ALL FOR ONE / ONE FOR ALL

THE LEGACY OF PROFESSOR ARON GOLDHIRSCH

40 years of advances in breast cancer research

BIG
Breast International Group

COLOPHON

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TRIBUTE TO ARON

By Martine Piccart, co-founder of BIG

Sadly, my dear friend, colleague and mentor, Professor Aron Goldhirsch, passed away at the age of 73 on 26 February 2020. Aron was like a brother to me. He was also often referred to as the 'father' of the Breast International Group (BIG).

BIG was 'born' over a dinner I had with Aron at the end of a meeting of the European Organisation for Research and Treatment of Cancer Breast Cancer Group (EORTC BCG) in 1995, at which he was an invited speaker. He was immediately enthusiastic about the idea of a new global network to strengthen and accelerate breast cancer research, starting in Europe. Aron already led the successful International Breast Cancer Study Group (IBCSG), but he saw the value of a larger collaboration to perform important clinical trials on a scale that no single organisation could do alone.

It was Aron who chose the name, BIG, when we were still a very small, fragile network of academic breast cancer research groups. This was not a random choice; Aron firmly believed in collaboration, cooperation, loyalty and friendship, and he was confident that BIG would grow into its name and become successful.

It wasn't all plain sailing. At the start, some research groups were concerned about being 'swallowed up', but that was never our aim. We knew there was a place for studies done by individual partners within the network and those performed together under the BIG umbrella. We also had the example of the North American Breast Cancer Group (NABCG), which successfully brought together a number of regional groups that still retained their independence.

Aron himself had a remarkable capacity for assessing whether a proposed trial would be best done by IBCSG or by BIG. At the heart of all his decisions was what was best for the patient. Whether he was in his clinic, planning a trial, or supporting his colleagues, the patient always came first. His presence – calm, thoughtful, and patient – was key to finding solutions and moving forward. Whenever I was discouraged, his energy, optimism and steadfastness took us through.

At quite an early stage in the history of BIG, the threatened withdrawal of funding for an important planned trial became the unlikely catalyst for uniting all our member organisations firmly behind BIG. On hearing of the looming disaster, Aron insisted we contact all the research groups that were members of BIG – as well as academic groups outside our network – and everyone agreed to boycott the trial unless it was led by BIG. As a result, the decision was reversed, BIG carried out the trial, and patient recruitment was so rapid that we were able to present the results alongside those of similar North American studies that had started well before ours.

This was a turning point for BIG because it gave our members confidence in the value of the network and what could be achieved if we all worked together. In the years that followed, Aron's input played an essential part in making BIG the organisation it is today – extending our presence across continents, bringing on board some of the finest breast cancer researchers, and completing multiple practice-changing clinical trials.

Over the years, many of Aron's collaborators have become firm friends and, in this special publication dedicated to him, some of them have come together to talk about his legacy to the breast cancer community – as a researcher, an educator and a mentor – and about some of the key BIG trials in which he played such an essential role.

We all miss Aron's wisdom, his generosity and the unique brightness in his eyes whenever a brilliant idea came to him. And there were many! During his working life, Aron dedicated himself to moving breast cancer care from the generalised to the personalised, so that every patient received treatment tailored to their cancer, their needs and their priorities. He and his collaborators made much exciting progress towards those goals. We continue that journey while always remembering Aron's extraordinary contribution and remaining true to his mantra: **'All for One, One for All'**.

Martine J. Piccart
Professor of Oncology at the Université Libre de Bruxelles and Scientific Director at the Jules Bordet Institute in Brussels, Belgium
Co-founder of BIG and Immediate Past Chair
President of *BIG against breast cancer* (BIG's philanthropy unit)

ABOUT ARON

Professor Aron Goldhirsch *(April 1946, Landsberg am Lech, Germany - February 2020, Lugano, Switzerland)* ***was an exceptional oncologist, scientist and teacher. He grew up in Israel and was married to Francesca, with whom he had three children (Tommy, Lea and Nina). His main hobbies were literature, photography and traveling.***

SOME KEY DATES

1999-2017 Founding Member and Vice-Chairman, Breast International Group (BIG)

1999 BIG became a legal entity

1996 with Martine Piccart, created and named BIG

1994-2004 President, Swiss Group for Clinical Cancer Research *(SAKK, member of BIG)*

1978 became Chairman, Scientific Committee, Foundation Council International Breast Cancer Study Group *(IBCSG)*

1972 obtained his degree in Doctor in Medicine and Surgery (M.D.)

1966 moved from Israel to Italy to study medicine at State University of Milan

PROFESSIONAL SOCIETIES

1998-2020 Co-Director of the WHO Collaborative Center for Cancer Control and Palliative Care

1997-2020 The Italian Medical Board, Milan (#34876)

1989-2020 European Society of Mastology (EUSOMA)

1985-2020 American Association for Cancer Research (AACR)

1982-2020 European Society for Medical Oncology (ESMO)

1981-2020 American Society for Clinical Oncology (ASCO)

1976-2020 Italian Association of Medical Oncology (AIOM)

1973-1974 The Italian Medical Board, Milan (#14458)

WORK EXPERIENCE

2016-2020 Medical Consultant, MedQualitas, Chiasso, Switzerland

2016-2020 Senior Consultant, Breast Health Program and Director of Melanoma, Skin Malignancies, Sarcoma and Rare Neoplasia Program, IEO, European Institute of Oncology, Milan, Italy

2013-2016 Director, Breast Health Program, IEO, European Institute of Oncology, Milan, Italy

2013-2016 Medical Consultant, EOC, Ospedale Italiano, Lugano-Viganello, Switzerland

2011-2012 Director, Swiss Center for Breast Health, Sant'Anna Clinic, Lugano-Sorengo, Switzerland

2010-2016 Deputy Scientific Director, IEO, European Institute of Oncology, Milan, Italy

1997-2013 Director, Department of Medicine, IEO, European Institute of Oncology, Milan, Italy

1996-2006 Invited Visiting Professor, Dept. of Medicine, Harvard Medical School, Dana-Farber Cancer Institute, USA

1994-2011 Physician-in-Chief, IOSI, Oncology Institute of Southern Switzerland, Bellinzona, Switzerland

1992 Professor of Medical Oncology (Titular Professor), University of Bern, Switzerland

From 1972 Various medical positions held in Israel, Italy and Switzerland

AWARDS

2014 Gianni Bonadonna Breast Cancer Award of the American Society of Clinical Oncology, USA

2013 St. Gallen Breast Cancer Award, Austria

2011 ECCO Clinical Research Award (Team Award together with Prof. Richard Gelber)

2010 Umberto Veronesi Award for the Future Fight Against Breast Cancer, Italy

2008 Brinker Award for Scientific Distinction in Clinical Research (Team Award together with Prof. Richard Gelber), USA

2006 ESMO lifetime Achievement Award (Team Award together with Prof. Martine Piccart. They were recognised for co-founding BIG, the Breast International Group)

2003 Lynn Sage Award, Chicago, USA

1999 Jean H. Lubrano Distinguished Visiting Scholar Award, Dana-Farber Cancer Institute, Boston, USA

1998 Jan Waldenström Award, Swedish Medical Society, Sweden

1995 Lavezzari Prize, Chiasso, Switzerland

1994 International Prize "la Madonina" of the City of Milan, Italy

1993 Doctor Honoris Causa, University of Göteborg, Sweden

1992 San Salvatore Prize, San Salvatore Foundation, Lugano, Switzerland

1987 Robert Wenner Prize, Swiss Cancer League, Switzerland

1987 Farmitalia Carlo Erba Prize, German Cancer Society, Germany

1984 Farmitalia Carlo Erba Prize, German Cancer Society, Germany

SCIENTIFIC PUBLICATIONS

Author of over 750 peer-reviewed articles and chapters in reference books and editor or co-editor of 10 books. Served on the editorial board of several oncology and breast cancer research journals.

Talk to any breast cancer specialist who knew Professor Aron Goldhirsch well and they will tell you about his extraordinary intellect, his professional generosity and his devotion to patients, family and friends.

ARON
HIS RESEARCH LEGACY

From his early days at the Bern branch of the Ludwig Institute for Cancer Research, Switzerland, through his pivotal role in establishing the Breast International Group (BIG) and the International Breast Cancer Study Group (IBCSG), to his ground-breaking initiatives in patient care at the European Institute of Oncology in Milan, Italy, Goldhirsch was a pioneer and visionary within the breast cancer community.

"One of the great privileges of working in international research is that you work with the best people in the world – and Aron was one of those people. We had a very close working relationship and it was probably the single most important academic, cultural and personal relationship of my clinical career," says **Professor Alan Coates,** Clinical Professor in the School of Public Health, at the University of Sydney, Australia.

By working with Goldhirsch for more than 40 years, initially through the Sydney branch of the Ludwig Institute and later the IBCSG, Coates saw first-hand the impact of Goldhirsch's radical thinking on breast cancer treatment.

"Aron will be most remembered for switching from thinking about the anatomy of breast cancer, in terms of how far it had spread, to the biology of breast cancer and how it was performing. Knowing the biology of the disease has enabled us to focus on targeted treatments, the first of which was endocrine treatment," Coates explains.

For another long-time collaborator and friend, **Professor Richard Gelber,** Professor in the Department of Biostatistics, Harvard University, and Dana-Farber Cancer Institute, Boston, USA, it was Goldhirsch's willingness and ability to bring together researchers from multiple specialties that was key to his success as a linchpin of international breast cancer research.

"As a statistician, some people I worked with saw me as a policeman telling them what they could and couldn't do, but he wanted to understand where I was coming from so that we could work together," says Gelber. "He had a great strength in being able to get people together from different backgrounds, and he taught me a huge amount about breast cancer."

By respecting the achievements of other researchers and sharing the decision-making and running of trials – and their success – Goldhirsch forged lasting collaborations in Europe and beyond.

"He could interact with people all over the world, and he could get to the point of mutual understanding much more quickly than those with limited ability with languages. He frequently used the motto **"All for One, One for All"** and he was very good at encouraging people to suppress their own egos for the greater good of the whole," Gelber explains.

At a time when few women had senior roles in oncology, Goldhirsch encouraged and promoted their involvement in breast cancer research, and women were principal investigators in a number of studies in which he played a major part.

Professor Giuseppe Viale, Professor of Pathology and Director of the Postgraduate Medical School in Pathology at the University of Milan School of Medicine, also felt the benefits of Goldhirsch's inclusive approach.

"In focusing on the biology of breast cancer to inform the choice of treatment, Aron wanted to have pathologists, surgeons and radiotherapists on board as well as oncologists. So we became a multidisciplinary team many years before this became common practice," says Viale.

Having played such a key role in the decades of research that led to more targeted breast cancer treatment, with fewer women requiring toxic chemotherapy, Goldhirsch turned his attention to new frontiers of research. **Professor Giuseppe Curigliano**, Associate Professor of Medical Oncology, University of Milan, Italy, explains that, latterly, he was interested in the impact of gender on response to treatment and in the microenvironment in which cancer cells exist.

In recent years, Goldhirsch had performed studies investigating response to cancer immunotherapy according to gender and had begun studies of low dose, long-term chemotherapy (metronomic chemotherapy), with the aim of treating both the tumour and the microenvironment.

"The idea was to treat the cancer not only through killing cancer cells but also through modulation of the cancer environment," says Curigliano. "Aron always had such an open mind and a curiosity about new approaches to breast cancer treatment and, in fact, for everything in life. He was methodical and he worked incredibly hard, and he was always looking for new ways of improving outcomes for patients."

A DRIVING FORCE AT IBCSG AND BIG

In the mid-1980s, when the Ludwig Breast Cancer Study Group evolved into the IBCSG, Goldhirsch was one of the founding members and became its natural leader.

"Aron's success as leader of the Group was due to his immense intellect and encyclopaedic knowledge of the research that was going on in the field. Sometimes he seemed to know more about what people were doing than they did themselves!" Coates recalls.

He explains that Goldhirsch played a major role in driving early trials of endocrine treatment in patients with endocrine-responsive disease. Although this approach was sometimes controversial at the time, subsequent history has shown that treating specific sub-groups of patients according to their breast cancer biology helps to optimise the balance between the effectiveness and side-effects of therapy for patients.

Gelber also highlights Goldhirsch's focus on the needs of patients when designing trials, and of taking account of geographic variations in clinical practice.

"When designing trials, we talked first about the science and then considered the perspectives of all the disciplines and how the study would be conducted in different countries. This was because in some countries surgeons were pre-eminent, in others radiation oncologists or medical oncologists. So we spent a lot of time discussing the inter-disciplinary science and then how it would be conducted. That became a standard way of doing things," says Gelber.

Despite the success of the IBCSG and national and regional networks of breast cancer specialists in collaborating on ground-breaking clinical trials, by the mid-1990s, it became apparent that something even larger was needed. A sort of 'network of networks', capable of carrying out the largest clinical trials that could take account of the huge heterogeneity of breast cancer and the need for a more personalised approach to treatment. This was BIG – the brainchild of Goldhirsch and his long-time collaborator and friend, **Professor Martine Piccart**, Professor of Oncology at the Université Libre de Bruxelles and Scientific Director at the Jules Bordet Institute in Brussels, Belgium. As co-founder, Martine Piccart is also BIG's Immediate Past Chair and President of *BIG against breast cancer* (the philanthropy unit of BIG).

"Aron and Martine made a fantastic team with their robust and principled approach, enthusiasm and shared vision of performing collaborative studies to get clear answers that could benefit patient outcomes," says BIG's current Chair, **Professor David Cameron**, Professor of Oncology, University of Edinburgh, UK.

When Cameron first joined BIG's Executive Board he was struck by the depth of knowledge and thought behind Goldhirsch's views on key issues:

"It was always clear that he spent a lot of time looking at the evidence and thinking things through so that he could stand up for what he felt was right. I had great respect for the fact that Aron always upheld his principles."

THE IMPORTANCE OF ACADEMIC INDEPENDENCE

With clinical trials of innovative medicines for breast cancer costing €50-100 million each, pharmaceutical company sponsorship of such studies is essential for progress to be made. Academic independence is just as important.

"We all recognised the importance of pharmaceutical support to carry out clinical trials of new therapies and the need to work together while remaining independent. Aron could always respond to any issues with numbers and logic. He enjoyed playing good cop, bad cop during discussions – I'll leave you to decide which was Aron!" Coates laughs.

In a paper published in *Nature* in 2007, Goldhirsch and colleagues said that, to keep faith with clinical trial volunteers, it was important that academic investigators should be responsible for making decisions about clinical trials, analysing data and preparing papers for publication.

"The initial draft of that paper was done in about two hours in an Istanbul hotel room after that year's meeting of the European Cancer Organisation, after we had been talking to representatives of patient organisations. The creative spark of writing with Aron is one of my greatest memories," says Coates.

As Cameron points out, Goldhirsch was not intransigent in discussions with pharmaceutical companies but he was always principled.

"He believed that clinical trials should not just be about testing lots of interesting new drugs, they should also be exploring opportunities for better use of older drugs or identifying what was best for patients based on their tumour biology," he says.

Equally, Goldhirsch was aware of the risks of uncoordinated academic research, adds Cameron, with potential for wasteful repetition of studies by competing institutions or groups with different philosophies pulling in different directions.

"What Aron and Martine set out to do with BIG was to build greater collaboration between academics so we would have larger studies that could more definitively answer the questions that needed answering. As a result, some studies are carried out with pharmaceutical support, some without, and the success of clinical research depends on collaboration between academics and between academics and industry," says Cameron.

ARON WOULD BE PLEASED ...

With over 750 papers bearing his name and many more continuing to be published, Goldhirsch's research legacy is assured.

"I think he would have been pleased with the enormous progress that has been made in improving breast cancer survival. This has a lot to do with the effective treatments that came out of the clinical trials which he and others did. The increasing acceptance of the importance of cancer biology would also have pleased him," says Coates.

Goldhirsch rarely took the sought-after first or last author position on the title page of the many papers he co-authored – an honour he frequently rejected in favour of colleagues. He did not need the official recognition of his role because everyone knew that, wherever his name appeared on the author list, he would have played a significant and valuable role in the research.

"By making clinical trials the bedrock of how we practise, he continues to offer hope to patients for future improvements in treatment," says Cameron. "In years to come, when they write the history of how breast cancer care was transformed, his name will keep appearing and he will be recognised as one of those who laid the foundations for that transformation. He made a difference."

ARON
THE BIG TRIAL LEGACY

Professor Aron Goldhirsch was, together with Professor Martine Piccart, the founder of BIG. He was also a driving force behind many of BIG's landmark clinical trials that have changed – and are still changing – the way that breast cancer is treated. Thanks to the pioneering ideas of Goldhirsch and his collaborators, the BIG network of academic research groups has become a global leader in running, facilitating and accelerating international breast cancer research, including pivotal trials that show how endocrine therapy can be personalised to each patient's cancer and their risk of recurrence.

ABOUT BIG 1-98 / IBCSG 18-98

The BIG 1-98 trial was designed to find out how best to use endocrine treatment in post-menopausal women with operable, hormone receptor-positive early breast cancer after surgery.

Between March 1998 and May 2003, approximately 8,000 women were recruited and enrolment included patients from 148 hospitals in 27 countries.[1,2] They were treated for five years in total, with one of four options: the aromatase inhibitor*, letrozole, letrozole followed by tamoxifen, tamoxifen, or tamoxifen followed by letrozole.[1]

After two years follow-up, letrozole had reduced the risk of breast cancer recurrence by 19% compared to tamoxifen. The greatest reduction (27%) was in distant metastases.[1]

At nearly nine years follow-up, letrozole significantly reduced recurrence (18%) and deaths (21%) compared to tamoxifen.[2] Recurrence and survival rates were similar for sequential treatment with letrozole followed by tamoxifen or tamoxifen followed by letrozole compared to letrozole alone.

The side effect profiles of tamoxifen and letrozole were different. Tamoxifen was more likely to cause blood clots, vaginal bleeding, hot flushes and night sweats. Letrozole was more likely to cause vaginal dryness, bone fractures, osteoporosis, joint and muscle pain, and more serious heart problems.

Additional analyses showed that, in women at lowest risk of recurrence, tamoxifen, letrozole and sequential treatment had similar five-year disease-free survival rates.[3]

For those at intermediate risk, letrozole and the two sequential treatment options were equally effective. Only in women at high risk of recurrence did letrozole give better outcomes than the other treatment options.

The researchers concluded that, although sequential treatments with tamoxifen and letrozole did not improve outcomes compared with letrozole alone, they could be useful for patients experiencing side effects of either tamoxifen or letrozole.

BIG 1-98 was sponsored and run by the IBCSG, under the BIG umbrella, and funded by a grant from Novartis.

BIG 1-98: FINDING THE RIGHT ENDOCRINE TREATMENT FOR THE RIGHT POST-MENOPAUSAL WOMEN

In 1998, when BIG 1-98 was set up, post-menopausal women with hormone receptor-positive early breast cancer were typically advised to take tamoxifen for at least five years after their surgery. Studies had shown that tamoxifen could reduce breast cancer recurrence by 47% and death by 26%.[1] The newer aromatase inhibitors, such as letrozole, also showed promise in reducing recurrence and improving survival. Doctors wanted to know which drug they should give to their patients, taking account of the different side effect profiles of tamoxifen and aromatase inhibitors and the greater cost of the newer agents.

Professor Alan Coates explains that initial proposals for BIG 1-98 were for a simple comparison between tamoxifen and one of the three aromatase inhibitors available at that time.

However, Goldhirsch and others felt that the study could be used to answer more complex scientific questions about the potential of sequential use of tamoxifen and aromatase inhibitors. They also wanted to include translational research to help identify patients who would do just as well with tamoxifen as with an aromatase inhibitor, especially in cases where aromatase inhibitor side effects or cost were important factors.

"Aromatase inhibitors have a different side effect profile from tamoxifen, which includes musculoskeletal and arthritis problems. So if we could reassure patients with these problems that they were not going to do worse if they switched back to tamoxifen, that would be very useful," recalls Coates.

Professor Richard Gelber agrees: "As a statistician, when I look at BIG 1-98, it was a fantastic study because it showed that patients at highest risk need an aromatase inhibitor while those at lowest risk only need tamoxifen. Those at intermediate risk do benefit from receiving an aromatase inhibitor initially, but might switch to tamoxifen before completing the full five years that are recommended for women at high risk. We would never have known all this if we hadn't had the four different treatment options in BIG 1-98."

Today, an on-line tool (#) is available free of charge to help physicians in decision-making – serving as a basis for discussion with post-menopausal patients and allowing an optimal choice of endocrine treatment.

(#) https://www.crib-calculator.com/

* Aromatase inhibitors (AIs) are endocrine (hormone-targeting) drugs (e.g. letrozole, anastrozole and exemestane). They work by blocking the enzyme, aromatase, which converts androgen hormones into oestrogen in the body. This means that less oestrogen will be available to stimulate the growth of hormone receptor-positive breast cancer cells.

Translational research: provides the link between the discoveries in the laboratory (basic science research) and their application for the benefit of patients (clinical research). It functions as a bridge between these two worlds and is based on two principles often referred to as "bench to bedside" and "bedside to bench".

BIG trials and research programmes always strive to incorporate translational research within them. Translational research is conducted using biological samples (such as tumour tissue or blood) collected in the context of BIG trials from patients who have consented to their use, either for specific projects, or for yet undefined future research. The biological samples collected are maintained in qualified biorepositories, which in general are independent from the partners involved in running a particular clinical trial. At a specific point in time, these samples – as well as clinical and other data collected during the course of a trial – are made available to scientists from around the world, both from within and outside of the BIG network.

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2. Regan MM, Neven P, Giobbie-Hurder A et al. Assessment of letrozole and tamoxifen alone and in sequence for postmenopausal women with steroid hormone receptor-positive breast cancer: the BIG 1-98 randomised clinical trial at 8·1 years median follow-up. *Lancet Oncol. 2011 Nov;*12(12):1101-8

3. Viale G, Regan MM, Dell'Orto P et al; BIG 1-98 Collaborative and International Breast Cancer Study Groups. Which patients benefit most from adjuvant aromatase inhibitors? Results using a composite measure of prognostic risk in the BIG 1-98 randomized trial. *Ann Oncol. 2011 Oct;*22(10):2201-7

ABOUT SOFT (BIG 2-02 / IBCSG 24-02) AND TEXT (BIG 3-02 / IBCSG 25-02)

Recruitment of patients to the international SOFT and TEXT trials started in November 2003 and was completed in April 2011. The studies included 5,738 women treated at over 500 hospitals and cancer centres in 27 countries. They investigated the optimal endocrine treatment for pre-menopausal women with hormone-sensitive early breast cancer after surgery.

Patients in SOFT had chemotherapy after surgery and then received one of the following three treatments: the aromatase inhibitor exemestane and ovarian suppression; tamoxifen and ovarian suppression; or tamoxifen alone. In TEXT, chemotherapy was optional, and patients then received one of two treatments: exemestane and ovarian suppression, or tamoxifen and ovarian suppression.

In SOFT, women who had treatment to suppress their ovarian function as well as tamoxifen had a 24% lower risk of breast cancer recurrence (4.2% absolute improvement) than those who had standard treatment with tamoxifen alone.

The studies also showed that women who were treated with the aromatase inhibitor exemestane and ovarian suppression had a 23% lower risk of breast cancer recurrence than those who received tamoxifen and ovarian suppression (4% absolute improvement).[1]

After nine years, 91.8% of the patients treated with exemestane and ovarian suppression were free of distant recurrence, compared with 89.7% for the women treated with tamoxifen and ovarian suppression.

The benefit of ovarian suppression was greatest in those at highest risk of recurrence and less in those at intermediate risk.[2] For those at low risk, there was no advantage of ovarian suppression over tamoxifen alone.

In the SOFT and TEXT trials, some women had chemotherapy, and some did not. Many patients who did not have chemotherapy did just as well with exemestane and ovarian suppression as those who did have chemotherapy. Doctors realised that, on the basis of routine diagnostic tests, they could identify patients with very hormone-sensitive breast cancer who would do well without chemotherapy. The trials taught when endocrine treatment escalation is needed and when it is possible to de-escalate.

SOFT and TEXT were sponsored and run by the IBCSG, under the BIG umbrella, and funded by grants from Pfizer, Ipsen, the IBCSG and the National Cancer Institute.

SOFT AND TEXT: SEARCHING FOR THE RIGHT HORMONE COMBINATION FOR PRE-MENOPAUSAL WOMEN

Having set up BIG 1-98 to establish optimal endocrine treatment for post-menopausal women with hormone-responsive early breast cancer, Goldhirsch and other BIG researchers were eager to discover the best option for pre-menopausal women with the same type of early breast cancer. As well as targeting the hormone receptors on breast cancer cells, the researchers needed to know how best to block the activity of the women's still functioning ovaries to minimise production of hormones that could stimulate cancer cell activity.

However, as **Professor Beat Thürlimann**, Chief Physician and Head of the Breast Centre, Kantonsspital St. Gallen, Past President of SAKK (Swiss Group for Clinical Cancer Research), Switzerland explains: "Some 20 years ago, at the time the research was being discussed, clinical practice for the treatment of pre-menopausal women with early breast cancer varied around the world. This made it difficult to design a trial that everyone would be happy to take part in."

"The most common approach was chemotherapy followed by tamoxifen but, in Europe, clinicians preferred ovarian function suppression followed by tamoxifen, and they used less chemotherapy," he says.

How could the different approaches be brought together to find out what was best for women?

"Aron was able to find a compromise and accommodate the differing views by establishing two trials, SOFT and TEXT, which were carried out alongside each other," explains **Professor Olivia Pagani**, Professor of Oncology at the University of Geneva, Switzerland, Past Co-President of the SAKK (Swiss Group for Clinical Cancer Research) breast cancer project group, Switzerland.

This turned out to be a very important solution because SOFT and TEXT revealed that, although ovarian function suppression plus endocrine treatment were generally better than endocrine treatment alone, some women did not need ovarian function suppression with all the related side effects, and many did not need chemotherapy.

"The size and complexity of SOFT and TEXT enabled us to tease out large enough sub-groups of women who benefitted in different ways, depending not only on established risk factors but also on the biology and hormone sensitivity of their tumours, allowing robust conclusions. Indeed, online tools (#) based on SOFT and TEXT results are now available and doctors can use them to calculate a patient's risk and guide treatment," says Thürlimann.

"In the end, Aron's compromise was very important for women," agrees Pagani. "He believed in asking multiple questions in clinical trials and hated studies that just compared one drug with another. SOFT and TEXT are a good example of the importance of his approach because they changed treatment for younger women with endocrine-responsive breast cancer worldwide."

Today, online-tools (#) are available free of charge to help physicians in decision-making – serving as a basis for discussion with pre- and post-menopausal patients and allowing an optimal choice of endocrine treatment:
(#) https://www.crib-calculator.com/
(#) https://rconnect.dfci.harvard.edu/CompositeRiskSTEPP/

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ABOUT POSITIVE (BIG 8-13 / IBCSG 48-14)

The POSITIVE study is a unique opportunity to find out whether young women with hormone-sensitive breast cancer can plan and try to become pregnant without waiting many years to complete their endocrine treatment – and to do this safely.[1] By helping to obtain solid data, it will also improve scientific understanding of many issues related to conception and pregnancy in young women who have had breast cancer.

Women who take part are able to stop their endocrine treatment for breast cancer for up to two years to give them time to try to have a baby. After that time, they will restart their treatment and will be followed up for 10 years after enrolment.

In December 2019, POSITIVE met its recruitment target, enrolling 518 women from 203 hospitals in 20 countries. At that time, 125 healthy babies had already been born.

POSITIVE is sponsored and run by the IBCSG, under the BIG umbrella, without pharmaceutical industry funding. We are therefore very grateful to the generosity of Fonds Baillet-Latour, the local resources of numerous participating groups and countries, and BIG's wider philanthropic community, with its on-going engagement in *BIG against breast cancer's* fundraising activities.

POSITIVE: BIG TIME FOR BABY

About one in six women with breast cancer are diagnosed at a time when they can still have children. As many women now delay starting a family, breast cancer occurs increasingly in those who would still like to become pregnant.

The POSITIVE study emerged from discussions of a working group between BIG and the North American Breast Cancer Group set up to develop international trials and chaired by Professor Aron Goldhirsch. However, as **Professor Olivia Pagani**, European Chair of the POSITIVE study, explains, the idea of women with breast cancer becoming pregnant has always been controversial, so there was a lot of reluctance among clinicians.

"POSITIVE had a very long gestation and, again, Aron needed to be flexible in order to get agreement for the study. This time he agreed to a simpler design than originally suggested because he realised this was the only way to get the study done," says Pagani.

In the absence of pharmaceutical support for the trial, Goldhirsch also provided substantial funding for POSITIVE through the Frontier Science Southern Europe initiative. This was a not-for-profit organisation that he started in southern Switzerland focused on patient-oriented projects such as improving consent forms and consultations.

"The POSITIVE trial has Aron written all over it. He was the 'father' of POSITIVE and he put a huge effort into getting it done. He lived to see recruitment of POSITIVE completed but sadly not the results," says Professor Richard Gelber. "When POSITIVE started some said it was doomed to failure because there weren't enough patients to recruit but Aron felt it was too important to give up. He was right."

References

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ABOUT SOLE (BIG 1-07 / IBCSG 35-07)

The SOLE trial was set up to find out whether taking 3-month treatment breaks during extended endocrine therapy would reduce the risk of recurrence in post-menopausal women with hormone receptor-positive, lymph node-positive early breast cancer.

Between December 2007 and August 2012, almost 4,900 patients who were free of breast cancer and had completed four to six years of endocrine therapy within the previous 12 months were enrolled at 240 centres in 22 countries.[1] They received an additional five years of continuous aromatase inhibitor treatment with letrozole, or five years of intermittent letrozole. Intermittent therapy involved taking letrozole for the first nine months during years 1 to 4, and then continuously for 12 months in year 5.

SOLE showed that intermittent letrozole did not improve disease-free survival compared with continuous use of letrozole, though there were improvements in quality of life.

The trial was sponsored and run by the IBCSG, under the BIG umbrella, and funded by IBCSG and Novartis.

SOLE: FROM LABORATORY TO CLINIC

Most patients with hormone-sensitive breast cancer take endocrine treatment with tamoxifen or an aromatase inhibitor for at least five years after surgery to prevent recurrence. Depending on the likelihood of benefits and side effects, some continue for longer but, over time, tumours may develop resistance to treatment.

Dr Marco Colleoni, now Director of the Division of Medical Senology at the European Institute of Oncology, Milan, Italy, lead author of the SOLE publication, explains that laboratory research carried out some years ago suggested that resistance to the aromatase inhibitor letrozole might be reversed by stopping and restarting treatment. Based on these laboratory findings, Professor Aron Goldhirsch designed the SOLE study to find out whether intermittent letrozole treatment could prolong sensitivity to treatment in patients with breast cancer.

"SOLE did not show improved disease-free survival with intermittent treatment, and it seems likely that the three-month interruption in letrozole wasn't long enough to restore sensitivity to treatment. However, intermittent treatment did have beneficial effects on quality of life for patients," says Colleoni.

While questions remain over the best way to give intermittent treatment, Goldhirsch's commitment to investigating the option in SOLE was important to patients with breast cancer, as the study supports the safety of temporary treatment breaks for those who need them.

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1. Colleoni M, Luo W, Karlsson P et al; SOLE Investigators. Extended adjuvant intermittent letrozole versus continuous letrozole in postmenopausal women with breast cancer (SOLE): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol. 2018 Jan;*19(1):127-138

ARON
THE EDUCATOR AND MENTOR

When Professor Aron Goldhirsch attended a major breast cancer congress, it could take him half an hour to move from one meeting room to another – so many people wanted to stop and chat with him about his and their own research.

As a young oncologist working in Milan in the early 1990s, **Professor Angelo Di Leo**, now Head of the Sandro Pitigliani Medical Oncology Unit and Chair of the Oncology Department, at the Hospital of Prato, Istituto Toscano Tumori, Italy, fondly remembers going to congratulate Goldhirsch on a presentation and starting a professional relationship that was to last over 20 years – despite the fact that they never worked in the same institution.

"I have never met anyone who was so generous and supportive of young oncologists," says Professor Di Leo.

In the early pre-email days of the friendship, he and Goldhirsch kept in touch by letter and fax, but when Goldhirsch moved to Milan as Head of Medical Oncology at the European Institute of Oncology, they would meet regularly to discuss research.

"Despite the fact that we were working in what could be seen as competing institutions, we would often meet and discuss our research. He was so kind and charismatic and it was a great opportunity for a young oncologist to interact and learn from him, and then to collaborate with him and others on clinical research," says Di Leo.

"One of the first things I learned from Aron was that it doesn't matter where you work, you need to be part of an international network of high quality researchers so that you can learn, grow and express yourself," he adds.

In the 1990s, Goldhirsch began to question the established belief that all patients with breast cancer would benefit from the same approach to treatment. At conferences and in publications, he urged clinicians to take account of the clinical behaviour and biology of each tumour and the personal characteristics of each patient – their age and expectations and, not least, how they wanted their cancer to be treated.

"Today, everyone talks about personalised treatment and understanding the wishes of patients, but in those days Aron's was an extraordinary message and not everyone was ready to hear it," explains Di Leo. "To me, as a young oncologist, it was like opening my eyes and seeing something completely unexpected."

Goldhirsch advocated that the first priority when diagnosing a patient with breast cancer was to establish whether they had a hormone receptor-positive tumour and, if this was the case, to establish its degree of sensitivity to endocrine therapy. Decades later, Di Leo teaches the same strategy to junior oncologists.

"It was a great change in the approach to breast cancer and the message is as true now as it was when Aron first proposed it," says Di Leo.

ENCOURAGING PATHOLOGISTS TO LOOK BEYOND THE MICROSCOPE

In the pathology lab, there were fundamental changes too. With the emphasis moving towards personalised therapy based on tumour biology, the pathologist's report became increasingly important in guiding treatment decisions. **Professor Giuseppe Viale**, who had 'grown up' looking at slides in the laboratory and reporting his findings, now needed to address the clinical implications of his findings.

"Aron taught me that there was a patient behind the microscope, and he wanted me to interpret the morphology and biology of each patient's tumour in the light of the patient's symptoms and treatment. He wanted me to understand that every single word and figure in my reports had clinical implications for the patient," Viale explains.

With the growing importance of the pathologist's report came an increased need to investigate inconsistencies in results – to check and double check data and, where necessary, to repeat tests.

"As a result of the lessons I learned from Aron, I now teach my colleagues and residents that, before they sign out any pathology report, they must not only read it, they must also try to assign the correct treatment for that patient. If you cannot do that, there is something wrong in your report and you must look again," says Viale.

Goldhirsch's message related not only to the biological and clinical personalisation of breast cancer therapy – the pathology results, the gene expression data and the scans – it also focused on the humanity of the patient.

"Aron told us to look beyond the test results at the patient in front of us – the young woman with children or the older lady who was still very active and valued her independence. As well as being doctors, we must be human beings who not only understand the cancer but also listen and respond to the personal needs of the patient," says Di Leo.

INVESTING IN YOUNG DOCTORS

For over 20 years, **Professor Marco Colleoni** also benefited from a close working relationship with Goldhirsch:

"Aron was convinced that we should invest in young doctors and researchers because they are the future. Each week we'd discuss a large number of cases at the multidisciplinary meeting and he spent a lot of time stimulating discussion, asking questions and giving explanations," he says.

Goldhirsch routinely included younger doctors in his clinical activities so they could learn from him how to listen and talk to patients. He also ensured that they understood the importance of these patient interactions for providing new ideas for clinical trials to answer clinical questions arising from consultations.

Like so many people who worked with Goldhirsch, Colleoni feels that he was years ahead of his time:

"Aron's mission was to provide the best personalised care for the individual patient with breast cancer,

with full respect for quality of life and proper communication. Personalised treatment is very popular now, but I started to learn about it more than 20 years ago when Aron came to the Institute and we started to work together."

WELCOMING CONTROVERSY AT ST. GALLEN

Amongst the many educational initiatives in which Goldhirsch was involved, the St Gallen International Breast Cancer Consensus Conference, of which he was Scientific Co-Chair for 30 years, has had implications for breast cancer care in clinics across the world. At this biennial meeting, leading specialists present state-of-the-art lectures with latest data on aspects of breast cancer research. Following extensive discussion, an expert panel makes recommendations on how these developments should be applied in daily practice.

Professor Beat Thürlimann explains that, in the early years of St. Gallen, the focus was on setting minimal standards of care. However, in the early 2000s, Goldhirsch proposed a change of direction.

"Aron suggested that St. Gallen should focus on controversies in breast cancer to try to provide clarity on questions of greatest importance to clinicians and patients. He wanted to produce recommendations that would form the basis of discussions between patients and doctors to help them decide treatment tailored to their medical needs as individuals," says Thürlimann.

He explains that, in making recommendations rather than drawing up guidelines, Goldhirsch wanted the St. Gallen consensus reports to provide flexibility for clinicians practising in different healthcare systems.

"Aron wanted doctors treating breast cancer to be guided by the same principles wherever they worked. But he didn't want the latest evidence alone to dictate how they worked, as this might not be possible in some countries," adds Thürlimann.

As a result, each update of the St. Gallen recommendations is highly respected worldwide, and the consensus views that are expressed are often reflected in national and international guidelines. While not prescriptive, the St. Gallen recommendations continue to summarise current thinking and, as Goldhirsch and his early collaborators intended, support clinicians in addressing the daily challenges of optimising patient care.

INSPIRATION AND ROLE MODEL

Dr Giuseppe Curigliano estimates he had over 10,000 early morning coffees with Goldhirsch in the 10 years he worked with him! At 7am, they would chat about their work, their families, their lives and their interests before starting their day.

"Aron was fundamentally a very good man. He was born in a refugee camp after the war, before moving to Israel, and so the Second World War was a big part of his history. But he would say: 'I don't want to waste my resources fighting the past, I want to invest them to build the future'. It was a lesson for me and one that I apply in my own life," says Curigliano.

He explains that Goldhirsch was a mentor par excellence. During many years of the weekly 'Journal Club', Curigliano and other young doctors learned to critique papers to understand their relevance for their own patients. Goldhirsch impressed upon them the importance of excellence and innovation.

"In his mind, the only way to drive excellence was to innovate and, through innovation, we would be able to help our patients," says Curigliano.

Goldhirsch was also a good listener, he says, always ready with the right words at the right time and always finding time to listen to, advise and support his colleagues.

"Everyone knows that Aron was a great scientist and researcher and had a beautiful mind, but he was also immensely loyal including to his juniors. He was a great man."

ARON INTERVIEW

20 years of progress in endocrine treatment for breast cancer

Two years ago, Professor Aron Goldhirsch discussed some of the most important developments in endocrine therapy for breast cancer with medical journalist, Jenny Bryan, drawing on a wealth of knowledge and his own many contributions to research and clinical practice. A shorter version of this interview was published in BIG's 2018 Annual Report and its 2019 publication "Hope and Progress", which celebrated 20 years of progress in breast cancer research since BIG was established. Now, we share Aron's more detailed insights and expectations for endocrine therapy as an essential part of breast cancer treatment.

What were the key stages in the evolution of endocrine therapy to its current role in women with breast cancer?

Endocrine therapy has made a major contribution to the improvement in breast cancer survival that we have seen in recent decades and was recognised as efficacious even before the existence and role of oestrogen receptors was understood.

Empirical application of hormonal treatment, such as ovarian ablation, was documented as causing regression of breast cancer, together with other endocrine therapies for pre-menopausal women with the disease. But decades elapsed before their role was defined in endocrine-responsive breast cancer.

The recognition of oestrogen receptors as essential for identification of endocrine responsiveness, and the appreciation that different endocrine modalities were needed for pre- and post-menopausal women, were essential steps in the development of the endocrine approach we use today.

The arrival of selective oestrogen receptor modulators (SERMs) and degraders (SERDs), non-steroidal and steroidal aromatase inhibitors, and more recently endocrine potentiating agents, such as m-TOR and CDK 4/6 inhibitors, has led to treatment changes in the adjuvant setting (after surgery) for early breast cancer and for women with advanced disease.

Defining standards of care for endocrine therapies can take a long time, especially in the adjuvant setting, because of slow event rates. Even so, clinical research has now enabled us to define new standards of care both for women needing adjuvant treatment in the earlier stages of breast cancer and for those with advanced disease, and this is an important achievement.

With the growing range of options for endocrine therapy, how do clinicians decide what to recommend for each patient?

Clinical trials are designed to define the efficacy and safety of a treatment but not how to treat each individual. Our patients don't just have a particular stage of breast cancer, they have their own history of past and concurrent diseases such as cardiovascular disorders, which may mean that some drugs are contraindicated. For example, tamoxifen is still a wonderful drug, but we now know that it is contraindicated in women who have had a deep vein thrombosis. Adapting treatment to each patient is complex but, in the adjuvant setting, we have, for many years, defined risk of relapse based on the grade of their tumour, the extent of their disease and the degree of proliferation. However, now that we have a broader range of effective treatments, especially for higher risk disease, we have been able to refine our risk classification so that patients can be treated according to their individual level of risk, with more intensive treatment for those at highest risk.

The BIG trials of endocrine therapy in early breast cancer – BIG1-98 (IBCSG 18-98) in post-menopausal women and SOFT (BIG 2-02 / IBCSG 24-02) and TEXT (BIG 3-02 / IBCSG 25-02) in pre-menopausal women – have played an important role in helping to define risk so that we can adapt treatment for each patient.

How effective is endocrine therapy for breast cancer today compared with 20 years ago?

This is a tricky question. Endocrine therapies are very effective in endocrine-responsive disease. They were effective in the past and continue to be effective. We have learned to better select patients according to risk, and we have learned how to combine endocrine approaches (ovarian function suppression, aromatase inhibitors, tamoxifen). We have also learned how to potentiate endocrine treatment by the addition of drugs, such as mTOR or CDK4/6 inhibitors.

Suffice it to say that these new treatments are more efficacious than treatments of the past. To quantify the degree of improvement in terms of disease-free survival or overall survival is impossible since it is entirely dependent upon patient selection and disease characteristics rather than on the treatment.

As well as the risk-adapted choice of adjuvant endocrine therapy for pre- and post-menopausal patients, we are seeing a fine-tuning of selection of patients whose disease has been defined as endocrine-responsive. As a result of the TAILORx (ECOG-PACCT-1) and MINDACT (BIG 3-04 / EORTC 10041) studies, we are seeing a reduction in the need for additional chemotherapy in patients whose disease has been defined as exclusively endocrine-responsive.

For patients with advanced disease, we are seeing the opportunity to increase the efficacy of available endocrine agents with the addition of compounds to potentiate response rate and duration.

For patients with "triple positive" disease – those whose tumours are oestrogen and progesterone receptor-positive, and HER2-positive – we are seeing promising results with the combination of endocrine therapy and anti-HER2 treatment, in association with a CDK 4/6 inhibitor, which may mean that we can avoid the use of chemotherapy in patients with HER2-positive breast cancer.

What are the goals of endocrine therapy research today?

We need to develop additional compounds which improve the efficacy of endocrine agents. The fact that less than half of patients with high oestrogen receptor levels have useful disease regression with endocrine therapy is an indication that we need to develop treatments to improve disease control when given with endocrine therapies.

We see endocrine responsiveness in 60% to 65% of patients with breast cancer, but the degree of responsiveness is defined by the proportion of cells that harbour oestrogen receptors, and this can be quite variable. Even when receptors are present on 90% or 95% of cells, we may see mechanisms that undermine or damage endocrine responsiveness. There may be overexpression of HER2 or the presence of cells with a tendency to proliferate despite endocrine agents. For example, in patients with high Ki-67 proliferation markers, endocrine responsiveness diminishes even in cells with a lot of oestrogen receptors. CDK4/6 inhibitors were developed to address this problem and introduce another method of blockade.

In contrast, in lobular breast cancer, which is responsible for about 50% of cases, tumours may be very responsive to endocrine treatments even if levels of oestrogen receptors are low. So, this is an important area for new investigation to find out how lobular cancers should be treated.

I would also like to see research into the potential of gonadotrophin-releasing hormone antagonists in the treatment of breast cancer. In the SOFT and TEXT trials we already showed the benefits of adding gonadotrophin-releasing hormone agonists, but antagonists are only used in prostate cancer. I've been trying for years to get these drugs tested in breast cancer, but without success.

Most of all, we need to ensure that promising new treatments are properly tested in well-designed clinical trials before they are widely used. We should never forget that over 10,000 patients with breast cancer were treated with high-dose chemotherapy and bone marrow support before clinical trials showed that it had no effect. We should have learned from this lesson, yet we are currently seeing patients routinely receiving adjuvant therapy with the CDK4/6 inhibitor palbociclib, despite the lack of data in the adjuvant setting. We should all be waiting for the results of the PALLAS trial (BIG 14-03 / ABCSG-42), before considering this treatment for our patients.*

Do you think that endocrine therapy will always be needed for breast cancer, or do you see a time when more specifically targeted treatment will have taken over?

This is an interesting question. Endocrine therapies are treatments targeted mainly towards oestrogen receptors. There is no doubt that some endocrine therapy will always be needed for blocking progression of a hormone-responsive breast cancer. The way to combine endocrine agents with other drugs that might either block endocrine resistance or add a non-endocrine effect where needed is the true challenge for the future.

Efficacy of endocrine therapies is hard to study in trials, because the event rates are distributed over a longer period of time than, for example, non hormone-responsive disease. This difficulty should indicate to researchers and to regulatory agencies that longer duration trials are needed, and longer duration of drug patents must be considered if we are to make an impact on the treatment of hormone-responsive breast cancer. It's a chronic disease that can continue for many years. We already have useful treatments that enable patients to lead symptom-free lives even after three, four or five lines of treatment, but there is still a need to find further treatments to potentiate the effects of endocrine therapy in the long term.

*In May 2020, following a pre-planned efficacy and futility analysis, the Data Monitoring Committee of the PALbociclib coLlaborative Adjuvant Study (PALLAS) determined that the trial was unlikely to show a statistically significant improvement in the primary endpoint of invasive disease-free survival and recommended to stop therapy with palbociclib. No new safety signals were observed in patients receiving palbociclib, which has been proven effective in advanced breast cancer. The study, run in collaboration with BIG and sponsored by the Austrian Breast & Colorectal Cancer Study Group (global sponsor) and Alliance Foundation Trials (sponsor for North America), compares the combination of palbociclib and standard adjuvant endocrine therapy for two years followed by continuing standard adjuvant therapy versus at least five years of standard adjuvant endocrine therapy in pre- and post-menopausal women or men with HR+, HER2- early invasive (Stage 2 and Stage 3) breast cancer, including those at moderate to high risk of recurrence. The study will continue to follow patients and conduct translational research.

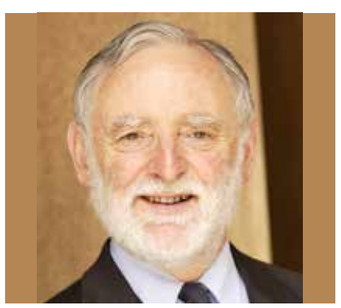
BIG THANK YOU

BIG would like to thank Aron's good friends and colleagues for their fascinating recollections and insights that have helped us honour an inspirational oncologist who leaves behind a lasting legacy.

"All for One, One for All"

DAVID CAMERON

Professor of Oncology, University of Edinburgh, UK
BIG Chair



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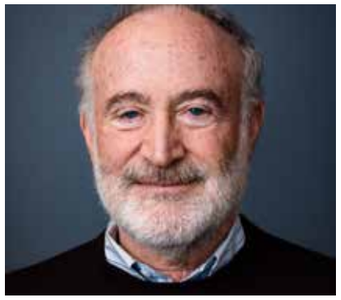

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ABOUT BIG

THE BIG NETWORK: GLOBAL RESEARCH COLLABORATION TO CURE BREAST CANCER

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

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

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

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

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

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

AFRICA

BGICS Breast Gynaecological International Cancer Society

ASIA

BDPCC Breast Disease Professional Committee of CMEA
BIEI Breast Intergroup of Eastern India
CTRG Cancer Therapeutics Research Group
HKBOG Hong Kong Breast Oncology Group
ICON ARO Indian Co-operative Oncology Network
IOSG Indian Oncology Study Group
JBCRG Japan Breast Cancer Research Group
KCSG Korean Cancer Study Group
SKMCH & RC Shaukat Khanum Memorial Cancer Hospital & Research Centre
TCOG Taiwan Cooperative Oncology Group
TSCO Thai Society of Clinical Oncology

AUSTRALASIA

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

EUROPE

ABCSG Austrian Breast & Colorectal Cancer Study Group
AGO-B Arbeitsgemeinschaft Gynäkologische Onkologie Breast Study Group
BOOG Borstkanker Onderzoek Groep
CEEOG Central and East European Oncology Group
CT-IRE Cancer Trials Ireland
DBCG Danish Breast Cancer Cooperative Group
EORTC BCG European Organisation for Research and Treatment of Cancer Breast Cancer Group
FBCG Finnish Breast Cancer Group
GBG German Breast Group
GCSG Georgian Cancer Study Group
GEICAM Spanish Breast Cancer Group
GOIRC Gruppo Oncologico Italiano di Ricerca Clinica
HSBS Hellenic Society of Breast Surgeons
HeCOG Hellenic Cooperative Oncology Group
HORG Hellenic Oncology Research Group
IBCG Icelandic Breast Cancer Group
IBCSG International Breast Cancer Study Group
IBIS International Breast Cancer Intervention Studies
ICCG International Collaborative Cancer Group
ICR-CTSU Institute of Cancer Research - Clinical Trials & Statistics Unit
IJB-CTSU Institut Jules Bordet Clinical Trials Support Unit
ITMO Italian Trials in Medical Oncology
MICHELANGELO Fondazione Michelangelo
NBCG Norwegian Breast Cancer Group
NCRI-BCSG National Cancer Research Institute - Breast Cancer Clinical Studies Group
SABO Swedish Association of Breast Oncologists
SAKK Swiss Group for Clinical Cancer Research
SLO Société Luxembourgeoise d'Oncologie
SOLTI Breast Cancer Research Group
SUCCESS Study Group
SweBCG Swedish Breast Cancer Group
UCBG Unicancer Breast Group
WSG Westdeutsche Studiengruppe

LATIN AMERICA

GAICO Grupo Argentino de Investigación Clínica en Oncología
GECO PERU Grupo de Estudios Clinicos Oncologicos Peruano
GOCCHI Chilean Cooperative Group for Oncologic Research
GOCUR Grupo Oncológico Cooperativo Uruguayo
LACOG Latin American Cooperative Oncology Group

MIDDLE EAST

IBG Israeli Breast Group
ICRC Iranian Cancer Research Center
SBCG Sheba Breast Collaborative Group

NORTH AMERICA

CCTG Canadian Cancer Trials Group

BIG
Breast International Group

BIG against breast cancer

TOGETHER

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