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IBCSG

BIG
Breast International Group

POSITIVE *Progress*

Finally a prospective clinical trial for young women with breast cancer who wish to have a baby !

Young breast cancer patients often face the disease before having addressed their family planning; they may not have time to wait for 5 to 10 years of treatment completion before considering pregnancy. The best available evidence suggests that pregnancy after breast cancer therapy does not negatively impact disease outcome and is safe for the offspring.

The IBCSG 48-14/BIG 8-13 POSITIVE Trial investigates endocrine therapy interruption to enable conception for young women between 18 and 42 years of age with endocrine-responsive early breast cancer, who received adjuvant endocrine therapy for 18 to 30 months and wish to attempt pregnancy.

Main objectives:

- To assess the risk of breast cancer relapse associated with temporary interruption of endocrine therapy to permit pregnancy.
- To evaluate factors associated with pregnancy success after interruption of endocrine therapy.

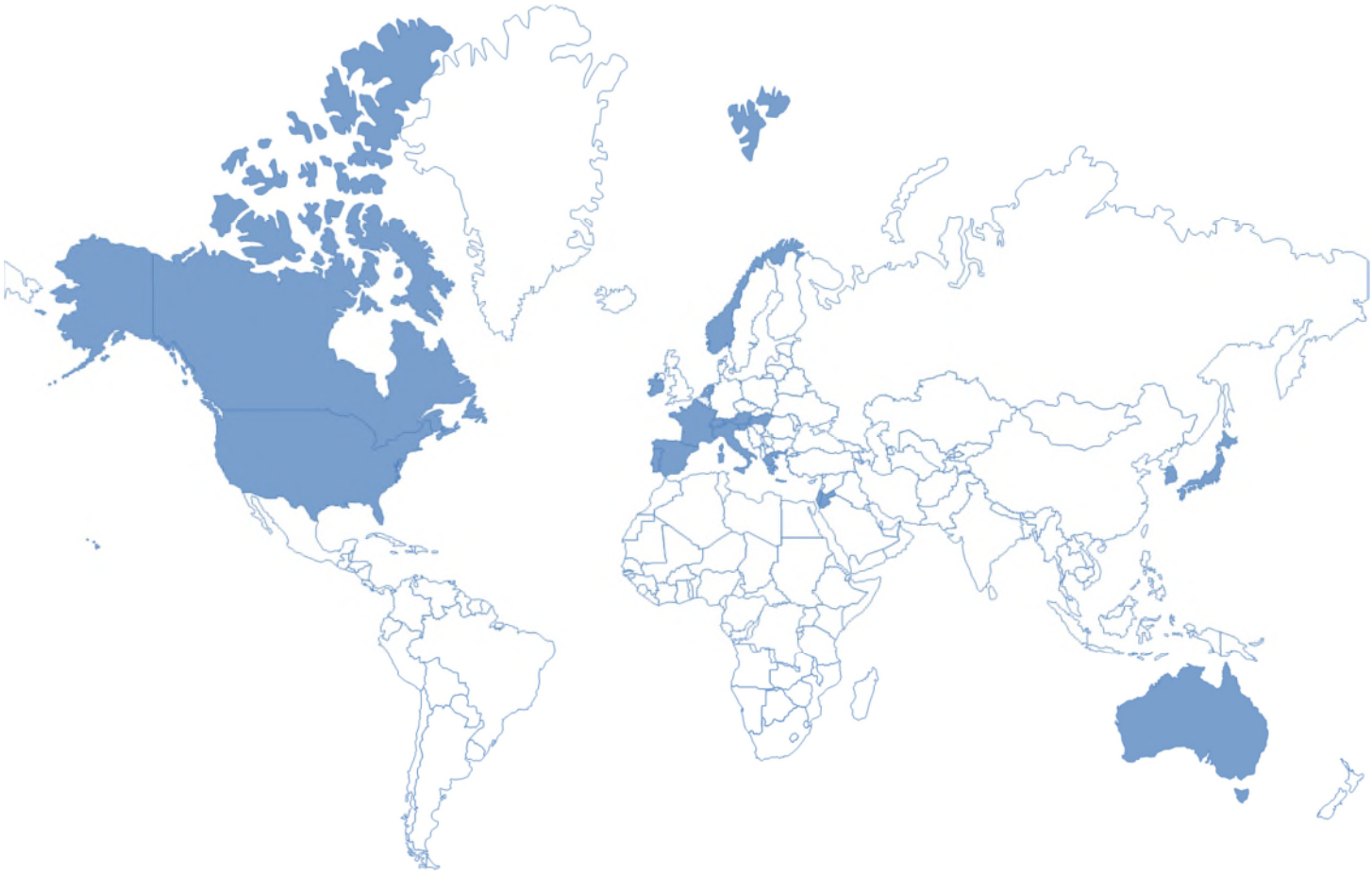
A major focus of the study is the testing of biological correlates of pregnancy and disease outcome. In addition, a psycho-oncology companion study, which explores psychological distress, fertility concerns and decisional conflicts, is being activated in interested sites capable to conduct it.

Inside this issue

The POSITIVE World Map

Launched in 2014, the POSITIVE trial was conceived and activated by the International Breast Cancer Study Group (IBCSG) as a project developed by the Endocrine Working Group of the Breast International Group (BIG) and the North American Breast Cancer Group (NABCG). The IBCSG has built up a coalition of participating Groups and Centers and has been leading the trial worldwide.

As of 31 December 2017, the trial has been activated in 175 Centers from 20 countries and many BIG groups (Switzerland/SAKK, Australia, Italy, Belgium, Spain/SOLTI/GEICAM, Greece/HORG, Slovenia, USA/Alliance, Canada/CCTG, Japan/JBCRG, Portugal/SOLTI, Netherlands/BOOG, Hungary, Ireland/CTI, Norway/NBCG, South Korea, Serbia, Israel, Austria/ABCSG and France) with an accrual of 197 patients overall in the main trial and 112 patients in the psycho-oncological companion study.



175 participating oncology centers in 20 countries around the world!

POSITIVE Facts

Trial Info	
Activation date	03.07.2014
Anticipated end date Patients are followed for 10 years after enrollment. Total trial duration including long-term follow up: 14 years.	31.12.2028
Target accrual (# patients)	500

Trial Progress *as of 31 December 2017*	
Accrual	
♦ Patients enrolled in the main trial	197
♦ Patients enrolled in the Psycho-oncological Companion Study	112
Number of patients pregnant	67
Number of babies born	19
Patients withdrawn but providing recurrence status	4
Patients withdrawn, no further participation	7
Number of patients lost to follow-up	0
An enrolled woman may need at least 1.5 years from enrollment to have a baby. Among the 45 patients enrolled prior to July 2016, 24 patients were pregnant and 12 births occurred.	

Participation *as of 31 Dec 2017*	
Continents	4
Countries	20
Centers	175

Top Ten Recruiting Countries

♦ Italy	44
♦ USA	39
♦ Spain	25
♦ Switzerland	20
♦ Japan	16
♦ Belgium	15
♦ Canada	9
♦ Norway	7
♦ Slovenia	6
♦ Portugal	3
♦ Ireland	3
♦ Netherlands	3

PATIENT SAFETY FIRST

Ethics, Data and Safety Monitoring

The IBCSG Ethics Committee and the referral ethics committees of all participating Centers reviewed and approved the POSITIVE protocol.

The IBCSG Ethics Committee reviews it annually.

The trial is presented for review to the IBCSG Data and Safety Monitoring Committee (DSMC) at each of their semi-annual meetings. Accrual and safety are monitored and interim analyses reviewed.

A Steering Committee has been established and is responsible for :

1 Maintaining the scientific integrity of the trial, for example, by recommending changes to the protocol in light of emerging clinical or scientific data from other trials.

2 Translating recommendations of the IBCSG Data and Safety Monitoring Committee into decisions.

The Steering Committee membership includes IBCSG officials, study co-chairs, trial statisticians, representatives from some Participating Centers and Patients Advocacy Groups.

Message from the Trial Chair

By Olivia Pagani, Oncology Institute of Southern Switzerland, Bellinzona

Young women with breast cancer who desire motherhood after the disease often face difficult decisions and are not always supported by their health providers in finding the right informed personal solution.

Scientific evidence is still not definitive and many questions are open, e.g., how long to wait to conceive after diagnosis and safety in women with endocrine responsive disease. In particular, women who need long-term endocrine therapy risk to end treatment at an age when fertility is decreased and conception can be definitively compromised.

The POSITIVE trial will finally provide the information young women with breast cancer and their physicians need to properly address and manage pregnancy after the disease, overcoming prejudice and misinformation.

"Women who need long-term endocrine therapy risk to end treatment at an age when fertility is decreased and conception can be definitively compromised ."

The Investigator in the Field

By Nadia Bianco, European Institute of Oncology (IEO), Milan—Italy

When I read the POSITIVE Trial for the first time, I was so enthusiastic; finally a study that will answer our crucial questions!
At first glance, it seemed very straightforward and easy to manage, but when we started to recruit patients, we realized that conducting a clinical trial in young patients with breast cancer is challenging.
Besides the effort to be compliant with the visit schedule, perform the tests for translational research and adhere to the protocol timetable, we faced the complexity of problems unique to this patient population.
In fact, although patients were committed to pursue a pregnancy, they were still very fatigued from their cancer journey; an experience that leaves them with many doubts, moments of uncertainty and even apprehension about facing such a happy a moment.

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It is necessary to have a dedicated team that supports patients even after pregnancy or in the event that things do not go well.

Despite many difficulties, often related to geographical distances, we experienced and shared with our patients the defeats but also the accomplishments and the joy of having a baby. It is without a doubt a very challenging and tiring path, but from my experience, this journey together is a chance of growth for both physicians and patients.

"I love being a mum."

Chris, Kirby and Easton. Image: Cassie Gunthorpe. Credit: The West Australian

Patient Voices

Kirby
Perth, Australia

Breast cancer can put baby plans on hold, so when Kirby was diagnosed at 26 she had to face the prospect that she may never realise her dream of being a mum. Three years later, Kirby became the first Australian woman to plan, conceive and deliver a healthy baby as part of the international POSITIVE Trial. Today, she and husband Chris are the proud parents of five-month old Easton, and they couldn't be happier. "I love being a mum," Kirby said. "It's absolutely wonderful."

Led by the International Breast Cancer Study Group, POSITIVE was launched globally in 2014 and is only offered in Australia through St John of God Subiaco Hospital, under the guidance of St John of God Subiaco Hospital Director of Breast Cancer Research Unit and Surgical Oncologist Professor Christobel Saunders. It aims to recruit about 500 women from around the world who wish to interrupt hormone therapy for up to two years to attempt conception.

To be eligible for this trial, women need to have oestrogen receptor positive (ER+) breast cancer, be aged 18 to 42 and pre-menopausal. Participation involves brief semi-annual clinic visits, blood tests at three, six and 12 months and a pelvic ultrasound performed at three and six months, as well as optional questionnaires.

Kirby said she found the lump in her breast after significant weight loss, and within a week of diagnosis was scheduled for a lumpectomy.

This was followed by six rounds of chemotherapy and a series of radiotherapy treatments.

Like many patients with ER+ cancer, she was then put on tamoxifen to reduce the risk of recurrence. "Before my treatment we tried fertility preservation, but they couldn't get any eggs, so unfortunately we had no backup plan," Kirby said. "When Professor Saunders asked if I wanted to take part in this trial, we jumped at the opportunity. Although there is a minor risk with interrupting the tamoxifen, we decided it was a risk worth taking and we couldn't be happier with the result." Kirby fell pregnant within a year of interrupting her tamoxifen treatment, without intervention. She is now about to restart the tamoxifen and said without the support of Professor Saunders and the POSITIVE Trial she and Chris may never have realised their dream of becoming parents. Professor Saunders said about 15 per cent of patients with breast cancer are diagnosed during their reproductive years. "As more women tend to delay childbearing, increasingly, breast cancer occurs before they have completed their families," she said. "This international study evaluates the pregnancy outcomes and safety of interrupting endocrine treatment.

Prof. Christobel Saunders. Image: Cassie Gunthorpe. Credit: The West Australian

It will also improve our scientific understanding of issues related to conception and pregnancy in young women who have had breast cancer by helping us obtain solid data."

Credit: The West Australian

Laura
Zurich, Switzerland

"n January 2015, it was 'BIG Time for Baby' for us – interrupt treatment and start planning a family. We were not sure whether we could succeed within the foreseen two years and whether the probability of a relapse would increase. Thanks to good medical care and participation in the study, we confidently jumped into the adventure.
The decision was right: Lenny is now an eight-month-old, healthy and curious boy. And no, there has been no relapse yet." said Laura, a young Swiss patient enrolled in the POSITIVE Trial, whose attempt to get pregnant was successful.

When Laura was invited by Monica Ruggeri, Head of Program for Young Patients at IBCSG, to join the Swiss PINK RIBBON GOLF TOUR 2017 , she was enthusiastic and said "I received so much from the POSITIVE Trial that I feel I need to give something back".
Laura, her husband Claudio and their smiling boy Lenny were the perfect testimonials!

For the 3rd consecutive year, the IBCSG was the beneficiary of the 3-golf tournaments and received 40'000 Swiss Franc to support the POSITIVE Trial. IBCSG is immensely grateful to PINK RIBBON Switzerland for their tireless work and continuous support .

"The decision was right: Lenny is now an eight-month-old, healthy and curious boy. And no, there has been no relapse yet. "

Claudio, Lenny, Laura and Monica Ruggeri. Crediit: Custom IMAGES

Challenges & Initiatives

Given the relatively small numbers and the emotional and preference-laden issues involved, the accrual of young patients in a prospective clinical study on pregnancy after breast cancer is the anticipated challenge. For this reason, the participation of many countries and Centers worldwide is a prerequisite to reach the target accrual of 500 patients.

Aiming to promote trial awareness and facilitate enrolment, IBCSG developed an informative leaflet to be displayed in the doctors' office or shared with colleagues and local Patient Advocacy Groups. In addition, a poster visualizing the translational research (TR) schedule was designed to support Investigators, Study Coordinators, Research Nurses and facilitate communication when explaining TR assessment time points to patients as well as the level of commitment needed throughout the first year of participation.

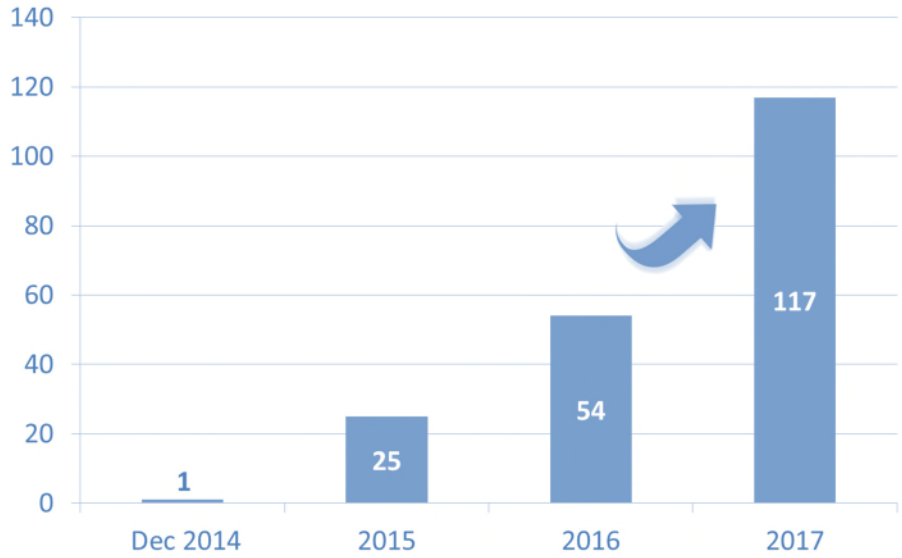
Thanks to these initiatives and, most importantly, to the involvement of other Centers and the support of Patient Advocacy Groups (i.e., Europa Donna and the Young Survival Coalition), the accrual has substantially increased.

Furthermore, IBCSG, with the collaboration and financial support of the young patient group of Southern Switzerland "Anna dai Capelli Corti", has produced the POSITIVE Study Awareness Video. https://youtu.be/rIPkvmQS_3g

The goal is to raise awareness among the scientific and patient communities about the availability of the POSITIVE Study for young patients with endocrine-responsive early breast cancer who wish to have a baby and to sensitize the health providers regarding the aspects unique to this population such as fertility and pregnancy. The video sees the participation of two young breast cancer survivors, Dr. Olivia Pagani and Dr. Fedro Peccatori as breast cancer experts and POSITIVE study scientific co-chairs.

It has been approved by the lead Ethics Committee in Switzerland and is spreading around the world through the European School of Oncology (ESO), Europa Donna, the Breast International Group (BIG) and several collaborative Groups and Centers .

Accrual over time (as of 31 December 2017)



On Sunday June 11, 2017, the IBCSG women (female co-workers with their families and friends), participated in the 5km walk at the well known Frauenlauf held in Bern every year.
We walked together for young women with breast cancer to demonstrate to young patients who face a variety of unique medical and psychosocial issues that because of their diagnosis and treatment, they are not alone. Infertility, premature menopause and sexual dysfunction following treatment are of deep concern for these young patients and may contribute to the greater distress observed in this population. We walk together to demonstrate that IBCSG is committed to the research **P**rogram for **Y**oung **P**atients with breast cancer (**PYP**).

Women 4 Women
walking together, stronger than ever !

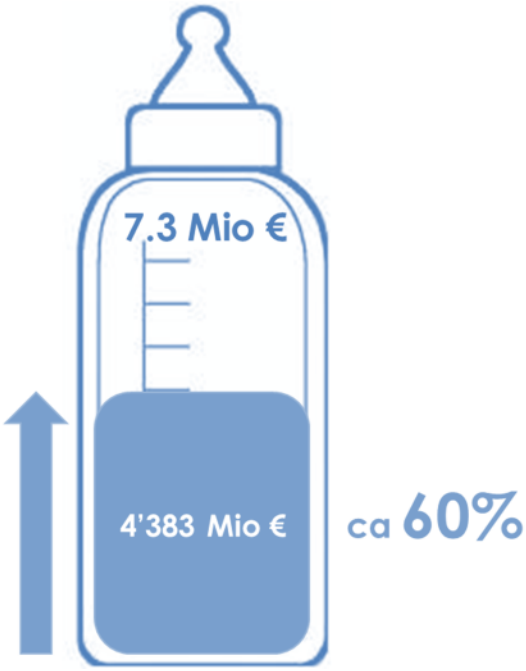
Funding

The acquisition of scientifically sound data for the benefit of young women with breast cancer requires a global effort and commitment by the scientific, patient and charitable communities.
While the international approach is a prerequisite for this trial to be successful and reach the target accrual, on the other hand, it requires enormous efforts in terms of management and thus funding.
The IBCSG is the international sponsor for the trial.

Central conduct (trial management and coordination, data collection, data management, safety and regulatory, statistical reporting, and biobank maintenance): with help from national funding bodies, resources have been identified to permit the start-up and to secure some central activities.

Local conduct
Substantial funding has been granted by local and national sources to support the collaboration of participating institutions worldwide. For example, the participation of North American institutions is supported by the Division of Cancer Prevention of the United States National Cancer Institute through a grant to the Alliance for Clinical Trials in Oncology. Grants are also in place for participation from several other countries. However, these local/national sources of support do not provide any funding for the essential core functions provided by IBCSG. Hence, IBCSG is committed to secure additional funding by establishing a consortium of funders to enable successful completion of the POSITIVE trial.

In 2017, thanks to the successful efforts of Prof Martine Piccart and the team at BIG Headquarters, IBCSG received a substantial grant from the Baillet Latour Fund to support the POSITIVE Trial. This grant has also enabled the IBCSG to provide some funding to help participating Centers that are struggling to find financial support in their country.



We need to secure additional funding by establishing a consortium of funders to enable successful completion of the POSITIVE trial.

A special THANK YOU goes to all foundations and donors for their generous support in making the POSITIVE Trial happen and available for the many young patients with endocrine-responsive early breast cancer who wish to have a baby.

- *Breast International Group (BIG) with Baillet Latour Fund, Belgium*
- *Frontier Science & Technology Research Foundation, Southern Switzerland (FSE)*
- *Pink Ribbon, Switzerland and Norway*
- *Estée Lauder, Switzerland*
- *Swiss Cancer League, Switzerland*
- *San Salvatore Foundation, Switzerland*
- *Swiss Cancer Research Group (SAKK), Switzerland*
- *Rising Tide Foundation, Switzerland*
- *Piajoh Fondazione di Famiglia, Switzerland*
- *Gruppo Giovani Pazienti "Anna dai Capelli Corti", Ticino, Switzerland*
- *Dutch Cancer Society, Netherlands*
- *Norwegian Breast Cancer Society, Norway*
- *Division of Cancer Prevention of the United States National Cancer Institute, USA*
- *Gateway for Cancer Research, USA*
- *Breast Cancer Research Foundation (BCRF), USA*
- *ELGC K.K., Tokyo, Japan*
- *Pink Ring, Tokyo, Japan*

thank you!

IBCSG Facts
as of 31 December 2017

- 35'000 patients
- 500 centers
- 5 continents
- 351 scientific publications

About the International Breast Cancer Study Group (IBCSG)

Since 1977, IBCSG conducts academic clinical trials in breast cancer, while respecting the highest scientific and ethical standards. The patients are at the center of its considerations; the patient's welfare and quality of life are important research topics.
IBCSG is dedicated to innovative clinical cancer research designed to improve the outcome of women with breast cancer. The goal of clinical research within IBCSG is to find answers to key questions. We wish to give our patients a longer survival, if we fail to cure, a longer symptom free period after the primary treatment and eventually to improve their quality of life.

The IBCSG has been a pioneer in research into combined hormonal therapy and chemotherapy, timing and duration of adjuvant therapies and the assessment of quality of life of breast cancer patients. In addition to the clinical trials research questions, the IBCSG conducts extensive programs in translational research, database studies, quality of life and statistical methodology.
The group conducts its trials with up to 500 participating Centers from 5 continents and involves both major research sites affiliated to universities and smaller institutions of the community health sector. It is one of the world's leading groups in the research on breast cancer with more than 35,000 patients participating in its trials so far.
IBCSG publishes the results of the research projects in high-ranking peer reviewed journals. As soon as the trials have reached maturity of the data allowing for the statistical analysis, the data are analyzed and the results presented at major international conferences and published. As of December 2017 the group has published 351 papers.

IBCSG Contact Details
Effingerstrasse 40
CH-3008 Bern
Switzerland

Monica Ruggeri
Head of Program for Young Patients
Phone +41 (0)31 511 94 15
Fax +41 (0)31 389 93 92
monica.ruggeri@ibcsg.org