Fighting breast cancer around the globe

Central and Eastern Europe
Farewell to Professor Aron Goldhirsch (1946 – 2020)

Professor Aron Goldhirsch, the “father” of the Breast International Group (BIG) and a founder of the International Breast Cancer Study Group (IBCSG), passed away at the age of 73 on 26 February 2020. He was much more than a brilliant medical oncologist; he was a truly remarkable person known for his very high sense of ethics, humanity and openness. He will be profoundly missed, not only by his family, friends and patients, but also by the scientific world and his extended BIG family.
Throughout his career, Professor Goldhirsch made significant contributions to breast cancer medicine and education, and worked tirelessly to foster international collaboration and preserve academic independence in cancer research. Over the years, his humanity and openness inspired people with different backgrounds and expertise to join efforts and build a genuine collaboration: “…a multidisciplinary approach across groups and institutions, working together with the spirit of ‘all for one and one for all’, is the most powerful attitude to improve results in breast cancer research”\(^1\). Much of this work was conducted in the context of his leadership within the International Breast Cancer Study Group.

In the early 1990s, while breast cancer research was highly fragmented, with academic groups running many similar trials and consequently duplicating efforts, and wasting time and resources, Professor Goldhirsch, together with Professor Martine Piccart, shared a different vision of the future: groups debating the latest research findings, sharing ideas for new clinical trials and working in harmony to conduct these trials together. He strongly believed that this was the only way forward to make significant advances in breast cancer research and answer pertinent therapeutic questions more rapidly and efficiently. In 1996, Professors Goldhirsch and Piccart created the Breast International Group (BIG) with the aim of bringing together academic research groups. BIG became a legal entity in 1999 and now, over 20 years later, more than 60 trials have been run under the BIG umbrella, many of them landmark, having a real impact on patients’ lives. It was Professor Goldhirsch’s idea to call this new network “BIG”, despite it being a very small and fragile collaborative network at the start. According to Professor Piccart, “This was not a random choice: because of Aron’s faith in collegiality, loyalty, friendship, and his passion for ‘academic freedom’, he knew that this construction would grow and become successful over the years.”

When asked about the future, Professor Goldhirsch was optimistic: “Improvement of patient care has been observed in each of the last four decades. There is no reason for this trend to stop! Our current degree of knowledge will increase and, with it, improve practice.”\(^2\) Throughout his career, he encouraged new generations of breast cancer experts to work together and to maintain the spirit of academic research, which includes better care for patients and better knowledge for advancing science.

Professor Goldhirsch was bestowed with numerous prestigious honours and awards for his work, including the Susan G. Komen for the Cure Brinker Award for Scientific Distinction (2008), the Umberto Veronesi Award for the Future Fight Against Breast Cancer (2010) and the Gianni Bonadonna ASCO Breast Cancer Award & Lecture (2014).

But his impact extends well beyond these prizes and the over 700 peer-reviewed articles he authored. Professor Goldhirsch’s greatest legacy is his vision: provide the best care for each individual patient through collaboration, academically independent research and education.

He will continue to live through and inspire future generations of cancer scientists, and everyone else who had the privilege to know him.

\(^1\) Interview with BIG HQ, BIG Research in Focus vol.7, September 2017

\(^2\) Interview with BIG HQ, BIG Research in Focus vol.7, September 2017
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As part of our multi-series newsletter "Fighting breast cancer around the globe", which explores breast cancer research scenarios in the various regions of the world where BIG member groups are present, we have come to the last continent of the series: Europe. Because many European countries and BIG member groups are involved in academic breast cancer research taking place in this part of the world, we will issue three editions of the newsletter in 2020, starting with this one, which focuses on Central and Eastern Europe. The next will focus on Southern Europe (September 2020), and we will close these series with Northern Europe (December 2020).

For this edition, the themed article, by science writer Jenny Bryan, includes interviews by Professor Jacek Jassem (Poland), Professor Gunta Purkalne (Latvia), Doctor Tanja Španić (Slovenia) and Professor Giorgi Dzagnidze (Georgia). They provide us with their insights into breast cancer research in their countries, and in Central and Eastern Europe in general.

Breast cancer is less common in Central and Eastern Europe than in other parts of Europe, but delayed diagnosis and limited access to newer treatments have resulted in poorer outcomes in many parts of the region.

The ratio of mortality to incidence is less favourable in Central and Eastern Europe than the rest of Europe, and the gap is not getting smaller. The most likely reason is the lower rate of women participating in breast screening, so cancers are diagnosed at a later stage than in other countries.

Alongside improvements in diagnosis and treatment of breast cancer, there is a growing emphasis on treatment de-escalation in specialist cancer centres in CEE countries – as there is in other parts of Europe. “Patients with early breast cancer are offered breast conserving surgery with sentinel node biopsy in Poland, and in most other countries of Central and Eastern Europe, and shorter courses of radiotherapy have been increasingly offered. Fewer patients receive chemotherapy, but we do still need to improve access to Oncotype® and MammaPrint® testing for risk of relapse to further reduce the use of chemotherapy,” says Professor Jacek Jassem, chair of the Central and Eastern European Oncology Group (CEEOG).

In Slovenia, Doctor Tanja Španić and her colleagues at Europa Donna are advocating strongly for wider availability of genomic testing and more personalised treatment based on test results.

Professor Gunta Purkalne has analysed the situation in Latvia and concludes that they are seeing more investment for cancer drugs. However, the newer, more expensive drugs for metastatic disease are not reimbursable, and this is contributing to a higher breast cancer mortality in Latvia than in many European countries.

The article also sheds a light on breast cancer research in Georgia. Professor Giorgi Dzagnidze, President of the Georgian Cancer Study Group (GCSG), is hopeful: “In the last 20 years, we have been educating the younger generation of oncologists, some of whom trained in other parts of Europe, and we have significantly expanded our clinical trial programmes – presenting our results at some major conferences. Step by step, we are making important progress, including education for clinicians in smaller private hospitals so we have a network of well-trained clinicians across the country.”

In 2019, BIG celebrated its 20th anniversary, 20 years of breast cancer research and hope. For the years to come, the BIG network aims to continue to play an important role in providing a platform for clinical research that is fast and effective and allows for the most efficient conduct of clinical trials within a network of countries across the world. Further collaboration with groups in countries where research is scarcer and availability of innovative trials is rarer could be a significant step towards improving treatment and care for women and men with breast cancer.

Finally, the following pages will also give you a peek at BIG members’ research and related activities around the world. We hope these articles will inspire you and welcome your stories.
Breast cancer is less common in Central and Eastern Europe than in other parts of Europe, but delayed diagnosis and limited access to newer treatments have resulted in poorer outcomes in many parts of the region. For breast cancer specialists, shaping future services, wider availability of breast screening, better access to Oncotype® and MammaPrint® testing and targeted therapies, and more specialist breast cancer centres, are high on the agenda – as science writer Jenny Bryan discovered.

With an estimated incidence of 73.7/100,000, breast cancer is less common in Central and Eastern Europe (CEE) than in Europe overall, where the disease affects 100.9/100,000. However, as mortality rates are very similar, breast cancer specialists across the region are working to improve the outlook for patients.

“The ratio of mortality to incidence is less favourable in Central and Eastern Europe than the rest of Europe, and the gap is not getting smaller. The most likely reason is the lower rate of women participating in breast screening, so cancers are diagnosed at a later stage than in other countries,” explains Professor Jacek Jassem, from the Medical University of Gdansk, Poland, and Chair of the Central and East European Oncology Group (CEEOG).

Participation in breast screening in Poland has almost doubled to 59% in less than 15 years and, in Slovenia, where breast cancer mortality is lower than in many CEE and other European countries, a national screening programme is helping to reduce late stage diagnosis.

In 2015, the South Eastern European Research Oncology Group (SEEROG) panel recommended that national cancer control plans (NCCPs) and national cancer registries should be established in all CEE countries. Other recommendations included greater availability of multidisciplinary and outpatient care, improved access to specialist expertise for clinicians and to primary and secondary prevention programmes for patients, increased cancer education and larger oncology budgets.

Five years on, considerable progress is being made. For example, a Cancer Control Strategy is gradually being implemented in Poland, including registries for breast and other cancers. However, such strategies are still lacking in some CEE countries, and a series of meetings and consultations have recently been held so that countries can share needs and experiences and achieve greater consistency of services and registries across the region.

“Without registries, we not only miss epidemiological data, we also miss important information about patient pathways, treatments, follow up and outcomes,” says Jassem.
There are fewer comprehensive breast cancer centres in the region than in Western Europe (WE). In Poland, for example, their development has only recently started, and there are just ten centres, compared with the 70 that are considered to be needed to care for the country’s 38 million population.

In Latvia, all patients are now treated at one of three comprehensive, multidisciplinary breast cancer centres – an advance that is having a major impact on patient care.

“Last year we celebrated ten years since the establishment of medical oncology as a separate specialty in Latvia, including specific training for breast cancer treatment for medical oncologists, though we do still have a shortage of doctors and especially nurses,” says Professor Gunta Purkalne, from the Clinic of Oncology, Pauls Stradiņš Clinical University Hospital, Riga, Latvia.

Alongside improvements in diagnosis and treatment of breast cancer, there is a growing emphasis on treatment de-escalation in specialist cancer centres in CEE countries – as there is in other parts of Europe. Jassem was a panel member of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer, which recommended de-escalation in low-risk patients, aimed at reducing morbidity associated with surgery, radiotherapy and chemotherapy.3

“Patients with early breast cancer are offered breast conserving surgery with sentinel node biopsy in Poland, and in most other countries of Central and Eastern Europe, and shorter courses of radiotherapy have been increasingly offered. Fewer patients receive chemotherapy, but we do still need to improve access to Oncotype® and MammaPrint® testing for risk of relapse to further reduce the use of chemotherapy,” says Jassem.

In Latvia, about 50% of patients continue to have mastectomy, which is more than in most European countries. This is partly due to a shortage of radiation technologies in Latvia, and limited availability of post surgical radiotherapy for those who have breast conserving procedures, though this is improving.

“Some patients choose mastectomy because they do not have the support to enable them to travel for daily radiotherapy. However, as well as less aggressive surgery with sentinel node biopsy, we can now offer hypofractionated and partial breast radiation. We also use the deep inspiration breath-hold technique to minimise cardiac damage during radiotherapy, and we are using less aggressive chemotherapy and more hormone and targeted therapies such as CDK4/6 inhibitors,” says Purkalne.

Tanja Španić, President of Europa Donna Slovenia, who participated in recent de-escalation meetings with North American and European representatives, explains that, in Slovenia, most clinicians will await changes to European guidelines before introducing treatment de-escalation.

“De-escalation has the potential to improve quality of life not only in the short term while treatment is underway, but also 10 or 20 years later if long term adverse effects can be prevented. We now have a lot of data about balancing the benefits of de-escalation against any possible increased risk of recurrence and I think we are ready to move forward,” she says.

Striving for treatment equality

While recommendations for breast cancer treatment are the same across Europe, resourcing is a major challenge in CEE. In 2015, average expenditure on cancer drugs was 2.5 times higher in WE than in CEE.4 Average availability of 35 key drugs was 91% across Europe and 100% in Germany. But, in CEE, it averaged 70% – ranging from 37% in Bosnia to 86% in Herzegovina.

The study also demonstrated much wider differences in treatment expenditure in CEE than WE. In WE, expenditure per new case of cancer ranged from €11,586 in Italy to €17,879 in Switzerland, a difference of 54%.3 However, the difference in expenditure between Serbia, which spent least on cancer drugs (€1,300 per new case), and Slovakia, which spent most (€12,700), was 907%. Annual cancer drug expenditure per new cancer case was significantly negatively correlated with mortality to incidence ratio.
For the novel breast cancer drug trastuzumab emantsine, expenditure ranged from €43-199 per new cancer case in WE compared to €0-22 in CEE, reflecting the very limited availability of this drug in CEE.

“In Central and Eastern Europe, there is delayed access to modern medicines for breast cancer. Many patients cannot afford molecular risk testing such as MammaPrint® or Oncotype®, and access to targeted medicines is delayed or these drugs are not reimbursed,” says Jassem.

In Slovenia, Španić and her colleagues at Europa Donna are advocating strongly for wider availability of genomic testing and more personalised treatment based on test results.

“After the European Medicines Agency registers a new treatment, in some cases it can take as long as two years of negotiations with payers to get reimbursement, and during that time patients don’t have access to the drug. Their only option is to go abroad for treatment,” says Španić.

“We are a small country so we can advocate directly with politicians, clinicians, healthcare providers and the media to get our message across. But we still need better access to the national medicines agency and to insurers,” she adds.

Though geographically close to each other, the Baltic states vary considerably in availability of newer, targeted agents.

“In Latvia, we are seeing more investment for cancer drugs, but the newer, more expensive drugs for metastatic disease are not reimbursable, and this is contributing to our higher breast cancer mortality compared to many European countries,” says Purkalne.

In Latvia, trastuzumab is reimbursed for neoadjuvant, adjuvant and metastatic disease, but pertuzumab is only reimbursed for metastatic disease. In contrast, in Estonia and Lithuania pertuzumab reimbursement includes adjuvant and neoadjuvant disease. However, CDK 4/6 inhibitors are reimbursed in Latvia (for first line treatment of metastatic disease in combination with endocrine therapy), but not in Estonia and Lithuania.

“The situation is changing all the time, but we continue to have differences in access to newer drugs across the Baltic states,” says Purkalne.

In Poland, systemic therapy follows recommended practice in Europe, though there are also delays in the availability of the newest drugs.

“We have had treatment guidelines for 20 years that are regularly updated. Since 2018 they have become an official state document with quality measures that are monitored. Selected quality indicators have been made publicly available so that patients can use the result to help them choose where to have their treatment,” says Jassem.

Hospitalisation rates and duration of stay for patients with cancer are higher in some CEE than WE countries, points out Professor Jassem, though longer stays for breast cancer surgery are also seen in Germany and Austria. In some CEE countries, patients may have supplemental private health insurance to pay for their care. Trastuzumab is reimbursed in all countries, but trastuzumab emantsine and CDK4/6 inhibitors are much less widely available.

Many patients with breast cancer have chemotherapy as inpatients rather than through ambulatory care, and too few radiotherapy centres means that patients are often treated in large centres as inpatients.

“De-escalation has the potential to improve quality of life not only in the short term while treatment is underway, but also 10 or 20 years later if long term adverse effects can be prevented. We now have a lot of data about balancing the benefits of de-escalation against any possible increased risk of recurrence and I think we are ready to move forward.”

Tanja Španić (Slovenia)
“Hospitalisation for chemotherapy is common because it is reimbursed in many healthcare systems of Central and Eastern Europe, so there is no incentive to change this practice even though patients could be treated as outpatients,” says Jassem.

In Poland, a Cancer Control Strategy is gradually being implemented for all cancers, though it is not yet an official state document.

“There is much more to be done in promoting education and screening, but progress is being made,” concludes Jassem.

Georgia: at the crossroads of Eastern Europe and Western Asia

Though higher than its CEE neighbours across the Black Sea, the incidence of breast cancer in Georgia is still lower than in some other parts of Europe (90.6/100,000). However, the fact that 20% of the country is occupied by Russia, and some of the population is transient, makes it difficult to provide accurate estimates, as Professor Giorgi Dzagnidze, Head of the Breast Unit at S.Khechinashvili University Hospital, Tbilisi, Georgia, and President of the Georgian Cancer Study Group (GCSG), explains:

“Half of Georgia’s four million population lives in Tbilisi but, in addition to movement of people in and out of the country in search of work, we have significant medical tourism from countries such as Chechnya and Azerbaijan because our facilities are better,” he says.

“We know that we are treating at least 1,200 cases of primary breast cancer annually, and the number may be as high as 1,500. In the last two years we have introduced an oncology registry and there is now greater collaboration between our main breast cancer centres, so we hope this will enable us to get a more accurate picture of breast cancer in Georgia,” he adds.

The profile of breast cancer diagnosed in Georgia appears similar to that of Eastern Europe, though there is evidence of a higher proportion of cases of triple negative disease. Through a collaboration with UK researchers, Dzagnidze plans to investigate familial breast cancer rates in Georgia and across the Caucasus region.

“Georgia is in the heart of the Caucasus, which is a region made up of many different countries and whose geographical barriers mean that populations have not mixed very much in the past with European or Asian populations. So it will be very interesting to collaborate on oncogenetic studies to find out if we have some particular types of inherited breast cancer,” he says.

Breast cancer screening was introduced in Georgia in 2008 and is available in all regions of the country. As a result, 70% of breast tumours are now diagnosed at an early stage, compared to 70% diagnosed at a late stage before screening was widely available. Oncotype® and MammaPrint® testing are not yet available, but Dzagnidze is optimistic that a cost-effective way of introducing such techniques can be found. Without a cyclotron in the country, radioactive tracers have not been available for sentinel node biopsy. However, positron emission tomography (PET) is being introduced at one cancer centre so progress is being made.

Treatment in the major breast cancer centres in Georgia where 70-75% of patients are treated, is largely comparable to that in Europe, with patients receiving breast conserving and reconstructive surgery, radiotherapy, hormone treatment and chemotherapy.
“Georgia is a fascinating country which holds great promise for breast cancer research – through the genetics of its population and the increasing quality of its clinicians and technologies. We have a lot to offer BIG and other research organisations.”

Giorgi Dzagnidze (Georgia)

“In the last 20 years, we have been educating the younger generation of oncologists, some of whom trained in other parts of Europe, and we have significantly expanded our clinical trial programmes – presenting our results at some major conferences. Step by step, we are making important progress, including education for clinicians in smaller private hospitals so we have a network of well-trained clinicians across the country,” says Dzagnidze.

The Georgian government has committed to funding 70% of all essential treatments for breast cancer so, for the last two years, trastuzumab has been available, though only a small proportion of patients can afford to pay for pertuzumab, lapatinib and CDK4/6 inhibitors. A major focus on biosimilar research has potential to extend availability of latest approaches to breast cancer treatment. Dzagnidze participated in a successful study of CT-P6, a trastuzumab biosimilar, along with colleagues from a number of CEE countries. The phase 3 trial showed equivalence of the two agents in terms of pathological complete response and adverse event profile. Dzagnidze and colleagues are participating in further, ongoing studies of trastuzumab biosimilars, including HD201 (Troika study) and TX05. They are also investigators in the MANTA Phase 2 study of fulvestrant in combination with the mTOR inhibitor, AZD2014, or everolimus vs fulvestrant alone in ER-positive metastatic breast cancer, and the PAKT Phase 2 study of the AKT inhibitor, AZD5363, combined with paclitaxel in triple negative advanced or metastatic breast cancer.

The GCSG works with leading breast cancer specialists from Europe and the USA to extend breast cancer training across Georgia – not only in implementing international guidelines but also enabling local clinicians to develop initiatives tailored to the needs of the local population.

“It is very important that these experts come to Tbilisi because it enables clinicians from across the region, not just Georgia, to hear about developments in breast cancer treatment and find ways to adapt them for their own patients in an affordable way, as well as forming research collaborations,” says Dzagnidze.

Earlier diagnosis of breast cancer and better clinical training are making it possible to introduce treatment de-escalation strategies, including individualised neoadjuvant endocrine therapy and intra beam radiotherapy. For patients with advanced, heavily treated breast cancer, Dzagnidze is investigating the potential of synthetic oestrogens – repurposing older agents for targeted use.

For the future, he hopes to further individualise therapy, using molecular biomarkers to determine the most appropriate approach and, ultimately, to detect breast cancer preclinically so that patients can have chemo- or surgical prevention. Another goal is to develop genetic testing to identify and hopefully eliminate the genetic causes of breast cancer in the region.

“Georgia is a fascinating country which holds great promise for breast cancer research – through the genetics of its population and the increasing quality of its clinicians and technologies. We have a lot to offer BIG and other research organisations,” concludes Dzagnidze.

### CEE participation in research

Breast cancer clinical trials scored well in a recent analysis of cancer research activity for 2007-2016 from 29 countries of the CEE and Russian Federation and Central Asian (R-CA) regions. Cancer biology and cancer drugs (including biomarkers, chemotherapy and targeted therapy) made up nearly 40% of research activities, but a significantly lower proportion of research focused on palliative care, screening and radiation oncology than is seen in comparable EU countries. International clinical trials, especially of new molecular targeted therapies, were responsible for 20% of overall research outputs across CEE and R-CA. The authors suggested that an increase in well-designed country- or region-specific studies is needed, with socio-economic models to help prioritise therapeutic interventions, introduction of new technologies and delivery of affordable and equitable care and better outcomes.
The research demonstrated a moderate increase in international collaboration between CEE researchers, mainly with EU countries, but Professor Jassem would like to see greater participation in international studies. CEEOG, which was set up in 1983 and now has members in most CEE countries, has coordinated many trials across the region, especially during the years when some countries were politically isolated, and it also acts as a bridge to international research groups.

“CEEOG has enabled many research groups to take part in international breast cancer trials and, as is well known, this type of participation also helps to improve standards of care,” says Jassem.

As well as participating in the HERA, APHINITY, BIG 1-98, ALTTO, OLYMPIA, SOLO, PALLAS and ALEXANDRA/IMpassion030 trials, CEEOG also conducted the LA-REMA study of molecular factors, predicting the efficacy of lapatinib in patients with HER2-positive advanced breast cancer, and was a part of the PathIES study to identify biomarkers that predict response to exemestane in postmenopausal women with early breast cancer. Molecular and clinical aspects of brain metastases of breast cancer have been the subject of a series of studies performed by the Polish Brain Metastasis Consortium, a working party of CEEOG.10-14

Jassem explains that, although Polish researchers take part in many breast cancer trials in collaboration with the European Organisation for Research and Treatment of Cancer (EORTC) and BIG, he would like to see more patients recruited to studies. Through large scale epidemiological studies of hereditary breast cancer in Poland, researchers now have a good understanding of the genetic and molecular profile of breast cancer in the country, and it appears that rates of breast cancer subtypes are similar to those of other countries in Europe.

“CEEOG has enabled many research groups to take part in international breast cancer trials and, as is well known, this type of participation also helps to improve standards of care.”

Jacek Jassem (Poland)

In Poland, there is limited funding for investigator-led trials, though cancer is one of the research programmes in the newly established Agency for Medical Research in Poland which will provide grants for academic clinical studies.

“At present, most breast cancer trials in Poland are sponsored by pharmaceutical companies or research associations such as BIG or its members, but this new agency is government sponsored. The budget is not large, but we have been campaigning for it for many years, and we are told the budget will increase in the years ahead,” says Jassem.

Research in Latvia is currently limited, mainly to basic research on inherited breast cancer, including collaborations with researchers in Poland, and to clinical trials sponsored by pharmaceutical companies. Attempted collaborations with researchers in other Baltic states have suffered from limited finance, and Professor Purkalne would welcome greater access to international breast cancer studies.

“We have enough knowledge and patients to participate, and we are working to overcome staffing shortages so that we can participate,” she says.
In Slovenia, clinicians have had fewer opportunities for taking part in research in recent years, and delays in gaining ethical approval for studies may have contributed to this reduction.

“It is very disappointing and frustrating for clinicians who want to participate in clinical trials, as potential sponsors are not prepared to wait many months for an ethical committee, especially for such a small country, but we hope this will change in the near future,” says Španić.

Two new trials are planned for 2020, and Slovenian breast cancer specialists are participating in BIG’s POSITIVE trial, which is investigating the safety of stopping hormone therapy in young women with endocrine-responsive early breast cancer in order to try to conceive.

For Španić in Slovenia and Purkalne in Latvia, the key goal for breast cancer research over the next few years is to achieve a more personalised approach.

“Breast cancer is such a heterogeneous disease, it is essential that we have greater access to genomic testing so that we can offer personalised treatment. We also need better rehabilitation for patients after treatment, and palliative care for those with more advanced disease so that we can improve quality of life for patients,” says Purkalne.

Španić agrees: “A personalised approach for every patient must be our goal for the next five to 10 years. It’s not just about personalising treatment to their cancer, but to their lifestyle and profession, and everything that is important to them.”

Jassem also hopes that research across CEE countries will contribute to more personalised treatment of breast cancer in the region tailored to individual tumour type, allowing further de-escalation of treatment. Alongside this more personalised approach, he would like to see growing use of immunotherapy and identification of new, targetable molecular drivers of breast cancer. He concludes: “I hope that we will be able to close the gap in breast cancer care between western and central and eastern Europe, and we are working hard to convince governments to prioritise cancer because it is not just an expense, but also a good investment. I remain optimistic!”

“Breast cancer is such a heterogeneous disease it is essential that we have greater access to genomic testing so that we can offer personalised treatment. We also need better rehabilitation for patients after treatment and palliative care for those with more advanced disease so that we can improve quality of life for patients.”

Gunta Purkalne (Latvia)
References


Meet the experts

**Jacek Jassem, MD, PhD**
Professor and Head, Dept. of Oncology and Radiotherapy
Medical University of Gdansk, Poland
Chair of the Central and East European Oncology Group (CEEOG)
Gdansk, Poland

**Gunta Purkalne, MD, PhD**
Professor and Head of the Clinic of Oncology, Pauls Stradiņš Clinical University Hospital
Riga, Latvia

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

**Giorgi Dzagnidze, MD, PhD**
Professor and Head of the Breast Unit at S.Khechinashvili University Hospital of Tbilisi
President of the Georgian Cancer Study Group (GCSG)
Tbilisi, Georgia
PINK OCTOBER: EORTC & BIG
Public educational session “Breast cancer: what do I need to know?”

The month of October is international breast cancer awareness month

On Tuesday 29 October, the European Organisation for Research and Treatment of Cancer (EORTC) and the Breast International Group (BIG against breast cancer) organised a public educational session on breast cancer, which took place in Brussels (Belgium).

The aim of this session was to raise awareness about breast cancer, highlight the importance of global breast cancer research, demonstrate the progress that has been made, and illustrate the promising future that new technologies could offer in treating, and hopefully curing, breast cancer.
The session included the following five presentations:

- **The BIG picture of breast cancer and the importance of international collaboration in cancer research**  
  By Dr Martine Piccart  
  BIG founder, former president of the EORTC and breast cancer oncologist at Institut Jules Bordet (Brussels, Belgium)

- **The importance and impact of breast cancer clinical trials**  
  By Dr Michail Ignatiadis  
  Secretary of the EORTC Breast Cancer Group and breast cancer oncologist at Institut Jules Bordet (Brussels, Belgium)

- **The future of breast cancer research and treatment**  
  By Dr Peter Vuylsteke  
  Member of the EORTC Breast Cancer Group and breast cancer oncologist at CHU UCL Namur (Belgium)

- **Testimonies of male breast cancer patients and presentation of the male breast cancer patients’ association BorstkankerMAN**  
  By Prof. Henk Van daele and Mr. André Pauwels  
  President and vice president of BorstkankerMAN (Flanders, Belgium)

- **Quality of life during and after breast cancer**  
  By Dr Erika Joos  
  Former president of Europa Donna (Belgium) and former breast cancer patient

During the session, participants - who were a mix of breast cancer patients, advocates, family members, students, researchers and breast cancer specialists - were also invited to ask the speakers any questions they had, allowing for a true learning and sharing experience.
In 2019, BIG celebrated its 20th anniversary

In 2019, BIG - through its philanthropy branch BIG against breast cancer - organised different events to celebrate its 20th anniversary with different audiences.

The aim was to strengthen BIG’s existing and new relationships by connecting and reconnecting, and to raise funds for academic breast cancer research.

2019 was marked by:
- 7 philanthropic initiatives
- A supporters’ network of over 1,500 attendees
- € 900,000 funds raised

19 May – 20 km of Brussels

Move for BIG!

For its 20th anniversary, BIG participated for the first time in the Brussels 20 km challenge - a popular annual race through the city of Brussels.

A fundraising campaign was set up and about a hundred runners supported BIG to raise more than € 11,000.

20 kilometres represent 20 years of research - each kilometre marks a year of BIG’s commitment to finding better treatments against breast cancer.

Today BIG can boast of having developed and conducted many studies that are considered landmark and whose results have already changed the way thousands of people are treated.

25 June – MoveforBIG.org launch event

The MoveforBig.org launch event’s purpose was to present a new way to support breast cancer research.

The MoveforBIG.org platform encourages BIG’s advocates to create their own fundraising initiatives by making a personal fundraising page. The fundraising page can be created for the occasion of a birthday, baby shower, in memoriam, sports challenge, corporate opportunity or by getting creative through any other means.

During the launch, supporters were presented a selection of BIG’s trials and studies to choose from and the platform’s possibilities were introduced. To top it all, composer and pianist Alain Lanty closed the event with an intimate concert.

17 September – Official celebration of 20 years of BIG, in the presence of HRM the Queen Mathilde

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 to talk about the evolution of breast cancer in the past, the present and the future.

Professor Martine Piccart (past chair and co-founder of BIG), Professor David Cameron (chair of BIG), and Dr Alberto Costa (CEO, European School of Oncology) gave overviews of yesterday’s treatments, those of today and those we are targeting for tomorrow.

At the end of the event, Her Royal Majesty the Queen of the Belgians, BIG ambassadors, partners, sponsors, foundations, companies and individual supporters of BIG blew out the twenty candles and shared the birthday cake together.

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 Israel, Prof Martine Piccart, Mrs Nathalie Misson, Baroness Jacques Brotchi, Mrs Mathilde Jooris, Baron Jacques Brotchi, Mr Alain De Waele, Mrs Patsy Israel, Prince Amaury de Merode, Mrs Betty Buligant
9 October – “The BIG Roaring Twenties” annual gala dinner

This seventh edition of BIG’s annual gala dinner was organised under the theme of “The Roaring Twenties” - a perfect way to celebrate two decades of hope and progress in breast cancer research.

The funds raised during the annual gala dinner will be invested in the AURORA study (public name: metastatic breast cancer GPS).

Over 600 attendees joined this event and participated in an auction full of exclusive and unusual prizes donated by BIG’s partners and individual benefactors.

24 October – “PINK is the new black” dinner and dance party

On 24 October, BIG held the second edition of its “PINK is the new black” dinner and dance party, in the presence of Professor Martine Piccart.

The theme was again “The BIG Roaring Twenties”, and the AURORA study was the beneficiary.

“Alone, we go faster. Together we go further. Together, let’s help save lives.”

14 November – “From Shadow to Light” corporate event

To celebrate twenty years of collaboration, a special event was organised to thank all of BIG’s partners.

“From Shadow to Light” was the theme chosen to symbolically illustrate, throughout the evening, the journey of a patient with breast cancer, from diagnosis of the disease to the completion of treatment. This was illustrated through five artistic performances conveying emotional experiences.

This event presented the perfect occasion to remind all our corporate donors about how to support BIG and, in so doing, breast cancer research.

27 November – Carmina Burana concert

This concert celebrated the 40th anniversary of the Brussels Choral Society and featured music by Carl Orff, Leonard Bernstein and Igor Stravinsky, three leading 20th century composers. BIG was a beneficiary of this cultural event and invited companies and individuals to attend.
FINESSE (BIG 2-13): main clinical and biomarker results published in the Clinical Cancer Research Journal

Results from the phase II FINESSE trial, which involved 76 patients from 24 hospitals in nine countries were published in the Clinical Cancer Research Journal in October 2019. They were first presented as a poster at ESMO in 2018.

The main objective of FINESSE was to evaluate the antitumour activity of lucitanib, an inhibitor of angiogenesis and FGFR proteins, in patients with hormone receptor-positive (HR+), HER2-negative (HER2-) metastatic breast cancer whose tumours harboured abnormalities in the FGFR1 and/or chromosome arm 11q genes/proteins, i.e. either amplified or non-amplified cancer cells. In particular, the trial aimed to determine whether lucitanib had the potential to slow down or stop such cancer cells from growing or spreading further.

Recruitment in the study was stopped prematurely by the sponsor following a risk/benefit analysis run on all available data of the lucitanib breast cancer clinical development programme showing that lucitanib was not likely to be superior to standard of care. Moreover, the drug was associated with less tolerability and more safety concerns than predicted, particularly with regard to hypertension-related side effects.

In FINESSE, lucitanib showed modest antitumour activity and significant hypertension-related toxicity. Although based on small sample sizes, exploratory biomarker analyses run in the study suggested however that patients with high FGFR1 amplification or expression might derive greater benefit from the drug. Higher ORR was observed in patients with high FGFR1 amplification (≥4 CNV) than those without high amplification (22% vs. 9%). ORR in patients with FGFR1-high tumours (IHC, H-score ≥50) was 25% versus 8% in FGFR1-low cancers.

Reference:

PALLAS (ABCSG 42 / BIG 14-03): second interim analysis
By ABCSG

PALLAS enrolment was successfully closed in November 2018 with nearly 5,800 patients from more than 400 sites in 21 countries worldwide. Of these, 3,381 patients were
randomised in 242 sites in 20 countries under the ABCSG/BIG umbrella. These numbers underscore both the successful collaboration between ABCSG and the US Alliance Foundation and within the BIG network and its sites. After completing enrolment, efforts were streamlined towards the first protocol-based interim analysis, which was triggered by the 157th globally reported invasive disease-free survival (iDFS) event in February 2019.

Based on the first interim analysis results, the PALLAS Independent Data Monitoring Committee (IDMC) recommended that the trial continue without modification. The treatment phase (in order to compare the CDK4/6-inhibitor palbociclib given in combination with standard adjuvant endocrine therapy versus standard adjuvant endocrine therapy alone for male and female patients with HR+/HER2-negative early breast cancer) is ongoing.

Currently, the main focus of ABCSG and the collaborating teams are to maintain data quality and keep patients on trial. All participating sites are working hard in order to keep arm A patients on study treatment and to have data documented in a timely manner. The second interim analysis was triggered by the 313th iDFS event (reported in early January 2020), and results will be assessed again by the IDMC regarding recommendations for further study conduct. ABCSG and the whole BIG network are looking forward to the results of this important trial and are very optimistic about the prospects of continuing this remarkable global academic collaboration.

**POSITIVE (IBCSG 48-14 / BIG 08-13): study has reached target accrual**

On 2 January 2020, the POSITIVE study (public name: BIG Time for Baby) met its target accrual, enrolling 518 patients from 203 centres from 20 countries around the world. The initial target accrual was 500 patients, but due to the interest shown by young women in this study, women who already had appointments with their oncologists to enrol in the study were still able to participate.

POSITIVE represents a unique opportunity to allow young women who have had breast cancer to plan and try to become pregnant without waiting many years after completing their endocrine treatment.

The study expects to provide an answer to the question of whether women can interrupt their endocrine treatment to try to have a baby, without increasing the risk of cancer recurrence.

The study has recruited pre-menopausal women, aged 42 years and younger, with ER+ early breast cancer who have received endocrine therapy for 18 to 30 months and who wish to interrupt endocrine therapy to become pregnant. During the study, they take a three-month break in treatment before attempting pregnancy and stop treatment for up to two years to allow time for conception, delivery and breastfeeding (or potential failure to conceive). Endocrine therapy then restarts and continues for the duration of treatment. Women will be followed up for 10 years after enrolment.

POSITIVE will improve our scientific understanding of issues related to conception and pregnancy in young women who have had breast cancer by helping us obtain solid data. Initial results are expected in the next few years.

As of 31 December 2019, 125 healthy babies had already been born.

The study is being led by IBCSG, under the BIG umbrella, and involves 11 collaborative research groups around the world. A poster session presenting POSITIVE took place at SABCS 2019.

**Reference:**

From 10 to 14 December 2019, the annual San Antonio Breast Cancer Symposium (SABCS) took place in Texas (USA). The symposium, which is now in its 42nd year, is the premier conference for basic, translational, and clinical research professionals focusing on breast cancer. It is well-known for presenting the latest breast cancer data from all over the world. More than 7,500 healthcare professionals from over 90 countries attended.

**APHINITY (BIG 4-11): presentation of data from a second interim overall survival analysis.**

*Presented by Dr Martine Piccart*

On the first day of SABCS, during a general session, Dr Piccart presented data from a second interim overall survival analysis of APHINITY after a median follow-up of 74 months. The data showed that adding pertuzumab to standard trastuzumab plus chemotherapy after surgery continued to show clinical benefit for patients with HER2-positive early breast cancer. Fewer deaths were seen among patients with pertuzumab but there was no statistical difference for overall survival (OS) at this time.

Descriptive analyses for invasive disease-free survival (IDFS) and cardiac safety were also performed. The greatest IDFS benefit was seen among patients with lymph node positive disease with a 28% relative risk reduction in recurrence or death, corresponding to 4.5% absolute benefit for IDFS at six years. No new cardiac safety issues emerged at this time.

Primary results of APHINITY were published in the *New England Journal of Medicine* in 2017.

APHINITY is a randomised, multicentre, double-blind, placebo-controlled comparison of chemotherapy plus trastuzumab plus placebo versus chemotherapy plus trastuzumab plus pertuzumab as adjuvant therapy in patients with operable HER2-positive primary breast cancer.

Its main aim is to investigate clinical benefit of adding adjuvant pertuzumab, a humanised monoclonal antibody targeting HER2 and acting in a complementary way to trastuzumab, in combination with the current standard of care (chemotherapy and trastuzumab). The hope is that this strategy can overcome the resistance to treatment that occurs in some patients when a single drug is used.

This study is conducted by BIG Headquarters, in collaboration with the Institut Jules Bordet Clinical Trials Support Unit (IJB/CTSU) and Frontier Science Foundation (FS), which serve respectively as independent data and statistical centres. Roche is the sponsor. The study is conducted according to BIG’s Principles of Research Conduct.

24 research groups from the BIG network are participating in this trial.

Reference:
IBIS-II (BIG 5-02): long-term follow-up results of the International Breast Cancer Intervention Study IBIS-II
Presented by Prof. Jack Cuzick

Long-term follow-up results of the International Breast cancer Intervention Study IBIS-II have demonstrated a 49% overall reduction in breast cancer occurrence with anastrozole. This was based on a 61% reduction during the 5-year treatment period and an additional 36% reduction in the 5-12 year post-treatment follow-up period. These results indicate a long-term preventive benefit with the aromatase inhibitor anastrozole based mostly on ER-positive breast cancer in postmenopausal women at increased risk of developing breast cancer, suggesting that anastrozole should be the first option in breast cancer prevention for most women with a higher risk of disease occurrence.

These results are very important, and substantially strengthen the findings from the initial report after a 5-year median follow-up, with no evidence of new late side effects. They provide crucial information about the effects of anastrozole in preventing breast cancer in women at high risk of the disease. It is hoped that they will lead to a change in clinical practice with anastrozole being routinely prescribed as preventive medicine for post-menopausal women at high risk of breast cancer. The results of the study were published in The Lancet on 12 December 2019.

This international, randomised, double-blind, placebo-controlled breast cancer prevention trial is analysing the use of anastrozole versus placebo in postmenopausal women at high risk of breast cancer. It aims to determine whether anastrozole can lower the risk of breast cancer in these patients.

In total, 3,864 high-risk postmenopausal women aged 40-70 years from 153 centres in 19 countries were recruited between February 2003 and January 2012. They were randomly assigned to receive 1 mg/day of anastrozole for 5 years (n = 1,920) or placebo (n = 1,944). After treatment completion, women were followed on a yearly basis. The primary outcome measure was development of histologically confirmed breast cancer, both invasive and non-invasive.

The IBIS-II Prevention trial is run by the International Breast Cancer Intervention Study group (IBIS), with the support of BIG. The study was funded by Cancer Research UK, the National Health and Medical Research Council Australia, Breast Cancer Research Foundation, Sanofi Aventis, and AstraZeneca. The funders played no role in the study design, data collection, data interpretations or writing of the report.

Reference:

Study details:
- **Official title**: International Breast Cancer Intervention Study
- **Current primary outcome**: development of histologically confirmed breast cancer, both invasive and non-invasive
- **Current secondary outcome**: breast cancer mortality
- **Study start date**: September 2003
- **Estimated study completion date**: January 2022
- **Recruitment state**: in follow-up - not recruiting
- **Brief summary**: RATIONALE: Chemoprevention therapy is the use of certain drugs to try to prevent the development of cancer. Anastrozole may be effective in preventing breast cancer
- **Purpose**: This randomised clinical trial is studying how well anastrozole works in preventing breast cancer in postmenopausal women who are at increased risk for the disease
- **Accrual**: a total of 3,864 high-risk postmenopausal women aged 40-70 years were recruited for this study over 10 years
- **Study type**: interventional (drug: anastrozole, aromatase inhibitor, other name: Arimidex vs drug: placebo, Arimidex placebo)
- **Study phase**: 3
- **Countries involved**: Australia, Belgium, Chile, Denmark, Egypt, Finland, Germany, Hungary, Ireland, Italy, Malta, New Zealand, Pakistan, Peru, Portugal, Russia, Switzerland, Turkey, United Kingdom
- **Study sponsor**: Queen Mary University of London
- **Investigators**: Study chairs: Jack Cuzick, PhD (Queen Mary University of London) and Anthony Howell (University of Manchester)
- **NCT number**: NCT00078832
Ki67 (BIG-NABCG): analytical validation and prognostic potential of an automated digital scoring protocol for Ki67: An International Ki67 Working Group Study  
Presented by Dr Balázs Ács

Results from the study conducted by the International Ki67 in Breast Cancer Working Group were also presented at SABCS. The open source and calibrated automated digital image analysis tool tested in the study was found to be successful for the analysis of core biopsies, but not for whole-tumour sections in a multi-institutional setting. The discrepancy is likely related to issues such as tissue handling and fixation or heterogeneity within tumours. More research is planned.

Although testing for Ki67 (a marker of cancer proliferation) can be useful, an unacceptable level of variability between laboratories has been identified by the Working Group before 1. A main aim of the study was - in very general terms - to see whether using a digital image analysis tool would lead to more reproducible results across laboratories than standard visual scoring done by pathologists. The study involved 17 laboratories.

The Ki67 Working Group of the BIG-NABCG (North American Breast Cancer Group) was formed to address the problem of inconsistent Ki67 assessment between laboratories, and it proposed guidelines for pre-analytic and analytic conditions for Ki67 assessment, as well as for interpretation, scoring, and related data handling. It generated the following manuscripts, among others. 2,3,4

References:  

Male breast cancer is a rare disease accounting for 1% of all breast cancers and less than 1% of all cancers in males. Treatment decision-making about male breast cancer is largely extrapolated from female breast cancers. To date, there is still limited information regarding the genomic landscape of male breast cancers, particularly in the context of identifying targeted treatments.

Coordinating groups/sponsors:  

Eight research groups from the BIG network are participating in this research programme.

MALE BREAST CANCER (BIG 2-07): the genomic landscape of male breast cancers using the Oncomine Comprehensive Assay for actionable mutations  
Presented by Dr Jane Bayani

The results of targeted gene sequencing (TGS) performed on 248 male breast cancer patients with non-metastatic, oestrogen receptor-positive, HER2-negative breast cancers enrolled in the retrospective part of the International Male Breast Cancer Programme were reported at SABCS. This represents the largest series of male breast cancers collected to date. Mutational and copy number variations were evaluated for genes that are prognostic or predictive to targeted therapies currently in use in the clinic or late-stage clinical trials.
MINDACT (BIG 3-04): should age be integrated together with clinical and genomic risk for adjuvant chemotherapy decision in early luminal breast cancer? 

*Presented by Dr Fatima Cardoso*

The results of a subgroup analysis of the MINDACT study, similar to one that was conducted in the context of the TAILORx study, were presented by the MINDACT researchers during a general session at SABCS.

In the TAILORx Study, which assessed the utility of the Oncotype DX® gene signature, an unplanned subgroup analysis suggested that women aged 50 years or younger, with an intermediate Recurrence Score (RS) and a high clinical risk as defined in MINDACT, derived benefit from the addition of chemotherapy to endocrine therapy in terms of distant recurrence rate at 9 years.

A similar analysis conducted in MINDACT showed that women with luminal breast cancer aged 40 to 50 years had a small numerical benefit in distant metastasis free survival at 5 years when they received chemotherapy compared to those who did not in the low genomic risk and high clinical risk group. Of note, this was an unplanned and underpowered analysis and the results are therefore hypothesis-generating rather than practice-changing and require further investigation. Moreover, only 8% of the women under 50 in this study received ovarian function suppression, suggesting that this age-dependent effect might be due to the chemotherapy-induced ovarian function suppression.

MINDACT is a prospective, randomised study combining the 70-gene signature MammaPrint® with the common clinical-pathological criteria in selecting patients for adjuvant chemotherapy in breast cancer with 0 to 3 positive nodes.

The primary results of MINDACT were published in 2016 in the *New England Journal of Medicine* and provided the highest level of evidence to show that using MammaPrint® in combination with clinico-pathological assessment can identify patients who might safely avoid chemotherapy, thereby substantially reducing the prescription of chemotherapy in patients with node-negative and 1-to-3 node positive breast cancer.

The trial is sponsored and run by the European Organisation for Research and Treatment of Cancer (EORTC) under the BIG umbrella, and many other partners, both from academia and the private sector, including the breast cancer patient advocacy network Europa Donna. The biotechnology company Agendia developed MammaPrint®.

Seven research groups from the BIG network are participating in this trial.

**Reference:**

SOLE (BIG1-07 / IBCSG-3507)
study of letrozole extension; a phase 3 randomised clinical trial of continuous vs intermittent letrozole in postmenopausal women who have received 4-6 years of adjuvant endocrine therapy for lymph node-positive, early breast cancer: final analysis and sole oestrogen sub-study (SOLE-EST)
Presented by Prof Guy Jerusalem

During SABCS, a poster on the final analysis of SOLE and on SOLE-EST - a sub-study of SOLE, looking specifically at changes in oestrogen levels - was presented. In SOLE, at 84 months median follow-up, disease free survival (DFS) in the interrupted treatment (extended intermittent letrozole) was not shown to be better compared to the standard administration of continuous treatment, confirming previous results. Similar outcomes were observed for breast cancer-free interval, distant recurrence-free interval, and overall survival.

SOLE-EST has so far shown that, in the intermittent treatment group, oestrogen levels show an important increase as soon as six weeks after stopping letrozole therapy. Further research is underway.

The first results of SOLE were presented at ASCO 2017. The study established that taking planned three-month treatment breaks during long-term treatment with letrozole does not improve DFS compared with taking the treatment continuously for five years for postmenopausal women with hormone-sensitive, node-positive early breast cancer who have already received four to six years of adjuvant endocrine therapy ¹.

However, investigators observed improvement with regards to patient-reported symptoms and quality of life (physical well-being, sleep disturbances, hot flushes, etc.) with the intermittent administration ².

This study is coordinated and sponsored by the International Breast Cancer Study Group (IBCSG) and is conducted under the BIG umbrella. Novartis is the pharmaceutical partner.

Nine research groups from the BIG network are participating in this trial.

References:
Other trials & activities by BIG member groups

ABCSG

ABCSG 45: a national study on olaparib in patients with positive homologous recombination deficit status

ABCSG 45 is a new prospective, open, randomised phase II study1, run by the Austrian Breast & Colorectal Cancer Study Group (ABCSG). The PARP inhibitor olaparib, which is administered in combination with carboplatin for 6 cycles in arm A, compared to 6 cycles anthracycline / taxane-based chemotherapy in arm B, is being tested in patients who have triple-negative breast cancer (TNBC) and test positive for homologous recombination deficit (HRD) status. The primary objective of the study is to determine the efficacy of olaparib / carboplatin, measured by centrally assessed residual cancer burden (RCB) at the time of surgery after treatment. Further secondary objectives include pathologic complete response (pCR) at the time of surgery and patients’ well-being, assessed by means of quality of life questionnaires. The study consists of two phases: in the dose-finding phase 1, the participants receive 4 different doses of olaparib, depending on the safety and tolerability of the individual dose level. After 10 patients have finished arm A, the maximum tolerated dose (MTD) of olaparib will be evaluated. The MTD will then be used in the phase 2 with 70 patients. Phase 1 is currently ongoing and six sites are participating, the last of these being activated in October 2019. By 13 January, 5 patients had been randomised, 22 screened, 15 screen-failed. After completion of phase 1, the MTD for phase 2 will be determined and submitted to the ethics committee. After approval, phase 2 will commence. The recruitment is currently planned until March 2021.

Reference
1. This research is conducted with support from AstraZeneca Austria GmbH.

ABCSG 50 / BRCA-P: global enrolment has started in prevention trial

ABCSG 50 / BRCA-P is an innovative phase-III study in which healthy women with a BRCA1 mutation are included to determine the preventive effect of denosumab. In this double-blind trial, there are two arms: in arm A participants receive preventive denosumab as subcutaneous injections (120 mg every 6 months for a total of 5 years); in arm B women receive placebo. A total of 2,918 women with a BRCA1 mutation are to be randomised worldwide. The first participant was enrolled in Austria in July 2019, and also in Australia the trial has already been activated. Enrolment is expected to increase once more sites are activated since sites can utilise their already established documentation registries of BRCA1 carriers to identify potential participants. In Spain, the trial was submitted to regulatory authorities in November 2019. Remaining countries (Israel, Germany, UK and US) are expected to come on board in 2020. As ABCSG president Professor Michael Gnant put it: “We are excited to finally enter the space of breast cancer prevention with this trial – ABCSG has a long-standing experience with denosumab and its effects. ABCSG’s trial Chief Investigator Professor Christian Singer added: “ABCSG 50 / BRCA-P is taking an important step in the direction of prevention of cancer in this population at particular risk of developing the disease”.

ABCSG 52 / ATHENE: new immunochemotherapy study in patients with HER2-positive early breast cancer

ABCSG 52 / ATHENE is an open-label, two-arm, randomised, single-stage phase II study with a complex study setting. The primary objective is to investigate the efficacy and safety of a neoadjuvant immunochemotherapy regimen consisting of atezolizumab, trastuzumab, pertuzumab and epirubicin in patients with HER2-positive early breast cancer.

A further objective of the trial is to explore translational potentials in terms of immunological and genetic biomarkers. ABCSG 52 / ATHENE is a national and multicentric study. Eight Austrian trial sites are planned to be activated and 58 patients to be randomised. The study start is intended for Q1 2020.
Breast Cancer Trials (BCT-ANZ) is a group of world-leading breast cancer doctors and researchers based in Australia and New Zealand, committed to the conduct of multicentre national and international clinical trials for the treatment and prevention of breast cancer.

Founded in 1978, BCT-ANZ’s breast cancer clinical trials research programme is a unique collaboration between researchers, clinical trial participants and supporters. It brings together almost 800 researchers in over 100 institutions in Australia and New Zealand. Almost 16,000 women have participated in the group’s clinical trials over the last 40 years.

New clinical trials

BCT-ANZ will activate two new trials in early 2020 called Neo-N and CAPTURE.

Neo-N is an international clinical trial lead by BCT-ANZ in collaboration with the International Breast Cancer Study Group (IBCSG) and will be open to both women and men with triple negative early breast cancer. The purpose of this study is to see if using the immunotherapy drug (nivolumab) together with standard chemotherapy (paclitaxel and carboplatin) is safe and effective in treating breast cancer before surgery. The BCT-ANZ Study Chair of Neo-N is Professor Sherene Loi.

The aim of the CAPTURE clinical trial is to determine whether treatment with alpelisib plus fulvestrant prolongs progression-free survival (PFS) compared to capecitabine in patients with oestrogen receptor positive (ER+), HER2-negative advanced breast cancer (ABC) who have PIK3CA mutant circulating DNA and have received prior treatment with a CDK4/6 inhibitor (CDK4/6i) and aromatase inhibitor (AI). The BCT-ANZ Study Chair is Professor Sarah-Jane Dawson.

Discretionary funding

BCT-ANZ has awarded discretionary funding to a new research project that will investigate the feasibility of prescribing vaginal oestrogen for women with breast cancer, to reduce genitourinary symptoms. The study will be conducted by Dr Antonia Pearson, with Dr Belinda Kiely, and has been awarded $100,000 over two years.

Recognition for BCT-ANZ researchers

Professor Geoffrey Lindeman and Professor Jane Visvader received the Susan G. Komen Brinker Award for Scientific Distinction in Basic Science at the 2019 San Antonio Breast Cancer Symposium.

Prue is the Chair of the BCT-ANZ Scientific Advisory Committee and recently received a Fellowship into the Australian Academy of Health and Medical Sciences. Sherene is the BCT-ANZ Study Chair of the CHARIOT and DIAmOND clinical trials, and was recently recognised on the Highly Cited Researchers 2019 list, which identifies scientists and social scientists who produced multiple papers ranking in the top 1% by citations for their field and year of publication, demonstrating significant research influence among their peers.
Clinical trials - current activities

The German Breast Group (GBG) continues to conduct promising trials to test the combination of immune checkpoint inhibitors with chemotherapy in different breast cancer settings. The 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 triple-negative breast cancer (TNBC)\(^1\). In the adjuvant setting the randomised phase II ALEXANDRA/IMpassion030 (GBG 98 / BIG 16-05) study, a collaborative study with BIG, is evaluating the efficacy, safety and pharmacokinetic profile of atezolizumab in combination with standard anthracycline/taxane-based adjuvant chemotherapy versus chemotherapy alone in early TNBC patients\(^2\).

The phase III SASCIA (GBG 102) study has been set up and will soon start recruitment to evaluate the efficacy and safety of postneoadjuvant treatment with sacituzumab govitecan compared to treatment of physician’s choice (capecitabine or platinum-based chemotherapy or observation) in primary HER2-negative breast cancer patients with high relapse risk after standard neoadjuvant treatment.

A prospective and retrospective registry study on breast cancer in pregnancy and young women (BCP), in cooperation with BIG (GBG 29 / BIG 03-02), is successfully ongoing. A new analysis is planned for 2020 to evaluate the outcome of breast cancer patients treated with chemotherapy during pregnancy compared with non-pregnant controls in cooperation with INCIP (International Network on Cancer, Infertility and Pregnancy).

The final analysis of the international PenelopeB study (GBG 78 / BIG 01-13), a study under the BIG umbrella, is expected by Summer 2020. Results will 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.

The first results of the GeparX (GBG 88) trial were presented at SABCS 2019 (San Antonio Breast Cancer Symposium, Texas, USA – December 14-19, 2019). In this phase II study, 780 primary breast cancer patients were randomised to neoadjuvant chemotherapy with or without the RANK-ligand antagonist denosumab and in addition to two different nab-paclitaxel schedules. The addition of denosumab to neoadjuvant chemotherapy did not increase the pathological complete response rate (41% with vs. 43% without; \(p=0.59\)). Nab-paclitaxel 125mg/m\(^2\) should be given continuously as it resulted in a higher pathological complete response rate than given in 2 out of 3 weeks (45% vs 39%; \(p<0.1\))\(^3\).
The translational research findings of GeparSepto were recently reported at SABCS 2019. In a biological approach, whole-transcriptome sequencing fresh-frozen paraffin embedded breast cancer core biopsies from clinical cohorts were found suitable to identify immune-cell signatures. Specifically, adaptive immunity through NK rather than T-cell response appears prevalent in high-risk TNBC. The patterns of these immune signatures, particularly the presence of T follicular helper cells, reflect the clinical behaviour of breast cancer and might be used to identify tumours with an increased response rate to neoadjuvant chemotherapy\(^4\). Clinically, tumour microenvironment profiling by RNA sequencing has been found to be a potential independent biomarker useful for predicting response to and prognosis after neoadjuvant chemotherapy, including taxanes and anthracyclines, for hormone receptor negative patients, confirming potential prognostic roles for CAV1/2. No significant differences in disease-free survival (DFS) and overall survival (OS) based on CAV1/2 expression were noted for patients who received nab-paclitaxel based treatment, but the odds of obtaining pathological complete response (pCR) were improved for patients with high CAV1/2 expression. These findings suggest that CAV1/2 expression may offset the negative prognostic factor associated with higher CAV1/2 expression in patients treated with nab-paclitaxel regimens by enhancing the efficacy of treatment, perhaps through increased nab-paclitaxel endocytosis/transcytosis\(^6\).

At ESMO 2019, GBG medical advisor Jenny Furlanetto, MD, received a Merit Award for her research project on the impact of chemotherapy-induced ovarian failure on long-term outcomes in young women with early breast cancer. In this pooled analysis of four GBG neo-/adjuvant trials, patients with chemotherapy-induced ovarian failure after anthracycline/taxane-based chemotherapy showed better DFS, especially in women with hormone-receptor positive tumours or younger than 30 years. The improvement in DFS translates in a survival advantage in patients with hormone-receptor positive early breast cancer\(^7\).

The GBG recently started to partner in the ONCOBIOME project under the EU research framework “Horizon 2020”, the biggest EU Research and Innovation programme ever, with nearly €80 billion of funding available over 7 years. The aim of ONCOBIOME is to determine the relationship between intestinal microbial signatures and the prognosis and treatment resistance in four common cancer entities (breast, colon, lung and melanoma). With its expertise in sample collections and clinical translational research, GBG is a valued partner and has already implemented stool sample collection as an amendment to the study protocol of GeparDouze. Samples will be used by cooperating partners in the ONCOBIOME project to isolate DNA and RNA for genomic and expression analyses.

References:

For another consecutive year, the Chilean Cooperative Group for Oncologic Research (GOCCHI) has been committed to spreading Good Clinical Practice (GCP) knowledge.

A new partnership with the Support Office for Clinical Research of the University of Chile Clinical Hospital encouraged the development of a two-day course for academics, researchers, residents and interns of the Faculty of Medicine, on 8-9 October 2019.

The course included the history of GCP, adherence, security, and adverse events, among other topics.

Almost 50 people attended the course, and most of them were first-time researchers, so this initiative allowed them to actively participate not only in the classes, but also in the workshops. The approval rate was 75%.

It is well known to us all that breast cancer is a very distinct disease; not only because it is the most common malignancy in women, but also because it affects the breast, femininity at its core, and occurs often in younger, productive age groups. And every procedure on the breast has implications on much more than just appearance, and these linger for years after the treatment has been completed.

Therefore, breast surgery bears distinct challenges, and it has to be a science as well as an art. The breast surgeon is required to remove the diseased tissue with oncological safety but leave an aesthetically satisfactory result at the same time. To achieve this, we have long and strenuous training and have to combine dexterities from different areas of surgery – oncology and reconstruction.

The Hellenic Society of Breast Surgeons (HSBS) considers it its duty to contribute to this complex training of young breast surgeons. Thus, it organises a 2-day “Hands-on Seminar on Breast and Oncoplastic Surgery” every December. The seminar takes place at the certified Training Centre of ELPEN Pharma in Pikermi, very close to Athens, where trainees practice on live tissue (pigs) many surgical and oncoplastic techniques, namely sentinel node biopsy, approach of axilla, different types of mammoplasty, the use of implants and ADMs, nipple reconstruction, latissimus dorsi reconstruction, the localisation of non-palpable masses with different types of markers, the use of ultrasonography in breast surgery for core biopsies, insertion of guidewires, markers, etc.

The theoretical part is limited to the absolutely necessary and emphasis is put on the hands-on practice. The trainees are split into groups of four, and each group is allocated to a surgical table. An experienced trainer guides the group through the techniques, and everyone has the opportunity to perform each technique at least once and assist/watch many more.

In December 2019 the seminar was organised in collaboration with the Hellenic Surgical Society under the auspices of the Medical School of the National and Kapodistrian University of Athens. Its success is reflected in the enthusiastic feedback from the trainees who arrived from different parts of the country and abroad, as well as the fact that many of the places for next year’s seminar are already booked.

With the hope that the breast surgical community will continue to find the “Hands-on Seminar on Breast and Oncoplastic Surgery” useful, HSBS is committed to maintaining the hard work and opening this fantastic training opportunity to as many colleagues as possible.
**JBCRG**

**On-going clinical trials and publications**

The Japanese Breast Cancer Research Group (JBCRG) 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, now recruiting.

- **JBCRG-C07 (REIWA)**: an observational study to evaluate the impact of the gene panel test FoundationOne® CDx on treatment decision-making in metastatic and recurrent breast cancer throughout Japan as a whole, now recruiting.

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

- **JBCRG-M05 (PRECIOUS)**: a randomised, open-label phase III trial to evaluate the efficacy and safety of pertuzumab retreatment in previously pertuzumab, trastuzumab and chemotherapy treated HER2-positive metastatic locally advanced and metastatic breast cancer, in follow-up.

Under the BIG umbrella, JBCRG is currently participating in POSITIVE, ALEXANDRA/IMpassion030, OlympiA, PenelopeB and PALLAS. Japanese recruitment to the POSITIVE study was surprisingly good: JBCRG achieved 12% of the global recruitment!

JBCRG’s publications include the following:

1) JBCRG-C06 (Safari) in Breast Cancer 2019
2) JBCRG-20 (Neo-Peaks) in Breast Cancer Research and Treatment 2020
3) JBCRG-C01 in Breast Cancer 2020

**JBCRG’s presentations at SABCS 2019**

1) **JBCRG-C06 (Safari)** - 3 posters sessions

Dr Norikazu Masuda and Dr Misato Hagi (Masuyama).

Dr Kenjiro Aogi

Dr Shinji Ohno and Dr Takahiro Nakayama

Dr Shigehira Saji
Other topics

Three young doctors and one nurse from Peking University First Breast Disease Center (China) visited JBCRG in December 2019. JBCRG introduced its history and structure, and had a warm discussion about the different medical structures and future visions of the respective countries.

JBCRG’s annual meeting

JBCRG’s 10th Educational Meeting from 12 October 2019 had to be postponed due to the terrible typhoon HAGIBIS, which caused a lot of damage to eastern Japan. The re-scheduled date became 15 February 2020. The theme was ‘Revolution of diagnosis and treatment for breast cancer through artificial intelligence and precision medicine’, and around 100 investigators attended.

“The same as our wish to conquer breast cancer, we also wish for all lives across the globe to be protected from natural disasters, which can occur anywhere.”
CURA PROJECT: Ready for Christmas event

On December 13, the major Christmas Show for the CURA Project was hosted in Miami, Florida (USA)

The Ready For Christmas event, by the Latin American Cooperative Oncology Group (LACOG), took place in partnership with the Journey Through Brazilian Experience event, a cultural activity of the Consulate General of Brazil in Miami, and included performances by the great Venezuelan singer-songwriter Marger, accompanied by Puerto Rican pianist and conductor José Negroni and his jazz band, which has been nominated three times for the Latin Grammy.

The show was organised to benefit “Proyecto Cura”, in which the proceeds from music and art go towards the battle against cancer and research.

The event was attended by an audience of 250 people, representing several Latin American and Caribbean countries (Venezuelans, Colombians, Mexicans, Peruvians, Argentines, Brazilians, Cubans, Puerto Ricans, among others). Also present was Dr Orlando Silva, Medical Oncologist in Miami and scientific director of CURA, as well as Dr Luis Fernando Correia, MD, journalist and CURA Ambassador.
Neoadjuvant chemotherapy (NAC) has become common practice in the primary treatment of breast cancer. Its effect is equivalent to adjuvant chemotherapy and can therefore be used in all patients with an indication for postoperative chemotherapy. Patients with large tumours and tumours with a poor prognosis such as HER2-positive and triple negative breast cancers are most appropriate candidates for NAC. The main advantages of NAC are two-fold:

- **NAC gives the clinician the opportunity to assess response to a given preoperative regimen in vivo; via imaging during NAC and by studying residual cancer in pathology tissue specimens taken at surgery.**
- **NAC also enables a de-escalation from mastectomy to breast conserving procedures in cases with large tumours. Furthermore, NAC can prevent fully axillary dissection if lymph node response upon imaging is favourable.**

The use of modern NAC regimens leads to a pathological complete response (pCR) of the tumour in more than 50% of cases. In these cases, open surgery serves only to prove full remission - indeed it could be argued that these invasive procedures could be de-escalated to interventional biopsies. According to the current literature, pCR is most accurately predicted using MRI. Nevertheless, imaging cannot predict pCR with sufficient accuracy. Therefore, following NAC, breast conserving surgery or mastectomy is conducted in accordance with clinical indications.

The main objective of this multicentre interventional cohort is the calculation of sensitivity, specificity, negative predictive value and positive predictive value for the post-NAC vacuum-assisted biopsy (VAB) in determining pCR compared to conventional surgical resection.

In patients scheduled for operation after NAC and MRI-proven complete response, vacuum-assisted biopsies will be taken in the tumour bed under general anaesthesia just prior to surgical intervention. Alternatively, this procedure can be done before surgery in the framework of localising the wire to the tumour bed. These biopsies will be taken in close proximity to the breast biopsy site marker. Subsequently, conventional surgery will be performed. If indicated, surgeons may perform axillary surgery. Results for both tissue samples will be compared to determine whether VAB can reliably predict pCR in patients who have undergone NAC.

This trial aims to study interventional biopsy in combination with MRI in comparison to classic open surgery. Our results may lead to a de-escalation of therapy in women and men with excellent response to NAC and open up broadly studies of interventional image-guided procedures of the breast.

SAKK plans to activate the study in 2020 and recruit 420 patients in Switzerland and Austria. The final treatment is scheduled for Q4 2022. The trial relevant examinations end 14 days after the operation.
First immunotherapy trial with T lymphocytes for breast cancer treatment in Spain

Last Autumn, the SOLTI-TILs-001 study, designed by researchers of the SOLTI Breast Cancer Research Group, received the prestigious AECC (Spanish Society Against Cancer) Scientific Foundation Award. Dr. Aleix Prat, President of SOLTI and Head of Medical Oncology Department at Hospital Clínic from Barcelona, collected the award during the ceremony that was held at the headquarters of the AECC in Madrid at the end of September.

With this grant, SOLTI will start the first clinical trial in Spain to employ adoptive cell therapy (ACT) with T lymphocytes in patients with advanced breast cancer. This is, among all immunotherapy techniques, one that drives the activation of the patient’s own immune system (mainly lymphocytes) to restore its ability to attack tumour cells. Using tumour biopsies, the patient’s lymphocytes from the tumour micro-environment will first be selected and cultured in the laboratory, and then expanded to obtain several billions of cells. Subsequently, these lymphocytes will be reinfused into the patient via a transfusion. An alternative technique using ACT, called CART19, has already shown efficacy for the treatment of other diseases such as acute lymphoblastic leukaemia.

To transfer ACT results to solid tumours, SOLTI investigators have designed this cooperative study. The study will be performed in four Spanish hospitals: Hospital Clínic from Barcelona, led by Dr. Aleix Prat and Dr. Manel Juan; the Hospital Universitario 12 de octubre in Madrid, led by Dr. Eva Ciruelos and Dr. Luis Álvarez-Vallina; the Vall d’Hebron Institute of Oncology (VHIO) in Barcelona, led by Dr. Cristina Saura, Dr. Ana Vivancos and Dr. Alena Gros; and the Clínica Universidad de Navarra, led by Dr. Marta Santisteban, Dr. Sandra Hervás and Dr. Juan José Lasarte.

Beyond being the first academic clinical trial to evaluate this personalised technique in breast cancer in Spain, with this trial, SOLTI is innovating with respect to patient selection criteria, as participants will be included according to their lymphocyte’s ability to express the PD1 protein. During the award ceremony, Dr. Aleix Prat pointed out that “We are at the forefront of personalised and precision medicine: we will use each patient’s own cells and, at the same time, we will treat only those that present the PD1 biomarker”.

Samples will require expert manipulation in isolated spaces called “clean rooms”. To this end, the laboratory for Advanced Therapies of Dr. Manel Juan, Head of the Immunotherapy Section of the Hospital Clínic in Barcelona, will host the patients’ lymphocyte manipulation. Dr. Juan added: “In the central laboratory, we will receive the biopsy samples for lymphocyte isolation and expansion. Later on, the final product will be sent back to their hospitals so that patients can receive treatment”.

SOLTI
The SOLTI-TILs-001 trial is aimed at patients with advanced triple-negative breast cancer (TNBC), the most aggressive subtype that usually affects young patients. “For TNBC, we still don’t have an effective approach beyond chemotherapy,” said Dr. Aleix Prat. This innovative technique could bring great benefits to these patients and could represent the starting point to explore a potential synergistic effect with other immunological therapies already under study.

The project will run for five years and is expected to include a maximum of 20 patients. With the funding from the AECC Scientific Foundation, the study will start including the first eight patients. SOLTI will centralise all main aspects of the trial: in an initial phase SOLTI will manage all regulatory requirements in order to include the first patient in the second half of 2020. “During the next two years these eight patients will receive treatment in parallel with our obtaining and analysing results, so that this can guide trial expansion decisions. To this end, it is essential to pursue the search for funding since it is an exclusively academic research project, led by a non-profit cooperative group such as SOLTI”, indicates Patricia Villagrasa, Scientific Director at SOLTI.
In 2020, SOLTI celebrates its 25th anniversary

SOLTI is an academic research group dedicated to conducting ground-breaking research in the field of oncology. It was established in 1995 and since then it has focused its efforts on the development of clinical trials with special focus on breast cancer. In 2020 it will be celebrating its 25th anniversary of working on and promoting excellence in independent clinical research, mainly designed from SOLTI’s members’ own ideas. Nowadays, 60% of SOLTI’s pipeline are trials promoted by the group. In addition, it has incorporated innovative translational research in all the projects in which the group participates.

Currently, SOLTI has more than 400 members with multidisciplinary profiles, as well as a network of more than 100 sites that are hospitals distributed in Spain, Portugal, France and Italy where clinical trials can be conducted. With an accumulated pipeline of 77 clinical trials, SOLTI is positioned among the reference groups in oncology, both nationally and internationally.

Through the promotion of strategic alliances, the recognised trajectory in the design of innovative trials, the promotion of the continuous medical education initiatives for members and the empowerment of patients using digital tools, SOLTI has become a reference point for breast cancer research in particular and aims to fulfil this role in other types of tumours as well.
The **DCIS study** is an academic, investigator-led, randomised phase III study of radiation doses and fractionation schedules for DCIS of the breast. It aims to individualise radiotherapy after breast conserving surgery for women with higher risk DCIS by tailoring radiation dose escalation to the tumour bed and fractionation schedules according to individual risks of recurrence.

The study was activated in Australia and New Zealand in 2007, and internationally in 2009 in collaboration with the BIG network including the Canadian Cancer Trials Group (CCTG), European Organisation for Research and Treatment of Cancer (EORTC), Scottish Cancer Trials Breast Group, International Breast Cancer Study Group (IBCSG) and Cancer Trials Ireland.

With the powerful momentum generated by the global investigator team, the accrual of 1,608 patients from 136 centres in 11 countries was completed on 30 June 2014, two years ahead of schedule. Preparation for 5-year main analysis on the primary endpoint of time to local recurrence is underway. Release of results is anticipated later in 2020 and will represent a key milestone of the DCIS study.

In the interim, the investigator team completed the first international study of cosmetic outcomes in patients with DCIS treated by breast conserving surgery and adjuvant radiotherapy. It is the largest prospective evaluation of cosmetic outcomes for women with DCIS and was published in Radiotherapy and Oncology in 2019. This sub-study highlights that cosmetic outcomes were independent of treating-centre geography; conventional (longer course) and hypofractionated (shorter course) whole breast radiotherapy achieved similar 3-year cosmetic outcomes; and the addition of radiation boost to the tumour bed doubled the risk of cosmetic deterioration. Together with the main efficacy analysis, it will provide robust data to support treatment decision-making by patients and clinicians.

In addition, the study team completed an analysis of patient-reported outcomes including fatigue, physical functioning, body image and perceived risk of developing invasive breast cancer following breast conserving surgery and radiotherapy for DCIS. In contrast to invasive breast cancer, there is little published evidence to date on the impacts of treatment on patient-reported outcomes for women diagnosed with DCIS. This BIG 3-07/TROG 07.01 sub-study is expected to be published in 2020 and will provide the evidence to complement efficacy data in guiding treatment decisions.

Importantly, the prospectively collected DCIS tumour specimens of BIG 3-07/TROG 07.01 are centrally reviewed by an international panel of expert breast pathologists and provide a unique biological resource to develop and validate a clinical diagnostic test that predicts the likelihood of recurrence, in particular invasive recurrence. The ability to distinguish patients with DCIS at high or low risk of recurrence will facilitate personalised patient management to optimise outcomes. This biological research is actively in progress.

The final 10-year analysis of the DCIS study is planned for 2024. The successful conduct to date of this academic, investigator-led study is made possible only by the strong and enduring international alliance of the BIG network.

For further information, please contact Study Chair, Professor Boon H Chua (Boon.Chua@health.nsw.gov.au).
### 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>
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</table>
| ALEXANDRA / IMpassion 030       | BIG 16-05  | A randomised phase III trial comparing atezolizumab (anti-PD-L1 inhibitor), given in combination with standard chemotherapy vs. chemotherapy alone as adjuvant treatment in patients with operable TNBC - NCT03498716 | M. Ignatiadis, H. McArthur | Lead trial  
(Co)-Leading partners: BIG HQ / IJB-CTSU (BreAST) / FSTRF and AFT  
Pharma partner: Roche/Genentech (sponsor)  
Funding: Roche / Genentech |
| APPALACHES                      | BIG 18-01  | A Phase II study of Adjuvant PALbociclib as an Alternative to Chemotherapy in Elderly patients with high-risk ER+/HER2- early breast cancer -NCT03609047 | H. Wildiers, E. Brain, K. Punie | Supporter trial  
Coordinating group: EORTC (sponsor)  
Pharma partner: Pfizer |
| AURORA (Metastatic Breast Cancer GPS) | BIG 14-01  | The AURORA programme: aiming to understand the molecular aberrations in metastatic breast cancer - NCT02102165 | P. Aftimos, M. Oliveira | BIG-sponsored programme  
(Co)-Leading partners: BIG HQ (sponsor) / IJB-CTSU(BreAST) / FSS  
Pharma partner: N/A  
Funding: BCRF, Fondation Cancer Luxembourg, NIF Trust, the National Lottery (Belgium), individual donors |
| Breast Cancer in Pregnancy     | BIG 2-03   | Prospective registry of women treated for breast cancer while pregnant - NCT00196833 | S. Loibl, G. von Minckwitz | Supporter trial  
(Co)-Leading partner: GBG (sponsor)  
Pharma partner: N/A  
Funding: GBG, Deutsches Konsortium für Translationale Krebsforschung |
| Exceptional Responders         | BIG 16-04  | A global hunt for exceptional responders in the BIG network: aiming to identify breast cancer patients with a truly remarkable clinical response to anticancer treatments, and to characterise their tumours molecularly | A. Irrthum (coordinator) | BIG-sponsored programme  
(Co)-Leading partner: BIG HQ  
Pharma partner: N/A  
Funding: Breast Cancer Research Foundation |
| EXPERT                          | BIG 16-02  | A randomised phase III trial of adjuvant radiation therapy vs observation after breast conserving surgery for patients with molecularly characterised low-risk luminal A early breast cancer - NCT02889874 | B. Chua | 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 |
| PEARLY                          | BIG 19-01  | 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 - NCT02441933 | J. Sohn | Supporter trial  
Pharma partner: N/A  
Coordinating group: KCSG (sponsor) |
| POLAR                           | BIG 18-02  | Palbociclib for HR+ isolated local or regional recurrence of breast cancer - NCT03820830 | E. Munzone, S.Aebi | Supporter trial  
Coordinating group: IBCSG (sponsor)  
Pharma partner: Pfizer |
## Follow-up or post-study activities

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<tr>
<th>Study name</th>
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<tr>
<td><strong>ALTO</strong></td>
<td>BIG 2-06</td>
<td>Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation: sequence and combination for patients with HER2/ErbB2 positive primary breast cancer - NCT00490139</td>
<td>M. Piccart, A. Moreno-Aspitia</td>
<td>Lead trial (Co)-Leading partners: BIG HQ / IJB-CTSU (BrEAST) / FSTRF / Alliance (former NCCTG; sponsor for the US) Pharma partner: Novartis (global sponsor for all countries with the exception of US) Funding: GSK (past) / Novartis</td>
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<td><strong>APHINITY</strong></td>
<td>BIG 4-11</td>
<td>Comparison of single-versus-dual anti-Her2 therapy (trastuzumab, pertuzumab) for patients with HER2-positive primary breast cancer - NCT01358877</td>
<td>M. Piccart, S. Loibl, J. Bines</td>
<td>Lead trial (Co)-Leading partners: BIG HQ / IJB-CTSU (BrEAST) / FSTRF Pharma partner: Roche (sponsor) Funding: Roche</td>
</tr>
<tr>
<td><strong>BRAVO</strong></td>
<td>BIG 5-13</td>
<td>Niraparib for patients with HER2-negative, germline BRCA mutation-positive, locally advanced or metastatic breast cancer - NCT01905592</td>
<td>N. Turner, J. Balmaña, D. Cameron, J. Erban</td>
<td>Co-lead trial (Co)-Leading partners: EORTC / BIG HQ Pharma partner: Tesaro (sponsor) Funding: Tesaro</td>
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<tr>
<td><strong>DCIS</strong></td>
<td>BIG 3-07</td>
<td>Radiation doses and fractionation schedules for women with DCIS - NCT00470236</td>
<td>B. Chua</td>
<td>Supporter trial (Co)-Leading partner: TROG (sponsor) Pharma partner: N/A Funding: National Health &amp; Medical Research Council Project Grant, Susan G. Komen</td>
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<td><strong>FINESSE</strong></td>
<td>BIG 2-13</td>
<td>Oral lucitanib for patients with FGFR1 ER+ metastatic breast cancer - NCT02053636</td>
<td>F. André, J. Cortès</td>
<td>Lead trial (Co)-Leading partners: BIG HQ / BrEAST / FSS Pharma partner: Servier (sponsor) Funding: Servier</td>
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<td><strong>IBIS-II</strong></td>
<td>BIG 5-02</td>
<td>Prevention study of anastrozole for postmenopausal women at increased risk of breast cancer; and of effects of tamoxifen vs. anastrozole in postmenopausal women with DCIS - NCT00072462</td>
<td>J. Cuzick</td>
<td>Supporter trial (Co)-Leading partner: IBIS Pharma partner: Astrazeneca Sponsor: Queen Mary University of London Funding: Cancer Research UK, Queen Mary University of London</td>
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<tr>
<td><strong>International Male Breast Cancer Programme</strong></td>
<td>BIG 2-07</td>
<td>Registration and biologic characterisation programme of breast cancer in men - NCT01101425</td>
<td>F. Cardoso, S. Giordano</td>
<td>Supporter programme (Co)-Leading partners: EORTC (sponsor) / NABCG (US) Pharma partner: N/A Funding: Breast Cancer Research Foundation</td>
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<tr>
<td><strong>LORELEI</strong></td>
<td>BIG 3-13</td>
<td>Neoadjuvant letrozole plus taselisib versus letrozole plus placebo in postmenopausal women with ER+, HER2-negative, early-stage breast cancer - NCT02273973</td>
<td>C. Saura, E. de Azambuja</td>
<td>Co-lead trial (Co)-Leading partners: ABCSG, SOLTI and BIG HQ Pharma partner: Genentech (sponsor) Funding: Genentech</td>
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<td>MA.32 Metformin</td>
<td>BIG 5-11</td>
<td>Effect of metformin on recurrence and survival in early stage breast cancer - NCT01101438</td>
<td>P. J. Goodwin</td>
<td>Supporter trial (Co)-Leading partner: CCTG (sponsor) Pharma partner: Apotex Funding: NCI/NIH grants, Cancer Research UK, Canadian Cancer Society, BCRF and Canadian Breast Cancer Foundation</td>
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<tr>
<td>MINDACT</td>
<td>BIG 3-04</td>
<td>Can addition of 70-gene signature to common clinical-pathological criteria safely spare patients with 0 to 3 node positive breast cancer from adjuvant chemotherapy? - NCT00553358</td>
<td>E. Rutgers F. Cardoso M. Piccart</td>
<td>Co-lead trial (Co)-Leading partners: EORTC (sponsor) / BIG HQ Commercial partners: Roche, Sanofi, Novartis and Agenda Funding: European Commission, Roche, Sanofi and Novartis grants, BCRF, Susan G. Komen for the Cure, Cancer Research UK, EORTC Charitable Trust, numerous national cancer societies and many other charitable grants*</td>
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<td>NEO-ALTTO</td>
<td>BIG 1-06</td>
<td>Comparison of dual HER2 inhibition (lapatinib, trastuzumab) plus chemotherapy before surgery versus single HER2-targeted therapy - NCT00553358</td>
<td>C. Saara J. Huober</td>
<td>Co-lead trial (Co)-Leading partners: IJB-CTSU (BrEAST) / FSS / SOLIT / BIG HQ Pharma partner: Novartis (global sponsor for all countries with the exception of US, where Alliance is the sponsor) Funding: GSK (past) / Novartis</td>
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<td>OLYMPIA</td>
<td>BIG 6-13</td>
<td>Olaparib vs. placebo for patients with BRCA-mutated, high-risk HER2-negative breast cancer, having completed local treatment and (neo)adjuvant chemotherapy - NCT020832823</td>
<td>A. Tutt B. Kaufman C. Geyer</td>
<td>Lead trial (Co)-Leading partners: NRG Oncology (sponsor in US), BIG HQ and FSTRF Pharma partner: Astrazeneca (sponsor in Rest of the World) Funding: Astrazeneca</td>
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<td>PALLAS</td>
<td>BIG 14-03</td>
<td>PALbociclib CoLaborative Adjuvant Study: palbociclib with standard adjuvant endocrine therapy versus standard adjuvant endocrine therapy alone for HR+ / HER2-negative early breast cancer - NCT02513394</td>
<td>E. Mayer M. Gnant</td>
<td>Co-Lead trial (Co)-Leading partners: ABCSG (RoW), AFT (US) (sponsors) and BIG HQ Pharma partner: Pfizer Funding: Pfizer grant</td>
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<td>PENEOLE.-B</td>
<td>BIG 1-13</td>
<td>Post-neoadjuvant palbociclib for patients with HR+, HER2-normal primary breast cancer with high relapse risk after neoadjuvant chemotherapy - NCT01864746</td>
<td>G. von Minckwitz</td>
<td>Supporter trial (Co)-Leading partner: GBG (sponsor) Pharma partner: Pfizer Funding: Pfizer grant</td>
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<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 - NCT0290085</td>
<td>O. Pagani</td>
<td>Supporter trial (Co)-Leading partner: IBCSG (sponsor) Pharma partner: N/A Funding: IBCSG, Fonds Baillet-Latour, national and local funding bodies, individual donors</td>
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<td>PYTHIA</td>
<td>BIG 14-04</td>
<td>Palbociclib plus fulvestrant for pretreated patients with ER+/HER2- metastatic breast cancer - NCT02536742</td>
<td>L. Malorni</td>
<td>Co-Lead trial (Co)-Leading partners: IBCSG (sponsor) and BIG HQ Pharma partner: Pfizer Funding: Pfizer grant</td>
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<td>SNAP</td>
<td>BIG 2-12</td>
<td>Schedules of nab-Paclitaxel: evaluation of different schedules of nab-paclitaxel for metastatic breast cancer - NCT01746225</td>
<td>A. Gennari G. Jerusalem</td>
<td>Supporter trial (Co)-Leading partner: IBCSG (sponsor) Pharma partner: Celgene Funding: Celgene grant</td>
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<td>SOFT</td>
<td>BIG 2-02</td>
<td>Evaluation of ovarian suppression and of exemestane as adjuvant therapy for premenopausal women with endocrine responsive breast cancer - NCT000666690</td>
<td>P. Francis G. Fleming</td>
<td>Supporter trial (Co)-Leading partner: IBCSG (sponsor) Pharma partner: Pfizer Funding: Grant support from Pfizer, Ipsen, US NCI, IBCSG and many participating collaborative academic groups, BCRF, as well as various charities</td>
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<td>SOLE</td>
<td>BIG 1-07</td>
<td>A phase III trial evaluating the role of continuous letrozole versus intermittent letrozole following 4 to 6 years of prior adjuvant endocrine therapy for postmenopausal women with hormone-receptor positive, node positive early stage breast cancer (SOLE - Study Of Letrozole Extension) - NCT00553410</td>
<td>M. Colleoni P. Karlsson S. Aebi J. Chingwin</td>
<td>Supporter trial (Co)-Leading partners: IBCSG Sponsor: IBCSG Pharma partner: Novartis Funding: Novartis</td>
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<td>SUPREMO</td>
<td>BIG 2-04</td>
<td>Selective Use of Postoperative Radiotherapy AfEr MastectOmy: adjuvant chest wall irradiation for ‘intermediate risk’ breast cancer following mastectomy - NCT00966888</td>
<td>I. Kunkler P. Canney</td>
<td>Supporter trial (Co)-Leading partner: SCTBG Sponsor: UK Medical Research Council Pharma partner: N/A Funding: UK Medical Research Council, EORTC, Cancer Australia, William and Elizabeth Davies Charitable Trust, Peter Chan Jee Yat Foundation, Yeung Ying Yin and May Yeung Foundation.</td>
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<td>TEXT</td>
<td>BIG 3-02</td>
<td>Tamoxifen and Exemestane Trial: evaluation of exemestane plus GnRH analogue for premenopausal women with endocrine responsive breast cancer - NCT00066703</td>
<td>O. Pagani B. Walley</td>
<td>Supporter trial (Co)-Leading partner: IBCSG (sponsor) Pharma partner: Pfizer Funding: Grant support from Pfizer, Ipsen, US NCI, IBCSG and many participating collaborative academic groups, BCRF, as well as various charities</td>
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<td>TREAT-CTC</td>
<td>BIG 1-12</td>
<td>TRastuzumab in HER2-negative Early breast cancer as Adjuvant Treatment for Circulating Tumor Cells (CTC) (&quot;TREAT-CTC&quot; Trial) - NCT01548677</td>
<td>M. Ignatiadis M. Piccart J.-Y. Pierga B. Rack C. Sotiriou</td>
<td>Supporter trial (Co)-Leading partners: EORTC BCG, SUCCESS, UNICANCER Sponsor: EORTC Pharma partner: Roche, Janssen Diagnostics Funding: Roche educational grant/medication; Janssen test kits</td>
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<td>ULTIMATE</td>
<td>BIG 16-01</td>
<td>Immunotherapy combined with standard endocrine therapy as neoadjuvant treatment for women with ER+/HER2-negative breast cancer - NCT02997995</td>
<td>F. André A. Prat</td>
<td>Co-lead trial (Co)-Leading partners: French Breast Cancer Intergroup Unicancer (UCBG) (sponsor) and BIG HQ Pharma partner: Astrazeneca Funding: Astrazeneca grant</td>
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* full information available on the BIG website


NB: This table does not include the trials in development and the closed trials. For more information, please visit: [www.BIGagainstbreastcancer.org](http://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.

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www.BIGagainstbreastcancer.org

The 57 breast cancer research groups of the BIG network

| ABCSG | Austrian Breast & Colorectal Cancer Study Group |
| BCT-ANZ | Breast Cancer Trials - Australia & New Zealand |
| BGCS | Breast-Gynaecological International Cancer Society |
| BIE | Breast Inter-group of Eastern India |
| BOOG | Barstünker Onderzoek Groep |
| CCGS | Breast Disease Professional Committee of CMEA (China) |
| CCTG | Canadian Cancer Trials Group |
| CEEOG | Breast-Gynecological International Cancer Society |
| BIE | Breast Breast Cancer Group Study Group |
| AGO-B | Arbeitsgemeinschaft Gynäkologische Onkologie Breast Study Group |
| ARCAAGY-GINECO | Association de Recherche dans les Cancers dont Gynécologiques – Groupe d’Investigateurs Nationaux pour l’Étude des Cancers Ovariens et du sein |
| BCT-ANZ | Breast Cancer Trials - Australia & New Zealand |
| ABCSG | Austrian Breast & Colorectal Cancer Study Group |
| EORTC BCG | European Organisation for Research and Treatment of Cancer, Breast Cancer Group |
| FBCG | Finnish Breast Cancer Group / Suomen Rintaisyöpäryhmä |
| GAICO | Grupo Argentino de Investigación Clinica en Oncologia |
| GBG | German Breast Group |
| GCOS | Georgian Cancer Study Group |
| GEOPERU | Grupo de Estudios Clinicos Oncologicos Peruano |
| GECAM | Spanish Breast Cancer Group |
| GOCCHI | Chilean Cooperative Group for Oncologic Research |
| GOCUR | Grupo Oncologico Cooperativo Uruguyano |
| GOLDRC | Italian Oncology Group for Clinical Research |
| HBSS | Hellenic Breast Surgical Society |
| HeCIOG | Hellenic Cooperative Oncology Group |
| HKBOG | Hong Kong Breast Oncology Group |
| HORG | Hellenic Oncology Research Group |
| IBCG | Icelandic Breast Cancer Group |
| IBG | Israeli Breast Group |
| IBIS | International Breast Cancer Intervention Studies |
| ICCG | International Collaborative Cancer Group |
| ICN | Indian Co-Operative Oncology Network |
| ICRC | Iranian Cancer Research Center |
| ICR-CTSU | Institute of Cancer Research – Clinical Trials & Statistics Unit |
| IB / CTSU | Institut Jules Bordet / Clinical Trials Support Unit |
| IOSG | Indian Oncology Study Group |
| ITMO | Italian Trials in Medical Oncology |
| JBCRG | Japan Breast Cancer Research Group |
| KCCG | Korean Cancer Study Group |
| LACOG | Latin American Cooperative Oncology Group |
| MICHELANELO | Fondazione Michelangelo |
| NRCG | Norwegian Breast Cancer Group |
| NCRI-BCSG | National Cancer Research Institute - Breast Cancer Clinical Studies Group |
| SABC | South African Breast Cancer Group |
| SKMCH & RC | Swiss Society for Clinical Oncology |
| SBCG | Sheba Breast Collaborative Group |
| SAKK | Swiss Group for Clinical Cancer Research |
| SBCG | Swedish Breast Cancer Group |
| TCOG | Taiwan Cooperative Oncology Group |
| TROG | Trans Tasman Radiation Oncology Group |
| TSCO | Thai Society of Clinical Oncology |
| UCBG | Unicancer Breast Group |
| WSG | Westdeutsche Studiengruppe |
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 sky is the limit: whatever your creative idea is to fundraise for breast cancer research, you can get started here!

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

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 to 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!
Today’s research for tomorrow’s cures

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or donate online:
www.BIGagainstbreastcancer.org/donate

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Blvd de Waterloo 76, B-1000 Brussels, Belgium
info@BIGagainstbc.org

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