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Like in most parts of the world, South Asia is not spared the global cancer epidemic. While breast cancer incidence is comparable to that in western countries, mortality rates, in contrast, do not tend to fall. Indeed, every year in South Asia one in two women diagnosed with the disease is likely to die from it.

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, this edition focuses on India and Pakistan.

Meet Dr Gouri Shankar Bhattacharyya from the Indian Co-operative Oncology Network (ICON ARO), Drs Mazhar Ali Shah and Farah Rasheed from the Shaukat Khanum Memorial Cancer Hospital & Research Centre (SKMCH & RC), Pakistan, and Dr Sudeep Gupta from the Indian Oncology Study Group (IOSG), who share their experience and in-depth insight into cancer research in their respective countries.

Among the major challenges faced by breast cancer specialists in South Asia, Dr Bhattacharyya and colleagues point out the limited access to cancer diagnosis procedures and treatments, especially in rural areas, as well as the struggle to get funding. Beyond this, there is a lack of awareness about breast cancer in some segments of the population, which often leads to late presentation and poor outcome.

These cancer experts are set on taming the disease in their countries by improving uniformity of care, developing education campaigns, and prioritising research to address the needs of their patient populations. Moreover, they are confident that South Asia can play a bigger role in global breast cancer research in the near future, by offering qualified physician-investigators and large numbers of patients. They would like to be more involved in international studies and strengthen collaboration with other research groups from around the world, hence their commitment to the BIG network.

ICON ARO, SKMCH & RC and IOSG are among the 59 collaborative member groups comprising the BIG network. Taking all groups together, BIG represents over 10,000 experts present across six continents, which makes it the largest international academic research organisation dedicated to finding a cure for breast cancer.

The specificity of BIG is to be both global and local. By joining efforts and sharing expertise, data and resources, BIG member groups are able to advance research more rapidly and tackle global challenges, all while being aware of the specific needs of each population.

This “glo-cal” approach is also reflected in our Executive Board (EB), which now represents 11 different countries and multiple cultures. Five new representatives joined the BIG EB in June 2018, bringing along their expertise, commitment and vision for a future without breast cancer. In this newsletter we are happy to introduce you to Drs Carlos Barrios (LACOG, Brazil), Philippe Bedard (CCTG, Canada), Etienne Brain (EORTC BCG, France), Eva Carrasco (GEICAM, Spain) and Nick Turner (NCRI BCSG and ICR-CTSU, UK).

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

We hope you enjoy the reading.
With at least 200,000 women diagnosed with breast cancer each year in South Asia and nearly 100,000 dying from the disease, healthcare providers face a formidable challenge. Add the fact that the South Asian population is spread across over 5 million km², and that most people live in rural areas hundreds of miles from major cities, some days, the task must seem overwhelming.

In India, where nearly three quarters of the region’s patients with breast cancer are diagnosed, incidence is rising but, in contrast to more developed countries, mortality is not yet starting to fall. According to different registries, 35-60% of women present late – with advanced or metastatic breast cancer – and nearly 30% have triple negative breast cancer (TNBC), so it is not hard to see why mortality remains static.

Lack of awareness of the disease and poor access to standard diagnostic procedures and treatment, especially for women living in rural areas, are at the root of the problem of late diagnosis.

Dr Gouri Shankar Bhattacharyya, consultant medical oncologist in Kolkata, India, and World Health Organisation Steering Committee Member for Oncology, believes that greater health literacy is the way forward: “In India, our main priority is to take away the fear and stigma of breast cancer so that women seek help earlier. Only by making them more ‘aware’ of breast cancer diagnosis and treatment, can we help them to ‘beware’ of the signs and symptoms which should take them to their doctor.”

Dr Bhattacharyya explains that progress is being made in improving awareness in schools and colleges in urban areas, but the message has yet to reach women in rural communities. Breast screening is not available in India and the aim is therefore to encourage self-examination and provide better clinical support, including from more nurse practitioners, with opportunities for mammography for those with a lump.
Breast cancer specialists in Pakistan have similar priorities. Breast cancer incidence is already comparable to that in the west, with a similar TNBC rate to India, and mortality is the highest in Asia. Dr Mazhar Ali Shah, consultant radiation oncologist at Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, is committed to running breast cancer awareness campaigns and wants to see sustained, far reaching education across Pakistan.

“We need to educate both women and men in rural areas that this is a curable disease in the early stages so that men understand the importance of taking their wives and other female relatives to hospital.”

Dr Mazhar Ali Shah (Pakistan)

Alongside better health literacy must come greater uniformity of care, including availability of infrastructure for diagnosing and treating breast cancer, says Professor Sudeep Gupta, professor of medical oncology at Tata Memorial Centre, Mumbai, India, and Past Convenor of the Breast Cancer Working Group. He explains that mammography and pathology facilities, including immunohistochemistry for ER, PR and HER2 testing, are available in major cities in India but less in tier-2 cities and smaller towns:

“In the last five years, a lot of progress has been made to standardise mammography and pathology testing in laboratories in India, but we now need to bring more laboratories to this level of quality control, and increase access. We also need to create nationwide expertise in all the specialties needed to deliver care for patients with breast cancer, from surgeons and oncologists to physiotherapists and lymphoedema specialists.”

In Pakistan, breast cancer care is also based mainly in larger cities and, although surgery and chemotherapy are typically available, there is a shortage of centres offering radiotherapy, explains Dr Shah. There is also limited availability of trastuzumab or pertuzumab to women with HER2+ disease, though a Roche-funded programme provides free drugs for half a course of treatment where funding can be found for the remaining treatment.

In India, the National Cancer Grid, coordinated by the Tata Memorial Centre, aims to boost uniformity of care (https://tmc.gov.in/ncg/). It already brings together over 130 public and private hospitals treating cancer to harmonise management guidelines for breast and other cancers, and monitor implementation of evidence-based treatment. As part of this initiative, clinicians from Grid centres come together each week for a Virtual Tumour Board to discuss cancer cases that would benefit from multi-institutional input.

The National Cancer Grid is a valuable resource for the ‘hub and spoke’ model of cancer care delivery being developed in India. The aim is to provide specialist diagnostic and treatment options at a relatively small number of hubs and to ensure that standard procedures and chemotherapy are available at ‘spoke’ hospitals closer to the homes of women living away from major cities.

“By harmonising guidelines in all these centres and agreeing minimal quality parameters, we believe we can go a long way towards achieving uniformity of care in India,” concludes Professor Gupta.
Making research relevant to South Asia

In addition to taking steps towards greater uniformity of care, there is a need for research addressing the specific needs of women with breast cancer in South Asia. Although some research priorities in South Asia are the same as those in the US and Europe, others reflect the very different patient population.

Despite its vast population and growing incidence of breast cancer, South Asia’s contribution to research is small – with 1.4% of breast cancer trials listed on clinicaltrials.gov being carried out in the region, nearly all of them in India. Nevertheless, South Asia’s breast cancer researchers are making important contributions to the world literature, together with advances that are locally relevant and implementable.

In 2015, Professor Gupta and colleagues published results of an open-label, randomised controlled trial which showed there was no survival advantage of locoregional treatment of the primary breast tumour in women with metastatic breast cancer at initial presentation.1 “This study showed, for the first time, that surgical removal of the primary tumour is not useful in women with metastatic cancer and has led to a change in practice,” says Professor Gupta.

Of local importance has been a breast cancer study carried out by the Tata group which showed that both sentinel node biopsy and low axillary sampling, based on defined anatomical correlates of the lower axilla, were associated with a similar false negative rate.2 “We showed that, in non-specialist hospitals, where gamma cameras and specialist expertise are not available, it is still possible to accurately assess lymph node involvement without needing to carry out full axillary dissection. As a result, this technique is now being used in many hospitals in India,” he says.

In a third piece of research, the group showed that a single injection of hydroxyprogesterone before primary breast cancer surgery was beneficial for women with node-positive operable disease.3 Through a collaboration with the National Institute of Biomedical Genomics in West Bengal, they subsequently showed progesterone-related upregulation of genes indicative of a favourable effect on surgical stress.4 “In several institutions in India, depot injection of progesterone has become the standard of care for women with node-positive breast cancer prior to surgery. However, as our original findings were from a sub analysis of a single-centre randomised trial, the results are now being validated in a multicentre randomised trial, and additional in vitro research is being carried out to further investigate the underlying mechanism,” says Professor Gupta.

As cost is an important consideration for diagnostic procedures and treatment for women with breast cancer in India, other research is focusing on reducing treatment costs and enhancing survivorship.

“Treatment has to be accessible and affordable, otherwise the benefits are offset by what I call financial toxicity. We need to identify treatments that women can afford and will still give them good results and quality of life,” explains Dr Bhattacharyya.

Dr Bhattacharyya points out that the best treatment may not always be optimal treatment, especially if the cost is far beyond the means of many Indian women.

With this in mind, he and colleagues have carried out studies of drug combinations for women with advanced breast cancer that avoid the latest, most expensive agents. For example, they have demonstrated the benefits of adding sirolimus to tamoxifen in women with metastatic ER+, PR+, HER2-breast cancer who could not afford aromatase inhibitor (AI) treatment.5 Sixty-eight per cent of women responded to the combination, with a time to progression of 16 months, compared to 36% and nine months for tamoxifen alone. In a second study of women with metastatic ER+, PR+, HER2-disease for whom tamoxifen and/or an AI failed, response rates were 40% with the tamoxifen/sirolimus combination versus 4% with tamoxifen. Time to progression was 11 months and three months respectively.
Similarly, Dr Bhattacharyya and his team showed that commonly used, affordable drugs (weekly cisplatin for six out of eight weeks, daily low dose endoxan and intermittent low dose methotrexate) are a realistic alternative to the bevacizumab and weekly paclitaxel and carboplatin combination that is used to treat women with TNBC who have relapsed after taxane and anthracycline treatment. They reported a 62% response to the cisplatin/endoxan/methotrexate combination, compared to 30% when platinum was left out of treatment. Time to progression was 13 versus seven months respectively, and they are now exploring further combination options in TNBC.

The strong generic drug industry in India means rapid availability of generic products when patents on branded drugs run out. For example, trastuzumab is now available to up to 65% of women with HER2+ breast cancer treated at Tata Memorial Centre, compared to just 4-5% when it was a branded product. However, Dr Bhattacharyya would welcome research aimed at identifying women less likely to benefit from trastuzumab, so even money spent unnecessarily on generic treatment can be put to better use.

To address the difficulty of getting access to novel treatments, Dr Bhattacharyya is taking a novel approach – exploring how to repurpose inexpensive drugs that are established in other areas of medicine. For example, he is investigating the potential anti-angiogenic effects of beta blockers in cancer, and the possibility that the anti-cyclooxygenase 2 effects of aspirin can be exploited to inhibit tumour cell proliferation.

“By repurposing drugs that are widely available in India and are affordable to a much larger population than the latest treatments, we hope to make valuable advances for women with breast cancer that improve survival and enhance quality of life.” – Dr Gouri Shankar Bhattacharyya (India)
Research priorities in Pakistan

Why is the prevalence of breast cancer in Pakistan so high when few women have the ‘textbook’ risk factors for the disease? This is the question which Dr Shah would very much like research to investigate.

He points out that most women in Pakistan marry young, are likely to be multiparous and breast feed each of their children for 18 months to two years. Women are not obese, do not smoke or drink or use oral contraceptives or hormone replacement therapy (HRT), and have a simple, non-western lifestyle. So it is difficult to understand why breast cancer is so common.

“There must be something else that has not been considered, and we would love to investigate – if we could get funding,” says Dr Shah.

At the Shaukat Khanum Memorial Cancer Hospital and Research Centre, in Lahore, which has state-of-the-art facilities comparable with those in Europe and the USA, he and colleagues have already conducted research on BRCA prevalence amongst the large numbers of women who come to their walk-in clinic from across Pakistan, and from Afghanistan. Funded by charitable donations, the Centre can treat about 1,200 new patients with breast cancer per year, but that is a fraction of those who come to the door.

Dr Shah explains that about 75-80% of patients receive free treatment, including hormone treatment for five to six years for those with hormone-sensitive tumours. As treatment is free, it is impossible to help everyone, and so the Shaukat Khanum team focuses on young women with newly diagnosed, aggressive disease.

“We have plenty of patients and well-trained doctors, so we could do far more breast cancer research in Pakistan than is currently being achieved. By getting more women into clinical trials, we would then have the resources to treat a higher proportion of those who come to our walk-in clinic,” he says.

Dr Farah Rasheed, Clinical Research Administrator at Shaukat Khanum, explains that, while clinicians at the Centre have participated in international clinical trials sponsored by pharmaceutical companies, researchers generally struggle to convince funding bodies to bring their studies to Pakistan.

“We have a pool of trained oncologists who are qualified physician-investigators with international experience, and they could help to address the under-representation of Pakistan in major international breast cancer trials – something which threatens the validity of global research,” she says.

She is frustrated that breast cancer specialists in Pakistan are routinely told they will not be considered for large clinical trials.

“Typically, we indicate our expression of interest and demonstrate that we have qualifying sites with infrastructure and expertise, but we are told we will not be considered, not because we do not qualify, but because of the decision of the sponsor,” says Dr Rasheed.

She highlights recent successful clinical trial collaborations with organisations such as the London School of Hygiene and Tropical Medicine, in which Pakistan was among the highest recruiting countries, as evidence that trials are not hindered by regulatory issues in Pakistan. She and Dr Shah are keen to encourage a national network of cancer research in Pakistan to enable clinicians to showcase achievements as evidence of their ability to contribute at international level. This will require government funding and a concerted effort to push cancer research higher up the national health agenda.

Dr Shah believes that, with national and foreign investment and commitment, it will be possible to build strong foundations for cancer research in Pakistan and a culture of encouraging and training researchers:

“We have so much to offer in terms of excellent doctors and large numbers of patients who would be prepared to get involved in research. We have the seeds, we just need the fertiliser to grow a research organisation that can bear plentiful fruit for the wider breast cancer community.”

Dr Farah Rasheed (Pakistan)
Clinical research in India is entering a new period of stability, following five years of uncertainty arising from regulatory reforms in 2013. Initial reforms enabled study participants to claim compensation if they gained insufficient benefit from investigational drugs or placebo treatment, and threatened to jeopardise Indian involvement in major trials. However, subsequent amendments mean that compensation is only payable if access to an available standard of care is not provided. As a result of the revisions, clinical research in India has started to recover and, currently, 282 breast cancer clinical trials are recorded on the Clinical Trials Registry – India, compared to 77 in 2012.8

“In the last two years, the regulatory situation has been largely resolved and processes simplified and streamlined so that most trials get speedy approval. As a result, a slew of trials that were previously held up are now being opened up to research centres in India,” says Professor Gupta.

He explains that there is still a shortage of investigator-led and cooperative group studies in India and, though he is optimistic that organisations such as the National Cancer Grid and the Indian Cooperative Oncology Group (ICON) will encourage greater collaboration, funding remains a major issue.

“There is no systematic funding mechanism for clinical trials. We have had a lot of discussions with the federal government and hope that this will change and that funding will soon become available for clinical trials in non-communicable diseases, such as cancer,” says Professor Gupta.

Through ICON (www.oncologyindia.org), there are growing opportunities for collaboration within India and beyond, and Dr Bhattacharyya explains that progress is being made in encouraging wealthy donors to fund research through corporate social responsibility initiatives. Considerable effort is also going into educational campaigns to overcome patient fear about taking part in clinical research, and it is hoped that better understanding of the new, more rigorous regulatory climate will go some way to dispelling these fears.

Although Indian researchers did contribute to some of BIG’s major trials, such as ALTTO and NeoALTTO, Dr Bhattacharyya regrets that cancer researchers in India are not included in more international trials and feels there is a misguided assumption that they will not deliver.

“People assume that setting up trials in India is too difficult, but that is not the case, and gaining regulatory approval for trials is not a big issue,” he says.

Both he and Professor Gupta would like to see more partnerships between Indian researchers and international research organisations, including technical expertise and support in setting up laboratory assays, which are increasingly important in translational and biomarker-guided studies.

“We are already collaborating with the Medical Research Council Clinical Trials Unit in the UK in the Add Aspirin study, which includes 3,400 patients with breast cancer. This has great clinical potential if we can see a benefit from using something as cheap as aspirin, and it has also been very worthwhile to understand the statistical and logistical aspects of setting up such a large trial,” says Professor Gupta.

Both he and Dr Bhattacharyya are optimistic that India can and will play a greater role in breast cancer research:

“I am convinced that, over the next five years we will see the road to India becoming established for clinical research and, in 10 years, India will be considered an established destination showing the way forward in research,” says Dr Bhattacharyya.

“We have the manpower, we are hard-working, and we have a lot of patients, so I am very optimistic that the conditions will be right for breast cancer research in India.”

“In the last two years, the regulatory situation has been largely resolved and processes simplified and streamlined so that most trials get speedy approval. As a result, a slew of trials that were previously held up are now being opened up to research centres in India.”

Professor Sudeep Gupta (India)
Breast cancer is the most common cancer in women in India and Pakistan, and the second most common in Bangladesh and Nepal, after cervical cancer.9-12 Although breast cancer incidence in India, Bangladesh and Nepal is much lower than the global average (Table 1),1,3 there are considerable variations around these countries. For example, incidence ranges from 12.4 per 100,000 in rural Barshi to 41 per 100,000 in Delhi.9

Recently published data from the Sri Lanka National Cancer Registry show a steady increase in breast cancer incidence of about 4% per year, with the greatest increase in women aged 60-64 years.14 While some of the increase was attributed to better diagnosis and recording of cases, worsening obesity, especially in older women, and trends towards delayed childbearing, smaller families and western lifestyle are likely to have played a part.

The incidence of TNBC in India and Pakistan appears to be the highest in the world, with estimates up to approximately 30% according to various analyses; moreover, the disease occurs at a younger age than in most other countries.15,16 Although testing facilities are limited in most of South Asia, an incidence of TNBC of just 9% has been reported in Bangladesh.17 In India, there is a familial link in approximately 5% of breast cancer cases, and BRCA1/2 mutations have been reported in 2.9%-24% of women with familial breast cancer.9

A higher proportion of women diagnosed with breast cancer in South Asia are premenopausal than in western countries. The mean age of women newly diagnosed with breast cancer at the National Institute of Cancer Research and Hospital in Dhaka, Bangladesh, from 2005-2010, was 41.8 years, and 56% were aged 15-44.17 Similar findings have also been reported in India but may partly reflect the fact that older women are more reluctant to seek help.15

Late presentation across South Asia is a major factor in the high mortality rate in the region, and approximately half of women with breast cancer in India and Pakistan present with Stage III/IV disease.18,19 This is reflected in a five-year survival rate of 66.1% in women diagnosed with breast cancer in India in 2010-2014, compared to 89.5% in Australia and 90.2% in the USA.20 While breast cancer kills one in two women diagnosed with the disease in India, only one in six women diagnosed in the USA is likely to die of it.21

Breast cancer treatment across South Asia is variable, with a small proportion of patients treated at specialist centres offering treatment comparable with that in Europe and the USA. Reports from Nepal and Bangladesh suggest that, without standardised treatment protocols, many women undergo inappropriate or incomplete surgical excision at district or community level and few women receive breast-conserving surgery or post-mastectomy reconstruction.12,17 A wide range of chemotherapy regimens are used, but outcomes and effectiveness are not reported, and palliative care is rarely available.17 Results of a recent study carried out in Nepal highlighted the negative impact of chemotherapy on women’s quality of life and the lack of emotional support.22 Participants also reported severe financial concerns. Researchers pointed out that Nepalese women are responsible for maintaining family harmony and expected to put family needs above their own, so families may be unaware of the needs of women undergoing chemotherapy for breast cancer.

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<th>South Asia</th>
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<th>Incidence ASR</th>
<th>Mortality</th>
<th>Mortality ASR</th>
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</tbody>
</table>

ASR= age-standardised rate


Meet the experts

Dr Gouri Shankar Bhattacharyya  
Consultant medical oncologist  
Indian Co-operative Oncology Network (ICON ARO)  
World Health Organisation Steering Committee Member for Oncology  
Kolkata, India

Professor Sudeep Gupta  
Professor of medical oncology  
Tata Memorial Centre  
Indian Oncology Study Group (IOSG)  
Mumbai, India

Dr Mazhar Ali Shah  
Consultant radiation oncologist  
Shaukat Khanum Memorial Cancer Hospital and Research Centre (SKMCH & RC)  
Lahore, Pakistan

Dr Farah Rasheed  
Clinical research administrator  
Shaukat Khanum Memorial Cancer Hospital and Research Centre (SKMCH & RC)  
Lahore, Pakistan
Expansion of BIG Executive Board

In continuation of the organisation’s governance review and expansion that began in 2017, BIG is proud to welcome five newly appointed BIG Executive Board (EB) members: Dr Carlos Barrios, Dr Philippe Bedard, Dr Etienne Brain, Dr Eva Carrasco and Dr Nick Turner.

They join Dr Judith Bliss, Dr Boon Chua, Dr Marco Colleoni, Dr Barbro Linderholm, Dr Shinji Ohno, Dr Aleix Prat, and Dr Ander Urruticoechea, members of the EB since 2017, as well as Dr David Cameron, Dr Angelo Di Leo and Dr Sybille Loibl, elected in 2018 to serve an additional term. Dr Martine Piccart remains on the EB as chair, but discussions to select new officers are planned in Q4 of this year.

The new EB assumed its role on 1 July 2018, following the BIG General Assembly at ASCO in June 2018.

This expanded board well reflects the multiculturality and scientific know-how of the BIG network and is the main scientific and decision-making authority of the organisation.

Dr Nick Turner and Dr David Cameron were unfortunately unavailable for an interview for this edition of BIG Research in Focus.

“I believe BIG can be instrumental in developing academic trials that are essential for answering important questions that will not be covered by pharma sponsored studies.”

Dr Carlos Barrios (Brazil)
Breast cancer represents a significant challenge in many aspects. Recent data showing a dramatic decrease in the mortality rates (39%) in the US indicates that it is possible to improve these results in other parts of the world and cure a significant proportion of patients. A broad approach will be necessary, as we will need to address prevention, screening and early diagnosis strategies, as well as surgical treatment, radiotherapy and access to new medications as part of the process. BIG members cover many areas of expertise and, through active collaboration, I believe the organisation can be instrumental in developing academic trials that are essential for answering important questions that will not be covered by pharma sponsored studies. At the end of the day, research globalisation is an extremely positive process that finds in BIG an ideal platform.

During ASCO 2018, you presented an educational session on how to improve global breast cancer research. How do you think BIG could better leverage international collaboration, particularly between regions that face many challenges when it comes to healthcare in view of regional obstacles?

Dr Carlos Barrios, Brazil

What particular expertise do you think you will bring to the BIG EB?

I believe that my experience in the process of developing a multinational research infrastructure (LACOG) over the last 10 years in low-middle income regions of the world, such as Latin America and the Caribbean, is something that can help BIG to expand its influence to other regions of the world. Of note, over the next decade, most new cancer cases and cancer related mortality will be seen in low and middle-income countries, and clinical research undoubtedly is one of the major strategies to provide access and improve cancer care in these regions.

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Dr Etienne Brain, France

What particular expertise do you think you will bring to the BIG EB?

Through the EORTC, I have been exposed to the European research environment since the early 2000s. This has been an incredible and formative experience, because of both the multicultural aspects found across Europe and the historical academic commitment of EORTC to surpass frontiers. I want to share these two acquired particularities within the board to help address research questions with global effects, rather than highly specific drug- or refined disease setting-dependent ones, especially for neglected groups of patients such as the elderly.

What inspired you to pursue a specialisation in older patients? What are the challenges faced by older patients and their treatment options?

Dr Philippe Bedard, Canada

Could you please explain what motivated you to apply and serve on the BIG EB?

BIG is critical to the future of breast cancer clinical research. There is increasing global fragmentation of clinical trials driven by pressures from spiralling drug costs and diminished national funding for cooperative groups. I believe strongly that we need to work together as international academic investigators to carry out research studies that matter for our patients. I am motivated to be part of the BIG EB team to meet these challenges and help BIG lead the next wave of practice-changing trials.

You were once a fellow at BIG and worked with the organisation in the early years. How do you think BIG could foster more learning opportunities for early-career breast cancer specialists?

My fellowship at BIG was a highlight of my career. I was fortunate to be mentored by great leaders throughout the BIG network and formed lasting friendships with other fellows and BIG members. As the fellowship director for our drug development programme at Princess Margaret, I see how fellows can benefit from opportunities to develop their own research ideas. BIG has incredible clinical data warehouses and biological data from biospecimens collected through more than two decades of practice-changing trials in breast cancer. An annual open competition for fellows to submit their projects that leverage these resources and interact with BIG researchers on an ongoing basis until completion of their projects would engage a new generation of early career investigators.

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The current cancer research scenario is extensively regulated, which makes daily research very complicated and costly. Pharma, although playing an important role to introduce new drugs to the market, doesn’t support the full development of drugs. As a consequence, academic investigators have to do this work, although there is very limited budget for that. Within this scenario, the role of cooperative groups is crucial to cover the unmet medical needs that physicians dealing with breast cancer patients face daily in the clinic. The role of local groups such as GEICAM is very important in this matter, but in order to respond quickly to these needs, it is critical to collaborate with counterparts in other countries. For this international collaboration, BIG represents the perfect mechanism. This is why, since I joined GEICAM more than 8 years ago, I have tried to attend all BIG meetings to foster GEICAM’s collaboration within this network. For all these reasons I decided to apply for a position on the BIG EB with the aim to work hard to serve the best interests of breast cancer patients.

Dr Angelo Di Leo, Italy

What are your hopes and vision for the future of BIG?

I hope BIG will promote more independent research addressing patients’ unmet needs, while maintaining a collaboration with pharma industries and academic partners. BIG will have to fill the current gap that exists between most clinical trial results and their application in the clinical practice context.

Dr Sibylle Loibl, Germany

What fields of research do you think BIG should focus on to better serve the needs of patients, and society as a whole?

Early breast cancer, especially ER+ and triple negative breast cancer, are still far from being cured, whereas in general HER2+ early breast cancer does seem curable now. The future focus here will lie in tailoring the treatment more specifically to the needs of patients and their tumour characteristics. However, de-escalation, as popular as it may seem, bears some risks. The breast cancer community, together with BIG and other large cooperative groups, has achieved a lot in terms of longer and better survival of breast cancer patients. This achievement should be maintained, and therefore de-escalation trials should only be conducted in specific groups of carefully selected patients.

How do you think BIG could encourage early-career breast cancer specialists to participate and conduct academic research?

This is a very difficult question, as the basic motivation for these individuals depends on the study groups located in different countries. BIG, together with its member groups, can offer training and fellowship positions to young, already motivated oncologists. But these young researchers also need to be introduced to the governance structure of trials to gain a full understanding of how international academic research works. They should be given the opportunity to lead trials, but also to participate in translational and tertiary endpoint research.

Read the full interviews on BIG’s website:
BIG is proud to present the members of the expanded Executive Board:

Our heartfelt thanks go to Drs Fabrice André, José Baselga, Karen Gelmon and Michael Gnant who are outgoing members of BIG’s EB. We wish them every success in their future endeavours.
ALEXANDRA / IMpassion030 (BIG 16-05)

The aim of this phase III trial, which opened its first site in the US last May, is to compare the efficacy and safety of the anti-PD-L1 inhibitor atezolizumab given in combination with chemotherapy versus chemotherapy alone as adjuvant treatment to prevent cancer recurrence in patients affected by operable triple-negative breast cancer.

ALEXANDRA / IMpassion030 is one of the international studies of immunotherapies combined with anticancer treatments recently undertaken by BIG with the aim to understand how we can work with patients’ immune systems to reinforce their responses against their tumours.

As we are writing these lines, the first patients are being randomised, including in Japan and in Europe. Investigators are working hard to launch the study in Latin American countries by the beginning of 2019.

The trial currently involves 20 BIG member groups from 30 countries overall, and approximately 2,300 patients are expected to participate in this global research effort for the treatment of triple-negative breast cancer, an aggressive form of the disease.
EXCEPTIONAL RESPONDERS (BIG 16-04)

A global hunt for exceptional responders in the BIG network
The BIG Exceptional Responders Programme aims to identify breast cancer patients with a truly remarkable clinical response to anticancer treatments, and to characterise their tumours molecularly. Until recently, these “exceptional responders” were largely regarded as clinical anecdotes, occasionally published in case reports, but with a limited direct bearing on research and practice.

With the recent developments in tumour sequencing, however, things have changed. Analysing the tumour genome of exceptional responders can help us uncover the molecular mechanisms underlying the response. The hope is to discover clinically useful biomarkers to predict a patient’s sensitivity to a specific drug. It might even revive our interest in drugs that have failed in past clinical trials by redefining their target population as a smaller, better stratified subgroup of patients. Finally, it could also accelerate the development of promising combination therapies, whereby the drug being studied and a drug targeting the newly discovered sensitivity are used together.

Sixteen BIG collaborative member groups are taking part in the programme, which allows us to reach investigators from many institutions in over 20 countries in Europe, Asia and Latin America. The initiative has elicited considerable interest from doctors throughout the BIG network and many candidate “Exceptional Responder” cases have already been submitted, covering various clinical subtypes of breast cancer (e.g., triple negative, HER2-amplified, hormone-positive, BRCA-mutated) and multiple drugs and treatment regimens (e.g., HER2-targeted therapies, anti-angiogenic therapy, hormone therapy, anti-mitotic chemotherapy).

A panel of experts will select the 10 most interesting cases that will be characterised using exome sequencing, RNA-sequencing and copy number variant analysis. This will provide a detailed view of the genetic make-up of these tumours, helping us to identify the molecular factors behind the exceptional response, and providing valuable insights into the mechanisms of drug sensitivity.

This international academic programme was launched within the BIG network in 2017 with the generous support of the Breast Cancer Research Foundation*.

EXPERT (ANZ 1601 / BIG 16-02)

EXPERT is an investigator-initiated trial that presents a unique opportunity to improve personalised use of radiation therapy in patients with early breast cancer according to their individual risks of local recurrence. The primary aim of EXPERT is to determine whether a genomic test of breast cancer tissue can be used to identify women who can safely avoid radiation therapy after breast cancer surgery. EXPERT was developed in Australia and is Breast Cancer Trials - Australia & New Zealand’s (BCT/ANZ) international study managed together with the Breast International Group (BIG).

EXPERT opened to recruitment in Australia and New Zealand in August 2017 and is reporting strong recruitment numbers, with approximately 90 patients enrolled so far. BCT-ANZ anticipates opening international sites in late 2018 and expects to recruit 1,170 participants worldwide by 2022.

PALLAS (ABCSG 42 / BIG 14-03)

Sample size increased
The remarkable collaboration of the global BIG network has made the PALLAS trial (Palbociclib Collaborative Adjuvant Study) a huge success, with worldwide recruitment ahead of projections.

In early May, the Austrian Breast & Colorectal Cancer Study Group (ABCSG) received the okay for a protocol amendment that increases the sample size by 1,000 patients worldwide to an updated total of 5,600. The trial objective is to investigate the addition of the CDK4/6-inhibitor palbociclib to standard adjuvant endocrine therapy in male and female patients with hormone receptor-positive (HR+) / human epidermal growth factor receptor 2 (HER2)-negative early breast cancer.

This outstanding achievement is the result of the tremendous efforts of the ABCSG’s and BIG’s partners worldwide. “I’m very proud of our network’s efforts, and it’s remarkable that BIG sites in 20 countries around the world are constantly ahead of projections in recruiting”, says Professor Michael Gnant, coordinating investigator for PALLAS and president of the ABCSG.
Every year in late May or early June, the ASCO Annual Meeting brings together more than 32,000 oncology professionals from around the world to discuss state-of-the-art treatment modalities, new therapies, and ongoing controversies in the field.

Several abstracts with updates or follow-on analyses from BIG trials were presented at ASCO 2018, including APHINITY, ALTTO / NeoALTTO, SOLE, POSITIVE, SOFT and TEXT.

Here is a glimpse at what was presented:

**ALTTO / NeoALTTO (BIG 2-06 / 1-06)**

Dr Matteo Lambertini, research fellow at the Institut Jules Bordet, Brussels, Belgium, presented further analyses from the NeoALTTO and ALTTO trials that aimed to evaluate the outcome of pregnancies occurring during or following trastuzumab and/or lapatinib treatment, as well as the prognostic effect of having a pregnancy in HER2-positive early breast cancer patients.1

Data from 92 patients (7 from NeoALTTO and 85 from ALTTO) were analysed and brought researchers to the following conclusions: firstly, having a pregnancy after trastuzumab and/or lapatinib treatment does not appear to impact disease-free-survival or overall survival of the mother. Secondly, unintentional exposure to trastuzumab and/or lapatinib during gestation does not seem to affect newborns’ outcomes upon treatment discontinuation.

For his research and important findings, Dr Lambertini received a 2018 Conquer Cancer Merit Award, which supports early-career oncology professionals who are first authors on selected abstracts.

**Other abstracts related to ALTTO/NeoALTTO**

- A RB-1 loss of function gene-signature (RBsig) as a tool to predict response to neoadjuvant chemotherapy (CT) plus anti-HER2 agents (H): A substudy of the NeoALTTO trial (BIG 1-06). Risi, E., et al.

- Association between adaptive immune signature and outcome in HER2-positive breast cancer treated with trastuzumab and lapatinib in the NCCTG-N9831 (Alliance) and NeoALTTO trials. Chumsri, S., et al.

- Impact of body mass index (BMI) and weight change after treatment in patients (pts) with HER2-positive (HER2+) early breast cancer (EBC): Secondary analysis of the ALTTO BIG 2-06 trial. Martel, S., et al.
SOFT and TEXT (IBCSG 24-02 & 25-02 / BIG 2-02 & 3-02)

Longer-term results from the SOFT and TEXT trials
Addition of ovarian suppression to adjuvant tamoxifen significantly improves disease-free and overall survival vs. tamoxifen alone in premenopausal women with HR+ breast cancer after median follow-up of 8 years.

The results from pre-specified updated analyses of SOFT and the combined analysis of data from SOFT and TEXT after a median follow-up of 8 and 9 years, respectively, were presented at the 2017 San Antonio Breast Cancer Symposium by Gini Fleming and Prue Francis and published in The New England Journal of Medicine.1

In the trials, premenopausal women with hormone receptor (HR)-positive breast cancer were randomised to receive 5 years of tamoxifen, tamoxifen plus ovarian suppression, or exemestane plus ovarian suppression in SOFT, and to tamoxifen plus ovarian suppression or exemestane plus ovarian suppression in TEXT. Randomisation was stratified by receipt of chemotherapy.

The 8-year disease-free survival rates in SOFT were 78.9% with tamoxifen alone, 83.2% with tamoxifen plus ovarian suppression, and 85.9% with exemestane plus ovarian suppression (for tamoxifen plus ovarian suppression versus tamoxifen alone: hazard ratio [HR] = 0.76, P = 0.009; for exemestane plus ovarian suppression vs. tamoxifen alone: HR = 0.65, 95% confidence interval [CI] = 0.53-0.81). Overall survival at 8 years was 91.5% with tamoxifen alone, 93.3% with tamoxifen plus ovarian suppression (HR = 0.67, P = 0.01, versus tamoxifen alone), and 92.1% with exemestane plus ovarian suppression (HR = 0.85, 95% CI = 0.62-1.15, versus tamoxifen alone); the respective survival rates among women who remained premenopausal after chemotherapy were 85.1%, 89.4%, and 87.2%.

In the combined analysis of the two trials including patients who were assigned to receive ovarian suppression, 8-year disease-free survival rates were 86.8% with exemestane plus ovarian suppression versus 82.8% with tamoxifen plus ovarian suppression (HR = 0.77, P <0.001) and 8-year overall survival rates were 93.4% versus 93.3% (HR = 0.98, P = 0.84). The majority of patients in the two trials had HER2-negative disease. Among these women who received chemotherapy, the 8-year rate of distant recurrence with exemestane plus ovarian suppression was lower than the rate with tamoxifen plus ovarian suppression by an absolute 7.0% in SOFT and 5.0% in TEXT. Adverse events of grade ≥3 occurred in 24.6% of the tamoxifen group, 31.0% of the tamoxifen plus ovarian suppression group, and 32.3% of the exemestane plus ovarian suppression group.

The authors concluded that, among premenopausal women with HR-positive early breast cancer, the addition of ovarian suppression to tamoxifen resulted in significantly higher rates of both disease-free and overall survival than tamoxifen alone.

The use of exemestane plus ovarian suppression resulted in even higher rates of freedom from recurrence. The frequency of adverse events was higher in the two groups that received ovarian suppression than in the tamoxifen-alone group.

Follow-up of the SOFT and TEXT trials continues. At the 2018 ASCO Annual Meeting, Meredith Regan presented a further analysis of the SOFT and TEXT results.2 Her presentation focused on patients with HR-positive, HER2-negative disease and detailed the absolute improvements in freedom from distant recurrence that might be achieved across the spectrum, from a very high risk of recurrence to a low risk of recurrence, utilising treatment with exemestane plus ovarian suppression, or tamoxifen plus ovarian suppression versus tamoxifen alone.


2. Regan, M. M., et al., Absolute improvements in freedom from distant recurrence with adjuvant endocrine therapies for premenopausal women with hormone receptor-positive (HR+) HER2-negative breast cancer (BC): Results from TEXT and SOFT. Journal of Clinical Oncology 36, 2018 (no.15_suppl; abstr 503)
SOLE (IBCSG 35-07 / BIG 1-07)

Poster discussion of SOLE results on molecular alterations and late recurrence

Women with hormone receptor-positive early breast cancer have a persisting risk of relapse even after 4 to 6 years of adjuvant endocrine therapy, and the question is whether there are any biomarkers to predict late recurrence and thereby improve the clinical management of these patients. From the 4,884 postmenopausal women enrolled in the extended adjuvant intermittent letrozole versus continuous letrozole (SOLE) trial, 3,162 had tumour samples of the primary breast cancer available and were eligible for molecular analysis, the aim of which was to identify prognostic factors and potential molecular targets.

The associations of genomic alterations with breast cancer-free interval and distant recurrence-free interval were assessed. This analysis showed that patients with hormone receptor-positive, node-positive breast cancer with copy number gain for FGFR1 had an increased risk of late recurrence despite extended therapy. FGFR1 analysis may improve the risk stratification in this population and represent a potential therapeutic target.

A poster with these results was presented by Elena Guerini Rocco et al. at ASCO 2018 and discussed by Erica L. Mayer, during the poster discussion session.

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

Two poster presentations

POSITIVE is a prospective, single arm, international trial to assess whether temporarily interrupting adjuvant endocrine therapy (for up to 2 years) for young women with endocrine responsive breast cancer who desire pregnancy is safe in terms of risk of breast cancer recurrence. **Sample size is 500 evaluable patients and, as of 30 June 2018, 262 patients have already been enrolled.**

A trial in progress poster was presented by Ann Partridge et al. at the ASCO Annual Meeting in Chicago last June. The poster generated a lot of interest, and we hope that this will further help to recruit patients in this very important trial.

Another poster for the POSITIVE trial presented at ASCO described the estimation of a historical control rate for single arm trials, presented by Zhuoxin Sun et al.

POSITIVE is a single arm trial and, in order to better estimate the historical control rate, methods were developed and applied using the data from the SOFT/TEXT phase III trials.

A cohort of 1,499 SOFT and TEXT patients who met the POSITIVE eligibility criteria – including having received 18 to 30 months of endocrine therapy – were identified. Two approaches were used and compared:

- Method I included all eligible patients and calculated the annualised hazard rate of breast cancer-free interval (BCFI) events directly over the first 3 years and the 3-year BCFI failure rate, based on Kaplan-Meier estimates.
- Method II was a more refined approach taking into account the potential selection of eligible patients who would enrol in POSITIVE by group-matching the patient characteristics of SOFT/TEXT patients to the first 149 POSITIVE patients who were enrolled until 1 October 2017.

These methods will aid in the interpretation of the final analysis of POSITIVE. In order to ensure a consistent and robust estimate of a historical control rate across the different cohorts, a next step is to apply these methods using data also from other sources.

1. Guerini E. et al., Molecular alterations and late recurrence in postmenopausal women with hormone receptor-positive node-positive breast cancer (BC): Results from the "SOLE" trial. *Journal of Clinical Oncology* 36, 2018 (no.15_suppl; abstr S17)

2. Sun Z. et al. Estimation of historical control rate for a single arm de-escalation study: Application to the POSITIVE trial. *Journal of Clinical Oncology* 36, 2018 (suppl; abstr TPS3596)
Other trials & activities by BIG member groups

**ABCSG**

DFS results from ABCSG-18 presented at 2018 ASCO Annual Meeting

A total of 3,425 patients with hormone receptor-positive breast cancer participated in the Austrian Breast and Colorectal Cancer Study Group’s (ABCSG) placebo-controlled, double-blind, multi-center phase-III breast cancer study. The standard therapy for postmenopausal women with this type of breast cancer is aromatase inhibitors. However, these may also have negative effects on bone density, and thus significantly increase the risk of osteoporosis. The use of the monoclonal antibody denosumab (60 mg twice yearly) in addition to the patients' antihormonal therapy, reduced the incidence of clinical bone fractures by 50% and generally improved bone health without additional toxicity. These results were presented at ASCO 2015 and published in The Lancet (Gnant et al, Lancet. 2015; 386: 433-43).

In June 2018, Prof Michael Gnant presented the six-year disease-free-survival (DFS) data of ABCSG-18 at ASCO. After an average of 73 months of follow-up, these DFS results are statistically significant, and the risk of relapse is reduced by approximately 18% with the administration of 60mg q6m denosumab. Of the patients who also received denosumab, 89.2% (versus 87.3% for placebo) at 5 years, and 80.6% (versus 77.5% for placebo) after 8 years were disease-free. This benefit comes in addition to the significant reduction of clinical fractures; thus adjuvant denosumab constitutes an effective and safe treatment option for postmenopausal patients with breast cancer on aromatase inhibitor therapy.

**BCT-ANZ**

Breast Cancer Trials-Australia & New Zealand (BCT-ANZ) 40th Annual Scientific Meeting

BCT-ANZ recently held their 40th Annual Scientific Meeting (ASM) in Sydney, Australia, with approximately 200 participants from Australia and New Zealand.

The ASM is an opportunity for BCT-ANZ members to discuss current and future clinical trials and research updates. This year’s event was a special celebration of BCT-ANZ formation in Australia and New Zealand 40 years ago. International guest speakers were Professor Carlos Arteaga, Associate Professor Peter Dubsky, Professor Hope S Rugo and Professor Timothy Whelan.

The ASM is also an opportunity to recognise BCT-ANZ researchers involved in the conduct of clinical trials and research excellence. The following awards were presented:

- The Alan Coates Award for Excellence in Clinical Trials Research was awarded to Professor Fran Boyle AM.
- The Robert Sutherland Award for Excellence in Translational Research was awarded to Professor Carlos Arteaga.
- The John Collins Medal was awarded to Dr Synn Lynn Chin.
- The Study Coordinator Prize was awarded to Ms Vicki Sproule.
GEICAM and Fundación Atlético de Madrid team up for breast cancer research

GEICAM, the Spanish Breast Cancer Group, in collaboration with the Atlético de Madrid Foundation, organised the fourth edition of its annual solidarity soccer 7 tournament “Together against Breast Cancer” to raise funds for research.

The funds raised during the event, which took place on 23 June, will be used to finance GEICAM’s EFiK study, which focuses on the benefits of physical exercise. The results are expected to clarify the biological mechanisms associated with the benefits of physical exercise as a prognostic modifier for patients with operable breast cancer.

For several years, GEICAM has been investing efforts into scientific research in the field of physical exercise and breast cancer.

Spanish women with a sedentary lifestyle have a 71% higher risk of developing breast cancer than those who follow the recommendations of the World Health Organisation (WHO) on physical exercise. In fact, according to an epidemiological study carried out by GEICAM¹, up to 13.8% of breast cancer cases could be prevented if inactive women started to follow these recommendations. This study was conducted to determine the impact of physical exercise on the risk of developing the disease, and if complying with the WHO recommendations can lower the probability of developing the disease.

Apart from developing the first Spanish epidemiological study aimed at determining the impact of physical exercise on the risk of developing breast cancer, and evaluating whether complying with the international recommendations on physical exercise is associated with less likelihood of developing the disease, GEICAM has launched the Programme on Oncological Physical Exercise with three objectives: to lead research on the benefits of exercise in the evolution of breast cancer, to generate a network of specialists in this field, and to communicate the importance of staying active to patients, institutions and the general population. With this initiative, GEICAM has become a benchmark in this field at a European level.

CIBOMA/2004-01_GEICAM/2003-11 Study
An international, multicenter, randomised phase III trial assessing adjuvant capecitabine after standard neo- and/or adjuvant chemotherapy (CT) for patients with early triple-negative breast cancer (TNBC)
This study was developed with the aim of evaluating the addition of adjuvant capecitabine after completion of standard treatment in patients with early-stage TNBC.

The results from this study will supplement the results from the CREATE-X study,1 which showed an improvement in disease-free survival (DFS) and overall survival (OS) with capecitabine in patients with HER2-negative breast cancer, this benefit being particularly notable among patients with TNBC. In contrast to the CIBOMA/2004-01_GEICAM/2003-11 study, patients at a higher risk of recurrence were included in the CREATE-X study, as they had residual invasive disease after neoadjuvant chemotherapy (CT) based on anthracyclines and/or taxanes.

CIBOMA/2004-01_GEICAM/2003-11 was developed in parallel to the creation of the Iberoamerican Coalition for Research in Breast Oncology (CIBOMA), integrating twelve Latin American countries (Argentina, Brazil, Chile, Colombia, Costa Rica, Ecuador, Guatemala, Honduras, Mexico, Peru, Uruguay and Venezuela), as well as Portugal, Spain and the United States of America (USA). Once the CIBOMA/2004-01_GEICAM/2003-11 study has completed, CIBOMA will be closed and its functions assumed by the Latin American Cooperative Oncology Group (LACOG).

Patients eligible for CIBOMA/2004-01_GEICAM/2003-11 have operable, node-positive, centrally confirmed hormone receptor-negative, HER2-negative breast cancer, and have received 6–8 cycles of standard anthracycline and/or taxane-containing CT or 4 cycles of doxorubicin-cyclophosphamide (for node-negative disease) in the (neo)adjuvant setting, followed by radiation therapy (if indicated).

Patients have been randomised to either 8 cycles of capecitabine (1,000 mg/m² bid, on days 1–14, every 3 weeks) or observation. Stratification factors include axillary lymph nodes involvement (0 versus 1-3 versus ≥ 4), prior taxane-based therapy (yes versus no), phenotype (basal: cytokeratin 5/6 positive and/or epidermal growth factor receptor (EGFR) positive versus non-basal), and center.

The primary objective is to compare DFS between both treatment arms, and secondary objectives include the comparison in terms of 5-year DFS, OS and safety.

From the translational research perspective, several projects have been developed in collaboration with different groups:
- To explore the predictive biomarkers and/or gene signatures of the benefit of adding capecitabine to previous standard CT, in collaboration with Dr Carlos Arteaga, from UTSW Harold C. Simmons Comprehensive Cancer Center, Dallas, USA.
- To identify actionable oncogenic targets associated with resistance and/or sensitivity to CT and clinical outcomes using a multigene expression NanoString platform, in collaboration with Dr Aleix Prat, from Hospital Clinic de Barcelona, Spain.
- To determine an optimal cut-off for predicting the expression levels of hormone receptors (estrogen and progesterone) and HER2 (assessed by immunohistochemistry and in situ hybridisation) by gene expression analyses of ESR1, PGR and ERBB2, as well as to evaluate its predictive value for treatment efficacy. Conducted in collaboration with Dr Aleix Prat, from Hospital Clinic de Barcelona, Spain, this analysis includes sample collections from ten different cohorts and has been submitted to SABCS 2018.

84 sites (54 in Spain and 30 in Latin America) have participated in the study, with 344 patients having been randomised in seven countries from Latin America (Brazil, Chile, Colombia, Ecuador, Mexico, Peru and, Venezuela) and 532 in Spain, for a total of 876 patients. The enrollment was completed between October 2006 and September 2011.

Preliminary data about patients’ baseline demographics and disease characteristics in addition to safety have been previously communicated.2-6 An abstract to present updated study data, including efficacy results, has been submitted to SABCS 2018.
SOLTI

SOLTI to launch two new window-of-opportunity studies

In an effort to accelerate the understanding of promising therapeutics, discovering biomarkers, and devising rational combinatorial strategies for breast cancer, the SOLTI Breast Cancer Research Group has launched VENTANA, a window-of-opportunity programme. This initiative consists of small proof-of-concept studies with biological endpoints, which allow for rapid data generation and decision-making in clinical development.

The first VENTANA clinical trial studied the effects of three weeks of metronomic vinorelbine with or without letrozole versus letrozole alone in patients with newly diagnosed luminal breast cancer amenable to surgery. Results will be presented at SABCS later this year.

In addition to the rich biological information generated by the first VENTANA study, this trial has served to optimise the operational, regulatory and financing processes required for this setting, allowing SOLTI to streamline the start-up of future VENTANA studies.

References


As the promise of immune-oncology in breast cancer rises, two new studies will be opening during the latter part of this year in SOLTI sites in Spain: **PROMETEO** and **AWARE-1**, both investigating the effects of combining oncolytic viruses and a checkpoint inhibitor.

**PROMETEO** is a study led by Dr Aleix Prat and Dr Tomás Pascual as principal investigators, with the objective to assess the effects of talimogene laherparepvec plus atezolizumab in patients with triple-negative or high-risk luminal early breast cancer with residual disease after standard neoadjuvant chemotherapy.

**AWARE-1**, by contrast, intends to identify which breast cancer subtypes may benefit from pelareorep based on activation of the immune system in the tumour. The study has five cohorts: two with luminal disease investigating the virus in combination with letrozole and letrozole plus atezolizumab, respectively; a triple negative breast cancer cohort that combines the virus with atezolizumab; and two HER2+ cohorts, hormone receptor-positive and negative, separately assessing the virus plus trastuzumab and atezolizumab. The principal investigators are Dr Luis Manso and Dr Joaquín Gavilá.

Even though trials requiring small numbers of patients are usually conducted within the realm of SOLTI, these proof-of-concept studies within the VENTANA Programme are intended to serve as the basis for larger confirmatory trials that may later be brought to the extended BIG network.

For more information about or potential collaborations in conjunction with the VENTANA Programme or any of its associated studies, please contact Dr Aleix Prat.
## Overview of the clinical studies run within the BIG network

### Open, recruiting patients

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<td>M. Ignatius, H. McArthur</td>
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<td>Exceptional Responders</td>
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<td>BIG-sponsored programme (Co)-Leading partners: BIG HQ. Pharma partner: N/A. Funding: Breast Cancer Research Foundation</td>
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<td>EXPERT</td>
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<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>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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**Legend:**
- AFT: Alliance Foundation Trials, LLC; BCRF: Breast Cancer Research Foundation; FSS: Frontier Science Scotland, Ltd; FSTRF: Frontier Science and Technology Research Council of Australia, and BIG HQ fundraising initiatives
- N/A: not applicable; NCCTG: North Central Cancer Treatment Group; NCI: US National Cancer Institute; SCTBG: Scottish Cancer Trials Breast Group; TBCRC: Translational Breast Research Consortium
- 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)
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<th>Model &amp; trial partners</th>
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<td>Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation: sequential and combination for patients with HER2+ErbB2-positive primary breast cancer NC108490319</td>
<td>M. Piccart A. Moreno-Arias</td>
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<td>G. van Minckwitz J. Basel</td>
<td>Lead trial (Co-Leading partners: BIG HQ / IB-CTSU (BrEAST) / FSTFR Pharma partner: Roche) Funding: Roche</td>
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<td>N. Tjirna M. Balducci D. Cameron J. Embus</td>
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<td>A randomised clinical trial of adjuvant chemotherapy for radically resected loco-regional recurrence of breast cancer NC100074752</td>
<td>S. Achi I. Wapnit</td>
<td>Supporter trial (Co-Leading partner: IBCSG (sponsor) Pharma partner: N/A Funding: IBCSG / IBCG)</td>
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<td>B. Chua</td>
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<td>E. Andre J. Loriot</td>
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<td>C. Saera E. de Azambuja</td>
<td>Co-lead trial (Co-Leading partners: ABCSG, SOLOI and BIG HQ Pharma partner: Genetech (sponsor) Funding: Genetech)</td>
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<td>J. Bueidt I. Fidler</td>
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<td>A. Gemmari G. Jerusalem</td>
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<td>P. Francois G. Fleming</td>
<td>Supporter trial (Co-Leading partner: IBCSG (sponsor) Pharma partner: Pfizer Funding: GSK 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>Supporter trial (Co-Leading partner: FBCG (sponsor) Pharma partner: Novartis Funding: Novartis)</td>
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<td>Supporter trial (Co-Leading partner: IBCSG (sponsor) Pharma partner: Pfizer Funding: GSK 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>
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<td>M. Ignatius M. Piccart J. V. Perugia</td>
<td>Supporter trial (Co-Leading partner: EORTC (sponsor) Pharma partner: Roche Funding: Roche grant)</td>
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The Breast International Group (BIG) is a not-for-profit organisation for academic breast cancer research groups from around the world.

Founded by leading European breast cancer experts in 1999, BIG now constitutes a network of 59 groups and data centres based in Europe, Canada, Latin America, the Middle East, Asia and Australasia. These entities are tied to several thousand specialised hospitals and research centres worldwide. About 30 clinical trials and several research programmes are run or are under development under the BIG umbrella at any one time. BIG also works closely with the US National Cancer Institute and the North American Breast Cancer Group, so that together they act as a strong interacting force in the breast cancer research arena.

www.BIGagainstbreastcancer.org

The 59 breast cancer research groups of the BIG network

- ABCSG Austrian Breast & Colorectal Cancer Study Group
- AGO-B Arbeitsgemeinschaft Gynäkologische Onkologie Breast Study Group
- ARCAVylGINECO Association de Recherche dans les Cancers dont Gynécologiques – Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens et du sein
- BCT-ANZ Breast Cancer Trials - Australia & New Zealand
- BDPCC Breast Disease Professional Committee of CMEA (China)
- BGICS Breast-Gynecological International Cancer Society
- BII Breast Intergroup of Eastern India
- BOOG Borskitranker Onderzoek Groep
- CCTG Canadian Cancer Trials Group
- CEESG Central and East European Oncology Group
- CT-IRE Cancer Trials Ireland
- CTRG Cancer Therapeutics Research Group
- DBCG Danish Breast Cancer Cooperative Group
- EORTC BCG European Organisation for Research and Treatment of Cancer, Breast Cancer Group
- FBCG Finnish Breast Cancer Group / Suomen Rintasyöpäpäryhmä
- FBI Frankcilian Breast Intergroup
- GAICO Grupo Argentino de Investigación Clínica en Oncología
- GBG German Breast Group
- GCSG Georgian Cancer Study Group
- GECO PERU Grupo de Estudios Clinicos Oncologicos Peruano
- GECAM Spanish Breast Cancer Group
- GOCCHI Chilean Cooperative Group for Oncologic Research
- GOCUR Grupo Oncologico Cooperativo Uruguayo
- GOIRC Italian Oncology Group for Clinical Research
- GONO Gruppo Oncologico Nord-Ovest
- HBSS Hellenic Breast Surgical Society
- HcCOG Hellenic Cooperative Oncology Group
- HKBOG Hong Kong Breast Oncology Group
- HORG Hellenic Oncology Research Group
- IBGG Icelandic Breast Cancer Group
- IBCSG International Breast Cancer Study Group
- IBG Israeli Breast Group
- IBB International Breast Cancer Intervention Studies
- ICGC International Collaborative Cancer Group
- ICON ARO Indian Co-Operative Oncology Network
- ICRC Iranian Cancer Research Center
- ICR-CTSU Institute of Cancer Research – Clinical Trials & Statistics Unit
- IE / CTsu (formerly BrEAST)
- Institut Jules Bordet / Clinical Trials Support Unit
- IOSG Indian Oncology Study Group
- ITMO Italian Trials in Medical Oncology
- JBCRG Japan Breast Cancer Research Group
- KCSG Korean Cancer Study Group
- LACOG Latin American Cooperative Oncology Group
- MICHIELANGELO Fondazione Michelangelo
- NBGC 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
- SCBG Sheba Breast Collaborative Group
- SKMCH & RC Shaukat Khanum Memorial Cancer Hospital & Research Centre
- SLO Société Luxembourgeoise d'Oncoologie
- SOUT South Africa Cancer Research Group
- SUCCESS – Study Group
- SweBCG Swedish Breast Cancer Group
- TCCG Taiwan Cooperative Oncology Group
- TCGN Trans Tasman Radiation Oncology Group
- TSCO Thai Society of Clinical Oncology
- UCBG Uncancer Breast Group
- WSG Westdeutsche Studiengruppe
16th St. Gallen International Breast Cancer Conference 2019
Primary Therapy of Early Breast Cancer
Evidence, Controversies, Consensus
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