particularly those who have previously received trastuzumab and pertuzumab in the early stages.

Given the positive results demonstrated by trastuzumab deruxtecan (T-DXd) in the HER2-positive

metastatic breast cancer population as observed in the DESTINYBreast-03 trial, GEICAM has initiated the TRANSCENDER study, with support from AstraZeneca. This national, multicentre single-arm phase II clinical trial aims to investigate the efficacy, safety and tolerability of administering of T-DXd in HER2-positive locally advanced or metastatic breast cancer patients who are resistant to trastuzumab plus pertuzumab plus taxane due to early relapse.

The study aims to enrol **41 patients**, with an estimated recruitment period of 24 months from the enrolment of the first patient. Currently, seven out of the 19 targeted sites are prepared to recruit patients, but no patients have been included yet. Efforts are underway to activate the remaining 12 sites.

More information: <https://clinicaltrials.gov/study/NCT05744375> ●

GOCCHI CHILEAN COOPERATIVE GROUP FOR ONCOLOGIC RESEARCH

Transforming breast cancer care in Latin America: The journey of cooperative research of LACRN

In 2009, the National Cancer Institute (NCI) established a groundbreaking initiative, **the Latin American Cancer Research Network (LACRN)**, forging bilateral agreements with the governments of Argentina, Brazil, Chile, Mexico, Peru, and Uruguay. This initiative marked a significant step in fostering international collaboration in cancer research, focusing on harnessing the strengths of governments, institutions, and researchers across the region.

LACRN's objective was to revolutionise cancer research and treatment in Latin America. One of its key projects, initiated in 2011, was the "Molecular Profiling of Clinical Stage I and II Breast Cancer in Latin American Women Receiving Standard Reference Treatment" (MPBC - NCT02326857). This study, conducted across 37 clinical sites, including 9 in Chile with GOCCHI as the coordinating centre, aimed to understand the molecular profile distribution of breast cancer in Latin American women. This understanding was pivotal in enhancing diagnosis and treatment strategies.

The MPBC study introduced several novel features to mainly public participating institutions

- > Harmonisation of diagnostic and therapeutic procedures.
- > Construction of biobanks for biological sample management.
- > Development of a bioinformatics platform for data and sample analysis.
- > Rigorous monitoring to maintain sample and data integrity.
- > Creation of comprehensive operating manuals.
- > Standardisation training for procedures and technologies.
- > Development of epidemiological questionnaires linked with clinical variables.



The fruits of this collaborative effort began to emerge with the publication of pivotal studies:

1. "Socioeconomic, Clinical, and Molecular Features of Breast Cancer Influence Overall Survival of Latin American Women" DOI: [10.3389/fonc.2022.835626](https://doi.org/10.3389/fonc.2022.835626)
2. "The Transcriptomic Portrait of Locally Advanced Breast Cancer and Its Prognostic Value in a Multi-Country Cohort of Latin American Patients" DOI: [10.3389/fonc.2022.845527](https://doi.org/10.3389/fonc.2022.845527)
3. "Implementing Standard Diagnosis and Treatment for Locally Advanced Breast Cancer through Global Research in Latin America - Results from a Multi-Country Pragmatic Trial" Accepted on JCO Global Oncology

These publications marked a significant milestone in understanding breast cancer in Latin American women, setting a new precedent in oncological research.

Recently, LACRN's commitment and success in cancer research were further recognised. Conquer Cancer®, the ASCO Foundation, in collaboration with Pfizer Global Medical Grants, awarded grants to support initiatives aimed at addressing inequities and enhancing metastatic breast cancer (mBC) patient care (picture). Among the funded projects is the "Pattern of care of metastatic breast cancer in five Latin American countries", led by Javier Retamales, Executive Director of GOCCHI. The objective of this study is to evaluate the overall survival of participants with stage II and III breast cancer enrolled in the MPBC study, with systemic recurrence, as a function of epidemiological, socioeconomic, molecular subtypes and care patterns in different Latin American countries. It focuses on treatment strategies, adherence to recommendations, and disparities in healthcare.

The journey of LACRN, from its inception to its current achievements, embodies the power of collaborative research in changing the face of medicine. Under the leadership of figures like Bettina Müller, President of GOCCHI, LACRN has not only changed the lives of thousands of patients who participated in its studies but also set a new standard in cancer care through continuous collaboration and dedication. This initiative stands as a testament to how cooperative efforts can effectively address healthcare disparities, making a dream of equitable and advanced cancer care a reality in Latin America. ●

The Latin America Regional Council at the review meeting for the programme. The meeting took place at the Argentina Association of Clinical Oncology in Buenos Aires, Argentina.

IBCSG INTERNATIONAL BREAST CANCER STUDY GROUP

The IBCSG 67-22 PREcoopERA window-of-opportunity study

The IBCSG 67-22 PREcoopERA study is a window-of-opportunity study for premenopausal women with hormone receptor-positive, HER2-negative early breast cancer, with the proliferation biomarker Ki-67 greater than or equal to 10%.

Window-of-opportunity trials are studies in which patients receive one or more new agents during a short period of time between their cancer diagnosis and the start of standard treatment, such as surgery. These trials typically include patients who are naïve to cancer treatment. They typically have a translational endpoint that is answered based on tumour biopsies taken before and after the window-of-opportunity treatment.

Adjuvant endocrine therapy for premenopausal women with hormone receptor-positive, HER2-negative early breast cancer often includes suppression of ovarian function with a GnRH or LHRH agonist plus an aromatase inhibitor or tamoxifen.

Younger age is associated with lower rates of compliance with endocrine therapy, suggesting that side effects are less acceptable to these women. Clinical development of new endocrine therapies with similar efficacy to conventional endocrine therapies but in an environment with higher oestradiol levels is warranted. New oral selective oestrogen receptor degraders (SERDs) are emerging as potentially useful endocrine therapies in the (neo)adjuvant setting. Giredestrant is an efficient and potent SERD and a full antagonist, resulting in better anti-proliferative activity than known SERDs. It is unknown whether LHRH agonists are needed in combination with SERD therapy in premenopausal women.

The aim of the PREcoopERA window-of-opportunity study is to determine whether giredestrant plus the LHRH agonist triptorelin has greater anti-proliferative activity, as measured by the ability to decrease Ki-67, than the aromatase inhibitor anastrozole plus triptorelin in premenopausal women with oestrogen receptor-positive, HER2-negative early breast cancer. Additionally, the study aims to evaluate whether giredestrant without LHRH agonists has similar or non-inferior anti-proliferative activity to giredestrant plus triptorelin. These results from the PREcoopERA trial would provide the rationale for subsequent (neo)adjuvant clinical trials.

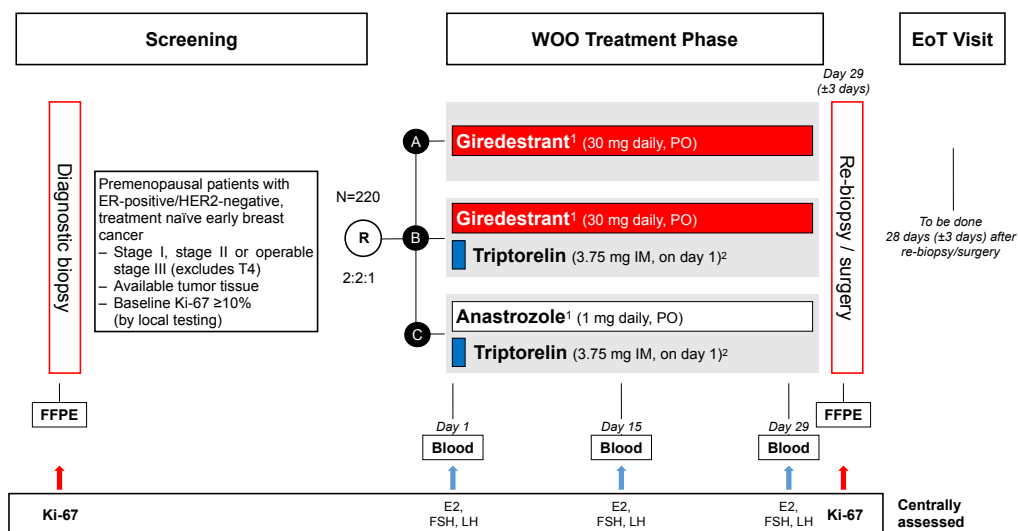
PREcoopERA (NCT05896566) is a randomised, open-label, 3-arm, window-of-opportunity study. The sample size is 220 women, randomised in a 2:2:1 ratio to giredestrant (30 mg/d po for 4 weeks until rebiopsy) plus triptorelin (3.75 mg IM on d1), giredestrant alone; or anastrozole (1 mg/d po for 4 weeks until rebiopsy) plus triptorelin. Rebiopsy is planned on day 29 after treatment initiation, either during primary surgery or as a stand-alone procedure if subsequent neoadjuvant therapy is planned. The primary endpoint is the change in the Ki-67 labelling index between the pre-treatment diagnostic tumour biopsy and the post-treatment rebiopsy, as assessed centrally by the IBCSG pathology office.

Dr. Elisabetta Munzone, Milan, Italy, and Dr. Peter Dubsy, Lucerne, Switzerland, are the study chairs.

The study is sponsored by the ETOP IBCSG Partners Foundation and funded by a grant from F. Hoffman-La Roche. It is conducted in collaboration with the German Breast Cancer Study Group, SOLTI, and Cancer Trials Ireland.

Sites in Switzerland, France, Italy, Hungary, Sweden, as well as in Germany (GBG), Ireland (CTI), and Spain (SOLTI), are participating in the PREcoopERA study.

The first patient worldwide was enrolled in Switzerland on 25 January 2024. ●



¹ Oral treatment (giredestrant or anastrozole) is given from day 1 until the day of re-biopsy/surgery

² If re-biopsy/surgery cannot be done on day 29 (± 3 days) from first injection, a second triptorelin injection should be given on day 29 (± 3 days).



JBCRG JAPAN BREAST CANCER RESEARCH GROUP

Ongoing clinical trials and publications

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

- **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.
- **JBCRG-M08 (AMBER):** innovation of the 1st line strategy optimised as abemaciclib with endocrine therapy based on the ESR1 mutation of ctDNA for HR-positive HER2-negative advanced metastatic breast cancer patients (JBCRG-M08) – a multi-institutional phase II trial.
- **JBCRG-C09 (OPTIMAL):** olaparib treatment in metastatic/advanced breast cancer patients using real world data in Japan (OPTIMAL study).
- **JBCRG-C10:** optimal therapeutic strategies with CDK4/6 inhibitors based on the real world evidence in patients with HR-positive/HER2-negative advanced and metastatic breast cancer.

Congress presentations

> ESMO 2023 (20-24 Oct 2023): JBCRG-M07TR

Poster presentation by Dr. Takayuki Iwamoto: Changes in cell-free DNA after short-term palbociclib and fulvestrant treatment for advanced or metastatic hormone receptor-positive and human epidermal growth factor 2-negative breast cancer: JBCRG-M07 (Future) TR study.

Recent publications

1) JBCRG-M07TR in *Breast Cancer Research and Treatment*, 2023

Takayuki Iwamoto, Naoki Niikura, et al. Changes in cell-free DNA after short-term palbociclib and fulvestrant treatment for advanced or metastatic hormone receptor-positive and human epidermal growth factor 2-negative breast cancer. *Breast Cancer Research and Treatment*, 2023 October.

DOI: <https://doi.org/10.21203/rs.3.rs-2909789/v1>

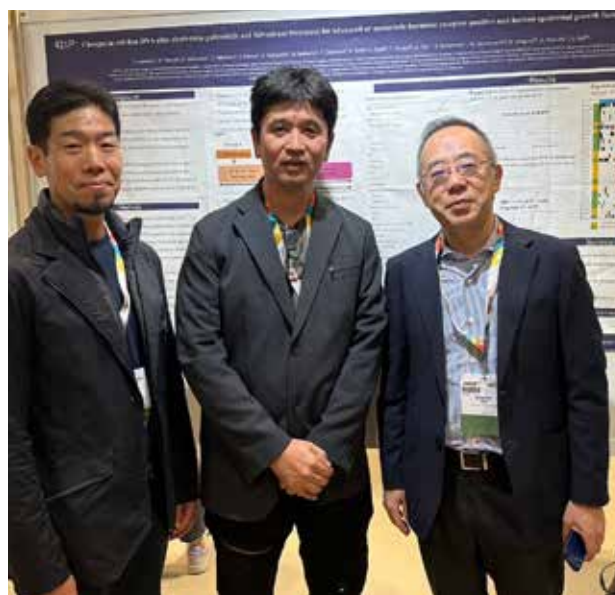
2) JBCRG-22TR in *British Journal of Cancer*, 2024

Kosuke Kawaguchi, Don Saldajeno, et al. Time-series blood cytokine profiles correlate with treatment responses in triple-negative breast cancer patients. *British Journal of Cancer*, 2024 January.

DOI: <https://doi.org/10.1038/s41416-023-02527-0>

Participation in global BIG trials

JBCRG is involved in the following studies run under the BIG umbrella: **ALEXANDRA/IMpassion030 (BIG 16-05)**, **OlympiA (BIG 6-13)**, **POSITIVE (BIG 8-13)**, **Penelope-B (BIG 1-13)** and **PALLAS (BIG 14-03)**. For details about the trial leadership, please refer to the overview of BIG trials on page 32-35. ●



Dr. Naoki Niikura, Dr. Takayuki Iwamoto, and Dr. Shigehira Saji

LACOG LATIN AMERICAN COOPERATIVE ONCOLOGY GROUP

2023 San Antonio Breast Cancer Symposium

From 5-9 December, the 2023 San Antonio Breast Cancer Symposium took place in Texas, USA. During this edition of the meeting, LACOG was honoured to have three abstracts selected, presented by LACOG Executive Director Dr. Gustavo Werutsky and other authors. These important works are the result of efforts by many investigators across Latin America to describe the current scenario of breast cancer care, as well as the challenges and disparities of optimal care in the region.

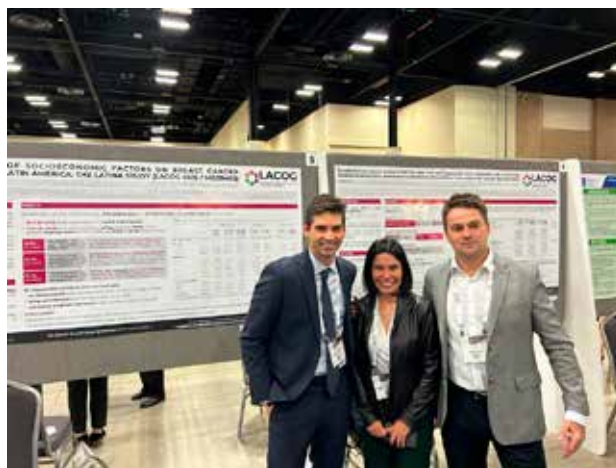
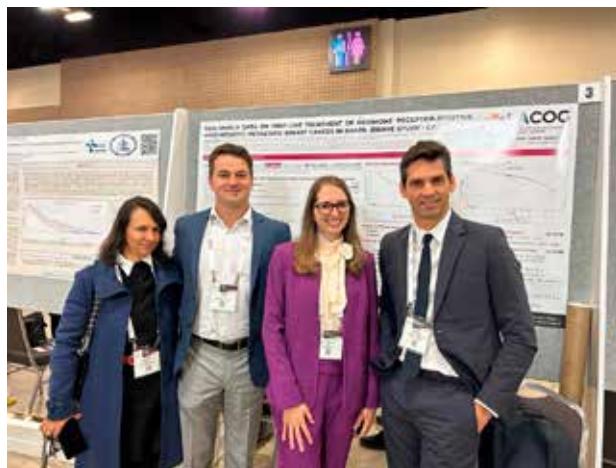
Poster: LACOG 0221 - BRAVE study: "Real-World Data on First-line Treatment of Hormone Receptor-positive, HER2-negative, Metastatic Breast Cancer in Brazil (BRAVE study - LACOG 0221)"

Poster: LACOG 0615/MO39485 - LATINA study: "The Impact of Socioeconomic Factors on Breast Cancer Diagnosis in Latin America: The LATINA study"

Educational Session: Treatment post-CDK4/6 inhibitors: single agent endocrine therapy

Dr. Carlos Barrios, president of LACOG, presented the lecture "Treatment Post-CDK4/6 Inhibitors: Single agent endocrine therapy" at an educational session of the San Antonio Breast Cancer Symposium.

The presentation addressed an important and evolving topic with a significant impact for clinical practice. With the adoption of cyclin inhibitors as first line therapy for HR+ MBC patients, what to offer for these patients is a common and pertinent question for clinicians all over the world. Many options are being explored in this situation and one potential strategy would be to continue endocrine therapy with single agents. ●



SOLTI BREAST CANCER RESEARCH GROUP

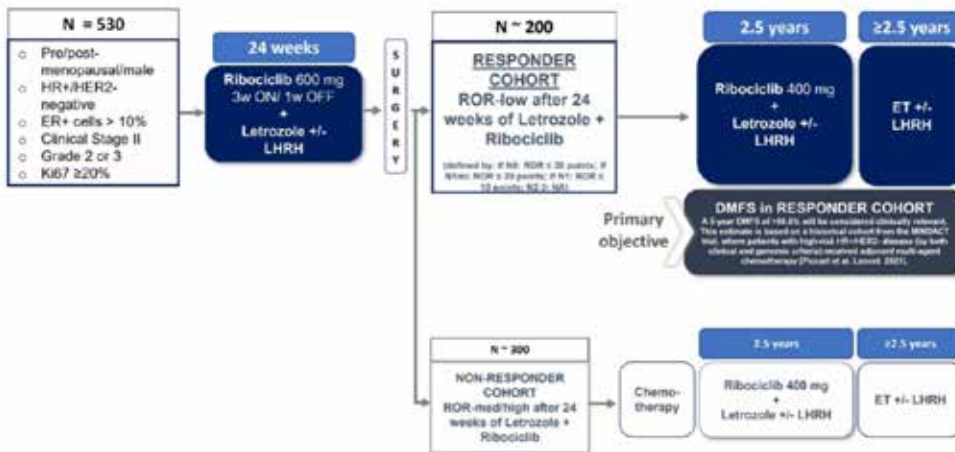
4 keys to the future

1. RIBOLARIS

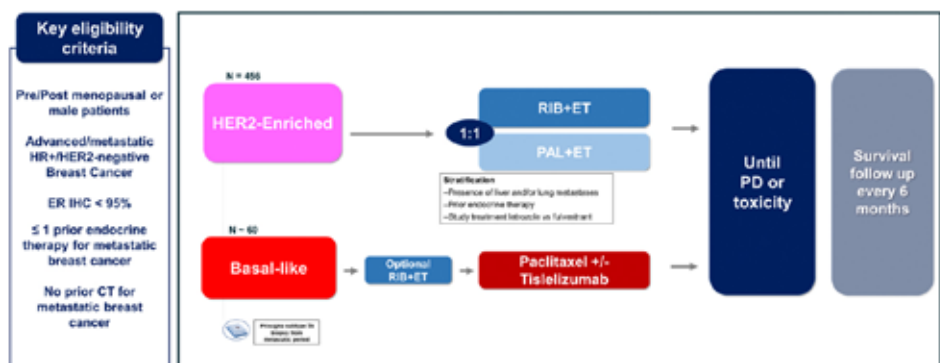
The RIBOLARIS study, which started in May 2022, is a Phase 2 clinical trial for patients with early-stage hormone receptor-positive and HER2-negative breast cancer. Promoted and developed by the academic cancer research group SOLTI, the study is coordinated together with UNICANCER, a counterpart group in France, and is run under the BIG umbrella as a supporter model study (BIG 21-02). The objective of the trial is to spare patients from chemotherapy treatment if, after neoadjuvant treatment combining ribociclib with letrozole, their tumours have shown a reduction in aggressiveness at a molecular level. These patients would continue treatment with the same drug combination for 2.5 years after surgery, thus avoiding chemotherapy and its associated toxic effects, favouring their quality of life.

RIBOLARIS Principal Investigators are **Aleix Prat, MD, PhD** (Hospital Clínic de Barcelona, Spain), **Joaquín Gavilá, MD, PhD** (Instituto Valenciano de Oncología), **Paul Cottu, MD, PhD** (Institut Curie, Paris) and **Thibault de la Motte Rouge, MD, PhD** (Pitié Salpêtrière Hospital, Paris).

Clinical trial design RIBOLARIS



Clinical trial design HARMONIA



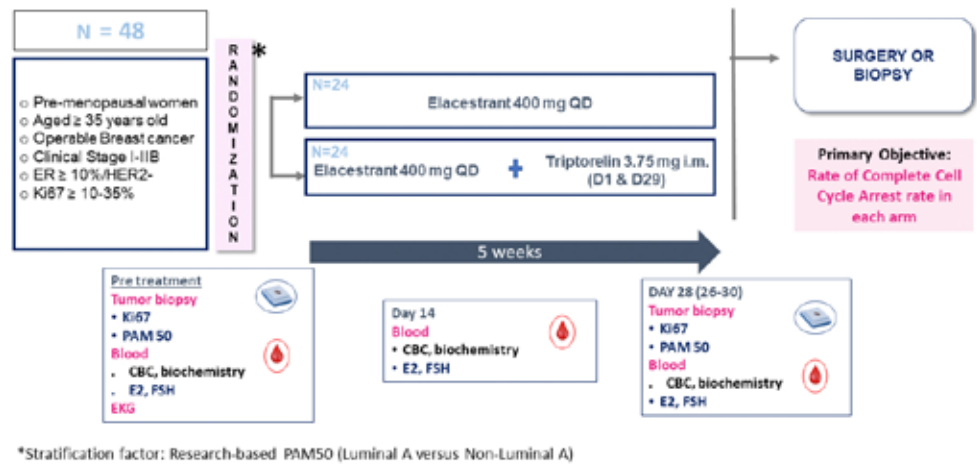
2. HARMONIA

Launched by SOLTI in September 2021, **HARMONIA** is the first phase III clinical trial that compares treatment options for patients with difficult-to-treat HR+/HER2-advanced breast cancer (ABC). There is an unmet 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 testing 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. 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.

Aleix Prat, MD PhD, Head of Translational Genomics & Targeted Therapeutics Group at the Hospital Clínic Barcelona (Barcelona, ESP), along with **Lisa A. Carey, MD ScM**, co-Chair of the Breast Cancer Committee at ALLIANCE and Deputy Director of Clinical Science at Lineberger Comprehensive Cancer Center (Chapel Hill, NC, US), are leading 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 as study chairs.

Clinical trial design
PREMIERE



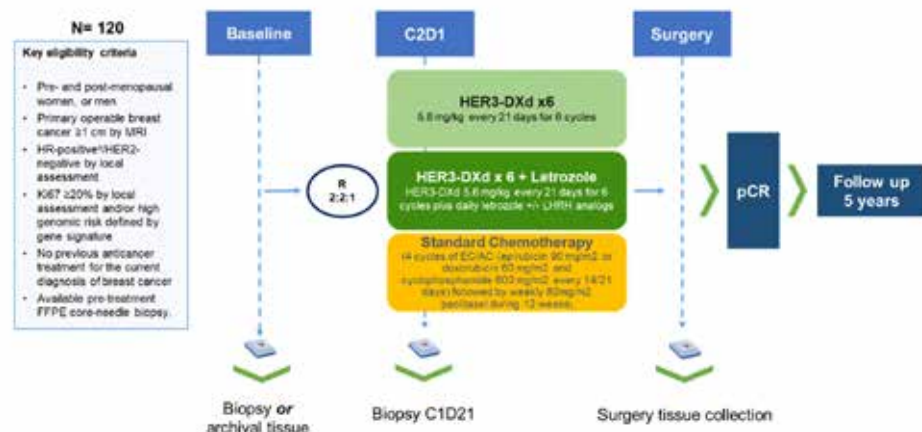
3. PREMIERE

The positive results of the ELIPSE study (aimed at determining the biological effect of elacestrant – a new SERD – for the first time in early-stage disease, after the drug had demonstrated its effectiveness in metastatic breast cancer), led to the opening of a second, larger study: the PREMIERE clinical trial. PREMIERE enrolls young, pre-menopausal, hormone receptor-positive breast cancer patients who have not yet received any cancer treatment. The trial will measure the ratio of cancer cells that are able to stop the division cycle completely, thus halting tumour proliferation, thanks to elacestrant in the neoadjuvant setting.

PREMIERE is a Phase II, multicentre, randomised, open-label study of premenopausal patients with luminal breast cancer investigating the effect of oral SERD elacestrant with or without triptorelin on the functional ER pathway and Ki67 proliferation.

Sponsored by SOLTI, PREMIERE Principal Investigators are **Meritxell Bellet, MD, PhD** (Hospital Vall d’Hebron de Barcelona), **Cristina Hernando, MD** (Hospital clínico de Valencia) and **Pablo Tolosa, MD** (Hospital 12 de Octubre, Madrid).

Clinical trial design
VALENTINE



4. VALENTINE

SOLTI-2103 VALENTINE was created with the aim of testing patritumab deruxtecan in a neoadjuvant setting, alone or in combination with endocrine therapy, to verify its efficacy against classical chemotherapy in RH+/HER2- breast cancer.

This study is based on the good results of SOLTI-TOTHER3, which confirmed the anti-tumour activity of a new drug-antibody conjugate for early-stage breast cancer. TOT HER3 is the first trial to test the drug-antibody conjugate patritumab deruxtecan in patients with previously untreated hormone receptor-positive (HR+)/HER2-negative early breast cancer.

Sponsored by SOLTI, VALENTINE Principal Investigators are **Alex Prat, MD, PhD** (Hospital Clínic de Barcelona) and **Mafalda Oliveira, MD, PhD** (Hospital Vall d’Hebron/VHIO, Barcelona).

*Overview of the***CURRENT STUDIES RUN WITHIN THE BIG NETWORK****Open trials / research programmes**

Study name	BIG number	Short description	Principal Investigator(s)	Trial model & partners
AURORA (Metastatic Breast Cancer GPS)	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 (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.
Breast Cancer in Pregnancy	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
DIANER	BIG 18-03	A Randomized Phase II Study to Evaluate the Incidence of Discontinuations due to Diarrhoea at 3 Cycles in patients with Early-stage HER2-positive (HER2+), Hormone Receptor-positive (HR+) Breast Cancer treated with Neratinib plus Loperamide prophylaxis versus Neratinib with Initial Dose Escalation plus PRN Loperamide prophylaxis versus Neratinib plus Loperamide plus Colesevelam prophylaxis. - NCT 05252988	M. Martin M. Gil	Supporter trial (Co)-Leading partner: GEICAM Pharma partner: Puma Biotechnology
EXPERT (BIG Radio Tuning)	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, National Lottery (Belgium), and BIG HQ fund-raising initiatives
OPTIMA	BIG 22-02	Optimal personalised treatment of early breast cancer using multi-parameter analysis	R. Stein A. Makris J. Dunn	Supporter trial Coordinating group: ICR Foundation (sponsor): University College London Pharma partner: / Funding: UK National Institute for Health Research (NIHR) Health Technology Assessment Programme
POLAR	BIG 18-02	Palbociclib for HR+ isolated local or regional recurrence of breast cancer - NCT03820830	E. Munzone S. Aebi	Supporter trial Coordinating group: ETOP IBCSG Partners Foundation (sponsor) Pharma partner: Pfizer Funding: Pfizer
RIBOLARIS	BIG 21-02	Neoadjuvant and Adjuvant Ribociclib and ET for Clinically High-risk ER+ and HER2-Breast Cancer	A. Prat P. Coftu J. Gavilá T. de La Motte Rouge	Supporter trial Coordinating group: SOLTI (sponsor) Pharma partner: Novartis Pharma AG Funding: Novartis Pharma AG

TREAT ctDNA Elacestrant	BIG 22-01	Elacestrant for treating ER+/HER2- breast cancer patients with ctDNA relapse	M. Ignatiadis E. Saloustros W. Janni	Supporter trial Coordinating group: EORTC Foundation (sponsor): EORTC Pharma partner: Menarini Ricerche (collaborator for ctDNA analysis: Invivata)
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Follow-up or post-study activities, recently closed studies

Study name	BIG number	Short description	Principal Investigator(s)	Trial model & partners
ALEXANDRA / IMpassion 030	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 / FSTRF and AFT Pharma partner: Roche/Genentech (sponsor) Funding: Roche / Genentech
ALPHABET	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 - NCT05063786	A. Pérez-Fidalgo C. Criscitiello P. Bedard	Co-lead trial (Co)-Leading partners: GEICAM (sponsor) / ETOP IBCSG Partners Foundation and BIG HQ Pharma partner: Novartis Funding: Novartis
ALTO	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
APHINITY	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
APPALACHES	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 Funding: Pfizer
BRAVO	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
DCIS	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
DECRESCENDO	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)
Exceptional Responders	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
IBIS-II	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

INTERNATIONAL MALE BREAST CANCER PROGRAMME	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 NCTN / TBCRC (US) Pharma partner: N/A Funding: Breast Cancer Research Foundation
LORELEI	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
MA.32 Metformin	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.
MINDACT	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*
NEO-ALTO	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
OLYMPIA	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 (global sponsor for all countries excluding the US) and Merck (co-developer of the drug) Funding: AstraZeneca
PALLAS	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, Alliance for Clinical Trials in Oncology Foundation (sponsors for Rest of the World and the US respectively) and BIG HQ Pharma partner: Pfizer Funding: Pfizer grant
PENELOPE-B	BIG 1-13	Post-neoadjuvant palbociclib for patients with HR+, HER2-normal primary breast cancer with high relapse risk after neoadjuvant chemotherapy - NCT01864746	S. Loibl	Supporter trial (Co)-Leading partner: GBG (sponsor) Pharma partner: Pfizer Funding: Pfizer grant
POSITIVE (BIG time for Baby)	BIG 8-13	Endocrine therapy interruption to enable conception for young women with ER+ breast cancer - NCT02308085	O. Pagani	Supporter trial (Co)-Leading partner: ETOP IBCSG Partners Foundation (sponsor) Pharma partner: N/A Funding: ETOP IBCSG Partners Foundation, Fonds Baillet-Latour, BIG HQ, national and local funding bodies, individual donors

* 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; NCTN: National Clinical Trials Network; NCCCTG: North Central Cancer Treatment Group; NCI: US National Cancer Institute; SCTBG: Scottish Cancer Trials Breast Group; TBCRC: Translational Breast Cancer Research Consortium

PYTHIA	BIG 14-04	Palbociclib plus fulvestrant for pretreated patients with ER+/HER2- metastatic breast cancer - NCT02536742	L. Malorni	Co-lead trial (Co)-Leading partners: ETOP IBCSG Partners Foundation (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.
SNAP	BIG 2-12	Schedules of nab-Paclitaxel: evaluation of different schedules of nab-paclitaxel for metastatic breast cancer - NCT01746225	A. Gennari G. Jerusalem	Supporter trial (Co)-Leading partner: ETOP IBCSG Partners Foundation (sponsor) Pharma partner: Celgene Funding: Celgene grant
SOFT	BIG 2-02	Evaluation of ovarian suppression and of exemestane as adjuvant therapy for premenopausal women with endocrine responsive breast cancer - NCT00066690	P. Francis G. Fleming	Supporter trial (Co)-Leading partner: ETOP IBCSG Partners Foundation (sponsor) Pharma partner: Pfizer Funding: grants from BCRF, Cancer Research CH, Pfizer, Ipsen, Debiopharm, TerSera Therapeutics, US NCI, IBCSG and many participating collaborative academic groups, as well as various charities. Pfizer and Ipsen provided the drugs for these studies.
SOLE	BIG 1-07	A phase III trial evaluating the role of continuous letrozole versus intermittent letrozole following 4 to 6 years of prior adjuvant endocrine therapy for postmenopausal women with hormone-receptor positive, node positive early stage breast cancer (SOLE - Study Of Letrozole Extension) - NCT00553410	M. Colleoni P. Karlsson S. Aebi J. Chirgwin	Supporter trial Coordinating group: ETOP IBCSG Partners Foundation Sponsor: ETOP IBCSG Partners Foundation Pharma partner: Novartis Funding: Novartis
SUPREMO	BIG 2-04	Selective Use of Postoperative Radiotherapy AfEr 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.
TEXT	BIG 3-02	Tamoxifen and Exemestane Trial: evaluation of exemestane plus GnRH analogue for premenopausal women with endocrine responsive breast cancer - NCT00066703	O. Pagani B. Walley	Supporter trial (Co)-Leading partner: ETOP IBCSG Partners Foundation (sponsor) Pharma partner: Pfizer Funding: grants from BCRF, Cancer Research CH, Pfizer, Ipsen, Debiopharm, TerSera Therapeutics, US NCI, IBCSG and many participating collaborative academic groups, as well as various charities. Pfizer and Ipsen provided the drugs for these studies.
TREAT-CTC	BIG 1-12	TRastuzumab in HER2-negative Early breast cancer as Adjuvant Treatment for Circulating Tumor Cells (CTC) - NCT01548677	M. Ignatiadis M. Piccart J.-Y. Pierga B. Rack C. Soliriou	Supporter trial (Co)-Leading partners: EORTC BCG, SUCCESS, UNICANCER Sponsor: EORTC Pharma partner: Roche, Janssen Diagnostics Funding: Roche educational grant/ medication; Janssen test kits

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

ABOUT BIG

THE BIG NETWORK: GLOBAL RESEARCH COLLABORATION TO CURE BREAST CANCER

2024 marks BIG's 25th anniversary! For the past quarter-century, BIG's academic research groups have relentlessly 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, 25 years later, BIG represents about 60 like-minded research groups from around the world and reaches across approximately 70 countries on 6 continents.

Through its network of groups, BIG connects several thousand specialised hospitals, research centres and world-class breast cancer experts who collaborate to

design and conduct pioneering breast cancer research. Each BIG group plays a crucial role. The combined expertise, collaborative spirit, dedication and hard work are essential to improving the lives of patients confronted with breast cancer. BIG is thus global and local.

More than 30 clinical trials are run or are under development under the BIG umbrella at any one time. BIG also works closely with the US National Cancer Institute and the North American Breast Cancer Group, to act as a strong integrating force in the field of breast cancer research. Thanks to this global collaboration, BIG 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.

www.bigagainstbreastcancer.org





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

ABCBSG Austrian Breast & Colorectal Cancer Study Group

AGO-B Arbeitsgemeinschaft Gynäkologische Onkologie Breast Study Group

BOOG Borstkanker Onderzoek Groep

CEEORG 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

EUBREAST The European Breast Cancer Research Association of Surgical Trialists Network (EUBREAST e.V./Germany and EUBREAST ETS./Italy)

FBCG Finnish Breast Cancer Group

FSS Frontier Science Scotland

GCSG Georgian Cancer Study Group

GEICAM Spanish Breast Cancer Group

GIM Gruppo Italiano Mammella

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-CTSU Institute of Cancer Research - Clinical Trials & Statistics Unit

IJB-CTSU 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



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