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Canada and the BIG-NABCG collaboration
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In the Feature article of this newsletter, focus is placed on BIG’s activities and collaborations in North America. The floor is given to Dr Philippe Bedard, who recently joined BIG’s Executive Board and is a member of the Canadian Cancer Trials Group (CCTG), one of the 59 collaborative research groups comprising the BIG network, and the only member based in North America.

Dr Bedard highlights the various challenges faced with the conduct of clinical trials in his country, but also the great contribution of Canadian researchers to practice-changing trials run with US cancer research groups, as well as their particularly collaborative spirit and involvement in international studies run under the BIG umbrella.

For over a decade now, BIG has been collaborating closely with its US counterpart, the North American Breast Cancer Group (NABCG), with the aim to improve international clinical trials and answer critical questions that really matter for patients much more quickly. Together, through joint research programmes, BIG and NABCG address the most challenging aspects of breast cancer research that are not supported by the pharmaceutical industry but are important for patients, such as male breast cancer.

BIG and NABCG share a same vision and goal: to eradicate breast cancer through truly international research. This vision and the longstanding collaboration are supported by the Breast Cancer Research Foundation (BCRF). Contributing to this newsletter, BCRF Co-Founder Dr Larry Norton, as well as Drs Nancy Davison and Martine Piccart, co-chairs of the BIG-NABCG Steering Committee, shed light on the early days of this collaboration, its shared successes and challenges, and future projects.

In 2019 BIG is celebrating its 20th anniversary! Together, and over the past 20 years, BIG researchers, patients and supporters have made real progress in better understanding breast cancer and improving the treatments of women and men with the disease. BIG is delighted to celebrate this anniversary with you through a large awareness campaign launched on 4 February, World Cancer Day.

Finally, the following pages will give you a peek at BIG members’ research projects and activities around the world.

We hope you enjoy the reading.
When BIG co-founder and chair, Professor Martine Piccart, first began to meet with the NABCG in the late 1990s to share research plans and priorities between the two organisations, she did not imagine the immensely fruitful collaboration that has emerged.

Starting with small, short, early morning meetings at each year’s American Society of Clinical Oncology (ASCO) congress, the collaboration has evolved into a major international partnership with multiple research and guideline programmes under its belt, and an annual one-day meeting of its own to discuss progress and plan ahead.

“It wasn’t long before we agreed that a one-hour meeting at ASCO only gave us a very superficial idea of the capabilities of these two important breast cancer research networks. We therefore set up a forum for much more in-depth discussions about how we could work together to our mutual benefit, and held our first formal meeting during the San Antonio Breast Cancer Symposium in 2005,” recalls Piccart.

Since then, the BIG-NABCG collaboration has established joint research programmes aimed at answering major questions currently facing clinicians and patients with breast cancer. Today, these include investigating the effects of interrupting hormone treatment for young women with luminal breast cancer so they can become pregnant, optimising treatment of metastatic breast cancer, and exploring the place of immunotherapy. In addition, the collaboration has helped to standardise aspects of diagnostic and research methodology, such as Ki67 assessment and endpoints in adjuvant and neoadjuvant trials, and led to a much-needed research initiative in male breast cancer.

Together, BIG and NABCG are addressing some of the most challenging aspects of breast cancer research, such as male breast cancer, that are not supported by the pharmaceutical industry.
What makes the BIG-NABCG collaboration different from other research partnerships is that it is a long-standing relationship that is particularly focussed on finding ways to improve translational and clinical research in breast cancer, and it is academically driven,” says Dr Nancy Davidson, Senior Vice President and Director of the Clinical Research Division at the Fred Hutchinson Cancer Research Center in Seattle, USA, and co-chair of the BIG-NABCG Coordinating Group.

At last year’s BIG-NABCG meeting, delegates discussed barriers to clinical trials and how these may be addressed and overcome. This year, the spotlight is on treatment de-escalation, and special emphasis is being placed on the input from patient representatives.

“We’ve come to realise that it may be possible to reduce the amount of treatment some women receive and therefore lessen the side effects they experience, while continuing to maintain therapeutic success,” explains Davidson.

None of the practice-changing findings from the BIG-NABCG partnership would have been possible without the generous financial support of the Breast Cancer Research Foundation (BCRF), which rapidly recognised the benefits of such a collaboration, and has provided funding since 2010.

“The goal of the BRCF has always been to see if we could do international trials more efficiently, so the BIG-NABCG collaboration was an obvious fit. We believe that, by working together, we can answer questions more quickly and move on to the next challenge that needs to be addressed,” says Dr Larry Norton, Founder and Scientific Director of BCRF.

He explains that the Foundation was established by philanthropist, Evelyn Lauder, in 1993 with the vision of identifying the most creative, energetic and productive breast cancer researchers and giving them the resources, freedom and security to accomplish their goals.

Norton points out that a lot of research funding is based on success, and researchers are often working with the knowledge that their funding will stop if they fail. However, not every great idea works and a negative finding can be just as important as a positive one.

“At the BCRF, we have a peer-review process through which we find and discuss the most productive areas for research and fund them accordingly, rather than going through the conventional competitive grant process through which money is allocated,” he says.

The BIG-NABCG collaboration is not without its own challenges, not least language and time differences, and regulatory and funding issues. Even so, Norton explains that, with each passing year, collaboration members are becoming more communicative and relaxed in discussing their common goals and challenges:

“We have yet to reach our goal of truly international breast cancer trials answering critical questions very quickly, but we are breaking down the various barriers and I believe we can fully realise our dream of working together as a global community,” he concludes.
NABCG – a major network of US and Canadian researchers

The NABCG is a network of US and Canadian research groups supported by the US National Cancer Institute (NCI), with major funding from the BCRF. For many years, breast cancer clinical trials in the USA were run through 10 different cooperative groups, each with its own breast cancer committee, but researchers decided there was a better way of doing things.

“We recognised that a lot of different groups were doing studies asking the same questions and agreed that it would be better to work together. We talked about it and the NABCG was actually set up on the basis of a handshake in a Toronto cafe,” laughs Norton.

Since then, the organisation has been further consolidated by the NCI into the National Cancer Trials Network (NCTN), consisting of four adult cancer groups in the USA (NRG, ECOG-ACRIN, SWOG and the Alliance for Clinical Trials in Oncology) and the Canadian Network Group. However, the overall group has kept its ‘legacy’ name of NABCG, through which it collaborates with BIG.

Breast cancer research in Canada: successes and challenges

Within the NABCG network, Canadian breast cancer researchers have consistently ‘punched above their weight’ – leading or making a major contribution to many practice-changing trials of breast cancer treatment, including those on aromatase inhibitors and accelerated and partial breast irradiation. Uniquely among NABCG members, Canada is also a member of BIG, through the Canadian Cancer Trials Group (CCTG).

“We’re geographically close to the US and have many collaborations with the US intergroups, and the CCTG also has a federally funded US grant that, in part, supports its activities. But we’re also part of BIG and participate in some of their international trials that do not include the US,” explains Dr Philippe Bedard, a member of BIG’s Executive Board since June 2018 and Associate Professor of Medicine at the University of Toronto.

He suggests that Canada’s single-payer healthcare system may make it easier for its researchers to participate in some breast cancer research, such as health economic aspects of real world clinical studies, than US researchers whose payer data sources are more fragmented.

“What makes the BIG-NABCG collaboration different from other research partnerships is that it is a long-standing relationship that is particularly focussed on finding ways to improve translational and clinical research in breast cancer, and it is academically driven”

Nancy Davidson

However, Canada’s vast territory and small population bring both advantages and disadvantages to the country’s research efforts.

“Our greatest strength is that breast cancer researchers in Canada are highly collaborative and work well together and with US groups and other academic groups in the rest of the world. However, our relatively small population can make it challenging for us to contribute to large international trials that focus on rare subpopulations of patients with breast cancer,” he says.
Bedard explains that, as in many countries, the rising costs of research are also hampering progress. He estimates that about two-thirds of breast cancer studies in Canada are funded by pharmaceutical companies and one-third investigator initiated.

“Government support for clinical research has decreased, particularly in breast cancer where some studies require long term follow up of patients for 10 years or longer, and it’s a big challenge for cooperative groups to adequately fund practice-changing clinical trials,” he says.

There are also growing concerns that funding challenges will deter young investigators from getting involved in research if they are overwhelmed by administrative and cost hurdles and sustainability issues.

The current focus of national breast cancer research – precision medicine, immunotherapy and treatment de-escalation – is similar to that in other developed countries, though successful recent initiatives to standardise care and bring radiotherapy and chemotherapy closer to patients in remote areas are more specific to Canada.

“Twenty years ago, patients had to be treated in large urban centres and we were sending patients to the US for breast radiotherapy because of resource limitations. Now, that’s all changed because the provinces have really tried to improve care delivery in more rural centres, especially for radiotherapy,” says Bedard.

As in many countries, Canada has a national body, the pan Canadian Oncology Drug Review (pCODR), to assess cost-effectiveness and make recommendations for use of cancer medicines, though provinces decide on local availability based on further price negotiations with manufacturers.

Major breast cancer trials currently led by Canadian researchers include MA32, a phase 3, placebo controlled, five-year trial of metformin in patients with high risk, early stage breast cancer, which is expected to report in the next few years, and MA39, a recently initiated radiotherapy de-escalation study in patients with limited node-positive disease, based on genomic risk scores.

Through the Breast Cancer Dream Team initiative, sponsored by StandUpToCancer Canada and the Canadian Cancer Society, research and development of three new biomarker-driven drugs for triple negative breast cancer has been accelerated. These drugs – CFI-400945 (a PLK4 inhibitor), CX5461 (an RNA Pol I inhibitor/GQ binder), and CFI-402257 (a TTK inhibitor) – are undergoing basic/translational development and phase 1/2 trials in patients with advanced breast cancer.

For the future, Bedard hopes that innovative trial designs that enable Canadian patients to take part through electronic follow up and video conferencing will allow greater participation by those living in rural areas – boosting the overall numbers of participants that Canadian researchers can contribute.

“We are proud to have contributed to BIG’s practice-changing breast cancer trials, and we believe we bring a unique perspective in that we are geographically close to the US but, in some aspects of care delivery, we favour a more European approach,” concludes Bedard.

“Our greatest strength is that breast cancer researchers in Canada are highly collaborative and work well together and with US groups and other academic groups in the rest of the world”
Ki67: BIG-NABCG research leads the way in standardising tests

Developing guidance aimed at standardising assessment of the nuclear proliferation marker, Ki67, in predicting breast cancer progression and determining clinical management, has been one of the most outstanding success stories of the BIG-NABCG collaboration.

“The Ki67 programme was a truly remarkable and practice-changing development, and it undoubtedly required the kind of international collaboration provided by BIG and NABCG to help standardise the different testing methods which were being used,” says Norton.

In 2009, the International Ki67 Breast Cancer Working Group of the BIG-NABCG was formed to address the problem of inconsistent Ki67 assessment between laboratories, and it proposed guidelines for pre-analytic and analytic conditions for Ki67 assessment, as well as for interpretation, scoring, and related data handling. However, a subsequent BIG-NABCG study, which included eight highly experienced laboratories using their own best practices for tissue microarray slides, showed substantial variation in Ki67 scores among laboratories, on both centrally and locally stained sections (intraclass correlation of 0.71 and 0.59, respectively). Tumour region selection, counting method and subjective assessment of staining positivity were identified as contributing to inter-laboratory discordance.

A second BIG-NABCG study was therefore set up to determine whether standardisation of Ki67 scoring methodology could improve score concordance among laboratories. In this study, 16 laboratories from eight countries calibrated assessment to a specific Ki67 scoring method using a web-based tool. They then scored 50 prestained 1-mm cores on a tissue microarray glass slide, following scoring instructions similar to those used in the calibration exercise.

For tissue microarray scoring, the intraclass correlation estimate was 0.94 (95% confidence interval: 0.90–0.97), which was markedly and significantly greater than 0.7, the prespecified minimum target for success.

Taking this approach a step further, in the most recently published BIG-NABCG study, automated machine-based methods were used for Ki67 testing of sets of prestained core-cut biopsy sections of 30 breast tumours at 14 laboratories. Seven unique scanners and 10 software platforms were used, and the prespecified intraclass correlation coefficient for success was over 0.8.

The intraclass correlation coefficient for automated average scores across 16 operators was 0.83 (95% credible interval: 0.73–0.91) and the intraclass correlation coefficient for maximum scores across 10 operators was 0.63 (95% credible interval: 0.44–0.80).

The study authors concluded that automated machine assessment of average Ki67 has the potential to achieve inter-laboratory reproducibility similar to that seen with rigorously standardised assessment by pathologists, but that the maximum score methods may be suboptimal for consistent measurement of proliferation. They recommended further standardisation and subsequent clinical validation.

“The Ki67 recommendations for standardised analysis demonstrate both the advantages and pitfalls of testing and will hopefully improve the quality of testing of this biomarker. This is very important, especially in countries where multigene prognostic signatures, such as MammaPrint® and Oncotype DX®, are not reimbursed and oncologists use Ki67 testing to distinguish between luminal A and B breast cancer, and treat patients according to their findings,” concludes Piccart.

The AURORA project in metastatic breast cancer

AURORA Europe and US are two of the most ambitious programmes ever carried out to improve understanding of metastatic breast cancer, and have been established through the BIG-NABCG collaboration, funded by the BRCF as a result of the sale of Evelyn Lauder’s jewellery.

“What astonishes me about AURORA is the enthusiasm with which all the international investigators of note have come together to study the molecular biology of metastatic breast cancer and identify potential targets to prevent tumour spread, in a way that has never been attempted before,” says Norton.

“There’s a lot to be said for competition in research, but AURORA is showing the value of cooperation so that everyone can benefit,” he adds.

AURORA is two parallel but closely linked initiatives, run respectively in North America and in Europe. AURORA in Europe is analysing primary and metastatic biopsy samples from approximately 1,000 patients with metastatic breast cancer and subjecting them to next generation sequencing of a panel of cancer-related genes. In addition, plasma samples are collected at study entry, every six months and at each disease progression. All clinical data are collected from these patients, including successive treatments and responses, and patients are followed up for 10 years.

“By performing the sequencing, we hope to gain a better understanding of the clonal evolution of the disease, and which clones become dominant, to help us understand why we are not curing metastatic breast cancer so that, hopefully, we can change this,” says Piccart.

The strength of AURORA Europe is that samples are collected from each patient at various timepoints throughout the course of the disease. This provides a unique opportunity to study tumour evolution and find molecular changes associated with disease progression and treatment sensitivity or resistance.
Alongside sequencing of a panel of cancer genes, the results of which are provided in real-time to the treating physician, the European AURORA programme also performs RNA and circulating tumour DNA sequencing, generating a comprehensive molecular portrait of each breast cancer.

Patients taking part in the European AURORA programme will be treated at the discretion of their physician according to local practice or depending on the molecular profile of their tumour sample, directed to innovative clinical trials of molecularly targeted agents.

To date AURORA Europe has generated molecular data from more than 600 patients with metastatic breast cancer. The first aggregated results of this programme will be presented this year.

The AURORA US programme is more focused on in-depth analysis of molecular changes in breast cancer over time, without the intention of using results to assign patients to clinical trials. Davidson explains that there are two distinct sub-studies within the US initiative. This first is a retrospective analysis of patients with metastatic breast cancer who very generously donated multiple tissue samples from all metastatic sites for immediate collection after they died. Researchers went back to existing tumour banks to find and study primary breast tumour samples alongside these metastatic samples and appropriate clinical data.

“This has enabled us to study the original tumour and the attributes of metastases in brain, lung, liver and bone to get a better idea of how primary and metastatic tumours change and what drives those metastases to grow,” says Davidson.

All the tissue samples for this part of the study have now been collected for analysis of DNA, RNA and methylation abnormalities and initial results are expected in 2019.

In the second, prospective part of AURORA US, which will soon get underway, several hundred women with metastatic disease undergoing tissue biopsy for clinical purposes will be asked to donate part of their sample to AURORA US. Researchers will again try to match patients’ primary and metastatic samples so they can identify disease drivers and, in this study, will follow their progress – clinically and through biopsies – over time.

The reference laboratories for the biopsy analysis will be those which took part in The Cancer Genome Atlas study which led to the characterisation of many different types of cancer, and the clinical work will be done through the Translational Breast Cancer Research Consortium (TBCRC) of 19 academic centres in the US.

Davidson points to the huge effort needed to get this study underway, and the importance of the advocate community who have ensured relevant questions are asked and helped raise awareness of the importance of the research.

“I’m very excited about the scientific questions we are attempting to answer, and the laboratories we’ve brought together in our clinical trial consortium. It’s taken longer to bring all this together than I may have hoped but this reflects the complexity of what we’re trying to do, bringing together nearly 20 different institutions,” she says.
The POSITIVE trial: answering an important question for young women

For many young women undergoing hormone treatment for endocrine-responsive early breast cancer, the question of if and when they can stop therapy to become pregnant is high on their list.33

Retrospective and population-based analyses support the safety of pregnancy and breast feeding after breast cancer in women at low risk of recurrence. However, there is no direct evidence about the risks of stopping hormone treatment within the typical five years and up to 10 years of therapy in the approximately 15% of patients who are diagnosed with breast cancer during their reproductive years.

Following extensive discussion through the BIG-NABCG collaboration, the large international POSITIVE trial has been set up to produce clear evidence about the safety of interrupting cancer treatment.

“This is a very important study for young women with breast cancer. At present, if a woman is diagnosed with breast cancer in her early 30s, by the time she has completed treatment, it may be too late to start a family. With the POSITIVE study, we hope to answer that important question of whether it is safe to take a break from treatment,” says Piccart.

The POSITIVE study is aiming to recruit 500 premenopausal women with ER+ early breast cancer who received endocrine therapy for 18 to 30 months, are 42 years of age or younger at enrolment, and wish to interrupt endocrine therapy to become pregnant. Women will take a three-month break in treatment before attempting pregnancy and stop treatment for up to two years to allow time for conception, delivery and breastfeeding (or potential failure to conceive). Endocrine therapy will then restart and continue for the duration of treatment.

By end of December 2018, 339 women with ER+ early breast cancer had been recruited to POSITIVE in 20 countries, and 57 healthy babies had been born. Women will be followed up for 10 years after enrolment and initial results are expected in the next few years.

Breast cancer in men

For the 1% of patients with breast cancer who are male, the International Male Breast Cancer Programme (IMBCP) is a key initiative to gain a better understanding of their disease. Conceived within the BIG-NABCG collaboration, it is led and sponsored by the European Organisation for Research and Treatment of Cancer (EORTC) and the Translational Breast Cancer Research Consortium (TBCRC).

“Male breast cancer is an excellent example of what a major international research collaboration can achieve. It is such a rare disease that it would take a very long time for smaller organisations to collect enough data to gain the knowledge we need,” says Piccart.

By characterising the biology of male breast cancer, the hope is to develop novel approaches to treatment. Following initial centralised analysis of data and tumour samples from 1,800 patients,34 and clinical and pathological disease characterisation, further research is using RNA sequencing and genomic profiling. The second part of the IMBCP consists of a prospective registry for male breast cancer through an international network of centres. In just 30 months, 570 patients were recruited through the network, indicating the potential for clinical trials carried out through the centres.

Previous IMBCP research has consistently shown that fewer men receive hormone therapy than would be expected, or radiotherapy for node positive disease. In absolute terms, breast cancer survival in men is worse than for women but, when data are adjusted for age and comorbidities, survival is similar.

A major goal of the programme is therefore to establish a clinical trial in the male breast cancer setting, possibly of neoadjuvant therapy. In the meantime, considerable effort is going into raising awareness of the unmet needs of men with breast cancer and to improve recruitment of male patients in large breast cancer trials that are often limited to female patients.

“Male breast cancer is an excellent example of what a major international research collaboration can achieve. It is such a rare disease that it would take a very long time for smaller organisations to collect enough data to gain the knowledge we need.”

Martine Piccart

BIG-NABCG: what's next in 2019 and beyond?

During 2019, the BIG-NABCG collaboration aims to consolidate progress in breaking down barriers to clinical trials and simplifying processes for investigators and patients to take part. As demonstrated by the focus of this year’s annual meeting, biomarker-guided treatment de-escalation is another priority as part of efforts to extend precision medicine to more patients with breast cancer.

Piccart points out that there has never been a systematic strategy on the best way to achieve safe de-escalation, so that patients do not lose out in terms of survival. There is also a need to agree the best statistical methodology for de-escalation studies.

The value of treatment de-escalation in women with small HER2+ breast cancers who can be treated with paclitaxel and trastuzumab, without the need for anthracyclines, has now been widely accepted by clinicians and is included in guidelines,
explains Piccart. However, it is proving more difficult to act on the results of the MINDACT trial showing that women with high risk, early-stage breast cancer and a favourable MammaPrint® signature may not need chemotherapy,\(^1\) because some regulatory organisations have been reluctant to approve or reimburse the test.

At the annual BIG-NABCG meeting, discussions will include patient input about the potential risks and benefits of treatment de-escalation:

“By working together on treatment de-escalation in breast cancer at our annual meeting, we hope to publish a consensus statement from BIG and NABCG which will make a more powerful contribution to the field than either organisation alone,” says Piccart.

Over the next few years, the collaboration will also build on recent evidence supporting the role of immunotherapy for breast cancer, as there is considerable interest in improving understanding about which patients are most likely to benefit from the immune approach.

“The ultimate goal is to see a truly international collaboration in which researchers from across the world contribute data from many, many patients in one study to answer one question. In that way, instead of answering questions in years, we will be able to answer them in months.”

Larry Norton

References

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BIG and 20 years of hope and progress

Thanks to global collaboration BIG has become a leading force in the breast cancer research arena

In 2019, BIG is celebrating its 20th anniversary. For the past two decades, BIG and its member groups have been conducting global clinical trials and research programmes to find better treatments against breast cancer. Numerous BIG trials and programmes are considered to be landmark, having introduced particularly innovative designs, studying unmet needs, or contributing to significant breakthroughs that pave the way towards more personalised treatment of breast cancer.

Today, BIG is the largest international network of academic research groups dedicated to finding cures for breast cancer. It consists of 59 national and international member groups from Europe, Canada, Latin America, Asia and Australasia, linking over 10,000 of the world’s leading breast cancer experts and representing several thousand hospitals. 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 has the ability to achieve faster results and greater patient benefits by enrolling larger numbers of patients into clinical trials more quickly, and doing so in many countries around the world.
How it all started

In the mid-1990s, the organisation was little more than an idea raised by two oncologists who had set their hearts on increasing the chances of finding a cure for breast cancer. At the time, breast cancer research in Europe was extremely fragmented, with many academic teams working on similar trials in isolation rather than collaborating. Dr Martine Piccart and Dr Aron Goldhirsch shared a different vision for the future, one where international teams could discuss the results of their latest research, share ideas for new clinical trials and conduct them together.

Today, over 30 clinical trials and several research programmes are currently being run or are under development under the BIG umbrella. Since 1999, more than 95,000 patients have participated in BIG’s clinical trials.

BIG’s ambition is to see the next generation reaping the fruits of its research to beat breast cancer.

To mark the occasion of BIG’s 20th anniversary, a short animation for BIG Member Groups has been produced. It can be found on the BIG website and BIG Member Groups are free to share it.

Today, over 30 clinical trials and several research programmes are currently being run or are under development under the BIG umbrella. Since 1999, more than 95,000 patients have participated in BIG’s clinical trials.

www.BIGagainstbreastcancer.org

Breast cancer incidence

According to recent figures (source: Globocan 2018), by end of 2018, approximately 2.1 million people, including twenty-one thousand men (1%), were estimated to be diagnosed with breast cancer. With no fewer than 627,000 deaths (72 deaths/hour) worldwide, it is the cancer that causes the most deaths in absolute terms.

Breast cancer incidence rates are the highest in Australia/New Zealand, Northern Europe (UK, Sweden, Finland and Denmark), Western Europe (Belgium, The Netherlands, France), Southern Europe (Italy) and Northern America. In women, these rates far exceed those for other cancers in both developed and developing countries, making it the most commonly diagnosed cancer in women: 24.2%, or about 1 in 4 of all new cancer cases in women worldwide. It is also the leading cause of cancer death in women (15%), and the 5th leading cause of death (6.6%) of all cancer deaths worldwide, for both women and men.

Fortunately, mortality rates are falling thanks to the research conducted to date. Women diagnosed with breast cancer 20 years ago had very few treatment options and a low survival rate. But today, patients have access to more individualised treatments.

Many BIG trials now focus on groups of patients having tumours with specific genetic aberrations. The objective is to develop increasingly personalised and precise cancer treatments. BIG trials also anticipate the future, collecting biospecimens for subsequent research to help us better understand tumour biology and learn why some patients respond well to therapies while others do not. This will ultimately help doctors and their patients make better treatment decisions.
CLINICAL TRIALS AND ACTIVITIES

BIG trial updates

PALLAS (ABCSG 42/ BIG 14-03): Enrolment successfully finished  By ABCSG

PALLAS (Palbociclib Collaborative Adjuvant Study) was a huge enrolment success across the world thanks to the remarkable academic collaboration of the global BIG network in this Austrian Breast & Colorectal Cancer Study Group (ABCSG)-sponsored trial.

The study randomisation – which aimed to include 5,600 early breast cancer patients – was closed on 30 November 2018 in all 21 participating countries and 409 sites worldwide, of which 244 sites were from the BIG network. Sites from the BIG academic network enrolled the majority of patients, for which the PALLAS team at the ABCSG office is very proud and grateful. This outstanding achievement was reached ahead of the planned timelines and is the result of the dedication and great efforts of ABCSG’s and BIG’s partners as well as their affiliated study sites worldwide.

Now the efforts are being streamlined to focus on the upcoming interim analysis planned in the investigation of adding the CDK4/6-inhibitor palbociclib to standard adjuvant endocrine therapy in male and female patients with hormone receptor-positive (HR+) / human epidermal growth factor receptor 2 (HER2)-negative early breast cancer.

DCIS (TROG 07.01 / BIG 3-07)  By TROG - the DCIS Trial Team

Since 2007, TROG Cancer Research and BIG have established a productive and successful collaboration on the BIG 3-07/ TROG 07.01 (DCIS) trial, an academic, investigator-led, international, phase III randomised trial of radiation doses and fractionation schedules for non-low risk ductal carcinoma in situ (DCIS) of the breast.

The study, activated in Australia in 2007 and internationally in 2009, is strongly supported by the BIG network, including the Canadian Cancer Trials Group (CCTG); Cancer Trials Ireland; the European Organisation for Research and Treatment of Cancer (EORTC); and the International Breast Cancer Study Group (IBCSG). The Scottish Cancer Trials Breast Group (SCTBG) is also participating in the study.

With the powerful momentum generated by the global investigator team, accrual of 1,608 patients from 136 centres in 11 countries was completed on 30 June 2014, a remarkable two years ahead of schedule. We are excited that the study is coming to fruition, with the main analysis due to be conducted in 2019.
Integral to BIG 3-07/TROG 07.01 trial is the translational research component that aims to develop and validate a clinical diagnostic test to predict the likelihood of recurrence of DCIS or invasive carcinoma. Our unique, prospectively curated and centrally reviewed DCIS tissue resource enables us to perform suitably powered biomarker analyses. In addition, we are analysing the correlative patient-reported outcomes to better understand the perspectives of patients with DCIS and inform shared decision-making in the future.

We would like to sincerely thank all of our collaborators for the strong and enduring support in the conduct of BIG 3-07/TROG 07.01 trial.

For further information, please contact the Study Chair Professor Boon Chua (Boon.Chua@health.nsw.gov.au).

POLAR (IBCSG 59-19 / BIG 18-02)
By IBCSG

The POLAR trial (IBCSG 59-19 / BIG 18-02) protocol was released on 17 December 2018.

POLAR is a multicentre, randomised phase III trial comparing adjuvant palbociclib in combination with endocrine therapy versus endocrine therapy alone in patients with hormone receptor-positive / HER2-negative resected isolated locoregional recurrence (ILRR) of breast cancer. Consistent with initiatives to generalise eligibility criteria, this is the first IBCSG-coordinated trial that will enrol male patients. In addition, both premenopausal and postmenopausal women will be enrolled, and exclusions with respect to prior malignancies have been reduced.

In a high proportion of patients, local or regional recurrence of breast cancer after mastectomy or lumpectomy indicates poor prognosis and accompanies or precedes distant metastasis. Patients with ILRR without evidence of distant metastasis hold a substantial risk of developing subsequent distant metastasis, with 5-year survival probabilities ranging between 45% and 80% after locoregional recurrence1,2. These outcomes show the powerful negative prognostic importance of ILRR events, and the need for treatments beyond surgical removal of the ILRR.

An updated, final analysis of the CALOR Trial (IBCSG 27-02 / BIG 1-02 / NSABP B-37) after median follow-up of about 9 years was published in the Journal of Clinical Oncology in April 2018, and confirmed that chemotherapy benefitted patients with resected ER-negative ILRR3. The CALOR results strongly suggest that tailoring treatment according to the characteristics of the recurrent lesion – in this case ILRR – provides a better indication of possible treatment response than tailoring according to the characteristics of the primary tumour.

Based on these results and on strong evidence suggesting the activity of CDK4/6 inhibitors combined with endocrine therapy, the POLAR study investigators hypothesise that the CDK4/6 inhibitor palbociclib given in combination with endocrine therapy may be effective as adjuvant therapy in patients with HR-positive / HER2-negative resected ILRR of breast cancer.

Trial design of IBCSG 59-19 / BIG 18-02 POLAR

Palbociclib
125 mg/day orally for 21 days, followed by 7 days rest for 3 years
Standard endocrine therapy (as per local practice)
- May consist of AI, fulvestrant or SERM, +/- LHRH analog if premenopausal or male
- Can have already started at time of randomisation
- Protocol endocrine therapy duration is at least 3 years from randomisation
- Patients are encouraged to continue ET beyond 3 years, according to Investigator’s decision
Surgery
- Randomisation must take place within 6 months from the complete gross excision of the isolated locoregional recurrence.

The trial will enrol 400 patients from approximately 35 centres in six different countries in Europe. The enrolment is expected to occur over a period of 3.5 years, with the targeted number of events required or the primary analysis expected 1.5 years after the inclusion of the last patient, and the updated analysis approximately 4 years later.

The POLAR trial, coordinated and sponsored by IBCSG, is being conducted under the BIG umbrella as a Supporter trial. It has garnered much interest from IBCSG centres and BIG member groups. If you would like to know more about this trial, please contact ibcsg59_polar@fstrf.org.

FINESSE (BIG 2-13)

Lucitanib for the treatment of HR+ HER2-negative metastatic breast cancer patients: results from the multicohort phase II study

Results of the FINESSE trial, which involved 76 patients with breast cancer from 24 hospitals in nine countries, were presented as a poster at ESMO 2018. Recruitment in the study was stopped prematurely as the drug was associated with less tolerability and more safety concerns than predicted. Additionally, lucitanib was not shown to be better for patients than available standard chemotherapy.

Still, the study data suggest that lucitanib might provide antitumour activity in patients with hormone receptor-positive (HR+), HER2-negative (HER2-) metastatic breast cancer. Exploratory biomarker analyses also show that patients with high FGFR1 amplification present a higher objective response rate (ORR) (25%) than those without amplification (8%). Investigators therefore hypothesise that patients with high FGFR1 expression might derive more benefit from lucitanib and recommend to further explore this patient population in a large trial.

The main objective of FINESSE was to evaluate the effects of lucitanib, an inhibitor of angiogenesis and FGFR proteins, and the response rate in patients with metastatic breast cancer whose tumours harboured abnormalities in the FGFR1 and/or chromosome arm 11q genes/proteins, i.e. either amplified or non-amplified cancer cells. In particular, the trial aimed to determine whether lucitanib had the potential to slow down or stop such cancer cells from growing or spreading further. The secondary objectives were to determine the clinical benefit rate and progression-free survival (PFS), as well as to evaluate the drug’s safety.

BIG 1-98 / IBCSG 18-98

Long-term follow-up results published

Last November Dr Thomas Rustaller and colleagues published the long-term follow-up (LTFU) analysis results of the BIG 1-98 / IBCSG 18-98 trial in the Journal of Clinical Oncology. Overall, results of the 12.6 years of median follow-up showed continued, although modest and decreasing, benefit of letrozole compared to tamoxifen as adjuvant endocrine therapy for postmenopausal women with receptor (ER and/or PgR) positive tumours. It was reported that contralateral breast cancer incidence was lower in the first 10 years with letrozole whereas, after 10 years, it was less frequent following tamoxifen.

In 2010, when pharmaceutical sponsorship ended at 8.4 years of median follow-up, the academic partners, i.e., the International Breast Cancer Study Group (IBCSG) together with the Breast International Group (BIG), decided to continue to follow up patients and initiated an observational, long-term follow-up extension collecting annual data on survival, disease status and adverse events.

As emphasised by the authors of the publication, this LTFU study illustrates the value of extended follow-up in trials with luminal breast cancer.

BIG 1-98 is a four-arm, phase III study designed to evaluate letrozole as adjuvant endocrine therapy compared to tamoxifen, for postmenopausal women with receptor (ER and/or PgR) positive tumours. The 8,010 women enrolled received either letrozole continuously for five years or received a sequence or two years of a letrozole plus three years of tamoxifen.

BIG research at SABCS 2018
(December 4-8, San Antonio, USA)

Every year in December, the San Antonio Breast Cancer Symposium (SABCS) brings together researchers and physicians from around the world to present and discuss the latest findings in breast cancer research. Several clinical trials conducted within the BIG network were presented at SABCS 2018. The below gives you a glimpse:

ALTTO (BIG 2-06)

Researchers investigated the prognosis of patients with hormone receptor-positive (HR+) or receptor-negative (HR-) HER2-positive early breast cancer, the risk of early and late recurrences, the risk factors and the patterns of relapse according to the HR status. This large analysis included 6,271 patients (median follow-up 6.93 years) treated with modern chemotherapy (CT) and trastuzumab (T)-based regimens from the ALTTO trial (the lapatinib-alone arm was not included).

The investigators concluded that their study provides strong evidence for two different diseases within the HER2+ population based on HR expression. This large analysis, they say, may be used as “historical” control for the design of future de-escalation or escalation trials separately in patients with HR+ and HR- HER2+ early breast cancer.

International Male Breast Cancer Programme (EORTC-10085-BCG / BIG 2-07)

Researchers presented the gene expression results of 380 out of the total 1,483 male breast cancer patients enrolled in the retrospective joint analysis (part 1) of the International Male Breast Cancer Programme (EORTC-10085-BCG / BIG 2-07) (Cardoso et al. Annals of Oncology, 2018*). This study was designed to generate and compare risk scores of the current commercial breast cancer multigene tests and demonstrate their clinical utility in male breast cancer, as well as the discrepancies and similarities with female breast cancer. While disagreement between test results at the individual patient level was found, the assays evaluated and already validated in female breast cancer were shown to provide similar information in male breast cancer patients as in female ones.

POSITIVE (IBCSG 48-14 / BIG 08-13)

A trials-in-progress poster was presented for the IBCSG 48-14/BIG 08-13 POSITIVE trial. POSITIVE is enrolling premenopausal patients with hormone receptor-positive early breast cancer who wish to conceive, and evaluates the pregnancy and disease outcomes as well as the safety of temporarily interrupting adjuvant endocrine therapy to allow for pregnancy. The poster outlined the study objectives, design, methods and accrual. By end of December 2018, POSITIVE had enrolled 339 out of 500 patients, with accrual completion expected mid-2020.

A study evaluating pregnancy, disease outcome and safety of interrupting endocrine therapy for premenopausal women with endocrine responsive breast cancer who desire pregnancy (IBCSG 48-14/BIG 8-13). Pagani O., et al. (OT1-01-06)

SOFT-EST, a substudy of the IBCSG 24-02/BIG 2-02 SOFT trial, aimed to describe estradiol, estrone and estrone sulphate during the first 4 years of treatment with monthly triptorelin plus either exemestane or tamoxifen, and to assess if there were patients with suboptimal estrogen suppression in the combined triptorelin-exemestane treatment group. Most patients in the triptorelin-exemestane group experienced a profound estradiol drop, consistent with postmenopausal status on aromatase inhibitors; however, over 20% of them had 2 or more estradiol values above the strict threshold for optimal suppression (2.72 pg/mL), and 4% reported vaginal bleeding. Women with higher estradiol levels prior to initiating the triptorelin-exemestane treatment more frequently experienced suboptimal estrogen suppression. The results were displayed as a poster.

BIG 1-98/ IBCSG 18-98

By IBCSG

A BIG 1-98/IBCSG 18-98 translational research (TR) project aimed to validate a novel integrated clinical-pathologic and genomic method derived from the METABRIC series to classify invasive ductal luminal breast cancers (IDLBC). Another objective was to explore whether including specific treatment information could differentiate between sensitivity or insensitivity to tamoxifen and/or letrozole. In the BIG 1-98 study, 8,010 postmenopausal women with hormone receptor-positive, operable invasive breast cancer were randomised into 1 out of 4 possible 5-year adjuvant treatments: monotherapy with either letrozole or tamoxifen, or sequential strategy of letrozole then tamoxifen, or tamoxifen then letrozole. Results of the TR project validated that, in the BIG 1-98 cohort, IDLBC3 status was associated with increased risk of distant recurrence and shorter overall survival. The results also showed that the magnitude of letrozole vs. tamoxifen treatment benefit was greater for IDLBC3 than for IDLBC1-2 tumours.
Other trials & activities by BIG member groups

BCT-ANZ

**DIAmOND and CHARIOT – New immunotherapy clinical trials**

Breast Cancer Trials (BCT-ANZ) has started two new clinical trials that are both looking at how patients may benefit from immunotherapy, which uses the patient’s own immune system to aid in their cancer treatment. Immunotherapy is not in routine use as a treatment option for breast cancer in Australia and New Zealand, but breast cancer researchers are learning from the results of research in other cancer types, such as melanoma, lung cancer and bladder cancer. The **DIAmOND** and **CHARIOT** clinical trials will use different combinations of immunotherapy in patients with different breast cancer subtypes that are more likely to respond to immune manipulation.

Professor Sherene Loi is the Study Chair of both of these new trials and a member of the BCT Scientific Advisory Committee. More information about these clinical trials are available at www.breastcancertrials.org.au.

**Breast Cancer Trials 2019 Annual Scientific Meeting**

BCT’s 41st Annual Scientific Meeting (ASM) will be held on 24-26 July 2019 at The Hilton Adelaide, South Australia. ASM registration and applications for travel grants will open in early 2019.

**Education campaign**

BCT has recently launched a public education campaign that pairs stories of women who have participated in past clinical trials with women today who have received a treatment that was proven effective in a trial. The aim of this campaign is to highlight the importance of clinical trials research and participation in clinical trials. To view the campaign videos and stories of some of BCT-ANZ’s ground-breaking past clinical trials, visit www.trialssavelives.com.au.
The China Medicine Education Association (CMEA) is a national level, academic non-profit organisation. The Breast Disease Professional Committee of CMEA (BDPCC) is a secondary branch of the CMEA, which was established on 30 January 2015. The BDPCC has 418 members, most of whom are breast surgeons, oncologists and pathologists. Our members come from over 300 hospitals, spreading over 30 provinces in China. The main activities of the BDPCC are to:

1) offer continuing education to community physicians with the purpose to train them in breast disease treatment;
2) hold the Breast Disease Multidisciplinary Symposium and the Great Wall Breast Cancer Conference every year;
3) launch a multicentre prospective observational study, with the purpose of collecting breast cancer tissue samples for further sequencing and analysis;
4) play a leading role in multicentre clinical trials in China and participate actively in international clinical trials.

Activities of BDPCC in 2018

1) The Breast Disease Multidisciplinary Symposium and the Great Wall Breast Cancer Conference
The Breast Disease Multidisciplinary Symposium and the Great Wall Breast Cancer Conference have been held four times since BDPCC was established. The fourth Great Wall Breast Cancer Conference took place in Shijianzhuang, Hebei province, on 16-18 March 2018 and gathered leading Chinese personalities in the breast disease field who shared their experience with colleagues from across China.

2) County education, China circuit
With the aim to improve the low level of breast disease diagnosis and treatment in district and community hospitals of China, BDPCC launched the County education, China circuit on 27 March 2016 to provide physicians in those institutions with free education and training. In 2018, BDPCC provided the same to over 2000 physicians in the provinces of Hebei, Shanxi, Gansu, Guangdong, Heilongjiang, Shandong, Jilin, Liaoning, Jiangsu, Zhejiang, Shaanxi, Sichuan, and Inner Mongolia Autonomous Region, among others.

3) Research launched by BDPCC
Breast cancer gene mutation screening in China (February 2016 - April 2020)
Breast cancer is a major public health problem worldwide and the most common female cancer in China. The therapeutic strategy for breast cancer is complex. With the development of precision medicine theory and the associated technology, it is increasingly possible to tailor treatments to individual patients. However, precision medical data so far have been obtained from European and American populations, which may not be suitable for Chinese breast cancer patients. The objectives of the breast cancer gene mutation screening study launched by BDPCC include using high-throughput technology to conduct sequencing analyses of tumour tissues and plasma specimens to search for drug targets, develop gene panels independently and validate them.

Future prospects of BDPCC
Since BDPCC became a BIG member group, it has been active in various meetings and other activities hosted by BIG, such as the Scientific Meeting held during the last EBCC Conference (Barcelona, March 2018) and the first BIG-East Asia Clinical Trial Workshop for Young Investigators that took place in Singapore in November 2018.

BDPCC’s vision is in accord with that of BIG: “We will find a cure for breast cancer through global research and collaboration”. What we are doing is pushing forward breast cancer therapy in China. By joining the BIG network, BDPCC aims to bond with the other member groups and collaborate together to make further progress in breast cancer research and therapy.
GBG

As a leading cooperative study group in the field of breast cancer in Germany, the German Breast Group (GBG) currently manages over 40 clinical trials across all major therapeutic areas: prevention, surgical palliative, adjuvant, and neoadjuvant, for which the group is best known.

Clinical trial status and results

In 2018, GBG continued to deliver consistent high-quality results that contribute to improving the treatment of breast cancer patients and their quality of life. Furthermore, the GBG-led clinical trials were also accompanied by broad translational research programmes, allowing for analysis of biomaterial in academic cooperations worldwide.

The first results of the neoadjuvant GeparNuevo trial were presented at ASCO 2018. In this phase II study of 174 patients with early stage triple-negative breast cancer, the addition of durvalumab to anthracycline/taxane based chemotherapy increased the pCR rate by an absolute 9%, although this was not statistically significant. The durvalumab effect was seen only in the window cohort of patients treated with durvalumab alone prior to starting chemotherapy, as compared to placebo. Hence, induction therapy with durvalumab seems beneficial.

Translational research findings of GeparNuevo were received with great interest at SABCS 2018 and support further investigation of durvalumab as treatment for patients with primary triple-negative breast cancer.

Another GBG success in 2018 was the publication of the first results of the KATHERINE study, which was a joint effort with the National Surgical Adjuvant Breast and Bowel Project (NSABP). In the interim analysis, T-DM1 showed a statistically significant and clinically meaningful improvement of invasive disease-free survival by an absolute value of 11% compared to trastuzumab as adjuvant treatment in patients with HER2-positive early breast cancer and residual disease after neoadjuvant therapy. The safety data were consistent with the known safety profile of T-DM1, with more adverse events associated with T-DM1 than with trastuzumab alone.

Results of the neoadjuvant GeparOcto trial were recently published, demonstrating no difference in pCR rates between patients with high-risk early stage breast cancer who received intensified dose-dense epirubicin, paclitaxel and cyclophosphamide, and those treated with weekly paclitaxel/liposomal doxorubicin plus carboplatin in triple-negative breast cancer patients only. Among the triple-negative breast cancer patients, those carrying germline BRCA1/2 mutations had a higher pCR rate compared with non-carriers; there was, however, no evidence for a benefit of carboplatin treatment in this setting.

Soon, the results of the international PenelopeB study (GBG 78/BIG 01-13), a study under the BIG umbrella, are expected to shed light on the addition of the CDK4/6 inhibitor palbociclib as postneoadjuvant treatment for HER2-negative, hormone receptor-positive patients with high relapse risk after neoadjuvant chemotherapy.

Ongoing trials and future research

Currently, a number of GBG trials and registries are ongoing in the neoadjuvant, adjuvant and palliative settings. GeparX is evaluating the addition of the RANK-ligand antagonist denosumab to neoadjuvant chemotherapy, while GeparDouce is investigating the addition of the immune-checkpoint inhibitor atezolizumab to preoperative treatment in patients with triple-negative tumours. In metastatic breast cancer, several trials of CDK4/6 inhibitors are recruiting (i.e. AMICA, PADMA).

A prospective and retrospective registry study on breast cancer in pregnancy and young women (BCP), in cooperation with BIG (GBG 29/BIG 03-02), is successfully ongoing. Data about the oncological management and survival of young non-pregnant patients with breast cancer diagnosed at the age of 40 years or younger was presented at SABCS 2018.

GBG will continue to develop clinical trials and translational research to investigate new therapeutic agents for breast cancer with an emphasis on immune-checkpoint inhibitors.

References:
1. Loibl S, Untch M, Burchardi N et al. Randomized phase II neoadjuvant study (GeparNuevo) to investigate the addition of durvalumab to a taxane-anthracycline containing chemotherapy in triple-negative breast cancer (TNBC). J Clin Oncol 36, 2018 (suppl; abstr 104).
6. Schneeweiss A, Mösbus V, Tsch H, et al. Intense dose-dense epirubicin, paclitaxel, cyclophosphamide and weekly paclitaxel, liposomal doxorubicin (plus carboplatin) in triple-negative breast cancer patients only. Among the triple-negative breast cancer patients, those carrying germline BRCA1/2 mutations had a higher pCR rate compared with non-carriers; there was, however, no evidence for a benefit of carboplatin treatment in this setting.
Important results of CIBOMA/2004-01 GEICAM/2003-11 study presented at SABCS 2018: Adjuvant capecitabine did not significantly improve outcomes for patients with early stage triple-negative breast cancer

Subgroup analysis suggested the treatment may benefit patients with non-basal-like disease.

During SABCS 2018, Professor Miguel Martín, GEICAM President, presented the results of CIBOMA/2004-01 GEICAM/2003-11 study* investigating the use of capecitabine to treat patients with triple-negative breast cancer (TNBC) in the adjuvant setting. This study, a collaboration between the Iberoamerican Coalition for Research in Breast Oncology (CIBOMA) and GEICAM, was presented on 5 December in General Session 2.

The study’s conclusion is that patients with early stage triple-negative breast cancer treated with adjuvant (maintenance) capecitabine, after having completed their standard treatment with neo/adjuvant chemotherapy (anthracyclines +/- taxanes), surgery and adjuvant radiation therapy according to local guidelines, did not show significantly improved disease-free survival and overall survival compared with those patients in the observation group.

Furthermore, in the subgroup analyses, it was found that, among the 248 patients with non basal-like disease, those randomised to receive adjuvant capecitabine were 49% less likely to experience a disease event and 52% less likely to die compared with those randomised to observation. Non-basal-like disease was defined by the absence of cytokeratins 5/6 and epidermal growth factor receptor expression, determined by central immunohistochemical assessment at the patient’s inclusion.

“We were disappointed to find that adding adjuvant capecitabine to the standard treatment did not significantly improve disease-free or overall survival,” said Professor Martín. “However, given that we found that the subset of patients with non basal-like disease seemed to have a significant benefit from capecitabine, and data from the CREATE-X trial showed that adjuvant capecitabine significantly reduces the rate of relapse and improves overall survival when administered to breast cancer patients with residual disease after neoadjuvant chemotherapy, we strongly recommend that patients with triple-negative breast cancer discuss adjuvant capecitabine with their oncologists.”

Although the results of the subgroup analyses need more extensive work to confirm their validity, if confirmed, these results will open new opportunities to investigate innovative approaches for patients with this type of breast cancer.

Recruitment just completed in the PEARL study (GEICAM/2013-02)

A phase III study of palbociclib with endocrine therapy vs. chemotherapy in HR+/HER2- metastatic breast cancer patients.

Endocrine therapy (ET) is the cornerstone treatment for hormone receptor (HR)–positive, HER2-negative breast cancer patients. However, endocrine resistance is a major clinical challenge. When the cancer of patients being treated with aromatase inhibitors (AIs) recurs or progresses, treatment options include giving sequential endocrine-based therapies, i.e. another AI or estrogen-receptor antagonists/degraders administered as monotherapy or in combination with a targeted therapy, or making a strategic change to chemotherapy.
Palbociclib is a CDK4/6 inhibitor approved for use in combination with AIs or fulvestrant in patients with HR-positive, HER2-negative metastatic breast cancer (MBC), both for patients being treated first-line or those who have been pretreated. However, the relative value of palbociclib plus hormones versus chemotherapy in pretreated patients has not been established yet.

PEARL is an international, multicentre, open label, controlled, randomised phase III study comparing the efficacy and safety of palbociclib given in combination with endocrine therapy (exemestane or fulvestrant) versus capecitabine in postmenopausal women with HR-positive/HER2-negative MBC whose disease was resistant to previous AIs.

We know that palbociclib combined with fulvestrant in second-line therapy is better than fulvestrant alone, and that capecitabine is a very active and well-tolerated drug in this setting. To our knowledge, PEARL is the first study comparing a CDK4/6 inhibitor given in combination with endocrine therapy to chemotherapy alone in this group of patients. Currently, there is no evidence of the superior clinical benefit of endocrine therapy plus palbociclib compared to capecitabine. The PEARL trial was developed to answer this very relevant question.

PEARL is already fully enrolled and we are now focusing on the progression-free survival analysis. The necessary number of events were reached in January 2019. The results will be presented and published very soon.

GOCCHI

On 20 December 2018, nearly 50 professionals from Fundación Arturo López Pérez (FALP) and working in clinical research participated in the first Good Clinical Practice (GCP) course organised by the Oncology Drug Research Unit of FALP, in collaboration with the Chilean Oncologic Group for Clinical Research (GOCCHI).

The GOCCHI group providing the training was headed by Dr. Bettina Müller, medical oncologist and Director of GOCCHI, Dr. Javier Retamales, radiation oncologist and Assistant Medical Director and Zdenka Zlatar, Senior CRA and Study Coordinator.

For Dr. Erika Saavedra, Head of the Oncology Drug Research Unit of FALP, updates on GCP are essential for anyone working in clinical research, while also being a requirement for all centers involved.
The Hellenic Cooperative Oncology Group (HeCOG)’s interest in conducting breast cancer research is ongoing and growing. As we have a very large biobank of both blood and tissue samples from patients treated in HeCOG’s clinical trials or recommended therapy programmes, lately most of our work has been translational research. Over the last 15 years, HeCOG has regularly published high-quality, original translational research articles. In 2018, our group published 14 papers on breast cancer, all in high-quality journals, and mainly in translational research. These include the following:


**HeCOG**

**IBCSG**

Last December at SABCS, the International Breast Cancer Study Group (IBCSG) presented two posters with interesting results from translational research projects exploring methylation markers and triple-negative breast cancer (TNBC). (P4-08-09, P5-12-04).

The first poster described a project investigating whether molecular markers of epigenetic processes, such as DNA methylation, could risk-stratify patients with TNBC. Genome-wide methylome marker discovery was performed on samples from patients having received locoregional therapy with and without chemotherapy from institutional and clinical trial cohorts of TNBC (the latter including IBCSG Trials VIII & IX). Methylation signatures that distinguished patients who remained recurrence-free from those with recurrent disease were identified in the discovery cohort consisting of 100 and 30 CpG markers. In the IBCSG no-chemotherapy cohort, high methylation of the signatures was associated with a shorter recurrence-free interval. Similarly, high methylation was significantly associated with recurrence in the combined institutional and IBCSG chemotherapy cohort (100 CpG, P=0.002; 30 CpG, P = 0.05).

A second poster presented a new approach to analysing methylome datasets. These studies suggest that high methylation confers increased risk of recurrence independently of whether patients receive chemotherapy or not. Methylation markers could have prognostic value in TNBC, and the findings should be validated in additional clinical trial cohorts.

**NBCG**

Several Norwegian neoadjuvant studies are being or have been conducted by the Norwegian Breast Cancer Group (NBCG), in order to perform in-depth molecular analyses of the effect of various systemic treatments on primary breast tumours. These studies aim to identify tumour signatures or factors associated with resistance or sensitivity to anthracyclines, taxanes, cyclophosphamide, carboplatin and targeted treatments (HER2-directed, PARP-inhibition, anti-angiogenic treatments):

- **NBCG6/NeoTAX**: Evaluation of epi-adriamycin versus paclitaxel for primary medical treatment (neo-adjuvant chemotherapy) in patients with locally advanced (stage III, T3/4 and/or N2) non-inflammatory breast cancer with or without limited distant metastases. Recruitment has completed and analyses are ongoing;
  - **Neoadjuvant Avastin in Breast Cancer (NeoAVA)**: Recruitment has completed, and analyses are ongoing;
  - **PERSONALIZED TREATment of high-risk MAMmary Cancer (PETREMAC/NBCG15)**: Recruitment has completed, and analyses are ongoing;
  - **Improved Breast Cancer Therapy (I-BCT-1)** (with carboplatin) in the Neoadjuvant and Metastatic Setting (I-BCT): Recruitment is ongoing.
NBCG has also played a leading role in conducting a study to test the efficacy of secondary adjuvant treatment in patients with presence of single disseminated tumour cells in the bone marrow 8 to 9 months after receiving anthracycline-containing chemotherapy. The primary endpoint results have been published, but additional analyses are ongoing. (NBCG9/SATT: recruitment completed).

The Energy Balance and Breast Cancer Aspects study (EBBA2/NBCG14) has randomised 600 patients after breast cancer surgery to compare intervention with an exercise programme versus control (i.e. no exercise programme during adjuvant treatment; recruitment and intervention have been completed). The first results were presented in a general session at SABCS 2018.

A study of hypo-fractionated locoregional treatment and integrated boost in breast cancer is being conducted by some of the NBCG investigators in collaboration with an international radiotherapy group (SKAGEN1 trial: ongoing).

Check-point blockades in advanced breast cancer are the focus of two recently launched Norwegian phase II studies testing immunogenic chemotherapy (liposomal doxorubicin 2qw + oral cyclophosphamide 2/4 weeks) +/- atezolizumab (anti-PD-L1) in triple negative breast cancer (NBCG17/ALICE) and immunogenic chemotherapy +/- nivolumab (anti-PD1) and low dose ipililumab (anti-CTLA4)(NBCG18/ICON) in Luminal B breast cancer.

With the primary aims to reduce overtreatment with adjuvant chemotherapy and to establish molecular breast cancer profiling within all Norwegian health regions, two large NBCG studies opened in October 2018, using the Prosigna® test to classify ER+HER2- patients into refined prognostic groups. Fifteen hospitals in Norway are planning to participate in these studies. NBCG19/EMIT1 is a decision-impact study for patients with node-negative disease, whereas NBCG20 is part of the OPTIMA trial randomising patients mainly with node-positive (pN1-2) disease to Prosigna® test-directed decision-making: chemotherapy plus endocrine treatment (patient group 1) or endocrine treatment alone versus chemotherapy plus endocrine treatment (patient group 2 according to the Prosigna test). The Norwegian part of the OPTIMA trial is being run in collaboration with the UK OPTIMA study group.

1 Cardiovascular function and the effect of exercise training during adjuvant breast cancer treatment. Results from the EBBA-II trial, Thune I, et al. General Session 45, Abstract #GS5-02, SABCS2018

Precision medicine through translational research

To be at the forefront of cancer research, SOLTIs scientific strategy focuses on three main types of programmes. These include clinical trials designed to answer questions of major scientific interest and clinical relevance.

Firstly, there is the Clinical Trial Research Programme. This comprises translational-oriented studies, mainly phase II proof-of-concept trials that are highly informative at the clinical level. This year, SOLTi will launch four such studies, all designed and sponsored by the group.

Secondly, the Window Programme concentrates on small, innovative window-of-opportunity trials devoted to better understanding the biological activity of a drug, alone or in combination with others. The group has already completed VENTANA-SOLTI-1501, the first study under this programme. One study is ongoing, and three more will begin in 2019, with a special focus on novel immunotherapies.

Finally, SOLTIs Biomarker Programme covers correlative analyses using tumour and blood samples to identify the prevalence or distribution of molecular alterations within different cohorts of patients of interest. Through retrospective and prospective approaches, this programme aims to deconstruct the biology of cancer and identify promising predictive biomarkers in selected scenarios, enabling us to shape the next steps in clinical trial design.

The three programmes together aim to prove that patient selection according to biological criteria is the most precise approach to ensure better outcomes for patients. With this in mind, three of the four studies being initiated in 2019, PATRICIA 2, TATEN and NEREA, will prospectively select patients according to their molecular intrinsic subtypes.

PATRICIA II

Based on the results reported at SABCS 2017 of the SOLTi-1303_PATRICIA study, an exploratory phase II study that evaluated the efficacy of combining palbociclib plus trastuzumab with or without letrozole in postmenopausal patients who had received at least two prior lines in their metastatic disease, SOLTi is starting the confirmatory study, PATRICIA II.

PATRICIA II will prospectively select patients with HER2-positive/hormone receptor (HR)-positive, luminal intrinsic
subtypes. The study’s aim is to confirm the significant statistical difference in progression-free survival that was seen in the PATRICIA study in the luminal intrinsic subtypes, defined by PAM50, compared to non-luminal disease (10.5 months vs. 3.5 months).

**TATEN and NEREA:**
Within advanced HR-positive/HER2-negative tumours, the prognostic value of the basal-like and HER2-enriched (E) intrinsic subtypes are associated with worse outcome than luminal subtypes. Thus, non-luminal HR-positive/HER2-negative tumours are aggressive and require novel therapeutic approaches.

TATEN will assess the efficacy of pembrolizumab and paclitaxel in treating PAM50 non-luminal disease within HR-positive/HER2-negative advanced breast cancer. NEREA will investigate the efficacy of combined neratinib and endocrine therapy to treat patients with advanced HR-positive/HER2-negative disease, whose tumours are HER2-E and resistant to endocrine treatment.

The results of these studies, and all the data collected through the associated comprehensive translational research, may contribute to a paradigm change in the patient selection process for future clinical trials.

Taking all this into account, and in its mission to promote excellence in clinical research, SOLTI is committed to moving towards precision medicine by developing translational-oriented studies and fostering international collaborations to improve the prognosis and well-being of breast cancer patients.

**TROG**

**TROG celebrates its 30th Anniversary in 2019**

This year marks the 30th Anniversary of the Trans-Tasman Radiation Oncology Group (TROG), with celebrations planned during the TROG Annual Scientific Meeting on 12-15 March 2019 in Melbourne, Australia. This meeting will bring together approximately 250 delegates, and feature plenary sessions and workshops, including a dedicated stream on breast cancer clinical trials. For more information: http://www.cmnzl.co.nz/trog-2019-asm/

TROG Cancer Research is the leading collaborative cancer trials group for research involving radiotherapy in Australia and New Zealand. Over the past 30 years TROG has gained national and international recognition in trial excellence, having accrued more than 14,500 patients to its studies. The group represents over 1,400 members, including oncologists, radiation therapists, medical physicists, data managers and other researchers, together conducting research across a range of cancers. TROG Cancer Research has completed over 100 cancer clinical trials via its collaboration with more than 200 public and private centres in Australia and internationally.
The Breast International Group (BIG) is a not-for-profit organisation for academic breast cancer research groups from around the world.

Founded by leading European breast cancer experts in 1999, BIG now constitutes a network of 59 groups and data centres based in Europe, Canada, Latin America, the Middle East, Asia and Australasia. These entities are tied to several thousand specialised hospitals and research centres worldwide. About 30 clinical trials and several research programmes 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, so that together they act as a strong interacting force in the breast cancer research arena.

www.BIGagainstbreastcancer.org

The 59 breast cancer research groups of the BIG network

ABCG
Austrian Breast & Colorectal Cancer Study Group
AGO-B
Arbeitsgemeinschaft Gynäkologische Onkologie Breast Study Group
ARCAGY-GINECO
Association de Recherche dans les Cancers dont Gynécologiques – Groupe d’Investigateurs Nationaux pour l’Étude des Cancers Ovariens et du sein
BCT-ANZ
Breast Cancer Trials - Australia & New Zealand
BDPCC
Breast Disease Professional Committee of CMEA (China)
BGICS
Breast-Gynecological International Cancer Society
BIBI
Breast Intergroup of Eastern India
BOOG
Borstkanker Onderzoek Groep
CCTG
Canadian Cancer Trials Group
CEEOG
Central and East European Oncology Group
CT-IRE
Cancer Trials Ireland
CTRG
Cancer Therapeutics Research Group
DBCG
Danish Breast Cancer Cooperative Group
EORTC BCG
European Organisation for Research and Treatment of Cancer, Breast Cancer Group
FBG
Finnish Breast Cancer Group / Suomen lintusäästöpäivätä
FBI
Francilien Breast Intergroup
GAGE
Grupo Argentino de Investigación Clínica en Oncología
GBG
German Breast Group
GCSC
Georgian Cancer Study Group
GECO PERU
Grupo de Estudios Clinicos Oncologicos Peruano
GECAM
Spanish Breast Cancer Group
GOCCHI
Chilean Cooperative Group for Oncologic Research
GOCUR
Grupo Oncologico Cooperativo Uruguayo
GORIC
Italian Oncology Group for Clinical Research
GONO
Gruppo Oncologico Nord-Ovest
HBSS
Hellenic Breast Surgical Society
HeCOG
Hellenic Cooperative Oncology Group
HKBOG
Hong Kong Breast Oncology Group
HORG
Hellenic Oncology Research Group
IBC
Icelandic Breast Cancer Group
IBCSG
International Breast Cancer Study Group
IBG
Israeli Breast Group
IBIS
International Breast Cancer Intervention Studies
ICCG
International Collaborative Cancer Group
ICON ARO
Indian Co-Operative Oncology Network
ICRC
Iranian Cancer Research Center
ICR-CTSU
Institute of Cancer Research – Clinical Trials & Statistics Unit
IJB / CTSU
Institut Jules Bordet / Clinical Trials Support Unit
IÖG
Indian Oncology Group
IOMO
Italian Oncology Group
JBCRG
Japan Breast Cancer Research Group
KCSG
Korean Cancer Study Group
LACOG
Latin American Cooperative Oncology Group
MICHIELANGELO
Fondazione Michelangelo
NBCG
Norwegian Breast Cancer Group
NCRI-BCSG
National Cancer Research Institute - Breast Cancer Clinical Studies Group
SAKO
Swedish Association of Breast Oncologists
SAXK
Swiss Group for Clinical Cancer Research
SBCG
Sheba Breast Collaborative Group
SKMCH & RC
Shaukat Khanum Memorial Cancer Hospital & Research Centre
SLO
Société Luxembourgeoise d’Oncoologie
SOBU
Breast Cancer Research Group
SUCCESS – Study Group
SweBCG
Swedish Breast Cancer Group
TCOG
Taiwan Cooperative Oncology Group
TROG
Trans Tasman Radiation Oncology Group
TSCO
Thai Society of Clinical Oncology
UCBG
Unicancer Breast Group
WSG
Westdeutsche Studiengruppe
Overview of the clinical studies run within the BIG network

### Open, recruiting patients

<table>
<thead>
<tr>
<th>Study name</th>
<th>BIG Number</th>
<th>Short description</th>
<th>Principal Investigator(s)</th>
<th>Trial model &amp; partners</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALEXANDRA / IMpassion 030</td>
<td>BIG 16-05</td>
<td>A randomised phase III trial computing atezololimus (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</td>
<td>Lead trial (Co-Leading partners: BIG HQ / IJB-CTSU / B(E)AsT / FSTRF and AFT) Pharma partner: Roche/Genentech (sponsor) Funding: Roche / Genentech</td>
</tr>
<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. Afittos, M. Oliveira</td>
<td>BIG-sponsored programme (Co-Leading partners: BIG HQ (sponsor) / IJB-CTSU (B(E)AsT) / FSS Pharma partner: N/A Funding: BCRF, Deutsches Konsortium für Translationale Krebsforschung</td>
</tr>
<tr>
<td>Breast Cancer in Pregnancy</td>
<td>BIG 2-03</td>
<td>Prospective registry of women treated for breast cancer while pregnant NCT01950833</td>
<td>S. Ledl, G. von Minckwitz</td>
<td>Supporter trial (Co-Leading partner: GBG (sponsor) Pharma partner: N/A Funding: GBG, Deutsches Konsortium für Translationale Krebsforschung</td>
</tr>
<tr>
<td>Exceptional Responders</td>
<td>BIG 16-04</td>
<td>A global hunt for exceptional responders in the BIG network: aiming to identify breast cancer patients with a truly remarkable clinical response to anticancer treatments, and to characterise their tumours molecularly.</td>
<td>A. Iorshium (coordinator)</td>
<td>BIG-sponsored programme (Co-Leading partner: BIG HQ Pharma partner: N/A Funding: BCRF</td>
</tr>
<tr>
<td>EXPERT</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</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>
</tr>
<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. Guirdano</td>
<td>Supporter programme (Co-Leading partners: EORTC (sponsor) / NABCG (US) Pharma partner: N/A Funding: BCRF</td>
</tr>
<tr>
<td>OLYMPIA</td>
<td>BIG 6-13</td>
<td>Olaparib vs. placebo for patients with BRCA-mutated, high-risk HER2-negative breast cancer, having completed local treatment and (neo) adjuvant chemotherapy NCT02032823</td>
<td>A. Tuut, 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>
</tr>
<tr>
<td>POSITIVE (BIG time for Baby)</td>
<td>BIG 8-13</td>
<td>Endocrine therapy interruption to enable conception for young women with ER+ breast cancer NCT02308085</td>
<td>O. Pagani</td>
<td>Supporter trial (Co-Leading partner: IBCSG (sponsor) Pharma partner: N/A Funding: IBCSG, Fonds Baillie-Latour, national and local funding bodies, individual donors</td>
</tr>
<tr>
<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>
</tr>
<tr>
<td>ULTIMATE</td>
<td>BIG 16-01</td>
<td>Immunotherapy combined with standard endocrine therapy as neoadjuvant treatment for women with ER+/HER- breast cancer NCT02997995</td>
<td>F. André, A. Prat</td>
<td>Co-lead trial (Co-Leading partners: UCBRG (sponsor) and BIG HQ Pharma partner: Astrazeneca Funding: Astrazeneca grant</td>
</tr>
</tbody>
</table>

**Legend:**

**NB:** This table does not include the trials in development and the closed trials. For more information, please visit: www.BIGagainstbreastcancer.org.
### Follow-up or post-study activities

<table>
<thead>
<tr>
<th>Study name</th>
<th>BIG Number</th>
<th>Short description</th>
<th>Principal Investigator(s)</th>
<th>Trial model &amp; partners</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALTO</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</td>
<td>N. M. Picart, A. Moreno-Araujo</td>
<td>Lead trial</td>
</tr>
<tr>
<td>AFinHTY</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</td>
<td>M. Picart, J. Bines</td>
<td>Lead trial</td>
</tr>
<tr>
<td>AZURE</td>
<td>BIG 1-04</td>
<td>Dose Adjutant Zoledronic acid redUxe REcurrence in patients with high-risk, locally advanced breast cancer</td>
<td>S. M. Lobit, J. Coleman</td>
<td>Supporter trial</td>
</tr>
<tr>
<td>BRaVo</td>
<td>BIG 5-13</td>
<td>Niraparib for patients with HER2-negative, gemline BRCA mutation-positive, locally advanced or metastatic breast cancer</td>
<td>N. Tjulera, J. Balaba, D. Cameron, I. Edem</td>
<td>Supporter trial</td>
</tr>
<tr>
<td>CALOR Loco-regional</td>
<td>BIG 1-02</td>
<td>A randomized clinical trial of adjuvant chemotherapy for radically resected loco-regional relapse of breast cancer</td>
<td>S. Aebi, I. Wagner</td>
<td>Supporter trial</td>
</tr>
<tr>
<td>DCIS</td>
<td>BIG 3-07</td>
<td>Radiation doses and fractionation schedules for women with DCIS</td>
<td>B. Chua</td>
<td>Supporter trial</td>
</tr>
<tr>
<td>FINESSe</td>
<td>BIG 2-13</td>
<td>Oral luteinising for patients with FGFR1 ER+ metastatic breast cancer</td>
<td>P. Andre, J. Cortes, E. Cordon</td>
<td>Lead trial</td>
</tr>
</tbody>
</table>
| IBIS-II    | BIG 5-02   | Prevention study of anastrozole for postmenopausal women at increased risk of breast cancer, and of effects of tamoxifen vs.
|            |            | anastrozole in postmenopausal women with DCIS | J. Cusick | Supporter trial | Supporting: Pfizer, Genentech, Roche, Novartis, Sanofi, and Agendia. Funding: Pfizer, Genentech, Roche, Novartis, Sanofi, and Agendia. |
| LOREELI    | BIG 2-13   | Different regimens of letrozole (or letrozole + cabazitib) in postmenopausal women with ER positive/HER2-negative, early stage breast cancer | C. Saura, E. de Azambuja | Supporter trial | Supporting: Pfizer, Genentech, Roche, Novartis, Sanofi, and Agendia. Funding: Pfizer, Genentech, Roche, Novartis, Sanofi, and Agendia. |
| MA.32 Meflofin | BIG 5-11 | Effect of meflofin on recurrence and survival in early stage breast cancer | P. J. Goodwin | Supporter trial | Supporting: Pfizer, Genentech, Roche, Novartis, Sanofi, and Agendia. Funding: Pfizer, Genentech, Roche, Novartis, Sanofi, and Agendia. |
| MINDACT    | BIG 2-06   | Can addition of 70-gene signature to common clinical-pathological variables impact outcome with N + to 3 node positive breast cancer | E. B. Bowers, M. Piccart | Co-lead trial | Supporting: Pfizer, Genentech, Roche, Novartis, Sanofi, and Agendia. Funding: Pfizer, Genentech, Roche, Novartis, Sanofi, and Agendia. |
| NEO-ALTO   | BIG 1-06   | Comparison of dual HER2 inhibition (lapatinib, trastuzumab) plus chemotherapy before surgery versus single HER2-targeted therapy | P. Nacif, J. Hauser | Co-lead trial | Supporting: Pfizer, Genentech, Roche, Novartis, Sanofi, and Agendia. Funding: Pfizer, Genentech, Roche, Novartis, Sanofi, and Agendia. |
| PANacea    | BIG 4-13   | Anti-PI-3, monoclonal Ab in AdvanCed, trastuzumab-resistant, HER2-positive breast cancer | S. Lei, F. Andre | Supporter trial | Supporting: Pfizer, Genentech, Roche, Novartis, Sanofi, and Agendia. Funding: Pfizer, Genentech, Roche, Novartis, Sanofi, and Agendia. |
| PALLAS     | BIG 4-03   | PALbociclib CoLlaborative Adjuvant Study: palbociclib with standard adjuvant endocrine therapy versus standard adjuvant endocrine therapy alone for HR+/HER2-negative early breast cancer | E. Moyer, M. Piccart, A. DeMichiele | Co-lead trial | Supporting: Pfizer, Genentech, Roche, Novartis, Sanofi, and Agendia. Funding: Pfizer, Genentech, Roche, Novartis, Sanofi, and Agendia. |
| PENELOPE-B | BIG 1-13   | Post-neoadjuvant palbociclib for patients with HR+ HER2-normal primary breast cancer with high relapse risk after neoadjuvant chemotherapy | G. von Minckwitz | Supporter trial | Supporting: Pfizer, Genentech, Roche, Novartis, Sanofi, and Agendia. Funding: Pfizer, Genentech, Roche, Novartis, Sanofi, and Agendia. |
| REACT      | BIG 1-03   | Randomised Europeana Clexelix Trial: clexelix versus placebo in primary breast cancer patients | C. R. Coombes, E. Bliss, G. von Minckwitz | Supporter trial | Supporting: Pfizer, Genentech, Roche, Novartis, Sanofi, and Agendia. Funding: Pfizer, Genentech, Roche, Novartis, Sanofi, and Agendia. |
| SNAP       | BIG 2-12   | Schedule of nab-Paclitaxel: evaluation of different schedules of nab-paclitaxel for metastatic breast cancer | A. Grunzy, G. Jerusalem | Supporter trial | Supporting: Pfizer, Genentech, Roche, Novartis, Sanofi, and Agendia. Funding: Pfizer, Genentech, Roche, Novartis, Sanofi, and Agendia. |
| SOFT       | BIG 2-02   | Evaluation of ovarian suppression and of exemestane as adjuvant therapy for postmenopausal women with endocrine responsive breast cancer | F. S. Chang | Supporter trial | Supporting: Pfizer, Genentech, Roche, Novartis, Sanofi, and Agendia. Funding: Pfizer, Genentech, Roche, Novartis, Sanofi, and Agendia. |
| SOLE       | BIG 1-07   | Study Of Letrozole Extension: continuous versus intermittent intraductal following endocrine treatment for postmenopausal women with disease-free survival of 5 years and node-positive early stage breast cancer | M. Collomb, G. Kaufman, S. Aebi, I. Chlebus | Supporter trial | Supporting: Pfizer, Genentech, Roche, Novartis, Sanofi, and Agendia. Funding: Pfizer, Genentech, Roche, Novartis, Sanofi, and Agendia. |
| SUPREMO    | BIG 2-04   | Selective Use of Postoperative Radiotherapy AfterMasteOmy: adjuvant chest wall irradiation for intermediate risk breast cancer following surgery | I. Kandir, C. Donnelly | Supporter trial | Supporting: Pfizer, Genentech, Roche, Novartis, Sanofi, and Agendia. Funding: Pfizer, Genentech, Roche, Novartis, Sanofi, and Agendia. |
| TEXT       | BIG 3-02   | Tamoxifen and Exemestane Trial: evaluation of tamoxifen plus prophylactic reductive breast cancer | F. R. Pagani, B. Waddley | Supporter trial | Supporting: Pfizer, Genentech, Roche, Novartis, Sanofi, and Agendia. Funding: Pfizer, Genentech, Roche, Novartis, Sanofi, and Agendia. |
| TREAT CTC  | BIG 1-12   | Trastuzumab treatment for HER2-negative early breast cancer in the presence of circulating tumour cells (CTC) | M. Ignatidou, P. Sicard, E. J.-Y. Pietra | Supporter trial | Supporting: Pfizer, Genentech, Roche, Novartis, Sanofi, and Agendia. Funding: Pfizer, Genentech, Roche, Novartis, Sanofi, and Agendia. |

*full information available on the BIG website*
We’re BIG about breasts.

What about you?

Together we will beat breast cancer. Be a part of it.

#BIGagainstBC