BIG

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contents

BIOBANKING: THE VIEW FROM THE PATIENT'S END OF THE MICROSCOPE

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NOTE FROM THE EDITOR

Dear Colleagues,

How do patients view the importance of biobanking in finding the best treatment for their disease? How involved should they be? And what can be done to encourage their participation in biobanking? Following *BIG Newsletter*'s May edition in which we focused on both the technical and legal challenges and potential of biobanking, we now turn to look at the issue from the patient's point of view. Bettina Borisch (President of Europa Donna), Doris Schmitt (PATH's managing committee member), and Hugh Davies (NERS Research Ethics Advisor) walk us through the subject on pages 3 to 6.

BIG, in partnership with Philips, Custodix, the Polytechnic University of Madrid, the Foundation for Research and Technology Hellas and the Institut Jules Bordet, has embarked on a new project called INTEGRATE. Funded by the European Commission under the Seventh Framework Programme "Information and Communications Technologies", it aims to address some key obstacles in oncology research today, namely a lack of harmonization, standardization and integration that impedes the optimal use of massive collections of data and valuable repositories of biological samples. To learn more about the project and the challenges of data sharing, go to page 7.

Our members continue to be very active and we are happy to report about their many projects and initiatives: recruitment to GBG and AGO-B's GeparSixto study has been launched; GOCCHI joined the United States-Latin America Cancer Research Network; the Study Nurse Forum launched some years ago by ABCSG is becoming ever more popular... And there is more to discover in the section dedicated to BIG members on pages 10 to 20. In particular, I invite you to read the interviews with Dr Barbro Linderholm and Dr Christos Christodoulou to learn more about the Swedish Association of Breast Oncologists (SABO) and the Hellenic Cooperative Oncology Group (HeCOG), two research groups that, together with the Francilian Breast Intergroup (FBI), joined the BIG network in 2011.

I certainly also recommend that you read the very interesting feedback from the MINDACT trial investigators, invited by the *BIG Newsletter* editors to share their experiences on the occasion of the successful end of accrual of this trial.

Finally, I would like to announce that the IMPAKT Breast Cancer Conference will take place in Brussels on 3 to 5 May 2012. I invite you to look at this edition's scintillating scientific programme on www.impakt.org.

I hope you enjoy the reading and wish you and your families a peaceful holiday season and a successful 2012.

Kind regards,

MARTINE PICCART-GEBHART

BIOBANKING: THE VIEW FROM THE PATIENT'S END OF THE MICROSCOPE

BY EMMA MASON

Following May's *BIG Newsletter* in which we focused on the challenges and potential of biobanking, we now turn to look at the issue from the patient's perspective. How do patients view the importance of biobanking in finding the best treatments for their disease? How involved should they be? And what can be done to encourage their participation and partnership in biobanking projects?

Empowered and well-informed patients are crucial to the success and effectiveness of biobanking, according to the president of the pan-European organisation that campaigns for better information and research into breast cancer.

Professor Bettina Borisch, president of Europa Donna (The European Breast Cancer Coalition) believes that, as with other aspects of medical research, biobanks are best set up and run with patient collaboration. In this way, biobanks are more likely to reflect accurately the needs and aspirations of patients, rather than just the (sometimes) narrow interests of particular researchers. However, she says the patients have to be well-informed first about all aspects of their disease before they can become effective advocates for themselves and others.

Empowering Patients

"Before patients start to get involved in biobanking, they need to be given information by pathologists and clinicians about very basic things such as what a pathology laboratory actually looks like, that pathologists are qualified doctors with at least six years medical training, what tissues and tumours look like when you look at them down a microscope, that all the genetic and protein information is in the tissue, and that the possible later treatments are already indicated by what's in the tissue. Only when patients properly understand these things can they play an informed role as patient advocates," says Borisch.

A trained pathologist herself, Borisch works with patients, showing them her laboratory at the University of Geneva in Switzerland, and helping them to peer down a microscope at tumour specimens.

"This is the first, very important information that patients have to have," she says. "If they don't know these things, then how can they understand about the importance of clinical trials, biobanks and so on? But if patients understand that their breast tissue belongs to them, what happens to it in a pathology lab or in a biobank, and how the tissues can be used to improve their treatments, then you have patients who are empowered."

Of course, not all patients are willing or able to be so involved in every aspect of their treatment in the way that Borisch describes, but she believes they should have the opportunity to if they want to.

Having access to this sort of information not only enables patients to acquire the information they need to become patient advocates, but also helps towards the success of biobanks and to preventing problems such as the organ retention scandal in the UK. Of this, Borisch says: "For the pathologists it seemed like the most normal thing in the world to collect these organs, but there was a missing communication. That's why I think that in the routine diagnostic process, it's important that patients know what is going on, where their tissue is going, and, if they want to, that they can have a look.

"INFORMED PATIENTS ARE NORMALLY VERY HAPPY TO SAY 'YES, YOU CAN USE MY LEFT-OVER TISSUE FOR FURTHER CLINICAL RESEARCH'."

I have never seen people who have said 'no' once they were completely informed."

Doris Schmitt, a member of the managing committee for PATH – the Patients' Tumour Bank of Hope (see also article on page 6) – agrees with Borisch about the importance of informed patients. PATH, based in Germany, is possibly the only breast tumour bank in the world to be set up and run by cancer patients.

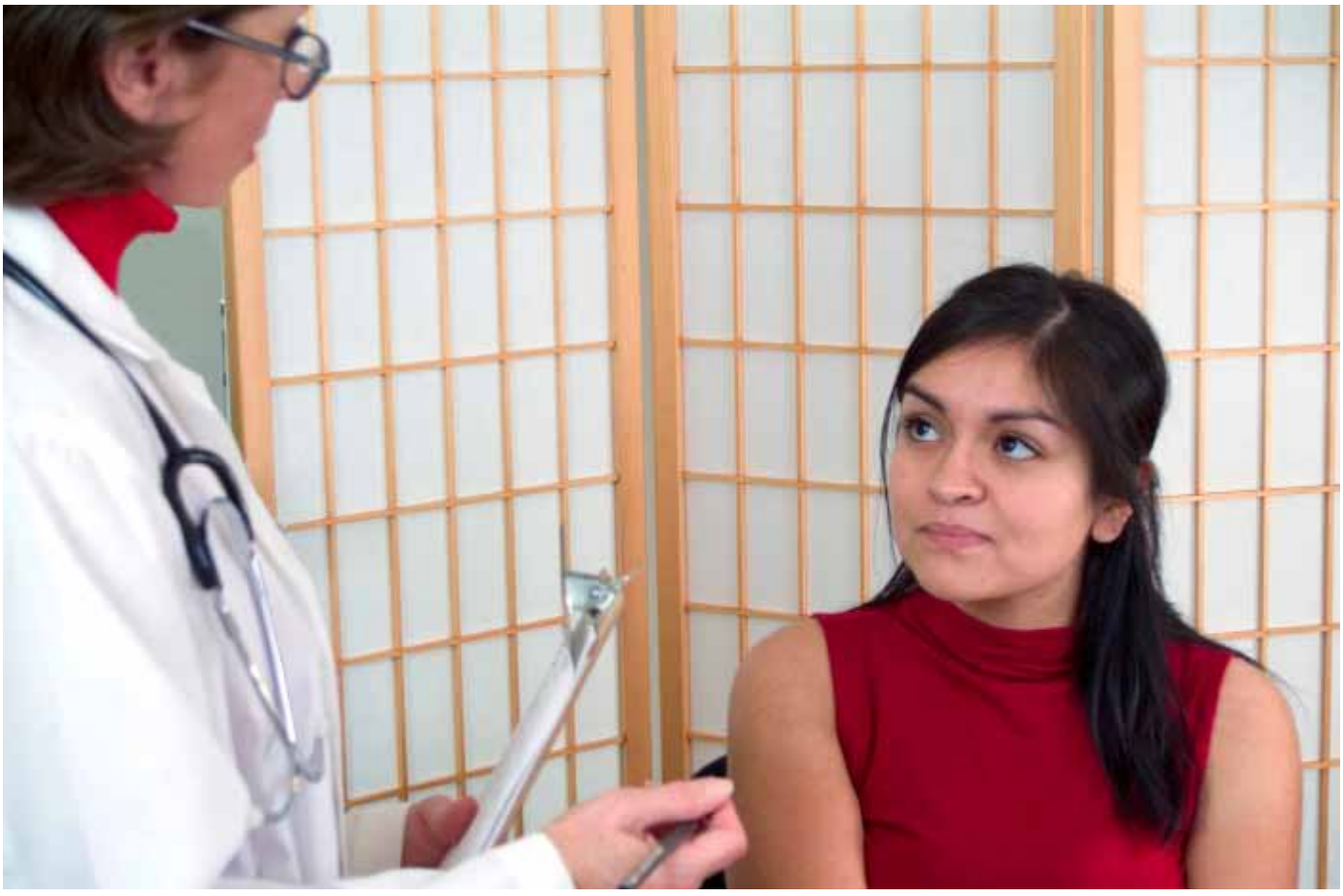
"It is essential for patient advocates to have knowledge and experience," she says. "This is also what I'd like to say to patients who are interested in doing something: you can't discuss in a steering committee for a clinical trial or biobank what is right and what is wrong if you don't know what the therapy does and if you don't know about side-effects, primary or secondary endpoints and things like that."

Schmitt was diagnosed with breast cancer in 1999 and joined PATH in 2008, following time spent as a member, board member and finally chairwoman of **mamazone**, a German breast cancer patient information organisation. She is a patient advocate on the steering committees for several studies because of her experience in these two organisations. But in 1999 she was given very little information about her disease.

"The only thing the physician told me was that it was a serious diagnosis and that I had to have chemotherapy, and that was about it. I didn't know about clinical studies. I didn't know that actually I was a guinea pig for sentinel nodes dissection. At that time, patients were not informed. They can't ask questions if they don't know anything about their disease. That's when I decided I had to do something; I had to inform women how to ask questions and how to get more information. So I'm now on advisory boards, looking at brochures for patients to check they can understand them, that it's not clinical language or physician language or medical language."

Schmitt has had no formal training in being a patient advocate; she has trained "on the job", learning via books, journals, the internet and attending conferences to talk to breast cancer researchers. By profession a communications trainer, she has used her skills to help doctors and patients talk to each other better.

"CLINICIANS ARE STARTING TO REALISE THAT THERE ARE VERY WELL-INFORMED AND PROFESSIONAL PATIENT ADVOCATES OUT THERE AND THEY SHOULD WORK TOGETHER WITH THEM," she says.



The fact that patient organisations can be an asset to researchers is something that is acknowledged by institutions, groups of investigators and individuals (see article on challenges and potential of biobanking published in the *BIG Newsletter* Vol. 13/1 in May 2011).

Patients' Added Value

Schmitt believes that a large part of the value that patients add to discussions between researchers on advisory boards and steering committees for biobanks and clinical trials relate to asking the obvious questions that doctors can sometimes overlook.

"A simple example is if you have a clinical trial where the physicians say that they'd like to see the patients every two weeks, but you are in a country where commuting back and forth between homes and hospitals is difficult. **Clinicians and scientists often don't think about the logistics, but if you have a patient advocate involved, the advocate can tell them that they need to consider travel times and distances for women who may still be quite weak after their primary treatment and that to expect them to do it every two weeks is too much."**

In the UK, the National Institute for Health Research (NIHR) makes a very explicit statement about the importance and value of patient involvement in medical research on its website:

"Involving patients and members of the public in research can lead to better research, clearer outcomes, and faster uptake of new evidence.

The NIHR encourages patients and the public to be actively involved in all NIHR-funded health and social care research to:

- *Set research priorities*
- *Identify the important questions that health and social care research needs to answer*
- *Give their views on research proposals alongside clinicians, methodologists, scientists, and public health and other professionals*
- *Help assess proposals for funding*
- *Take part in clinical trials and other health and social care research studies, not just as subjects but as active partners in the research process*
- *Publicise the results."*

Hugh Davies, Research Ethics Advisor at the UK's National Ethics Research Service (NERS), says that patient involvement is something that the NERS promotes, but points out that the degree of involvement can vary depending on the nature of the project.

"If you are just going to do a new stain on a breast cancer tissue that is already being used in research, then there might not be much point in involving patients in decisions about this. We don't want to burden researchers with more demands if it's not relevant to their research.

"However, if you are going to do a clinical trial, it's important that your end points match the end points that patients consider relevant to their needs. So, when appropriate, patients should be involved at a very early stage. They are the people who know which questions are relevant to them and which are not. They are the people in the midst of their disease."

He concludes with the important point that patient involvement is also about public trust in research. "Patient involvement makes a difference, although the reality can be less clear. However,

> IT'S CRUCIAL THAT WE INVOLVE PATIENTS IN ORDER TO MAINTAIN TRUST IN RESEARCH.

If you lose public trust in research, you lose public participation." ■

Meet the Interviewees

Prof Bettina Borisch

President of Europa Donna (The European Breast Cancer Coalition)
MD and Pathologist at University of Geneva, Switzerland

Doris Schmitt

Member of the managing committee for PATH – the Patients' Tumour Bank of Hope

Hugh Davies

Research Ethics Advisor at the UK's National Ethics Research Service (NERS)

PATH – THE PATIENTS' TUMOUR BANK OF HOPE RUN BY PATIENTS FOR PATIENTS

PATH was founded in 2001 by a group of German breast cancer patients to organise and fund a breast cancer biobank. Its objectives are to support clinical and genetic research, and to offer tissue storage to breast cancer patients at no cost to them.

The biobank is run by volunteers (all breast cancer survivors), with one paid member of staff, and is a non-profit organisation, financed by donations and sponsors. It collects tissue and blood samples and data under uniform standard operating procedures. Since 2009, PATH has been collecting follow-up data from all patients.

"PATH sets out to prove that patients, physicians and researchers can join forces to operate a tumour bank at the highest ethical standards, while collecting tumour specimens and blood serum at the highest, standardised quality," says Doris Schmitt.

"It is important for breast cancer patients to realise the tumour belongs to them. Most cancer patients are not aware of this, and that it is they who can decide what has to be done to it. We have seven cooperating breast cancer centres in Germany, and they inform the patients after their diagnosis that they are able to have their tumour frozen. If they decide to, and most of them do, half of the tumour belongs to the patient, and any portion that remains goes to research. **This is unique: we freeze their tumour specimen for them, free of charge, and the patient has lifelong access to her tissue, so that she can take advantage of newly developed diagnostic or treatment approaches that are developed in the future**. Many of these women also do it for the sake of their daughters, their nieces and their grand-daughters, so that we support research to find targeted therapies to treat breast cancer more effectively."

PATH is very successful at recruiting breast cancer patients: over 90% of patients at its partner breast cancer centres give informed consent to have their samples stored in the biobank. Since 2004, over 4500 patients have consented to biobank storage with PATH.

"The beauty of our organisation is that we are not a commercial tissue bank," says Schmitt. "We are a foundation and a not-for-profit organisation and this gives patients confidence in it. This is why we have such a high percentage of informed consent, because they know that it's in all of our interests to fight breast cancer and one of these days to find a cure."

The biobank is open to requests from researchers (academic and industry) to use samples for their investigations. If the PATH's advisory boards give approval, the samples are donated for the research, with only expenses being charged. Since 2008, PATH has given away samples for five projects in Germany, The Netherlands and the USA.

Schmitt says of herself and the colleagues who work with her at PATH and other patient organisations: "We are driven and inspired by a passionate desire to live. We have all had the shock of being told we have cancer, and there are some women in the world who think that we have to do something about it, do something more. These are the women who are involved with PATH, **mamazone** and other patient organisations." ■

For more information visit:
www.stiftungpath.org

A NEW BENCHMARK IN COLLABORATIVE DATA SHARING IN CANCER CLINICAL TRIALS

BY LINA PUGLIANO, ALEXANDRE IRRTHUM, KAMAL SAINI

INTEGRATE is partially funded by the European Commission under the 7th Framework Programme.

In the modern era, multiple types of data can be generated from clinical trials: clinical, pathology, imaging, molecular signature and sequencing. The explosion of clinical trials, targeted agents and technological advances in genomics has resulted in vast amounts of data being generated. However, optimal exploitation of this data to improve patient outcome has lagged behind because of several obstacles.

Current Obstacles in Oncology Research

The ability to use, merge and take advantage of data generated by different clinical trials is hindered by differences in methodology, lack of standards, and suboptimal collaboration between and among academia and the pharmaceutical/biotechnology industry. Additionally, inadequately developed bioinformatics tools and difficulties imposed by national regulations (governing intellectual property rights, data privacy, patient informed consent, secondary use of data, etc.) further hamper sharing of such data. This results in duplication of effort, a high financial burden, and slow transfer of new discoveries and technologies into clinical practice. One of the main challenges for future cancer research is to develop and enable an environment where widespread data sharing and collaboration becomes possible.

Obstacles for Data Integration

Various ways of expressing the same data point add complexity to integrating data from different clinical trials and datasets. For example, a date of birth can be written as 13/09/2011 or as 13-09-2011 or 09/13/2011 and so on. The human brain is capable of interpreting the three formats and arriving at the conclusion that the date of birth is 13 September 2011, but that is not the case for the normal computer system. However, a process called semantic mapping can provide a computer system with the means to do this, thus giving data both the meaning and context needed for uniform storage and ease of use. The use of semantic mapping and other manoeuvres to "curate" data can make it possible to pool data from different trials to enlarge the sample size, increase statistical power, and enable better exploitation of data and information.

Obstacles for Biological Sample Analysis

Different types of biological samples (e.g., blood and tumor) are collected from patients enrolled in clinical trials. The samples and the related clinical data together form a biospecimen inventory. With the patients' consent, linking this bioinventory with clinical and imaging data means that the data and samples can later be re-used, new tests applied and new hypotheses generated by researchers. Biotracking refers to the database associated with a biospecimen inventory, together with a tracking tool able to locate particular biological samples of interest at any given time, right down to the shelf position in the storage facility. It is also vital to be able to track and link a biosample to the type of test or analyses to which a patient has consented. Currently, individual trials use different and diverse biotracking systems. As the requirement of biological sample testing grows in clinical trials, and aliquots from these samples are tested in different specialized laboratories, more robust and standardized systems will need to be established to meet the future demands.

What is INTEGRATE?

INTEGRATE is a project funded by the European Commission under the Seventh Framework Program "Information and Communications Technologies" that is aimed at addressing some of these issues in oncology research, data integration, and biological sample analysis. It is a collective effort that brings together six European partners (Philips, Custodix, the Polytechnic University of Madrid, the Foundation for Research and Technology Hellas, Institut Jules Bordet and BIG), representing experts in the fields of clinical medicine, knowledge engineering, information technology, basic and translational science, as well as security, legal and ethical bodies and local health services. BIG has been involved since the project's inception and continues, in close cooperation with the partners, to develop the INTEGRATE environment. The objective is to provide solutions and construct an infrastructure for collaboration in the form of a data sharing platform that will integrate multidisciplinary data from clinical trials.

INTEGRATE Environment

The INTEGRATE environment will house multiple features built on a service-oriented architecture. Firstly, data from multiple clinical trials will be incorporated into INTEGRATE with the semantic mapping process described above. Secondly, a series of existing and newly developed analysis services and tools will be employed. These will consist of molecular and pathology/imaging analysis tools and a biotracking service, as well as tools that will facilitate the future linkage to electronic health records (eHR) of participating hospitals.

The INTEGRATE platform will also support the development, preservation and sharing of multi-scale predictive models. Lastly, the INTEGRATE environment will possess the highest standards in data security, access control, and privacy.

Prospective Molecular Testing
Molecular testing of pathology samples consists of several different analyses to identify a patient's specific molecular profile. It is a patient's unique molecular signature that may guide future treatment decisions. As further advances are made in personalized medicine, specific mutation(s), gene expression profiles or signatures are likely to become a requirement for entry into specific clinical trials. INTEGRATE will allow a platform for prospective molecular testing to help determine if a patient is eligible for a specific clinical trial based on his/her specific molecular profile.

Users
The INTEGRATE environment will provide the biomedical research community with access to complex datasets. Users of INTEGRATE will encompass basic and translational scientists, biostatisticians and bioinformaticians, and clinical researchers from both academia and the pharmaceutical and biotechnology industry. A secure system will ensure data protection, and access to different datasets will be granted to different users based on appropriate legal agreements.

Assisting Oncology Research
INTEGRATE will initially be tested and validated using data from select BIG trials. A key feature of the INTEGRATE platform is that it will integrate high quality data from multiple clinical trials. Another important feature of INTEGRATE is that it will enable molecular testing to select appropriate patients into targeted therapy trials.

By tapping into this rich collection of data – whether from trials or molecular testing – users will be able to share and re-use all incoming data in order to conduct meta-analyses, generate and test hypotheses, identify new biomarkers, design innovative clinical trials, and set contemporary benchmarks in cancer therapy in a shared environment.

However, INTEGRATE will be more than just a data mining and molecular screening system. Collaboration with existing systems in and beyond Europe offer complementary and valuable data sharing opportunities that will strengthen global oncology research, and INTEGRATE will seek to interface with these systems to achieve this goal.

What are the goals of INTEGRATE?

- Removal of obstacles to collaborative research
- Superior use of high quality data to drive international standards in breast cancer care
- Analysis across datasets to develop hypotheses related to clinical and molecular biomarkers and therapies
- Fruitful collaboration between the pharmaceutical / biotechnology industry and academia
- Reduced duplication of research efforts
- Reduced economic burden of cancer research
- Linkage to electronic health records of collaborating hospitals

In summary, INTEGRATE represents a novel data sharing platform that will possess the capability of molecular testing in addition to the potential for multiple forms of analysis. This will expedite our knowledge of the biology and therapeutics of breast cancer to allow for increasingly more personalised therapy. ■

For more information visit:
www.fp7-integrate.eu

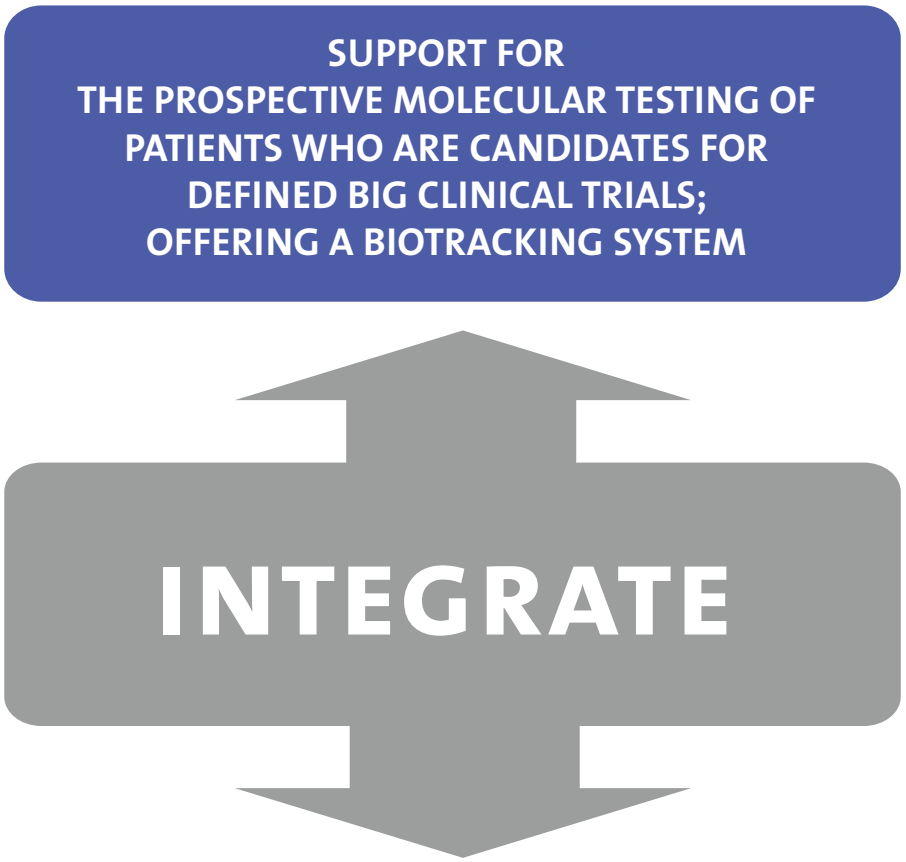
FP7 CORDIS ICT:
http://cordis.europa.eu/fp7/ict

European Commission/INFSO section of Europa:
http://ec.europa.eu/information_society

What are the key features of INTEGRATE?

- Integration of data from multiple clinical trials
- Secure IT platform capable of storage of large amounts of multi-scale data
- Data sharing based on strict access control
- Legal framework specified (intellectual property rights, patient privacy, informed consent, regulatory compliance)
- Allocation of patients to clinical trials based on molecular testing
- Tools for tracking of biological specimens and consents
- Tools for central review of pathology and imaging
- Generation of predictive models

INTEGRATE aims to construct solutions and infrastructure for collaboration via a data sharing platform that will integrate multidisciplinary data from multiple clinical trials.



BIG encompasses 50 members worldwide, which are collaborative research groups or trials data centres represented by one voting and several non-voting delegates within the BIG network. The final decision-making body of BIG is its General Assembly, consisting of the members embodied by their voting representatives. Some BIG groups are regional, some are national and several are international. Each is associated with several to several hundred member hospitals and investigators. This represents several thousand institutions worldwide.

Three new members joined BIG in 2011, bringing along their own local experience and further enriching BIG's capabilities as an international network:

- **Francilian Breast Intergroup (FBI), France**
- **Hellenic Cooperative Oncology Group (HeCOG), Greece**
- **Swedish Association of Breast Oncologists (SABO), Sweden**

Dr Linderholm, SABO voting representative, and Dr Christodoulou, HeCOG voting representative, introduce their respective groups, sharing their expectations and challenges.

SABO

Swedish Association of Breast Oncologists (SABO)
BIG Voting representative: Barbro K Linderholm

The Swedish Association of Breast Oncologists (SABO), set up in 2010, is an academic non-profit organisation open to all medical oncologists in Sweden. Specialists, but also younger colleagues training in medical oncology, can apply for membership.

The overall aim is to promote and develop high quality diagnostic procedures, treatment and care of patients with breast cancer in Sweden. This will be achieved through the exchange of knowledge, education, and the initiation and implementation of clinical trials as well as quality registries. The group collaborates with the Swedish Breast Cancer Group, the Swedish Group of Breast Surgeons and the Breast Cancer Patient Association in Sweden.

INTERVIEW WITH DR LINDERHOLM

BIG: Why did SABO join the BIG network? What does SABO expect from this affiliation?

Dr Linderholm: SABO joined BIG because we believe in the necessity of large cooperative groups to achieve results from clinical trials within shorter time periods, thus improving breast cancer therapy faster. Taking into account the further subdivision of breast cancer into several molecular subgroups, we do not believe that single research groups can solve relevant issues in an effective way anymore. We consider BIG, acting as umbrella organisation for many academic groups, to have an invaluable qualification to discuss and conduct studies aiming to answer several aspects of breast cancer care. By joining the BIG network, we will no longer be solely dependent upon study proposals from pharmaceutical companies.

The improving connection between preclinical discoveries and the consequent effort to implement new targeted therapies has put light on the necessity of translational studies. Fortified by the TRANSBIG Consortium experience, we expect BIG to keep on developing new and interesting study proposals with a translational research focus. As members of BIG, we appreciate the opportunity to take part in discussions about ongoing trials as well as upcoming proposals.

Lastly, we consider the educational scope of BIG to be very important and value very much the efforts BIG puts into fulfilling these needs for early-career scientists and clinicians-in-training, whether through training or by involving them in clinical trials. For example, the IMPAKT meeting, with its training course for young investigators, is valued as one of the top breast cancer conferences, and SABO colleagues are encouraged to actively participate.

What are the biggest challenges for SABO? Do you think these are likely to be shared by other BIG member groups?

As SABO is a young group, we need time to develop our structure and working frame, but we hope this will be settled shortly. One of our main missions is to educate and engage young physicians in clinical translational studies and we encourage them to apply for the Pre-IMPAKT training course. Besides the challenges linked to establishing our group, we struggle against an increasing shortage of clinical doctors. This results in diminished opportunities to do more than basic clinical work – a scenario that is not exclusive to Sweden, I guess.

What does the Swedish breast cancer research scenario look like today and how do you think it will evolve in the next decade?

Sweden is a small country with a small population of around nine million inhabitants. Thus we cannot conduct randomised adjuvant trials on our own within a decent time frame, and this has become much clearer, because a substantial number of today's study proposals focus on smaller molecular subgroups of breast cancer. With this in mind, it is obvious that we will gain from participating in international studies rather than in national ones. The fast development and validation of new prognostic and/or treatment predictive signatures also needs international collaboration, which we aim to adhere to.

How are clinical trials run at SABO? In which clinical trials or research programmes is SABO currently involved?

SABO is represented in the Swedish Breast cancer Group (SweBCG) and several of our centres have participated in the recently closed adjuvant PANTHER trial, led by the SweBCG in collaboration with the German Breast Group (GBG) and the Austrian Breast & Colorectal Cancer Study Group (ABCSG). For many years there have been several trials successfully conducted within Scandinavia. At present several Swedish centres are actively involved in the SOLD trial initiated by the Finnish Breast Cancer Group and supported by BIG (BIG 1-10).

SABO is still struggling with some "childhood diseases", and so far only one phase II translational study has been initiated by our group. In accordance with BIG's objectives we have recruited one young physician as co-principal investigator at each site.

SABO also encourages projects looking at patient care and handling of side effects. Such aspects may vary between countries and we estimate that meaningful descriptive projects can be run at a national level. For example, a project looking at compliance of adjuvant endocrine therapy, as well as the possible delay in return to work due to this therapy has been initiated. This project has received financial support from the patient advocacy group in Sweden.

We hope to have the opportunity to become an active group following our first trial invitation from BIG, the TREAT CTC trial, and look forward to other future proposals. ■

HeCOG

Hellenic Cooperative Oncology Group (HeCOG)
BIG Voting representative: Dr Christos Christodoulou
Website: www.hecog.gr

The Hellenic Cooperative Oncology Group (HeCOG) was founded in 1990 by four medical oncologists who shared a common vision and scientific goals, but most of all the willingness to offer their patients optimal care based on the latest achievements in medical oncology. HeCOG was a pioneer in introducing collaborative clinical trials in medical oncology in Greece to evaluate new anticancer agents and treatment schemes.

Over time more oncologists and physicians from other specialties, as well as scientists from other biomedical research fields, joined the group and have consequently expanded the horizons of its research activities. Today HeCOG numbers over 70 members from 18 oncology institutions/departments in Greece and Cyprus. It promotes interdisciplinary collaborations to advance research among radiologists, radiotherapists, biostatisticians, pathologists, molecular biologists, geneticists and economists.

Research done by HeCOG led to more than 400 publications in peer reviewed journals, with a cumulative impact factor of >800, having received >5500 citations.

The main goals of the group are the study and development of novel anticancer therapies; the promotion of innovative clinical and translational research both in Greece and internationally; and the organisation of scientific seminars and symposia aimed at informing and educating physicians, other scientists interested in oncology, and medical students.

The group has a 7-member Board of Directors chaired by Professor George Fountzilas, a Scientific Committee chaired by Professor Dimitrios Pectasides and 12 Working Parties.

The HeCOG Central Data Office is located in Athens and coordinates clinical data management, monitoring of trials, programming, biostatistical analysis, collection of biological materials, translational research projects that are integrated into clinical trials.

INTERVIEW WITH DR CHRISTODOULOU

BIG: Why did HeCOG join the BIG Network? What does HeCOG expect from this affiliation?

Dr Christodoulou: HeCOG is an oncology research group founded in 1990, incorporating investigators from 18 academic, public and private oncology departments throughout Greece and Cyprus. Over the years our group has grown in numbers and scientific expertise, holding an important position and reputation among the international breast cancer scientific community.

We believe that, at this stage we are mature enough as a group to join a network like BIG. BIG's achievements stand as a hallmark of international collaboration at its best. From this affiliation we expect to participate in, design and initiate large and complex phase II-III studies that few research organisations could accomplish without structured and supportive collaboration. We expect to join state-of-the-art studies, to be able to have access to front-line new drugs that could change oncology practice, and to learn about and have access to innovative research technologies. Over the years we have made it routine practice within the group to collect biological material from all patients participating in our studies. We would like to be able to contribute such material to large tissue banks for the design of novel diagnostic and therapeutic strategies that

could open new horizons for our patients. We expect that, while keeping our identity, we can offer our experience, integrate and share our ideas with other opinion leaders and breast cancer experts within BIG. As a leading national research group, we believe that our affiliation with BIG can add another "building block" for the advancement of breast cancer research. We also believe that the future of innovative personalised diagnostic and therapeutic strategies for breast cancer can only be achieved through committed large collaborations, structured partnerships and innovative, large-scale teamwork; this is why we wanted to join BIG, and that is what we expect from this alliance.

What are the biggest challenges for HeCOG? Do you think these are likely to be shared by other BIG member groups?

HeCOG has been running clinical studies for a number of years in a variety of cancer types. Several of our collaborators have participated in multinational studies, experience that has paved the way to our joining BIG. The strength of our commitment to clinical research is demonstrated by the number of our studies, the quality of our studies and the quality of the biological materials we collect – all these aspects will grow through further collaboration. The challenges we face by joining BIG – which we believe are shared by most smaller national research groups – are to be able to keep our identity as investigators and as a group; to be heard and participate with ideas and work (and not only with patient accrual); and, finally, to benefit as a group by gaining access to new technologies and new drugs and by being present in the scientific community and literature. We are all committed to improving patient outcomes and we join with the trust and confidence that all our hopes and ideas will flourish within the BIG network.

What does the Greek breast cancer research scenario look like today and how do you think it will evolve in the next decade?

As is the case in many smaller countries, disparity in collaboration combined with geographical isolation has resulted in the establishment of several different research groups. A significant proportion of breast cancer research in Greece is represented by studies led and run by our own research group, allowing patient access to innovative strategies. State financial support is limited, however, and most of these studies are funded by the pharmaceutical industry. Structural changes in the health system, involvement in several international groups and the recognition of breast cancer experts in Greece of the need for stronger collaboration both at a national and international level represent the main challenges – and opportunities – of the next decade, in order to improve the overall quality of research and access to novel therapies.

How are clinical trials run at HeCOG? In which clinical trials or research programmes is HeCOG currently involved?

HeCOG's Central Data Office coordinates all clinical trials and ensures that all trial-related activities are performed according to the principles of the International Conference on Harmonisation Good Clinical Practice standards (ICH GCPs) and all applicable laws and regulations. HeCOG employs at least one study assistant and/or a research associate in each one of its 18 collaborative institutions. The Central Data Office handles clinical data management, monitoring procedures, pharmacovigilance, biostatistical analyses, collection of biological materials and coordination of translational research projects. ■

Ongoing clinical trials sponsored by HeCOG

- **HE 3/07** Gemcitabine combined with the mTOR inhibitor temsirolimus (CCI-779) in patients with inoperable or metastatic pancreatic cancer. A phase I-II study with biomarker evaluation.
- **HE 4/09** Study of the mTOR inhibitor temsirolimus (CCI-779) in patients with CA125 only relapse of ovarian cancer. A phase II study.
- **HE 17/08** Investigation of the efficacy of lapatinib monotherapy and temozolomide plus lapatinib combination, in recurrent high-grade gliomas. A phase I-II study.
- **HE 21/10** Efficacy and safety of bevacizumab/temsirolimus combination after first-line bevacizumab/IFN combination in advanced renal cell carcinoma.
- **HE 6A/09** A single-arm, muliticenter, phase II study of panitumumab in combination with capecitabine/oxaliplatin in first-line, wild-type KRAS metastatic colorectal cancer.
- **HE 42/09** Lapatinib and Whole Brain Radiotherapy for patients with brain metastases from lung and breast tumors. A phase II study.

GEPARSIXTO: RECRUITMENT LAUNCHED!

BY ANDREA MAISCH, IOANNIS GKANTIRAGAS, SIBYLLE LOIBL AND GUNTER VON MINCKWITZ

GeparSixto (GBG 066) is a randomized phase II neoadjuvant trial to investigate the addition of carboplatin to paclitaxel / liposomal anthracycline-based neoadjuvant chemotherapy.

GeparSixto is the 10th neoadjuvant study conducted by the BIG member groups GBG (German Breast Group) and AGO-B (Arbeitsgemeinschaft Gynäkologische Onkologie Breast Study Group). The study is sponsored and co-ordinated by the GBG, with Gunter von Minckwitz and Michael Untch as principal investigators.

The study enrolled its first patient on 29 August, and at 26 October already 54 patients have already been randomized. Overall, 45 German centers recruit patients for the study.

Designed for patients with triple-negative (TNBC) and HER2+ early breast cancer, the main objective of the trial is to evaluate the role of carboplatin in addition to an optimal neoadjuvant treatment. Baseline neoadjuvant treatment for all patients will be weekly paclitaxel, non-pegylated liposomal doxorubicin (NPLD, Myocet®) and bevacizumab (B) for TNBC, and trastuzumab plus lapatinib for HER2+ disease.

Rationale

Anthracycline/taxane-based chemotherapy for at least 18 weeks represents today's standard of care in the neoadjuvant setting. The addition of platinum compounds might improve the activity of taxanes in patients with TNBC, as these tumors are genetically unstable and thus more sensitive to DNA-damaging agents. Carboplatin might also improve activity in HER2+ breast cancer, because in vivo data have demonstrated that the highest synergism exists between trastuzumab, taxanes and carboplatin[1,2]. However, data from two metastatic trials are conflicting, although the negative BCIRG 007 trial was biased because of different taxane dosages in the control and experimental arms[3,4].

The recent results of the GeparQuinto trial demonstrated that in patients with TNBC, the addition of bevacizumab to anthracycline-taxane-based chemotherapy resulted in a significant increase in pathological complete response (pCR) rates (hazard ratio 1.67). Higher pCR rates in patients with HER2+ disease might also be achieved with lapatinib given in addition to trastuzumab. Data from the recent Neo-ALTTO and Neosphere trials[5,6] suggest that a dual HER2-receptor blockade reaches significantly higher pCR rates than trastuzumab alone.

NPLD has a better cardiac tolerability profile than conventional anthracyclines. It was therefore selected to reduce the overall cardiac toxicity of a combination with a taxane, carboplatin, trastuzumab, lapatinib or bevacizumab.

Design

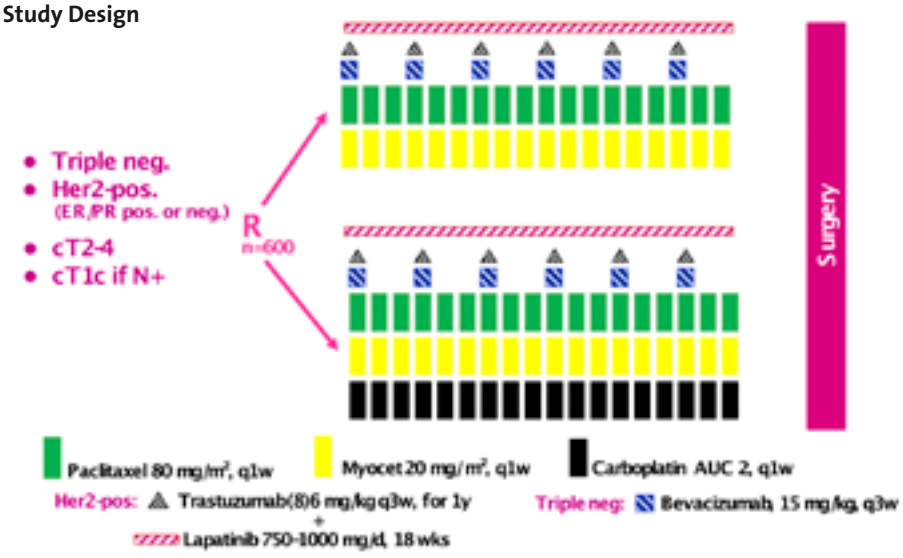
GeparSixto is a prospective, multicenter, randomized, open-label phase IIb study. A total of 600 patients with clinical T2-T4, or cT1c if cN+/pNSLN+ TNBC or HER2+ primary breast cancer with no increased cardiac or bleeding risks will be enrolled. Stratification will be performed according to ER/PR/HER2 status of the core biopsy, defining HER2+ as IHC 3+ or FISH ratio >2,2 and ER/PR+ status as >1% and Ki-67 status (ffi20% and >20%). All four markers will be centrally tested before randomization.

As shown in the figure (see Study Design), all patients will be treated for a total duration of 18 weeks with paclitaxel 80 mg/m² weekly and NPLD 20 mg/m² weekly. Patients with TNBC will be treated simultaneously in all cycles with bevacizumab 15mg/kg given intravenously every 3 weeks. Patients with HER2+ disease will receive simultaneously in all cycles trastuzumab 6 (8) mg/kg every 3 weeks and lapatinib at a daily dose of 750(-1000) mg. In addition, patients will be randomized to receive simultaneous carboplatin with AUC 2 weekly, versus no carboplatin. An integrated safety analyses will take place after the first 60 patients with TNBC and HER2+ disease have entered the study, with timely collection of toxicity data.

The primary aim of GeparSixto is to compare the pCR rates - defined as ypTo ypNo - of neoadjuvant cytotoxic-targeted therapy with or without carboplatin. The trial's secondary aims are to assess 1) compliance and toxicity, 2) the pCR rates separately per treatment arm, and 3) loco-regional relapse-free survival, regional relapse-free survival, local recurrence-free survival, distant disease-free survival, invasive

(*continued on page 15*)

Study Design

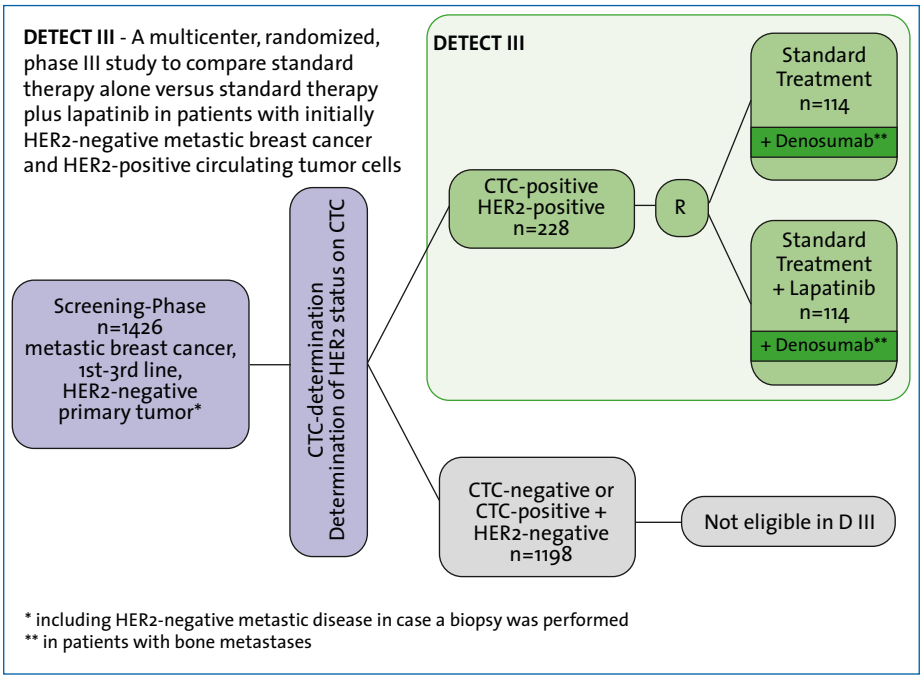


INNOVATIVE INTERVENTIONAL TRIAL IN METASTATIC BREAST CANCER WITH CTCs

BY CARSTEN HAGENBECK, WOLFGANG JANNI AND TANJA FEHM

The HER2 status in breast cancer patients may change during the course of the disease. In 30% of patients who initially had HER2-negative disease with circulating tumor cells (CTCs), HER2-positve CTCs can be detected in peripheral blood samples[1]. At present, it is unclear whether therapy based on the HER2 status of CTCs offers a clinical benefit for these patients. DETECT III is a multicenter, randomized, phase III trial that compares lapatinib as HER2-targeted therapy in combination with standard therapy versus standard therapy alone in patients, with initially HER2-negative metastatic breast cancer and HER2-positive CTCs.

As one of the first interventional trials based on the assessment of CTC phenotypes, DETECT III aims to evaluate the efficacy of HER2-targeted therapy in patients with metastatic breast cancer and HER2-postive CTCs, as well as the significance of CTCs as an early predictive marker for treatment response.



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(*continued from page 14*)

disease-free survival and overall survival. Analyses of molecular markers will be performed to identify possible relationships between biomarkers and drug activity.

Several sub-studies have been integrated into the trial, such as the detection of circulating tumor cells in the blood, a pharmacogenetic substudy of genetic markers to predict tumor biology, treatment response and prognosis, and a substudy on ovarian function in patients under the age of 45 to evaluate the rate of premature ovarian failure following treatment.

GeparSixto is among the first studies to investigate in a randomized design the efficacy of using carboplatin to treat patients with TNBC and HER2+ breast cancer. Recruitment is planned to end by the last quarter of 2012. ■

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MAMMARY PREVENTION MAP.3 TRIAL RESULTS

BY JOSÉ E ALÉS-MARTÍNEZ

The BIG member Grupo Español de Investigación del Cáncer de Mama (GEICAM) has contributed to the MAP.3 trial led by Paul Goss and the NCIC-CTG, the first randomized trial to assess an aromatase inhibitor as a breast cancer preventive in healthy women. The study, which recruited 4560 women from the US, Canada, Spain (432 women) and France, compared 5 years of exemestane vs. 5 years of placebo in women with one or more of the following risk factors: Gail score >1.66%, prior atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), lobular carcinoma in situ (LCIS) or ductal carcinoma in situ (DCIS) with mastectomy, or age over 60. The trial was designed to show a 65% reduction in the relative risk of developing a new invasive breast cancer in the population treated with exemestane in comparison with placebo.

The results of the trial were presented at ASCO 2011[1] and recently published in the *New England Journal of Medicine*[2].

Both groups under study were well balanced for baseline demographic characteristics such as age 62.5 years (37-90), Gail Score 2.3 % (0.6-21) or BMI 28.0 kg/m2 (15.9-65.4). 57% had a history of hormone-replacement therapy use. In an exploratory analysis performed in the 432 Spanish women, mean age (60.3 years), Gail Score (2.6 %) and BMI (28.5 kg/m^2) were similar to the general MAP.3 cohort. In contrast, only 15.5% had a history of hormone-replacement therapy. However, the Spanish participants had a higher proportion of prior breast lesions than the general population. At a median follow-up of 35 months, there were 11 invasive breast cancers (IBCs) on exemestane and 32 on placebo (this is an annual incidence of 0.19% vs. 0.55%; HR 0.35, 95% CI 0.18-0.70, p = 0.002). Results were almost identical among women from North America (HR 0.34; 95% CI, 0.16 to 0.71) or Europe (>95% from Spain) (HR, 0.39; 95% CI, 0.07 to 1.99). Most tumors were early stage and ER-positive (7E/27P). Exemestane was superior in all subgroups. The relative risk reduction of IBC or DCIS combined was 53% (HR 0.47; 95% CI 0.27-0.79; p = 0.004) based on 64 IBCs or DCIS (20 exemestane /44 placebo).

Adverse events occurred in 88% of the exemestane group and 85% of the placebo group (P = 0.003), with no significant differences in clinical bone fractures, osteoporosis, hypercholesterolemia or cardiovascular events. No clinically meaningful differences in quality of life (QOL) were detected. Arthritis (P = 0.01) and hot flashes (P<0.001) were more common in the exemestane group, but differences in the frequency of those with grade 2 or higher symptoms were modest (arthritis, 6.5% vs. 4.0%; hot flashes, 18.3% vs. 11.9%).

A very important finding from the study is that the number of patients who needed to be treated (NNT) with exemestane therapy in order to prevent one case of IBC was 94 in 3 years and only 26 in 5 years. This figure, which matches the best NNT obtained with any cardiovascular risk-preventing drug, gives us hope that we can begin to effectively implement an effective chemopreventive strategy in wide segments of the population of postmenopausal women at increased risk of developing invasive breast cancer.

In summary, MAP.3 is a large, well-designed study involving a substantial number of European women, which has shown in a conclusive manner that exemestane can provide a 65% reduction in the incidence of breast cancer in the target population and that it does so with a good side effect profile and acceptable tolerability. This has the potential to translate into a significant reduction in the breast cancer burden if there is an adequate population uptake. There are associated bone health substudies within MAP.3 assessing the influence of exemestane on bone density and structure. We await the results with great interest. Future ongoing trials with other aromatase inhibitors could reinforce this approach. The trial has proven the ability of GEICAM to undertake primary prevention trials in collaboration with other groups. Now it is the time to try and explore what the preventive potential is of this intervention in the general population. ■

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GOCCHI PARTICIPATES IN US-LA CRN BREAST CANCER PROJECT

BY BETTINA MÜLLER

The Chilean Cooperative Group for Oncological Research (GOCCHI), a BIG member, has joined the United States-Latin America Cancer Research Network (US-LA CRN), an initiative of the Center for Global Health's Office of Latin American Cancer Program Development (OLACPD) led by the US National Cancer Institute (NCI). US-LA CRN was created to develop and implement mutually beneficial cancer research programs in Latin America.

With an emphasis on increasing the capacity of Latin American countries to participate and partner in cancer research, the initiative emphasizes the critical development of clinical research networks and advanced technology centers, as well as training personnel to be better informed to deliver state-of-the-art cancer care to patients. This network will also enable investigators to conduct high-quality clinical cancer research so that important information on treatment response and related pharmacogenomic pathways can be studied in the Latin American population.

The first project launched by this network is a breast cancer study aiming to characterize the distribution of molecular profiles in Latin American women with stage II or III breast cancer. The molecular profiles will be correlated with epidemiological, histological and clinical characteristics, including pathologic response, to standard neoadjuvant chemotherapy. Moreover, this study intends to define a molecular signature that will predict response to neoadjuvant therapy in breast cancer. This is a prospective cohort study in which no investigational drugs will be administered to patients. The study will be conducted at participating institutions in Argentina, Brazil, Chile, Mexico, and Uruguay. This project was awarded as a subcontract by SAIC-Frederick, Inc., the operations and technical support contractor for the National Cancer Institute. This project is 100% supported with federal funds.

To develop and conduct this first project, the OLACPD has created multidisciplinary committees composed of representatives from the five countries, including a Steering Committee, and committees for pathology, clinical oncology, breast surgery, basic research and applied technologies, epidemiology, bioinformatics, bioethics, and communications. The work of these committees so far has enabled clinical and oncological procedures to be harmonized, and pathology and basic research procedures standardized.

In Chile this study will allow the participating community hospitals to set up the country's first public tumor bank, which in turn will ensure the collection and storage of fully annotated tissue and blood samples of the enrolled patients following well defined SOPs. Furthermore, this study will provide a collection of relevant high-quality clinical data. Collaboration between clinical researchers and basic scientists will take place from the beginning of the study, creating the basis for future translational clinical research studies and clinical trials.

Until now GOCCHI has not been able to participate in BIG trials that included the collection and storage of snap-frozen tissue or blood samples for molecular profiling, genomic and genetic analyses, because the infrastructure for these procedures was not available at clinical sites. Participation in the US-LA CRN will enable Chile to create a sustainable infrastructure for high quality cancer research in the future. In so doing, it will enhance capabilities and capacity to develop and conduct clinical research studies, including clinical trials and translational research focused on the pressing unsolved questions in oncology research in Chile. ■

To learn more about OLACPD and US-LA CRN visit: http://olacpd.cancer.gov

THE STUDY NURSE FORUM

BY GITTI GROBBAUER

Several years ago the Austrian Breast & Colorectal Cancer Study Group (ABCSG), a BIG member group, launched its "Study Nurse Forum" project to enhance the exchange of experience and communication among study nurses. A success from early on, the Forum is becoming more and more popular.

Together with clinical investigators and research associates, study nurses rank high among the experts responsible for carrying out clinical studies at specific trial centers. They arrange and coordinate diagnostic investigations, sample shipping and trial medication administration. They thus ensure that the work associated with clinical studies is optimally organized and integrated into everyday clinical life. Trial quality clearly depends to a large extent on the training and competence of the study nurses involved.

This is what the ABCSG Study Nurse Forum recognizes. Courses and workshops are set up via this platform, as well as hands-on seminars at large trial centers for "newcomers". Study nurses rapidly gain thorough insight into the various tasks and requirements of their profession, while improving their knowledge and being given the opportunity to turn to more experienced colleagues. Their training is topped off by annual meetings that focus on topics of relevance to ongoing clinical trials.

"The rush to our courses is growing year by year, and we even receive requests from abroad. This lets us know we truly provide practice-related training and information suited to daily use. We are right on track with this forum", explains its coordinator Natalija Frank.

The web portal www.studynurses.at is also visited by many insiders, including clinics seeking personnel reinforcement. In turn, freelance study nurses offer their services on the web portal.

ABCSG President Michael Gnant is the initiator and most prominent supporter of the Study Nurse Forum. Prof Gnant stresses that study nurses are indispensable members of the study teams: "Today, high quality standards apply to clinical trials internationally. Qualified study nurses thus are in greater demand than ever, their professional abilities and experience being essential in trial conduct. Of course, this also goes for Austria and its exemplary clinical study setting". ■

METASTATIC BREAST CANCER SURGICAL STUDY

BY GITTI GROBBAUER

New basic knowledge about the emergence and development of breast cancer are expected from a novel clinical trial recently initiated by the Austrian Breast & Colorectal Cancer Study Group (ABCSG), a BIG member. The ABCSG 28 study, or POSYTIVE (Primary operation in synchronous metastasized invasive breast cancer), explores the currently non-standard option of initial in-breast tumour resection in women with primary metastatic breast cancer (MBC). The desired effects include reducing and perhaps even completely eliminating cancer stem cells or signals such as growth factors emanating from the primary tumour.

Prof Florian Fitzal, Coordinating Investigator of the trial at Vienna Medical School's Department of Surgery, says: "Thanks to this simple treatment, and the associated low rate of side effects, we have the unique opportunity both to establish new ways to improve our patients' survival and to revolutionise basic knowledge about breast cancer pathogenesis. Complete re-thinking will become necessary should we show that local treatment can indeed improve survival in the presence of metastatic breast cancer. This has already been documented in renal cell carcinoma".

Retrospective analyses[1-7] of more than 10 000 women already substantiate the hypothesis according to which crucial advantages can be gained with primary tumour resection in patients with MBC. As Prof Fitzal explains, "If you extrapolate these data, you may see a 50% relative improvement in overall survival with a rather elementary intervention that has few side effects".

Dealing with both clinical outcomes and causal analyses in translational research, the ABCSG 28 – POSYTIVE trial may, in future, reveal novel treatment options for patients with systemic disease. A series of experimental sub-studies are being planned to investigate stem cells, growth factors and proteomics. ■

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The Netaji Subhash Chandra Bose Cancer Research Institute in Kolkata, India, shares with BIG *Newsletter* readers a progress report about two of its projects:

1) a comprehensive analysis of the association between human leukocyte antigen class I and class II alleles and breast cancer in the population of Eastern India;
2) a study to detect and follow-up on germline BRCA 1 and BRCA 2 gene mutations in breast cancer families in West Bengal.

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HLA CLASS I AND II ASSOCIATION WITH RISK OF BREAST CANCER

BY SOMA MUKHOPADHYAY, DEBOSHREE BHATTACHARYYA, ABHIJIT CHAKRABORTY, JAYASRI BASAK AND ASHIS MUKHOPADHYAY

Breast cancer is the most common malignancy and the second leading cause of cancer deaths among women worldwide. In India, breast cancer accounts for 21% of female cancers and 23% of West Bengal female cancers. With these numbers in mind, we should try not only to treat patients, but also to detect and anticipate the susceptibility of breast cancer at an early stage whenever possible. The Human Leukocyte Antigen (HLA) is potentially an interesting tool for early detection of breast cancer, given that ethnicity-specific HLA allele haplotypes play a significant role in the increased risk of breast cancer.

The analysis we are conducting aims to determine the correlation between different HLA class I and II alleles and breast cancer susceptibility in the Eastern Indian population – an unexplored area so far. The single or multi-locus analysis of single or multiple allele haplotypes will help to evaluate the relative risk or protective effect of any allele(s), if present. Therefore, through this study, we expect to be able to assign to cohort(s) those women with an increased risk of breast cancer.

The objectives of our analysis are to:
- Find correlations between the associations of HLA subtypes that are prevalent among breast cancer patients
- Assess the prevalent HLA subtypes among the normal control group
- Inform women who have susceptible HLA subtypes and take appropriate preventive measures aimed at reducing their future breast cancer burden
- Closely follow-up on those women with HLA subtypes susceptible to the development of breast cancer
- Detect the protective roles of HLA alleles from control groups

As researchers, we hope that by taking adequate preventive measures and by establishing a HLA database, this study will help reduce the breast cancer burden in Eastern India. ■

GENETIC SUSCEPTIBILITY

Genetic susceptibility plays a role in the development of most human cancers. T cell responses are dependent on the inheritance of specific alleles of the highly polymorphic HLA class I and class II genes. Somatic alteration in many tumors can contribute to the down-regulation of HLA class I gene expression in tumor cells. HLA class I genes are expressed in all cells; immune responses also require the presentation of antigenic peptides to T cells by HLA class II molecules. The molecular analysis of ethnicity-specific HLA alleles in patients with breast cancer and controls (who are relatives of the patients) might provide information on the potential existence of alleles that could confer susceptibility or resistance to breast cancer.

GERMLINE BRCA 1 AND 2 GENE MUTATION DETECTION AND FOLLOW UP

BY ABHIJIT CHAKRABORTY, JAYASRI BASAK, DEBOSHREE BHATTACHARYYA AND ASHIS MUKHOPADHYAY

Every year in India, an average of 80 000 women are diagnosed with breast cancer, and 40 000 women die from it. Although it is currently the second most common cancer among Indian women (19%) after cervical cancer (30%), in the urban cancer registries of Kolkata, Delhi and Mumbai, breast cancer has rapidly overtaken cervical cancer in frequency – the Indian Council of Medical Research (ICRM) already observed this trend in 2005.

In this context, our institute has developed a study to detect and follow-up on germline BRCA 1 and 2 gene mutations in breast cancer families in West Bengal.

The objectives of the study are to:
- Detect BRCA1 and BRCA2 mutations in patients with breast cancer and their first and second degree relatives
- Detect BRCA1 and BRCA2 mutations in those women who have a strong familial history of breast cancer
- Study BRCA1 and BRCA2 gene expression in healthy individuals (as controls)
- Establish a genetic profile of the studied population
- Study BRCA1 and BRCA2 gene-positivity as prognostic factor in breast cancer patients
- Search for new mutations in the Eastern Indian population

Epidemiological studies have revealed several risk factors associated with increased susceptibility to breast cancer[1-3]. Among these, familial history is one of the most important. About 30% of young sufferers, and 5% to 10% of breast cancers in general, are believed to be hereditary. The majority of breast cancer patients with BRCA1 or BRCA2 mutations also reveal a family history of breast and/or ovarian cancer in at least one first-degree relative.

In general, women who carry BRCA1 mutations have about an 80% probability of developing breast cancer, and for women who carry BRCA2 mutations, the likelihood increases to 85%[4,5]. But to date there are no data about such mutations in the West Bengal population. To assess the contribution of BRCA1 and BRCA2 mutations to breast cancer in young Indian women, a hospital-based pilot study is being undertaken.

Our institute is planning to analyze the samples of young breast cancer patients treated at different hospitals in West Bengal (especially in Kolkata and surrounding areas). We will screen approximately 200 individuals (100 patients, 50 family members of patients and 50 healthy individuals with no family history) for mutations throughout the entire coding region of both BRCA1 and BRCA2. The complete sequencing of germline mutations on both genes will be conducted.

Inclusion Criteria:
- Probands with at least two first-degree relatives with breast and ovarian cancer
- Probands with only two first-degree relatives with breast cancer, of which one must be diagnosed when under the age of 50
- A first degree relative with cancer diagnosed in both breasts
- Patients with breast and ovarian cancer, bilateral breast cancer, breast cancer diagnosed before the age of 40 and male breast cancer without any other cancer in the family.

Our long-term objectives include:
- Detection of new BRCA gene mutations in the Eastern Indian population
- Maintenance of a hospital-based registry to assess the contribution of BRCA1 and BRCA2 mutations to breast cancer in young Indian women
- On the basis of the results of this pilot study, we may undertake future studies across a wider range of the population, including different ethnicities and geographical distributions. ■

Work Plan

Selection of areas for the collection of samples

⇩

Selection of female individuals complying to the inclusion criteria

⇩

Collection of peripheral blood sample

⇩

DNA isolation from peripheral blood

⇩

Detection of mutations through PCR-SSCP, PTT, direct sequencing

⇩

Individuals with detected mutations will be referred to medical practitioners and regularly monitored

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BIG TRIALS

- **Open trials** – Ongoing trials open to recruitment
- **In follow-up trials** – Trials closed to recruitment, but in active follow-up phase
- **Closed trials** – Trials that have ended activity

Between the time of writing and printing the newsletter, some references and figures in the trial updates texts can become out of date. To get the latest information, we invite you to contact the trial coordinators indicated, or big@bordet.be.

BIG 1-03 / GBG 27 / ICCG C-20-01

OVER HALF WAY TO TARGET RECRUITMENT!

BY LAURA MAHER AND KELLY MOUSA ON BEHALF OF THE TRIAL MANAGEMENT GROUP

REACT is an academically-led trial co-ordinated by two BIG members, the International Collaborative Cancer Group (ICCG) and the German Breast Group (GBG). It is designed to assess the adjuvant benefit of COX-2 inhibition on treatment of primary breast cancer. Patients are randomised to either 400mg celecoxib p.o. or placebo daily for 2 years in a 2:1 ratio in favour of celecoxib. The trial is reviewed on a regular basis by an Independent Data Monitoring Committee.

Celecoxib is a selective COX-2 inhibitor licensed for the treatment of chronic arthritis. However, an association between non-steroidal anti-inflammatory drug use and decreased breast cancer risk in women has also been demonstrated, believed to be due to inhibition of the COX-2 enzyme. It has been shown that COX-2 inhibitors can prevent mammary tumour formation, inhibit angiogenesis and reverse resistance to apoptosis.

Recruitment is increasing steadily and has now reached 1411 patients, 54.5% of our target of 2590. The average monthly accrual for 2011 is 47, a considerable increase on 36 patients per month in 2010. There are currently 153 sites recruiting, with plans to open further sites over the coming months.

Protocol version 35 (dated 23 March 2011) is now in effect. The main changes include:

- Widening of inclusion criteria so that patients are eligible regardless of menopausal status
- Widening of inclusion criteria so that there are no restrictions on age other than a minimum age of 18
- Exclusion of T1No patients who are Grade 1, removing the need for reference to the St. Gallen criteria

To date, 378 FFPE tumour blocks have been collected as part of the pathology sub-study. The sub-study analysis will investigate modulators of tumour response using tissue micro-arrays as we have hypothesised that elevated COX2 expression drives distant tumour recurrence and progression in a sub-group of breast cancers. ■

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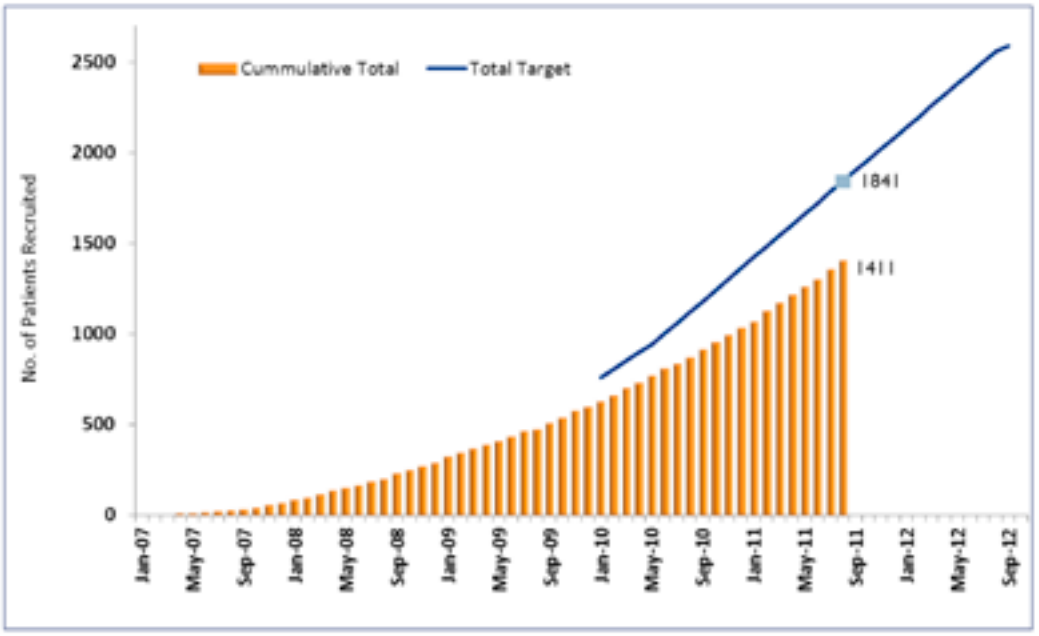

BIG 2-04 SUPREMO / MRC 05-S0501-106 / EORTC

ACCRUAL RATE EXPECTED TO INCREASE

BY IAN KUNKLER, EVE MACDONALD, JULIAN LIPSCOMBE AND LEIGH FELL

SUPREMO (Selected Use of Postoperative Radiotherapy after MastectOmy) has a target accrual of 1600 patients with a primary endpoint of overall survival after ten years. The intended closing date for recruitment to the trial is 31 December 2012.

At the end of August 2011, there had been 1170 patients recruited to the trial (831 UK, 240 EORTC, 99 Non-EORTC International) from a total of 157 open sites (117 UK, 26 EORTC, 14 Non-EORTC International). Recruitment is progressing well and the trial now needs to recruit an average of 27 patients per month to meet the recruitment target. Through the first eight months of 2011 the trial has been recruiting at an average of 29.5 patients per month and is therefore on track.

New Protocol Version to Increase Recruitment

Protocol Version 29 was released to sites in February 2011. Recruitment is now expected to increase because of the widened eligibility criteria as detailed below:

- cT1-2,N0-1 or cT2,N0 patients with additional risk factors (grade 3 or LVI) who have neoadjuvant therapy followed by mastectomy, even if downstaged to pathological stage type T0-2,N0-1
- Patients with pN1 (1-3 positive nodes) in which a minimum of 8 nodes (previously required a waiver) were obtained from an axillary clearance
- Patients with pathologically involved internal mammary nodes on sentinel node biopsy (stage pN1b or pN1c)
- T3,N0 patients
- T3,N0 who receive neoadjuvant systemic therapy followed by mastectomy
- BRCA1 or BRCA2 mutation carriers

The updated protocol was submitted to the EORTC Protocol Review Committee (PRC) in March 2011 and was approved by the PRC in April. Subsequently all relevant documents will be translated, with the expectation to implement the protocol in all the EORTC sites during the autumn.

As of this writing, 124 out of 152 sites have received ethical approval for Version 29 (UK: 116 out of 117, EORTC: 2 out of 26, Non-EORTC International: 6 out of 9). The five China sites will continue to work to Version 27.

Grant from Cancer Australia

We would like to congratulate the BIG voting representative and member of the BIG Advisory Council, Associate Professor Boon Chua (Peter MacCallum Cancer Centre, Australia) on successfully obtaining funding from Cancer Australia for support for the trial under the auspices of TROG (Trans-Tasman Radiation Oncology Group). This may lead to an additional ten new sites from Australia. In addition, the two existing standalone Australian sites at the Royal Adelaide Hospital and the Sir Charles Gairdner Hospital in Perth will now come under the TROG umbrella.

New Grant to Support Long Term Follow Up in China

Breast cancer is a rising health care issue, particularly among young urban women in China. Mastectomy is a common operation for operable breast cancer in China so the results of SUPREMO will be highly relevant to many Chinese patients.

(*continued on page 23*)

1. Chinese Acaemy of Medical Sciences, Beijing
2. Zhejiang Cancer Hospital, Hangzhou
3. Cancer Center, West China Hospital, Chengdu
4. Sun Yat-sen University Cancer Center, Guangzhou

BIG 3-02 / IBCSG 25-02 TEXT

GEARED UP FOR TRANSLATIONAL RESEARCH

BY OLIVIA PAGANI AND RUDOLF MAIBACH

TEXT aims to compare adjuvant endocrine therapy with ovarian function suppression plus either tamoxifen or exemestane for premenopausal women with steroid hormone receptor positive early breast cancer.

Two years ago the International Breast Cancer Study Group (IBCSG) launched a major translational research program in the context of TEXT, supported by a Susan G Komen for the Cure® Promise Grant.

As of this writing, blood samples for DNA isolation from about 2000 of the 2639 TEXT patients have been collected and DNA extraction has been performed in almost a third of them. The goal is to assess patient-related pharmacogenetics and disease-related gene polymorphisms that could possibly give an indication about whether one or the other therapy compared in TEXT is better for the individual woman.

Bone Sub-study

The TEXT bone sub-study, which collects serial blood and bone mineral density measurements to assess any possible differential role of study treatments on bone health, was amended to also include patients at post-baseline visits, with the assumption that baseline bone mineral density and serum bone markers would be normal for these premenopausal women.

Amendment 3 was released with two purposes. The first is to revise the statistical section, taking into account the lower than anticipated event rate and introducing a time-driven analysis plan (with a cut-off set for Fall 2013 at a median follow up of approximately 6 years). The second purpose is to collect additional targeted adverse event information on glucose intolerance (diabetes) and anti-diabetic concomitant medications, since increased risk of diabetes has been suggested by epidemiological studies in men being treated with GnRH agonists for prostate cancer. ■

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(*continued from page 22*)

SUPREMO is the first BIG radiotherapy trial to include a network of investigators from China under the very effective leadership of Professor Yexiong Li and Associate Professor Shulian Wang at the National Cancer Centre in Beijing. An initial generous grant of HKD 1 million to the University of Edinburgh from the William and Elizabeth Davies Foundation funded the recruitment of 60 patients from China and five years of follow-up. Currently there have been 58 patients recruited from four centres (Chinese Academy of Medical Sciences, Beijing [22], Sun Yat-sen University Cancer Centre, Guangzhou [19], Cancer Hospital of Zhejiang Province [10], West China Hospital, Chengdu [7]). Only two more patients are required to reach our target.

A subsequent grant of GBP 68 140 for the monitoring and follow up of Chinese patients for ten years has been awarded by the HSBC Trustees from the Chan Jee Yat Foundation and the Yeung Ying and May Yeung Foundation in April 2011. We are very grateful for this generous support to a BIG trial. ■

BIG 4-11/BO25126/TOC4939G

DUAL HER2 INHIBITORS TESTED IN ADJUVANT BREAST CANCER PATIENTS: THE APHINITY TRIAL

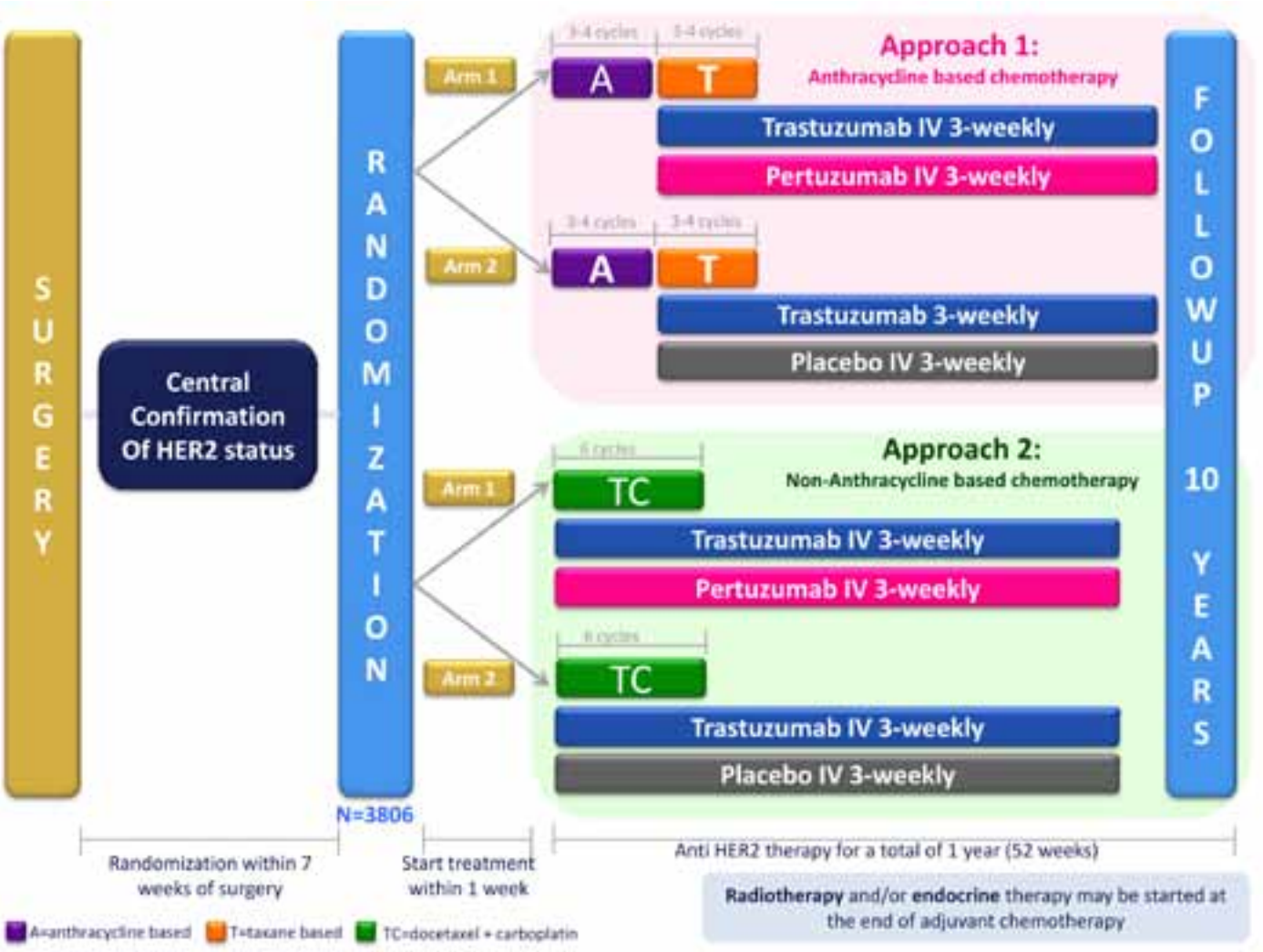
BY LINA PUGLIANO, KAMAL S SAINI AND EVANDRO DE AZAMBUJA

Trastuzumab was approved for use in metastatic breast cancer in 1998 and in the adjuvant setting in 2006. Despite its significant benefit in the adjuvant treatment of HER2-positive breast cancer, not all patients benefit from this therapy. For this reason, new anti-HER2 drugs, such as pertuzumab, have been sought.

Like trastuzumab, pertuzumab is a monoclonal antibody, but with an alternate and complementary mechanism of action. While trastuzumab targets domain IV of the extracellular HER2 domain, pertuzumab's main mechanism of action is to inhibit dimerisation of HER2 with other HER family members. Pertuzumab achieves this by binding to domain II of the extracellular domain of HER2, also known as the dimerisation site.

Pertuzumab has been shown to be efficacious in the metastatic and neoadjuvant settings and it is now moving towards adjuvant therapy. In the NeoSPHERE trial, the addition of pertuzumab to docetaxel and trastuzumab in neoadjuvant treatment of breast cancer patients resulted in a pathologic complete response rate of 45%[1].

APHINITY (Adjuvant Pertuzumab and Herceptin in Initial Therapy of Breast Cancer, NCT 01358877) is an international collaborative study involving scientists, oncologists, academia and the pharmaceutical industry that aims to recruit approximately 3806 patients. It is a prospective, two-arm randomized, multicenter, multinational, double-blind, placebo-controlled study in patients with centrally tested HER2-positive primary breast cancer who have had an excision of their primary breast tumor. Patients will be randomized (1:1 ratio) prior to any chemotherapy to one of 2 treatment arms:



Approach 1: Anthracycline-based Chemotherapy

Treatment Arm 1: anthracycline therapy can consist of 3-4 cycles of chemotherapy from an approved list followed by 3-4 cycles of taxane chemotherapy given concomitantly with trastuzumab and pertuzumab. Anti-HER2 therapy continues for a total duration of 1 year (52 weeks)

Treatment Arm 2: anthracycline therapy can consist of 3-4 cycles of chemotherapy from an approved list followed by 3-4 cycles of taxane chemotherapy given concomitantly with trastuzumab and placebo. Anti-HER2 therapy continues and for a total duration of 1 year (52 weeks)

Approach 2: Non-Anthracycline-based Chemotherapy

Treatment Arm 1: consists of docetaxel and carboplatin for 6 cycles given concomitantly with a trastuzumab and pertuzumab. Anti-HER2 therapy continues for a total duration of 1 year (52 weeks)

Treatment Arm 2: consists of docetaxel and carboplatin for 6 cycles given concomitantly with a trastuzumab and placebo. Anti-HER2 therapy continues for a total duration of 1 year (52 weeks)

All patients must have a central pathology review of HER2 to be considered eligible for participation in the study. In addition, central assessment of hormone receptor status (ER and PgR) will be conducted for the purpose of stratification. Other stratification factors include nodal status, type of chemotherapy (anthracycline vs non-anthracycline containing regimens) and geographical region.

Primary objective: to compare invasive disease-free survival (IDFS), excluding second non-breast cancers.

Secondary objectives are: invasive disease-free survival (IDFS), including second non-breast cancers, disease-free survival (DFS), overall survival (OS), recurrence-free interval (RFI), distant recurrence-free interval (DRFI), cardiac safety, overall safety, and health-related quality of life (HRQL) in the two treatment arms.

A key feature of APHINITY is the prospective collection of biosamples for future translational research. Tissue and blood samples will be collected to evaluate a number of biomarkers either for prognostic purposes or to potentially identify patients whose disease is more likely to respond to treatment. Mandatory samples that will be collected are formalin fixed paraffin embedded (FFPE) tumor blocks, whole blood, serum and plasma. Optional consent for donation of fresh frozen tissue (FFT) is provided for patients at selected centers.

This trial will recruit patients worldwide with approximately 700 centers from 44 countries. Patients will be followed for 10 years. The Breast International Group (BIG) and Roche/Genentech have designed and developed this trial that will be led by Drs Gunter von Minckwitz, Jose Baselga and Jose Bines as the principal investigators. The central data management will be performed by the Breast European Adjuvant Study Team (BrEAST) located at Jules Bordet Institute in Brussels, Belgium, and the statistical analyses will be conducted by Frontier Science & Technology Research Foundation, with offices in Scotland and the US. ■

Reference

1. Gianni L, et al. Neoadjuvant pertuzumab (P) and trastuzumab (H): Antitumor and safety analysis of a randomized phase II study (NeoSphere). SABCS 2010; Abstract S3-2

BIG 2-02 SOFT / IBCSG 24-02

PHARMACOGENETICS PROGRAM

BY PRUE FRANCIS AND RUDOLF MAIBACH

SOFT focuses the ovarian function suppression question on the subset of women who biologically would be most likely to benefit, i.e. premenopausal women with hormone receptor positive breast cancer, either following surgery alone or after completion of adjuvant/neoadjuvant chemotherapy.

In collaboration with Dr Matt Goetz from the North Central Cancer Treatment Group (NCCTG), the International Breast Cancer Study Group (IBCSG) has started a program of pharmacogenetic investigations to understand whether common variations in the genes involved in tamoxifen and exemestane metabolism may affect how these drugs work. All patients enrolled in SOFT by North American sites (1030 of the study total of 3066) are being asked to participate in this program by donating a single blood sample. The collection of samples is currently ongoing.

The one-time blood sample will help determine the role of CYP2D6 as a predictor of disease-free survival in premenopausal women who receive adjuvant therapy with tamoxifen alone and tamoxifen plus ovarian function suppression. It will also be used to determine whether there is an increased incidence of musculoskeletal events in women who receive either tamoxifen or exemestane according to whether they have a SNP (single-nucleotide polymorphism) on chromosome 14 (e.g., TCLIA) or not,. In addition, DNA will be stored for future research, thus allowing us to explore whether currently undiscovered genes whose protein products are involved in the metabolism, uptake or distribution of tamoxifen or exemestane or other plasma biomarkers are associated with either disease-free survival or toxicity.

In parallel with the TEXT trial amendment 3, amendment 2 for SOFT has been prepared and distributed. The purpose of these amendments is to adapt the statistical analysis plan to the lower than anticipated event rate and to add diabetes to the case report forms as a targeted adverse event (cf. article on TEXT on page 23). It is anticipated that the SOFT analysis will be performed in the fall of 2013 with a median follow-up of approximately five years. ■

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BIG 1-07 SOLE / IBCSG 35-07

CONTINUED INTEREST IN INNOVATIVE RESEARCH QUESTION

BY MARCO COLLEONI AND RUDOLF MAIBACH

The Study Of Letrozole Extension (SOLE) is a worldwide trial coordinated by the International Breast Cancer Study Group (IBCSG, a member of BIG). It is designed to compare extended continuous letrozole for five years with intermittent letrozole over a 5-year period for postmenopausal women who are disease-free following four to six years of prior adjuvant endocrine therapy with SERM(s) and/or AI(s) for endocrine-responsive, node-positive, operable breast cancer.

More than 3200 of the planned 4800 patients have now been included in the trial, and recruitment continues at a high pace. This year centers in Austria, France and the US have started contributing to the recruitment. Two Greek groups, the Hellenic Breast Surgeons Society (HBSS) and the Hellenic Oncology Research Group (HORG), as well as the Ireland Co-operative Oncology Research Group (ICORG), all three BIG members, are in the activation process. With over 220 participating centers spread over the 6 continents, SOLE has become a truly international study!

SOLE EST Sub-study

SOLE EST is a small sub-study conducted in selected sites which assesses the serum level of the estrogens estradiol (E2), estrone (E1) and estrone sulphate (E1S) as well as sex hormone binding globulin (SHBG) during letrozole treatment. The degree of recovery of these markers during the 3-month treatment gap in the intermittent arm of the study will be of particular interest. The first patient was enrolled in January 2011 and currently two-thirds of the planned sample size of 100 patients have been recruited. ■

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BIG 2-06 ALTTO / N063D / EGF 106708

ACCRUAL TARGET REACHED AND CHANGES AFTER IDMC RECOMMENDATION

BY IVANA BOZOVIC, MARTA CAPELAN AND EVANDRO DE AZAMBUJA

The Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation study (ALTTO) is a multi-centre, phase III study of lapatinib, trastuzumab, their sequence, and their combination in patients with HER-2 positive early breast cancer. This trial is coordinated by the BrEAST Data Centre (Brussels, Belgium) and Frontier Science & Technology Research Foundation (Boston and Scotland) provides statistical leadership. In North America, the trial is coordinated by the North Central Cancer Treatment Group (NCCTG). GlaxoSmithKline (GSK) is the trial sponsor.

ALTTO reached its target accrual and randomisation of new patients was closed in July 2011. **We would like to congratulate all investigators worldwide who have contributed to this great achievement, and express our gratitude to all patients and to all people who made this possible by maintaining their commitment to ALTTO.** ALTTO has once more proved that a large global phase III trial in adjuvant breast cancer is feasible.

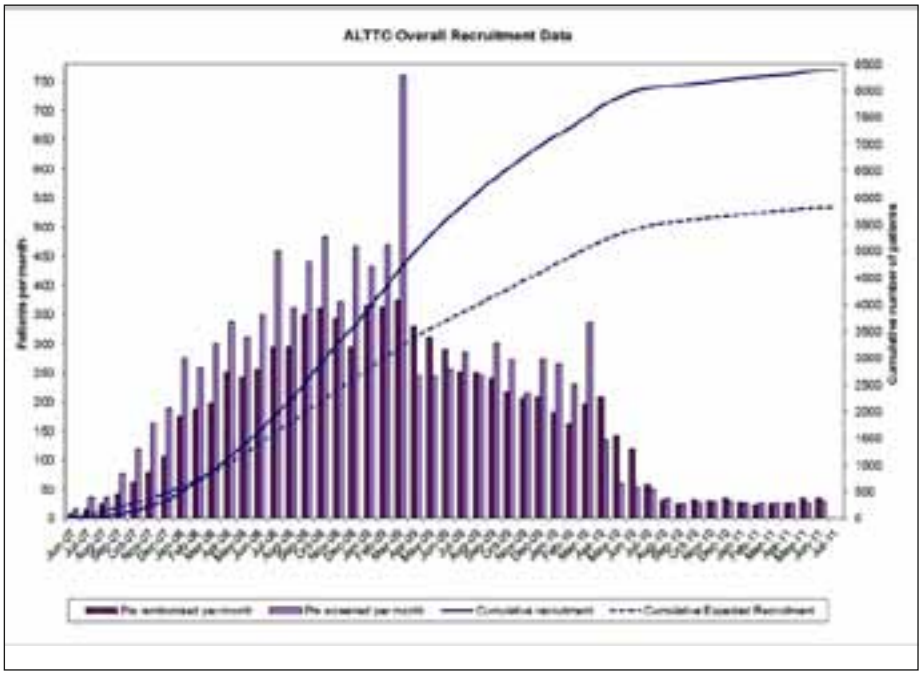

Figure 1: ALTTO overall recruitment data

In four years, a total of 8381 patients from 945 active enrolling sites were randomised: 4566 into Design 1 (targeted therapy starting after completion of chemotherapy), 3370 into Design 2 (targeted therapy started concomitantly with taxanes chemotherapy) and 444 into Design 2B (carboplatin plus docetaxel, the so-called "TCH" regimen given concomitantly with the targeted therapy) (see figure 1). These impressive numbers reflect a truly unique collaboration involving two major academic research networks – The Breast International Group (BIG) and the North American Breast Cancer Group (NABCG) – and an industry partner, GlaxoSmithKline. ALTTO involves 44 countries across Europe, North America, South America, Asia and Australia.

From October 2010 to July 2011 recruitment into ALTTO was limited to Design 2B, open only to patients from the US and Canada, where the TCH regimen is FDA approved and clinicians are experienced in managing side effects related to this regimen. In the future, ALTTO will be able to provide detailed information about the safety of the TCH regimen given in combination with anti-HER2 agents (trastuzumab or lapatinib alone, their combination or their sequence). Importantly, all patients will be followed for up to ten years after randomisation, in an effort to shed new light on the toxicity profiles of the two anti-HER2 agents, especially regarding cardiac safety.

ALTTO also embeds an ambitious translational research component in its design, including central HER2 testing by IHC and FISH, ER and PgR status, and TMAs for all randomised patients. The vast majority of patients have contributed with two additional cores for future research, providing the potential to better understand HER2 disease and its mechanisms of resistance / sensitivity to anti-HER2 drugs. It has already been possible to collect blood and other body fluid derivates (such as plasma, serum, and CTCs) from a subset of patients. The results of research involving analyses on these samples are eagerly awaited in the future.

ALTTO is part of a visionary breakthrough in the treatment of breast cancer patients, because at the time the trial was being designed there were no data available about the efficacy of a dual HER2 blockade (lapatinib and trastuzumab). Since then, the dual blockade has been proven to be more efficacious than a single blockade in the metastatic[1,2] and neoadjuvant[3,4] settings. However, the translation of efficacy as measured by short outcome surrogates (progression-free survival and pathologic complete remission) into long outcome benefit (disease-free and overall survival) can only be confirmed in a few years' time.

In August 2011 the first ALTTO interim analysis was triggered after a predefined number of events were reached. The Independent Data Monitoring Committee

(*continued on page 28*)

BIG 1-98 / IBCSG 18-98

LONG-TERM FOLLOW-UP AND TRANSLATIONAL RESEARCH

BY BEAT THÜRLIMANN AND RUDOLF MAIBACH

Since the first publication in 2005, the BIG 1-98 Collaborative Group has published several updates with increasingly longer observation time. The 12-year update of the monotherapy comparison is currently in preparation with a median follow-up time of eight years. Is this the end of the story? By no means!

At the beginning of 2011 the group started an observational, non-interventional long-term follow-up study as an extension of the BIG 1-98 trial to collect a yearly, simplified update of survival, disease status, and long-term adverse events for patients from centres participating in the 4-arm option. The objective is to report on the long-term outcomes and side effects of the four treatment groups. Long-term follow-up, as well as all the questions on the long-term follow-up CRFs, were foreseen in the original BIG 1-98 trial protocol and CRFs. Many centres have already activated this part of the study; in others, activation is ongoing.

Although all patients have completed treatment as indicated in the protocol, BIG 1-98's focus on long-term follow-up and translational research will continue to provide useful information beyond the primary questions of efficacy.

The translational research reports on known biomarkers, and the composite assessment obtained by putting the available tumour characteristics together to assess the risk of recurrence, provide a basis upon which to make informed decisions about the selection of patient treatment. Future translational research will further clarify individual patient differences relevant to making treatment decisions, as will the detailed safety data.

BIG 1-98 long-term follow-up data will be used to weigh the risks and benefits of the various treatment options in terms of efficacy in tumour-defined subgroups, adverse events, and tumour biology not yet determined. Tumour tissue was secured from over 5000 patients treated in the trial, and DNA has been extracted for about 4900 patients. Genotyping of CYP2D6 and CYP19A1 has been completed, and the correlation of CYP2D6 with patient outcome was presented at SABCS 2010 by Giuseppe Viale. At ASCO 2011, Mark Bouzyk presented an analysis of the relationship of ESR1 and ESR2 with outcome. The comparison of the role of tumour PgR expression, HER2-status and Ki-67 LI as predictors of responsiveness to sequential treatment with what was previously observed for monotherapy has been published in the *Annals of Oncology*[1]. Several other projects are ongoing. The BIG 1-98 translational research programme is funded in part by a Susan G Komen for the Cure® Promise Grant. ■

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(*continued from page 27*)

(IDMC) reported that the lapatinib alone arm (Arm 2) is unlikely to meet the pre-specified criteria to demonstrate non-inferiority at the final analysis in terms of disease-free survival as compared to the trastuzumab alone arm (Arm 1). As a consequence, ALTTO amendment 10 and an amended Informed Consent Form (ICF) were released in October 2011 to discontinue the lapatinib arm and allow a switch to trastuzumab for those patients who were assigned to the lapatinib alone arm and were still on treatment. The other three arms (trastuzumab alone, sequential trastuzumab and lapatinib treatment, and their combination) should continue as planned. Also, for those patients randomised to lapatinib alone (Arm 2) who have already finished their therapy, a discussion between patients and their treating physicians should take place to evaluate whether they should also receive trastuzumab treatment. ■

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2. Blackwell KL, Burstein HJ, Storniolo AM, et al: Randomized study of Lapatinib alone or in combination with trastuzumab in women with ErbB2-positive, trastuzumab-refractory metastatic breast cancer. *J Clin Oncol* 28:1124-30, 2010

3. Gianni L, Pienkowski T, Im YH, et al: Neoadjuvant Pertuzumab (P) and Trastuzumab (H): Antitumor and Safety Analysis of a Randomized Phase II Study ('NeoSphere'). Presented at: 33rd Annual San Antonio Breast Cancer Symposium; December 8-12, 2010; San Antonio, TX

4 Baselga J, Bradbury I, Eidtmann H, et al: First Results of the NeoALTTO Trial (BIG 01-06 / EGF 106903): A Phase III, Randomized, Open Label, Neoadjuvant Study of Lapatinib, Trastuzumab, and Their Combination Plus Paclitaxel in Women with HER2-Positive Primary Breast Cancer. Presented at: 33rd Annual San Antonio Breast Cancer Symposium; December 8-12, 2010; San Antonio, TX

BIG 3-04 MINDACT / EORTC 10041

SUCCESSFUL END OF ACCRUAL AND FEEDBACK FROM SITES

BY CAMILO MOULIN, GUSTAVO WERUTSKY, KRISTEL ENGELEN, ROEL GOOSSENS, VIRGINIE SOETE, JAN BOGAERTS AND FATIMA CARDOSO ON BEHALF OF THE TRANSBIG-MINDACT EXECUTIVE COMMITTEE

The European Organization for Research and Treatment of Cancer (EORTC), BIG, and collaborators are pleased to announce the completion of patient accrual for the BIG 3-04/EORTC 10041 MINDACT (Microarray In Node negative and 1-3 positive lymph node Disease may Avoid Chemotherapy Trial) study. MINDACT is a multi-center, prospective, randomized phase III trial, sponsored and coordinated by the EORTC and run under the TRANSBIG network. The MINDACT trial investigates the added clinical value of the 70-gene profile (Mammaprint™) to standard clinicopathological criteria for the selection of breast cancer patients for adjuvant chemotherapy (CT). The trial also aims to explore two additional questions in the adjuvant setting: the validation of a non-anthracycline regimen (docetaxel plus capecitabine) and the evaluation of the switching strategy and extended duration of endocrine therapy (7 years of letrozole vs. 2 years of tamoxifen followed by 5 years of letrozole).

The trial started recruitment in February 2007 and as of October 2011 more than 6694 patients in 111 institutions across ten European countries were enrolled, out of more than 11 000 registered.

Country	Open sites	Enrolled patients
Belgium	10	828
The Netherlands	21	2092
Spain	11	546
France	25	2066
Slovenia	2	37
Germany	21	835
UK	8	66
Italy	12	199
Switzerland	1	25

Figure 2: Enrolled patients per country

During accrual, the results of the pilot phase, which included the first 800 patients, were presented at the EBCC-7 in 2010[1]. The main conclusions were that this logistically complex trial is feasible in a multinational setting, and that the proportion of patients with discordant results, the expected reduction in CT indication in the Mammaprint™ low-risk group, and the compliance to treatment assignment in the risk-discordant groups were according to plan.

Later, a late-breaking abstract[2] was presented at ECCO 16 – ESMO 36 in Stockholm in September 2011. The presentation shared that MINDACT accrual has been success fully completed and the trial's complex logistics, including real-time collection of frozen tumor tissue, were proven feasible in a multinational, multicentric setting.

Figure 1: Recruitment curve of registered and enrolled patients

We would like to thank all the patients who have participated in MINDACT and all the investigators and their staff for their continual commitment, support, and efforts made to achieve this important milestone.

We are also grateful to all our funding bodies, without whom MINDACT would not be possible: the European Commission Framework Programme VI (FP6-LSHC-CT-2004-503426), the Breast Cancer Research Foundation, Novartis, F. Hoffman-La Roche, Sanofi-Aventis, the US National Cancer Institute (NCI), the EBCC-Breast Cancer Working Group, the Jacqueline Seroussi Memorial Foundation, Prix Mois du Cancer du Sein, Susan G. Komen for the Cure®, Fondation Belge Contre le Cancer, Dutch Cancer Society (KWF), Association Le Cancer du Sein, Parlons-en!, Deutsche Krebshilfe, and the Grant Simpson Trust and Cancer Research UK. The whole genomic analyses have been kindly provided by Agendia.

The Study Coordinators also want to give a warm thank you to all the members of the EORTC MINDACT team over these years! ■

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MINDACT: INVESTIGATORS' EXPERIENCES

"The apparent complexity of MINDACT led us to examine the consenting and sample procurement for perioperative clinical trials in Dundee and brought together the multidisciplinary team to successfully address the logistical issues. MINDACT was challenging, yes, but very worthwhile for team building and patient-focused care."

Dr Alastair Thompson, University of Dundee, UK

"The outstanding partnership with EORTC and BIG in managing such an innovative trial has provided a real growth opportunity for the Gruppo Oncologico Italiano di Ricerca Clinica (GOIRC). The technical and clinical issues encountered on the way turned out to be a stimulating challenge for a qualification that continues to improve."

Dr Rodolfo Passalacqua & Dr Renata Todeschini, Azienda Istituti Ospitalieri, Cremona, Italy

"When speaking about MINDACT there are two main points to highlight: the logistics (MINDACT involved almost all the specialists managing breast cancer patients!), and the patients' views about enrolling in this particular clinical trial. Setting up the study proved to be hard for us in terms of communication between specialists, and especially because of the need to work with fresh frozen tissue.

To determine the pitfalls and improve our results we organised a team meeting every two months. The crucial issue was to inform the entire team when a patient was enrolled in the trial and to make sure that, at the time of surgery, the frozen material was correctly collected for the genomic test. If something went wrong with the material collection, then the patient would become ineligible.

It was a onetime shot. So to avoid any miscommunication and "loss of patients", we used to send an email to all involved in the study informing them about the date of surgery at the time the patient signed the informed consent form. I should say that there was no reluctance from the specialists involved and that everyone has worked hard to accomplish the study.

One of the most remarkable things about MINDACT has been the reaction of patients to this new type of clinical trial: 99% of patients received the trial with hope and were willing to participate. Additionally, after the MINDACT Patients' Workshop held during EBCC-7 in March 2010 in Barcelona, we were approached by several newly diagnosed breast cancer patients wanting to join the study,

which is something quite unusual. Most clinical trials are driven by the medical oncologist, but in MINDACT the surgeon was the first to receive and consent the patient. This has made the interaction between the surgeons, pathologists and medical oncologists much closer."

Dr Isabel Rubio, Hospital Universitario Vall d'Hebron, SPAIN

"The MINDACT study has been a great success in The Netherlands: with 20 actively participating hospitals, we have been very effective in drawing attention to translational research, including MammaPrint™. Stella Mook – back then still a fellow – coordinated the MINDACT pilot study, which showed that MINDACT was logistically feasible[1]. Inge Eekhout joined Stella from October 2007.

The NKI-AVL was the first Dutch hospital to initiate MINDACT in March 2007. The experience gained there was very helpful in starting up other sites. We facilitated this by having guidelines and checklists in place, and by serving as a local 'help desk' in our capacity as designated National Coordinating Centre). The help desk proved to be extremely helpful for investigators, especially during their busy consultation hours. We believe that this was instrumental to the success of MINDACT in the Netherlands.
To make sure everyone was informed and remained motivated we circulated national newsletters at least three times a year and organized three Investigators' Meetings with inspiring presentations and delicious food! We also developed a Dutch website (www.mindact.nl), where the different disciplines/sites can find all the required documents and read about the latest developments.
In 2009 Valesca Rètel, a PhD student in the NKI-AVL involved in a MINDACT side study ('Impact of genomic testing'), and Jolanda Remmelzwaal joined the Dutch MINDACT team. Some obstacles in the coordination of the trial emerged, and Inge and Jolanda had to find creative solutions, which were very effective.

Having completed recruitment, we can now reflect on a very challenging study, but one that was embraced by many enthusiastic participants, all of whom will ensure that MINDACT will become a landmark in the field of breast cancer. Finally, we would like to thank the EORTC, and particularly Kristel Engelen, Jillian Harrisson, Miet Celis, Roel Goossens and Virginie Soete, for the very pleasant cooperation. We can try, as a NCC, to do our utmost to offer the best service to everyone, but without good cooperation and communication with the EORTC this would be impossible."

Dr Emiel Rutgers, Ms Inge Eekhout and Ms Jolanda Remmelzwaal, NKI-AVL, THE NETHERLANDS

Reference

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NEWS FROM THE LAST TRANSBIG TRAINEES

With the end of the formal support by the European Commission under Framework Programme VI to the TRANSBIG Consortium, the 2010-2011 TRANSBIG traineeship programme, dedicated to translational research, was the last one of a series of five.

We asked Camilo Moulin and Carmen Criscitiello to talk us through their experience and to tell us how the TRANSBIG traineeship will be useful in their professional future.

CAMILO MOULIN
TRANSBIG Trainee
EORTC, Brussels, Belgium

I am a Brazilian physician who graduated from the Federal University of Espírito Santo, Brazil. After finishing medical school I moved to São Paulo to do my residency training in internal medicine (at the University of São Paulo) and medical oncology (at the Sírio-Libanês hospital). Back then I was already proud and delighted to be able to work in very renowned places, without knowing what was yet to come in my professional endeavors.

After finishing my medical oncology training, I started working as an associate oncologist in a large comprehensive cancer center, the Hospital de Câncer de Barretos, in São Paulo state's countryside. Nonetheless, since early in my training, I realized that more experience in cancer research would be important to me, both from the perspective of a caregiver, and to better understand patients' needs. A lack of clinical trials for some breast cancer patients and a wide range of unanswered questions in my daily practice further increased my feeling that I needed to acquire experience in research.

With great excitement – both for the professional opportunity and the experience of living abroad – I accepted the challenge of moving to Brussels to join the Breast European Adjuvant Study Team at the Jules Bordet Institute as a research fellow, under the supervision of Dr Evandro de Azambuja and Dr Martine Piccart. There, I started getting acquainted with large international phase III trials and took my first steps in the implementation and running of translational research in breast cancer clinical trials.

After the fruitful experience at Jules Bordet, I decided to go one step further in translational research: I applied to and was awarded a TRANSBIG traineeship position at the European Organisation for Research and Treatment of Cancer (EORTC). I started working there in November 2010, and was mainly involved in the BIG 3-04 / EORTC 10041 MINDACT trial quality assurance and quality control program. MINDACT is investigating the added clinical value of the 70-gene profile (Mammaprint™) to standard clinico-pathological criteria for the accurate selection of breast cancer patients for adjuvant chemotherapy.

MINDACT is a large phase III trial with a strong translational component and very complex logistics, including real-time collection of frozen tumor tissue. MINDACT is a pivotal trial when it comes to personalized medicine and genomic risk profiling. Such aspects of the trial made my tasks more challenging and diverse – but in a very positive way! Among my broad range of assignments, I was in charge of providing medical advice to sites, developing and organizing their questions in FAQs, and assessing patients' SAEs and safety issues. Moreover, I actively participated in the Executive Committee meetings, implemented a protocol amendment, helped to develop a pathology quality assurance assessment and provided medical input on statistical issues.

In addition, because MINDACT represents a major collaboration between the EORTC and the BIG networks and involves investigators from around Europe, I experienced first-hand some of the important milestones of this trial, such as the successful end of accrual (6694 enrolled patients out of 11291 registered) and a late-breaking abstract in the presidential session at ECCO-ESMO 2011 in Stockholm[1].

Being a TRANSBIG trainee has been a very positive experience. Beyond that, being situated at EORTC Headquarters made my experience even more pleasant, because I had the opportunity to interact with statisticians and peers with different research expertise, get to know fellows from all over the world and make new friends. From an educational point of view, the TRANSBIG traineeship at EORTC also gave me the opportunity to stay updated in both oncology and research by attending the most renowned oncology meetings in the world (e.g., ASCO, ECCO, St. Gallen) and a myriad of internal and local training sessions in medical oncology, statistics, and translational research, not only as a participant but as a speaker as well.

I am sure that this one-year traineeship will be very helpful in my future career, whether in Brazil or elsewhere, whether as a clinician or researcher. Especially in our field there will always be something to learn and we should be open and prepared for that. Life is never static, nor is our knowledge. But we have to bear in mind that the knowledge should be used and shared, otherwise science will not evolve. This is one of the principles of the TRANSBIG traineeship program, and although this was the last year it was offered, I am sure that we TRANSBIG trainees and academic researchers in general will benefit tremendously from the study results that will emerge in the coming years.

Last, I would like to thank my colleagues, friends, and co-workers at EORTC, especially Dr Gustavo Werutsky, for all their help getting me oriented, and their support and partnership. My warm thanks also go to the BIG team, and especially to Dr Fátima Cardoso, for offering me such a precious opportunity and the always harmonious and synchronized sharing of tasks. ■

Reference

1. Rutgers E, Bogaerts J, Cardoso F, Werutsky G, Delaloge S, Van 't Veer L, Rubio IT, Moulin C, Engelen K, Viale G, Thompson AM, Passalacqua R, Nitz U, Vuylsteke P, Pierga JY, Piccart-Gebhart M. The EORTC 10041/ BIG 03-04 MINDACT (Microarray in Node Negative and 1 to 3 Positive Lymph Node Disease May Avoid ChemoTherapy) Trial: Patients' Baseline Characteristics and Logistics Aspects After a Successful Accrual. LBA 10, presidential session at ECCO 16th – ESMO 36th Multidisciplinary Congress, Stockholm, Sweden, 2011

TRANSBIG TRAINEESHIP

CARMEN CRISCITIELLO
TRANSBIG Trainee
IJB, Brussels, Belgium

I have been working in breast cancer research since 2005, when I started my specialization in clinical oncology at the Università Federico II in Naples, Italy. I have always been fascinated by translational research and the way it is conducted, and it did not take much time for me to develop a special interest in breast cancer. During the last year of specialization I was given the opportunity to receive special training in translational research at the Jules Bordet Institute in Brussels, renowned for its research in the field of breast cancer. After obtaining my specialization I attended a PhD program, in the context of which I applied for a TRANSBIG traineeship position at the same institute. It was important to me to be able to continue my research at the Breast Cancer Translational Research Laboratory J.C. Heuson at the Institute, as I had the feeling that I had not yet spent sufficient time there to learn everything required to enhance my competencies in the field and that would be needed for my career my future career. This traineeship enabled me to learn a wide range of skills and to broaden my knowledge of techniques such as gene-expression profiling and detection of circulating tumor cells.

The main project I worked on during the traineeship period is a large-scale epigenetic and gene expression characterization of Luminal A breast cancers aiming to interpret their heterogeneous clinical behavior. Although first generation multigene signatures have improved breast cancer prognostication, their ability to provide information useful for guiding treatment decision-making for patients with advanced tumor stages is scarce. Indeed, breast cancer patients with advanced disease (i.e., presence of positive lymph nodes), namely the "genomic low risk" Luminal A tumors as defined by first generation signature, show poor clinical outcome, suggesting that these are a clinically distinct entity from the "classic" luminal A tumors. We hypothesized that this more aggressive behavior might be the consequence of accumulations of genetic and epigenetic alterations during breast cancer progression.

Therefore, our work consisted in interrogating in an unbiased manner epigenetic and gene expression aberrations to molecularly characterize advanced stage Luminal A breast cancer. Ultimately we hope that this work will serve to individualize and optimize breast cancer management in this subgroup of patients for whom first generation signatures add little or no information to current clinico-pathological parameters.

Furthermore, I received mentoring and broad training in translational research, which included areas such as ethics, designing translational clinical trials, statistics, bioinformatics and writing papers. In addition, I was able to interact with and learn from clinicians and scientists of different scientific backgrounds, as well as to attend seminars and lecturers given by prominent speakers.

This experience will be invaluable for my professional future. It has provided me with the skills necessary to pursue a career in breast oncology, combining clinical practice with a strong laboratory and clinically-oriented research program in translational medicine. I am sure that there would have been no better way for me to advance my professional growth. ■

TRANSBIG TRAINEES & HOST INSTITUTIONS 2006 - 2011

2006-2007	Stella Mook, NL	Nederlands Kanker Instituut (NKI), The Netherlands
	Alexandar Celebic, ME	Institut Gustave Roussy (IGR), France
2007-2008	Philippe Bedard, CA	Institut Jules Bordet (IJB), Belgium
	Roman Sreseli, GE	Ninewells University Hospital & Medical School, UK
2008-2009	Camelia Colichi, RO	Institut Gustave Roussy (IGR), France
	Gustavo Werutsky, BR	European Organisation for Research and Treatment of Cancer (EORTC), Belgium
2009-2010	Ivana Bozovic, SP	BIG HQ, Belgium
	Carlos Castaneda, PE	Hospital Universitario 12 de Octubre, Spain
2010-2011	Carmen Criscitiello, IT	Institut Jules Bordet (IJB), Belgium
	Camilo Moulin, BR	European Organisation for Research and Treatment of Cancer (EORTC), Belgium

IMPAKT 2012: EXCELLENT ABSTRACTS SHOWCASE & TRAINING OPPORTUNITIES

Co-chaired by Sherene Loi and Fabrice André, the IMPAKT Breast Cancer Conference will be back in 2012, 3 to 5 May in Brussels, with an outstanding panel of speakers, excellent training opportunities for early-career researchers and some "firsts" in its scientific programme, including, among others:

- Session to develop a consensus opinion about the clinical relevance of prognostic multigene signatures in daily practice and about defining medically useful molecular sub-classification of breast cancer
- Overview of novel drugs and biomarkers still under development but close enough to be relevant for the clinic
- A guided demonstration of biotech advances and related discussions

Abstract submission deadline is 18 January 2012

Submit your abstract at www.impakt.org in one of the following categories and attend IMPAKT, now at its 4th edition:

Submission categories include:
- Adjuvant medical therapy
- Biomarkers
- Detection and diagnosis
- Loco-regional therapy
- Imaging
- Molecular biology (pre-clinical)
- New drug development
- Miscellaneous

Best Abstract Sessions and Poster Walk
Abstracts will have excellent showcase opportunities at the conference:

- Authors of abstracts with original data of superior quality will be invited to present their research orally in Best Abstract Sessions. Presentations will be followed by expert discussion on relevant research perspectives.
- Abstracts selected for poster presentation will be on display for the duration of the conference. During dedicated Poster Walk sessions participants will have the opportunity to discuss selected posters with both their authors and experts in the field.

IMPAKT 2011: training course

A restricted number of travel grants are available.

Pre-IMPAKT Training Course
The IMPAKT conference will be preceded by a training course for early-career researchers on 2 to 3 May. This course will help participants understand key topics of translational research that are relevant to patient care in breast cancer, including:
- PI3K biology; PIK3CA, PTEN and AKT gene alteration in human breast cancer
- Drug development concepts: illustration based on PI3K inhibitors
- Translational research on host-tumour interactions
- Updates on latest technological advances: gene expression, MiRNA, SiRNA screens, CTCs

To ensure an interactive learning environment, attendance is limited to 50 people. Application deadline is 1 February 2012. ■

For more information visit www.impakt.org

IMPAKT 2011: Poster Walk

BIG PUBLICATIONS

MARCH - DECEMBER 2011

- Loi S, Symmans WF, Bartlett JM, Fumagalli D, Van't Veer L, Forbes JF, Bedard P, Denkert C, Zujewski J, Viale G, Pusztai L, Esserman LJ, Leyland-Jones BR. Proposals for uniform collection of biospecimens from neoadjuvant breast cancer clinical trials: timing and specimen types. *Lancet Oncol*. 2011 Nov;12(12):1162-8.

- Coleman RE, Marshall H, Cameron D, Dodwell D, Burkinshaw R, Keane M, Gil M, Houston SJ, Grieve RJ, Barrett-Lee PJ, Ritchie D, Pugh J, Gaunt C, Rea U, Peterson J, Davies C, Hiley V, Gregory W, Bell R for the AZURE Investigators. Breast-Cancer Adjuvant Therapy with Zoledronic Acid. *N Engl J Med* 2011; 365:1396-1405 October 13, 2011

- Chirgwin J, Sun Z, Smith I, Price KN, Thürlimann B, Ejlertsen B, Bonnefoi H, Regan MM, Goldhirsch A, Coates AS., The advantage of letrozole over tamoxifen in the BIG 1-98 trial is consistent in younger postmenopausal women and in those with chemotherapy-induced menopause. *Breast Cancer Res Treat*. Epub 2011 Sep 4.

BIG MEETINGS IN 2012

BIG Scientific Meeting
Wednesday, 21 March 2012
To coincide with EBCC-8, 21-24 March 2012, Vienna, Austria

BIG Advisory Council Meeting
Thursday, 22 March 2012
To coincide with EBCC-8, 21-24 March 2012, Vienna, Austria

4th IMPAKT Breast Cancer Conference
3-5 May 2012
Brussels, Belgium
www.impakt.org

BIG-NABCG Annual Meeting
5-6 May 2012
Brussels, Belgium (by invitation only)

BIG General Assembly
Sunday, 3 June 2012
To coincide with ASCO, 1-5 June 2012, Chicago, IL, USA

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Deadline: **18 January 2012**

4TH IMPAKT BREAST CANCER CONFERENCE

3-5 May 2012
Brussels, Belgium

HIGHLIGHTS

- New trends in pathology research
- Updates on recent landmark translational aspects in breast cancer
- Biomarker approval and reimbursement policies (Satellite Symposium)
- Biomarker consensus and guidelines (New!)
- Biotech walk (New!)
- Triple negative breast cancer

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