Hope and Progress
20 years of breast cancer research
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By medical journalist Jenny Bryan

In 2000, a year after the Breast International Group (BIG) was founded, approximately one million women and men were diagnosed with breast cancer and nearly 470,000 died from the disease.\(^1\) By 2018, when the latest data were published, just over two million people were diagnosed and nearly 627,000 died.\(^2\)

The increase in cases is mainly because widespread screening and greater awareness of breast cancer have meant that more tumours are found and treated, though growing rates of obesity – an important risk factor – have also played a role.

The good news is that people with breast cancer – women and men – are living longer than ever before. This is largely due to earlier diagnosis, more effective treatment and, increasingly, better tailoring of treatment to the specific characteristics of each patient’s tumour.

Here, some of BIG’s leading researchers discuss the impact of advances in the understanding and treatment of breast cancer since 1999 and look forward to developments that are likely to improve the outlook for people with breast cancer in the years ahead.

References


BREAST CANCER: NO LONGER A SINGLE DISEASE, BUT MANY

OVER THE LAST TWO DECADES, MAJOR ADVANCES IN GENETIC PROFILING MEAN THAT MULTIPLE DIFFERENT TYPES OF BREAST CANCER ARE NOW RECOGNISED, AND TREATMENT IS INCREASINGLY PERSONALISED TO THE MOLECULAR CHARACTERISTICS OF EACH PATIENT’S TUMOUR.

Targeted treatment for hormone sensitive tumours has been available since the 1970s, but it wasn’t until the early 2000s that breast cancer was divided into luminal A and B tumours, which carry receptors for oestrogen and/or progesterone (ER+, PR+); HER2 receptor-positive (HER2+) tumours; and basal tumours, which carry no receptors and are often called triple negative breast cancer (TNBC).1

“Thanks to our improved understanding of the biology of breast cancer, we can now diagnose it earlier when it is minimally invasive, and we are developing better therapies to cure more patients, improve survival and quality of life, and reduce the number of patients who need chemotherapy,” says Dr Ander Urruticoechea, medical oncologist and scientific director, Onkologikoa Foundation, San Sebastian, Spain.

In recent years, researchers have dug ever deeper into the genetic make-up of breast tumours and discovered that, within the four main types, there are many more differences that can help drive new approaches to treatment.2

“We now have detailed information on many different biological alterations in breast tumours, which is enabling us to design clinical trials to define new targets for treatment. There are many drugs in early-phase clinical trials, and the challenge is now to match them with the tumour alterations and show that they are useful to patients,” says Professor Aleix Prat, head of medical oncology at the University of Barcelona, Spain.

In the last few years, three drugs (palbociclib, ribociclib and abemaciclib) have become available for patients with luminal B, HER2- breast cancer that inhibit CDK4/6 – cyclin dependent kinases, which are essential for cell division and are often overactive in cancer cells. Combined with hormone treatment in patients with metastatic ER+, HER2-breast cancer, they have been shown to prolong progression-free survival by about 50%, and researchers are optimistic that clinical trials will also show survival benefits in early stage luminal B, HER2- breast cancer.

The drawback of CDK4/6 inhibitors and some other promising targeted therapies is that there are, as yet, no diagnostic tests to identify patients who will benefit most.

“It is very important to have tumour or blood tests for DNA mutations or other biological determinants in breast cancer, so we can identify patients most likely to benefit from the new targeted treatments. Without such tests, we risk ‘diluting’ the efficacy of these drugs by giving them to patients who are unlikely to respond and end up losing valuable new treatments,” says Urruticoechea.

Promising results have been reported with the alpha-specific PI3K inhibitor alpelisib, which targets mutations in the PI3K cell-signalling pathway to prevent cancer cell proliferation.

For patients with metastatic breast cancer and the inherited BRCA1/2 mutation, the PARP inhibitor olaparib exploits deficiencies in DNA repair mechanisms in cancer cells. Preliminary evidence suggests that PARP inhibitors may also work in women with normal BRCA genes but with other DNA repair deficiencies.

For the 15% of patients with TNBC, targeted therapy is still elusive. They have so many different genetic mutations that it is difficult to identify

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targets for novel treatments for large numbers of patients. The most common mutations are in the cancer suppressor gene p53, and gene therapy and novel targeted treatments are being explored to restore the anti-cancer effects of this gene.

Owing to the high immunogenicity of TNBC, immunotherapy is one of the most promising strategies.

> Relevant BIG studies/trials:
AURORA (BIG 14-01)
PYTHIA (BIG 14-04)
PALLAS (BIG 14-03)
LORELEI (BIG 3-13)

References
HOW TRASTUZUMAB HAS TRANSFORMED THE OUTLOOK FOR WOMEN WITH HER2+ DISEASE

When the monoclonal antibody trastuzumab was first licensed for the treatment of women with HER2+ metastatic breast cancer in 1998, HER2+ tumours were among the hardest to treat forms of the disease. Fast forward two decades and anti-HER2 therapy is one of the biggest success stories in modern cancer treatment – not only for metastatic but also for early stage HER2+ breast cancer.

“In the last 20 years, progress has been astonishing, and anti-HER2 therapies are now lifesaving for women with early stage disease because they increase the chance of cure. For women with advanced disease, they prolong survival without altering quality of life because most are extremely well tolerated,” says Professor Martine Piccart, professor of oncology at the Université Libre de Bruxelles and Jules Bordet Institute, Brussels, Belgium. Dr. Piccart is also co-founder and chair of Breast International Group (BIG).

In the first phase III study in women with HER2+ metastatic breast cancer, published in 2001, adding trastuzumab to standard chemotherapy prolonged median survival by over five months, with a 20% reduction in risk of death compared with standard chemotherapy alone.1 The subsequent HERA trial, as well as the results of two North American trials5, demonstrated the value of adjuvant trastuzumab in prolonging disease-free survival in patients with early stage HER2+ breast cancer too.2

Since these initial studies, relapse rates with trastuzumab and chemotherapy have been substantially reduced, for example, from 15-20% at four years, to 10%. This suggests that, in countries that cannot afford the latest anti-HER2 therapies, patients can do well with trastuzumab, often in less expensive generic formulations.
Even so, one in four women with node-positive HER2+ breast cancer still relapses and dies within 10 years, despite trastuzumab therapy, so the battle is far from won.

Considerable hope rests on the newer anti-HER2 therapies – the monoclonal antibody pertuzumab, the anti-HER1/2 tyrosine kinase inhibitor lapatinib, and the antibody-drug conjugate trastuzumab emtansine (T-DM1). But the path to success has been far from smooth.

Adding pertuzumab to trastuzumab and docetaxel in patients with metastatic breast cancer improved survival by over 15 months. However, in women with early stage breast cancer, the benefits of combination treatments were a lot more modest. The lapatinib/trastuzumab combination was also disappointing as adjuvant therapy, despite initial success in the neoadjuvant setting.

"HER2+ breast cancer is a very heterogeneous disease and we have so far failed to identify biomarkers that can differentiate women most likely to benefit from trastuzumab or from a combination of anti-HER2 therapies," says Piccart.

Early experience with T-DM1 in advanced breast cancer has been quite impressive. Using trastuzumab to target chemotherapy directly at HER2+ cells reduces toxicity so there are fewer adverse effects on everyday life for patients. Further trastuzumab-targeted agents are being developed for patients who become resistant to T-DM1, and they are also being explored in patients who have low HER2 expression levels and are not candidates to be treated with trastuzumab.

For the future, it appears that more sophisticated, biomarker-driven trials are needed to identify better ways of tailoring anti-HER2 treatment. Patients with HER2-enriched disease may benefit from dual anti-HER2 therapy and may need little or no accompanying chemotherapy, while those with non-enriched disease may do better with single-agent anti-HER2 therapy combined with CDK4/6 inhibitors or immunotherapy. As treatment is streamlined, researchers also stress the importance of investigating optimal duration of anti-HER2 combinations at an early stage of regulatory clinical trials, possibly with government funding for shorter duration treatment arms.

“By including shorter duration arms in the initial trials of expensive new targeted treatments, we can get answers that may have important clinical and financial implications for the future of adjuvant anti-HER2 and other therapies in breast cancer,” concludes Piccart.

> Relevant BIG studies/trials:
  HERA (BIG 1-01)
  APHINITY (BIG 4-11)
  ALTTO (BIG 2-06)
  NeoALTTO (BIG 1-06)
  SOLD (BIG 1-10)

References
5. National Surgical Adjuvant Breast and Bowel Project (NSABP) trial B-31 (Doxorubicin and Cyclophosphamide Plus Paclitaxel With or Without Trastuzumab in Treating Women With Node-Positive Breast Cancer That Overexpresses HER2. ClinicalTrials.gov Identifier: NCT00004067) and the North Central Cancer Treatment Group (NCCCTG) trial N9831 (Studying Tissue Samples From Women With Breast Cancer Who Were Treated on Clinical Trial NCCCTG-N9831. ClinicalTrials.gov Identifier: NCT00898898)
SURGERY: SMALLER OPERATIONS WITH BETTER RESULTS

“Over 30 years ago, when I started training, any woman with a tumour larger than 2 cm was thought to need a mastectomy, but not now. Our surgical techniques are better, and the use of systemic therapies to shrink tumours means that 90-95% of women can now have breast conserving surgery,” says Professor Michael Gnant, MD, FACS, Austria.

For women who do still need a mastectomy, there have also been advances in techniques for breast reconstruction, which can often be done at the same time as the mastectomy—reducing the need for repeat surgery and offering women more rapid resolution of their cancer surgery.

Unfortunately, many women with breast cancer in regions such as Africa and Asia do still have a mastectomy. There is also growing concern that some women, mainly in the US, are having prophylactic mastectomy even in the absence of BRCA mutations associated with high risk of breast cancer.

“This is mastectomy as a treatment for fear, and it would be tragic if we lose the success we have achieved over the last decades in reducing mastectomy rates,” says Gnant.

After breast conserving surgery, few patients now need large numbers of lymph nodes removed from under their arm (axilla) to look for signs of spread. This is because, in the late 1990s, it was confirmed that finding and checking one key node (the sentinel node) could accurately predict risk of metastasis.

“Removing large numbers of lymph nodes is now so rare that we have trouble teaching it to our junior colleagues! In the last 20 years, sentinel node biopsy has become the standard of care, and we have become much less invasive in our surgery,” says Gnant.
Local recurrence rates have fallen significantly in many countries, due jointly to better surgery, pathology, radiotherapy and radiology and greater standardisation of procedures.

Even so, there are still questions to be answered. While new anti-cancer drugs are subjected to rigorous clinical trials, surgical issues are rarely addressed in such studies. This is why BIG has established a task force to consider how surgical questions can be integrated into clinical trials.

“We need to be more systematic in the way we challenge and re-challenge new surgical strategies and techniques. To get the required quality of information, we need to find ways to piggy-back surgical questions onto clinical trials of new drugs and other therapies, and that is what the BIG community is discussing,” says Gnant.

Research is also exploring whether, in the future, some patients with breast cancer may be able to avoid surgery. This will depend on the identification of biomarkers to predict which women will get such a good response from non-surgical therapy that they will be left with no tumour tissue to remove. However, as surgery continues to become less invasive, any non-surgical approach will need to compare favourably in terms of both survival and quality of life.

“I shall be the first to support an end to breast cancer surgery if alternatives are shown to be as effective but, realistically, I don’t think that will happen in the next decade,” concludes Gnant.

References


For many years, radiotherapy has been an integral part of treatment for early stage and advanced breast cancer, and remarkable technological advances over the last three decades have improved treatment precision and decreased toxicity. More recently, growing understanding of breast cancer biology has enabled researchers to investigate how radiotherapy may be more precisely tailored to individual patient needs and optimise treatment outcomes.

Following the shift from routine mastectomy to breast conserving surgery for early breast cancer, it was shown that post-operative breast radiotherapy decreased the rate of local recurrence. Subsequent landmark publications reported that it also improved the survival.1,2 It was shown that radiotherapy to the conserved breast halved the rate of recurrence and reduced breast cancer deaths by about a sixth.3

“Individual studies had shown that radiotherapy after breast conserving surgery reduced the rate of recurrence in the breast. However, it was not until the results of these studies were analysed together that it became clear radiotherapy also improved survival of patients with early breast cancer,” explains Professor Boon Chua, radiation oncologist and director of Cancer and Haematology Services, University of New South Wales and Prince of Wales Hospital in Sydney, Australia.

More recent research in early breast cancer has focused on minimising the toxicity and burden of radiotherapy without compromising local control and survival. After breast conserving surgery, conventional radiotherapy administered daily over five to six weeks has been found to have no safety or effectiveness benefits compared with modestly larger daily doses of radiation given in fewer treatment sessions, typically over three weeks. The newer approach, called hypofractionated radiotherapy, has obvious advantages for patients and healthcare providers.

Boon Chua, MD, PhD - radiation oncologist
Member of BIG’s Executive Board
TROG & BCT-ANZ (Trans Tasman Radiation Oncology Group & Breast Cancer Trials - Australia & New Zealand)
AUSTRALIA
“As a result of the studies, hypofractionated whole breast radiotherapy is being adopted as a standard of care for women with early breast cancer in an increasing number of countries,” says Chua.

To further reduce treatment burden and toxicity, researchers have investigated whether some patients may only need partial breast irradiation, targeting the primary tumour site where recurrence is most likely to occur. As a result of the limited volume of breast tissue irradiated, further acceleration of treatment delivery to one week or less, including a single treatment, has become possible.

“More mature data on safety and efficacy are necessary for definitive evaluation of this approach. Until then, use of partial breast irradiation should be limited to low-risk patients defined by international and national guidelines,” says Chua.

If partial breast irradiation becomes an accepted treatment option for some patients, is there a possibility that some women may not need radiotherapy after breast conserving surgery? Could their individual risks of recurrence be sufficiently low that the benefit of radiotherapy may be outweighed by its toxicity and burden?

Preliminary reports suggest that the genomic profiles of breast cancer may improve the prognostic precision in identifying these low-risk patients. Large studies of these new-generation genomic markers are underway.

“Data on new-generation biomarkers for predicting the risk of local recurrence are promising but exploratory, hence continuing research is critical. I think the future of personalised radiotherapy will be driven by integrating our current knowledge with new understanding of tumour biology and efficacy of systemic therapy in a multidisciplinary setting,” concludes Chua.

> Relevant BIG studies/trials:

**EXPERT (BIG 16-02)**
**SUPREMO (BIG 2-04)**
**DCIS (BIG 3-07)**

References


HORMONE THERAPY: LEADING THE WAY IN TARGETED TREATMENT

AS THE FIRST TARGETED TREATMENT FOR BREAST CANCER, HORMONE THERAPY FOR PATIENTS WITH OESTROGEN AND PROGESTERONE RECEPTOR POSITIVE TUMOURS (ER+ AND PR+) HAS LED THE WAY TOWARDS A MORE INDIVIDUALISED APPROACH, TAILORED TO EACH PATIENT’S TUMOUR.

Many of the drugs in use today were available long before the turn of the century. However, research in the last 20 years has helped to differentiate the roles of tamoxifen, aromatase inhibitors (AIs) and other forms of hormone therapy, based on disease severity and risk of recurrence. In the last few years, research has also demonstrated that it is possible to boost the effectiveness of hormone therapy with other drugs.

“Tamoxifen is still a wonderful drug as adjuvant therapy in women with low risk, hormone sensitive early breast cancer and no contraindications, but for women at intermediate and high risk of recurrence, we now have clear standards of care based on results of trials in the last two decades,” says Professor Aron Goldhirsch, medical oncologist, Italy/Switzerland. Professor Goldhirsch is also co-founder and, until recently, was vice-chair of Breast International Group (BIG).

For premenopausal women, research has shown that women at intermediate risk of recurrence benefit from tamoxifen combined with ovarian suppression, while those at highest risk may do better with exemestane combined with ovarian function suppression.1 In postmenopausal women, results of the BIG 1-98 showed that adjuvant treatment with the AI letrozole is more effective at preventing recurrence than tamoxifen alone.2

Even if 90-95% of a patient’s cancer cells have hormone receptors (HR+), other mechanisms may diminish their response to hormone treatment. Indeed, only 50% of patients with HR+ disease get significant tumour regression with hormone

Aron Goldhirsch MD, PhD (Hon)
Co-founder and until recently vice-chair of BIG IBCSG (International Breast Cancer Study Group)
ITALY/SWITZERLAND
treatment. For this reason, newer agents, such as CDK4/6 and mTOR inhibitors, have been used to boost the effectiveness of hormonal treatment. Tests such as Ki-67 staining are used to measure cell proliferation as an indication of the proportion of cancer cells that are growing. A series of Ki67 measurements during hormone treatment may thus indicate the degree of therapeutic efficacy.

In patients with advanced breast cancer, the addition of a CDK4/6 inhibitor to endocrine therapy has been shown to prolong progression-free survival. In subsequent lines of treatment, hormone therapy may also be combined with the mTOR inhibitor everolimus, though new, less toxic inhibitors are needed.

“Thanks to the success of the newer treatment options, many patients live with advanced breast cancer for longer periods and have multiple lines of therapy. As a result, it has become increasingly important that treatment is well tolerated, and side effects well controlled, so that patients can experience good quality of life,” explains Goldhirsch.

Following reassuring long-term safety data in advanced disease, the combination of hormone treatment and CDK4/6 inhibitors is being investigated as adjuvant hormone therapy in early stage breast cancer.

“Endocrine therapy will always be needed for blocking progression of hormone responsive breast cancer, and improved selection of patients for additional tailored therapies will enable us to optimise results. Identifying the best way of combining these agents is the true challenge for the future,” concludes Goldhirsch.

> Relevant BIG studies/trials:
SOFTEXT (BIG 2-02 / BIG 3-02)
AROMATASE INHIBITORS
(BIG 1-97 / BIG 2-97 / BIG 1-98)

References


CHEMOTHERAPY: FEWER WOMEN NEED TOXIC DRUGS FOR BREAST CANCER THAN EVER BEFORE

IN THE LAST THREE YEARS TWO MAJOR TRIALS, MINDACT AND TAILORX, HAVE CONFIRMED THAT FEWER WOMEN WITH EARLY BREAST CANCER NEED CHEMOTHERAPY THAN EVER BEFORE,1,2 – PROVIDING CLEAR EVIDENCE OF HOW PRECISION MEDICINE IS TRANSFORMING THE USE OF CYTOTOXIC DRUGS.

“In the 1990s and early 2000s, the vast majority of patients with early stage breast cancer received chemotherapy, but we now know that patients with tumours that are highly sensitive to hormone treatment do not need chemotherapy,” says Dr Angelo Di Leo, medical oncologist, head of Sandro Pitigliani Medical Oncology Unit, Istituto Toscana Tumori, Prato, Italy.

Even patients with early stage, hormone sensitive (luminal A) breast cancer that has spread to axillary lymph nodes are no longer automatic candidates for chemotherapy.3 Instead, the biology of a tumour is becoming more relevant to such treatment decisions than whether lymph nodes are positive, especially if only a small number of nodes are affected.

“It is great, great progress that we can confidently skip chemotherapy in women with luminal A breast cancer and only one to three positive nodes, without compromising cure, and just treat with adjuvant hormone therapy after surgery,” adds Di Leo.

Despite this success in luminal A breast cancer, chemotherapy does still play an important role in many patients with early breast cancer. It is needed by the 25-30% of patients with luminal B breast cancer, as this is less sensitive to hormone therapy than luminal A disease. It is also needed by the 15-18% of patients who have triple negative breast cancer (TNBC), and it is given in combination with anti-HER2 therapy in the 15-20% of patients with HER2+ breast cancer.

As well as the reduced need for chemotherapy in early breast cancer over the last two decades, many patients can have ‘kinder’ chemotherapy with fewer side effects.4

Angelo Di Leo, MD, PhD - medical oncologist
Member of BIG’s Executive Board
IBCSG (International Breast Cancer Study Group)
ITALY
“Chemotherapy is evolving, and we try to give the most appropriate treatment for individual cases. It is now tailored to individual tumour biology, stage and size and, not least, to patient wishes and expectations,” says Di Leo.

For patients with advanced breast cancer, the place of chemotherapy has also changed. Patients whose tumours are hormone-sensitive are offered chemotherapy later than in the past – if the tumour becomes resistant to hormone treatment. As in early breast cancer, chemotherapy remains the only option for TNBC but, once again, every effort is made to give the least toxic treatment possible with limited side effects.

Metronomic chemotherapy – frequent, low dose, oral treatment taken at home – often replaces more traditional cycles of high-dose treatment requiring hospital visits, even in metastatic TNBC.

“Metronomic chemotherapy is a kinder option for less aggressive metastatic disease, including some triple negative tumours. By hitting the cancer every day, we are targeting the tumour while the patient remains relatively well and gets on with his or her life,” says Di Leo.

For the future, cancer specialists are researching ways to target chemotherapy ever more specifically at patients most likely to benefit, and there is great interest in how it can be combined with immunotherapy.

“Chemotherapy continues to play a key role in a significant proportion of patients with early and metastatic breast cancer. But we can now be more selective and creative in the way we use it and adapt regimens to different situations to get the greatest benefit for our patients. In the future, it will be increasingly combined with immunotherapy and other forms of targeted therapy,” concludes Di Leo.

References


> Relevant BiG studies/trials:
  MINDACT (BiG 3-04)
IMMUNOTHERAPY REVEALS POTENTIAL IN BREAST CANCER

In 1999, the possibility of activating the immune system to destroy breast cancer cells was little more than an idea. But, following the success of novel forms of immunotherapy in the treatment of melanoma, lung and other cancers, recent research suggests it has a role in breast cancer too, with dozens of clinical trials underway.

At the heart of this potential breakthrough in the treatment of breast cancer are checkpoint inhibitors—drugs that release the brakes on the immune system’s natural response against cancer cells.

“During the last 20 years, advances in scientific understanding of how immune cells recognise cancer cells as abnormal and, most importantly, how cancer cells inhibit that immune response, have provided the foundation for today’s immunotherapy,” explains Professor Fabrice André, medical oncologist, professor of medical oncology at the Institut Gustave Roussy, Villejuif, France.

The checkpoint inhibitors of greatest interest in breast cancer are antibodies that interfere with the way cancer cells deactivate immune cells called T lymphocytes when they arrive in tumours to kill them. Novel drugs prevent a protein called PD-L1 on tumour cells from interacting with a second protein called PD-1 on activated T cells.1 Research shows that treatment is most effective in patients with large numbers of tumour infiltrating lymphocytes (TILs) in their tumours, and studies are investigating how TIL levels can be increased in all tumours.

“These are really exciting times for immunotherapy research, and there is a lot of work ahead. Recent results herald the use of checkpoint inhibitors in metastatic triple negative breast cancer and are expected to accelerate the clinical development of this class of drugs for patients with early and metastatic breast cancer,” says Dr Michail Ignatiadis, senior attending physician, Medical Oncology Department at the Jules Bordet Institute, Brussels, Belgium.
Results have been reported from studies in over 500 patients with metastatic breast cancer treated with an anti-PD-L1 (atezolizumab or avelumab) or anti-PD1 antibody treatment (pembrolizumab). Combining anti-PD-L1/PD-1 therapies with chemotherapy has helped boost responses from around 20% with monotherapy to over 40% with combination treatment.

“In triple negative breast cancer, there appears to be strong synergy between chemotherapy and immunotherapy, probably because chemotherapy induces the immune system and anti-PD-1 therapy then activates it,” says André.

In the most promising study to date, IMpassion 130, first-line treatment with atezolizumab and standard chemotherapy (nab-paclitaxel) in patients with metastatic triple negative breast cancer (TNBC) prolonged progression-free survival by nearly two months compared to placebo and standard chemotherapy. There was also an encouraging overall survival benefit of 9.5 months in patients with PD-L1+ tumours.

Preliminary data suggest that immunotherapy may also play a role in patients with HER2+ breast cancer, and that it can be combined with chemotherapy or a CDK4/6 inhibitor in a subset of patients with luminal B breast cancer. Although initial immunotherapy studies were carried out in advanced breast cancer, researchers are optimistic that it can be used successfully in early disease, as either neoadjuvant or adjuvant therapy. As with other novel cancer treatments, biomarker tests are needed to predict which patients will benefit most from immunotherapy, and to monitor early responses.

Progress is also being made in developing cancer vaccines to ‘educate’ the immune system to recognise abnormal protein markers (neoantigens) on breast cancer cells and attack them.

“Over the next five to 10 years, we can expect increasingly sophisticated types of immunotherapy for treatment of breast cancer, including personalised cancer vaccines and adoptive T-cell therapy, and we will hopefully start to develop vaccination strategies for breast cancer prevention,” concludes Ignatiadis.

References
3. Schmid P, Adams S, Rugo HS et al. IMpassion130: Results from a global, randomised, double-blind, phase 3 study of atezolizumab (atezo) + nab-paclitaxel (nab-P) vs placebo + nab-P in treatment-naive, locally advanced or metastatic triple-negative breast cancer (mTNBC). Annals of Oncology, 2018; 29 (suppl 8): LBA1

> Relevant BIG studies/trials:
ALEXANDRA / IMPASSION 030 (BIG 16-05)
PANACEA (BIG 4-13)
ULTIMATE (BIG 16-01)
GETTING MALE BREAST CANCER ON THE RESEARCH AGENDA

For the 1% of patients with breast cancer who are male, the most significant changes of the last 20 years have been the growing awareness and diagnosis of the condition, together with efforts to get more men into large clinical trials of novel treatments.

“If men participate in clinical trials of new treatments – even in small numbers – they are more likely to be included among the patient groups who can access those treatments when they are approved by the regulatory authorities. In this way, we hope to improve standards of care for men with breast cancer to the same level as women,” says Dr Fatima Cardoso, director of the Breast Unit of the Champalimaud Clinical Center, Lisbon, Portugal.

Nearly all men with breast cancer have ER+ tumours, with only 5-10% HER2+, and fewer than 1% TNBC. Diagnosis is often delayed, so cancer is more advanced. Treatment recommendations are largely extrapolated from the findings of breast cancer studies in women, with tamoxifen the most commonly used adjuvant therapy for early breast cancer. For advanced breast cancer, AIs are combined with luteinising hormone releasing hormone (LHRH) agonists to block testicular hormones that may stimulate tumour growth.

> Relevant BIG studies/trials:
  MALE BREAST CANCER (BIG 2-07/EORTC 100-85P/BCG)
Research carried out through the International Male Breast Cancer Programme (IMBCP)* has consistently shown that fewer men receive hormone therapy than would be expected, or radiotherapy for node-positive disease. In absolute terms, breast cancer survival in men is worse than for women but, when data are adjusted for age and comorbidities, survival is similar.

Men are not yet benefitting as much as women from recent advances in breast cancer treatment, partly due to reimbursement issues for newer agents. In addition, trial sponsors may be wary of including men in breast cancer trials in case they ‘dilute’ treatment benefits achieved in female patients.

“If the inclusion of a handful of men in a large breast cancer trial can dilute a treatment effect, then the trial must be looking for a very small, unimportant benefit, which should not be the case. So we say to researchers – ‘unless you need to exclude male patients for a strong scientific reason, please don’t,’ “ says Cardoso.

The IMBCP is characterising the biology of male breast cancer to gain a better understanding of novel treatment approaches. Following initial centralised analysis of data and tumour samples from 1800 patients,1 and the initial clinical and pathological characterisation of this disease, further research is using RNA sequencing and genomic profiling. Considerable interest is focused on the role of the androgen receptor in male breast cancer2 and how this differs from female breast cancer, especially as novel agents are becoming available that target this receptor.

The second part of the IMBCP consists of a prospective registry for male breast cancer through an international network of centres. In just 30 months, 570 patients were recruited through the network, indicating the potential for clinical trials carried out through the centres. Even so, it remains extremely difficult to find sponsorship and interest for such studies.

“I remain optimistic that, if we work together, we can change attitudes and get more male patients into breast cancer trials. I also believe that, as academic researchers, it is our role to work together to improve understanding of the biology of male breast cancer, and to educate all clinicians and the public about the need to recognise symptoms so that it can be diagnosed and treated earlier,” concludes Cardoso.

* coordinated by BIG, the European Organisation for Research and Treatment of Cancer (EORTC), the Translational Breast Cancer Research Consortium (TBCRC) and the North American Breast Cancer Group (NABCG)

References
BIG CLINICAL TRIALS & RESEARCH PROGRAMMES

BIOLOGICAL THERAPIES

PRENEADJUVANT

LORELEI

Neo-ALTTO

PENELOPE-B

NeoPHOEBE

ADJUVANT

IMPassion 030

ALTTO

APHINITY

AZURE

HERA

MA.32

MINDACT

OlympiA

PALLAS

REACT

SOLD

METASTATIC

BRAVO

FINESSE

PYTHIA

ANTI-HER2

ALTO

APHINITY

HERA

NeoALTTO

SOLD

TBP

IMMUNOTHERAPY

ALEXANDRA /
IMPassion030
PANACEA
ULTIMATE

FGFR1
FINESSE

BISPHOS-PHONATES
ICE
AZURE

PI3K
LORELEI
NeoPHOEBE

CDK 4/6
PALLAS
PENELope-B
PYTHIA

SURGERY
LAMANOMA

RADIOTHERAPY
DCIS
EXPERT
SUPREMO

View all clinical studies run within the BIG network on BIG's website here
RESEARCH PROGRAMMES

EXPLORING TUMOUR MOLECULAR BIOLOGY
AURORA
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TRANSBIG

DATA SHARING
EURECA INTEGRATE

SPECIAL POPULATIONS
MALE BREAST CANCER
PREGNANCY:
- REGISTRY
- POSITIVE
FERTILITY SURVEY

CHEMOTHERAPY
CALOR
P53
TAX 315
SNAP
CASA

METABOLISM
MA.32

HORMONOTHERAPY
BIG 1-98
IBIS-II
IES
MA.17
SOFT / TEXT / PERCHE
SOLE
HABITS

NSAIs
REACT

View all clinical studies run within the BIG network on BIG’s website here.
ABOUT BIG

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.

BIG was founded as a network of collaborative groups in 1999 to address fragmentation in European breast cancer research. However, groups from other parts of the world rapidly expressed interest in joining BIG, and in 2018 it represented 59 like-minded research groups from around the world and reached across more than 65 countries and 6 continents.

Through these groups, BIG connects thousands of hospitals and world-class breast cancer experts who collaborate on pioneering breast cancer research.

BIG’s mission is to facilitate and accelerate breast cancer research at an international level. We are proud to be both global and local, helping breast cancer patients from all over the world.

www.BIGagainstbreastcancer.org
Once you choose **HOPE**, anything’s possible

**PROGRESS** is impossible without collaboration

#BIGAGAINSTBC

WWW.BIGAGAINSTBREASTCANCER.ORG

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