SUBSCRIBE NOW to keep up to date with trending topics in the world of breast cancer and BIG member groups’ academic research.

For your FREE bi-annual digital or print copy of “BIG Research in Focus” simply scan the QR code with your smartphone or type in the link to be directed to the sign-up form.

www.BIGnews.BIGagainstbreastcancer.org
## Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Pages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Note from the editor</td>
<td>4</td>
</tr>
<tr>
<td>Breast cancer research in Australia and New Zealand</td>
<td>5-13</td>
</tr>
<tr>
<td>BIG is celebrating its 20th anniversary in royal style</td>
<td>14-15</td>
</tr>
<tr>
<td>Clinical trials and activities</td>
<td>18-28</td>
</tr>
<tr>
<td>Overview of BIG trials</td>
<td>36-37</td>
</tr>
<tr>
<td>BIG member groups</td>
<td>38</td>
</tr>
</tbody>
</table>
As part of the series on “Fighting breast cancer around the globe”, the feature article of this edition of BIG’s bi-annual newsletter focuses on Australia and New Zealand.

Australia and New Zealand have some of the highest incidences of breast cancer in the world. In 2019, it is estimated that 19,535 new cases of breast cancer will be diagnosed in Australia. The corresponding number for New Zealand is 3,504 new cases. In Australia, the incidence rate for breast cancer is expected to increase with population ageing but the age-standardised mortality rate is decreasing (source Australian Institute of Health and Welfare). In New Zealand, outcomes of patients with early breast cancer are comparable with other developed countries but clinicians and patients are addressing the relatively unfavourable outcomes of patients with advanced disease (source Breast Cancer Foundation New Zealand).

In Australia, healthcare is publicly funded and standard treatments for early breast cancer (except neoadjuvant pertuzumab) are available free of charge. In conjunction with the concerted efforts of the governments and communities in addressing the barrier of distance in a large country to improve equity of access to treatment, breast cancer clinical trials have played a significant part in the falling breast cancer mortality rates in Australia. Indeed, Australia and New Zealand have a strong track record in clinical trials accrual, proving that distance from the rest of the world is no barrier to successful research leadership and partnership.

Like researchers worldwide, investigators in Australia and New Zealand are developing strategies to evolve from the conduct of large adjuvant trials to smaller, molecular subtype-specific breast cancer trials. Breast Cancer Trials Australia & New Zealand (BCT-ANZ) has been a BIG member group since inception and participated in many BIG studies over the past two decades. The Trans Tasman Radiation Oncology Group (TROG) also has a long history of productive collaboration with BIG. Undoubtedly BIG membership has provided a most valuable platform through which investigators in Australia and New Zealand actively engage with the global network to provide patients with access to novel therapy through clinical trials participation.

Importantly, the BIG global network has enabled BCT-ANZ and TROG in the conduct of large-scale, non-industry sponsored academic trials for which international collaboration is integral to success. For example, EXPERT, a co-lead study of BCT-ANZ and BIG, is the only actively accruing, investigator-led and competitively funded randomised trial that investigates the use of genomic profiling in the identification of biologically low-risk patients to personalise adjuvant radiation therapy for luminal A breast cancer. Although accrual is strong in Australia and New Zealand, international support of the BIG network is critical to success.

Finally, I sincerely congratulate BIG on its 20th anniversary. This milestone signifies our unwavering collective commitment to collaboration, innovation and leadership in facilitating and accelerating breast cancer research to deliver the best in breast cancer care for optimal patient outcomes. In all that we do, there is no greater purpose.

Enjoy the reading.

Boon H Chua
Professor and Director of Cancer and Haematology Services, University of New South Wales and Prince of Wales Hospital, Sydney, Australia
Radiation Oncology Craft Group Lead, Breast Cancer Trials Australia & New Zealand (BCT-ANZ)
Chair of Breast Working Party, Trans Tasman Radiation Oncology Group (TROG)
Executive Board Member, Breast International Group (BIG)
Fighting breast cancer around the globe

Australia and New Zealand

Despite their relatively small populations spread over large and often remote areas, Australia and New Zealand have played an important part in many practice-changing breast cancer trials. Faced with some of the highest incidence of breast cancer in the world, clinicians are all too aware of the need to implement the findings of such research and make the highest standards of care available to all patients – whatever their cultural background and wherever they live. Science writer Jenny Bryan discusses recent progress, ongoing studies and future strategies with some of those at the forefront of breast cancer research in Australia and New Zealand.

When radiation oncologist Professor Boon Chua is seeking research collaboration or funding from organisations thousands of miles from her Sydney base, she isn’t averse to getting on a plane for a 24-hour trip to make her case.

“If you’re developing a research partnership or applying for competitive funding, I believe it’s harder for people to say ‘no’ if you go in person!” says Chua, Director of Cancer and Haematology Services, at the University of New South Wales and Prince of Wales Hospital in Sydney, Australia, Radiation Oncology Craft Group Lead for Breast Cancer Trials Australia & New Zealand (BCT-ANZ), Chair of Breast Working Party for Trans Tasman Radiation Oncology Group (TROG), and member of the BIG Executive Board.

With their enviable track record in recruiting patients to major breast cancer trials, researchers in Australia and New Zealand, like Chua, are eager to demonstrate that distance should not be an obstacle to participation.

From the landmark IBIS-1 trial of tamoxifen in breast cancer prevention, for which Australia and New Zealand recruited over 2,600 patients nearly 30 years ago, to the more recent SOFT and TEXT trials of exemestane and ovarian suppression in young women with breast cancer, to which they contributed nearly 500 patients, researchers from the two countries have consistently proved their worth.

“Our success in recruiting patients to major international trials is partly because we participate in trials where we believe we can achieve good recruitment levels,” explains Soozy Smith, Chief Executive Officer of BCT-ANZ, the largest academic oncology research group in Australia and New Zealand. “Our clinicians know their patient population and can give a realistic estimate of recruitment success, thus not opening a study at their site for which they may not be able to recruit many patients.”
Dr Prue Francis, who chaired the international steering committees for SOFT and TEXT, explains that limitations on the number of participating sites available to researchers in Australia and New Zealand can be frustrating and points to their world-leading expertise in many areas of clinical and translational breast cancer research. She highlights the growing contribution of researchers to advances in immunotherapy in breast cancer, such as in the recently published PANACEA trial, supported by the International Breast Cancer Study Group (IBCSG) and BIG, which demonstrated the safety and activity of the combination of pembrolizumab and trastuzumab in patients with PD-L1-positive, trastuzumab-resistant, advanced, HER2-positive breast cancer.1

“PANACEA was the first trial of trastuzumab and immunotherapy to show a role in HER2-positive metastatic breast cancer, and we are following that up with the DIAMOND trial, which uses another immunotherapy regimen in combination with trastuzumab in a similar group of patients,” says Francis, from the Peter MacCallum Cancer Centre and the University of Melbourne, Australia, and Chair of the Scientific Advisory Committee of BCT-ANZ.

Alongside such immunotherapy studies, recently published research, led by Melbourne translational researcher Professor Sherene Loi, has enhanced understanding of the role of tumour infiltrating lymphocytes (TILs) in residual disease in predicting survival in patients with triple negative breast cancer (TNBC) following neoadjuvant chemotherapy and prognosis in early stage disease.4,5

“Prognosis has previously been based on tumour size and lymph node involvement, but this type of translational research is adding another important factor to our understanding and is very relevant to the rapidly advancing field of immunotherapy,” explains Francis.

State-of-the-art genomic analysis is a key element of the international EXPERT trial, the first international trial to be led by BCT-ANZ from Australia, in collaboration with BIG. In this potentially practice-changing study, developed by Chua, 1,170 patients with luminal A, early stage breast cancer will be enrolled, and a genomic test used to find out if it is possible to reliably select women who can avoid radiation therapy after surgery. The trial aims to improve personalised use of radiation therapy in patients aged 50 and older with early breast cancer, according to individual risk of local recurrence. Over 200 patients have already been recruited in centres in Australia and New Zealand, and recruitment in centres outside these countries will start at the end of 2019.

“EXPERT is the only randomised study which is using genomic testing to complement conventional clinical and pathological markers to investigate de-escalation of radiation treatment for breast cancer, and accrual is going very well in Australia and New Zealand. However, international recruitment is essential for such a large trial, and the BIG network is therefore critical to the success of the study,” says Chua.

Addressing the needs of patients with breast cancer in Australia

For the approximately 18,500 patients who are diagnosed with breast cancer each year in Australia,6 treatment options are comparable with those in other developed countries. BreastScreen Australia, a national screening programme that offers two-yearly mammograms to women aged 50-75 years, has contributed to earlier diagnosis and treatment. Age standardised mortality has fallen steadily over the last 20 years from 16.4/100,000 in 2000 to 12.3/100,000 in 2018 – comparing well with Europe (14.9/100,000) and the USA (12.7/100,000).7
Dr Prue Francis explains that breast tumour types are similar to those seen in European populations and there is, as yet, no evidence of breast cancer predominating in younger patients as seen in Asian populations.

“Only about 10% of the population has an Asian background, but many have not reached the age when breast cancer might occur. We also don’t yet know whether the move to a different country may affect their breast cancer risk profile, as has been seen in demographic studies of other diseases,” says Francis.

Healthcare in Australia is publicly funded and all standard treatments for early breast cancer are available free of charge, except neoadjuvant pertuzumab. The biggest challenge is ensuring that patients living hundreds of miles from major towns can access treatment, particularly radiation therapy. Professor Boon Chua explains that, without good access to radiation therapy, some patients have, in the past, chosen mastectomy over breast conserving treatment, but hopefully that is changing.

“The Australian government is making a concerted effort to develop radiation oncology services in regional towns in order to break down geographical barriers to equity of access,” she says.

During the last two decades, patients with breast cancer have benefited from a number of advances in local and systemic treatments arising from studies initiated in Australia or in which Australian researchers have participated.

In the early 2000s, Australian and Canadian researchers joined forces for the MA.20 trial, which showed that, among women with node-positive or high-risk node-negative breast cancer, the addition of regional nodal irradiation to whole-breast irradiation did not improve overall survival but reduced the rate of breast-cancer recurrence. Subsequent radiation oncology research was methodically planned and conducted to focus on individualising the extent and dose fractionation, including partial breast irradiation, to minimise the toxicity and burden of radiation therapy without compromising local control and survival.

Australian researchers participated in the TARGIT-A trial, which showed that targeted intraoperative radiation therapy could be considered as an alternative to conventional external beam radiation therapy in selected patients with early breast cancer.

In December 2018, data from the RAPID study, carried out through a collaboration between the Ontario Clinical Oncology Group and TROG, showed that accelerated partial breast irradiation was non inferior to whole breast irradiation in preventing local recurrence among selected women with invasive breast cancer or ductal carcinoma in situ (DCIS).

Compared to invasive breast cancer, there have been few trials for patients with DCIS, and TROG is the primary sponsor of a major international trial investigating the optimisation of radiation therapy for DCIS. This trial, carried out through a collaboration with multiple international breast cancer research groups, is investigating whether targeted radiation dose escalation can reduce the risk of recurrence, and if a shorter radiation dose-fractionation schedule can achieve the same results as a conventional longer course of treatment.

“This DCIS trial is very much an academic trial made possible by strong international support and the goodwill of the BIG network. We successfully completed recruitment of over 1,600 patients two years ahead of schedule, and results are expected soon,” explains Chua.

“Our overarching purpose is to show how best to individualise radiation therapy for each patient with breast cancer so that we can reduce the adverse effects and burden of treatment without compromising cancer control or survival, in a similar way to targeted systemic therapies,” she adds.

“It’s very important to understand where we come from in terms of the research that has been carried out in Australia and New Zealand over the last 40 years, so that we can implement our findings in daily practice, and plan for the future”
Francis explains that, as well as contributing to major BIG trials of systemic therapies, such as the HERA and APHINITY studies of HER-2 therapies in women with HER2-positive breast cancer, and leading the SOFT and TEXT trials, Australian and New Zealand breast cancer specialists have made other important contributions to patient care over many years.10-12

“...over 30 years since a study led by one of the founders of BCT-ANZ, Professor Alan Coates, showed that patients with advanced breast cancer whose disease responded or stabilised with chemotherapy experienced better quality of life if they continued chemotherapy until disease progression than if they stopped treatment and only restarted when their cancer came back,” she explains.

“This was an important and much cited study because most people assumed quality of life would be worse but it showed that, with good symptom control with chemotherapy, quality of life was better,” she adds.

In another BCT-ANZ conducted trial, researchers showed that capecitabine is a good first-line option for women with advanced breast cancer who are unsuited to more intensive chemotherapy12 and, in contributing to the POEMS trial, led by the South Western Oncology Group (SWOG), clinicians helped show that goserelin can reduce the risk of premature menopause and improve chance of future pregnancy in premenopausal women with breast cancer receiving chemotherapy.13

“It’s very important to understand where we come from in terms of the research that has been carried out in Australia and New Zealand over the last 40 years, so that we can implement our findings in daily practice, and plan for the future,” concludes Francis.

Breast Cancer Trials Australia & New Zealand: providing end-to-end support for research

In 1978, breast cancer specialists set up a clinical trials group in Australia and New Zealand committed to exploring and finding better treatments. Now called Breast Cancer Trials Australia & New Zealand (BCT-ANZ), the organisation provides financial and practical support to take clinical studies from initial idea to completion. It offers Discretionary Funding for small-scale research studies, such as pilots for prospective BCT-ANZ trials, sub-studies of existing protocols, and small-scale translational research, and Clinical Trial Development Funding for longer-term, high strategic value, unfunded research projects coordinated by the BCT-ANZ Trials Department.

“We are unique in both raising funds for breast cancer research and conducting the trials, which includes protocol preparation, making ethics submissions, monitoring sites, and storing tissue samples. We have recently streamlined our review processes, so we aim to consider an investigator’s proposal and give them an answer on funding in about three months,” explains Soozy Smith.

The organisation works with national and international grant-giving bodies and with pharmaceutical companies but, thanks to its built-in fundraising arm that raises AUD 3-4 million annually, is not reliant on external sources to support the two or three clinical trials it gets up and running each year. BCT-ANZ is a first port of call for international research groups, such as BIG, the International Breast Cancer Study Group (IBCSG), the German Breast Group (GBG), the Austrian Breast and Colorectal Cancer Study Group (ABCSG), Translational Research in Oncology (TRIO) and the Alliance Foundation Trials, when they look for investigators in Australia and New Zealand to participate in their studies.
“BCT is the largest academic oncology trials group in Australia and probably one of the largest of all the clinical trial groups in the country. Through our fundraising we have built an investment portfolio which enables us to draw down the money we need to support trials and ensures we have sufficient funds to complete any trial that we start,” says Smith.

In recent years, we have noticed that more breast cancer studies are being restricted to European centres and, as we understand that budgets may be tight, we want research organisations to understand that we can contribute financially to studies if they are extended to clinicians in Australia and New Zealand”

Soozy Smith

In addition to EXPERT and DIAMOND, current trials being conducted by BCT-ANZ include:

- **CHARIOT** – a phase 2 study of immunotherapy and neoadjuvant chemotherapy in high risk triple negative early breast cancer
- **PATINA** – exploring the addition of palbociclib to first-line maintenance treatment of HER2 positive metastatic breast cancer to delay therapeutic resistance and prolong survival
- **POSNOC** – investigating whether routine adjuvant treatment is sufficient in women with early stage breast cancer and one or two positive axillary sentinel nodes without the need for further axillary surgery or radiation therapy

At an early stage in its history, BCT-ANZ recognised the importance of patient input in defining research priorities and acceptability of studies to potential participants, and the Consumer Advisory Panel (CAP) was formed in 1999.

“It is essential that we do research that patients feel is needed, together with what researchers identify would benefit their patients. Our CAP members are very engaged not only in advising about our trials but also in helping us with our communications for participants and in education and training of consumer advocates for other research groups in Australia,” says Smith.

BCT-ANZ’s membership of BIG has advantages for both organisations. It enables researchers in Australia and New Zealand to engage with breast cancer experts in many countries and to access international trials that allow patients access to treatment they wouldn’t otherwise receive. It also enables BCT-ANZ to support BIG in conducting international studies in Australia and New Zealand in terms of securing grants and raising funds if budgets are limited.

“In recent years, we have noticed that more breast cancer studies are being restricted to European centres and, as we understand that budgets may be tight, we want research organisations to understand that we can contribute financially to studies if they are extended to clinicians in Australia and New Zealand,” concludes Smith.

**New Zealand: challenging times for patients and clinicians**

Twelve months after publication of I’m Still Here – a disturbing report about breast cancer service use and outcomes issued by the Breast Cancer Foundation New Zealand – patients and clinicians are endeavouring to address inequalities that have left the country near the bottom of international survival tables for advanced disease. The report showed that, despite a nationwide breast screening programme and free healthcare, patients with advanced breast cancer had a median overall survival of 16 months – approximately 10-12 months less than that reported in other developed countries.

“In early breast cancer, we do very well and our results are comparable with Europe and North America but in advanced breast cancer we do poorly, particularly in the Maori population, which has the highest known incidence of breast cancer in the world and one of the highest mortality rates,” says Dr Marion Kuper-Hommel, Clinical Director Medical Oncology, at Waikato District Health Board, Hamilton, New Zealand.

Each year, about 3,000 of New Zealand’s 4.8 million population are diagnosed with breast cancer, including 300 with advanced disease, and there are over 600 deaths. Breast screening is offered to women aged 45-70 years every two years, and women at high risk are offered mammograms from age 40.
Over the last 20 years, breast cancer incidence has risen, especially in Maori and Pacific Island groups, which together make up over 20% of the population, and mortality in this latter group is also high.

Overall, breast tumour subtypes in New Zealand are comparable with those in western populations, though triple-negative breast cancer (TNBC) is less common in Maori and Pacific groups, and HER2-positive disease is more common in those of Pacific Island origin. In the Waikato area where Dr Kuper-Hommel works, there is a higher incidence of inflammatory breast cancer than in other developed countries, and this is slightly more common in New Zealand patients of European ancestry.

Dr Kuper-Hommel explains that differences in tumour type are unlikely to be responsible for the poor outcomes in Maori and Pacific Island patients. Instead, these groups have more comorbidities such as obesity and they present later – with more advanced disease. She adds that there may be greater reliance on traditional remedies, and economic inequalities may mean that Maori and Pacific Island patients are unable to pay for more expensive cancer drugs not included in free healthcare services.

“The first priority is to encourage greater participation in breast cancer screening, because we know that if tumours are picked up earlier in Maori and Pacific Island patients, outcomes are similar to New Zealand European patients,” says Dr Kuper-Hommel. “We also need better health literacy, so patients understand the importance of continued adherence to endocrine and other treatments.”

The Breast Cancer Foundation NZ report highlighted the significant proportion of patients with advanced breast cancer of all ethnicities who went untreated. This is partially explained by late presentation, close to end of life when patients were not fit for treatment, and under-reporting of endocrine therapies in the breast cancer registries. However, it may also have been due to failure to access hospital services.

Support services are spreading the word about the importance of screening and treatment and providing assistance for those with transport difficulties, as well as offering general health education to reduce comorbidities such as cardiovascular problems that may limit treatment options. However, national restrictions on the availability of newer medicines are a continuing issue for all patients with breast cancer in New Zealand, and are likely to have contributed to the particularly poor survival rates in patients with advanced HER2-positive disease reported in I’m Still Here.

“Trastuzumab emtansine will at last be publicly funded for HER2-positive disease from 1 December (more than four years after it was funded in Australia), though CDK4/6 inhibitors for hormone receptor-positive, advanced breast cancer have not yet been approved by Pharmac, the government body that decides which medicines are publicly funded in New Zealand.

“In early breast cancer, New Zealand does very well and our results are comparable with Europe and North America; but in advanced breast cancer we do poorly, particularly in the Maori population which has the highest known incidence of breast cancer in the world and one of the highest mortality rates” Marion Kuper-Hommel

“The drug budget has increased, but not to the extent that has been seen in other countries such as Australia and the UK, and we have no insight about if and when drugs will be funded. So, at present, if patients want non-funded drugs they have to pay or get access through medical insurance,” says Kuper-Hommel.

There is also frustration that decisions about funding are driven by costs rather than on health economic parameters such as quality adjusted life years (QALYs), as happens in many other countries.

Breast cancer is not alone in having funding problems for new treatments. A recent publication commissioned by Medicines New Zealand reported that only six new cancer medicines were reimbursed in New Zealand between 2011 and 2017, compared to 26 in Australia, 50 in the UK and 55 in Germany. The average time from registration to public reimbursement of new cancer drugs was 580 days in New Zealand compared to an average 244 days in 20 Organisation for Overseas Economic Cooperation and Development (OECD) countries.

In early breast cancer, New Zealand does very well and our results are comparable with Europe and North America; but in advanced breast cancer we do poorly, particularly in the Maori population which has the highest known incidence of breast cancer in the world and one of the highest mortality rates” Marion Kuper-Hommel

“The drug budget has increased, but not to the extent that has been seen in other countries such as Australia and the UK, and we have no insight about if and when drugs will be funded. So, at present, if patients want non-funded drugs they have to pay or get access through medical insurance,” says Kuper-Hommel.

There is also frustration that decisions about funding are driven by costs rather than on health economic parameters such as quality adjusted life years (QALYs), as happens in many other countries.

Breast cancer is not alone in having funding problems for new treatments. A recent publication commissioned by Medicines New Zealand reported that only six new cancer medicines were reimbursed in New Zealand between 2011 and 2017, compared to 26 in Australia, 50 in the UK and 55 in Germany. The average time from registration to public reimbursement of new cancer drugs was 580 days in New Zealand compared to an average 244 days in 20 Organisation for Overseas Economic Cooperation and Development (OECD) countries.

In early breast cancer, New Zealand does very well and our results are comparable with Europe and North America; but in advanced breast cancer we do poorly, particularly in the Maori population which has the highest known incidence of breast cancer in the world and one of the highest mortality rates” Marion Kuper-Hommel

“The drug budget has increased, but not to the extent that has been seen in other countries such as Australia and the UK, and we have no insight about if and when drugs will be funded. So, at present, if patients want non-funded drugs they have to pay or get access through medical insurance,” says Kuper-Hommel.

There is also frustration that decisions about funding are driven by costs rather than on health economic parameters such as quality adjusted life years (QALYs), as happens in many other countries.

Breast cancer is not alone in having funding problems for new treatments. A recent publication commissioned by Medicines New Zealand reported that only six new cancer medicines were reimbursed in New Zealand between 2011 and 2017, compared to 26 in Australia, 50 in the UK and 55 in Germany. The average time from registration to public reimbursement of new cancer drugs was 580 days in New Zealand compared to an average 244 days in 20 Organisation for Overseas Economic Cooperation and Development (OECD) countries.

In early breast cancer, New Zealand does very well and our results are comparable with Europe and North America; but in advanced breast cancer we do poorly, particularly in the Maori population which has the highest known incidence of breast cancer in the world and one of the highest mortality rates” Marion Kuper-Hommel

“The drug budget has increased, but not to the extent that has been seen in other countries such as Australia and the UK, and we have no insight about if and when drugs will be funded. So, at present, if patients want non-funded drugs they have to pay or get access through medical insurance,” says Kuper-Hommel.

There is also frustration that decisions about funding are driven by costs rather than on health economic parameters such as quality adjusted life years (QALYs), as happens in many other countries.

Breast cancer is not alone in having funding problems for new treatments. A recent publication commissioned by Medicines New Zealand reported that only six new cancer medicines were reimbursed in New Zealand between 2011 and 2017, compared to 26 in Australia, 50 in the UK and 55 in Germany. The average time from registration to public reimbursement of new cancer drugs was 580 days in New Zealand compared to an average 244 days in 20 Organisation for Overseas Economic Cooperation and Development (OECD) countries.

In early breast cancer, New Zealand does very well and our results are comparable with Europe and North America; but in advanced breast cancer we do poorly, particularly in the Maori population which has the highest known incidence of breast cancer in the world and one of the highest mortality rates” Marion Kuper-Hommel

“The drug budget has increased, but not to the extent that has been seen in other countries such as Australia and the UK, and we have no insight about if and when drugs will be funded. So, at present, if patients want non-funded drugs they have to pay or get access through medical insurance,” says Kuper-Hommel.

There is also frustration that decisions about funding are driven by costs rather than on health economic parameters such as quality adjusted life years (QALYs), as happens in many other countries.

Breast cancer is not alone in having funding problems for new treatments. A recent publication commissioned by Medicines New Zealand reported that only six new cancer medicines were reimbursed in New Zealand between 2011 and 2017, compared to 26 in Australia, 50 in the UK and 55 in Germany. The average time from registration to public reimbursement of new cancer drugs was 580 days in New Zealand compared to an average 244 days in 20 Organisation for Overseas Economic Cooperation and Development (OECD) countries.

In early breast cancer, New Zealand does very well and our results are comparable with Europe and North America; but in advanced breast cancer we do poorly, particularly in the Maori population which has the highest known incidence of breast cancer in the world and one of the highest mortality rates” Marion Kuper-Hommel

“The drug budget has increased, but not to the extent that has been seen in other countries such as Australia and the UK, and we have no insight about if and when drugs will be funded. So, at present, if patients want non-funded drugs they have to pay or get access through medical insurance,” says Kuper-Hommel.

There is also frustration that decisions about funding are driven by costs rather than on health economic parameters such as quality adjusted life years (QALYs), as happens in many other countries.

Breast cancer is not alone in having funding problems for new treatments. A recent publication commissioned by Medicines New Zealand reported that only six new cancer medicines were reimbursed in New Zealand between 2011 and 2017, compared to 26 in Australia, 50 in the UK and 55 in Germany. The average time from registration to public reimbursement of new cancer drugs was 580 days in New Zealand compared to an average 244 days in 20 Organisation for Overseas Economic Cooperation and Development (OECD) countries.
Given the lack of general access to newer treatments, clinicians in New Zealand are eager to get patients with breast cancer into clinical trials of novel therapies such as those funded by pharmaceutical companies. However, they have found themselves excluded from some of these studies because it is not seen as worthwhile to include New Zealand patients given the country’s track record in allowing access once efficacy of new agents is confirmed.

Mature, high quality breast cancer registries are providing useful information about tumour subtypes and outcomes, though most clinical research studies in New Zealand are carried out through collaborations with BCT-ANZ, with additional support from Clinical Trials Group New Zealand. Some breast cancer specialists have links with the US National Cancer Institute and, for example, participated in the TAILORx trial of the role of chemotherapy in early-stage breast cancer.

“With such good outcomes in early disease, we are now looking at de-escalation trials to see if we can reduce treatment without any deterioration in outcomes. For advanced breast cancer we are now also focusing on trials that monitor and aim to improve the health-related quality of life of our patients, who should have not only a longer but also a better cancer journey in the near future. However, it’s very frustrating to have to inform patients about treatment options that have become standard of care in many countries but are still not publicly available in New Zealand,” concludes Kuper-Hommel.

Like researchers around the world, investigators in Australia and New Zealand are having to adapt to the move from large, ‘all-comer’ breast cancer trials to smaller, niche studies of treatments targeted at specific tumour types.

“We are moving from trials such as IBIS-1 (a prevention trial with thousands of participants), to studies of TNBC or other tumour types with maybe 40 or 50 patients, and this is inevitably reducing the number of sites which can take part. We need to manage and share these “niche” trials by looking carefully for centres that have the specialist skills and equipment that are increasingly needed,” says Smith.

Kuper-Hommel points out that, with their limited patient populations, it can be particularly challenging for researchers at New Zealand’s six cancer centres to take part in these new generation trials unless they can join forces.

“Hospitals are reluctant to treat patients out of region because they already have waiting lists for treatment but, unless we can group together to contribute patients, we will miss out on the more niched trials and our patients won’t have the opportunity to try the new treatments in a clinical trial setting,” she says.

In Australia, Chua is eager to nurture a culture that does not separate research from care – with every patient considered for a clinical trial whenever appropriate.
“From the radiation oncology viewpoint, I am a strong believer in multidisciplinary trials that are often most likely to pave the way to significant advances in personalised breast cancer treatment. I also recognise the importance of integrating preclinical sciences in the design and conduct of clinical trials. Trials which focused on technologies and techniques of radiation therapy have served our patients well, but we now need to leverage our understanding of breast cancer biology into the design of multidisciplinary local-regional therapy trials,” she says.

For Francis, the goals of the next few years include de-escalating therapy for appropriate patients and maximising the potential of immunotherapy, especially in HER2-positive disease and TNBC:

“We also need a greater understanding of the factors that contribute to poorer outcomes in younger patients, particularly those with oestrogen receptor positive disease, so we can improve their prognosis,” she says. “Things are enormously better than when I saw my first oncology patient more than 30 years ago, and it’s very gratifying to see how far we’ve come. But we need to carefully design our future trials so we can maximise the benefits of research for all patients in our daily practice.”

References

Meet the experts

**Boon H Chua, MD, PhD**  
Professor and Director of Cancer and Haematology Services, University of New South Wales and Prince of Wales Hospital, Sydney, Australia  
Radiation Oncology Craft Group Lead, Breast Cancer Trials Australia & New Zealand (BCT-ANZ)  
Member of the Breast Cancer Trials Scientific Advisory Committee  
Chair of Breast Working Party, Trans Tasman Radiation Oncology Group (TROG)  
Executive Board Member, Breast International Group (BIG)  

Sydney, Australia

**Prue Francis, MD**  
Clinical Lead Breast Medical Oncology, Peter MacCallum Cancer Centre, University of Melbourne, Australia  
Chair of Scientific Advisory Committee, Breast Cancer Trials Australia & New Zealand (BCT-ANZ)  

Melbourne, Australia

**Marion Kuper-Hommel, MD, PhD**  
Clinical Director Medical Oncology, Dept of Oncology  
Waikato District Health Board  

Hamilton, New Zealand

**Soozy J Smith, PhD**  
Conjoint Professor, Chief Executive Officer of Breast Cancer Trials Australia & New Zealand (BCT-ANZ)  

Newcastle, Australia
BIG is celebrating its 20th anniversary in royal style

In 2019, BIG has been organising numerous events to celebrate its 20th anniversary.

On 17 September, and in the presence of its Honorary President, Her Royal Majesty the Queen of the Belgians, BIG invited leading breast cancer specialists such as Professor Martine Piccart (Chair and Co-founder of BIG), Professor David Cameron (Chair-elect of BIG), and Dr Alberto Costa (CEO, European School of Oncology) to shed a light on the past, present and future of breast cancer treatment. For a broad audience of BIG supporters, as well as for press, topics included new therapeutic regimens and therapeutic de-escalation of treatment.

In addition to the celebratory event with the Queen, BIG is organising various gala events connecting BIG ambassadors, individuals, partners, sponsors, foundations and companies. Thanks to the dedication of the organising team and the support of all participants, these philanthropic events – as well as other fundraising initiatives – will bring together more than 2,000 enthusiasts.
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.

BIG’s dedicated philanthropy unit conducts vital fundraising to support BIG’s academic clinical trials and research programmes. These have no commercial interest but are crucial for patients.

With a global network of 57 international academic research groups dedicated to finding a cure for breast cancer, BIG has the ability to achieve faster results and greater patient benefits by enrolling large numbers of patients into clinical trials more quickly, and doing so in many countries around the world.

Some BIG figures

Between 2012 and 2018, BIG invested €97,000,000 in its breast cancer research

57 international academic research groups in the BIG network

Several 1,000 hospitals in the network

> 10,000 doctors and researchers collaborating as part of the BIG network

> 30 ongoing clinical trials and research programmes

> 95,000 patients involved in BIG clinical studies

Yesterday’s research results in today’s treatment and tomorrow’s future

TOGETHER WE WILL FIND A CURE FOR BREAST CANCER

From left to right:
Dr Alberto Costa, Mr Serge Schmitz, Dr Theodora Goulioti, Mr Guy van Wassenhove, Princess Amaury de Merode, Mrs Jessica Parser, Prof David Cameron, Her Royal Highness the Queen of the Belgians, Mr Nissim Israël, Prof Martine Piccart, Mrs Nathalie Misson, Baroness Jacques Brotchi, Mrs Mathilde Jooris, Baron Jacques Brotchi, Mr Alain De Waele, Mrs Patsy Israël, Prince Amaury de Merode, Mrs Betty Baligant
Prof David Cameron appointed as BIG Chair

Following BIG’s General Assembly of 2 June in Chicago, BIG has appointed as new Chair Prof David Cameron. He will officially assume his role in November 2019. At the same time, Dr Ander Urruticoechea was appointed Treasurer.

Involved in BIG since 2001 and a member of its Executive Board (EB) since 2010, David Cameron connects deeply with the history and evolution of the organisation, understanding and sharing its core principles of academic independence, global collaboration and high-quality research. He is an unfailing advocate of BIG’s vision to unite groups from around the world to conduct clinical trials asking the most relevant scientific questions to serve the needs of patients with breast cancer.

Among the main challenges and priorities for the future, emphasised by BIG’s new Chair, are the changing landscape of clinical research, with novel research structures emerging around the world and ever more advanced technologies, the need to engage better with patients and to hear their voices, and the necessity to maintain scientific integrity and academic independence. To continue to find funding for academic studies, which are essential to patients but have no commercial interest, is also a priority for the BIG network in the years to come.

Prof Martine Piccart, co-founder of BIG, will stay active as Immediate Past Chair and President of BIG against breast cancer, the philanthropy unit of BIG.

“The role of Chair is perhaps less of that of the ‘leader’ but more of the helmsman steering a ship who is totally dependent on his fellow crew members – Executive Board members, headquarters staff and of course all the member groups.”

Prof Martine Piccart

Prof David Cameron appointed as BIG Chair

“David embodies all the qualities required to be an inspiring and committed leader for BIG. He has the necessary expertise and, most importantly, essential human values such as altruism, integrity and trust. His determination and strong collaborative spirit, combined with that of the other Executive Board members, will bring a renewed dynamic and a strengthened strategic thinking to the network, and this is essential for the future of BIG as an academic and patient-centred organisation,” explains Prof Martine Piccart.

Prof Martine Piccart and Prof David Cameron
2019 BIG-NABCG meeting: de-escalating therapies in breast cancer

In May, BIG and the North American Breast Cancer Group (NABCG) – a network of major US and Canadian-based research groups supported by the US National Cancer Institute (NCI) – held their annual meeting in Chicago, USA, prior to ASCO 2019.

About 60 world-class cancer researchers – oncologists, radiotherapists, surgeons, statisticians, psychologists, etc. – gathered to brainstorm on the topic of ‘de-escalating systemic adjuvant therapy for breast cancer’, tackling two main challenges: how to develop clinical trials that will, in the future, help doctors better identify which patients will really benefit from adjuvant treatment and which can safely be spared, and how to better involve patients in the design of these de-escalation trials.

Patient workshops

In preparation for this important meeting, two patient workshops were organised in April, one in New York and one at BIG Headquarters in Brussels, Belgium. About 20 patient advocates, men and women, were invited to share their experience as cancer patients and express their thoughts about the de-escalation of clinical trials. Among the questions asked were what is the level of cancer recurrence risk that they would be willing to accept in a de-escalation trial, how is the balance between risks and benefits communicated to them, and which factors influence their decision to participate in a clinical trial.

At the end of each workshop, patients responded to a survey that probed what factors prevail in deciding to participate in clinical trials with a de-escalation objective. Four patients were subsequently invited to attend the annual meeting in Chicago to share the workshop conclusions.

Several de-escalation trials have emerged on both sides of the Atlantic in recent years, including those aiming to evaluate the utility of genetic tests to characterise the biological profile of tumours and identify their potential aggressiveness. This is the case of the two BIG trials MINDACT and EXPERT, for example.

Several topics were discussed at the annual BIG-NABCG meeting, including the psychological aspects of treatment de-escalation, the statistical design of such trials, the rationale behind reducing loco-regional and other adjuvant chemotherapy or endocrine therapies, and what type of biomarkers can be used as tools to facilitate de-escalation trials.

At the end of the meeting, experts agreed that the patient perspective is essential in the development and design of new de-escalation trials. Both BIG and NABCG will work together to increasingly involve patients in the research development process.
CLINICAL TRIALS AND ACTIVITIES

BIG trial updates

ALEXANDRA / IMpassion030 (BIG 16-05): milestone achieved

ALEXANDRA / IMpassion030 is one of the international studies recently undertaken by BIG that combines immunotherapy with an anticancer treatment in order to understand how we can work with the patient’s immune system to reinforce its response against the tumour.

This phase III trial, which opened its first site in the US in May 2018, reached a milestone in July 2019 with over 250 patients randomised from 254 sites in 24 countries around the globe. In total, about 2,300 patients are expected to participate in this global research effort for the treatment of triple-negative breast cancer, an aggressive form of the disease.

ALEXANDRA / IMpassion030 aims to compare the efficacy and safety of the antiPD-L1 inhibitor atezolizumab given in combination with chemotherapy versus chemotherapy alone as adjuvant treatment to prevent cancer recurrence in patients affected by operable triple-negative breast cancer. The trial involves 20 BIG member groups worldwide.

A poster presenting ALEXANDRA/IMpassion030 was displayed at ASCO:


LORELEI (BIG 3-13): primary results published

The primary results of the LORELEI trial were published in Lancet Oncology this August.

These results, which were first presented by principal investigator Dr. Christina Saura at the ESMO conference in 2017, showed that the addition of the PI3K inhibitor taselisib to the standard neoadjuvant endocrine treatment (letrozole) increased the objective response rate from 38% to 56.2% in patients with PIK3CA mutation and from 39.3% to 50% across all patients in the study compared to letrozole alone. Patients with tumours harbouring a PIK3CA mutation seemed to benefit the most from the combined treatment. However, investigators suggest that more research be done to confirm this.

LORELEI is a phase II randomised, double-blind study of neoadjuvant letrozole plus taselisib versus letrozole plus placebo in postmenopausal women with ER-positive/HER2-negative early-stage breast cancer. It enrolled 334 patients from 85 hospitals in 22 countries around the world and involves the collaboration of eight BIG member groups.
NeoALTTO (BIG 1-06): updated results published

In the September issue of the European Journal of Cancer, Dr Jens Huober and colleagues reported the updated results of the NeoALTTO study.

The current updated analysis, performed with a median follow-up of 6.7 years, reported a 6-year event free survival (EFS) rate of 67%, 67% and 74% for lapatinib, trastuzumab and the combination, respectively. The difference in EFS rates between the combination group and the groups treated with a single anti-HER2 agent was not significant. Similarly, no significant differences were found in overall survival (OS) rates, with 6-year OS rates of 82%, 79% and 85% being reported for lapatinib, trastuzumab and the combination, respectively.

Notably, a landmark analysis did show that patients who had achieved a pathological complete response (pCR) did have a significantly better EFS and OS rate than those who had residual disease after neoadjuvant treatment, reporting EFS and OS rates of 77% vs 65% and 89% vs 77%, respectively. This effect was limited to the patients with hormone receptor-negative tumours.

NeoALTTO is a randomised multicentre open-label phase III study which enrolled 455 women with early HER2-positive breast cancer. These women were treated with weekly paclitaxel plus either lapatinib, trastuzumab or the combination of lapatinib and trastuzumab in the neoadjuvant setting.

Previous analyses of the NeoALTTO study had shown that the pCR rate was higher in the group of patients treated with the combination of lapatinib and trastuzumab compared to those who received either lapatinib or trastuzumab alone. However, an analysis performed after a median follow-up of 3.75 years found no significant differences between the treatment groups for 3-year EFS and OS rates.

OLYMPIA (BIG 6-13): target accrual reached

In April 2019, a milestone was reached for the OLYMPIA trial, which met its target accrual of 1,836 patients enrolled. Randomisation was completed in May.

The study investigates whether the PARP inhibitor olaparib can reduce the risk of breast cancer recurrence in patients with high-risk HER2-negative germline BRCA1/2 mutated primary breast cancer.

OLYMPIA was launched in 2014 with over 600 sites activated in 23 countries around the globe and involving 23 BIG member groups.

POSITIVE (IBCSG 48-14 / BIG 08-13): recruitment update

By 31 August 2019, POSITIVE (also known as the ‘BIG Time for Baby’ study) had enrolled 449 out of 500 patients.

Projections indicate that the study might reach its target accrual by mid-2020.

The POSITIVE study 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. Launched in 2014, the study gives hope to thousands of women wishing to have a baby after breast cancer. This trial involves 11 groups, covering 20 countries from within the BIG network.

PYTHIA (BIG 14-04): recruitment completed

Recruitment in the PYTHIA trial, a downstream trial of the AURORA academic programme, was completed in May 2019, with a total of 124 patients enrolled into the study. These patients all have participated in the AURORA programme.

PYTHIA aims to evaluate the anti-tumour activity, safety and tolerability of the combination of palbociclib and fulvestrant in postmenopausal women with HR+/HER2- metastatic breast cancer whose disease has progressed after prior endocrine therapy.

Coupling the molecular data with the clinical outcomes of patients receiving the PYTHIA study treatment will allow researchers to identify specific molecular abnormalities that could possibly predict treatment outcomes.
The first edition of the annual ESMO Breast Cancer congress took place early May in Berlin, Germany.

AURORA (BIG 14-01): first report

The initial results of AURORA were announced at the ESMO Breast Cancer Congress held on 2-4 May 2019 in Berlin, Germany, by Dr Philippe Aftimos, Co-Principal Investigator of the programme and Clinical Trials Development Leader at the Jules Bordet Institute in Brussels, Belgium.

The AURORA research programme aims to better understand the molecular characteristics and evolution of recurrent or metastatic breast cancer, in the hope of treating more effectively, and possibly blocking the disease in the future.

Dr Aftimos presented the results for the first 381 patients included out of a planned total of 1,000. The researchers have identified molecular alterations present in excess in metastases that may be correlated with the spread of cancer and increased resistance to standard treatments. In addition, the researchers estimate that in almost 50% of cases the genomic alterations identified could provide treating oncologists with additional information useful for patients.

Liquid biopsies were also analysed. This technique could have an important role in characterising and monitoring the disease, since, in some patients, analysis of circulating tumour DNA revealed genetic alterations not observed in the biopsy of the tumour lesion.

Analyses of the tumour immune environment are also underway and will be presented at future congresses.

Reference:
• First report of AURORA, the breast international group (BIG) molecular screening initiative for metastatic breast cancer (MBC) patients (pts). Aftimos P, et al.

63% of AURORA funding secured

AURORA is a purely academic programme made possible by grants and donations from various sources.

BIG is proud to announce that it is being awarded a grant of EUR 1 million from Fondation Cancer Luxembourg, adding to a previous contribution from the Fondation of over EUR 1,200,000.

ALTTO (BIG 1-06):
long-term cardiac outcomes presented

Dr Daniel Eiger, clinical research fellow at the Institut Jules Bordet, Brussels, Belgium, presented a mini oral session on the long-term cardiac outcomes of HER2+ breast cancer patients treated in the ALTTO trial.

Researchers reported the cardiac data from 4,190 patients who did not have any serious cardiac illness and who received one year of adjuvant trastuzumab alone, or trastuzumab and lapatinib concomitantly. Symptoms of heart failure in these patients were assessed tri-monthly during treatment, every 6 months until 2 years of treatment, and then once a year until 10 years after start of treatment.

It was found that dual HER2 blockade does not increase the rate of cardiotoxicity in comparison to trastuzumab alone.

ALTTO is a randomised, multi-centre, open-label, phase III study of adjuvant lapatinib, trastuzumab, their sequence and their combination in patients with HER2/ErbB2 positive primary breast cancer.

Reference:
• Long-term cardiac outcomes of HER2+ breast cancer patients treated in the ALTTO trial. Eiger D., et al.
Every year in late May or early June, the ASCO Annual Meeting brings together more than 32,000 oncology professionals from around the world to discuss state-of-the-art treatment modalities, new therapies, and ongoing controversies in the field.

APHINITY trial: biomarker analysis to predict prognosis and drug benefit

The first results of the pre-planned biomarker analysis performed on a subgroup of patients from the APHINITY trial were presented at ASCO 2019 by Dr Ian Krop, co-Principal Investigator of the study and Clinical Research Director of the Breast Oncology Center at the Dana-Farber Cancer Institute. The aim of this comprehensive genomic analysis was to identify prognostic and predictive biomarkers beyond clinical parameters (nodal and hormone receptor status) that can predict benefit of pertuzumab among patients with HER2-positive early stage breast cancer enrolled in the study. Two main questions were addressed: can a specific biomarker help physicians anticipate if the patient will have a cancer recurrence (good/bad prognosis)? Are there biomarkers that can predict the benefit of adding the drug pertuzumab to the standard treatment (chemotherapy plus trastuzumab) in patients with HER2-positive early stage breast cancer?

This is the largest biomarker analysis done so far in early-stage HER2-positive breast cancer, providing comprehensive molecular data essential for future research. Various types of analyses were performed: DNA and RNA sequencing were performed on 1,023 samples and tumour-infiltrating lymphocytes (TILS) and HER2 analysis on 4,804 samples from the APHINITY study.

The DNA analysis revealed that PI3K pathway alterations (i.e., PI3K/PTEN/AKT alterations), which occurred in 37% of the subgroup of patients analysed, were associated with unfavourable prognosis. Amplification of the MYC and ZNF703 genes were also associated with poor patient outcomes. In contrast, TOP2A amplification was associated with a better prognosis, independent of treatment. However, none of these biomarkers predicted benefit of adding pertuzumab to the standard treatment.

Researchers reported that higher levels of immune markers (both TILs and T cell related genes) were associated with favourable prognosis and predicted greater pertuzumab benefit. These data support an immune-mediated mechanism of action of pertuzumab, which needs to be further investigated. Finally, the HER2 analyses showed that cancers with high HER2 copy number (≥ 6) had better prognosis and may be associated with greater benefit with pertuzumab.

This is the most comprehensive molecular analyses in early stage HER2-positive breast cancer. These results will be useful to identify treatment targets and develop better trials for this patient population.

APHINITY is a phase III study of 4,805 patients with operable HER2-positive primary breast cancer which was set up to test whether adding pertuzumab to the standard adjuvant treatment (trastuzumab and chemotherapy) improves patient outcome. The last patient was recruited in August 2013 and all patients will be followed up for about ten years. The first study results were presented at ASCO 2017 and published in the New England Journal of Medicine. The trial is being conducted in 42 countries, with a total of 563 hospitals worldwide. 290 of the participating hospitals are affiliated with the 24 participating BIG groups.

Several abstracts with updates or follow-on analyses from other BIG trials were also presented at ASCO 2019, including ALTTO/NeoALTTO, ALEXANDRA/Impassion, LORELEI and BIG 1-98:

- Treatment completion and toxicity of trastuzumab or trastuzumab + lapatinib in older patients (pts): BIG 2-06; NCCTG N063D (Alliance), Ponde N. E., et al.
- On-treatment changes in tumor-infiltrating lymphocytes (TIL) during neoadjuvant HER2 therapy (NAT) and clinical outcome, Luen S. J., et al.
- Exploratory analysis of the effect of taselisib on downstream pathway modulation and correlation with tumor response in ER-positive/HER2-negative early-stage breast cancer from the LORELEI trial, Nuciforo P., et al.
Innovative prevention trial ABCSG 50/BRCA-P starts enrolment

On 8 July 2019, the Austrian Breast and Colorectal Cancer Study Group (ABSG) announced the “First Patient Included” in an innovative prevention trial with the monoclonal antibody denosumab.

ABCSG 50/BRCA-P is a randomised, double-blind, placebo-controlled phase 3 study to determine the preventive effect of denosumab on breast cancer in women carrying a BRCA1 germline mutation. It is important to emphasise that this study includes healthy women with a BRCA1 mutation, not breast cancer patients. “We want to evaluate the reduction in breast cancer risk in healthy women who carry a BRCA1 germline mutation. If successful, denosumab could turn out to become a real alternative for the bilateral mastectomy that is currently used for risk reduction”, explained ABCSG’s Study Principal Investigator Christian Singer, pointing out the primary objective. “It wasn’t so easy to realise this project, but we finally managed to put together a truly global consortium of collaborators who are all experts in the identification and management of BRCA mutation carriers. I am very happy about this remarkable achievement!” By July 2019, there were already three trial participants at Singer’s site at the Medical University Vienna; three more sites in Austria opened subsequently.

The trial contains two treatment arms: In arm A, participants receive 120mg denosumab as a subcutaneous injection (every six months for a total of five years); in the control arm, women receive placebo at the same rate. A total of 2,918 healthy women with a BRCA1 mutation are to be randomised worldwide. In addition to Austria, centres in Australia, Germany, Israel, Spain, the UK and the US are also involved, and will soon start recruitment.

ABCSG is conducting this study together with local sponsors and hopes to use this international study to find out whether denosumab could have a positive effect on the risk of breast cancer associated with this mutation in women with BRCA1 mutation.

“ABCSG has a long-lasting experience with denosumab and its effects on breast cancer patients”, says Professor Michael Gnant, MD, Principal Investigator of the successful phase-3 trial ABCSG 18, in which a total of 3,425 patients with hormone receptor-positive breast cancer participated. The use of denosumab in addition to the patients’ antihormonal therapy reduced the incidence of osteoporotic bone fractures by 50% and generally improved bone health without additional toxicity.

In June 2018, Prof Gnant presented the analysis of six-year disease-free survival data of the trial at ASCO: After an average of 72.6 months of follow-up, these results on disease-free survival are statistically significant, and the risk of relapse is reduced by approximately 18% with the administration of denosumab. Of the patients who also received denosumab, 89.2% (versus 87.3) and 80.6% (versus 77.5) were disease-free after five years. These significant differences are especially noteworthy because the survival rates of patients with this type of breast cancer are already quite high. Also, this benefit comes in addition to the significant reduction of clinical fractures.

“We with our fascinating and innovative ABCSG 50/BRCA-P study, we are taking an important step in the direction we have always wanted to go - from the treatment to the prevention of cancer”, emphasises Prof Gnant about the possible impact of ABCSG’s most recently launched trial.

Reference:
The Breast and Gynecological International Cancer Society (BGICS), based in Egypt, is one of the international multidisciplinary organisations dedicated to fostering the science of breast and gynaecological oncology as well as improving the care of cancer patients and their families throughout the world. It aims to lessen the human suffering from cancer. BGICS also holds the largest international Breast-Gynecological and Immunooncology International Cancer Conference (BGICC) in the Middle East and Africa.

Highlights from 11th Breast-Gynecological and Immunooncology International Cancer Conference (BGICC): “One World Against Cancer” (17-18 January 2019, Egypt)

Introduction
This global, multidisciplinary conference, with representatives from 80 nations and every continent, brought together stakeholders from around the world who are committed to providing optimal cancer care to patients. This year, attendance rose by 15% and abstract submission increased by 30%, with newly participating countries such as Russia and some African nations. The abstracts represented cutting edge research and focused on the most current treatment strategies. BGICC welcomed 3,000 visitors, 300 regional and international key opinion leaders and 80 members from the press. BGICC is now accredited by the European Accreditation Council for Continuing Medical Education (EACCME).

BGICC partnered with leading societies of oncology and well recognised cancer foundations worldwide, such as the American Society of Clinical Oncology (ASCO), the European School of Oncology (ESO), the European Society of Surgical Oncology (ESSO), the Society of Geriatric Oncology (SIOG), the African Palliative Care Association (APCA), the European Society of Radiotherapy (ESTRO), the European Society of Gynecology (ESGO), the European Society of Oncology Imaging (ESOI), the Russian Association of Oncomamoplastastic (RAOM), the Faculty of Medicine at Ain Shams Research Institute (MASRI), the Breast Gynecological International Cancer Society (BGICS), Breast Surgery International (BSI), the Society for Immunotherapy of Cancer (SITC), and the Biobank and Cohort Building Network (BCNet) and Nature Research.

Educational and interactive courses
The scientific programme covered the spectrum of oncology from basic science to palliative care on the treatment of breast and gynaecological cancer, with consideration of pathology, surgery, radiology, radiotherapy, neo-adjuvant, adjuvant and metastatic systemic therapy, nursing, clinical pharmacy, palliative care, scientific research, as well as genetics, molecular biology of breast cancer and industry sponsored symposia. Clinical research was most cited by the participants as their primary topic of interest. In view of personalised medicine, there was an intensive course on molecular biology, followed by a post-conference three-day “hands-on” workshop in collaboration with Thermofisher and Fudan University focusing on the first Next Generation Sequencing (NGS).

A full report on the 11th BGICC conference was published on ecancermedicalscience: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6592708/

References:

3. Swain SM, Im YH, Im SA. Safety profile of PertuzumabwithTrastuzumab and Docetaxel in patients from Asia with human epidermalgrowth factor receptor 2-positive metastatic breast cancer: results from the phase III trial CLEOPATRA. Oncologist 2014; 19: 693-701
CTRG (Cancer Therapeutic Research Group) comprises several major oncology institutions in Asia including:

- The Chinese University of Hong Kong (Hong Kong SAR, China)
- National University Cancer Institute, Singapore / National University Health System
- Johns Hopkins Singapore International Medical Centre (Singapore)
- National Cancer Centre (Singapore)
- Yonsei Cancer Centre (Seoul, Korea)
- Sir Charles Gairdner Hospital (Perth, Australia)
- National Taiwan University Hospital (Taipei, Taiwan)
- Department of Haematology, Singapore General Hospital

Prof Winnie Yeo from the Chinese University of Hong Kong is the Chairman of the CTRG’s Breast Site. She has received grants from US NCI CTEP (US National Cancer Institute, Cancer Therapy Evaluation Program) to conduct clinical trials under the auspices of CTRG. Prof Yeo is also a grant recipient of the World Cancer Research Fund (WCRF) and the Wereld Kanker Onderzoek Fonds (WCRF, The Netherlands) and leads two on-going studies that assess the influence of dietary isoflavone and lignan on long term breast cancer outcomes. Prof Soo Chin Lee from the National University of Singapore is the principal investigator representing the CTRG in the BIG study Impassion030. Apart from the National University of Singapore, other sites participating in this study include the National Cancer Centre and the Tan Tock Seng Hospital (Singapore).

EORTC Breast Cancer Group

Spanning across Europe and the world, the EORTC Breast Cancer Group (European Organisation for Research and Treatment of Cancer) is a leading force in clinical cancer research. Consisting of over 300 members from 30 countries, the EORTC Breast Cancer Group has been engaged in numerous clinical and translational studies.

Its current strategy relies on three main and interlaced directions:

1. better targeting of specific tumour populations (molecularly defined)
2. improving the many unmet clinical needs found in the expanding group of older patients
3. increasing patient-driven research, positioning health-related quality of life as a genuine first endpoint matching more faithfully patients’ interests and goals.

Selected trials and projects

APPALACHES – a phase II study of Adjuvant PALbociclib as an Alternative to CHEmotherapy in Elderly patients with high-risk ER+/HER2-early breast cancer

This phase II study assesses the efficacy of the combination of at least 5 year-endocrine therapy and 2 year-palbociclib as adjuvant systemic treatment instead of adjuvant chemotherapy followed by endocrine therapy in older patients with stage II-III ER+/HER2- early breast cancer. This is a two-arm open-label multi-centre randomised non-comparative study in elderly patients, aged 70 years and older, with stage II/III, ER+, HER2-early breast cancer for whom treatment with chemotherapy is indicated.

366 patients will be randomised with a 2:1 allocation rate to the following treatment arms:

1) Experimental palbociclib arm: standard adjuvant endocrine therapy for a duration of at least 5 years plus palbociclib for a total duration of up to 2 years
2) Control chemotherapy arm: adjuvant chemotherapy - 4 cycles of docetaxel/doxorubicin/epirubicin-cyclophosphamide; or of weekly paclitaxel, followed by standard adjuvant endocrine therapy for a duration of at least 5 years

The primary endpoint of the study is the 3-year distant recurrence-free interval rate in the experimental arm. The study is currently recruiting and the completion date is expected in 2031.

This study is being run under the BIG umbrella in collaboration with Pfizer, Swedish Association of Breast Oncologists, International Breast Cancer Study Group, German Adjuvant Breast Cancer Group, SOLTI and UNICANCER/GERICO.

Follow-up in patients with early and locally advanced breast cancer

An EORTC QLG-BCG-ROG Protocol is a new study that EORTC Breast Cancer Group will be opening in collaboration with EORTC Quality of life Group and Radiation Oncology Group. This is a multicentre cross-sectional study of early and locally advanced breast cancer patients after primary therapy with curative intent. The study aims to assess the well-being needs of early breast cancer patients across Europe following treatment with curative intent and to describe current follow-up patterns of EBC in different countries (length and frequency of follow-up).

Translational research studies

The EORTC Breast Cancer Group is also embarking on a number of translational research projects assessing biological attributions from trials such as MINDACT or p53: specific subpopulations (lobular and HER2+ tumours), confrontation of different genomic signatures, or immune biomarkers.

In this regard, immune checkpoint inhibitors have shown promising results in some cancer types, but biomarkers to select patients that might respond to the treatment still need to be established in most indications. One of the main challenges is the limited amount of comprehensive empirical data that integrate molecular, cellular and clinical information to guide future translational and clinical research development.
Therefore, the group is a partner of the Innovative Medicine Initiative (IMI) programme IMMUcan, an inclusive and integrated European immuno-oncology profiling platform to share data resources. IMMUcan stands for “Integrated IMMUnoprofiling of large adaptive CANcer patient cohorts”. The IMMUcan consortium is composed of 28 academic institutions and pharmaceutical companies under the leadership of Merck and EORTC. The project was started in March 2019 and will end in August 2024. It will focus on colorectal, lung, head & neck, gastric, renal and breast cancers, to which the EORTC Breast Cancer Group is contributing. The majority of the patients will be recruited via SPECTA, the integrated EORTC research platform.

IMMU can will generate broad molecular and cellular profiling data of the tumour and its micro-environment from high-risk cancer patients. The molecular and cellular information will be integrated with clinical data to better understand both how the immune system and tumours interact and the impact of current therapeutic interventions.

The aim is to develop a sustainable data platform and legal framework in which participants from both academia and industry can pursue their own independent investigations using the IMMUcan data.

Dr Etienne Brain, EORTC Breast Cancer Group Chair, says, “The group has a long history in practice-changing programmes. As we move forward with innovative strategies that are as exciting as immunotherapy, we need to focus more intensely on academic and patient-centred questions. Indeed, understanding the molecular and cellular biology of how new treatments react gives us the foresight needed to develop future research. But we need to learn standing out from the standard development of new treatments while bringing to the community important supplemental information, helping to fine-tune the indications of these, avoiding over-treatment and matching better our ageing society landscape. Only through such effort will we be able to improve patient care globally and fairly.”

Clinical trials - current activities

Given the promise of immune checkpoint inhibitors combined with chemotherapy to treat triple-negative breast cancer (TNBC), the GBG (German Breast Group) continues to conduct trials with immunotherapeutic agents in different breast cancer settings. For example, the ongoing phase III GeparDouze (GBG 96 / NSABP B-59) trial, a joint study with the National Surgical Adjuvant Breast and Bowel Project (NSABP), aims to explore the efficacy and safety of neoadjuvant and adjuvant administration of atezolizumab/placebo in patients with high-risk TNBC. In the adjuvant setting, the randomised phase III ALEXANDRA/Impassion030 (GBG 98 / BIG 16-05) study being run by BIG, is evaluating the efficacy, safety and pharmacokinetic profile of atezolizumab in combination with standard anthracycline/taxane-based adjuvant chemotherapy versus chemotherapy alone in patients with early TNBC.

Furthermore, the results of the neoadjuvant GeparNuevo study (GBG 89) were published in the Annals of Oncology. This randomised phase II trial conducted with early-stage TNBC patients showed that, when compared to placebo, the addition of durvalumab, a monoclonal antibody targeting PD-L1, to anthracycline/taxane-based neoadjuvant chemotherapy increased the pathological complete response (pCR) rate, particularly in patients treated with durvalumab alone prior to start of chemotherapy.

A prospective and retrospective registry study on breast cancer in pregnancy and young women (BCP), in co-operation with BIG (GBG 29 / BIG 03-02), is proceeding to plan. The follow-up of the international PenelopeB study (GBG 78 / BIG 01-13), also being run under the BIG umbrella, is still ongoing. Results 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.

Recently, the neoadjuvant phase IIb GeparX (GBG 88) trial completed recruitment. The study evaluated denosumab, a RANK-ligand antagonist, as an add-on treatment to neoadjuvant chemotherapy and two different nab-paclitaxel schedules in a 2x2 design in primary breast cancer. Between February 2017 and March 2019, a total of 780 patients were randomised. Analysis of the primary endpoints is ongoing.
The first results of the GeparOLA (GBG 90) trial were presented at ASCO 2019. In this phase II study, 106 patients with early stage HER2-negative breast cancer and homologous recombination deficiency (HRD) were randomised to either paclitaxel weekly plus olaparib or paclitaxel weekly plus carboplatin, both followed by standard epirubicin/cyclophosphamide. While the addition of olaparib to paclitaxel was well tolerated, a pCR rate of 55.1% (90% CI 44.5%-65.3%) was not sufficient to exclude the predefined pCR rate of 55% in the olaparib arm. However, in the subgroup analyses, the pCR rates were higher in the group receiving olaparib than in the carboplatin group with regard to hormone receptor-positive tumours, specifically in patients younger than age 40 and those with HRD (homologous recombination deficiency) scores high for the BRCA1/2 wildtype. Therefore, we suggest that olaparib as part of neoadjuvant therapy should be further investigated in patients with HRD. Further exploratory and translational research is ongoing.4

The long-term outcomes of the neoadjuvant GeparSepto trial (GBG 69) were recently published in the Journal of Clinical Oncology. The results demonstrated that the higher pCR rate with nab-paclitaxel when compared to solvent-based paclitaxel translated into significantly improved invasive disease-free survival in patients with early breast cancer. Moreover, treatment-related peripheral sensory neuropathy improved much faster with 125 mg/m2 nab-paclitaxel than with 150 mg/m2 nab-paclitaxel.5

Translational research – current activities

The translational research findings of GeparNuevo were received with great interest at recent international meetings and support further investigation of induction therapy with immune-checkpoint inhibitors for treatment of primary TNBC.6,7

One of GeparSepto’s translational research projects showed high genetic heterogeneity in different breast cancer subtypes and confirmed that NGS (next-generation sequencing) using fresh-frozen, paraffin-embedded tissue can be used to identify markers of therapy resistance in clinical study cohorts, with PIK3CA mutations being a potential major mediator of therapy resistance in breast cancer.8

Another investigation that recently stimulated interest in the breast cancer community was a retrospective pooled analysis based on GBG’s meta-database that aimed to identify factors predicting relapse despite pCR. A total of 2,188 patients with pCR from five major neoadjuvant trials were included. It was shown that despite favourable prognosis following a pCR, around 15% of patients still had a relapse and 10% a distant relapse after 5 years. Interestingly, initial tumour load (tumour size and nodal status) and histological tumour type remained prognostic factors for long-term outcome even when a pCR was achieved. Thus, this could be helpful for further treatment decision-making following surgery.9

References:


7. Seliger B, Karn T, Denkert C, et al. Correlation of the tumour mutational burden with the composition of the immune cell subpopulations in peripheral blood of triple-negative breast cancer patients undergoing neoadjuvant therapy with durvalumab: Results from the prospectively randomised GeparNuevo trial. J Clin Oncol 37, 2019 (suppl, abstr 588)


GEICAM-AECC collaboration agreement

GEICAM (Spanish Breast Cancer Group) and Asociación Española Contra el Cáncer (AECC, the Spanish Association Against Cancer) have signed a collaboration agreement to promote activities aimed at improving knowledge and information about breast cancer.

Through this agreement, both entities seek to promote the study of this disease by collaborating in oncological research projects and programmes. They also intend to raise public awareness through joint talks and workshops on breast cancer (its clinical and molecular characteristics, therapeutic options and consequences on patients’ short and long-term quality of life) and on the indispensable role of healthy lifestyle habits in cancer prevention. The agreement also provides mutual support for campaigns and actions developed by both organisations, as well as any other activity with benefits for patients or society in general, with a special focus on breast cancer prevention.

AECC is a non-profit organisation founded in 1953 and composed of cancer patients, their families, volunteers, collaborators and professionals. The association develops its activity throughout Spain, with its course of action focused on health education, accompanying and giving support to patients and their families, as well as research promotion.

From shadow to light. GEICAM (Spanish Breast Cancer Group) and BIG team up to support breast cancer research

GEICAM and BIG have come together to support breast cancer research through the philanthropic initiative “From shadow to light. Together to support breast cancer research and save lives”, an exclusive gala dinner experience being organised by both entities. The aim is to raise awareness about the power of clinical research and international collaboration in a unique, memorable, multisensory and emotional event.

This gala will take place on 26 March 2020 in Madrid.

Women leading innovative companies with a strong commitment to social causes will be joining this unique event to support BIG’s and GEICAM’s clinical trials, in particular to boost funding for academic research projects. At GEICAM and BIG, we believe that combining the efforts of researchers, companies and communities will bring us closer to the first generation of women who will overcome breast cancer.
**GOCUR**

**GOCUR activities**

GOCUR (Grupo Oncológico Colaborativo Uruguayo) has been active in clinical trials since 1998. In the beginning, the group collaborated mainly with the BCIRG (Breast Cancer International Research Group) and thus participated in many international, phase III breast cancer trials (TAX 306, TAX 316, TAX IMA 301, BCIRG 005, BCIRG 006, RIBBON 1), as well as in trials for other cancers such as prostate cancer (TROPIC).

Last year, GOCUR participated in the phase IIIb PERUSE clinical trial, which was completed in August 2019. This single-arm, multicentre study aimed to evaluate the safety and efficacy of taxane treatment with pertuzumab and trastuzumab in patients with metastatic HER2 positive breast cancer. GOCUR included many patients who received the treatment and showed very good tolerance.

Between 2018 and 2019 GOCUR participated in two retrospective clinical trials in lung cancer: the PANORAMA study, which evaluated real-life results of patients with stage IV lung cancer diagnosed in 2017, and the pattern of requests for molecular tests and therapeutic results related to this study.

GOCUR is also participating in the KINDLE study, which has been recruiting patients diagnosed with stage III lung cancer. This study seeks to assess the demographic and clinical characteristics of patients and treatment patterns across multiple countries. Clinical outcomes, such as progression-free survival, time to progression, objective response rate and disease control rate are described for each treatment line. Overall survival will be described, when available. Global survival will be evaluated, and the use of resources for medical care will be described, as available in medical records.

In 2019, GOCUR became a member of the SWOG group (South West Oncology Group), through its SLAI initiative (SWOG Latin American Initiative). GOCUR is looking to integrate clinical trials of the SWOG group into its activities in the foreseeable future.

GOCUR is led by Gabriel Krygier, MD, associate professor of Medical Oncology at Universidad Clínicas Hospital, Montevideo, Uruguay. He’s an active member of ASCO (American Society of Clinical Oncology) and ESMO (European Society for Medical Oncology).

---

**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 translational research, inspired by the extensive collection of breast cancer related biospecimens in its biobank. These tissue and blood samples have been collected from patients who either participated in HeCOG clinical trials or who were treated within recommended therapy programmes.

Reflective of this interest in translational research is an increase in HeCOG publications. In 2018, seven articles on breast cancer were published, while by July 2019, already ten articles had been published. It is worth highlighting the group’s work in hereditary breast cancer and the effort made to map the genes involved.

So far in 2019, members of HeCOG’s Breast Group have been involved in organising several conferences and educational events focused on the biology, prevention and treatment of breast cancer.

Finally, in collaboration with the Greek charter of Women for Oncology (W4O), the founding members of which are also members of HeCOG, a public awareness meeting on cancer in women and heredity was organised. (W4O Hellas Awareness Week, 17-23 September 2018, Athens, Greece).

---

**HSBS**

**History and current activities**

The HSBS (Hellenic Society of Breast Surgeons) is the main scientific association of breast surgeons in Greece. It was founded in 2000 as a non-profit organisation with the aim to promote surgical research related to prevention, diagnosis and treatment of breast cancer; to encourage communication and interaction among breast cancer specialists nationally and across borders to organise local and national conferences on breast cancer; to educate surgeons on the updates and developments on breast cancer management; to facilitate breast cancer awareness for the public; to organise breast cancer screening activities; to publish relevant newsletters and bulletins; and to contribute to the training of younger breast surgeons through workshops, seminars, and courses, among other activities.

Nearly two decades later, many of the targets have been achieved and new ones are being set. One of HSBS’s major activities is the annual National Breast Cancer Conference, held each November in Athens. It attracts hundreds of international delegates and participants. The annual conference is the largest breast cancer conference in Greece and has...
been the forum where breast specialists interact and update their knowledge. Latest developments are presented and cooperation among different disciplines is confirmed. The conference is reputed for its high-quality presentations and vigorous debates. HSBS also regularly organises other meetings of local or regional interest outside Athens. These provide opportunity for local medical societies and patients to interact with HSBS.

With Continuing Medical Education (CME) at the heart of HSBS, a hands-on seminar on “live-tissue for surgical and oncoplastic techniques for surgeons” is also organised annually. This is held under the auspices of the University of Athens and in co-operation with the Hellenic Surgical Society. This two-day seminar provides CME points for the trainees and, apart from the practice on live tissue, it familiarises them with modern medical instruments and relevant techniques. The training slots are highly sought-after and participants are encouraged to register many months in advance.

HSBS also communicates with breast cancer specialists through a bimonthly newsletter. This provides a platform for all to participate, express their opinions and have their voices heard.

One of HSBS’s most rewarding achievements has been its close co-operation with breast cancer patient societies. HSBS greatly appreciates the recognition shown by patient organisations and has signed memoranda of cooperation with them. Worth noting is that, due to geographical or social reasons, there are groups of women with suboptimal access to healthcare provision which HSBS members continuously strive to address.

The main achievement of HSBS through the years is, however, not directly measurable, as it relates to raising the public’s consciousness about the role of breast surgeons in Greece: a very specific category of doctors, breast surgeons treat a sensitive group of patients with various needs and expectations, by applying knowledge and practical skills that require continuous updating, needing to work in teams (possibly more than in any other medical field) and realising that research is an integral part of modern medical practice.

Over the years, HSBS has successfully expanded nationwide. This has been achieved by participating in large randomised surgical trials, affiliating with medical societies from abroad and, recently, becoming more active in BIG, through which HSBS is now seeking to play a more important international role. HSBS members are all convinced of the importance of internationally coordinated surgical research in the field of breast cancer. HSBS’s strong points are the large number of patients treated by its members in different centres, as well as the breast surgeons’ enthusiasm to contribute to trials with surgical endpoints. Members of HSB already run local trials or registries on breast reconstruction, oncoplastic surgery and axillary surgery after neoadjuvant chemotherapy. The challenge, now, is to bring this to an international level.

BIG Task Force for Breast Cancer Surgery

As part of its mission to address clinical unmet needs in breast cancer research, BIG created several task forces, including one dedicated to breast cancer surgery. It aims to propose research projects or clinical trials that will evaluate innovative surgical strategies appropriate for different breast cancer disease settings. The task force also aims to develop projects that will facilitate implementation of high-quality surgery and a multidisciplinary approach, which are the cornerstones of breast cancer treatment.

The members of the task force are:

- Shinji Ohno - JBCRG (Coordinator, BIG Executive Board Member)
- Viviana Galimberti - IBCSG/SAKK
- Michalis Kontos - HBSS
- Niels Thorndahl Kroman - DBCG
- Roman Rouzier - UCBG
- Isabel Rubio - EORTC
- Anita Rohini Skandarajah - BCT-ANZ
- Marie-Jeanne Vrancken Peeters - BOOG
- Carmela Caballero - BIG HQ

IBCSG

Current IBCSG (International Breast Cancer Study Group) trials targeting CDK4/6 inhibition

Uncontrolled cell proliferation is the hallmark of cancer, and tumour cells have often acquired damage to genes that directly regulate their cell cycles.2,3

In the human cell cycle, the cyclin-dependent kinase 4 (CDK4) and the homologous CDK6 control progression from the G1 into the S phase, and their primary target is the retinoblastoma susceptibility gene product (Rb). Rb mediates cell cycle arrest in the G1 phase through sequestration of the transcriptional factors of the E2F family.3-5 Active Rb inhibits cell proliferation by binding the E2F transcription factors to halt the G1/S transition. Phosphorylation of Rb (pRb) by the cyclin D1-CDK4/6 leads to inactivation of Rb and the subsequent transcription of requisite genes for S phase entry, permitting cell division to proceed (Figure 1).6

![Figure 1: The Cyclin D1-CDK4/6-Rb pathway to regulate cell proliferation (adapted from1).](image-url)
The cyclinD1-CDK4/6-Rb axis is important in a number of malignancies, particularly oestrogen receptor-positive (ER+) breast cancer. Oestrogen has been shown to drive cyclin D1 transcription, which increases the rate of progression from the G1 to the S phase.\(^7\)\(^9\)

The development of the potent, highly selective CDK4/6 inhibitors palbociclib, abemaciclib and ribociclib have greatly improved the management of hormone receptor (HR)-positive metastatic breast cancer.\(^10\)\(^11\)

Several trials have demonstrated the benefit of CDK4/6 inhibitors plus endocrine therapy in ER+ advanced breast cancer in first or subsequent lines of therapy and the trials PALOMA-2 and -3 (palbociclib), MONALEESA-2, -3 and -7 (ribociclib) and MONARCH-2 and -3 (abemaciclib) have led to FDA drug approvals of these agents.\(^11\)

CDK4/6 inhibitors are also under investigation for HR-positive / HER2-negative early breast cancer, including the PALLAS trial in which IBCSG participates (ABCSD 42 / BIG 14-03 / IBCSG 52-15).

The IBCSG has developed and is currently sponsoring three ongoing trials in the early and advanced disease settings, where the CDK4/6 inhibitor palbociclib is combined either with endocrine therapy or with endocrine therapy and HER-blockade.

PYTHIA is the first IBCSG sponsored trial with palbociclib. It is a multi-centre, prospective single arm phase II trial of palbociclib plus fulvestrant in postmenopausal patients with HR-positive / HER2-negative, endocrine-resistant metastatic breast cancer. The strength of PYTHIA lies in its translational research focused. The main objective will assess a series of potential biomarkers of disease responsiveness - gene mutations, copy number aberrations, and gene-expression signatures - measured in primary and metastatic tumour material. PYTHIA (IBCG 53-14 / BIG 14-04) is conducted in conjunction with BIG and the AURORA platform (IBCG 51-14 / BIG 14-01), and centres in Belgium, Italy and the UK are participating in this trial. The trial reached its final sample size of 124 patients in March 2019. Treatment and follow-up continue as per protocol, and we expect the primary analyses to begin during early 2020.

Building on the results from the CALOR Trial (IBCG 27-02 / BIG 1-02), IBCSG developed POLAR, another CDK4/6 inhibitor trial targeting CDK 4/6 inhibition in the HR-positive / HER2-negative setting.

POLAR is a multi-centre, randomised phase III trial comparing adjuvant palbociclib in combination with endocrine therapy versus endocrine therapy alone for patients with HR-positive / HER2-negative resected isolated locoregional recurrence (ILRR) of breast cancer.

Isolated local or regional recurrence of breast cancer after mastectomy or lumpectomy indicates an increased risk of metastases and decreased survival. The results from CALOR strongly suggested that tailoring treatment according to the disease characteristics of the local recurrence provides a better indication of the possible responsiveness to treatment than reliance on the characteristics of the primary tumour.

POLAR is sponsored and coordinated by the IBCSG and conducted under the BIG umbrella (IBCG 59-19 / BIG 18-02) in collaboration with GEICAM (Spanish Breast Cancer Group) / SOLTI (Breast Cancer Research Group), UCBG (Unicancer Breast Group, France) and the ABCSG (Austrian Breast & Colorectal Cancer Study Group). The trial will enrol 400 patients from approximately 35 centres in Austria, France, Hungary, Italy, Spain and Switzerland.

The cyclinD1-CDK4/6 pathway is not only critical for the development of HR-positive tumours. Molecular alterations involving the Rb pathway frequently also occur in HER2-positive breast cancer.\(^12\)\(^13\) Preclinical studies demonstrated that ER-positive and HER2-positive cell lines are sensitive to CDK4/6 inhibitors, and that the combination of CDK4/6 inhibitors and endocrine therapy, or CDK4/6 inhibitors and anti-HER2 agents, are synergistic in these breast cancer models.\(^14\)

TOUCH is a multi-centre, randomised phase II trial investigating neoadjuvant therapy for elderly patients with HR-positive / HER2-positive early breast cancer. TOUCH is assessing the efficacy, in terms of pathological complete response at surgery, of a chemotherapy-free regimen of palbociclib in combination with endocrine therapy and dual HER2-blockade versus a regimen of paclitaxel in combination with HER2-blockade. The trial has a strong translational research rationale, built on the gene-signature of functional loss of Rb (RBsig). This signature is prognostic in luminal breast cancer subtypes and can predict response to the CDK4/6 inhibitor palbociclib. Among patients with ER-positive / HER2-positive breast cancer, those with RBsig HIGH derive benefit from chemotherapy and might be resistant to CDK4/6 inhibitors. On the other end, patients with RBsig LOW breast cancer, who derive little benefit from chemotherapy, may benefit from CDK4/6 inhibitors.\(^15\)

The TOUCH trial is sponsored and coordinated by IBCSG (IBCG 55-17) in collaboration with UCBG (Unicancer Breast Group, France) and GERICO (French Geriatric Oncology Group). The target sample size is 144 randomised patients. The trial was launched in December 2018 and is currently activated in Switzerland, Italy, Belgium, and will soon be launched in France.
IJB-CTSU

Professionalism, drive and dedication to help cancer patients

As an academic non profit organisation, the Clinical Trials Support Unit (CTSU) of the comprehensive cancer centre Institut Jules Bordet (IJB) is fighting cancer through the design, set-up and conduct of innovative clinical trials that matter to patients. It strongly believes that its work contributes to improve the understanding of the disease and to improve diagnosis, care and cancer treatments.

Over the last two decades, the IJB-CTSU has been collaborating with the Breast International Group (BIG) to conduct international clinical trials such as TAX 315, HERA, ALTTO, APHINITY, FINESSE, ALEXANDRA/IMpassion030 and AURORA.

Since 2013, the IJB-CTSU has also been assisting researchers to develop and run investigator-initiated trials (phases I, II and III) for all cancer types, as well as for all treatment and diagnostic modalities.

The strength of the IJB-CTSU team lies in its proximity to and interactions with the “real-world” of cancer care. The ideas for the clinical trials that it conducts come from oncologists, surgeons, and radiotherapists who treat patients daily. The IJB-CTSU understands the challenges and limitations of running clinical trials in hospitals faced with the evolution of health care systems, especially the various financial constraints and rapidly changing environments. Therefore, while promoting innovative clinical trial design (umbrella trials, basket trials, platform trials, de-escalation trials), it can ensure that trials are feasible in current hospital environments.

The IJB-CTSU team learns from every success as well as from every setback, yet ultimately it remains motivated to take up new challenges to help cancer patients by promoting quality cancer research.

References:
8. Muangrove EA, Lee CS, Buckley ME, Sutherland RL. Cyclin D1 induction in breast cancer cell shortens G1 and is sufficient for cells arrested in G1 to complete the cell cycle. Proc Natl Acad Sci U S A 1994; 91(17): 8022-6.

IJB-CTSU’s multidisciplinary team of highly motivated, dynamic and experienced professionals take charge of:

• Clinical study management: operational coordination, communication
• Contract management: legal expertise, financial management
• Pharmacovigilance: safety reporting, adverse events oversight
• Data management: eCRF design, data quality control
• Central imaging: standardisation, collection, expert review
• Statistics: study design and methodology, analysis plans, data analysis, publication
• Medical and scientific expertise: study design, medical oversight
• Regulatory affairs: submissions in the EU, regulatory compliance
• Site monitoring: site initiation visits, on- and off-site visits
• Biosample management: standardisation, collection, analysis
• Information technology: development and maintenance of software, user support

Managing clinical trials from A to Z, IJB-CTSU works with academic partners or pharmaceutical companies on specific activities.
**History**

The **Italian Trials in Medical Oncology Group (ITMO)** was founded in 1991 by Prof Emilio Bajetta. Since the beginning, it has aimed to promote clinical research by conducting multicentric trials that could offer patients the chance to receive qualified medical expertise and assistance all over Italy. The group has also always striven to spread and share knowledge about the latest developments in oncology. In this spirit, ITMO’s XXIV National Congress was held on 10 July, and was a great success. Topics discussed included updates on breast cancer, neuroendocrine tumours, gastrointestinal tumours, genitourinary cancer, lung cancer, immunotherapy, nutrition before, during and after cancer, and associations that support patients with cancer during and after their illness.

Since its foundation, ITMO has participated in 42 international clinical trials, written 46 scientific publications and organised 47 educational meetings. It is also currently participating in three trials and has other projects in development.

ITMO focuses on clinical and scientific research. Indeed, the ultimate goal is to beat cancer once and for all, with one of its main priorities being the study and treatment of breast cancer in elderly patients.

**JBCRG**

**Ongoing clinical trials and publications**

JBCRG (Japan Breast Cancer Research Group) is running the following studies:

- **JBCRG-M06 (EMERALD)**, a phase III clinical study to compare the combination therapy of eribulin mesylate + pertuzumab + trastuzumab with paclitaxel or docetaxel + pertuzumab + trastuzumab in breast cancer,

- **JBCRG-M07 (FUTURE)**, a multi-centre study evaluate fulvestrant with additional palbociclib in advanced or metastatic HR-positive HER2-negative breast cancer after progression to fulvestrant monotherapy.

JBCRG’s publications include the following:

1) JBCRG-07 in *Cancer Medicine 2018*
2) JBCRG-07TR in *IJ Molecular Sciences 2019*
3) JBCRG-12/15 in *Breast Cancer 2018*
4) JBCRG-C02 in *Basic and Clinical Research 2018*
5) JBCRG-10 in *JCO 2019*
6) JBCRG-11TC in *Cancer Medicine 2019*
7) JBCRG-11CPA in *Cancer Medicine 2018*

Under the BIG umbrella, JBCRG is currently participating in POSITIVE, ALEXANDRA/ Impassion030, OlympiA, PenelopeB and PALLAS (see trials table on pages x-y). The results of the POSITIVE study are particularly eagerly awaited by investigators and patients alike, given the impact of breast cancer on young women during their childbearing years.

**JBCRG and ELC Japan**

Representative Director Shinji Ohno and Director Chikako Shimizu visited ELC Japan K.K. and met with Ms. Sue Fox, the President of ELC Japan, the Japanese affiliate of Estee Lauder Companies Ltd. Since 2014, ELC Japan K.K. has continuously supported JBCRG research activities, including the POSITIVE study.

**JBCRG’s Annual Meeting**

JBCRG’s 10th Educational Meeting will be held on 12 October 2019 in Tokyo. This year’s theme is “Revolution of diagnosis and treatment for breast cancer through artificial intelligence and precision medicine”. It is expected that 150 investigators will attend.

**JBCRG’s Board**

JBCRG’s board members were renewed at the board meeting held on 8 June 2019. Five new members, Dr. Toshinari Yamashita, Dr. Takayuki Ueno, Dr. Shoichiro Ohtani, Dr. Yasuaki Sagara and Dr. Naoki Niikura, joined as directors.
KCSG

One step forward in clinical trials for premenopausal hormone receptor-positive breast cancer

A pivotal role played by KCSG (Korean Society of Cancer Prevention)

About half of breast cancer patients in Asia are diagnosed in women younger than 50 years, compared with approximately 20% in Western countries. Specifically, the peak age of breast cancer onset has been approximately 45 to 49 years in Korea, China, Hong Kong, Japan, and Taiwan, compared to 70 years in Western countries. Premenopausal breast cancers at younger age have been known to be more aggressive, less hormone receptor (HR)-positive, and less responsive to hormonal agents. Although breast cancer that develops in premenopausal women may differ biologically from the disease that develops in postmenopausal women, the recommended treatment is similar to that for postmenopausal breast cancer at older age with the addition of ovarian suppression.

Young-PEARL (KCSG BR15-10) is a randomised phase II study of ribociclib plus exemestane with GnRH agonist versus capecitabine in premenopausal women with HR-positive metastatic breast cancer. A total of 189 patients previously treated with 0 or 1 line of chemotherapy for metastatic breast cancer were enrolled from 14 KCSG institutions. Median progression-free survival, the primary endpoint, showed superiority for endocrine therapy plus ribociclib over capecitabine (20.1 vs. 14.4 months, P=0.0235 by log-rank test; hazard ratio 0.659 (0.437–0.994)). This is the first study to compare treatment with the CDK4/6 inhibitor palbociclib plus endocrine therapy with single-agent capecitabine chemotherapy exclusively in premenopausal women. This work was selected as an oral presentation at the annual meeting of the American Society of Clinical Oncology (ASCO), May 31-June 4, 2019, in Chicago, IL.

In conjunction with the Young-PEARL study, MONALEESA-7 is a ribociclib clinical trial in which Korean investigators have focussed their initiatives for premenopausal HR-positive, HER2-negative breast cancer. This is a phase 3 trial comparing ribociclib with placebo, in addition to endocrine therapy exclusively evaluated in premenopausal or perimenopausal women with HR-positive, HER2-negative advanced breast cancer. The addition of ribociclib resulted not only in longer progression-free survival, but also in longer overall survival. The estimated overall survival at 42 months was 70.2% vs. 46.0% in the ribociclib and in the placebo groups, respectively [hazard ratio for death, 0.71 (0.54–0.95); P=0.00973 by log-rank test]. Addressing unmet needs prevalent in Asian countries were the starting point for the concept of this international collaborative trial in CDK4/6 inhibitors era, and many Asian investigators including KCSG’s members played a pivotal role from trial design to patient recruitment.

KCSG hopes that these efforts will represent new milestone in the treatment of premenopausal breast cancer, which is relatively under-recognised and under-represented in many clinical trials. KCSG is also optimistic that, together with other Asian groups, its investigators will continue to play an important role in expanding knowledge in this area and helping patients with breast cancer.


LACOG

The Cure Project (Projeto Cura), set up by LACOG (Latin American Cooperative Oncology Group), encourages oncological research by launching the Renata Thommann Proicianoy Award

Established by “The Cure Project”, the Renata Thommann Proicianoy Award intends to create a culture of philanthropy, raise funds to support scientific research and encourage young oncologists to conduct research that helps in the search for a cure for cancer. The award was launched during the Best of ASCO (American Society of Clinical Oncology) congress, which was held on 14-15 June 2019 in São Paulo, Brazil.

For its first edition, papers submitted to the 2019 ASCO Annual Meeting were taken into consideration for the award. A scientific committee composed of research physicians associated with LACOG selected the work submitted by Dr Thiago Bueno as the winner.

Dr Thiago Bueno works in one of the leading hospitals in Brazil, the Antonio Prudente Foundation, also known as Hospital AC Camargo. More information about Dr Thiago Bueno’s work can be found at projetocura.org.

Dr Thiago Bueno, winner of the first edition of the Renata Thommann Proicianoy Award, established by LACOG’s Cure Project (Projeto Cura)
The award was inspired by Nora Thorrmann Procianoy, who could count on the help of her daughter Renata Thorrmann Procianoy to support research that helped diagnose the problem she was facing with her breast prosthesis. Renata quit all her activities and dedicated herself solely to this mission. Two years later, this resulted in the inclusion of Nora’s case in research coordinated by Dr Roberto Miranda at the MD Anderson Hospital, University of Texas, USA. Thanks to this research, the issue was detected and Nora could be treated. Some years later, when Nora totally recovered from the cancer, her daughter was killed in a car accident.

The family decided to transform pain into love by supporting research aimed at finding a cure for cancer. Through “The Cure Project”, they donated funds to LACOG, an institution that develops and coordinates multicentric oncology research in Latin America, with headquarters in Brazil.

The Projeto Cura award trophy was created and donated by the artist Fernanda Frangetto Maksoud. She is a visual artist who works with different media: sculpture, installation, painting and drawing. She studied at the Centro Universitário de Belas Artes and specialised in sculpture at the Museu Brasileiro da Escultura (São Paulo).

“Jazz to Support Oncology Research” brings together the medical community and members of the general public

The evening of 14 June was marked by good music and solidarity. Participants of the 2019 Best of ASCO and members of the general public joined the event “Jazz to Support Oncology Research” with maestro Osmar Barutti and singer Alba Santos. The event also included the announcement of the winner of the first Renata Thorrmann Procianoy Award for Oncology Research, Dr. Thiago Bueno. The creation of a philanthropy culture, raising funds to support scientific research and encouraging young oncologists to develop research that helps with finding a cure for cancer are among the objectives of the award created by “The Cure Project”.

The show was held at the Blue Note in the city of São Paulo, with the support of Armazem Entretenimento.

SOLTI

Prospective molecular profiling: new SOLTI Governing Board’s focus on cancer research

SOLTI renewed its Governing Board last May, drawing up the strategy for the coming years to consolidate the academic group as an international reference in clinical research in oncology.

As presented in the last Issue, at SOLTI we classify our studies into three research programmes: the Clinical Trial programme, the Window programme and the Biomarker programme. The group’s commitment remains focused on increasing its portfolio with new and challenging studies aimed at precision oncology. Many of our trials are being designed to prospectively validate molecular alterations already identified as clinically relevant for patient stratification. We believe genomic analysis is the path towards more accurate treatments with potentially higher benefit for our patients. Proof of this is the inclusion of the first two patients in our PATRICIA II trial, with more undergoing screening phase. The other two trials to be initiated this year, NEREA and TATEN, are in the final stages awaiting authorities’ approval (trial details available in Issue 10). These studies are intended to drive a shift in the selection criteria of patients for clinical trials. Thus, SOLTI is reinforcing its focus on more innovative and better designed biomarker-driven trials and expects to contribute to a paradigm change in patient-treatment selection in the future.
Besides being mainly dedicated to clinical research, at SOLTI we also promote medical education initiatives, which is also one of the top priorities of SOLTI’s Governing Board. To this end we have been offering several training workshops for young investigators focused on trial design and a complementary biostatistics/bioinformatics course. In fact, one of our most-cited trials, PAMELA, was initially designed during one of our workshops, and it has been internationally recognized as a precedent for HER2 therapy deescalation. In a different setting, from SOLTI we organize two annual scientific meetings to promote networking within the community: our SUMMITS are designed to create a collaborative atmosphere around the latest scientific news. Renowned international speakers share the stage with our experts and interact with the audience to discuss the future medical needs we face. Altogether we expect to motivate our experts and challenge them with the most relevant topics in the field. Summary-videos area available on our YouTube channel (SOLTIREsearchGroup).

The last (but not least) of our cornerstones is patient empowerment. Derived from a social study conducted a few years ago, patients’ limited understanding of their disease arose as an issue to be addressed. Fears and doubts were also pointed out as barriers that prevented them from participating in clinical trials. With this in mind, SOLTI launched a series of patient workshops carried out by our Board experts, intended to deliver accurate information to patients about the benefits of trials for them. During the activity, all participants feel comfortable and have time to share their experiences. From patients we have learned that their engagement and implication in treatment decision-making are key for better performance in breast cancer clinical research.

For the next three years, excellent science, motivated experts and patient-centric thinking will be SOLTI’s trademark: by promoting fruitful collaborations with other academic groups we expect to contribute to the advancement of cancer research.

Finally, the MyPeBS study, which UCBG coordinates (the Principal Investigator is Suzette Delaloge), will start at the end of 2019 and will randomise 85,000 women (Belgium, France, Israel, Italy, UK, Netherlands, USA) in order to define the future place of stratified breast cancer screening according to individual cancer risk. This study, which has been made possible by a European grant (European Union’s Horizon 2020 research and innovation programme), is the first of its kind and may bring changes to screening policies.

References:
2. Bachet T, Treilleux I, Schliffer C et al. mTORC1 activation assessed in metastatic samples predicts outcome in patients with metastatic breast cancer treated with everolimus-exemestane: results from the SAFIRTOR study, ASCO 2019, Abstract#1024
### 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 / IMpassion030</td>
<td>BIG 16-05</td>
<td>A randomised phase III trial comparing avelozimab (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 (BrEAST) / FSTRF and AFT Pharma partner: Roche/Genentech (sponsor) Funding: Roche / Genentech</td>
</tr>
<tr>
<td>APPALACHES</td>
<td>BIG 18-01</td>
<td>A Phase II study of Adjuvant PALbociclib 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>
</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. 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, NIF Trust, the National Lottery (Belgium), individual donors</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 - NCT0196833</td>
<td>S. Loibl, G. von Minckwitz</td>
<td>Supporter trial (Co)-Leading partner: GBG (sponsor) Pharma partner: N/A</td>
</tr>
<tr>
<td>Exceptional Responders</td>
<td>BIG 16-04</td>
<td>A global hunt for exceptional responders in the BIG network: aiming to identify breast cancer patients with a truly remarkable clinical response to anticancer treatments, and to characterise their tumours molecularly</td>
<td>A. Irrthum (coordinator)</td>
<td>BIG-sponsored programme (Co)-Leading partner: BIG HQ Pharma partner: N/A Funding: Breast Cancer Research Foundation</td>
</tr>
<tr>
<td>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 - NCT0288974</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>PEARLY</td>
<td>BIG 19-01</td>
<td>A randomised, multicenter, open-label, phase III trial comparing anthracyclines followed by taxane versus anthracyclines followed by taxane plus carboPlatin as (neo)adjuvant therapy in patients with EARLY triple-negative breast cancer - NCT02441935</td>
<td>J. Sohn</td>
<td>Supporter trial Pharma partner: N/A Coordinating group: KCSG (sponsor)</td>
</tr>
<tr>
<td>POLAR</td>
<td>BIG 18-02</td>
<td>Palbociclib 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>
</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 - NCT023088085</td>
<td>O. Pagani</td>
<td>Supporter trial (Co)-Leading partner: IBCSG (sponsor) Pharma partner: N/A Funding: IBCSG, Fonds Baillier-Latour, national and local funding bodies, individual donors</td>
</tr>
</tbody>
</table>
**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>Principal trial model &amp; partners</th>
</tr>
</thead>
</table>
| ALTI0      | BIG 2-06   | Adjunctive Lapatinib and/or Trastuzumab Treatment Optimization: sequence and combination for patients with HER2+/ER2+ positive primary breast cancer - NCT00490319 | M. Piccart, A. Moreira-Apina | Lead trial  
(Co-Leading partners: BIG HQ / IJB-CTSU / EDESTHF / Alliance (former NCCTG, sponsor for the US)  
Pharma partner: Novartis (global sponsor for all countries with the exception of US)  
Funding: GSK (past) / Novartis |
| APHINITY   | BIG 4-11   | Comparison of single-agent diad anti-HER2 therapy (trastuzumab, pertuzumab) for patients with HER2-positive primary breast cancer - NCT01358877 | M. Piccart, S. Loibl, J. Ines | Lead trial  
(Co-Leading partners: BIG HQ / IJB-CTSU / EDESTHF)  
Pharma partner: Roche (sponsor)  
Funding: Roche |
| AZURE      | BIG 1-04   | Does Adjunctive Zoledronic acid and/or REcurrence in patients with high-risk, localized breast cancer? - NCT00792020 | R. Coleman | Supporter trial  
(Co-Leading partners: NCRHI  
Pharma partner: Novartis  
Sponsor: University of Sheffield  
Funding: Cancer Research UK, Experimental Cancer Medicine Centre (ECMC), National Institute for Health Research Cancer Research Network (NCRN), Novartis and Immunotherm |
| BRAVO      | BIG 5-13   | Neoadapt treatment for HER2-negative, germline BRCA mutation-positive, locally advanced or metastatic breast cancer - NCT01955922 | N. Tumer, J. Balmaña, D. Cameron, J. Erban | Co-lead trial  
(Co-Leading partners: EORTC / BIG HQ  
Pharma partner: Teva (sponsor)  
Funding: Texas |
| DCIS       | BIG 3-07   | Radiation doses and fractionation schedules for women with DCIS - NCT00740236 | B. Chua | Supporter trial  
(Co-Leading partners: TBGLP (sponsor)  
Pharma partner: NIA  
Funding: National Health & Medical Research Council Project Grant, Susan G. Komen |
| FINESSE    | BIG 2-13   | Oral gilterad for patients with FGFR1 ER+ metastatic breast cancer - NCT02053636 | E. André, J. Gorin | Lead trial  
(Co-Leading partners: BIG HQ / BREAST / FISS  
Pharma partner: Servier (sponsor)  
Funding: Servier |
| 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 - NCT00727462 | J. Czock | Supporter trial  
(Co-Leading partners: JBS  
Pharma partner: Arantheus  
Sponsor: Queen Mary University of London  
Funding: Cancer Research UK, Queen Mary University of London |
| International Male Breast Cancer Programme | BIG 2-07 | Registration and biologic characterization programme of breast cancer in men - NCT01101425 | F. Cardoso, S. Giordano | Supporter programme  
(Co-Leading partners: EORTC (sponsor) / NABCG (US)  
Pharma partner: N/A  
Funding: Breast Cancer Research Foundation |
| LORELI     | BIG 3-13   | Different regimens of letrozole (or letrozole + tamoxifen) in postmenopausal women with ER positive/HER2-negative, early stage breast cancer - NCT02727973 | C. Saura, E. de Aramburu | Co-lead trial  
(Co-Leading partners: ABCSG, SO21 and BIG HQ  
Pharma partner: Genentech (sponsor)  
Funding: Genentech |
| MA.32 Metformin | BIG 5-11 | Effect of metformin on recurrence and survival in early stage breast cancer - NCT01101438 | P. J. Goodwin | Supporter trial  
(Co-Leading partner: CCTG (sponsor)  
Pharma partner: Astra  
Funding: NCI/NIH grants, Cancer Research UK, Canadian Cancer Society, BCRF and Canadian Breast Cancer Foundation |
| MINDACT    | BIG 3-04   | Can addition of 70-gene signature to common clinical-pathological criteria safely spare patients with 0 to 3 node positive breast cancer from adjuvant chemotherapy - NCT00435589 | E. Rutgers, F. Cardoso, M. Piccart | Co-lead trial  
(Co-Leading partners: EORTC (sponsor) / BIG HQ  
Commerical partners: Roche, Sanofi, Novartis and Agenda  
Funding: European Commission, Roche, Sanofi and Novartis grants, BCRC; Susan G. Komen for the Cure; Cancer Research UK, EORTC, Charitable Trust, numerous national cancer societies and many other charitable grants* |
| NEO-ALTI0  | BIG 1-06   | Comparison of dual HER2 inhibition (lapatinib, trastuzumab) plus chemotherapy before surgery versus single HER2-targeted therapy - NCT00553538 | C. Saura, J. Hudis | Co-lead trial  
(Co-Leading partners: IBCT-CTSU (BRCA) / FISS / SO21 / BIG HQ  
Pharma partner: Novartis (global sponsor for all countries with the exception of US, where Alliance is the sponsor)  
Funding: GSK (past) / Novartis |
| OLYMPIA    | BIG 6-13   | Olaparib vs. placebo for patients with BRCA-mutated, high-risk HER2-negative breast cancer, having completed local treatment and (neo)adjuvant chemotherapy - NCT02032823 | A. Tutt, B. Kaufman, J. Garber, C. Geyer | Lead trial  
(Co-Leading partners: NRG Oncology (sponsor in US), BIG HQ and EDESTHF  
Pharma partner: AstraZeneca (sponsor in all other countries)  
Funding: BreastCancer.org (funder of the world) |
| FALLAS     | BIG 14-03  | Randomized, Open-label, Adjunct Study: palbociclib with standard adjuvant endocrine therapy versus standard adjuvant endocrine therapy alone for HR+ / HER2-negative early breast cancer - NCT02525394 | M. Grant, A. DeMichele | Co-lead trial  
(Co-Leading partners: ABCSG (RoW), AFT (US) (sponsor) and BIG HQ  
Pharma partner: Pfizer  
Funding: Pfizer grant |
| PYTHIA     | BIG 14-04  | Palbociclib plus placebo for premenopausal patients with ER+/HER2- metastatic breast cancer. NCT02536742 | L. Maluski | Co-lead trial  
(Co-Leading partners: IBCSG (sponsor) and BIG HQ  
Pharma partner: Pfizer  
Funding: Pfizer grant |
| PENELope-B | BIG 1-13   | Post-neoadjuvant palbociclib for patients with HR+, HER2-negative primary breast cancer with high clinical risk after neoadjuvant chemotherapy - NCT01846746 | G. von Minckwitz | Supporter trial  
(Co-Leading partners: BIG HQ (past)  
Pharma partner: Pfizer  
Funding: Pfizer grant |
| SNAPP      | BIG 2-12   | Schedules of sub-Paclitaxel: evaluation of different schedules of sub-paclitaxel for metastatic breast cancer - NCT01746225 | A. Gennari, G. Jerusalem | Supporter trial  
(Co-Leading partners: IBCSG (sponsor)  
Pharma partner: Celgene  
Funding: Celgene grant |
| SOFT       | BIG 2-02   | Evaluation of ovarian suppression and of exemestane as adjucent therapy for premenopausal women with node positive breast cancer - NCT00666090 | P. Francis, G. Fleming | Supporter trial  
(Co-Leading partners: IBCSG (sponsor)  
Pharma partner: Pfizer  
Funding: Pfizer grant |
| SUPREMO    | BIG 2-04   | Selective Use of Postoperative Radiotherapy in Axillary Dissection of Patients with Early Breast Cancer: short-term follow-up of the randomized trial NCT00966888 | T. Künkler, P. Canney | Supporter trial  
(Co-Leading partner: SCTBIG  
Sponsor: UK Medical Research Council  
Pharma partner: Pfizer  
Funding: UK Medical Research Council, EORTC, Cancer Australia, William and Elisabeth Davies Charitable Trust, Peter Cahn for Va Foundation, Young Ying Yin and Mac Young Foundation. |
| TEXT       | BIG 3-02   | Tannazolfin and Exemestane Trial: evaluation of exemestane plus GnRH analogue for premenopausal women with endocrine responsive breast cancer - NCT00666703 | O. Pignatelli, B. Walley | Supporter trial  
(Co-Leading partners: 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 |
| ULTIMATE   | BIG 16-01  | Immuno-therapy combined with standard endocrine therapy as neoadjuvant treatment for women with ER+/HER2-negative breast cancer - NCT02979795 | F. Andrei, A. Piot | Co-lead trial  
(Co-Leading partners: French Breast Cancer Intergroup Unioncancer (UCBRG) (sponsor) and BIG HQ  
Pharma partner: AstraZeneca  
Funding: AstraZeneca grant |

* Full information available on the BIG website.  
N/A: not applicable; NCCTG: North Central Cancer Treatment Group; NCU: 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.
The Breast International Group (BIG) is a not-for-profit organisation for academic breast cancer research groups from around the world.

For the past 20 years, BIG has been dedicated to finding treatments to cure breast cancer. Thanks to the support of a network of BIG member groups, and thanks to global collaboration, we have strengthened our research efforts to find more solutions.

Founded by leading European breast cancer experts in 1999, BIG now constitutes a network of 57 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 57 breast cancer research groups of the BIG network

- ABCSG
  Austrian Breast & Colorectal Cancer Study Group
- AGO-B
  Arbeitsgemeinschaft Gynäkologische Onkologie Breast Study Group
- ARACAY-GINECO
  Association de Recherche dans les Cancers dont Gynécologiques – Groupe d’Investigateurs Nationaux pour l’Étude des Cancers Ovariens et du sein
- BCT-AMZ
  Breast Cancer Trials - Australia & New Zealand
- BDPPC
  Breast Disease Professional Committee of CMEA (China)
- BGICS
  Breast-Gynecological International Cancer Society
- BIE
  Breast Intergroup of Eastern India
- BOOG
  Borstkanker Onderzoek Groep
- CCTG
  Canadian Cancer Trials Group
- CEEOG
  Central and East European Oncology Group
- CT-IREE
  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
- FBCG
  Finnish Breast Cancer Group / Suomen Rintatyöpärlä
- GAICO
  Grupo Argentino de Investigación Clínica en Oncología
- GBG
  German Breast Group
- GCG
  Georgian Cancer Study Group
- GEOC
  Group de Estudios Clinicos Oncologicos Peruano
- GECAM
  Spanish Breast Cancer Group
- GOCCHI
  Chilean Cooperative Group for Oncologic Research
- GCUR
  Grupo Oncologico Cooperativo Uruguayo
- GODIC
  Italian Oncology Group for Clinical Research
- HBSS
  Hellenic Breast Surgical Society
- HeCOG
  Hellenic Cooperative Oncology Group
- HKBGC
  Hong Kong Breast Cancer Group
- HORG
  Hellenic Oncology Research Group
- IBCG
  Icelandic Breast Cancer Group
- IBCSG
  International Breast Cancer Study Group
- IBG
  Israeli Breast Group
- IBIS
  International Breast Cancer Intervention Studies
- ICRC
  International Collaborative Cancer Group
- ICBN ARO
  Indian Co-Operative Oncology Network
- ICRC
  Instituto de Cancer Research – Clinical Trials & Statistics Unit
- UB / CTSU
  Institut Jules Bordet / Clinical Trials Support Unit
- IOCSG
  Indian Oncology Study Group
- ITMO
  Italian Trials in Medical Oncology
- JBCRG
  Japan Breast Cancer Research Group
- KCSS
  Korean Cancer Study Group
- LACSS
  Latin American Cooperative Oncology Group
- MICHELANGELO
  Fondazione Michelangelo
- NBCG
  Norwegian Breast Cancer Group
- NCRI-BCSG
  National Cancer Research Institute - Breast Cancer Clinical Studies Group
- SABO
  Swedish Association of Breast Oncologists
- SAKK
  Swiss Group for Clinical Cancer Research
- SBCG
  Sheba Breast Collaborative Group
- SKMCH & RC
  Shaukat Khanum Memorial Cancer Hospital & Research Centre
- SLO
  Société Luxembourgeoise d’Oncologie
- SOLEI
  Breast Cancer Research Group
- SUCCESS – Study Group
- SweBCG
  Swedish Breast Cancer Group
- TCDO
  Taiwan Cooperative Oncology Group
- TROG
  Trans Tasman Radiation Oncology Group
- TSOCO
  Thai Society of Clinical Oncology
- UCBG
  Unicancer Breast Group
- WSG
  Westdeutsche Studiengruppe
European Breast Cancer Conference
Discussing the burning issues at each step of the breast cancer journey

ABSTRACT SUBMISSION NOW OPEN

KEY DATES

2019
15 Nov: Abstract submission closing
17 Nov: Fellowship grant closing

2020
1 Feb: Late breaking abstract submission open
14 Feb: Late breaking abstract submission closes
19 Feb: Regular rate closing
20 Feb: Late rate opening

Translating clinical research into best practice for patients

eortc.org/ebcc
#EBCC12
Motivated by the love of their wives, mothers and daughters, a group of six entrepreneurs called ‘Over our Top’ took up a swimming challenge to push their limits for a good cause.

To mark the occasion of David’s 80th birthday, he generously invited his friends and family to make a donation to BIG instead of buying a gift.

The money you raise will go directly to an important research programme led by BIG and destined to one day find a way to block the progression of metastatic breast cancer.

Discover the many occasions you can continue to move for BIG by creating your own fundraiser!

Isabelle opted for donations to fund breast cancer research in lieu of baby shower presents.

Motivated by the love of their wives, mothers and daughters, a group of six entrepreneurs called ‘Over our Top’ took up a swimming challenge to push their limits for a good cause.

Having lost a loved one, Marie rallied her friends and family to donate to innovative research.

To mark the occasion of David’s 80th birthday, he generously invited his friends and family to make a donation to BIG instead of buying a gift.

Do you have an idea, engage your colleagues to fundraise for breast cancer research? Get started here!

The sky is the limit, whatever your creative idea is to fundraise for breast cancer research, you can get started here!