Fighting breast cancer around the globe

Southern Europe

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First and foremost, we at BIG wish you, your families, friends and colleagues good health and continued safety. As 2020 is coming to an end, we look back at a year that has been marked by an unprecedented health crisis, with the COVID-19 pandemic affecting our daily lives on a scale none of us have experienced before. Our thoughts are with all of those who have suffered during this difficult time. Let’s hope 2021 will bring us all together again.

BIG’s Editorial Board would like to take this opportunity to say THANK YOU to all the BIG member groups who contributed to this issue of BIG Research in Focus. In particular, thank you to the breast cancer experts who accepted to be interviewed for the themed article “Fighting breast cancer around the globe: Southern Europe”. You provided us with very valuable insights into breast cancer research in your countries. The Mediterranean countries have seen major improvements in breast cancer care over the last 20 years, despite the heterogeneity of healthcare systems and research infrastructure. Promising initiatives are underway to reduce inequalities of care, build and extend cooperative research groups, encourage academic research and address the challenges of COVID-19. For the full article, see as of page 5.

THANK YOU also to each BIG member group that contributed to this issue with an article for the recurrent section “Other trials & activities by BIG member groups”, which gives a peek at BIG members’ research and related activities around the world. We are happy to see that the number of contributions has increased considerably over recent years. This strengthens our belief that the BIG Research in Focus is a valued platform for sharing information about your expertise and the crucial work you do on a daily basis to improve the lives of women and men with breast cancer. We are grateful for your spirit of collaboration and commitment to the BIG network. We hope these articles will further inspire you and welcome your stories to be published in the next editions. See as of page 24.

BIG against breast cancer, BIG’s dedicated philanthropy unit, conducts vital fundraising to support BIG’s clinical trials and research programmes that have no commercial interest but are crucial for breast cancer patients. The funds raised provide the means for BIG member groups and their affiliated hospitals, and other partners, to finance their efforts and patient participation in a study. This is made possible by the generosity of foundations, companies, ambassadors and individuals. The section “BIG Network” provides an overview of activities carried out by BIG HQ and BIG against breast cancer. Due to the COVID-19 pandemic and related public health measures, planned events had to be cancelled and we had to re-invent how to reach BIG’s community of supporters. See as of page 14.

The section “Clinical Trials and Activities” gives an update on BIG trials, their status and abstracts presented at ESMO Virtual Congress 2020 and EBCC Virtual Congress 2020. See as of page 19.

Finally, you will find the “Overview of the current clinical studies run within the BIG network” as of page 46.

We hope you enjoy the reading.
Southern Europe has seen major improvements in breast cancer care over the last 20 years, despite the heterogeneity of healthcare systems and research infrastructure of Mediterranean countries. Promising initiatives are underway to reduce inequalities of care, build and extend cooperative research groups, encourage academic research and address the challenges of COVID-19. Medical journalist Jenny Bryan talks to leading breast cancer researchers from across the region.

Dr Angelo Di Leo, Head of the Sandro Pitigliani Medical Oncology Unit and Chair of the Oncology Department at the Hospital of Prato, Istituto Toscano Tumori, Italy, points out that Greek studies were among the first to advance understanding of breast cancer biology and signal the potential of liquid biopsy. Spanish researchers provided valuable information about the use of drugs, such as taxanes, in the treatment of early breast cancer, and Italian studies demonstrated the value of adjuvant therapy and treatment de-escalation based on tailoring treatment to breast cancer biology.

“For南方欧洲 has made substantial contributions to improvements in breast cancer care and research thanks to pioneering individuals and many highly trained teams of investigators,” says Di Leo.

He also highlights the contribution of researchers in Southern Europe to current BIG studies of novel biologic agents, and the POSITIVE trial, which is evaluating interruption of endocrine therapy for young women with ER-positive breast cancer who wish to become pregnant.

“It is extremely rewarding to see Southern Europe so well represented in these and other collaborative trials, and it is a measure of the success of current care and research in a region that may previously have been thought to be a little behind other parts of Europe,” says Di Leo.

Dr Etienne Brain, Chair of the European Organisation for Research and Treatment of Cancer - Breast Cancer Group (EORTC-BCG), agrees the substantial progress made by breast cancer researchers in Southern Europe, particularly in clinical studies. However, he explains that the increasing complexity and cost of trials continue to prevent some countries from getting involved. This not only limits the patient population for recruitment, it introduces inequity of access to novel treatments.
“At the EORTC we are trying to be flexible and to extend opportunities for participation in our trials, but the regulatory, ethical and other bureaucratic requirements can make it difficult for even highly skilled and committed researchers in smaller countries to participate,” says Brain.

He adds that the growing need to identify specific subgroups from large patient populations for clinical trials means that study organisers do need to go beyond the core countries that traditionally recruit.

“If we extend the populations from which we recruit, we can speed up our studies and get results more quickly. However, if investigators do not have the molecular screening tools to identify the subgroups and we need to arrange centralised testing, this can add to the trial costs,” says Brain.

Di Leo explains that BIG is also eager to foster research capacity in Southern Europe so there is more homogeneous access to experimental drugs across the region.

“We are planning to activate scholarships for young doctors from countries that are unable to participate in clinical trials so that they can come and experience established research infrastructure in other countries. However, we need to ensure that these young doctors are able to use their new knowledge when they go home, and BIG is exploring how this may be achieved through collaborations with the most advanced research centres in their countries,” he says.

Both Di Leo and Brain hope that it will be possible to standardise patient care and research across Southern Europe by reducing the bureaucracy and hence the costs of clinical trials, simplifying study designs and making better use of what is already available.

“If we can collaborate with cancer centres in countries outside Europe in very different settings from our own, we should not have research borders within Southern Europe. Over the next five to 10 years, I would expect a more consistent approach, more equal access to trials and clinical research, and a better match between the research that we do and the patient populations we treat,” says Brain.

As Di Leo concludes: “It’s only a two-hour flight from Firenze in Italy to Albania, and it is simply not acceptable in 2020 that women in Albania do not have access to the same treatments and the same clinical trial opportunities as those in Italy.”

### Conducting cancer trials in the era of COVID-19

With high levels of COVID-19 in many parts of Southern Europe during the early stages of the pandemic, clinicians such as Dr Aleix Prat, Head of Medical Oncology and Associate Professor at the Hospital Clinic of Barcelona, Spain, and Dr Gabriele Zoppoli, Assistant Medical Director of the Internal Medicine and Oncology Unit and Internal Medicine Assistant Professor at the Ospedale Policlinico San Martino, Genoa, Italy, were concerned about its impact on breast cancer research.

“In Spain, trial recruitment fell and research facilities closed but, by the summer, things were back to normal. I am optimistic that, unless there is a change in the next few months, clinical, translational and basic research will not be hugely impacted overall,” says Prat.

His main concern is that the huge investment being made in COVID-19 prevention and patient care will affect resources for treatment of patients with cancer.

“It is understandable that COVID-19 was the priority, but we now need to catch up with breast cancer screening because of the risk of delayed diagnosis and the potential for worsening mortality a few years down the line,” he says.

In Italy, which was the first European country to be hit by COVID-19, telemedicine played an important part in supporting patient care and, in Lombardy and Emilia Romagna – two of the worst hit regions of Italy – huge efforts were made to deliver cancer treatment in patients’ homes and ensure continuation of clinical trials.
“Lombardy and Veneto were the hotspots of the pandemic in Italy but, in several centres, they actually managed to increase accrual of new patients in clinical trials through a structured parallel care pathway for those with cancer,” recalls Zoppoli. “I think we can be very proud of how Italian centres dealt with the crisis and cared for patients,” he adds.

Spain: a major focus for collaborative research

Over the last 20 years, the introduction of free nationwide breast screening and multidisciplinary breast cancer units has transformed patient care in Spain, and breast cancer mortality is one of the lowest in Europe.1

“We now have a good public health system across much of Spain’s 17 regions and there is a good uptake for breast cancer screening. People know that if they go to their hospital, they can get specialist diagnosis and treatment. This has had an important impact on outcomes in Spain,” says Aleix Prat.

Each year, approximately 33,000 patients are diagnosed with breast cancer in Spain and there are about 6,400 deaths.2

Dr Ander Urruticoechea, Scientific Director, Onkologikoa Foundation, San Sebastián, Spain, explains that patients are offered guideline-based therapies, delivered by multidisciplinary teams comparable to those in other parts of Europe, with a similar emphasis on treatment de-escalation.

“In parallel with the rest of the world, we have seen the impact of prognostic platforms in the adjuvant setting that have allowed a reduction in the need for adjuvant chemotherapy in advanced disease and a move towards sequential monotherapies and novel agents,” he says.

Spain consistently achieves one of the highest recruitment rates in international breast cancer clinical trials and is making a major contribution to practice-changing studies.

“Doctors and, just as importantly, patients are willing to participate in both clinical and translational studies. It is partly a cultural thing that Spanish people are happy to contribute and, in addition, research is closely linked to the public health system so patients know they will get good care, making it generally easy to recruit,” says Prat.

In Spain, two organisations with similar goals and complementary approaches have evolved to coordinate independent breast cancer research, though many clinicians belong to both groups. The Spanish Breast Cancer Group (GEICAM) has 900 members in 200 institutions in Spain (including hospitals and R&D centres) while the SOLTI Breast Cancer Research Group has more than 400 members at 80 sites in Spain, Portugal, France and Italy.

“Bringing clinicians and scientists together to perform studies in these collaborations has had an important impact not only on research in Spain, but also in helping to define strategies for improving care for patients with breast cancer,” points out Dr Eva Carrasco, Scientific Director and CEO of GEICAM.

Traditionally, GEICAM research has prioritised large clinical trials such as Target 0, which explored docetaxel in node negative disease and led to the drug’s approval by the European Medicines Agency (EMA) in this indication. SOLTI studies, often proof-of-concept or window-of-opportunity studies, have been smaller with a strong element of translational research including molecular screening. However, the two organisations frequently collaborate to make best use of the expertise of their members.

Carrasco highlights the importance of GEICAM’s decision in 2003 to focus studies on breast cancer subtypes, such as in the CIBOMA trial in early triple negative disease, and more recently in studies, such as COMETA, based on tumour biology. COMETA-Breast is being carried out in patients with triple negative disease and CARABELA in those with very high-risk luminal breast cancer.

Amongst other recent studies, Prat draws attention to the ongoing PATRICIA trial, carried out jointly by SOLTI and GEICAM, which is one of the first studies in patients with
pre-treated HER2-positive advanced breast cancer who are being selected for targeted treatment according to genomic biomarkers. Following previous promising research, investigators are using PAM50 tumour profiling in the trial.

“We don’t often perform prospective studies in breast cancer using biomarkers, and this trial has the potential to change clinical practice for the 40% of patients with luminal A or B disease, so it is very exciting to be getting closer to subdividing HER2-positive disease in this way,” says Prat.

In a SOLTI pilot study that is scheduled to start soon, patients with triple negative advanced breast cancer will receive personalised immunotherapy using adoptive T cell transfer – a technique that has already shown promise in patients with leukaemia. Using fresh biopsy material, specific subtypes of T cells will be expanded in the laboratory and then reinfused.

“This is a very innovative approach in breast cancer, but SOLTI managed to raise funding for it to be carried out as an academic study in four hospitals in Spain with the specialist expertise that is needed,” says Prat.

Despite the widely available research expertise available in Spanish breast cancer centres, many clinicians are hampered by time limitations, which can make it difficult to participate in studies as much as they would like.

“The main challenge for clinical oncologists is the overwhelming workload in daily practice in Spain. This is increasing every year because the rising prevalence of breast cancer and improved outcomes mean that we need to spend more time on patient care. To do research, we need two or three days a week, but hospital clinicians are seeing patients five days a week,” says Prat.

He is particularly concerned about the diminishing levels of academic research due to lack of funding as well as limited time.

“Governments don’t seem to believe in academic research and will not invest. We risk paying a big price in the future because our best researchers will go to countries where it is easier to get grants,” says Prat.

Both he and Urruticoechea point to the lack of public fundraising in Spain to address the shortfall in research funding.

“Fundraising support is under-developed across Southern Europe, especially in Spain. Without sufficient research time and funding, it is amazing that Spanish researchers are such active recruiters to international trials,” says Urruticoechea. “Altruistic support for research is improving, but there is still a long way to go.”

His main priority for the future is to ensure that clinical trials are underpinned by robust translational research that can lead the way to personalised cancer care. He and Carrasco are very proud of the biobank (bGEICAM) that includes more than 40,000 samples from patients in GEICAM studies, linked to a huge amount of clinical information.

“bGEICAM is helping us and other researchers around the world to understand the pathogenesis and biology of breast cancer in order to personalise therapies for this disease,” says Urruticoechea.

This continuing focus on the biology of breast cancer is shared by Prat, who believes that research must establish how the disease evolves – how tumours behave before and after treatment and the processes that occur at cellular level.
“Our tools are improving and we are almost at the stage of being able to monitor processes at the level of single cells. Once we can do this and really understand cancer evolution in early stage disease, we will be able to make huge advances,” he concludes.

Greece: ready to show its full potential in international trials

For patients with breast cancer in Greece, the availability of novel diagnostic tests and innovative therapies is comparable with the rest of Europe, but the economic crisis of the last decade has had a major impact on research – now exacerbated by the COVID-19 pandemic.

Dr Evangelia Razis, Director, 3rd Department of Medical Oncology, Hygeia Hospital, Athens, Greece, points out that CDK4/6 inhibitors, immunotherapy and newer anti-HER2 agents are all available in appropriate settings, and clinicians have been using molecular testing to inform treatment de-escalation for more than 10 years.

“Breast cancer care is the same as in other countries, but it has been very difficult to carry out clinical studies in the last five to 10 years, and we are not currently running any prospective clinical trials,” she says.

A notable recent achievement by the Hellenic Cooperative Oncology Group (HeCOG), which represents physicians and scientists working in medical oncology, is the creation of a large biobank of tissue and blood samples from women with breast cancer who have undergone standard-of-care or clinical trial treatment over the last several years.

“We have paired samples with clinical data, and this will be extremely useful for our ongoing translational research. As treatment evolves, we will also be able to use the biobank samples for individual patients to guide their subsequent therapy,” says Razis.

Previously, HeCOG and the Hellenic Oncology Research Group (HORG), which focuses on clinical and basic research, played a significant role in raising awareness of the importance of cancer research among clinicians and patients.

“HeCOG was also involved in training younger oncologists in the nuts and bolts of doing research but, in the last 10 years of economic problems, research has been one of the areas that has suffered most,” adds Razis.

However, lack of funding and now COVID-19 are only part of the problem for Greek investigators wanting to participate in major breast cancer trials. Razis explains that it is more cost-effective for pharmaceutical sponsors to open multiple sites in a large country such as France than to recruit centres from a small country such as Greece. In addition, obstructive legislation, such as a requirement for clinical trial sponsors to pay the costs of standard-of-care treatment in comparator arms, and ethical committee and other delays, make it difficult for potential Greek investigators to compete for inclusion in major studies.

“We need to improve the Greek framework for conducting clinical trials but we also need support from sponsoring organisations to include us in international clinical trials so that we can show the value of our contribution and demonstrate our full potential. Participating in clinical trials will help us convince the Greek authorities of the importance of a better regulatory framework for the future,” says Razis.

Portugal: reducing research bureaucracy and encouraging future leaders

Without a formal national cooperative research group, it is not easy for breast cancer triallists in Portugal to participate in international studies. However, the creation of an informal group of breast cancer centres with research expertise is enabling Portuguese clinicians and patients to contribute to important trials via membership in the EORTC, SOLTI, and the International Breast Cancer Study Group (IBCSG).

“Research funding was cut as a result of Portugal’s recent economic crisis, but our core centres that perform the majority of clinical trials can provide good quality data on large numbers of patients, and these are the two key requirements for participating in national and international studies,” explains Dr Fatima Cardoso, Director, Breast Unit, Champalimaud Cancer Center/Champalimaud Foundation, Lisbon, Portugal.
According to European cancer data, Portugal has lower breast cancer incidence and mortality than some countries. But Cardoso advises caution in interpreting such figures, owing to registry variations and regional differences in Portugal and in other European countries. While patients in Portugal have equal access to treatment through the public health system, regional differences in the organisation of care and breast cancer expertise can affect outcomes.

“In Portugal, we need to make it mandatory by law that all patients are treated at specialist, certified breast cancer centres, as this is the only way to improve quality of care. People would like to be treated close to home, but there needs to be a balance, with treatment decisions taken by expert multidisciplinary teams and then treatment delivered near to patients’ homes,” says Cardoso.

Novel therapies are approved in parallel with EMA registration. However, delays may occur in agreeing pricing and performing the necessary cost-effectiveness analyses for reimbursement, and inadequate access to molecular profiling is still a significant barrier to treatment de-escalation for patients in Portugal.

“At the moment, only a very small proportion of patients have genomic testing reimbursed but, after years of trying to change this, a group of clinicians have got together to study the cost-effectiveness of testing in Portugal. That way, we can put more pressure on the authorities to agree to wider access,” says Cardoso.

For breast cancer specialists wanting to take part in clinical trials, improved regulatory processes have reduced the time for national approval of studies from over 12 months a decade ago, to four to six months today. Ethics and other reviews can be carried out in parallel, enabling trials to be opened more quickly in Portugal than was previously possible.

“We are a small country, so we will never have the opportunity to be as involved in trials as larger countries but, if we can speed up the processes even further, I think that our core group of research centres can be attractive to sponsors of both academic- and pharmaceutical-led studies,” says Cardoso.

She explains that, as EORTC members, these centres are very pleased to be participating in BIG’s AURORA trial in metastatic breast cancer, with its focus on translational research. In addition, investigators are trying to get access to the newer anti-HER2 agents for their patients by participating in trials such as the DESTINY studies of trastuzumab, and studies of tucatinib.

Despite the challenges of getting funding for academic studies, Cardoso’s own group has successfully applied for grants to support the NEOTARGET trial of sentinel lymph node marking and the CINDERELLA study of aesthetic outcomes and patient satisfaction following oncoplastic surgery.

“With EU funding, we created a simulator that uses patient photos and MRI scans to show how the breast will look after different procedures so patients can choose the technique they prefer, and we are moving ahead with further artificial intelligence-based interventions to address important clinical problems,” says Cardoso.

Her group is also participating in a large EU consortium, contributing to Onco-brain, part of the BOUNCE project that is investigating predictors of patient resilience in early breast cancer over time and identifying targets for intervention (https://www.bounce-project.eu).

For the future, Cardoso hopes that the national implementation of the EU’s Clinical Trial Regulation – with its single portal for all EU clinical trials and streamlined application and assessment processes – will facilitate Portuguese involvement in European breast cancer studies. She would like to see expansion of Portugal’s breast cancer research network, as well as further reductions in trial approval times, making the country attractive to external sponsors, not only as participants but as leaders and coordinators of studies.

“We have a lot of very bright young people who could develop great ideas for new trials in breast cancer. It would be very exciting to see them initiating research in Portugal and becoming leaders in international research, rather than having to go abroad in search of research experience and to advance their careers,” she concludes.
For Gabriele Zoppoli, over the last 20 years, universal breast screening and national standardisation of treatment guidelines top the list of advances for patients in Italy. Treatment de-escalation, either in the form of less aggressive surgery or optimisation of chemotherapy, have also been important.

“Ensuring that women over 40 in every region of Italy have universal, free access to breast screening and that adequate treatment is available to all appropriate women throughout Italy are among the greatest advances our country has made. In addition, Italian physicians were among the pioneers of sentinel lymph node biopsy and breast sparing surgery,” says Zoppoli who is also a Member of the Board of Directors of the Gruppo Oncologico Italiano di Ricerca Clinica (GOIRC).

“Large trials, including those led by the Gruppo Italiano Mammella (GIM), have helped to identify dose-dense anthracyclines and cyclophosphamide followed by taxanes as a common standard-of-care chemotherapy in high risk, early breast cancer,” he adds.

Zoppoli anticipates that molecular profiling to predict risk of recurrence will be next on the list when reimbursement, already available in Lombardy and some other regions, is agreed across Italy.

Italian researchers continue to play a prominent role in advances in breast cancer treatment but, for Zoppoli, the biggest issues inhibiting progress are the reductions in state funding practised by successive Italian governments, resulting in fragmented research and continuing competition between academic and commercially sponsored trials.

To address these problems, GOIRC is encouraging the development of loosely based networks of large breast cancer centres and smaller satellite hospitals to facilitate the pooling of expertise and resources to patient care and research. The aim is for initial consultations and surgery to be carried out at large specialist centres, and drug treatment to be given at satellite centres with fewer but well-trained oncology staff near patients’ homes.

“We are making progress and we try to share opportunities for research between specialist and satellite centres so that it isn’t always the same people who get the studies. We do still need to improve the electronic record system so that everyone has the same software and patients have their own electronic folder which can be accessed wherever needed,” says Zoppoli.

While GOIRC promotes and supports research and training in general in oncology, it frequently collaborates with Italy’s other major oncology research cooperatives – the Italian Trials in Medical Oncology group (ITMO) and Fondazione Michelangelo – and many clinicians are members of more than one group. GOIRC is currently coordinating joint participation with ITMO in BIG’s EXPERT trial of personalised radiotherapy in low risk breast cancer.

“We are very happy to recommend trials from other groups to our centres when they fit with our goals, and we try to be as integrative and open as possible while maintaining our non-profit, academic approach to research,” says Zoppoli.

He highlights collaborations with GIM in the CONSENT (GIM10) study comparing concurrent versus sequential chemotherapy and aromatase inhibitors in post-menopausal endocrine-responsive early breast cancer, and with BIG on the AURORA study in metastatic breast cancer.

“AURORA is currently the single greatest platform for translational metastatic breast cancer research in Europe, and GOIRC and Italian centres are very committed to this study because it is so important in improving our understanding of the evolution of breast tumours and their resistance to treatment,” says Zoppoli.

Among GOIRC’s own portfolio of largely Phase 2 trials is a translational clinical study of neoadjuvant treatment in HER2-positive breast cancer assessing immune responses to different combinations of trastuzumab and pertuzumab versus trastuzumab alone. GOIRC centres have also initiated a clinical and translational study of radiation-induced angiosarcoma – a late complication of breast cancer radiotherapy – and are extending this project through a collaboration with two research centres in Belgium.

“As well as extending our network of research collaborators in Italy and enhancing our structures for trial administration, we hope that GOIRC and other Italian breast cancer researchers will increasingly be able to propose and initiate studies in collaboration with BIG and other large groups. Through our growing network, we have the expertise and patients, so we’re aiming for the stars!” concludes Zoppoli.
References


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Meet the experts

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The month of October is international breast cancer awareness month. In this context, on Wednesday 14 October, the European Organisation for Research and Treatment of Cancer (EORTC) and the Breast International Group (BIG) organised a webinar on breast cancer addressed to the general public.

The purpose of the webinar, which counted 169 participants, was to raise awareness about breast cancer and the importance of international academic research.

The main topic of the session focused on the growing importance of treatment de-escalation to improve breast cancer patients’ quality of life by avoiding unnecessary overtreatment. Breast cancer experts from the EORTC and BIG networks gave examples of de-escalation clinical trials and explained how they may help breast cancer patients by safely reducing treatment burden. A patient advocate from Europa Donna also gave her perspective on this topic.
The session included the following presentations:

- **Brief introduction on global breast cancer research and de-escalation of breast cancer treatments** – By Prof. Etienne Brain, EORTC Breast Cancer Group Chair & BIG Executive Board member (Brussels, Belgium)

- **Brief presentation of DESCRESCENDO study and introduction of the speakers** – By Prof. David Cameron, BIG Chair and EORTC Breast Cancer Group member (Edinburgh, UK)

- **Tailoring radio therapy after surgery to an individual patient’s risk of recurrence (EXPERT study – BIG Radio Tuning). Tailoring radiation dose escalation after surgery: cosmetic results and patient reported outcomes informing treatment decision-making (DCIS study)** – By Prof. Boon Chua, BIG Executive Board member & Study Principal Investigator of EXPERT and DCIS (Sydney, Australia)

- **Using the biological characteristics of a tumour and novel diagnostic tests to help safely exclude chemotherapy (MINDACT study)** – By Prof. Fatima Cardoso, EORTC Breast Cancer Group and BIG member & Study Principal Investigator of MINDACT (Lisbon, Portugal)

- **Getting the patient’s perspective: Importance of giving patients the right information about de-escalation risks** – By Ms Elizabeth Bergsten Nordstrom, EUROPA DONNA Executive Board member (Stockholm, Sweden)

During the session, participants – who were a mix of breast cancer patients, advocates, family members, students, researchers and breast cancer specialists – were also invited to ask the speakers any questions they had, allowing for a true learning and sharing experience.

David Cameron’s interview for UK’s Breast Health Campaign (*The Guardian*)

As part of a large Breast Health awareness campaign organised in the UK, an article on BIG was published in *The Guardian* newspaper and online on Monday 28 September. The article was based on an interview with BIG’s Chair, Prof David Cameron and focused on “Rethinking breast cancer research and funding”.

The goal of this campaign, which also took place during the Breast Cancer Awareness Month, was to raise awareness of breast cancer signs and symptoms and to showcase innovations in breast cancer research, screening, testing, and treatment.

https://www.healthawareness.co.uk/breast-health/rethinking-breast-cancer-research-and-funding/
First virtual BIG Scientific Meeting

Bi-annual BIG Scientific Meetings usually take place during major cancer conferences, such as ESMO, EBCC or St Gallen, where most of BIG member group representatives get the opportunity to meet in person. Due to the COVID-19 pandemic, BIG’s Scientific Meeting 2020 was moved to a virtual format and took place on 30 September, just before EBCC-12. This first virtual meeting was attended by 123 BIG group representatives and experts. It proved to be very interactive, with lots of exchanges and about 10 new clinical trials and research projects presented.

Dr Martine Piccart received the 2020 Giants of Cancer Care® Award

On 5 November, during a virtual ceremony, Dr Martine Piccart, co-Founder and immediate Past Chair of BIG, was honored with the 2020 Giants of Cancer Care® Award for Breast Cancer for her contribution to advancing breast cancer research and the crucial impact she has had in oncology.

The Giants of Cancer Care® recognition programme honours researchers and scientists who have realised groundbreaking achievements in the global field of oncology.
Due to the COVID-19 pandemic and related public health measures, we at BIG against breast cancer, BIG’s philanthropic unit, had to cancel all of our usual events and activities planned for 2020, such as the annual gala and Pink is the New Black dancing dinner, both traditionally held in October. We had to re-invent how to reach BIG’s community of supporters.

24 June to 31 July
Move for BIG Research virtual challenge

Together against metastatic breast cancer!
Organised at the height of the lockdown in Belgium, during this first ever BIG virtual challenge, our community was invited to run, walk, garden, do yoga and cycle at home, all with the goal of reaching 28,800 steps each.

In just 26 days, 38 participants reached a total of 2,100 km altogether!

Months of September & October
“1 note, 1 donation” crowdfunding campaign in collaboration with Fanny Leeb

4,860 notes, for one song of hope for women and men with breast cancer.

From September till the end of October, a crowdfunding campaign was launched in collaboration with French singer Fanny Leeb.

For each donation of 11 euros, a note of her song “Show them how it goes”, which she specifically produced for BIG, was revealed.

In total, €9,513 was raised via social media and e-newsletters.

About Fanny Leeb and her most recent album called The Awakening.

For several months in 2018, Fanny Leeb led a fierce fight against breast cancer. She was able to turn her illness into a real strength, and this daily battle against her illness inspired her album “The Awakening”, composed with the help of her friend Keni Arifi and her brother Tom Leeb, and produced by Remark records (Vanessa Paradis, Raphaël, Christine and the Queens ...). She decided to expose herself without taboo, to try with humility to be the voice of all those who are fighting the disease and to speak about it openly and without fear within her networks and in the media.

11 songs that express her full sincerity about the perils of love or sickness.

“The Awakening” is her tribute to life.
Conference “Toi cancer, ce que tu m'as pris, ce que tu m'as donné – Bienvenue à bord de ma montagne russe émotionnelle, attachez vos ceintures, ça monte et ça descend !”

(You, cancer, what you took from me, what you gave me – Welcome aboard my emotional rollercoaster, buckle your seatbelt, we’ll be going up and down.)

On 28 September, during a conference attended by 100 people, Delphine Remy gave a talk about her journey from being diagnosed with breast cancer, through treatment, and now in remission. During her treatment, Delphine wrote a blog (cancer-je-gere.blog) chronicling this chapter of her life, which she then turned into a book titled “Cancer? Je gère!” (Cancer? I’ve got this!). Dr Martine Piccart, who wrote the preface of Delphine’s book, gave a brief introduction during the conference. The event concluded with a question and answer session, where participants could ask questions to both Delphine and Dr Piccart.

Delphine Remy has pledged to give the proceeds from the copyright sales of her book to support BIG’s research against breast cancer. It may be purchased via Amazon, or in bookstores in Belgium, France, Quebec, Switzerland and Luxembourg.
BIG trial updates

**AURORA (BIG 14-01)**
Target recruitment reached with 1,000 patients enrolled

Last August, BIG’s landmark programme AURORA, also known as the Metastatic Breast Cancer GPS, had enrolled 1,000 patients, an important milestone for this international academic study aiming to unlock the biology of metastatic breast cancer. This milestone was made possible through the efforts of researchers and patients from 11 European countries, 10 BIG groups and 66 hospitals and cancer centres. An ambitious plan to include up to 1,000 additional patients is now underway.

The analysis of the first 381 patients included in AURORA demonstrated important genetic differences between the primary and metastatic tumours. Moreover, these analyses identified tumour characteristics associated with the length of time between first diagnosis and disease recurrence, and characteristics associated with how long patients live with their disease. The analysis of the full cohort of patients will be essential to validate the first results obtained and to study rare subtypes of breast cancer.

From the first 1,000 patients enrolled in AURORA, the programme will have collected some 30,000 blood and tumour samples as well as large amounts of clinical and genomic data. Those will be available to experts to improve our understanding of metastatic breast cancer.

By comparing the molecular landscape of metastatic tumour samples with their counterparts from primary tumours, and by correlating this with molecular analyses carried out in prospectively collected serum and plasma samples, AURORA offers a unique opportunity to generate robust findings that will shed light on the evolution of metastatic breast cancer – the leading cancer-related cause of death among women worldwide.

Because of the great interest from around the globe in AURORA's very rich and unique data, BIG plans to extend the study to recruit an additional 1,000 women and men, if enough funding can be secured.

The AURORA programme is being led by BIG in collaboration with the Clinical Trials Support Unit of the Jules Bordet Institute (JJB-CTSU) and the Frontier Science Technology & Research Foundation. It is a purely academic programme made possible by generous grants from the Breast Cancer Research Foundation®, Fondation Cancer (Luxembourg), the National Lottery (Belgium), NIF Foundation, Barrie and Deena Webb, Think Pink Belgium (SMART Fund) and individual donors.
The BIG-NABCG collaboration developed a road map to improve the design and implementation of future de-escalation trials of systemic adjuvant therapy. Integrating insights from patients and expert statisticians in the road map, the aim is to obtain robust, practice-changing, and patient-centered results in future de-escalation trials. This opinion paper was published in the *Journal of Clinical Oncology* in early October. The work was funded by the Breast Cancer Research Foundation (BCRF), which also supports the annual meetings between BIG and its counterpart the North American Breast Cancer Group (NABCG).

This important paper is the result of the 2019 BIG-NABCG annual meeting, during which experts focused on treatment de-escalation in clinical trials, tackling various topics including the psychological aspects confronted by patients, the statistical design of such trials, the rationale behind the reduction of loco-regional and other adjuvant chemo or endocrine therapies, and the type of biomarkers that can be used as tools to facilitate de-escalation.

A representative group of patients from Europe and North America was invited to participate in the meeting to discuss their own experiences and express their thoughts about de-escalation clinical trials.

The authors of the paper unanimously observed that, while efforts are being made to de-escalate systemic adjuvant therapy in selected cancer patients, in order to improve quality of life and benefit health economics, only a few of the de-escalation trials conducted in the past have provided clear answers. Some of these trials suffered from poor accrual or had study designs that led to conflicting results. To move research forward, it is essential to understand the lessons from these trials and listen more carefully to the patient voice, which is essential in designing new de-escalation trials.

This consensus paper presents considerations for the development of de-escalation trials with systemic adjuvant treatment including non-inferiority trial design, choice of endpoints and prioritisation of patient’s perspectives. It is a useful tool to help investigators conduct de-escalation trials with robust, practice-changing, and truly patient-centred results.

Reference:
The second interim analysis results of PALLAS indicated that the addition of palbociclib to adjuvant endocrine therapy did not prolong invasive disease-free survival (iDFS) compared to endocrine therapy alone in patients with early-stage hormone receptor-positive (HR+), HER2-negative breast cancer. No new toxicities were observed in patients receiving adjuvant palbociclib compared with the metastatic breast cancer setting, where it has proven to be effective. Based on the Independent Data Monitoring Committee’s recommendation, the Steering Committee decided that patients still on active therapy should stop palbociclib and move to the long-term follow-up as planned in the study protocol.

An official press release was issued by all study partners last May and the results were publicly presented by one of the Principal Investigators, Dr Erica Mayer, during ESMO’s virtual conference 2020.

Although the analyses showed no effect on iDFS, the PALLAS trial contributes to our better understanding of CDK4/6 inhibition, of the use of palbociclib, and the treatment of patients diagnosed with HR+ HER2- early breast cancer. Moreover, the study provides scientists with a rich collection of samples (almost 6,000 tumour blocks and 10,000 blood samples) for future translational research projects.

Co-led by the Austrian Breast & Colorectal Cancer Study Group (ABCSG), Alliance for Clinical Trials in Oncology Foundation and BIG Headquarters, PALLAS started in September 2015 and reached its target accrual of 5,795 patients in November 2018. It represents a great example of global collaboration between academia and industry, involving 21 countries and 409 sites worldwide, to run a huge pivotal clinical trial and answer important questions about breast cancer management. This was possible thanks to the patients and to the dedication and tremendous efforts of all study partners as well as their affiliated sites worldwide.

NeoALTTO (BIG 1-06)
Nine-year survival results available
Presented by Dr Paolo Nuciforo

On Saturday 3 October Dr Paolo Nuciforo presented the nine-year event free survival (EFS) and overall survival (OS) rates of the NeoALTTO trial, with a highlight on the relationship between survival and pathological complete response (pCR) in the overall population and according to hormonal receptor status and treatment arm.

This long-term analysis, based on a median follow up of 9.7 years, showed that women who achieved pCR have significantly higher survival rates (EFS and OS) compared to those who did not. It confirms that pCR is likely an indicator of long-term benefit in HER2-positive breast cancer. This trend is more important in patients whose disease is hormone receptor-negative and in the population receiving the combination of lapatinib and trastuzumab. In the overall population, the survival rates by treatment arm did not differ significantly; however, patients who reached a pCR in the combination arm were nearly double compared to patients in the single drug arms. The analysis did not report any new or long-term safety concerns.

Developed in parallel with its sister trial ALTTO (BIG 2-06), the NeoALTTO study included 455 patients and was set up to investigate whether combining trastuzumab (Herceptin®) with another drug called lapatinib (Tykerb®) – given either alone, together or one after the other – could benefit patients with HER2-positive primary breast cancer in the neoadjuvant (pre-surgical) setting. To our knowledge, NeoALTTO is the neoadjuvant study with dual HER2 blockade in early breast cancer with the longest clinical follow-up (almost 10 years).

NeoALTTO is a study co-led by SOLTI Breast Cancer Group, BIG Headquarters, Institut Jules Bordet’s Clinical Trials Support Unit (IJB-CTSU) and Frontier Science & Technology Research Foundation (FSTRF). The primary analysis, published in The Lancet in 2012, showed that dual HER2-targeted therapy with lapatinib and trastuzumab resulted in more patients achieving a pCR, meaning a disappearance of all visible signs of cancer, compared to a single HER2-targeted therapy (trastuzumab).

For this exploratory subgroup analysis from the large MINDACT study, researchers investigated the clinical utility of the MammaPrint® genomic test (the 70-gene prognosis signature) in patients diagnosed with early-stage invasive lobular carcinoma (ILC), a patient population for which the decision-making around chemotherapy treatment remains controversial.

In MINDACT, patients were categorised into risk groups based on MammaPrint for genomic risk (g-risk) and modified Adjuvant!Online for clinical risk (c-risk). Those with c-low/g-low risk were spared chemotherapy, while those with c-high/g-high risk received the treatment. Discordant cases were randomised to receive CT based on the c- or g-risk.

Among the 6,693 women with early-stage breast cancer enrolled in MINDACT, 5,313 patients were included in this sub analysis and centrally classified as ILC (n=487, including 255 classic ILC and 232 non-classic ILC variants) or invasive ductal carcinoma (IDC) (n=4826).

They observed that, compared to IDC, ILC were associated with larger tumour size, and were more often of histologic grade 2. Furthermore, ILC and IDC had a similar distribution of c-risk, while 16% of ILC were high g-risk, with unfavourable survival outcomes. 38% of patients with ILC were classified as c-high/g-low risk. Higher rates of gH were observed in non-classic ILC variants than in classic ILC. Distant metastasis-free survival (DMFS) and overall survival (OS) estimates were similar for ILC and IDC classified as either low or high-g-risk.

**Based on their analysis, researchers concluded that MammaPrint also has prognostic value in ILC and may be a clinically useful tool for adjuvant treatment decision-making in ILC.**

Coordinated and sponsored by the European Organisation for Research and Treatment of Cancer (EORTC) in collaboration with BIG Headquarters, the MINDACT study delivered its main results in 2016 (published in the *New England Journal of Medicine*). The study proved that using MammaPrint in combination with clinico-pathological assessment could identify patients who might safely avoid chemotherapy, thereby substantially reducing the prescription of chemotherapy in patients with node-negative and 1-to-3 node positive breast cancer.
For the Austrian Breast and Colorectal Cancer Study Group (ABCSG), the implications of the pandemic are impacting daily operations as well as strategic scenarios. Professor Michael Gnant, President of the ABCSG, describes challenges, opportunities and lessons learned in recent months.

The last six months have been a great challenge for clinical routine and study groups. How does the COVID-19 pandemic affect clinicians, and the study landscape? What are the learnings for ABCSG so far?

Professor Gnant: “The pandemic has hit us unexpectedly, as everybody else. Probably the biggest challenge for clinicians in late winter and spring of 2020 was the uncertainty about how dramatic the impact on our health care systems would be. As everybody else in Europe, I was greatly moved and concerned after the alarming reports from our brave colleagues in Northern Italy came in. Some countries suffered more than others (in terms of health care capacity), and obviously the reaction (times) by political leaders was difficult. Personally, I would have hoped for a bit more unity and solidarity between EU countries and globally, but obviously politics is not yet as mature as we have developed in international research collaboration. While hospital capacities were blocked by and / or for COVID-19 patients, “non-essential” patient visits were postponed in many environments, which clearly affected clinical trials. However, with a lot of spirit and dedication, the study teams were able to maintain “damage control”, also supported by regulators and ethics committees, who helped in conquering the extraordinary situation.”

The PALLAS trial (Palbociclib Collaborative Adjuvant Study; ABCSG 42 / BIG 14-03) second interim analysis in early summer this year did not show a likely statistically significant improvement in the primary endpoint of invasive disease-free survival (iDFS) as the predefined futility boundary was crossed. What does the future of PALLAS look like?

Professor Gnant: “We have become used to “positive” clinical trial results, and therefore clearly the fact that PALLAS is unlikely to demonstrate a significant benefit of adjuvant palbociclib was disappointing for all of us. However, sometimes we learn more from scientific disappointment than from success – I am personally convinced that this will also be the case here. After presentation and publication of the interim results, we will intensify our (translational) research efforts in the years to come. Remember, PALLAS is a great global research collaboration involving more than 400 centres in 21 countries around the world, and all of this under academic sponsorship! With the mandatory biomaterial collection, which was actually just extended to the follow-up phase to come until patients complete 10 years on the study, there will be numerous research opportunities for young people and, despite an unexpected interim result, this model of collaboration – also supported by tremendous enrolment success – will be the role model for pivotal clinical trials in the future.”

In addition to the things you have mastered in your study activities with the ABCSG, what is your personal motivation to continue clinical breast cancer studies in these difficult times?

Professor Gnant: “Clinical research multiplies the creativity and dedication of caregivers. Developing ideas, discussing improvements in diagnosis and therapy, transforming exciting new achievements into clinical practice, mentoring young people – all of this keeps me going. In the last 30 years of clinical research, we have saved thousands of lives, achieved improvements in patient quality of life through modernisation and de-escalation, de-ciphered part of the enemies’ code – and made important friendships around the globe. I am very grateful for all of that.”
Breast Cancer Trials (BCT-ANZ) presently has eight clinical trials open to participants:

- **BRCA-P** is an international breast cancer prevention clinical trial that will enrol 2,918 patients worldwide. It is open to women with a confirmed BRCA1 gene mutation who have not had a diagnosis of breast cancer. The BRCA-P study will investigate whether using denosumab is a safe and effective way of preventing breast cancer. Professor Geoffrey Lindeman is the Australian Study Chair.

- **BCT 2001** (Breast MRI Evaluation) is an Australian study that will enrol at least 400 patients. It is open to women diagnosed with breast cancer and for which the medical treatment team suggests that Magnetic Resonance Imaging (MRI) of the breast will help plan treatment. This study aims to find out whether having a breast MRI after being diagnosed with breast cancer might change plans for treating the breast cancer and how this might affect patient outcomes. Professor Christobel Saunders is the Australian Study Chair.

- **CAPTURE** is an Australian clinical trial that will enrol 140 patients. It is open to both women and men diagnosed with oestrogen receptor (ER)-positive and human epidermal growth factor receptor 2 (HER2)-negative breast cancer that has returned after treatment with a CDK4/6 inhibitor (such as ribociclib, palbociclib, abemaciclib). The CAPTURE clinical trial will investigate whether treatment with a PI3K inhibitor (alpelisib), in combination with fulvestrant, will improve outcomes for patients with metastatic breast cancer when compared with standard treatment. Professor Sarah-Jane Dawson is the Australian Study Chair.

- **DIAmOND** is an Australian clinical trial that will enrol 50 patients. It is open to both women and men diagnosed with HER2-positive metastatic breast cancer. The DIAmOND clinical trial will investigate whether the addition of two monoclonal antibodies, tremelimumab and durvalumab, to trastuzumab therapy will improve outcomes for patients with metastatic breast cancer. Professor Sherene Loi is the Australian Study Chair.

- **EXPERT** is an international clinical trial, led by BCT-ANZ in partnership with BIG, which will enrol 1,170 patients worldwide. It is open to women aged 50 years or older, with hormone receptor (HR)-positive, HER2-negative, early stage breast cancer. EXPERT will use a genomic test of breast cancer tissue to select women who can safely avoid radiation therapy. The trial aims to improve personalised use of radiation therapy in early breast cancer patients, according to individual risk of local recurrence. EXPERT will be opened in BIG groups with centres in Ireland, Spain, Italy, Switzerland, Argentina and Chile and Taiwan will participate as an independent group. Professor Boon Chua is the Australian Study Chair and Dr Gunther Gruber is the international Co-Chair.

- **Neo-N** is an international clinical trial that will enrol up to 108 patients worldwide. It is open to both women and men diagnosed with unilateral triple negative early breast cancer. The Neo-N clinical trial will investigate whether using an immunotherapy drug alone prior to the combination of immunotherapy and standard chemotherapy is safe and effective in treating breast cancer before surgery. Professor Sherene Loi is the Australian Study Chair.

- **PATINA** is an international clinical trial that will enrol 496 patients worldwide. It is open to both women and men diagnosed with HR-positive, HER2-positive metastatic breast cancer. The PATINA clinical trial will investigate whether the addition of palbociclib to first-line treatment of HER2-positive breast cancer will delay the onset of therapeutic resistance and prolong survival. Associate Professor Elgene Lim is the Australian Study Chair.

- **POSNOC** is an international trial that will enrol 1,900 women worldwide, the aim of which is to find out whether further axillary treatment is of benefit in women with macrometastases found in one or two lymph nodes. Professor Bruce Mann is the Australian Study Chair.
Discretionary Funding Project Results

Full Members of BCT-ANZ are eligible for discretionary funding support to develop collaborative, high quality research projects and clinical trials that aim to find new and better treatments and prevention strategies for breast cancer. Recent results of discretionary funding projects include the following, led respectively by Associate Professor Elgene Lim (Garvan Institute of Medical Research) and Professor Sherene Loi (Peter MacCallum Cancer Centre):

- A new proof-of-principle laboratory study has shown promising results for the treatment of ER+ breast cancers resistant to current approaches, providing support for a potential new clinical trial.

- New proof of concept research that has found that patients with metastatic breast cancer may benefit from having their genome profiled, to help identify tumours that could be treated with a targeted treatment. Called the SEGMENT study, the aim of this research was to examine the feasibility of characterising genomic alterations using a customised next generation multi-gene sequencing panel on tumour specimens obtained from patients with incurable and/or advanced breast cancer.

The Breast Cancer Trials (ANZ) Podcast

BCT-ANZ produces a podcast that features breast cancer research news, clinical trial updates, and an explanation of breast cancer related topics such as recurrence, myths, and treatment during COVID-19. You can subscribe to the podcast by searching for Breast Cancer Trials in Apple podcasts, Spotify or Google Podcasts.

BOOG

The Borstkanker Onderzoek Groep (BOOG), or Dutch Breast Cancer Research Group in English, is a collaborative study group that was founded in April 2001 with the aim of initiating, promoting, coordinating and facilitating breast cancer clinical trials. In particular, the group’s focus lies on the development and conduct of phase II and III trials.

BOOG conducts national as well as international (BIG, EORTC, GBG, IBCSG) breast cancer trials relevant for the current state of the Dutch healthcare system on a broad basis in the Netherlands. BOOG has acquired a good reputation among many Dutch scientific researchers and supporters. Each hospital in the Netherlands is participating in at least one BOOG study, and over 70 clinical institutions and 500 investigators are working to facilitate the entry of their patients into an appropriate BOOG trial.

Founded in 2001, over 28,600 Dutch patients have participated in the group’s clinical trials over the last 20 years. This is an impressive number, considering the annual incidence of newly diagnosed breast cancer patients in The Netherlands.

The SONIA trial

The SONIA trial is a unique trial concept selecting the optimal position of CDK4/6 inhibitors in HR+, HER2-negative advanced breast cancer.

Cyclin dependent kinase 4 and 6 (CDK4/6) inhibitors are a valuable addition to the treatment armamentarium of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer. CDK4/6 inhibitors can be used in the first- or second-line treatment, but it is currently unknown which strategy is preferable in terms of clinical outcome and/or quality of life.

The SONIA study (BOOG 2017-03) is an investigator-initiated, randomised controlled trial involving 73 Dutch hospitals. BOOG is the sponsor of the study, which is registered in the European Clinical Trials Database (2015-000617-43) and ClinicalTrials.gov (NCT03425838). Funding is provided by the Netherlands Organization for Health Research and Development (ZonMw) and Health insurers Netherlands (ZN).

Patient participation

The Dutch Breast Cancer Society (BVN) represents Dutch breast cancer patients and supports the SONIA study. BVN was involved in the trial design and collaborates with the study team every step of the way. BVN feels it is important to investigate at which time point patients benefit the most from the addition of new drugs. In this respect, efficacy is obviously important but quality of life and impact on a patient’s everyday life (able to carry out daily activities or work, etc.) are also very important parameters. Health care costs will also be taken into account.
BVN is also involved in the communications about the SONIA study. The patient information sheet and informed consent form was reviewed by patient advocates and a video was developed (available in Dutch), providing additional study information, such as its goal, design and execution, which are explained by the three principal investigators. In addition, a representative of BVN and a participating patient express their opinion about the study.

**Design and status**

The SONIA study is designed for women with advanced, hormone receptor-positive breast cancer who will start palliative endocrine therapy\(^2\). A total of 1,050 patients will be randomised to receive a CDK4/6 inhibitor in either first- or second-line. The primary endpoint is progression-free survival after two lines (PFS2), with quality of life and overall survival as important secondary endpoints. The figure below depicts a schematic study overview.

The SONIA study opened in November 2017 and the site initiation and inclusion of patients went very well, with 73 of the 74 Dutch hospitals participating! As of 14 September 2020, we have accrued 793 patients. All three CDK4/6 inhibitors (abemaciclib, palbociclib and ribociclib) are available for use in the study.

In August 2020, the pre-planned interim analysis was performed. This analysis was designed to check for protocol compliance in terms of switch from first- to second-line treatment; if too many patients receive a different second-line treatment than the one defined in the SONIA protocol, this will devalue the results. We are pleased to announce that the Data Safety Monitoring Board (DSMB) unanimously decided to continue accrual in SONIA based on the interim analysis results.

**Side studies**

To answer other relevant questions about the use of CDK4/6-inhibitors, several side studies have been set up. These are optional: patients who do not want to participate can still enroll in the main study. The side studies being conducted are analysing circulating tumour DNA, pharmacodynamics and – genetics, extra imaging and cognitive testing.

We hope to finish accrual in spring 2021, and our first results are expected beginning of 2023.

**References:**


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**CCTG**

The current trial activity of the Canadian Cancer Trials Group (CCTG) (www.ctg.queensu.ca) is focused on ensuring the continued development and safe conduct of cancer clinical trials during the COVID-19 pandemic in addition to the activation of new trials aimed at improving outcomes in patients with cancer.

Three COVID-19 trials which allow enrolment of patients with breast cancer are:

- CCTG IC.8: COV-IMMUNO – a Randomised, Phase III Trial of Immunisation with IMM-101 versus Observation for the Prevention of Severe Respiratory and COVID-19 Related Infections in Cancer Patients at Increased Risk of Exposure (NCT04442048)
- CCTG ICC.1: NCI COVID-19 in Cancer Patients Study (N-CCaPS) – a Longitudinal Natural History Study (NCT04387656)

Our Breast Disease Site Committee has remained very active under the leadership of Co-Chairs Drs Stephen Chia (Medical Oncology) and Eileen Rakovitch (Radiation Oncology), Senior Investigators Drs Wendy Parulekar and Lois Shepherd, and Study Coordinator Cathy Davidson. Dr Philippe Bedard, a current member of BIG’s Executive Board, also functions as the Investigational New Drugs Liaison for the Breast Committee and is an engaged member of the investigator network.

The CCTG portfolio of breast cancer trials is extensive and spans early phase trials testing novel therapies to practice-changing phase III trials. Important research themes in our trial portfolio include biomarker identification for prognostication and prediction of response to anticancer therapy, de-escalation of therapy to reduce toxicity and improved QOL for patients with low risk breast cancer, incorporation of tissue collection and biobanking for integral and integrated biomarker studies, and inclusion of patient reported outcomes and economic analyses for all late phase trials led by CCTG.
CCTG MA.32 (BIG 5-11): a phase III randomised trial of metformin versus placebo on recurrence and survival in early stage breast cancer (NCT01101438). Dr Pamela Goodwin is the Study Chair.

This CCTG-led trial under the BIG umbrella (as a supporter trial) enrolled 3,694 patients with early stage high-risk breast cancer from August 2010 to March 2013 with participation from the Alliance, ECOG-ACRIN, NRG, SWOG, IBCSG and NCRI-BCSG - ICR-CTSU. The protocol defined final primary analysis will compare invasive disease-free survival (IDFS) between the metformin and placebo arms in the receptor-positive cohort and is planned for 2021.

CCTG MA.39: TAILOR RT: a randomised trial of regional radiotherapy in biomarker low-risk node positive breast cancer (NCT03488693). Dr Tim Whelan is the Study Chair.

This CCTG-led, international multi-centre, randomised, non-inferiority phase III trial evaluates the impact of omission of regional radiotherapy (RT) in patients with oestrogen receptor-positive (ER), HER-2 negative biomarker low-risk breast cancer defined by Oncotype DX recurrence score and nodal tumour burden. The trial is currently active across North America with participation from Alliance, ECOG-ACRIN, NRG and SWOG. Discussions are underway regarding participation of international centres that meet the requirements of participation in a CTEP (Cancer Therapy Evaluation Programme) sponsored trial.

CCTG MA.40: a double-blind placebo controlled randomised phase III trial of fulvestrant and ipatasertib as treatment for advanced HER-2 negative and oestrogen receptor-positive (ER+) breast cancer following progression on first line CDK 4/6 inhibitor and aromatase inhibitor (FINER). Dr Stephen Chia is the Study Chair.

This CCTG phase III trial is slated to open in the last quarter of 2020 and represents a collaboration with the Breast Cancer Trials Group (Australia/New Zealand) and Hoffmann-La Roche Ltd. The primary objective of this trial is to compare progression-free survival (PFS) in patients with ER-positive, HER2-negative advanced breast cancer treated with ipatasertib and fulvestrant versus placebo and fulvestrant after progression on first-line CDK 4/6 inhibitor plus AI treatment.

DECRESCEND: de-escalation of adjuvant chemotherapy in HER2-positive, oestrogen receptor-negative, node-negative early breast cancer subjects who achieved pathological complete response after neoadjuvant chemotherapy and dual HER2-blockade. Dr Martine Piccart is the global Principal Investigator and Dr Philippe Bedard is the CCTG Study Chair. This is a BIG-led multicentre, open label, dual phase, single arm, phase II trial that evaluates the treatment of HER2-positive/ER-negative/node-negative early breast cancer. The primary objective of the trial is to evaluate 3-year RFS in patients with HER2-enriched, ER-negative, node-negative breast cancers who achieve a pCR after neoadjuvant treatment with weekly paclitaxel (or docetaxel every 3 weeks) and dual HER2-blockade with pertuzumab and trastuzumab fixed dose combination given subcutaneously. The trial has been officially endorsed by CCTG to move forward within the investigator network.

CCTG remains committed to the conduct of high impact clinical trials in breast cancer that are made possible by international research collaborations.

**DBC&G & SweBCG**

**Neoadjuvant MASTER and NordicTrip to be launched**

**The MASTER study (MAmnary cancer STatin ER positive study)**

The MASTER study is a randomised, multicentre, double-blind, placebo-controlled comparison of standard (neo)adjuvant therapy plus placebo versus standard (neo)adjuvant therapy plus atorvastatin in patients with early breast cancer.

Cholesterol-lowering drugs such as statins are currently used to lower cholesterol levels and prevent cardiovascular events. Statins have, however, received substantial scientific attention as cancer-inhibiting drugs. Previous findings were recently supported in a large-scaled study within the BIG-98 trial, again demonstrating the beneficial effects of statins on breast cancer outcome - this time nested within a large, international, randomised clinical trial of modern adjuvant cancer therapy. Given the compelling evidence supporting a protective effect of statins on breast cancer recurrence, calls for prospective clinical trials have been expressed. In this trial – called MASTER – we hypothesise that the addition of statin treatment to the current breast cancer treatment will improve the prognosis of women with early breast cancer. Thus, the primary objective of MASTER is to determine the clinical efficacy of the statin atorvastatin, as measured by invasive disease-free survival among patients with primary breast cancer.

The trial is nationwide throughout Denmark and a total of 3,360 women are to be included. Women eligible for the trial have been diagnosed with an oestrogen receptor-positive breast cancer and are candidates for systemic cancer therapy, either prior to or following breast surgery. Upon eligibility confirmation and signed informed consent, trial participants will be randomised in a 1:1 manner to either standard treatment and placebo. The treatment with atorvastatin or placebo will continue for two years unless side effects are experienced and further treatment with atorvastatin or the placebo is deemed inadequate. The standard (neo)adjuvant treatment will continue as planned. The trial participants will follow the standard clinical routines in terms of follow-up, and in addition they will be asked to participate in the translational trial protocol and to fill in quality-of-life questionnaires, up to ten years following inclusion.
The study is initiated within the Danish Breast Cancer Group (DBCG) as a nationwide collaborative effort. The PI of the study is Professor Signe Borgquist (MD, PhD), Chair of the Department of Oncology, Aarhus University Hospital, Denmark. The study is gratefully supported by the Novo Nordisk Foundation. For further information, please contact signe.borgquist@auh.rm.dk

The Nordic Trip trial

NordicTrip is a randomised controlled trial exploring the effect of adding oral capecitabine to platinum-based preoperative chemotherapy in ER- and HER2-negative breast cancer stage 2 to 3.

The primary endpoint of the study is pCR rate at time of radical surgery, and secondary endpoints include IDFS, DFS and OS. The primary translational outcome is to describe the pCR rate in the different study arms, stratified for homologous repair deficiency status of the primary tumour. The inclusion goal is 820 randomised patients.

The study has been initiated within the Swedish Breast Cancer Group (SweBCG) and the Association of Swedish Breast Oncologists (BOF). It is being run as a collaborative effort with the national breast cancer groups of Sweden, Denmark, Iceland and Finland. The Principal Investigator of the study is Dr Niklas Loman MD, PhD at the department of Hematology, Oncology and Radiation Physics at Skåne University Hospital, Sweden. The study has received support from The Swedish Research Council, Nordic Cancer Union, Mrs Bertha Kamprad’s Foundation, Region Skåne and Bröstcancerförbundet.

For further information, please contact Niklas.Loman@med.lu.se

Fondazione MICHELANGELO

Fondazione Michelangelo per l’Avanzamento dello Studio e della Cura dei Tumori is a non-profit research organisation that was formally established in December 1999. It has its headquarters in Milano and promotes innovation in oncology treatments by designing, proposing and conducting clinical trials in several disease areas, including breast. Fondazione Michelangelo has always been very active in the area of neoadjuvant trials in breast cancer, such as the NOAH study – the only neoadjuvant trial that directly compared standard chemotherapy with chemotherapy and trastuzumab in women with HER2+ locally advanced breast cancer – and the NeoSphere trial, which compared the benefit of dual HER2 blockade with trastuzumab and pertuzumab with or without docetaxel with the therapeutic effect of conventional trastuzumab and docetaxel. These two trials have been the basis for label indications of neoadjuvant trastuzumab and of the dual blockade with trastuzumab and pertuzumab.

In 2013, Fondazione Michelangelo promoted a phase III, international multicentre study in collaboration with GEICAM (the Spanish Breast Cancer Group), and BCRC-WA (Breast Cancer Research Centre Western Australia). The study, known as ETNA (Evaluating Treatment with Neoadjuvant Abraxane), aimed at comparing the rate of pathologic complete response (pCR) for abraxane versus paclitaxel given for 4 cycles and followed by an anthracycline-containing regimen for 4 cycles before surgery in patients with early or locally advanced HER2-negative breast cancer. The improved rate of pCR after abraxane failed to reach statistical significance. The multivariate analysis revealed that tumour subtype (triple negative versus luminal B-like) was the most significant factor (odds ratio 4.85) influencing treatment outcome. Extensive collection and banking of tumour and blood was done, and translational studies are in progress and will provide clues for factors that can be of greater predictive value of tumour response.
In 2015, a neoadjuvant exploratory Phase II trial (NA-PHER2) was activated in 7 Italian centres to study changes of Ki67 from baseline before therapy, at 2 weeks and at surgery. Eligible patients had invasive unilateral non-metastatic ER-positive breast cancer overexpressing HER2 and had to be suitable for neoadjuvant therapy. They were treated every 3 weeks with trastuzumab and pertuzumab for 6 cycles combined with palbociclib 125 mg po q.d. x 21 q. 4 weeks and fulvestrant i.m. 500 mg, both given for 5 cycles. The evidence collected in the study supports previously available evidence by showing a profound effect of the concomitant block of ER, HER2 and Rb with the combination of trastuzumab and pertuzumab, fulvestrant, and palbociclib on Ki67 at 2 weeks and at surgery after 16 weeks of therapy. The effect is major, rapid and more profound at week 2 than at surgery, and is linked to good therapeutic activity, including pCR produced by this chemotherapy-free regimen. The findings of the initial cohort of cases were published in Lancet Oncology in 2018. Two additional cohorts of patients have been enrolled. In HER2+ cases the combination was used without administration of fulvestrant to explore whether an ER-directed therapy is needed in cases of triple-positive breast cancer. In addition, the possibility that concomitant targeting of ER, HER2 and Rb can produce favourable results was tested in cases of “luminal B”-like tumours characterised by HER2 1+/2+ non amplified; ER+, PgR+ and Ki67 >20%. The study’s completed findings have been submitted for publication.

In 2017, Fondazione Michelangelo launched a new neoadjuvant study in patients with early or locally advanced triple negative breast cancer (NeoTRIPaPDL1 - Neoadjuvant therapy in TRIPle negative breast cancer with antiPDL1), in which event-free survival after 8 cycles of carboplatin and abraxane with and without atezolizumab is the primary aim of the trial. All randomised patients completed the neoadjuvant part of the study. The addition of atezolizumab to carboplatin and abraxane did not significantly increase the rate of pCR in women with TNBC. Molecular studies of tumours at baseline, after 1 month of therapy, and in surgical samples are ongoing together with continuous follow up for efficacy end points.

Early 2018, a new neoadjuvant study (APTneo - Atezolizumab, Pertuzumab and Trastuzumab with chemotherapy as neoadjuvant treatment of HER2 positive early high-risk and locally advanced breast cancer) was activated. The primary aim is to compare the 5-year event-free survival in patients receiving trastuzumab, pertuzumab, carboplatin and paclitaxel with or without atezolizumab. In the study there is also a test of the potential benefit of anthracyclines owing to their well-established effects of favourable immune modulation.

Over the years, and especially since the conduct of NeoSphere, Fondazione Michelangelo has established that all patients participating in the group’s trials should be asked to contribute tissue and blood samples to Michelangelo’s bio-bank in order for translational ancillary studies, in search of prognostic and predictive biomarkers, to be conducted.
Two study concepts are currently being set up:

- The phase II APPALACHES (GBG 100, EORTC 1745 ETF-BCG) study that is run under the BIG umbrella and under the leadership of the EORTC Breast Cancer Group is evaluating adjuvant palbociclib as an alternative to chemotherapy in elderly patients with high-risk ER+/HER2- early breast cancer.

- The phase III TAXIS (GBG 101; SAKK 23/16/IBCSG 57-18/ABCSG-53) study, a collaboration led by the Swiss Group for Clinical Cancer Research (SAKK), is investigating the value of tailored axillary surgery, a new technique that aims at selectively removing the positive lymph nodes either before any systemic treatment or after neoadjuvant systemic treatment.

Final analysis of the international GBG-led Penelope-B study (GBG 78 / BIG 01-13), a study under the BIG umbrella, is currently ongoing and results will be presented at SABCS 2020. The phase III study is evaluating the addition of the CDK4/6 inhibitor palbociclib as post-neoadjuvant treatment for HER2-negative, hormone receptor-positive patients with high relapse risk after neoadjuvant chemotherapy. The results are eagerly awaited considering that the second interim analysis of the PALLAS study, presented at the ESMO Virtual Congress 2020, showed that adjuvant palbociclib with endocrine therapy did not improve iDFS compared to endocrine therapy alone.

**Research insights**

Survival results of the phase III GeparOcto (GBG 84) trial were recently presented at the ESMO Virtual Congress 2020. No difference was found in invasive disease-free and overall survival following neoadjuvant chemotherapy between intense dose-dense epirubicin, paclitaxel, and cyclophosphamide, and weekly paclitaxel/liposomal doxorubicin (plus carboplatin in TNBC), in the high-risk breast cancer population. The subgroup of hormone receptor-positive, HER2-negative breast cancer, however, significantly benefitted from treatment with intense dose-dense epirubicin, paclitaxel, and cyclophosphamide, supporting the concept of effective therapy beyond pathological complete response in patients with luminal breast cancer.

The GAIN-2 (GBG 68) trial compared efficacy and safety of intense, dose-dense epirubicin, nab-paclitaxel, and cyclophosphamide (iddEnPC) versus dose-dense, dose-tailored epirubicin/cyclophosphamide followed by dose-dense, dose-tailored docetaxel (dtEC-dtD) as adjuvant or neoadjuvant chemotherapy for node-positive or high-risk node-negative early breast cancer. The safety results and interim analysis of the primary endpoint, invasive disease-free survival (iDFS), were presented at ASCO 2020 showing no new safety concerns and no difference in iDFS between arms. Results of the GAIN-2 substudy on the preference for different administration routes of trastuzumab were presented at the ESMO Breast Cancer Virtual Meeting 2020. While the subcutaneous was preferred over the intravenous regimen, there were no safety signals or differences in compliance regarding the different areas of subcutaneous injection. However, due to higher bioavailability, the thigh remained the preferred site of injection.

Results of the GeparX (GBG 88) trial had already been presented in 2019, concluding that the addition of denosumab to neoadjuvant chemotherapy did not increase the pCR rate, but weekly nab-paclitaxel compared to three-weekly did. Two analyses related to GeparX have recently been presented. A high RANK expression was associated with significantly higher pCR rates, an effect that was pronounced in patients with luminal breast cancer, as shown at the ESMO Virtual Congress 2020. However, a clinical benefit of denosumab in relation to RANK expression could not be shown. A substudy investigating a potential eradication of disseminated tumour cells (DTCs) by denosumab was presented at ASCO 2020. While DTC-eradication was observed at a higher rate after denosumab plus chemotherapy than after chemotherapy alone, the presence of DTCs at baseline or DTC-eradication after denosumab treatment did not influence pCR rates. With regard to breast cancer subtypes, a potential effect of denosumab on DTC-eradication could be observed in TNBC.

The randomised phase II clinical trial GeparOLA (GBG 90) compared a neoadjuvant olaparib/taxane treatment to neoadjuvant platinum/taxane chemotherapy in patients with a homologous recombination deficiency (HRD), HER2-negative early breast cancer. While efficacy seemed to be similar, the treatment with olaparib resulted in a more favourable toxicity profile. Additional analyses concerning germline BRCA1/2 (gBRCA1/2) and other panel genes were presented at the ESMO Virtual Congress 2020. Germline BRCA1/2 mutation status predicted therapy outcome even in patients with HRD tumours. For patients without gBRCA1/2 mutations, higher pathological complete response (pCR) rates were observed in the paclitaxel plus olaparib compared to the paclitaxel plus carboplatin arm.
A retrospective analysis including 882 patients from the GBG brain metastases in breast cancer (BMBC) (GBG 79) registry, with data available from three Graded Prognostic Assessment (GPA)-scores (original-GPA, breast-GPA and updated breast-GPA scores), was recently conducted. The results presented at the ESMO Breast Cancer Virtual Meeting 2020 revealed that several clinical parameters, as well as the GPA-scores, were significantly associated with overall survival. However, all GPA-scores show only moderate diagnostic accuracy in predicting overall survival in the cohort analysed.

A translational research project of the GeparNuevo (GBG 89) trial revealed that tumour mutational burden and immune gene expression profile add independent value for the prediction of pCR. The results were recently published in *Annals of Oncology*.

Translational research – current activities

GBG, as a longstanding expert in multicentre trials and large tumour banks with well-characterised samples, is participating in national and international translational research projects. **INTEGRATE-TN** is a grant project funded by Deutsche Krebshilfe, which started in 2019. The project aims to understand molecular mechanisms of therapy response and resistance in tumours from patients with TNBC. Therefore, organoid cultures derived from sequential tumour samples will be established to identify and analyse novel biomarkers on a single-cell level. **ONCOBIOME** is funded by the EU research framework “Horizon 2020” and is investigating the relationship between intestinal microbial signatures and the prognosis and treatment resistance in four common cancer entities (breast, colon, lung and melanoma). GBG has already implemented a stool sample collection (as an amendment to the study protocol of GeparDouze), which will be used by cooperating partners in the ONCOBIOME project for isolation of DNA and RNA for genomic and expression analyses.

**References:**

4. Fauching PA, Jackisch C, Rühm K, et al. GeparOALA: A randomized phase II trial to assess the efficacy of paclitaxel and olaparib in comparison to paclitaxel/carboplatin followed by epirubicin/cyclophosphamide as neoadjuvant chemotherapy in patients (pts) with HER2-negative early breast cancer (BC) and homologous recombination deficiency (HRD). *J Clin Oncol 2019*, 37 (suppl; abstr 506)
Spanish Breast Cancer Group (GEICAM) guidelines for COVID-19 cancer management

The COVID-19 pandemic has deeply affected Spain. Due to its suddenness and the high impact of this public health crisis, the GEICAM Steering Committee decided to develop some practical guidelines to define the most appropriate way to manage breast cancer patients during the pandemic, a limited resources situation for which there has been no precedent. The publication is available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7405405/

GEICAM/2014-12 (FLIPPER Study) at ESMO Virtual Congress 2020

The combination of palbociclib plus fulvestrant as first-line therapy in postmenopausal women with HR-positive/HER2-negative, endocrine sensitive, metastatic breast cancer increases progression-free survival.

Dr Joan Albanell, from the Hospital del Mar Barcelona and coordinator of the GEICAM Scientific Committee, presented these important results at ESMO Virtual Congress 2020: the study met the primary endpoint of a significant improvement in progression-free survival (PFS) rate at 1 year for fulvestrant plus palbociclib (83.5%) compared to fulvestrant plus placebo (71.9%) in the first-line treatment of patients with endocrine sensitive HR-positive/HER2-negative metastatic breast cancer.

These findings answer a pragmatic question in clinical practice for this hormone-sensitive, first-line population of patients with metastatic disease.

Breast Cancer and COVID-19: information for patients and professionals

During the first months of the COVID-19 pandemic, GEICAM opened a new section on its website to keep patients and professionals informed about the latest information, evidence and guidelines regarding the SARS-CoV-2 virus and its impact on breast cancer patients, research and treatment. The Group also hosted two webinars on this subject, aimed at patients and researchers, respectively.


GEICAM launches new podcast channel for patients

GEICAM T – Habla, which translates into GEICAM Speaks to You, is the new podcast channel that GEICAM has launched as a space aimed at patients, and society as a whole, containing rigorous and simple information about breast cancer and cancer research explained by experts.

Listen to the podcast here: https://geicam-t-habla.geicam.org/

GEICAM’s RegistEM project wins Spanish Cancer Patients Group award

The GEICAM RegistEM project, the first prospective registry with real data on patients with advanced breast cancer in Spain, received the first prize from the Spanish Group of Cancer Patients (GEPAC) in the category "Social and Scientific Research in Oncology" at the virtual Gala that this group of patients organised last July. The registry’s objective is to obtain information about the characteristics of metastatic breast cancer in Spain, the effectiveness of the interventions carried out in clinical practice, and the identification of areas for improvement.

GEICAM and INVI Association sign a collaboration agreement on male breast cancer research

GEICAM and the Male Breast Cancer Association (INVI – Asociación Cáncer de Mama Masculino) signed a collaboration agreement that aims to promote research on the particularities of breast tumours in men. This agreement falls in line with the roadmap established by the Group with the launch of studies such as the Male Breast Cancer Registry, which retrospectively analyses 1,000 cases diagnosed in Spain between 2000 and 2017.
From 9 until 13 November 2020, the Chilean Cooperative Group for Oncologic Research (GOCCHI), together with colleagues from SWOG (formerly South West Oncology Group), Cancer Research and Biostatistics (CRAB) and The Hope Foundation, organised an open symposium entitled “Clinical Research as a Tool for Addressing the Cancer Burden in Latin America”.

The purpose of this symposium was to provide a high-quality scientific forum focusing on the cancer burden in Latin American countries, with the aim of generating studies to address that burden.

Experts from across the Americas gathered to discuss the design, conduct, and analysis of clinical trials in oncology, as well as the infrastructure for clinical trials in the region, and opportunities and challenges to collaborative trials.

This symposium was offered as an open, no-cost conference in both English and Spanish.

For information, visit: https://es.surveymonkey.com/r/W7YM9KQ and www.gocchi.org

DOMONCOVID project: a homecare model for cancer patients during and after the COVID-19 pandemic

Cremona, a city in the Lombardy region in the north of Italy, was the Italian city with the 5th highest incidence of COVID-19. The pandemic added a significant strain on healthcare resources due to the sheer volume of patients presenting to emergency departments, often within a short space of time. It became very difficult for cancer patients to be assisted and hospitalised. COVID-19-positive (COV-19 +) cancer patients, even with mild symptoms, were hospitalised in COVID wards and completely isolated from their family members and from the treating oncologists themselves. Patients were faced with enormous stress and terror due to the risk of death in a situation of isolation and total abandonment.

In the middle of March 2019, during the crucial phase of the pandemic, we decided to create a homecare project called DOMONCOVID with the aim of avoiding hospital admissions of cancer patients and their families, by following patients with mild to moderate symptoms at home and admitting only those with severe symptoms who needed invasive respiratory support.

In agreement with the hospital management, within a few days we formed a team composed of oncologists and nurses from the Oncology Division of Cremona Hospital and supported by a secretary with a dedicated telephone number. The team worked for 6 days a week from 8 AM to 5 PM in collaboration with local operators and general practitioners. We assisted cancer patients at home with confirmed diagnosis or symptoms suggestive of COVID-19, without clear clinical or radiological criteria for hospitalisation.

The assistance was provided for residents living within a radius of 50 km from the hospital, from Monday to Saturday, 8 AM to 5 PM. Cancer patients and their cohabitants were tested with at least two nasopharyngeal swabs (NPS). Blood tests, medical examinations and vital parameters were performed. We advised all screened individuals to follow the quarantine procedures, providing them with an information leaflet. We administered oral / infusion treatments, including antiviral drugs.

From 23 March to 30 April 2020, 71 cancer patients were assisted at home, with a total of 191 visits. Of the 71 patients tested with NPS, 26 were COV-19+. Twelve COV-19+ cancer patients had mild symptoms, such as low grade fever, cough, olfactory alterations, and mild dyspnea. Seven patients showed clinical and radiological signs of initial pneumonia with stable parameters; they were successfully treated at home with hydroxychloroquine, antivirals and NSAIDs and did not require hospitalisation. Seven patients with severe symptoms...
were promptly hospitalised. Four of them died, two due to the infection and two due to disease progression. 52 cohabitants were screened with NPS, of which 28 lived with a COV-19+ cancer patient; in this subgroup, more than half (n = 16) were COV-19+ by NPS. Interestingly, most of them (n = 15) were totally asymptomatic. In Italy, NPS screening is not routinely performed, not even in cohabitants of COV-19+ patients.

This project demonstrated the feasibility of an innovative model based on homecare assistance for COV-19+ cancer patients with mild symptoms. This strategy, limiting hospital access for COV-19+ patients, might be useful to contain the spread of the infection. Further studies are needed to test this strategy in COV-19-negative cancer patients, and we are planning to implement this model of assistance in this population, who will receive oral therapy at home. Finally, our experience indicates a high probability of identifying asymptomatic COV-19+ individuals among cohabitants, and there is an urgent need to extend the screening to this population.

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Acknowledgement
This work has been supported by MEDeA OdV and the United for the Province of Cremona organisation. The DOMONCOVID Project was designed by Rodolfo Passalacqua, Director of the Oncology Department of Cremona and member of the Gruppo Oncologico Italiano di Ricerca Clinica (GOIRC), and by the oncologists Federica Negri, Margherita Ratti, Maria Bonomi, Giulia Grizzi, Bruno Perrucci, Maria Olga Giganti, Matteo Brighenti, Stefano Panni, Maddalena Donini, Benvenuto Ferrari, Alessandra Curri, and the nurses Roberta Marchi and Gianvito Donati. The results of the DOMONCOVID Project was presented by Margherita Ratti as an oral presentation at the ESMO Virtual Congress in September 2020.

HeCOG

HeCOG (Hellenic Cooperative Oncology Group) is Greece's largest oncology research group. In the field of breast cancer, the group has developed a special and steadily growing interest in both clinical and translational research. HeCOG has collected extensive biological material, including both tumour tissue and blood samples, from breast cancer patients treated in the context of HeCOG's clinical or translational research trials. Breast cancer related biospecimens have been collected and stored in HeCOG's biobank, which has been constantly enriched by new biological material over the past few years.

Reflecting this scientific interest is an increase in HeCOG publications. While in 2019, 10 articles were published on breast cancer, by August 2020 already a total of five articles had been published and by September 2020, three more had been submitted.

Recently, HeCOG conducted and published the first study in Greece, evaluating real-world data on the clinical outcome, toxicity and economic aspects of cyclin dependent kinase 4/6 (CDK 4/6) inhibitors.

It is also worth highlighting the group's significant contribution to the research of hereditary breast cancer and the effort to map the genomic landscape in Greece.

Members of HeCOG’s Breast Group have been participating regularly in European and international conferences to present the group’s work and to be informed about any scientific updates in the management and treatment of breast cancer. At the same time, they have also been involved in the organisation of several national conferences and educational events with a main interest in the biology, prevention and treatment of breast cancer.

HeCOG has also been a member of the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) and has shared data of multiple clinical trials for metanalyses published in high impact journals.

Both translational and clinical research are part of the Institute’s DNA, aiming to bring research discoveries to the patient's bedside quickly. This report reflects the spirit of commitment and collaboration of the Institute healthcare professionals, researchers and operational support teams and, above all, of the patients who trust our teams and volunteer to participate in clinical trials.

For several decades, the Institut Jules Bordet has played a particularly strong role in promoting academic research by being directly involved in the creation of prestigious international networks such as the European Organisation of Research and Treatment of Cancer (EORTC), the Breast International Group (BIG) and, more recently, the Oncodistinct Network.

The oncology landscape has changed rapidly during the last 15 to 20 years. It became important to think how the Institut Jules Bordet could continue to play a leadership role in innovations along a patient’s cancer path from diagnosis to palliative care. In the Scientific Report 2020, the Institute presents its strategic vision for research, its organisation, its research projects and achievements as well as its research support units, including the Clinical Trials Support Unit (IJB-CTSU, formally known as the BrEAST Data Centre), which is a member of BIG. The IJB-CTSU provides operational support to researchers in academia and industry in the development and conduct of phase I, II, III clinical trials. IJB-CTSU is involved in BIG studies such as HERA, (Neo)ALTTO, AURORA, APHINITY, OLYMPIA and, more recently, ALEXANDRA and DECRESCEDENDO.

Looking towards the future, a new Institut Jules Bordet is being built on the campus of the Université Libre de Bruxelles alongside other research laboratories and the general academic Erasmus Hospital. This 80,000 m² new Institut Jules Bordet, with up-to-date equipment and technologies as well as 10,000 m² for cancer research activities, will increase its capacity from 160 to 250 beds. The building is now entering the final stretch with the move planned for the end of 2021.

The new Institut Jules Bordet will offer a range of possibilities for our research teams and university or private partners, present and future, both in Belgium and abroad – all with the common aim of discovering new strategies for fighting cancer and its consequences for patients.

You can watch the video and discover the major project for the new Institut Jules Bordet (https://www.youtube.com/watch?v=fHyg8y96OZo)

Recent trials and activities

The Japanese Breast Cancer Research Group (JBCRG) is running the following clinical trials:
- JBCRG-M06 (EMERALD): a phase III clinical study to compare the combination therapy of eribulin mesylate + pertuzumab + trastuzumab with paclitaxel or docetaxel + pertuzumab + trastuzumab
- JBCRG-C07 (REIWA): an observational study to evaluate the impact of the gene panel test on treatment decision-making in breast cancer throughout Japan as a whole
- JBCRG-ABCD project: Advanced Breast Cancer Database (ABCD) project

The following recent original JBCRG papers were published:
- JBCRG-M03 in Investigational New Drugs 2020
- JBCRG-M06 in Trials 2020
- JBCRG-C05 in Breast Cancer 2020

Participation in global trials:
JBCRG is involved in the following studies run under the BIG umbrella: ALEXANDRA/IMpassio030 and OlympiA studies, POSITIVE, PenelopeB and PALLAS. For details about the trial leadership, please refer to the Trials Table on pages 46-49.
The Latin American Cooperative Oncology Group (LACOG) Breast Group aims to develop real-world data studies and clinical trials in Latin America as well as to collaborate with international intergroup studies to improve breast cancer care in the region. Currently, there are over 80 investigators from several countries in Latin America participating in LACOG breast group studies.

“2020 has been a challenge and the pandemic forced us to adapt our schedules, improve our structure and adopt home office, but now we are at the office following all the safety measures. The group has been growing rapidly and the studies motivate the investigators in Latin America to contribute with breast cancer research globally. BIG has been a key partner in this process, and we expect to strengthen our collaboration within the BIG network”, said Gustavo Werutsky, LACOG Chair.

Ongoing studies

LACOG is currently participating in the BIG trials ALEXANDRA/IMpassion 030 (BIG 16-05) and PALLAS (BIG 14-03), which had its first results presented at ESMO Virtual Congress 2020.

LACOG is conducting the LATINA study (LACOG 0615), the most comprehensive breast cancer prospective registry in Latin America. The study has already included 800 of the 4,500 planned patients from 35 sites in 11 countries. “LATINA will provide for the first-time detailed information on socio-economic factors, clinical pathological data, and outcomes of breast cancer in Latin America; this study may identify gaps for optimal therapy in our continent” said Dr Gustavo Werutsky, study Principal Investigator.

In 2020, the LACOG Breast Group and the Grupo Brasileiro Estudos Câncer Mama (GBECAM) published the first results of the AMAZONA III prospective registry regarding the impact of sociodemographic factors and health insurance coverage in the diagnosis of breast cancer in Brazil. The results of the study show that patients with public health coverage were diagnosed with symptomatic disease at later stages, and with more aggressive subtypes of breast cancer than patients with private health coverage. This study brings to light important information that allows us to not only have a better understanding of tumour and patient characteristics but also to help to identify gaps within healthcare systems in Brazil.

An important and historical recent achievement of the LACOG group was the fact that for the first time an abstract of a LACOG trial was selected for oral presentation at ASCO. The results of LACOG 0415, a prostate cancer study, were presented in the Oral Abstract Session at the 2020 ASCO Annual Meeting.

Several proposals from breast investigators in Latin America are being evaluated to be developed by LACOG in the coming years.

Educational events

In collaboration with GBECAM, LACOG organises annually the Brazilian Breast Cancer Conference and the official Best of SABCS in Brazil. Both events bring together breast cancer specialists from all over the country. Another event that LACOG organises every year is the licensed Best of ASCO.

Patient advocacy collaboration is also part of the LACOG strategy to improve clinical trials awareness in Latin America. LACOG and Projeto CURA have been supported by educational events to show the benefits of cancer research and the importance of patient and societal engagement to improve access to clinical trials.

LACOG’s new visual identity

In 2020, an update of LACOG’s visual identity and communication strategy was developed to accompany the group’s latest steps in growth. The LACOG logo was updated and a specific logo for each LACOG cancer group and specialty, such as the LACOG Breast Group, was created. Additionally, LACOG launched a new website, where current information regarding studies, groups and events can be found.

More information is available at: www.lacogcancerresearch.org
The UK contribution to BIG is via partnership between NCRI Breast Research Group (NCRI-BRG) and Institute of Cancer Research - Clinical Trials & Statistics Unit (ICR-CTSU) as the two BIG member groups. The UK has contributed to numerous BIG studies, including AURORA and OLYMPIA.

A major focus of breast cancer research in the United Kingdom is centred around the risk-adaptation of treatment, and response-directed therapy, tailoring treatment to the individual in order to optimise oncological outcomes while minimising toxicities.

**High-risk breast cancer**
Consistent with international practice, the treatment paradigm in UK is for primary medical therapy to be standard of care for all patients with HER2-positive and triple negative breast cancer, when systemic anti-cancer therapy is to be used.

The NCRI-BRG has developed a platform for HER2-positive breast cancer whereby, for patients who have achieved pathological complete response (pCR), reduced treatment burden and toxicity is the goal while maintaining excellent breast cancer free survival. We have provisional approval from the Health Technology Assessment (HTA) Programme for the HER2-RADiCAL trial, which will assess the long-term efficacy and cost effectiveness of response-adapted therapy in patients with HER2-positive early breast cancer of good prognosis defined by pCR (ypT0/is ypN0) following non-anthracycline containing neoadjuvant chemotherapy and dual anti-HER2 therapy.

The HER2-PHOENIX trial: the corollary of this will be to develop a multi-arm study to test new therapies for patients for whom pCR is not achieved.

PHOENIX DDR/Anti-PD-L1 is the pioneering trial funded by CRUK of a pre-surgical window-of-opportunity, post-neoadjuvant chemotherapy and post-surgical adjuvant biomarker study of DNA damage response inhibition and/or anti-PD-L1 immunotherapy in patients with residual triple negative breast cancer that is resistant to neoadjuvant chemotherapy. Patients for whom pCR is not achieved receive novel therapies before surgery to accelerate the understanding of the biology of resistance and how to overcome this.

Standard neoadjuvant chemotherapy for breast cancer usually includes both a taxane and an anthracycline, in addition to other chemotherapeutic agents. Translational work from the UK NEAT study suggests that a combination of TOP2A and CEP17 copy number is predictive for the advantage of adding anthracyclines to adjuvant chemotherapy1. We are prospectively exploring this in the ROSCO study to determine the potential for this dual biomarker assay to select optimal neoadjuvant chemotherapy, potentially eliminating the need to expose all patients to both taxanes and anthracyclines, without loss of efficacy but reducing the risks of experiencing the toxicities to each of these agents.

Two studies in the UK portfolio will look at the feasibility of de-escalating breast and axillary surgery after neoadjuvant systemic therapy. The omission of surgery in women achieving pCR after neoadjuvant systemic therapy has been a discussion topic for decades, with historic studies demonstrating poor local control but seemingly without a survival penalty. The advent of more effective therapy, better radiology and the improved technology for non-operative sampling give hope that omission of surgery is safely achievable in some women2.
Studies to date using vacuum biopsy have not reached the accuracy required in the groups studied. **NOSTRA FEASIBILITY** is using an alternative sampling technique involving both protocol-specified tumour marking and comprehensive tumour bed sampling under ultrasound guidance after neoadjuvant therapy. This study is confined to HER2-positive, hormone receptor-negative disease where chemotherapy and dual targeted therapy achieved the highest probability of pCR. If successful, this study may provide the safety data required to proceed to a randomised study of omission of surgery where pCR is highly likely to have been achieved.

Continuing the theme of surgical de-escalation, the **ATNEC** study will examine the feasibility of de-escalating axillary surgery in patients receiving neoadjuvant systemic therapy. Patients with node-positive disease at presentation will have involved lymph nodes marked and, following neoadjuvant therapy, will undergo targeted axillary dissection. Patients who have no evidence of histopathological nodal involvement following this procedure will be randomised to either further axillary treatment (surgery or radiotherapy) or no further axillary treatment, with co-primary endpoints of axillary recurrence-free survival and lymphoedema.

**POETIC-A** is a phase III, multicentre, biomarker-stratified randomised trial for patients with ER-positive HER2-negative breast cancer. The trial has two stages: i) a screening-registration stage, where patients enriched for the subsequent eligible population will undergo two weeks of aromatase inhibitor treatment pre-surgery followed by ii) randomisation between standard endocrine therapy alone or abemaciclib with standard endocrine therapy when other standard-of-care treatment (chemotherapy, bisphosphonates, radiotherapy) are completed.

In lower risk breast cancer, NCRI BRG has developed several studies de-escalating the surgical treatment of breast cancer. The **SMALL trial** is an innovative multicentre, phase III, randomised controlled trial comparing standard surgery with minimally invasive, vacuum-assisted excision (VAE) of small, screen-detected breast cancers with favourable biological features.

Further studies in the UK portfolio also aim to adapt adjuvant therapies according to individualised assessment of patient risk. The **PRIMETIME** study is a biomarker-driven, interventional cohort study to determine the risk of local disease recurrence following omission of radiotherapy in patients with low-risk disease. Following surgery, patients over 60 with biologically favourable disease undergo risk stratification using the IHC4+C, which incorporates Ki67 into a prognostic tool utilising ER, PR and HER2 expression together with clinical features to estimate recurrence risk. In PRIMETIME, patients designated to have a very low risk of recurrence by IHC4+C will be offered the opportunity to avoid radiotherapy according to patient preference.

With respect to adjuvant chemotherapy, the **OPTIMA** study is evaluating the role of genomic assays in identifying a group of patients with high clinical risk, ER-positive, HER2-negative breast cancer, who can potentially be spared chemotherapy. In this trial, patients will be randomised to either standard-of-care chemotherapy or test-directed treatment. Patients receiving test-directed treatment using the Prosigna® assay will be allocated to endocrine therapy alone if they have a low risk of recurrence, or chemotherapy plus endocrine therapy alone if they are at high recurrence risk. OPTIMA is recruiting patients successfully in both the UK and Norway.

From the imaging and translational perspectives, research is concentrated on three areas:
- Optimisation of screening strategies
- Novel imaging technologies
- Development and application of artificial intelligence technologies.
Exploring optimisation of screening strategies Breast Screening – Risk Adaptive Imaging for Density (BRAID) is a randomised trial of imaging modalities for personalised screening of women with dense breasts, including abbreviated magnetic resonance imaging (MRI), contrast enhanced spectral mammography (CESM), and automated breast ultrasound (ABUS). The FAST MRI study aims to investigate the utility of abbreviated MRI in a screening setting. Prospective Randomized Trial of Digital Breast Tomosynthesis (DBT) Plus Standard 2D Digital Mammography (2DDM) or Synthetic 2D Digital Mammography (S 2D) Compared to Standard 2D Digital Mammography in Breast Cancer Screening (PROSPECTS) is investigating the use of DBT in screening.

With regard to novel imaging and pathological analysis PREvent ductal Carcinoma In Situ Invasive Overtreatment Now (PRECISION) is a CRUK Grand Challenge award to support an international collaboration building on multiple studies conducted in the UK, Europe, and the US over the last two decades. A range of established and innovative laboratory methods have been applied to DCIS pathology sample collections to identify and validate features distinguishing aggressive from “harmless” DCIS. PRECISION aims to establish tests to reduce the burden of unnecessary surgery, radiation and hormone-blocking therapies used in managing DCIS, reducing overtreatment without compromising the excellent outcomes for DCIS presently achieved.

The CAlicification Physicochemistry captures TUmour Remodelled Environment (CAPTURE) study has been launched, and samples of a range of breast pathologies are being analysed (imaging characteristics, microstructure, and fundamental chemistry of calcifications and adjacent tissues).

A rapidly evolving field is the development and application of artificial intelligence (AI) in medical imaging and pathology. OPTIMAM has developed technologies to build anonymised imaging databases suitable for training and testing AI products. A collaborate project with Deep Mind using artificial intelligence to analyse screening mammograms from the USA and UK resulted in a publication in Nature at the beginning of the calendar year. The OPTIMAM group has been commissioned by NHSx to evaluate some AI products. Further collaborative projects using mammograms from more UK screening sites are in development.

In all the projects there has been input from multiple members of the main Cancer Study Group and subgroups. In common with the rest of the UK breast cancer trials portfolio, these studies have all shared a high level of patient input into their design, development and delivery. The key role of patient advocates in UK breast cancer research ensures that it remains focused on answering questions that our patients consider of key importance, and that studies remain acceptable to our patients, enabling us to recruit successfully and foster engagement with regard to understanding how data is being utilised.

References:
1. Bartlett JMS, McGonkey CC, Munro AF et al. Predicting anthracycline benefit: TOP2A and CEP17 - Not only but also. Journal of Clinical Oncology. 2015 May 20;33(15):1680-1687
The SOLTI Breast Cancer Research Group launches Scientific Bites, the first e-learning platform in the field of oncology created by a cooperative research group

SOLTI, coinciding with its 25th anniversary, launched an initiative called Scientific Bites, a virtual space where health professionals can find educational content in the field of oncology. The goal of this e-learning platform is to facilitate access to the latest developments in translational research in a simple and didactical way to help create a more informed and discerning scientific community.

Dr Aleix Prat, SOLTI President and BIG Executive Board member says: “As an academic research group, our aim is to bring the latest advances to healthcare professionals. This freely available platform is a new and novel step in that direction. All topics selected are based on the educational needs we detect among our members throughout our educational programmes and activities”.

In the form of “Bites”, Scientific Bites offers on a regular basis relevant educational content in the field of oncology. Each “Bite” is a self-contained thematic block that consists of different modules and is coordinated by an oncologist with tremendous expertise and several publications on the addressed topic. It is an open-access tool for both SOLTI members and any professional involved in cancer research and treatment.

Participants will find the same tandem-structure in each module: an educational video (with its downloadable educational file) and a video-debate. Leading professionals present their views on controversial issues and hot topics related to the subject at hand, making the content more qualitative and relevant to the professional completing the training. To conclude each module, an assessment must be completed in order to receive an official accreditation for continuous medical education.

Scientific Bites kicked-off with the publication of the first “Bite”, called “Current scenario regarding HER2- and HER3-positive disease” and coordinated by Dr Aleix Prat, Chief Medical Oncology at Hospital Clinic in Barcelona. Currently, the platform and its content are only available for Spanish professionals, but SOLTI is working to translate it into English.

Scientific Bites, an original idea developed at the end of last year in conjunction with SOLTI President, Dr Aleix Prat, and the Office Communications Team, is an effort to design a more user-friendly and attractive format through which knowledge could be spread.

This is how Scientific Bites was born and we are glad to share it with anyone who may be interested and can take advantage of it. Enjoy!
Breast cancer ranks as having the highest prevalence among women who suffer from cancer in Taiwan, with approximately 15,000 newly diagnosed cases every year. Recent studies have found that young-age onset of breast cancer in East Asia presents numerous variances compared with their counterparts in Western countries, such as subtype classification, clinical pathology characteristics, patient prognosis and genetic mutations.

Terry Gou, chairman of the YongLin Healthcare Foundation (founder of FOXCONN), launched the "YongLin Sino Cancer Alliance" in 2017 to fully support "Genomic testing and clinical research for breast cancer and leukemia patients in Taiwan". As of today, 10 clinical studies have been activated, covering nearly 8,000 breast cancer and leukemia patients each year, and performing about 12,000 genomic tests.

The Taiwan Breast Cancer Society (TBCS) is proud to be responsible for convening experts composed of physicians and study staff for this project. In the past two years, several clinical research results have been published in highly recognised medical journals and presented at conferences, including: TP53 mutations in circulating tumor DNA associate with Klebsiella pneumoniae in breast cancer as a biomarker for early detection and prevention of breast cancer, by Professor Ming-Feng Hou from the Chung-Ho Memorial Hospital of Kaohsiung Medical University; Analysis of circulating tumor DNA (ctDNA) after neoadjuvant therapy to predict disease relapse in patients with stage II-III breast cancer to explore the relationship with the biomarkers, by Professor Chiu-Sheng Huang from the National Taiwan University Hospital; and The genomic variation of breast cancer patients in Taiwan to achieve the goal of precision medicine, by Professor Ling-Ming Tseng from the Taipei Veterans General Hospital.

Dr Ling-Ming Tseng, president of TBCS, said: "The Taiwan Breast Cancer Society looks forward to closely collaborating with the YongLin Healthcare Foundation, along with domestic and foreign biotechnology industries, to accumulate the genomic profiles of patients and better identify the pathogenic mechanisms of complicated cancer gene mutations. These studies will significantly contribute to new discoveries and breakthroughs in cancer treatment and prevention."

The Taiwan Breast Cancer Society, which was founded in 1997, is a non-governmental organisation (NGO) encouraging the study, research and education through physicians specialised in the field of breast cancer. The main objective is to provide a platform enabling breast cancer experts to engage, share experiences through academic conferences and lectures, both at a national and international level.

References
For the French UniCancer Breast Group (UCBG), this year has been a year of transition. Several major studies have been completed and are entering the exploitation phase; others are entering their last stretch. At the same time, new projects have been activated, and yet others are in the making and promise years of fruitful research ahead.

The huge CANTO programme (QOL assessment by self-administered questionnaire of patients with early breast cancer) was completed in January 2019 with 12,012 patients. Several important publications have already been produced, one of them stressing the problem of adherence to hormone therapy and the necessity to implement specific action for that matter, taking into account toxicities of hormonal treatment, particularly in the youngest patients. Furthermore, following the precise description of treatment-associated cognitive impairment in this cohort, we are currently working on a randomised, prospective trial with a specific intervention to try to address this problem.

The important PADA-1 trial, including patients with metastatic ER-positive/HER2-negative breast cancer on first-line letrozole + palbociclib and which assesses the interest of switching from an aromatase inhibitor (AI) to faslodex in case of detection of ESR1 mutation in sequential ctDNA analysis, completed accrual in January 2019. Among the 1,017 patients enrolled, we have now randomised 150 patients with rising ctDNA and we anticipate to reach the expected 200 at the end of the year. We already have significant results from the initial cohort. Specifically, we found that 3.2% of the patients had ESR1 mutations detectable in their serum at inclusion, mostly in patients who had already received an AI in the adjuvant setting (7.1%), and that this was correlated with a worse prognosis. This was presented by Francois Clément Bidard at the ASCO Annual Meeting 2020.

Among the recently activated projects, two trials in the metastatic setting are particularly important: in the area of first-line treatment, the AMBRE study will test the question of direct comparison between hormone therapy plus CDK inhibitor (abemaciclib) and chemotherapy alone for patients with hormone-sensitive but aggressive disease. Regarding second-line treatment after progression on anti-CDK therapy, and after molecular screening to select for homologous recombination deficiency, the DOLAF trial is testing an original combination of olaparib-durvalumab and fulvestrant. This study, conducted in collaboration with the SOLTI group, intends to screen 790 patients and select 158 for treatment.

Several projects are almost ready and should start in the months to come. Among them, the INTERCEPT study will include patients with HER2-positive metastatic breast cancer on pertuzumab plus trastuzumab who experience isolated brain progression. These patients will be treated with a triple trastuzumab, pertuzumab and tucatinib combination, with the expectation to significantly delay further progression. Finally, we are eagerly awaiting the activation of the large TRAK-ER study that we are setting up with the Royal Marsden group and that is the first to associate an iterative screening of patients with high-risk localised cancer using ctDNA followed by early therapeutic intervention in the presence of a resistance mutation. We plan to include 1,150 patients within two years and expect 110 to be randomised.

References:
17TH ST. GALLEN INTERNATIONAL BREAST CANCER CONFERENCE 2021
Primary Therapy of Early Breast Cancer Evidence, Controversies, Consensus
17 – 20 March 2021, Vienna/Austria and virtual

St. Gallen Oncology Conferences (SDNK)
c/o Tumor and Breast Center Zentrum für Tumor- und Brustkrankheiten (ZeTuP)
Rorschacherstrasse 150, 9006 St. Gallen/Switzerland
info@onconferences.ch, www.sg-bcc.org

www.sg-bcc.org
**Overview of the current clinical studies run within the BIG network**

### Open trials / Research programmes

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<tr>
<td>ALEXANDRA / IMpassion 030</td>
<td>BIG 16-05</td>
<td>A randomised phase III trial comparing atezolizumab (anti-PD-L1 inhibitor), given in combination with standard chemotherapy vs. chemotherapy alone as adjuvant treatment in patients with operable TNBC - NCT03498716</td>
<td>M. Ignatiadis, H. McArthur, S. Saji</td>
<td>Lead trial (Co)-Leading partners: BIG HQ / IJB-CTSU (BrEAST) / FSTRF and AFT Pharma partner: Roche / Genentech (sponsor) Funding: Roche / Genentech</td>
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<tr>
<td>APPALACES</td>
<td>BIG 18-01</td>
<td>A Phase II study of Adjuvant PALbocilb as an Alternative to CHemotherapy in Elderly patientS with high-risk ER+/HER2- early breast cancer - NCT03609047</td>
<td>H. Wildiers, E. Brain, K. Punie</td>
<td>Supporter trial Coordinating group: EORTC (sponsor) Pharma partner: Pfizer</td>
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<tr>
<td>AURORA (Metastatic Breast Cancer GPS)</td>
<td>BIG 14-01</td>
<td>The AURORA programme: aiming to understand the molecular aberrations in metastatic breast cancer - NCT02102165</td>
<td>P. Aftimos, M. Oliveira</td>
<td>BIG-sponsored programme (Co)-Leading partners: BIG HQ (sponsor) / IJB-CTSU (BrEAST) / FSS Pharma partner: N/A Funding: BCRF, Fondation Cancer (Luxembourg), NIF Foundatin, the National Lottery (Belgium), Barrie and Deena Webb, Think Pink Belgium (SMART Fund) and many individual donors</td>
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<tr>
<td>Breast Cancer in Pregnancy</td>
<td>BIG 2-03</td>
<td>Prospective registry of women treated for breast cancer while pregnant - NCT00196833</td>
<td>S. Loibl, G. von Minckwitz</td>
<td>Supporter study (Co)-Leading partner: GBG (sponsor) Pharma partner: N/A Funding: GBG, Deutsches Konsortium für Translationale Krebsforschung</td>
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<td>Exceptional Responders</td>
<td>BIG 16-04</td>
<td>A global hunt for exceptional responders in the BIG network: aiming to identify breast cancer patients with a truly remarkable clinical response to anticancer treatments, and to characterise their tumours molecularly</td>
<td>A. Irrthum (coordinator)</td>
<td>BIG-sponsored programme (Co)-Leading partner: BIG HQ Pharma partner: N/A Funding: Breast Cancer Research Foundation</td>
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<td>EXPERT (BIG Radio Tuning)</td>
<td>BIG 16-02</td>
<td>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</td>
<td>B. Chua, G. Gruber</td>
<td>Co-lead trial (Co)-Leading partners: BCT-ANZ (sponsor) and BIG HQ Pharma partner: N/A Funding: BCT-ANZ, the National Health and Medical Research Council of Australia, and BIG HQ fundraising initiatives</td>
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<tr>
<td>International Male Breast Cancer Programme</td>
<td>BIG 2-07</td>
<td>Registration and biologic characterisation programme of breast cancer in men - NCT01101425</td>
<td>F. Cardoso, S. Giordano</td>
<td>Supporter programme (Co)-Leading partners: EORTC (sponsor) / NABCG (US) Pharma partner: N/A Funding: Breast Cancer Research Foundation</td>
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<tr>
<td>POLAR</td>
<td>BIG 18-02</td>
<td>Palbocilb for HR+ isolated local or regional recurrence of breast cancer - NCT03820830</td>
<td>E. Munzone, S. Aebi</td>
<td>Supporter trial Coordinating group: IBCSG (sponsor) Pharma partner: Pfizer</td>
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## Follow-up or post-study activities

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<th>Study name</th>
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<th>Principal Investigator(s)</th>
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<td>ALTTO</td>
<td>BIG 2-06</td>
<td>Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation: sequence and combination for patients with HER2/ErbB2 positive primary breast cancer - NCT00490139</td>
<td>M. Piccart, A. Moreno-Aspitia</td>
<td>Lead trial (Co)-Leading partners: BIG HQ / IJB-CTSU (BrEAST) / FSTRF / Alliance (former NCCTG; sponsor for the US) Pharma partner: Novartis (global sponsor for all countries with the exception of US) Funding: GSK (past) / Novartis</td>
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<td>APHINITY</td>
<td>BIG 4-11</td>
<td>Comparison of single-versus-dual anti-HER2 therapy (trastuzumab, pertuzumab) for patients with HER2-positive primary breast cancer - NCT01358877</td>
<td>M. Piccart, S. Loibl, J. Bines</td>
<td>Lead trial (Co)-Leading partners: BIG HQ / IJB-CTSU (BrEAST) / FSTRF Pharma partner: Roche (sponsor) Funding: Roche</td>
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<td>BRAVO</td>
<td>BIG 5-13</td>
<td>Niraparib for patients with HER2-negative, germline BRCA mutation-positive, locally advanced or metastatic breast cancer - NCT01905592</td>
<td>N. Turner, J. Balmaña, D. Cameron, J. Erban</td>
<td>Co-lead trial (Co)-Leading partners: EORTC / BIG HQ Pharma partner: Tesaro (sponsor) Funding: Tesaro</td>
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<tr>
<td>DCIS</td>
<td>BIG 3-07</td>
<td>Radiation doses and fractionation schedules for women with DCIS - NCT00470236</td>
<td>B. Chua</td>
<td>Supporter trial (Co)-Leading partner: TROG (sponsor) Pharma partner: N/A Funding: National Health &amp; Medical Research Council Project Grant, Susan G. Komen</td>
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<td>FINESSE</td>
<td>BIG 2-13</td>
<td>Oral lucitanib for patients with FGFR1 ER+ metastatic breast cancer - NCT02056363</td>
<td>F. André, J. Cortés</td>
<td>Lead trial (Co)-Leading partners: BIG HQ / BrEAST / FSS Pharma partner: Servier (sponsor) Funding: Servier</td>
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<td>IBIS-II</td>
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<td>Prevention study of anastrozole for postmenopausal women at increased risk of breast cancer; and of effects of tamoxifen vs. anastrozole in postmenopausal women with DCIS - NCT0072462</td>
<td>J. Cuzick</td>
<td>Supporter trial (Co)-Leading partner: IBIS Pharma partner: Astrazeneca Sponsor: Queen Mary University of London Funding: Cancer Research UK, Queen Mary University of London</td>
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<tr>
<td>LORELEI</td>
<td>BIG 3-13</td>
<td>Neoadjuvant letrozole plus taselisib versus letrozole plus placebo in postmenopausal women with ER+, HER2-negative, early-stage breast cancer - NCT0273973</td>
<td>C. Saura, E. de Azambuja</td>
<td>Co-lead trial (Co)-Leading partners: ABCSG, SOLTI and BIG HQ Pharma partner: Genentech (sponsor) Funding: Genentech</td>
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<td>MA.32 Metformin</td>
<td>BIG 5-11</td>
<td>Effect of metformin on recurrence and survival in early stage breast cancer - NCT0110438</td>
<td>P. J. Goodwin</td>
<td>Supporter trial (Co)-Leading partner: CCTG (sponsor) Pharma partner: Apotex Funding: NCI/NIH grants, Cancer Research UK, Canadian Cancer Society, BCRF and Canadian Breast Cancer Foundation</td>
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<td>MINDACT</td>
<td>BIG 3-04</td>
<td>Can addition of 70-gene signature to common clinical-pathological criteria safely spare patients with 0 to 3 node positive breast cancer from adjuvant chemotherapy? - NCT00433589</td>
<td>E. Rutgers, F. Cardoso, M. Piccart</td>
<td>Co-lead trial. (Co)-Leading partners: EORTC (sponsor) / BIG HQ. Commercial partners: Roche, Sanofi, Novartis and 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*</td>
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<td>OLYMPIA</td>
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<td>Olaparib vs. placebo for patients with BRCA-mutated, high-risk HER2-negative breast cancer, having completed local treatment and (neo)adjuvant chemotherapy - NCT02032823</td>
<td>A. Tutt, B. Kaufman, J. Garber, C. Geyer</td>
<td>Lead trial. (Co)-Leading partners: NRG Oncology (sponsor in US), BIG HQ and FSTRF. Pharma partner: Astrazeneca (sponsor in Rest of the World). Funding: Astrazeneca</td>
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<td>PALLAS</td>
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<td>PALbociclib CoLaborative Adjuvant Study: palbociclib with standard adjuvant endocrine therapy versus standard adjuvant endocrine therapy alone for HR+ / HER2-negative early breast cancer - NCT02513394</td>
<td>E. Maye r, M. Gnant, A. DeMichele</td>
<td>Co-Lead trial. (Co)-Leading partners: ABCSG (RoW), AFT (US) (sponsors) and BIG HQ. Pharma partner: Pfizer. Funding: Pfizer grant</td>
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<td>POSITIVE (BIG time for Baby)</td>
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<td>Endocrine therapy interruption to enable conception for young women with ER+ breast cancer - NCT02308085</td>
<td>O. Pagani</td>
<td>Supporter trial. (Co)-Leading partner: IBCSG (sponsor). Pharma partner: Pfizer. Funding: Pfizer grant</td>
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<td>PYTHIA</td>
<td>BIG 14-04</td>
<td>Palbociclib plus fulvestrant for pretreated patients with ER+/HER2- metastatic breast cancer - NCT02536742</td>
<td>L. Malorni</td>
<td>Co-lead trial. (Co)-Leading partners: IBCSG (sponsor) and BIG HQ. Pharma partner: Pfizer. Funding: Pfizer grant</td>
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<td>SNAP</td>
<td>BIG 2-12</td>
<td>Schedules of nab-Paclitaxel: evaluation of different schedules of nab-paclitaxel for metastatic breast cancer - NCT01746225</td>
<td>A. Gennari, G. Jerusalem</td>
<td>Supporter trial. (Co)-Leading partner: IBCSG (sponsor). Pharma partner: Celgene. Funding: Celgene grant</td>
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<td>SOFT</td>
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<td>P. Francis, G. Fleming</td>
<td>Supporter trial. (Co)-Leading partner: IBCSG (sponsor). Pharma partner: Pfizer. Funding: Grant support from Pfizer, Ipsen, US NCI, IBCSG and many participating collaborative academic groups, BCRF, as well as various charities</td>
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* full information available on the BIG website.

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

**NB:** This table does not include the trials in development and the closed trials. For more information, please visit: www.BIGagainstbreastcancer.org.
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<td>SOLE</td>
<td>BIG 1-07</td>
<td>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</td>
<td>M. Colleoni&lt;br&gt;P. Karlsson&lt;br&gt;S. Aebi&lt;br&gt;J. Chirgwin</td>
<td>Supporter trial&lt;br&gt;(Co)-Leading partner: IBCSG&lt;br&gt;Sponsor: IBCSG&lt;br&gt;Pharma partner: Novartis&lt;br&gt;Funding: Novartis</td>
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<td>SUPREMO</td>
<td>BIG 2-04</td>
<td>Selective Use of Postoperative Radiotherapy After Mastectomy: adjuvant chest wall irradiation for 'intermediate risk' breast cancer following mastectomy - NCT00966888</td>
<td>I. Kunkler&lt;br&gt;P. Canney</td>
<td>Supporter trial&lt;br&gt;(Co)-Leading partner: SCTBG&lt;br&gt;Sponsor: UK Medical Research Council&lt;br&gt;Pharma partner: N/A&lt;br&gt;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</td>
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<td>TEXT</td>
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<td>Tamoxifen and Exemestane Trial: evaluation of exemestane plus GnRH analogue for premenopausal women with endocrine responsive breast cancer - NCT00066703</td>
<td>O. Pagani&lt;br&gt;B. Walley</td>
<td>Supporter trial&lt;br&gt;(Co)-Leading partner: IBCSG (sponsor)&lt;br&gt;Pharma partner: Pfizer&lt;br&gt;Funding: Grant support from Pfizer, Ipsen, US NCI, IBCSG and many participating collaborative academic groups, BCRI, as well as various charities</td>
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<td>TREAT-CTC</td>
<td>BIG 1-12</td>
<td>TRastuzumab in HER2-negative Early breast cancer as Adjuvant Treatment for Circulating Tumor Cells (CTC) - NCT01548677</td>
<td>M. Ignatiadis&lt;br&gt;M. Piccart&lt;br&gt;J.-Y. Pierga&lt;br&gt;B. Rack&lt;br&gt;C. Sotiriou</td>
<td>Supporter trial&lt;br&gt;(Co)-Leading partners: EORTC BCG, SUCCESS, UNICANCER&lt;br&gt;Sponsor: EORTC&lt;br&gt;Pharma partner: Roche, Janssen Diagnostics&lt;br&gt;Funding: Roche educational grant/medication; Janssen test kits</td>
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<td>ULTIMATE</td>
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<td>Immunotherapy combined with standard endocrine therapy as neoadjuvant treatment for women with ER+/HER2-negative breast cancer - NCT02997995</td>
<td>F. André&lt;br&gt;A. Prat</td>
<td>Co-lead trial&lt;br&gt;(Co)-Leading partners: French Breast Cancer Intergroup Unicancer (UCBG) (sponsor) and BIG HQ&lt;br&gt;Pharma partner: Astrazeneca&lt;br&gt;Funding: Astrazeneca grant</td>
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THE BIG NETWORK:
GLOBAL RESEARCH COLLABORATION TO CURE BREAST CANCER

For over 20 years, BIG’s academic research groups have been working together to find better treatments and cures for breast cancer

The Breast International Group (BIG) is an international not-for-profit organisation that represents the largest global network of academic research groups dedicated to finding cures for breast cancer. Its mission is to facilitate and accelerate breast cancer research at an international level.

In 1999, BIG was founded with the aim to address fragmentation in European breast cancer research. Research groups from other parts of the world rapidly expressed interest in joining BIG and, two decades later, BIG represents over 55 like-minded research groups from around the world and reaches across approximately 70 countries on 6 continents.

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

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

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

www.BIGagainstbreastcancer.org
The breast cancer research groups of the BIG network

AFRICA
BGICS Breast Gynaecological International Cancer Society

ASIA
BDPCC Breast Disease Professional Committee of CMEA
BIIEI Breast Intergroup of Eastern India
CTRSG 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 Shaukat Khanum Memorial Cancer Hospital & Research Centre
TCOG Taiwan Cooperative Oncology Group
TSCO Thai Society of Clinical Oncology

AUSTRALASIA
BCT-ANZ Breast Cancer Trials Australia and New Zealand
TROG Trans-Tasman Radiation Oncology Group

EUROPE
ABCSG Austrian Breast & Colorectal Cancer Study Group
AGO-B Arbeitsgemeinschaft Gynäkologische Onkologie Breast Study Group
BOOG Borskanker Onderzoek Group
CEEGG Central and East European Oncology Group
CT-IRE Cancer Trials Ireland
DBCG Danish Breast Cancer Cooperative Group
EORTC-BCG European Organisation for Research and Treatment of Cancer - Breast Cancer Group
FBGC Finnish Breast Cancer Group
GBG German Breast Group
GCSG Georgian Cancer Study Group
GEICAM Spanish Breast Cancer Group
GOIRC Gruppo Oncologico Italiano di Ricerca Clinica
HSBS Hellenic Society of Breast Surgeons
HeCOG Hellenic Cooperative Oncology Group
HORG Hellenic Oncology Research Group
IBCG Icelandic Breast Cancer Group
IBCSG International Breast Cancer Study Group
IBIS International Breast Cancer Intervention Studies
ICCG International Collaborative Cancer Group
ICR-CTSU Institute of Cancer Research - Clinical Trials & Statistics Unit
UI-BCTSU Institut Jules Bordet / Clinical Trials Support Unit
ITMO Italian Trials in Medical Oncology
MICHELANGELO Fondazione Michelangelo
NBOG 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 Clinicos Oncologicos 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
Together we will cure breast cancer

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