Clinical trials with a BIG impact

CHANGING THE LIVES OF BREAST CANCER PATIENTS
Today’s research, tomorrow’s cures

The Breast International Group (BIG) is a not-for-profit organisation that forms the largest international network of academic research groups dedicated to finding cures for breast cancer.

We are proud to be both global and local, helping breast cancer patients from all over the world.

www.BIGagainstbreastcancer.org
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The international randomised SOFT/TEXT clinical trials – together involving 5,738 patients from 510 hospitals and cancer centres linked to 13 BIG groups in 27 countries – were developed in parallel to test the optimal adjuvant endocrine treatment in premenopausal women with hormone-sensitive early breast cancer.

These trials demonstrated that, when combined with ovarian function suppression, exemestane, compared to tamoxifen significantly improved patient disease outcome, reducing the risk of cancer recurrence by 34%. Patients with a high risk of relapse who had received adjuvant chemotherapy especially benefitted from this treatment.

The primary results of SOFT and TEXT, which were published in the New England Journal of Medicine in 2014, were supported by a 5-year analysis presented at the 2017 San Antonio Breast Cancer Symposium.

While the patient follow-up continues, SOFT and TEXT have already delivered practice-changing results, providing a new post-operative treatment option for young women with hormone-sensitive early breast cancer who may have a higher risk of cancer recurrence after surgery.
The trials enrolled 5,738 premenopausal patients with hormone-responsive breast cancer.

- **510 hospitals**
- **27 countries**
- **13 BIG groups**

Set a new standard of treatment for reducing cancer recurrence:

Exemestane combined with ovarian function suppression (OFS) reduced the risk of recurrence by 34% and a five-year survival rate of 92.8%.

**SOFT/TEXT**

testing the optimal adjuvant endocrine treatment for young women with hormone-sensitive early breast cancer.

**Giving new hope to young women with hormone-sensitive early breast cancer**

- **Tamoxifen + OFS**
  reduced the risk of developing further breast cancer by 28% compared to tamoxifen alone.

- **Exemestane + OFS**
  reduced the risk of developing further breast cancer by 34% compared to tamoxifen + OFS.
APHINITY
Overcoming resistance to treatment and reducing the risk of invasive breast cancer returning

The APHINITY trial – involving 4,805 patients and 599 sites linked to 24 member groups covering 42 countries – tested whether adding pertuzumab to the standard adjuvant treatment (trastuzumab and chemotherapy) in patients with operable HER2-positive primary breast cancer improved the outcome of patients with the disease. Indeed, previous studies including HERA, had shown that trastuzumab combined with chemotherapy improved the chances of disease-free survival for this category of patients, and is now the standard of care. However, 40% of patients with this subtype of breast cancer may become resistant to trastuzumab.

APHINITY analysed whether adjuvant pertuzumab – which also acts on the HER2 marker – in combination with trastuzumab and chemotherapy in patients was better than standard treatment. It was found that this new dual anti-HER2 therapy regimen reduced the risk of breast cancer recurrence or death by 19% compared to trastuzumab and chemotherapy alone. At three years, 94.1% of patients treated with pertuzumab in combination with trastuzumab and chemotherapy did not see a breast cancer recurrence, compared to 93.2% of patients treated with trastuzumab and chemotherapy alone.

The results of the APHINITY trial show a modest benefit from adding pertuzumab to trastuzumab. However, it is an important step in advancing cancer care for patients – especially for women with the highest risk – those with node-positive and hormone-receptor negative breast cancer.

Over the course of the clinical trial, samples were collected from all participating patients for future research. These samples will help identify biomarkers, which can help to predict response or toxicity of the dual anti-HER treatment, and better understand the biology of HER2+ tumours as well as develop and validate diagnostic tests.

PUBLICATIONS

- Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer - von Minckwitz G et al., New England Journal of Medicine, 5 June 2017
The trial enrolled 4,805 women with known hormone receptor-negative disease and confirmed HER2+ early breast cancer.

Important step in advancing cancer care for patients with node-positive and hormone-receptor negative breast cancer.

The APHINITY Study (BIG 4-11/B025126/T0C4939G)

40% patients with HER2+ breast cancer may become resistant to trastuzumab

Trastuzumab + Pertuzumab + Chemotherapy reduced the risk of breast cancer recurrence or death by 19% compared to trastuzumab and chemotherapy alone.
The MINDACT trial – involving 112 hospitals in 9 countries from 7 BIG collaborative groups – represents a large academic effort towards de-escalating therapies.

The study was designed to evaluate the utility of adding the 70-gene test (MammaPrint®) to the standard clinico-pathological criteria used to identify those patients with early-stage breast cancer who could be safely spared adjuvant chemotherapy without this significantly affecting their risk of disease recurrence.

Between 2007 and 2011 the trial enrolled 6,693 women with node-negative or 1-to-3 node positive breast cancer.

46% of the patients identified as high-risk for cancer recurrence based on traditional factors were identified as low-risk when adding the MammaPrint test. Based on good outcome results without chemotherapy, the data suggested that chemotherapy provided no clinically meaningful benefit for these patients and could be safely omitted.

MINDACT gives hope to many women with node-negative or 1-to-3 node positive early breast cancer. The study’s results provide the highest level of evidence showing that Mammaprint could significantly de-escalate the use of adjuvant chemotherapy in the future, thereby improving the quality of life of a great many women confronted with the disease.

The primary results of MINDACT were published in 2016 in the New England Journal of Medicine.

PUBLICATIONS

- **70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer** - Cardoso F et al., New England Journal of Medicine, 25 August 2016

- **The EORTC 10041/BIG 03-04 MINDACT trial is feasible: results of the pilot phase** - Rutgers E et al., European Journal of Cancer, 1 November 2011

- **The MINDACT trial: the first prospective clinical validation of a genomic tool** - Cardoso F et al., Molecular Oncology, 22 October 2007
The trial enrolled 6,693 early-stage HER2-positive breast cancer patients.

- 112 hospitals
- 9 countries
- €47 million to fund the trial

**MINDACT**

70-gene prognosis signature

Can help doctors decide which patients would benefit from chemotherapy or not.

Clinical & genomic tests indicate **low risk of recurrence**.
Clinical & genomic tests indicate **high risk of recurrence**.

If the tests disagreed, patients were randomly assigned to be treated either on the basis of the clinico-pathological assessment or on the basis of the genomic test results.

- De-escalation of therapies
- Pioneering precision medicine
- Better and personalised treatment
- Potential savings for society
- 52,000 samples are stored in a biorepository for long-term storage, enabling future research.

46% of patients could be spared unnecessary chemotherapy.
ALTTO & NeoALTTO

Valuable resources for future translational research

The ALTTO and NeoALTTO trials – together involving more than 8,000 patients and establishing a huge prospective collection of biological materials for future translational research – are a testimony to the strength and richness in terms of scientific expertise, creativity and flexibility of BIG’s network of research groups to conduct complex international clinical studies.

ALTTO is considered to be the largest-ever adjuvant clinical trial in HER2-positive breast cancer, comparing single adjuvant trastuzumab therapy to dual HER2-targeted treatment (trastuzumab plus lapatinib).

Developed in parallel, NeoALTTO’s objective was to evaluate the benefit of dual HER2-targeted therapy, compared to a single anti-HER2 drug (either trastuzumab or lapatinib alone) given before cancer therapy. The results showed a near doubling of the pathologic complete response rate (pCR) with the dual HER2-targeted therapy rather than the single agent alone.

These results were considered promising for ALTTO and the adjuvant setting. However, the 2014 ALTTO findings did not confirm the predicted benefit of using both anti-HER2 therapies (trastuzumab plus lapatinib).

Despite its unexpected results, the ALTTO trial can be considered to be a landmark study. Not only did this large collaboration trial answer important questions about the adjuvant treatment of women with HER2-positive breast cancer – namely, the findings confirmed that the standard adjuvant treatment for early stage HER2-positive breast cancer should remain trastuzumab in combination with chemotherapy – but the data and samples collected are very valuable for the conduct of promising translational research.

PUBLICATIONS

- *Adjuvant Lapatinib and Trastuzumab for Early Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer: Results From the Randomized Phase III Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization Trial* - Piccart-Gebhart M et al., Journal of Clinical Oncology, 1 April 2016

- *Analysis of regional timelines to set up a global phase III clinical trial in breast cancer: The adjuvant lapatinib and/or trastuzumab treatment optimization experience* - Metzger-Filho O et al., The Oncologist, 28 January 2013

- *Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): survival outcomes of a randomised, open-label, multicentre, phase 3 trial and their association with pathological complete response* - de Azambuja E et al., The Lancet Oncology, September 2014

- *Lapatinib with trastuzumab for HER-positive early breast cancer (NeoALTTO): a randomised, open-label, multicentre, phase 3 trial* - Baselga J et al., The Lancet, 18 February 2012
Large scale collaboration & valuable resource for translational research

The results of the trials confirmed that the standard adjuvant treatment for early stage HER2+ breast cancer should remain trastuzumab in combination with chemotherapy.

A treasure trove for translational research

Huge prospective resource of data and biological materials collected during the trials.

ALTTd
Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation Trial
Study of adjuvant lapatinib, trastuzumab, their sequence and their combination in patients with HER2/ErbB2 positive primary breast cancer

Neo-ALTTd
Neo-Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation Trial
Study of neoadjuvant lapatinib, trastuzumab and their combination plus paclitaxel in women with HER2/ErbB2-positive primary breast cancer

The trials enrolled 8,836 Early-stage HER2-positive breast cancer patients

+/- 1000 hospitals
+/- 40 countries
18 BIG Groups
HERA

A new standard treatment for HER+ breast cancer

Recruiting 5,102 women from 480 sites across 39 countries in just over four years – in itself a remarkable achievement – HERA contributed to a new standard of treatment for women with HER2-positive, early breast cancer, a highly aggressive form of the disease. The study’s main results, published in 2005 and in 2017, indicated that one year of treatment with trastuzumab had a significant and sustained benefit in preventing cancer recurrence and improving overall survival among this group of patients.

A study involving the participation of 27 BIG collaborative groups, HERA helped accelerate the approval of trastuzumab, which has cut relapse rates by 50% and is now the standard treatment for HER2-positive breast cancer.

The final analysis of HERA was published in The Lancet in April 2017. As noted in the paper, to our knowledge, this 11-year follow-up provides the longest survival data of any trial that assessed the addition of anti-HER2 therapy to standard treatment for HER2-positive early breast cancer.

PUBLICATIONS

- [Herceptin Adjuvant (HERA) Trial Study Team. 11 years’ follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)31129-3/fulltext) - Cameron D et al., The Lancet, 25 March 2017

The trial enrolled 5,102 early-stage HER2-positive breast cancer patients from 480 hospitals in 39 countries across 27 BIG Groups.

Breast cancer relapse rates cut by 50%.

Randomised three-arm multicentre comparison of one year and two years of trastuzumab versus no trastuzumab in women with HER2-positive primary breast cancer who have completed (neo)adjuvant chemotherapy.

1 year vs. 2 years or none.

A new standard treatment for HER2+ breast cancer: Trastuzumab used in preventing cancer recurrence.

1 year of treatment with trastuzumab had a significant and sustained benefit in preventing cancer recurrence.
BIG 1-97, BIG 2-97 & BIG 1-98

The effectiveness of aromatase inhibitors

Three studies, BIG 1-97/MA.17, BIG 2-97/IES and BIG 1-98, together recruiting a total of 17,958 patients, contributed to the body of evidence that aromatase inhibitors could be used as a safe alternative to tamoxifen, a drug used to treat oestrogen receptor (ER) positive breast cancer that is associated with dangerous side effects for some women.

Not only did these trials prove the effectiveness of the new drugs, but they also answered important additional questions about whether the drugs should be given in combination or in sequence with others, the likelihood of side effects with long-term use, and patients' overall quality of life.

These trials gave women with ER-positive early breast cancer more treatment options than tamoxifen alone, and hence contribute to improving the quality of life for countless women around the globe, an important step forward towards personalised treatments for women with ER-positive disease.

PUBLICATIONS

- A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer - Goss PE, et al., New England Journal of Medicine, 9 October 2003

- Letrozole therapy alone or in sequence with tamoxifen in women with breast cancer - BIG 1-98 Collaborative Group, Mouridsen H, et al., New England Journal of Medicine, 20 August 2009

- Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-responsive early breast cancer: update of study BIG 1-98 - Coates AS, et al., Journal of Clinical Oncology, 10 February 2007

- A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer - Breast International Group (BIG) 1-98 Collaborative Group, Th rlimann B et al., New England Journal of Medicine, 29 December 2005

- Survival and safety of exemestane versus tamoxifen after 2–3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial - Coombes RC et al., The Lancet Oncology, 17 February 2007

- Disease-related outcomes with long-term follow-up: an updated analysis of the intergroup exemestane study - Bliss J et al., Journal of Clinical Oncology, 1 March 2012
BIG 1-97
Letrozole after completion of standard TAM Rx significantly improves disease-free survival

BIG 2-97
The study found that in postmenopausal women, switching to exemestane after 2-3 years of tamoxifen significantly improves disease-free survival

BIG 1-98
Letrozole significantly improves disease-free survival compared with tamoxifen for postmenopausal women with endocrine responsive breast cancer

The trials enrolled
17,958 patients

± 500 hospitals
± 40 countries
± 20 BIG groups

Aromatase inhibitors: providing more options for ER+ patients

Give women with ER-positive early breast cancer more treatment options than tamoxifen alone, contributing to improving the quality of life for countless women around the globe