FIGHTING BREAST CANCER AROUND THE GLOBE

The unmet needs of older patients with breast cancer
NOTE FROM THE EDITOR

As the month of October is Breast Cancer Awareness Month, and at 1 October marks the International Day of Older Persons (declared by the United Nations), the themed article of this edition of BIG Research in Focus highlights “The unmet needs of older patients with breast cancer”.

The BIG Headquarters communications team would like to thank Professors Etienne Brain, Hans Wildiers, Masataka Sawaki, Laura Biganzoli and Nicola Battisti, who kindly accepted to be interviewed on this topic. “Older patients are under-represented in breast cancer clinical trials and, although drug regulators discourage studies with upper age limits, exclusion criteria still mean that patients over 65 years old are frequently left out of important research. Without clinical trial evidence of efficacy and safety in older people, clinicians may be reluctant to prescribe novel agents, especially to their frailer patients, and getting reimbursement for drug doses, schedules and combinations adapted for older patients can be challenging. How are leading breast cancer researchers addressing the need to include more of the growing population of older patients in clinical trials?”, medical journalist, Jenny Bryan, reports. She also discusses the background of the APPALACHES clinical trial and the implications for breast cancer care with some of those closest to this important trial. See from page 2.

For the fourth consecutive year, BIG and the EORTC are combining their efforts and expertise by organising an annual Pink October webinar for a scientific audience. For this year’s theme, we have also chosen to focus on “The unmet needs of older patients with breast cancer”. This BIG-EORTC webinar takes place on 19 October. Registration is free but mandatory. For programme, speakers and registration, please see page 16.

The BIG network makes it possible to rapidly enrol a large number of patients into complex international clinical trials, to share best practices, expertise, and data. We are very pleased to welcome a new Italian breast cancer research group joining BIG: the Gruppo Italiano Mammella (GIM), represented by Dr Matteo Lamberti. See page 11.
Older patients are under-represented in breast cancer clinical trials and, although drug regulators discourage studies with upper age limits, exclusion criteria still mean that patients over 65 years old are frequently left out of important research. Without clinical trial evidence of efficacy and safety in older people, clinicians may be reluctant to prescribe novel agents, especially to their frailer patients, and getting reimbursement for drug doses, schedules and combinations adapted for older patients can be challenging. How are leading breast cancer researchers addressing the need to include more of the growing population of older patients in clinical trials? Medical journalist, Jenny Bryan, reports.

Nearly 50% of patients with cancer are aged 65 years and over, as are 55% of those with breast cancer but older patients are poorly represented in clinical trials. Eligibility criteria, concerns about toxicity and patient age, and the burden of trial participation have been identified as the main barriers. Older patients who are included in breast and other cancer trials are generally fitter than expected for their chronological age, with fewer comorbidities, and study results may not be indicative of outcomes in frailer, older patients eligible for newly approved therapies.

“Patients in trials tend to be younger and fitter or, if they are older, they have minimal heart, kidney or other end organ damage,” explains Etienne Brain, Institut Curie - Hôpital René Huguenin, Saint-Cloud, France, and past Chair of the EORTC Breast Cancer Group. “This creates a gap between the trial population and the patients we see in clinical practice. When a drug is approved, the label may say that it works irrespective of age, but that only means for the type of older patient in the clinical trials.”

Laura Biganzoli, Hospital of Prato, ASL Toscana Centro, Prato, Italy, points out that a lack of older patients in clinical trials can lead to delays in prescribing new agents to fit older patients, and frailer patients may miss out altogether. “Everybody recognises that this is an important issue, and we need to encourage pharmaceutical and other sponsors to support trials in older patients. These studies may require innovative designs and different endpoints from standard trials, but accrual of older patients can be really fast at centres where geriatric clinics are held alongside cancer clinics and there is a culture of oncogeriatrics,” she says.

Hans Wildiers, University Hospital Leuven, Belgium, past President of the International Society of Geriatric Oncology (SIOG) and past Chairman of the Cancer in the Elderly task force of the EORTC, suggests that some trial sponsors are concerned that if less fit, older patients are included in clinical trials, they will be more likely to experience toxicity, leading to poorer overall results.

“There is also the problem that very few frailer, older patients are likely to tolerate the side effects of standard chemotherapy, which is the comparator in many studies of new agents, and there is a reluctance to reduce the doses of any of the drugs in clinical trials to adapt to the needs of older patients,” he says.

When new agents are introduced for breast cancer, oncologists may give them to their frailer, older patients at lower than recommended doses to reduce toxicity, with different and empirical schedules including combinations with less harsh forms of chemotherapy. But, as Brain points out, this is rarely based on clinical evidence from registration trials and may lead to reimbursement or administrative issues.
“Like Biganzoli, he would also like to see different endpoints in older patients, with stepwise dose escalation strategies. Opportunities in major studies for using lower drug doses and reducing exclusion criteria, Brain favours more to older people, together with geriatric tools and scales.”

Biganzoli agrees. “We also need to include primary endpoint in trials with older patients, and the regulatory agencies are looking carefully at this,” says Brain.

He believes that ‘hidden ageism’ needs to be addressed in clinical trial recruitment, as there may be an assumption that older people will not understand the purpose of a trial or the inconvenience of taking part.

“It may take more time to explain and to listen to older patients, but we need to take that time as part of being a clinician. We are used to being in a rush to use the latest technology, make the diagnosis and get people on treatment but it’s just as important to know when to take time to explain things to our older patients. When they understand that we need to answer an important question in a trial, they can be just as likely to want to participate as younger patients,” Brain concludes.

THE IMPORTANCE OF GERIATIC ASSESSMENT

Inclusion of geriatric assessment (GA) in clinical trials to determine physiological age is widely recommended to differentiate older patients who are likely to tolerate treatment from those who are not. In their most recent guidance on the management of older patients with breast cancer, the European Society of Breast Cancer Specialists (EUSOMA) and the International Society of Geriatric Oncology (SIOG) recommended that a screening tool should be considered as the gateway or minimum starting point to any treatment decision-making in older patients with cancer. SIOG also carries out extensive educational and awareness initiatives about the importance of GA and collaborates with BIG and other organisations at national and global level to advocate for greater inclusion of older patients in clinical trials.

“In an ideal world, we would do a comprehensive geriatric assessment (CGA) for all older patients with breast cancer before making a treatment decision but this is time consuming. However, we now have geriatric screening tools that accurately predict the results of a CGA, and identify patients who need a full CGA, and these can often be done in minutes,” says Nicolò Battisti, Royal Marsden Hospital, London, UK, and SIOG President-Elect.

A key tool to identify older patients warranting an oncogeriatric approach is the Geriatric8 (G8) screening tool, which was developed to identify older cancer patients who would benefit from CGA, and is popular in clinical trials. In order to predict treatment benefits in this population, the PORTRET tool, developed in the Netherlands, has been designed to predict recurrence, overall survival and other-cause mortality in older patients with breast cancer. Similarly, the online Age Gap decision tool, developed in the UK, is designed to guide choices about surgery versus endocrine therapy as primary treatment in older patients with breast cancer, and in relation to chemotherapy after surgery. In order to predict the risk of severe side effects, the Cancer Aging Research Group (CARG) score has been externally validated for predicting chemotherapy toxicity in older adults with cancer, and CARG-BC has been developed to predict severe chemotherapy toxicity in older patients with early stage breast cancer. The CRASH score stratifies patients into four risk categories of severe toxicity.

A number of studies have now demonstrated the value of incorporating GA in cancer clinical trials for optimising care and health outcomes in older patients, including reducing treatment toxicity and discontinuation.

“If we combine tools that can predict need for CGA, life expectancy, efficacy of treatment and side effects, this enriches the discussion with older patients both in clinical trials and clinical practice,” says Battisti. “These tools are now being used in good quality clinical trials in geriatric oncology. We are also making progress in convincing pharmaceutical sponsors about the importance of geriatric assessment methods in order to include more older patients in clinical trials of breast cancer.”

He believes it is a lost opportunity if older patients are missed out of clinical trials because GA tools are not included in study design.

“In some types of breast cancer, over 50% of our patients are older, and if these are excluded from clinical trials of new medicines because there is no GA, many frailer patients will miss out on new treatments when they reach the clinic,” warns Battisti.

WHAT RESEARCH IS BEING DONE IN OLDER PATIENTS?

Although older patients are still infrequently enrolled in many breast cancer trials, some recent and ongoing studies have focused on the needs of older patients. In a Phase 2 study coordinated by Wildiers of pertuzumab and trastuzumab with or without metronomic chemotherapy in older patients (EORTC 75111-10114), 70% of patients had a potential frailty profile demonstrated by their G8 score. Results suggested that adding metronomic cyclophosphamide increased progression-free survival and might delay or supersede the need for taxane chemotherapy in this population.

In the Phase 2 EFFECT trial coordinated by Biganzoli in women with advanced breast cancer aged ≥ 65 years, survival outcomes were comparable for nab-paclitaxel 100 mg/m2 and 125 mg/m2, but the lower dose was better tolerated with significantly less neurotoxicity.

The Phase 3 ASTER 70s study investigated the benefits of adjuvant chemotherapy and endocrine therapy compared to endocrine therapy alone in patients with high grade oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer aged 70 years and over. In the primary intention-to-treat analysis, there was no statistically significant difference in overall survival between the two groups – suggesting that chemotherapy may not be needed in these older patients. There was a 20% non-adherence to treatment in the chemotherapy arm, which it has been suggested, contributed to the failure to see a survival difference between the two treatment options. However, as Brain points out, the non-adherence rate in ASTER 70s was very similar to that seen in other major trials, including TAILORx, in younger patients.

The Phase 2 APPALACHES trial, being carried out through the EORTC and BIG network of investigators, is the first study to compare palbociclib with chemotherapy in patients with high risk ER-positive breast cancer treated with standard adjuvant
endocrine therapy. About 340 of a planned 366 patients (women and men) with stage II or stage III, ER-positive, HER2-negative, early invasive breast cancer aged 70 years and over had been randomised by August 2022.

As Wildiers explains, the APPALACHES population is at high risk of relapse after surgery and, if they were younger, would probably have preventive chemotherapy with their hormone treatment to reduce their risk of metastases. However, in clinical practice, some older patients decide against chemotherapy due to its side effects and associated reduction in quality of life.

“Palbociclib has different anti-cancer effects to chemotherapy and is much better tolerated, and there is evidence that it may be as effective as chemotherapy. In APPALACHES, we are therefore looking to see if palbociclib can reduce the risk of metastases and avoid the need for chemotherapy in older patients with hormone-sensitive breast cancer,” says Wildiers who is principal investigator for APPALACHES.

The primary endpoint of the study is the 3-year disease recurrence-free interval (D-RFI) rate in the experimental arm. Secondary endpoints are breast cancer specific survival, overall survival, and incidence of permanent treatment discontinuation – all at five years.

Wildiers explains that, in common with a growing number of breast cancer trials, a threshold has been set for assessing the primary endpoint, so that fewer patients are needed than for showing a statistically significant difference for an outcome that may be very similar for palbociclib and chemotherapy. For APPALACHES, this bar has been set at 92% of patients treated with palbociclib achieving distant disease-free survival at three years.

“My goal is also to evaluate outcomes at eight to 10 years, so we can see how fast these cancers are growing in older patients. Did they die of breast cancer, or were we able to prevent that so they died of something else? Alternatively, if a lot of people do develop metastatic disease, then perhaps it is not a good choice to omit chemotherapy,” says Wildiers.

For Biganzoli, the feasibility of using novel cancer treatments in older patients is also important. With this in mind, the FACILE trial is investigating the feasibility of using another CDK 4/6 inhibitor, ribociclib, in patients with advanced breast cancer aged ≥70 years. The primary endpoint is the proportion of patients who have not experienced disease progression six months after first drug administration and are still on treatment with ribociclib.

“All patients in FACILE will undergo a full geriatric assessment, and we hope that this will enable us to evaluate the feasibility of treatment related to the true health status of individual patients,” says Biganzoli.

Geriatric assessment is also a feature of the Phase 2 TOUCH trial, which is comparing neoadjuvant palbociclib, hormonal therapy and HER2 blockade, with paclitaxel and HER2 blockade in postmenopausal patients with HR positive/HER2 positive early breast cancer.

“Women over 65 years of age are receiving geriatric assessment to enable us to better understand the treatment effects in the older patients in the trial,” explains Biganzoli.

EXPERIENCE IN JAPAN

At 87 years, Japanese women have the highest life expectancy in the world, and breast cancer is the most common form of the disease in this population. In 2017, approximately 28% of the 94,612 patients diagnosed with breast cancer were over 70 years of age, 41.6% over 65 years.

Masataka Sawaki, Department of Breast Oncology, Aichi Cancer Center Hospital, Nagoya, Japan, explains that data from the Japanese Breast Cancer Registry (JBCR) show that older patients (> 75 years) have more advanced disease at diagnosis, are more likely to have mastectomy, and are less likely to have radiotherapy or primary systemic chemotherapy after breast cancer surgery than younger patients.15 If they have chemotherapy, older patients are more likely to have cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) or oral 5FU than standard anthracycline and taxane chemotherapy. In a survey amongst institutions in the Japanese Oncology Group, 34% of responders said that an upper age of 80 years was an important factor when choosing surgery, and 20% put the upper age at 70 years.16 Seventy five years was generally considered to be the upper age for giving chemotherapy and 80 years the upper age for giving radiation.

“Despite the differences in stage at diagnosis and treatment, the Registry data showed similar breast cancer specific survival rates for all age groups, though the rate of other causes of death was higher in the older age groups,” says Sawaki.

To better understand the need for chemotherapy in patients with breast cancer in Japan, the RESPECT trial was set up to investigate the efficacy and tolerability of adjuvant trastuzumab with or without chemotherapy in 275 patients aged 70-80 years with surgically treated, HER2-positive early breast cancer.17 Three-year disease-free survival (DFS) was 89.5% with trastuzumab monotherapy compared to 93.8% with trastuzumab-chemotherapy (hazard ratio [HR] 1.36; 95% confidence interval [CI] 0.72 to 2.58; p=0.51). Common adverse events (AEs) were less frequent with trastuzumab monotherapy than with trastuzumab-chemotherapy: anorexia (7.4% vs 44.3%; p<0.0001), alopecia (2.2% vs 71.7%; p<0.0001), and grade 3/4 non-haematologic AEs (11.9% vs 29.8%; p=0.0003) respectively. Clinically meaningful deterioration in health-related quality of life was significantly less with trastuzumab alone than with trastuzumab-chemotherapy at two months (31 vs 48%; p=0.016) and at one year (19% vs 38%; p=0.009).

“Although the primary objective of noninferiority for trastuzumab monotherapy was not met, the observed loss of survival without chemotherapy was less than one month at three years, so this supports the use of trastuzumab monotherapy in this group of older patients with HER2-positive early breast cancer,” says Sawaki.

A sub-study of RESPECT did not show any negative effects of chemotherapy on cognitive functioning, which was reassuring as some older patients prefer to have combination treatment, explains Sawaki.

As yet unpublished GA data from patients in the RESPECT trial showed that comorbidities, increased creatinine, and Hospital Anxiety and Depression new Score (HADS) all affected AEs; comorbidities, reduced neutrophil count and Philadelphia Geriatric Center (PGC) Morale Scale new score affected DFS.

A validation study of geriatric assessment using the G8 score is now being carried out to confirm the probability of predicting AEs and prognosis in patients over 70 years with operable breast cancer. Sawaki reports that, as of July 2022, 646 patients had been recruited to the study, in which G8 assessment is carried out at baseline and after three months of treatment according to investigator and patient choice. Observational outcomes include DFS and overall survival (OS).

A further ongoing study of breast cancer treatment in older patients (65 years and over) in Japan is the non-inferiority, Phase 3 HERB TEA trial. Patients with advanced HER2-positive breast cancer are being randomised to docetaxel, trastuzumab and pertuzumab or T-DM1, and 126 patients had been recruited by July 2022.

FUTURE BREAST CANCER TRIALS IN OLDER PATIENTS

If positive, APPALACHES may set a new standard of care for older patients with ER-positive breast cancer, but what of those with other forms of the disease? Wildiers would like to see studies in older patients with HER2-positive disease and also in those with metastatic disease.

“We need studies that will test dosing and pharmacodynamics of breast cancer treatments in older patients to find out if we can start with lower doses and up-titrate slowly so that treatment is better tolerated. Doctors already do this but we need to investigate it properly so that we are using evidence-based dosing schedules,” he says.

Building on this approach to better understand how older patients respond to different dosing schedules, Biganzoli is involved in metabolomic research to predict the toxicity of chemotherapy in different patients.
“Blood samples from patients involved in geriatric assessment studies are being analysed to see if we can identify a metabolic signature that is predictive of severe toxicity in older patients with breast cancer and other tumour types. Implementing metabolomics in clinical practice will be quite complex, but the metabolic practice is a first step,” says Biganzoli.

She also wants to find out if genomic research can be used to identify a patient’s ‘epigenetic clock’ to see if that can predict their biological age more effectively than current geriatric assessment and whether this will give information about their risk of treatment toxicity.

Battisti believes that, in planning future clinical trials with older patients, investigators and sponsors should introduce GA and achieve more targeted, precision oncology in this age group,” concludes Battisti.

He also supports pragmatic designs for trials of older patients, for example, with fewer hospital visits and interventions that discourage some older patients from taking part. Moving forward, he would like to see studies investigating whether or not older patients with locoregional breast cancer need radiotherapy and if systemic treatment de-escalation is possible in the metastatic and advanced setting. In addition, he would like to see studies of non-chemotherapy options in older patients with triple negative breast cancer based on a better understanding of the biology of the disease, and more research on antibody drug conjugates and immunotherapy in older patients.

“We also need to investigate the economic impact of an integrated oncogeriatric approach to find out if — as I believe we will — we can reduce costs if we introduce GA and achieve more targeted, precision oncology in this age group,” concludes Battisti.

REFERENCES


MEET THE EXPERTS

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We are extremely happy and proud that GIM has joined the BIG network. This is a unique opportunity for our national group to be more actively involved in international academic trials in order to give our patients the opportunity to participate in such important studies. We will do our best to add our expertise to such an extraordinary network and group of leading breast cancer experts.

Dr Matteo Lambertini

GIM is an independent breast cancer research group acting in more than 100 Italian centres and including more than 200 investigators. GIM studies are sponsored by Oncotech, a not-for-profit organisation and public-private consortium formed by the Department of Medicine & Oncology of the University of Naples Federico II (Italy) and a CRO (Clinical Research Technology).

Oncotech is dedicated to clinical research, training, dissemination and scientific communication in the oncology field. Its aims are:

> To foster collaboration and interaction between university institutions and national and international research bodies
> To promote advanced scientific training courses, from Master’s degrees to Continuing Medical Education

GIM’s main research efforts are:

- Dose-dense adjuvant chemotherapy
- Fertility preservation
- Optimising adjuvant endocrine therapy

BIG now represents 57 like-minded research groups from around the world and reaches across more than 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.

“We are extremely happy and proud that GIM has joined the BIG network. This is a unique opportunity for our national group to be more actively involved in international academic trials in order to give our patients the opportunity to participate in such important studies. We will do our best to add our expertise to such an extraordinary network and group of leading breast cancer experts.”

Dr Matteo Lambertini
PRESTIGIOUS ONCOLOGY AWARDS

We are proud to announce that three world-class breast cancer experts and long-time friends of BIG, Dr Martine Piccart, Dr Etienne Brain and Dr Fatima Cardoso, have recently been honoured with prestigious awards in the field of oncology. We extend them our warmest congratulations!

DR PICCART RECEIVES VICTORIA’S SECRET GLOBAL FUND FOR WOMEN’S CANCERS 2022 MERITORIOUS AWARD

Dr Piccart founded the Breast International Group (BIG) together with Dr Aron Goldhirsch in 1999. She is currently President of BIG against breast cancer, the philanthropy unit of BIG, and Scientific Director at the Institut Jules Bordet, Brussels, Belgium.

Dr Piccart received the Victoria’s Secret Global Fund for Women’s Cancers 2022 Meritorious Award, in Partnership with Pelotonia & AACR. This new scientific award recognises the work and outstanding contributions of five prominent and influential female researchers to the fundamental understanding, prevention or treatment of breast or any form of gynaecologic cancers. Each of the five awardees received a prize amounting to $100,000. Moreover, they will be invited to nominate 3 to 5 outstanding early-stage investigators to be considered for a broader cancer research grant programme funded by The Victoria’s Secret Global Fund for Women’s Cancers and administered by the AACR and Pelotonia, and for which they will serve as mentors.

“I am grateful for this prize, which will support important research. We have definitely come a long way. Most women with early breast cancer are now able to get through it because they receive increasingly targeted treatments. However, the disease is not yet under control. It’s our duty to continue carrying out research, in particular for advanced or rare forms of the disease. It’s vital, patients need us,” says Dr Martine Piccart.

DR ETIENNE BRAIN RECEIVES 2022 B.J. KENNEDY GERIATIC ONCOLOGY AWARD

At the latest ASCO Annual Meeting 2022 (June 3-7) Dr Etienne Brain received the B.J. Kennedy Geriatric Oncology Award for his longstanding commitment and contribution to improving the treatment and care of older patients with cancer.

Treating older patients with cancer is complex and requires specific treatment approaches that take into account the additional symptoms and specific health conditions related to age. Although older adults now represent the majority of patients with cancer, there is still a lack of research and robust data in geriatric oncology, and this patient group is underrepresented in clinical trials (at most, 15% of all patients enrolled in studies are older than 75).

In his lecture, Dr Brain called for more representation of these patients in clinical trials, more education in geriatric oncology, and better collaboration between oncologists and geriatricians in order to prioritise and coordinate treatments and care.

“We need more diverse research and specific education to fight ageism and improve cancer care in the older patients. They deserve it. The onus is on us,” says Brain.

Dr Etienne Brain, MD, PhD, is a world-renowned oncologist and researcher, involved in both French and international studies on breast cancer in older women, such as ASTER 70s, one of the largest clinical trials conducted in the postoperative setting in women with breast cancer older than 70 (NCT01564056), and BIG’s APPALACHES (NCT03609047) study.

Dr Brain is senior medical oncologist at Institut Curie, in Saint-Cloud, France, and Secretary General of the European Organisation for Research and Treatment of Cancer (EORTC). He was President of the International Society of Geriatric Oncology (SIOG) from 2014 to 2106 and has been a member of BIG’s Executive Board since 2018.

Source: https://dailynews.ascopubs.org/doi/10.1200/ADN.22.201040

Visit also: https://www.esmo.org/about-esmo/awards/esmo-women-for-oncology-award

DR FATIMA CARDOSO HONOURED WITH ESMO WOMEN FOR ONCOLOGY AWARD 2022

The 2022 ESMO Women for Oncology Award was presented to Fatima Cardoso, Director of the Breast Unit of the Champalimaud Clinical Center (CCC) in Lisbon (Portugal) and President of the Advanced Breast Cancer (ABC) Global Alliance, for her outstanding commitment to oncology and patients. Cardoso forged her way in oncology, becoming a role model to a whole generation of women working in oncology in Portugal and beyond.

Fatima Cardoso will deliver her Award Lecture during the ESMO Congress 2023 Opening Ceremony on Friday, 9 September 2022, entitled “Women’s rights and gender balance: one step forward, two steps back?”

Fatima Cardoso, on receiving this award: “I am very honoured to receive the 2022 ESMO WHO Award. Motivating, educating and helping other female oncologists and students has been a central part of my career, and one that has been very rewarding. It is a pleasure (and a little bit of pride) to see fellow friends reaching leadership positions”.

And she continues: “Women now represent more than 80% of the workforce in healthcare but in leadership positions they still represent only about 20-30%. Gender balance is widely discussed but remains an unsolved problem. Why? I believe we all need to reflect carefully on the reasons and potential solutions. Are women really sufficiently helping each other, with real action, not just words?”

She adds: “The last few years, we have also seen frightening steps back in women’s rights, from Afghanistan to the United States, and in the terrible Ukrainian situation.”

And she concludes: “I have dedicated my life to the fight against breast cancer, the most ‘gender imbalanced’ cancer that exists! While never forgetting the needs of the 1% of male breast cancer patients – both through research, quality of care and advocacy –, it has mostly been with all the wonderful women I have known that I have learnt the most important lessons as an oncologist and as a human being. Breast cancer has taken too soon the lives of so many friends! A reminder that there is still so much to be done. It is to each of them, specially to all women with advanced/metastatic breast cancer, that I dedicate this award and the continuous promise to keep on fighting.”

Visit also: https://www.esmo.org/about-esmo/awards/esmo-women-for-oncology-award
Dr Fatima Cardoso was also the 2021 recipient of the ESO Umberto Veronesi Memorial Award, which aims at recognising a physician’s leading role in advancing science and care of breast cancer patients. In the interview BIG held with her last year, part of which can be found below, she talks about the progress we are seeing in the field of de-escalation of early breast cancer therapy, the importance of collaboration and the advantages of a global network such as BIG.

What progress have we seen in the field of de-escalation of early breast cancer therapy? Are these practice-changing?

I think that the best word is not “de-escalation” but rather “optimisation”; it’s not always about providing less treatment, but optimising treatment based on several characteristics of the disease and the patient.

In the early breast cancer setting, there are various examples of de-escalation trials that have been practice-changing. The MINDACT study (EORTC 100641 / BIG 3-04) is a typical example of treatment de-escalation. In this study we decreased the use of chemotherapy through the help of a genomic signature, the MammaPrint® test. This study has been practice-changing, since it showed that patients considered as high-risk of cancer recurrence based on traditional factors, but identified as low risk by the MammaPrint test and treated with endocrine therapy alone (without chemotherapy), still had very good outcomes at 8 years of follow-up. Particularly for post-menopausal women, we see no clinically meaningful benefit from chemotherapy and, therefore, it can be safely omitted.

I think it’s important to emphasise that the notion of de-escalation should not be limited to the treatment of early breast cancer. We are seeing a shift in mentalities also in the metastatic setting. While the old way of thinking is that, since metastatic disease is incurable, you have to give everything and as much as you can in the hope that you can somehow control the disease and prolong the life of the patient. Doctors and researchers now understand the need to metastatic setting.

How have academic cooperative groups contributed to this process in the past and how can a network like BIG continue to contribute?

MINDACT was a great example of academic collaboration that led to practice-changing results and impacted the lives of many patients with early breast cancer.

For the future, I think that we, investigators, need to discuss with statisticians about how to run these de-escalations trials in an appropriate way that provides the level of evidence that we need, but without taking so many years as MINDACT did, for example (about 15 years). We need to start changing mentalities in drug development itself, in terms of doses and in terms of trial design.

What we typically do is find the maximum tolerated dose. This traditionally comes from chemotherapy development. The problem is that we keep on trying to give the maximum tolerated dose even with targeted agents. But these agents were developed to hit a certain target and the efficacy is linked to “hitting the target”. We should therefore be looking for the minimum dose required, sometimes called “minimum biological effective dose”, to hit the target. This would allow us to retain efficacy and greatly decrease toxicity.

We need to start changing this from the preclinical stage up until the way phase I and then phase III trials are run. As academic groups, I believe that we need to pay attention to that, particularly in the field of targeted and biological therapies.

From my perspective, to run effective de-escalation studies, we also need innovative trial designs, and this must be done in close collaboration with regulators and pharmaceutical companies. These studies have to be statistically sound and accurate, but they can’t be run as non-inferiority trials, which demand a huge patient population. The same happened in the field of biosimilars, and a new methodology was developed and is approved by regulators. I strongly support the development of an equally effective methodology, approved by regulators, for de-escalation trials as well as for trials that aim at approving a new drug formulation or the use of lower (but similarly effective) doses.

I think that an academic network like BIG has the potential to play a key role here, to help change mentalities from the beginning of drug development, and to raise a voice in the discussions with pharmaceutical companies and regulators.

The academic community took a long time to pay attention to metastatic breast cancer. There are now different research programmes dedicated to the metastatic disease, such as AURORA (BIG 14-01), but the majority of studies run in this setting are still pharma driven and that leaves a lot of important questions unanswered for the patients.

Because metastatic breast cancer clearly has fewer patients (about 1/3 compared to 2/3 of patients with early breast cancer), international cooperation between academic groups is crucial to run trials in the metastatic setting that may not have commercial interests but tackle questions that really matter to patients.

For the full interview, go to: BIG Research in Focus, Vol 14 (April 2021).
For the fourth consecutive year, BIG and the EORTC (European Organisation for the Research and Treatment of Cancer) are combining their efforts and expertise by organising an annual Pink October webinar for a scientific audience.

This one-hour webinar will take place on Wednesday 19 October 2022 from 13:00 to 14:00 CET. Registration is free but mandatory. See link below.

The theme of this year’s webinar is “The unmet needs of older patients with breast cancer”. The objective is to create further awareness about the need to include more of the growing population of older patients in clinical trials. We will provide facts and figures, focus on the importance of geriatric assessment, recommend screening tools and highlight examples of recent research being done in elderly patients, e.g., the phase 2 APPALACHES trial, being carried out through the EORTC and BIG network of investigators. This is the first study to compare palbociclib with chemotherapy in patients with high-risk ER-positive breast cancer treated with standard adjuvant endocrine therapy.

Speakers include the following breast cancer experts from the BIG and EORTC networks:

> **Dr Etienne Brain** – senior medical oncologist involved in both French and international studies on breast cancer in older women. Institut Curie - Hôpital René Huguenin, Saint-Cloud (France), past chair of the EORTC Breast Cancer Group, member of BIG’s Executive Board, past president of SIOG (International Society of Geriatric Oncology), and co-Principal Investigator of the APPALACHES trial.

> **Dr Hans Wildiers** – medical oncologist dedicated to breast cancer research and geriatric oncology. University Hospitals Leuven, Belgium, past Chairman of the Cancer in the Elderly task force of the EORTC and member of the Breast Cancer Group, past President and current board member of SIOG (International Society of Geriatric Oncology), and Principal Investigator of the APPALACHES trial.

> **Dr Laura Biganzoli** – medical oncologist with a long-standing interest in improving the clinical management of older breast cancer patients. She has served as principal investigator of several clinical trials focused on geriatric oncology: Director of the breast centre at the Oncology Department of the Hospital of Pistoia, ASL Toscana Centro, Pisto (Italy) and Member of the Board of Directors at SIOG (International Society of Geriatric Oncology).

> **Tanja Spanic** – a patient advocate and president of Europa Donna Slovenia. Tanja has been involved in BIG’s Patient Partnership Initiative, participating in BIG-NCTN (National Clinical Trials Network, former NABCG - North American Breast Cancer Group meeting) among other activities.

The sessions will be presented in English and will be followed by a panel discussion.

For the programme and on-line registration form of the webinar, click on this link.
AMEERA-6 (BIG 20-01)
Study to be terminated
On 17 August 2022, the study sponsor, Sanofi, announced that they will stop the global clinical development programme of amcenestrant and therefore terminate the AMEERA-6 study. This decision follows the recommendation of the Independent Data Monitoring Committee (IDMC) and is based on the outcome of a prespecified interim analysis of the phase III AMEERA-5 trial in advanced breast cancer that showed that amcenestrant in combination with palbociclib did not meet the prespecified boundary for continuation in comparison with the control arm. No new safety signals were observed.

Trial participants will be transitioned to letrozole in combination with palbociclib or another appropriate standard of care therapy, as determined by their physician.


AMEERA-6 is a randomised, multicentre, double-blind, phase III study of amcenestrant (SAR439859) versus tamoxifen for the treatment of patients with hormone receptor-positive, human epidermal growth factor 2-negative or positive, stage IIIB-III breast cancer who have discontinued adjuvant aromatase inhibitor therapy due to treatment-related toxicity.

**Study information:**
- Study PIs: David Cameron, Etienne Brain and Otto Metger
- Co-lead partners: EORTC, AFT and BIG HQ
- 18 BIG member groups planned to participate in the study
- Pharmaceutical partner: Sanofi (sponsor)
- Study start date: 12 January 2022
- Target accrual: 3,738 randomised patients from 650 sites in about 29 countries
- ClinicalTrials.gov Identifier: NCT05128773

**Note from the BIG HQ**
This is of course disappointing news, after all the hard work done to set up and launch the study, but obviously this is not unusual in the oncology world. The BIG EB and the BIG HQ would like to thank all the BIG members and centres that were involved in the study setup and conduct. Given the significant progress made so far – including over 2,647 patients enrolled from 24 BIG member groups participating in the study – the BIG EB and the BIG HQ believe that the study was a success even though it has been stopped.

**APHINITY (BIG 4-11)**
Eight-year results presented at ESMO Virtual Plenary (14 July 2022)
On 14 July, full findings from the phase III APHINITY study in HER2-positive early breast cancer were presented at the European Society for Medical Oncology (ESMO) Virtual Plenary (VP6-2022).1

**Eight-year data from the APHINITY study show Roche’s Perjeta-based regimen continues to reduce the risk of disease recurrence for people with HER2-positive early breast cancer.**

- **Greatest benefit continued to be seen in people who are at a high risk of recurrence (those with lymph node-positive disease).**
- **With longer follow-up, treatment effect continues to be seen regardless of hormone receptor status; however overall survival data remain immature.**
- **The majority of HER2-positive breast cancer cases are diagnosed at an early stage, when the aim of treatment is cure.**

Results at 8.4 years median follow-up (101 months) showed the continued benefit of the combination of pertuzumab (Perjeta®), trastuzumab (Herceptin®) and chemotherapy (the Perjeta-based regimen), versus Herceptin, chemotherapy and placebo, when given as post-surgery (adjuvant) intravenous (IV) treatment for people with lymph node (LN)-positive, HER2-positive early breast cancer, who are at high risk of recurrence. For patients with lymph node (LN)-positive disease, results showed a 28% reduction in the risk of recurrence or death, corresponding to an absolute benefit at eight years of 4.9% (invasive disease-free survival [iDFS], hazard ratio [HR]-0.72, 95% confidence interval [CI] 0.60-0.87). The safety profile was consistent with previous studies.

Based on the primary analysis of the study in 2017, the clinical value of the Perjeta-based regimen has been recognised by health authorities worldwide. The regimen is approved for the treatment of people with early breast cancer who are at a high risk of recurrence in more than 100 countries, including the United States (US), the European Union (EU) and China. It has also been recognised in multiple international treatment guidelines, including those from the American Society of Clinical Oncology (ASCO), ESMO, the National Comprehensive Cancer Network (NCCN) and St Gallen International Breast Cancer Conference, which recommend it as a standard of care for the post-surgery treatment of people with HER2-positive early breast cancer at high risk of recurrence.2,5-8,10

More than 500,000 people worldwide who have HER2-positive breast cancer and are at high risk of recurrence have received the Perjeta-based regimen so far.2

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

**Study information:**
- Study PIs: Sibylle Loibl, Martine Piccart and José Bines
- Lead partners: BIG HQ in collaboration with Institut Jules Bordet – Clinical Trials Support Unit (IJB-CTSU) and Frontier Science & Technology Research Foundation (FSTRF)
- 24 BIG member groups participating in the study
- Pharmaceutical partner: Roche (sponsor)
- Final accrual: 4,805 patients enrolled, 2,647 of them from the BIG groups
- ClinicalTrials.gov Identifier: NCT0358877

**REFERENCES**
3. ESMO APHINITY abstract – VP6-2022
6. Roche data on file.
The DCIS study (BIG 3-07 / TROG 07.01) is an academic, investigator-led, randomised phase III study of radiation doses and treatment schedules in patients with non-low risk DCIS of the breast. Ductal carcinoma in situ (DCIS) of the breast is characterised by abnormal cells in the milk ducts which have not spread into the breast tissue. The international DCIS study shows that after breast conserving surgery, higher radiation doses to the part of the breast where the DCIS was found, in addition to radiotherapy of the whole breast, significantly reduced the risk of returning in patients with higher-risk DCIS. Compared to 5 weeks of whole breast radiotherapy, the study also shows that the shorter, more convenient 3 weeks of radiotherapy did not increase recurrence.

These primary results have recently been published in The Lancet (6 August 2022), which concludes: “In patients with resected non-low-risk DCIS, a tumour bed boost after whole breast irradiation (WBI) reduced local recurrence with an increase in grade 2 or greater toxicity. The results provide the first randomised trial data to support the use of boost radiation after postoperative WBI in these patients to improve local control. The international scale of the study supports the generalisability of the results.”

This achievement demonstrates that research on DCIS is a high priority for many patients and researchers. The ongoing challenge is to ensure that this academic study is completed successfully, as the study patients need to be followed-up for 10 years in order to achieve the purpose of the study. Considerable resources are required for the study to yield meaningful practice-changing outcomes, particularly to obtain the cutting-edge biomarker information that will allow personalised treatment of patients with DCIS.

Practice-changing potential, scientific advances and social benefits

Tailing radiation doses and number of treatments to the recurrence risks in patients undergoing radiotherapy for DCIS after surgery are of intense international interest. The study is one of the few large-scale clinical trials in DCIS that used highly standardised protocols for radiation treatment, detailed patient data collection, robust quality assurance, and development of one of the world’s largest DCIS tissue resource. Collectively, this comprehensive study has the potential to generate the high-quality evidence necessary for improving radiotherapy in patients with DCIS to improve patient outcomes.

Research using the unique DCIS resource of the study may identify markers for recurrence, in particular invasive recurrence. If this future research is successful, a test could be developed to predict the recurrence risks of DCIS and guide treatment decisions by patients and clinicians.

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

Study information:
- Study PI: Boon Chua
- Lead partners: Trans-Tasman Radiation Oncology Group (TROG) Cancer Research is the coordinating group and study sponsor
- 6 BIG member groups participating in the study
- Funding: the study is funded by the Australian National Health and Medical Research Council, Susan G. Komen for the Cure®, Breast Cancer Research Foundation (FSTRF), and US collaborative groups through NRG Oncology (sponsor in the USA)
- 21 BIG member groups are participating in the study
- Final accrual: 1,608 patients from 136 centres in 11 countries (completed on 30 June 2014, two years ahead of schedule)
- ClinicalTrials.gov Identifier: NCT00470236

REFERENCES

OLYMPIA (BIG 6–13)

The OLYMPIA trial: a global collaborative effort

Patients with high-risk HER2-negative primary breast cancer who carry BRCA1 or BRCA2 mutations in their genes could see the risk of death from their breast cancer cut by about 32% when treated with Astra Zeneca’s olaparib (Lynparza®). Highly encouraging results from the OLYMPIA trial published last year were greeted with great interest and enthusiasm across the breast cancer community. For the first time, research showed that patients who carried a mutation in the BRCA1/2 genes and developed a high-risk, HER2-negative, early breast cancer benefited from adjuvant treatment with the PARP inhibitor, olaparib (Lynparza®), after completing local treatment and neoadjuvant or adjuvant chemotherapy.

In the USA, olaparib underwent priority review by the Food and Drug Administration and, in March 2022, received regulatory approval for the adjuvant treatment of patients with BRCA-mutated HER2-negative high-risk early breast cancer who have already been treated with chemotherapy either before or after surgery. Regulatory agencies in Europe and Japan approved the new indication in June and August, respectively.

After OLYMPIA data were presented at the 2021 Annual Meeting of the American Society of Clinical Oncology (ASCO), ASCO guidance for the management of hereditary breast cancer was updated to include a recommendation for use of olaparib in patients with early stage, high-risk breast cancer with BRCA1/2 mutations. The National Comprehensive Cancer Network also added olaparib for a similar indication to its breast cancer guidelines and the St Gallen International Consensus Guidelines for Treatment of Early Breast Cancer 2021 endorsed the use of olaparib for patients meeting OLYMPIA inclusion criteria.

The results of the second interim overall survival (OS) analysis were presented during the ESMO Virtual Plenary session on 16 March 2022 and further discussed on 17 March during the Virtual Plenary Expert Insights (see the press release). A manuscript on the OS interim analysis is being prepared.

The results of the quality of life (QoL) analysis were presented during SABCS 2021. An updated QoL analysis is ongoing, and a manuscript will be prepared afterwards.

An abstract on the Japanese subset analysis has been accepted as an oral presentation during the JBCS congress (Yokohama, 30 June to 2 July 2022).

Study information:
- Study PI: Andrew Tutt, Judy Garber, Charles Geyer and David Cameron
- Lead partners: BIG HQ, in collaboration with Frontier Science & Technology Research Foundation (FSTRF), and US collaborative groups through NRG Oncology (sponsor in the USA)
- Pharmaceutical partners: Astra Zeneca (global sponsor for all countries excluding the USA) and Merck (co-developer of the drug)
- 21 BIG member groups are participating in the study
- Study start date: 22 April 2014
- Final accrual: 1,836 patients from 546 sites in 23 countries worldwide
- ClinicalTrials.gov Identifier: NCT02032823

REFERENCES
ALTO (BIG 2–06)
Agostinetti E, Ameye L, Martel S, et all. PREDICT underestimates survival of patients with HER2-positive early-stage breast cancer. npj Breast Cancer, 20 July 2022.

ALPHABET (BIG 18–04)
Article describing the study design, published in Future Oncology, 5 May 2022, 25 April 2022.

APHINITY (BIG 4–11)
“Effect of young age at diagnosis on the clinical outcomes of women with HER2-positive early-stage breast cancer receiving adjuvant trastuzumab with or without pertuzumab in the APHINITY trial”, manuscript published in the Journal of the National Cancer Institute, 5 May 2022.

Regional timelines variation to initiate a multinational clinical trial: the Aphtinity experience”, manuscript accepted at cancermedicalscience.
“Cardiotoxicity related to dual anti-HER2 blockade in the APHINITY Trial”, abstract presented at ASCO 2021, manuscript under peer-review.

DCIS (BIG 3–07 / TROG 07.01)
Study’s primary results published in The Lancet, 6 August 2022.

PYTHIA (BIG 14–04)
ESMO BREAST CANCER 2022

ESMO Breast Cancer 2022 took place as a hybrid meeting, onsite in Berlin, Germany, on 3-5 May 2022, and online, through a virtual platform.

ESMO Breast Cancer is a congress designed for breast cancer researchers and clinicians who have a specific interest in innovation (including translational research, new agents, molecular and functional diagnostics, biomarkers and cutting-edge research applications in the clinical setting) and care.

The following BIG study was presented:

AMEERA-6 (BIG 20-01) poster
"Adjuvant Study of Acmenestrant (SAR439859) Versus Tamoxifen for Patients With Hormone Receptor-positive (HR+) Early Breast Cancer (EBC), Who Have Discontinued Adjuvant Aromatase Inhibitor Therapy Due to Treatment-related Toxicity (AMEERA-6)"

Please see update on page 18.

ASCO ANNUAL MEETING 2022

(USA and online, from 3 to 7 June 2022)

> Dr Etienne Brain received the 2022 B.J. Kennedy Geriatric Oncology Award for his longstanding commitment and contribution to improving the treatment and care of older patients with cancer. See also page 12.

> ALTTO Abstract: "Effect of mevalonate pathway inhibitors on outcomes of patients (pts) with HER2-positive early breast cancer (BC) in the ALTTO trial"

> AMEERA-6 (BIG 20-01): "Adjuvant study of amcenestrant (SAR439859) versus tamoxifen for patients with hormone receptor-positive (HR+) early breast cancer (EBC), who have discontinued adjuvant aromatase inhibitor therapy due to treatment-related toxicity (AMEERA-6)"

> APHINITY (BIG 4-11): "Cardiotoxicity related to dual anti-HER2 blockade in the APHINITY Trial", manuscript under peer-review.

> DECRESCEO: A Trial in Progress poster: “DECRESCEO: De-escalation of adjuvant chemotherapy in patients with HER2+/HR-/node-negative early breast cancer who achieve pCR after neoadjuvant taxane and subcutaneous dual anti-HER2 blockade"

> NEOALTTO: “Prognostic and predictive implications of the intrinsic subtypes and gene expression signatures in early-stage HER2+ breast cancer: A pooled analysis of CALGB 40601, NeoALTTO, and NSABP B-41 trials”

> NEOALTTO: “Impact of Anti-HER2 Therapy Alone and in Association with Weekly Paclitaxel on the Ovarian Reserve of Young Women with HER2-positive Early Breast Cancer: Biomarker Analysis of the NeoALTTO Trial”

> PALLAS poster: “Impact of Body Mass Index on treatment and outcomes in early hormone receptor-positive breast cancer patients receiving endocrine therapy with or without palbociclib in the PALLAS trial”

> NEOALTTO: “Impact of Anti-HER2 Therapy Alone and in Association with Weekly Paclitaxel on the Ovarian Reserve of Young Women with HER2-positive Early Breast Cancer: Biomarker Analysis of the NeoALTTO Trial”

> PALLAS poster: “Impact of Body Mass Index on treatment and outcomes in early hormone receptor-positive breast cancer patients receiving endocrine therapy with or without palbociclib in the PALLAS trial”
CLINICAL TRIALS AND ACTIVITIES

OTHER TRIALS AND ACTIVITIES

BY BIG MEMBER GROUPS

ABCSG

The significance of meeting the unmet needs of older patients with breast cancer

AN INTERVIEW WITH PROFESSOR MICHAEL GNANT, PRESIDENT OF THE AUSTRIAN BREAST AND COLORECTAL CANCER STUDY GROUP (ABCSG)

It is known that bone mineral density decreases with age. It is also known that patients undergoing adjuvant treatment for breast cancer suffer from osteoporosis and bone fractures as a long-term side effect of endocrine therapy. The important ABCSG-18 study, with a primary endpoint being fractures, was first presented by Prof Gnant at the ASCO Congress in 2015 and then published in The Lancet. In 2018, also at ASCO, Prof Gnant presented preliminary data on disease-free survival (DFS).

Now the final results of the study show that taking the anti-RANK-ligand denosumab reduces the risk of breast cancer recurrence, but also demonstrates a beneficial effect on overall survival.

As the study’s Principal Investigator, please give us a short outline of this important study.

Professor Gnant: ABCSG-18 recruited 3,400 postmenopausal patients with HR+ breast cancer in Austria and Sweden – it is a double-blinded, placebo-controlled, randomised phase III trial that compares the adjuvant use of the anti-RANK-ligand denosumab with placebo. The primary endpoint results of the trial (Gnant M, et al., The Lancet 2015) showed that denosumab dramatically reduces treatment-induced clinical fractures, HR = 0.5. The trial also shows that the adjuvant use of the antibody at the dose of 60 mg twice yearly (the same dose as for the treatment of osteoporosis) is very safe – we could not identify any major toxicity in this huge trial. Finally, ABCSG-18 also confirms long-term outcome benefits in terms of DFS, bone-metastasis-free survival and even overall survival – very comparable to those of bisphosphonates in the postmenopausal patient group (EBCTCG 2015, The Lancet).

Would you only give denosumab to postmenopausal patients with HR+ breast cancer or are there other cohorts where these benefits may apply?

Professor Gnant: Experience tells us that we must not extrapolate from the results of one trial to other patient groups. I understand that it is tempting, but it can also be dangerous – we have for example seen in the bisphosphonate era that “extrapolating” the results of the ABCSG-12 trial (NEJM 2019) in premenopausal patients with HR+ breast cancer to patients with receptor-negative disease not only did not work but may even have ended in some harmful effects on the other patient cohort. Scientific discipline is important – this means that, in general, we have to stick with the patient subgroup that was studied. The “art of medicine”, however, may allow us to sometimes treat individual patients who would not have fulfilled the inclusion/exclusion criteria of a pivotal trial – we have to do this cautiously, and in full transparency with patients. Particularly the elderly patient subgroup, which for a long time has not been allowed into clinical trials, despite the fact that it constitutes the numerically most important patient group.

The results of the ABCSG-18 study – after the outstanding results of the postmenopausal breast cancer study ABCSG-16 / S.A.L.S.A in 2021 – may once more be practice changing, also given the consideration for routine clinical use. Could you please comment on the implications of these findings and, whether, secondly further studies (maybe in the ABCSG project pipeline) will address related questions, particularly for an older patient cohort?

Professor Gnant: Currently, the ABCSG-18 trial results are being scrutinised and discussed by several guideline bodies, particularly ASCO. Clearly, there are arguments for and against a routine recommendation but, in my personal practice, my consideration is: I have an “easy” intervention (2 subcutaneous injections per year!), almost no side effects (not a single case of osteonecrosis of the jaw at this dose!), reasonably cheap (as compared to other innovations in breast oncology), and it definitely cuts treatment-induced fractures in half – even long-term outcomes are markedly improved. I find it difficult to argue with these facts, and so do patients.

ABCSG has quite a number of projects and trials in the pipeline and starting this year or in early 2023. Because of the particular importance of the elderly breast cancer population, we have long raised the age limit of trial inclusion to 80 years, or even no limitation at all – we do however need to consider methodological issues of trial patients in that age group (“competing causes” of events and/or adherence), and thus it will probably remain unrealistic to have no age limit whatsoever in the future.

Professor Michael Gnant, President of ABCSG

JBCRG

Ongoing clinical trials and publications

The Japanese Breast Cancer Research Group (JBCRG) is running the following clinical trials:

JBCRG-C07 (REIWA):
- an observational study to evaluate the impact of a gene panel test on treatment decision-making in breast cancer throughout Japan as a whole

JBCRG-ABCD project:
- the Advanced Breast Cancer Database (ABCD) project

JBCRG-C08 (ATTRIBUTE):
- Atezolizumab in patients with TRiple-negative Breast cancer, mUlticenter observational study for Treatment safety and Efficacy

JBCRG-C07-A1 (REIWA2):
- an exploratory study
  a) using gene expression analysis to assess the predictability of resistance to hormone therapy and chemotherapy sensitivity in luminal breast cancer patients who have a treatment history of CDK4/6 inhibition and
  b) investigating patients with luminal or triple negative breast cancer showing FGF-FGFR mutation/ amplification detected using FoundationOne® comprehensive gene expression analysis

JBCRG-M08 (AMBER):
- innovation of the 1st line strategy optimised as abemaciclib with endocrine therapy based on the ESRI mutation of ctDNA for HR-positive HER2-negative advanced metastatic breast cancer patients (JBCRG-M08) – Multi-institutional phase II trial

RECENT PUBLICATIONS

1) JBCRG-M05 (PRECIOUS) in Cancer Science 2022
- Pertuzumab retreatment for HER2-positive advanced breast cancer: a randomised, open-label phase III study.
  Yutaka Yamamoto, et al. doi: 10.1111/cas.15474.2
2) JBCRG-M04 (BOOSTER) in Lancet Oncol 2022
Switch maintenance endocrine therapy plus bevacizumab after bevacizumab plus paclitaxel in advanced or metastatic oestrogen receptor-positive, HER2-negative breast cancer (BOOSTER); a randomised, open-label, phase II trial. Shigehira Saji, et al. doi: 10.1016/S1470-2045(22)00196-6.

3) JBCRG-22TR in BMC Medicine 2022

4) JBCRG-C06 in Japanese Journal of Clinical Oncology 2022
Factors associated with overall survival after recurrence in patients with ER-positive/HER2-negative breast cancer: an ad-hoc analysis of the JBCRG-C06 Safari study. Hidetoshi Kagawachi, et al. https://doi.org/10.21203/rs.3.rs-190374/v1

PARTICIPATION IN GLOBAL TRIALS
JBCRG is involved in the following studies run under the BIG umbrella: AMEERA-6, ALEXANDRA/1Mpassio30, OlympiaA, POSITIVE, PenelopeB and PALLAS. For details about the trial leadership, please refer to the Trials Table on page 32.

LACOG
The Brazilian Breast Cancer Conference 2022 – LACOG/GBECAM and Best of SABCS Brazil
The Brazilian Breast Cancer Conference 2022 was held on 29 and 30 April in São Paulo, alongside the official licensed event, Best of SABCS Brazil. The event was organised by the Latin American Cooperative Oncology Group (LACOG) and the Brazilian Group for Breast Cancer Studies (GBECAM). The conference, carried out in a hybrid format with in-person participants and online transmission, involved 34 national and two international speakers. 1,117 participants from different states in Brazil attended the scientific sessions during those two days.

The LACOG Geriatric Oncology Group begins its activities

When we talk about oncology, several gaps need to be filled in the care of elderly patients with cancer, especially in the construction of scientific evidence that can be applied to the elderly population,” according to Dr Lucíola Pontes, Chair of the LACOG Geriatric Oncology Group. The LACOG Geriatric Oncology Group was created to gather information on the current scenario of geriatric oncology in Latin America and develop research projects in the region.

Recent Publication
The abstract “Delay in postoperative radiation in patients with breast cancer in Brazil: a sub-analysis of AMAZONA III” was presented at the ESTRO (The European Society for Radiotherapy and Oncology) Congress by Dr Gustavo Marta, LACOG Radiation Group Vice-Chair, and other authors. The event was held from 6 to 10 May 2022 in Copenhagen, Denmark. In 582 patients evaluated, most patients (58.9%) had clinical stage III, were treated in the public health system (74.1%), and had a monthly household income of level 1-3 minimum wage (45.9%). The majority of breast cancer patients in Brazil initiate post-operative radiotherapy (PORT) within an adequate timeline. However, patients from the public health system have a significantly higher risk of delayed PORT and thus strategies to facilitate and streamline the access to PORT must be implemented.

Project with the participation of LACOG develops and supports the structuring of six new cancer research centres in Brazil
To help promote the growth of clinical research in Brazil, the Instituto Vencer o Câncer, in partnership with LACOG, developed the project “Love for Research Against Cancer” in Brazil. The objective is to develop and support the structuring of new research centres, especially in regions where research is underserved. In addition to developing and organising the operational and personnel structure, LACOG will monitor the implementation of clinical studies and activities for a period of two years. In this first stage, six institutions were selected in the north and northeast of Brazil in the following cities: Manaus, Feira de Santana, Belém do Pará, Campo Grande, João Pessoa and São Luís.
TOT-HER3 trial results confirm anti-tumoural activity of a novel immunoconjugate for early-stage breast cancer

Results of SOLTI’s TOT-HER3 study in patients with untreated HR-positive/HER2-negative early breast cancer demonstrate that a single dose of patritumab deruxtecan produces a clinically significant response, an increase in immune clearance and a decrease in cell proliferation.

In addition, the safety of the treatment in patients with early breast cancer has been confirmed, in line with the results previously reported.

Due to the high anti-tumour activity of the drug in this subgroup of patients, the study will be extended to test an alternative drug dosage pattern.

In parallel, a new trial – SOLTI-2103 VALENTINE – will be launched to evaluate the usefulness of this immunoconjugate compared to chemotherapy in early hormone-sensitive disease.

The latest results of SOLTI’s TOT-HER3 study, the first trial to test the immunoconjugate drug patritumab deruxtecan in patients with previously untreated hormone-sensitive (HR+), HER2-negative (HER2-) early breast cancer, show biological changes such as infiltration of immune cells into the tumour, a decrease in proliferation, and high anti-tumour activity with tumour shrinkage in 45% of the 78 patients enrolled in the trial. The safety of the treatment has also been confirmed. Based on these data, the study will be extended to include patients with triple-negative breast cancer and, in addition, a new study, the SOLTI-2103 VALENTINE trial, will be initiated to test patritumab deruxtecan alone or in combination with endocrine therapy as neoadjuvant treatment in HR-positive/HER2-negative early breast cancer.

The results of TOT-HER3 were presented on 3 May at ESMO Breast Cancer 2022, and update and confirm the trend reported last December at the San Antonio Breast Cancer Symposium (SABCS) 2021 after analysis of the response in the first 30 patients. The study is led by Dr Aleix Prat, president of SOLTI and head of the Medical Oncology Service at Hospital Clinic de Barcelona, as well as member of the IDIBAPS group for translational genomics and targeted therapies in solid tumours, and Dr Mafalda Oliveira, member of SOLTI’s Executive Board and medical oncologist at Hospital Vall d’Hebron and Vall d’Hebron Institute of Oncology (VHIO).

“The results of TOT-HER3 are especially relevant because they have demonstrated for the first time the efficacy of this immunoconjugate drug in an early context, which until now had only been tested in patients with metastatic breast cancer. It also shows that the tumours that benefit most from this treatment are those with a more aggressive profile, regardless of their levels of HER3 protein and mRNA. These data lay the groundwork for future studies to conclude whether these drugs can partially or completely replace the use of chemotherapy in early HR+/HER2- disease, a pathology that affects 70% of breast cancer patients,” says Dr Aleix Prat, Principal Investigator of TOT-HER3.

According to Dr Mafalda Oliveira, co-Principal Investigator of TOT-HER3, “This is a unique study for many reasons, one of them being its innovative design: it is the first window trial with an immunoconjugate or ADC, these studies, which constitute a distinctive research programme at SOLTI, take advantage of the short window of time between the diagnosis of the neoplasm and surgery to test new therapeutic strategies, which makes it possible, in a very short period of time, to obtain fundamental biological information to then design larger studies that can lead to the approval of the drug being tested. In this case, and for the first time, positive biological changes and tumour shrinkage have been demonstrated in patients with HR+/HER2- breast cancer with the ADC patritumab deruxtecan, after a single administration of the drug”.

TOT-HER3 results open new lines of investigation

Given the efficacy demonstrated by the ADC patritumab deruxtecan in the entire subgroup of patients with early hormone-sensitive disease HR+/HER2-, a new study – SOLTI-2103 VALENTINE – is being planned to test this treatment in the neoadjuvant context to check its efficacy compared to chemotherapy for the same patient population. Furthermore, based on its current results, the TOT-HER3 study will be extended with two additional cohorts: the first one will analyse whether a lower dose of the drug – which translates into greater tolerability – results in equal efficacy, and the second one will include patients with triple-negative breast cancer.

TOT-HER3 has made it possible to explore, for the first time, the expression of HER3

HER3 is a member of a family of key proteins, but has so far been little studied in cancer research. Within this family, there are four types of growth factors or cell division pathways involved in tumour development: HER1, HER2, HER3 and HER4. HER3 overexpression occurs in metastatic breast cancer and other tumour subtypes and is a poor prognostic factor. However, so far, no HER3-targeted agent has been approved in this setting or in any type of tumour, so this study is a major translational effort, and the data collected will improve our knowledge of this biomarker in order to determine its suitability as a therapeutic target.

“It is a study with a high translational component, which has allowed us to prove that the activity of the drug is independent of HER3 levels in the tumour, which is extremely interesting”, says Dr Prat.

The TOT-HER3 study, promoted by SOLTI Breast Cancer Research Group, involves 78 patients from 10 Spanish hospitals and is carried out in collaboration with the pharmaceutical company Daiichi Sankyo.

REFERENCE
1. HER3 is a protein found on the surface of cells that is a clear predictor of poor prognosis when overexpressed in breast tumours.
Overview of the
CURRENT STUDIES RUN WITHIN THE BIG NETWORK

Open trials / research programmes

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<td>A randomised phase III trial of trastuzumab + Alpelisib +/- fulvestrant vs. trastuzumab + chemotherapy in patients with HER2+ mutated breast cancer - NCT02841974</td>
<td>A. Pérez- Fidalgo C. Cristofani P. Bardot</td>
<td>Co-Leading partners: GEICAM (sponsor) / BCSC and BIG HQ Pharma partner: Novartis Funding: Novartis</td>
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<td>H. Wildiers E. Brain K. Ponie</td>
<td>Supporter trial Coordinating group: EORTC (sponsor) Pharma partner: Pfizer</td>
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<td>P. Aftimos M. Benelli A. Guerrero Zolano</td>
<td>BIG-sponsored programme Co-Leading partners: BIG HQ (sponsor) / UB-CTSU / FSS Pharma partner: N/A Funding: Breast Cancer Research Foundation® (BCRF) as the main funder, Fondation Cancer Luxembourg, Pfizer grant for non-drug research, Fondation centre le Cancer (Belgium), National Lottery (Belgium), NIF Foundation, Rhone Trust, Banque and Dana Webb, Canondale, Fondation Fuku 21, Sogorim, Think Pink Belgium (SMART Fund), Cognazine Foundation, Eurofins Foundation and many individual donors. AURORA has also been supported by the Fund Friends of BIG, managed by the King Baudouin Foundation.</td>
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<td>S. Lobli G. von Mindelwitz</td>
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<td>M. Piccart G. Zopoli</td>
<td>Co-Lead trial Co-Leading partners: UB-CTSU (sponsor) and BIG HQ Pharma partner: Roche Funding: Roche (grant)</td>
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<td>E. Munzone S. Abls</td>
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NB: This table does not include the studies in development and all closed trials. For more information, please visit: www.BIGagainstbreastcancer.org.*

*All information available on the BIG website.

Legend: AFT: Alliance Foundation Trials, LLC; BCRF: Breast Cancer Research Foundation; FG: Frontier Genetics; HHS: Health Services Scotland, LTD; IBCSG: International Breast Cancer Study Group; ICBST: Italian Breast Cancer Study Group; ICBT: Italian Breast Cancer Tissue Bank; IBIS: International Breast Cancer Intervention Study; ITR: International Treatment Research Foundation; MA.32: Metformin; MINDACT: Motivating Individualized Neoadjuvant Decisions About Chemotherapy Treatment; NCT: National Cancer Institute; NCI: National Cancer Institute; NCI/NIH grants: Cancer Research Societies and many other charitable grants; Novartis and Agendia Charitable Trust, numerous national cancer societies and many other charities; Pfizer and Ipsen provided the drugs for these studies.
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. 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 research.

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

BIG represents about 60 like-minded research groups from around the world and reaches across approximately 70 countries on 6 continents. The Breast International Group and its network of groups serve 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.

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AFRICA
- BGCIS Breast Gynaecological International Cancer Society
- AFRICA

ASIA
- BDPC Cancer Breast Disease Professional Committee of CMEA
- BIB Breast InterTumor of Eastern India
- CTRG Cancer Therapeutics Research Group
- HKBCG Hong Kong Breast Oncology Group
- ICON ARO Indian Co-operative Oncology Network
- IOSG Indian Oncology Study Group
- JBCRG Japan Breast Cancer Research Group
- KCSC Korean Cancer Study Group
- SMKCM & RC Shaukat Khanum Memorial Cancer Hospital & Research Centre
- TCGO 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 Arztagemeinschaft Gynaekologische Onkologie Breast Study Group
- BBOG Boeretancer 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
- GCSC Georgian Cancer Study Group
- GEICAM Spanish Breast Cancer Group
- GIM Gruppo Italiano Mammella
- GOIRC Gruppo Oncologico Italiano di Ricerca Clinica
- HSBS Hellenic Society of Breast Surgeons
- HeCoG Hellenic Cooperative Oncology Group
- HORG Hellenic Oncology Research Group
- IBCCG Icelandic Breast Cancer Group
- IBCSG International Breast Cancer Study Group
- IBIS International Breast Cancer Intervention Studies
- ICGO International Collaborative Cancer Group
- ICR-CTSG Institute of Cancer Research - Clinical Trials & Statistics Unit
- LB-CTSG Institut Jules Bordet Clinical Trials Support Unit
- ITMO Italian Trials in Medical Oncology
- MICHELANGELO Fondazione

LATIN AMERICA
- GACO Grupo Argentino de Investigación Clínica en Oncología
- GECO PERU Grupo de Estudios Clinicos Oncologicos Peruano
- GOCCHI Chilean Cooperative Group for Oncologic Research
- GOCUR Grupo Oncologico Cooperativo Uruguayo
- LACOG Latin American Cooperative Oncology Group

MIDDLE EAST
- IBG Israeli Breast Group
- ICRG Iranian Cancer Research Center
- SBCG Sheba Breast Collaborative Group

NORTH AMERICA
- CCGT Canadian Cancer Trials 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 Luxembourgoise d’Oncologie
- SUITI Breast Cancer Research Group
- SUCCESS Study Group
- SweBCG Swedish Breast Cancer Group
- UCSB Unicancer Breast Group
- WSG Westdeutsche Studiengruppe
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